

Redacted Data Submitted by the Primary Manufacturer and Other Interested Parties for Imbruvica

Below are redacted versions of the data submitted by the Primary Manufacturer and other interested parties in response to the Negotiation Program information collection request.¹ These redacted data have been redacted consistent with the confidentiality standards described in section 40.2 of the revised guidance and do not contain proprietary information, protected health information (PHI)/personally identifiable information (PII), or other information that is protected from disclosure under applicable law.

Respondents were permitted to include citations and attachments (hereinafter, collectively called “supplemental materials”) within their submissions for certain questions specified in the information collection request; therefore, you may observe that the number and order of any supplemental materials included as part of each response below will vary.

¹ The Negotiation Program information collection request is available on the Office of Management and Budget’s (OMB’s) website at the following link: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202306-0938-013 and described in section 50 of revised guidance.

Section 1194(e)(1) Data Factors

IPAY Year: 2026

Manufacturer: Pharmacyclics LLC

Drug: Imbruvica (Ibrutinib)

Background: For the first year of the Medicare Drug Price Negotiation Program (“the Negotiation Program”), CMS selected 10 Part D high expenditure, single source drugs for negotiation. Section 1194(e) of the Act requires Centers for Medicare & Medicaid Services (CMS) to consider two sets of factors as the basis for determining the offer and counteroffer throughout the negotiation process: (1) certain data that must be submitted by the manufacturer of each drug selected for negotiation and (2) evidence about alternative treatments, as available, with respect to each selected drug and therapeutic alternative(s) for each selected drug. After entering into an agreement under the Negotiation Program with CMS and in accordance with section 1193(a)(4) of the Act, the Primary Manufacturer of each selected drug submitted to CMS the following information with respect to a selected drug: information that CMS required to carry out negotiation, including but not limited to the factors listed in section 1194(e)(1) of the Act. For IPAY 2026, the Primary Manufacturer of each selected drug were tasked to provide the following data factors for each of its selected drug(s), which were specifically:

- C: Research and Development Costs and Recoupment,
- D: Current Unit Costs of Production and Distribution,
- E: Prior Federal Financial Support,
- F: Patents, Exclusivities, and Approvals, and
- G: Market Data and Revenue and Sales Volume Data.

The Primary Manufacturer is responsible for aggregating and reporting all necessary data on its selected drug(s) from other parties, as applicable.

Disclaimers: With the exclusion of publicly available data, all manufacturer submitted data is considered proprietary and confidential. The data contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Note: Primary Manufacturers submitted required data in the Health Plan Management System (HPMS). Please note that the format of manufacturer responses is dependent on the data element requested. For example, some requested responses are “yes or no”, while other response options in HPMS provided a drop-down menu. However, some responses could be more complex and subjective, such as dollar

amounts, cost per unit, etc. For many questions, the ICR instructs the manufacturer to include an explanation. In some instances, an explanation is required and in other instances, the ICR directs the user to include an explanation “as necessary.” CMS instructs manufacturers to indicate “n/a” if they choose not to include an explanation in this case.

C. Research and Development Cost							
<p>Description: Section C contains five questions, related to different types of R&D costs incurred by the Primary Manufacturer, including acquisition costs. Each of these questions required the Primary Manufacturer to report, as applicable: (1) dollar amounts for R&D costs, which must be reported in the numerical response field and (2) explanations of how those costs were calculated in the free response field. Section C also contains one question about the Primary Manufacturer’s global and U.S. total lifetime net revenue for the selected drug. This question required the Primary Manufacturer to report, as applicable: (1) the dollar amount for global, total lifetime net revenue, which must be reported in the numerical response field, (2) an explanation of how this amount was calculated in the free response field, (3) the dollar amount for U.S. lifetime net revenue, which must be reported in the numerical response field, and (4) an explanation of how this amount was calculated in the free response field.</p>							
Primary Manufacturer Acquisition Costs of the Selected Drug	Total Acquisition Costs for the Selected Drug	Basic Pre-Clinical Research for All Approved Indications of the Selected Drug	Post-IND Costs for All Approved Indications of the Selected Drug	Costs of Failed or Abandoned Products Related to the Selected Drug	Direct Costs of Other R&D for the Selected Drug Not Accounted for Above	Global Total Lifetime Net Revenue for the Selected Drug	U.S. Total Lifetime Net Revenue for the Selected Drug

Explanations:

Explanation of Allocation of Total Acquisition Costs for the Selected Drug

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AbbVie/Pharmacyclics submits this information under CMS's assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42).

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On May 26, 2015, AbbVie acquired Pharmacyclics, a biopharmaceutical company that developed and commercialized IMBRUVICA (ibrutinib), a Bruton's tyrosine kinase (BTK) inhibitor, targeting B-cell malignancies for people impacted by select forms of cancer.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

As previously reported in AbbVie's Form 10-Q for Q1 2023 filed with the SEC on May 5, 2023, and Form 10-Q for Q2 2023 filed with the SEC on August 7, 2023, the selection of Imbruvica for the Drug Price Negotiation Program under the Inflation Reduction Act could unfavorably impact AbbVie's ability to recover the carrying value of Imbruvica, resulting in an intangible asset impairment which may have a material effect on AbbVie's results of operations."

Explanation of Basic Pre-Clinical Research Costs

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

AbbVie/Pharmacyclics and JBI are under a collaboration agreement for the joint development and commercialization of Imbruvica where AbbVie/Pharmacyclics has exclusive license to commercialize Imbruvica in the United States. Under this agreement JBI and AbbVie/Pharmacyclics share costs and revenue globally. Costs reported are net of JBI reimbursement to AbbVie/Pharmacyclics for study-specific expenses.

The pre-clinical R&D costs reported here are for the development of the oral suspension formulation of Imbruvica the NDA for which was approved by FDA in 2022. R&D for the oral formulation focuses on pediatric patients and those with difficulty swallowing. This research, and the ensuing formulation, which facilitated approval of an indication for a rare disease, pediatric patients with chronic Graft Versus Host Disease (cGVHD), addressed an unmet need for these pediatric patients. . In addition, the oral suspension formulation is used off-label to mitigate unmet medical needs for pediatric patients in other indications as well as geriatric patients and others unable to swallow a capsule or tablet. The

oral suspension gives patients another option to access the medicine they need in an approachable formulation. Additionally, oral suspension of Imbruvica serves a unique unmet need as other available BTKis do not offer an oral formulation.

While valuable, the success of pre-clinical research is not fully predictive of how effective or safe a molecule will be in humans. Moving molecules from pre-clinical research to humans carries a great inherent risk of failure that the manufacturer must bear. Imbruvica was a first-in-class small molecule inhibitor of Bruton's tyrosine kinase which made its development especially high-risk due to the lack of research in humans at the time of Imbruvica development. Greater upfront investment is required with the goal of getting medicine to patients as quickly as possible to help them sooner. This high-risk investment is a necessary contribution to the fields of science and healthcare but must continue to be incentivized. This research investment, in addition to other R&D-related overhead, enables a robust R&D organization to pursue these types of indications and formulations, undertaking great risk, to continue to find new ways to serve patients."

Explanation of Post-IND Costs

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[REDACTED]

[REDACTED]



Imbruvica received accelerated approval for Chronic Lymphocytic Leukemia (CLL), Marginal Zone Lymphoma (MZL), and Mantle Cell Lymphoma (MCL). However, MZL and MCL have since been withdrawn, and therefore are included in the Question 4 costs of failed/abandoned products. Costs associated with Phase IV CLL studies are reported here.



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Imbruvica is a first-in-class small molecule inhibitor of Bruton's tyrosine kinase (BTKi). Before Imbruvica's approval in 2013, chemo-immunotherapy was the standard of care for managing patients with B-cell malignancies, but it had several limitations, such as severe side effects compared to newer oral agents and requiring administration at a cancer infusion center. Imbruvica has significantly transformed the treatment paradigm for CLL and other B-cell malignancies addressing a significant unmet need. As Imbruvica was a first-in-class molecule, extensive R&D was performed to demonstrate Imbruvica's safety and efficacy.

Presently, Imbruvica stands as the most extensively studied targeted therapy across B-cell malignancies in both clinical and real-world settings with 15+ years of ongoing clinical development which includes 18+ phase 3 studies across multiple B-cell malignancies (CLL, MCL, MZL, Waldenström Macroglobulinemia (WM), chronic Graft Versus Host Disease (cGVHD), Follicular Lymphoma, Diffuse Large B cell Lymphoma) and 8+ years of long-term data in the CLL setting. Imbruvica has demonstrated substantial benefit in unique and fragile patient populations, including elderly patients, high-risk patients, patients with multiple comorbidities, other cancers, and vulnerable patient populations.

These post-IND costs also include significant investment in studies of indicated patient populations that represent the most significant usage of Imbruvica in Medicare, including first-line CLL, first-line WM, and second-line cGVHD. Imbruvica is the only approved BTKi in adult and pediatric

patients with cGVHD. Imbruvica has also shown consistent efficacy and safety in vulnerable patients and across diverse racial and ethnic populations. R&D investments were critical to approval of these indications. Clinical trials sought to include a broad set of patients, including patients with unmet medical need. Imbruvica largely serves an elderly population as its main usage is in CLL where the median age of the patient is over 65. Note that per CMS guidance, this submission excludes indirect R&D investments in activities like investigational studies, data readouts, and other meetings and other non-R&D overhead that are critical to the success of R&D, both of which account for significant additional investment."

Explanation of Costs on Allowable

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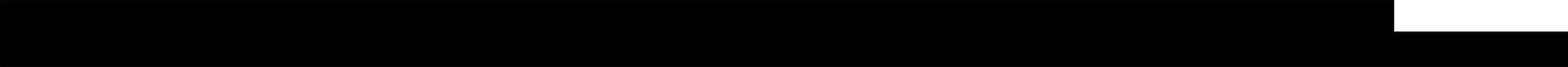
The costs in the submission for Question 4 include direct costs for completed Phase I-III studies and FDA-required post-marketing requirements related to unapproved indications/those no longer being pursued: Mantle Cell Lymphoma (MCL) & Marginal Zone Lymphoma (MZL), Solid Tumor, Multiple Myeloma, Acute Myeloid Lymphoma, Diffuse Large B-Cell Lymphoma, first-line chronic Graft Versus Host Disease, and Imbruvica + Venclexta combination research in Chronic Lymphocytic Leukemia.

[REDACTED]

[REDACTED]



Basic pre-clinical research costs were not included given that the INDs for all unapproved/no longer pursued indications were incurred prior to acquisition. Therefore, all of the costs submitted under this question were for Post-IND clinical research.



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Note that MCL and MZL were previously approved but have since been withdrawn from the market, and therefore the associated costs are captured in this question. Imbruvica has a large body of clinical evidence in B-cell malignancies, including MCL and MZL. These costs represent significant R&D investment and exploration in new indications, while assuming the risk that some indications will fail—rewarding this investment, despite the risk of failure, is an extremely important part of continuing to fund innovation in the industry and expansion into new therapeutic areas for approved products. In particular, the FDA requested that AbbVie/Pharmacyclics pursue MCL and MZL as indications and granted accelerated approval to address significant unmet need in these disease areas. Though now withdrawn from the market, this level of investment and rapid financial support through all cycles of development illustrates a high willingness to invest in disease areas with unmet need.

The spend across several indications in this category of failed or abandoned products highlights that research and development outcomes are difficult to predict. Efficacy and safety both need to be demonstrated for FDA approval. There is significant uncertainty and a strong sense of urgency in drug development to get patients much-needed treatments as quickly as possible. Imbruvica's significant effort for the initial research in these indications and mechanisms also provided a foundation for the further development of drugs with similar mechanism of action."

Explanation of Costs of Other R&D

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[Redacted]

[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

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Imbruvica is a first-in-class small molecule inhibitor of Bruton's tyrosine kinase (BTKi). As a first-in-class molecule, Imbruvica transformed the treatment paradigm for Chronic Lymphocytic Leukemia and other B-cell malignancies. Additionally, Imbruvica paved the way for follow-on BTKis that launched in more recent years. The uncertainty and risk that AbbVie/Pharmacyclics took in acquiring and investing in R&D for Imbruvica cannot be fully captured in the reported costs here. The uncertainty and risk that AbbVie/Pharmacyclics undertook is demonstrated by the fact that it has yet to recoup its R&D investment. [REDACTED]

[REDACTED] Beyond its benefit in high-risk patients and unique populations, Imbruvica is the only BTKi with formulation optionality allowing for personalization of therapies and offers convenient one pill once daily administration. Additionally, as a first-in-class molecule, significant expertise and technical know-how was required to guide the development of Imbruvica that AbbVie/Pharmacyclics has obtained through decades of bringing innovative therapies to patients. The full costs of Imbruvica development must also consider the full breadth of knowledge and expertise of AbbVie/Pharmacyclics which is difficult to quantify."

Explanation of Global

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Global lifetime net revenue was calculated from the date AbbVie/Pharmacyclics acquired Pharmacyclics (May 26, 2015) through the date of the publication of selected drug list (August 29, 2023). Revenue was calculated to include the following:

- 1) United States product revenue, less the following: a) profit sharing payments to collaboration partner JBI, and b) royalty payments to Celera;
- 2) Outside United States “collaboration” revenue received from collaboration partner JBI.

[REDACTED]

[REDACTED]

Explanation of U.S. Lifetime Net Revenue

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U.S. lifetime net revenue was calculated from the date AbbVie/Pharmacyclics acquired Pharmacyclics (May 26, 2015) through the date the of the publication of selected drug list (August 29, 2023). Revenue was calculated to include United States Product Revenue, less the following: a) profit sharing payments to collaboration partner JBI, and b) royalty payments to Celera. [REDACTED]



D. Current Unit Costs of Production and Distribution

Background: Manufacturers were required to report production and distribution unit costs separately for each NDC-11 of the selected drug, including any NDC-11 of the selected drug marketed by a Secondary Manufacturer. A free response field was provided to explain the methodology for calculating the amount reported.

NDC-11	Average Per Unit Production Cost	Average Per Unit Distribution Costs	Indicate Unit Used	Total Unit Volume
57962-0014-28			EA	
57962-0280-28			EA	
57962-0007-12			ML	
57962-0140-09			EA	
57962-0070-28			EA	
57962-0560-28			EA	
57962-0140-12			EA	
57962-0420-28			EA	

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[Redacted]

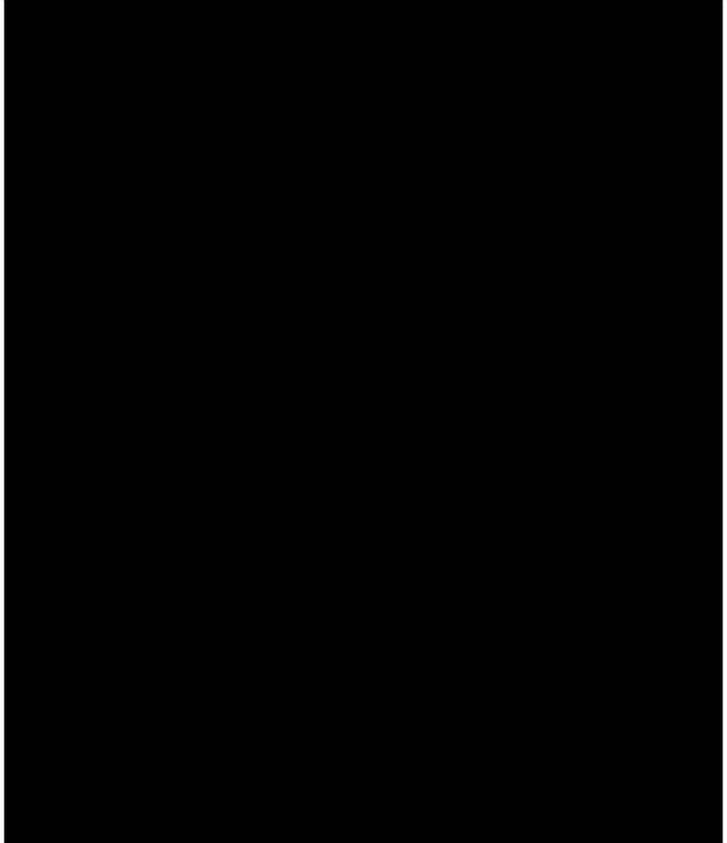


Note: Two NDC's, 57962042071 and 57962056071, are included in Section A as NDC's that were registered and active earlier in the Imbruvica lifecycle. The NDC's were active from February of 2019 to December of 2020. However, these NDC's were not active over the requested time period (12 month period ending May 31, 2023) and thus data related to these NDCs are not included in our submission.

E. Federal Financial Support				
Description: This section pertains to all prior federal financial support provided by federal agencies or federally supported grants or contracts that contributed to direct costs for the basic pre-clinical research and clinical trials phase of research and development for FDA-approved indications of the selected drug to the Primary Manufacturer only. It also pertains to prior federal financial support received for indirect costs of developing the selected drug.				
Total Federal Financial Support	Federal Financial Support	Type of Agreement	Federal Agency(ies) Participating in Agreement	Nature of Agreement
		OTH	US Health and Human Services & National Cancer Institute	AbbVie/Pharmacyclics and NCI have entered into a Cooperative Research and Development Agreement ("CRADA") to collaborate on the non-clinical and clinical development of

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Total Federal Financial Support	Federal Financial Support	Type of Agreement	Federal Agency(ies) Participating in Agreement	Nature of Agreement
				PCI-32765, a Bruton's tyrosine kinase (BTK) inhibitor. 

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Total Federal Financial Support	Federal Financial Support	Type of Agreement	Federal Agency(ies) Participating in Agreement	Nature of Agreement
	 <p>**Footnotes**: A. August 24, 2022 is the date of the last NDA approval for Imbruvica. To account for the short 2022 period from January 1, 2022 to August 24, 2022, we used a pro rata proportion of the 2022 R&D credit (i.e., 236/365 of the total 2022 credit calculated for Imbruvica). - B. August 24, 2022 is the date of the last NDA approval for Imbruvica. To account for the short 2022 period from</p>			

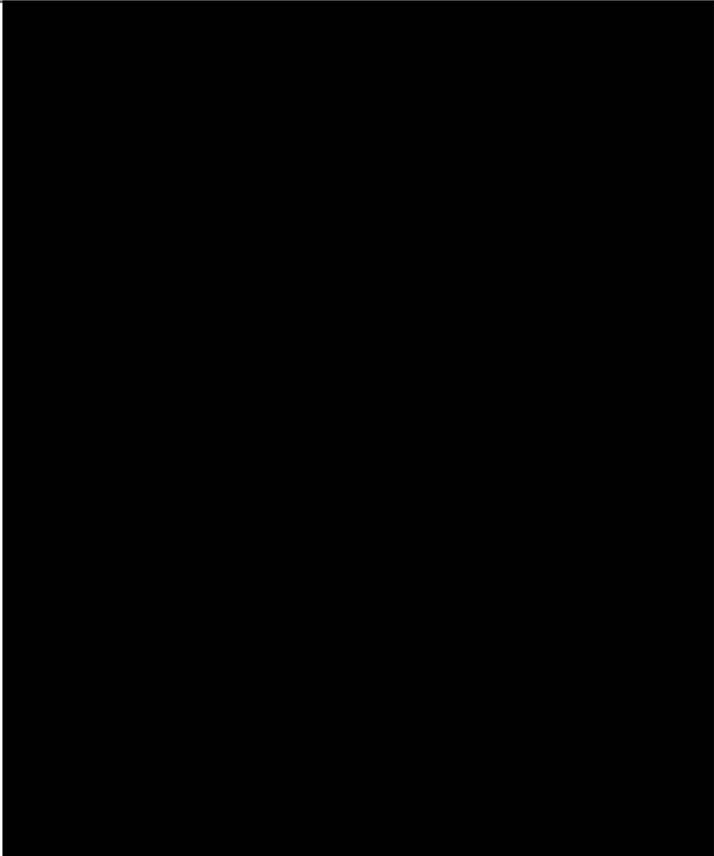
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Total Federal Financial Support	Federal Financial Support	Type of Agreement	Federal Agency(ies) Participating in Agreement	Nature of Agreement
	January 1, 2022 to August 24, 2022, we used a pro rata proportion of the 2022 Orphan Drug Act credit (i.e., 236/365 of the total 2022 credit calculated for Imbruvica).			
[REDACTED]	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p> <p>[REDACTED]</p>	OTH	The National Heart, Lung, and Blood Institute	<p>NHLBI and AbbVie/Pharmacyclics, have entered into a CRADA to collaborate on a phase II clinical study of ibrutinib in combination with fludarabine and pembrolizumab for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). [REDACTED]</p>

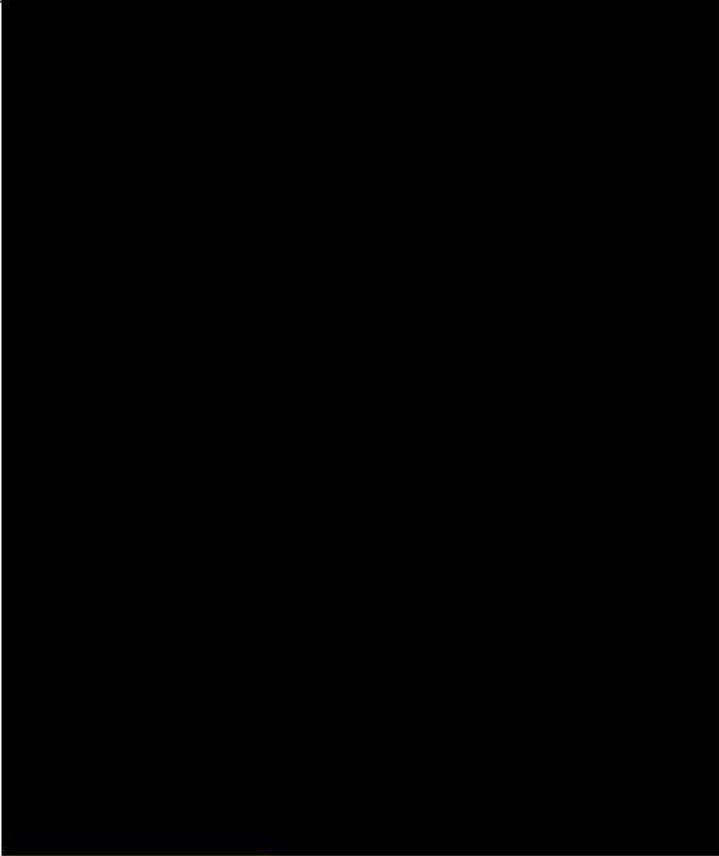
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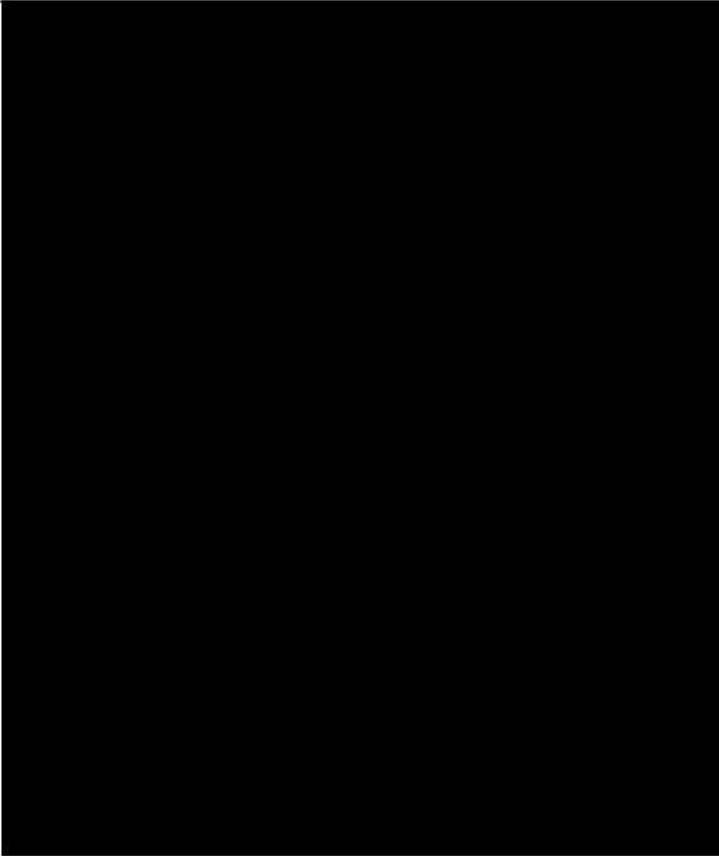
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	<p>**Footnotes**:</p> <p>A. August 24, 2022 is the date of the last NDA approval for Imbruvica. To account for the short 2022 period from January 1, 2022 to August 24, 2022, we used a pro rata proportion of the 2022 R&D credit (i.e., 236/365 of the total 2022 credit calculated for Imbruvica).</p> <p>-</p> <p>B. August 24, 2022 is the date of the last NDA approval for Imbruvica. To account for the short 2022 period from January 1, 2022 to August 24, 2022, we used a pro rata proportion of the 2022 Orphan Drug Act credit (i.e., 236/365 of the total 2022 credit calculated for Imbruvica).</p>			
<p>[REDACTED]</p>	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p> <p>[REDACTED]</p>	<p>OTH</p>	<p>National Cancer Institutes</p>	<p>This is a three party CRADA and collaboration between NCI, Washington University, and AbbVie/Pharmacyclics to perform a phase two pilot study of ibrutinib, in subjects with newly diagnosed chronic graft versus host disease (cGVHD). [REDACTED]</p>

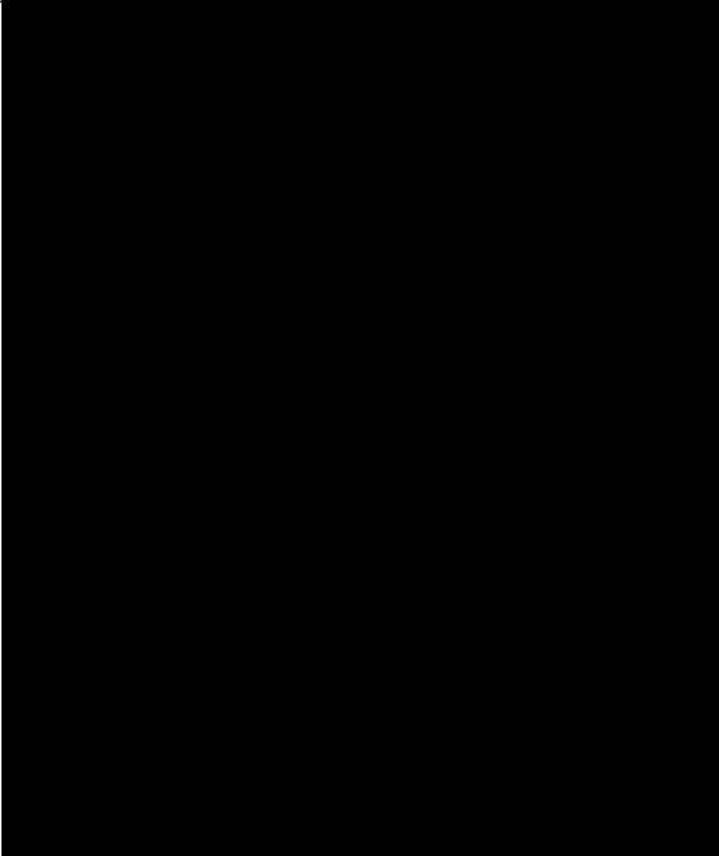
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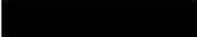
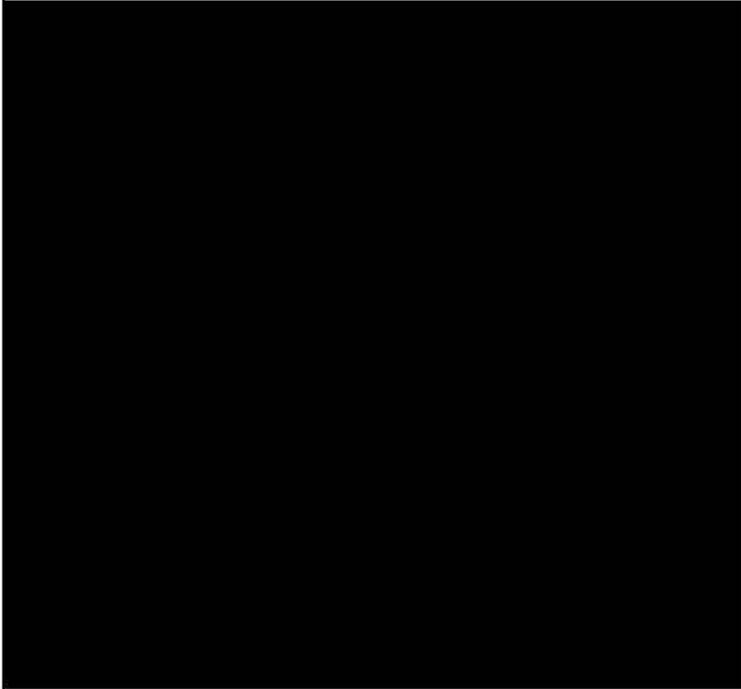
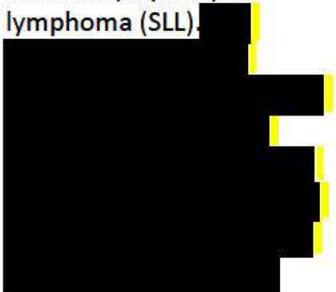
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	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p> 	OTH	The National Heart, Lung, and Blood Institute	<p>CRADA between NHLBI and AbbVie/Pharmacyclics on a phase II clinical study of ibrutinib, for the treatment of patients with chronic lymphocytic leukemia (CCL) or small lymphocytic lymphoma (SLL).</p> 

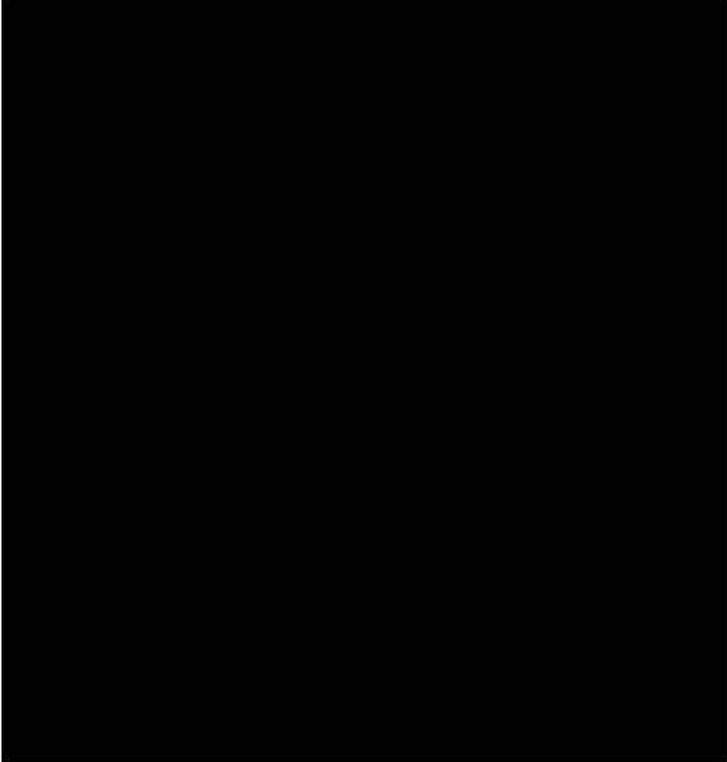
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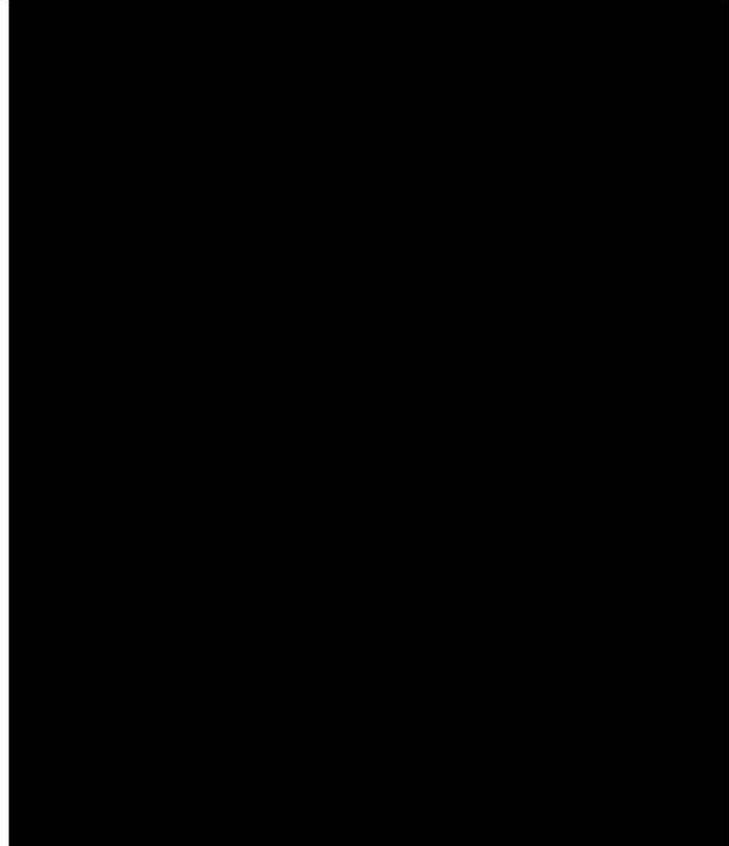
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<p>[REDACTED]</p>	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p> <p>[REDACTED]</p>	<p>OTH</p>	<p>THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE</p>	<p>This is a three party CRADA between NHLBI, Cornell Weill School of Medicine, and AbbVie/Pharmacyclics on a phase II clinical study of ibrutinib for the treatment of patients with chronic lymphocytic leukemia (CCL) or small lymphocytic lymphoma (SLL). [REDACTED]</p>

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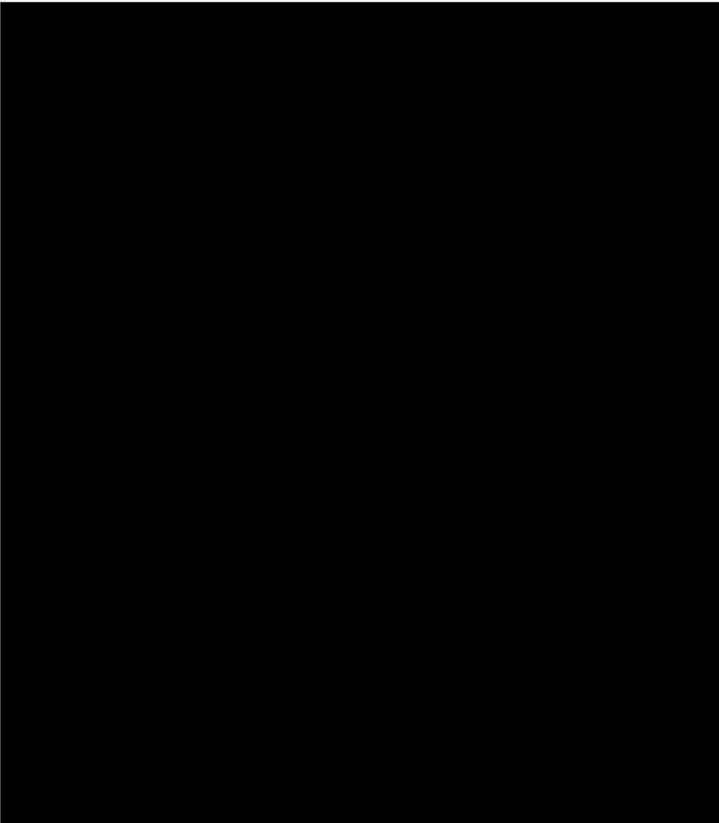
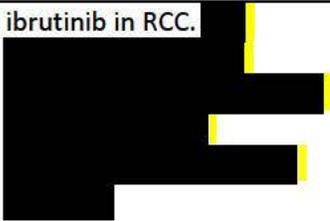
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<div style="background-color: black; width: 100%; height: 20px;"></div>	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p>	OTH	Department of Veteran's Affairs Long Beach System	This is a CRADA between the VA and AbbVie/Pharmacyclics for research on everolimus and

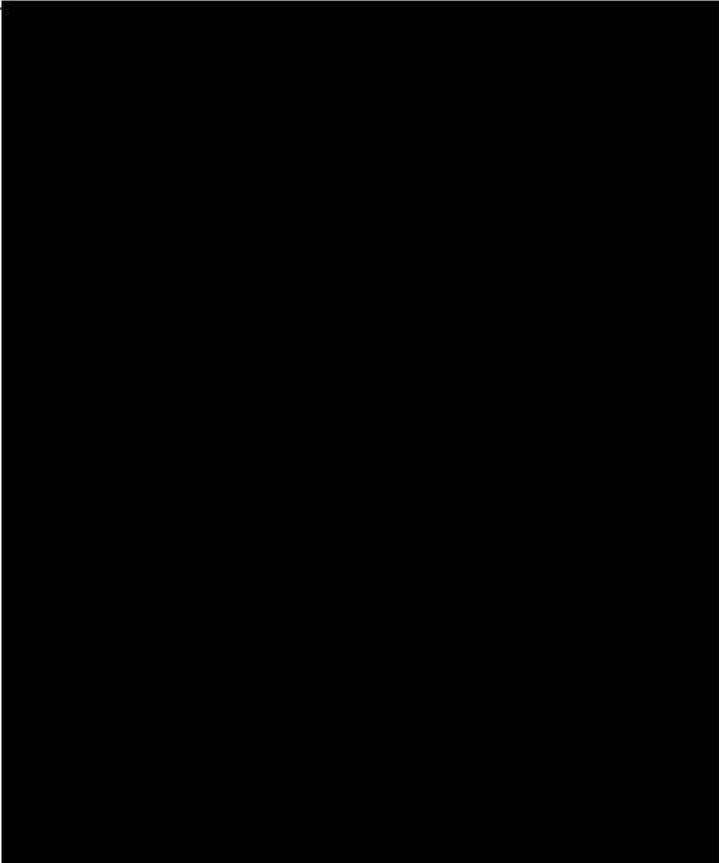
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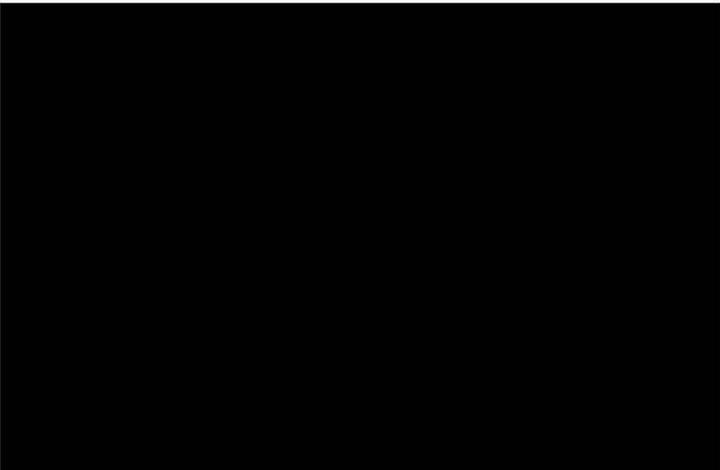
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	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p> 	OTH	Department of Veteran's Affairs Bay Pines	<p>This is a CRADA between AbbVie/Pharmacyclics and the Bay Pines VA System for a Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal and Genitourinary Tumors.</p> 

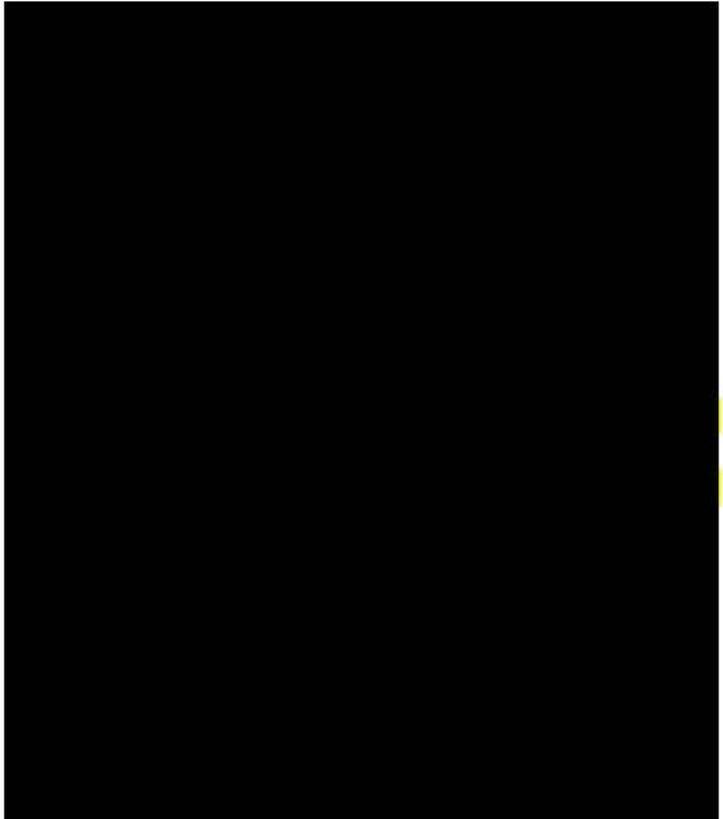
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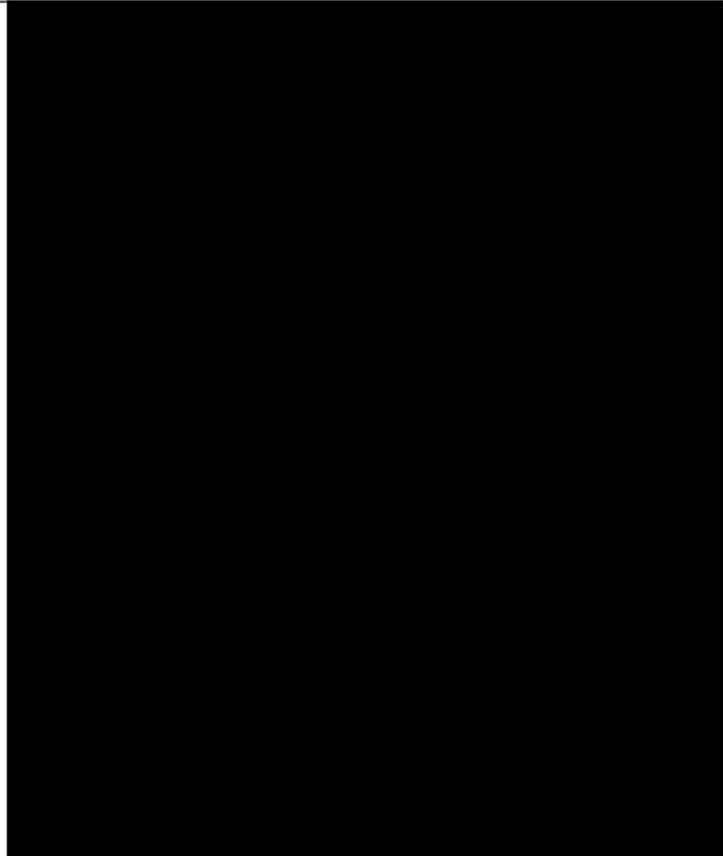
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<div style="background-color: black; width: 100%; height: 20px;"></div>	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p> <div style="background-color: black; width: 100%; height: 30px; margin-top: 10px;"></div>	OTH	NIH	<p>This is a CRADA for a Phase 2 pilot study of ibrutinib, in subjects with newly diagnosed chronic graft versus host disease (cGVHD) with Washington University and the NIH. [REDACTED]</p>

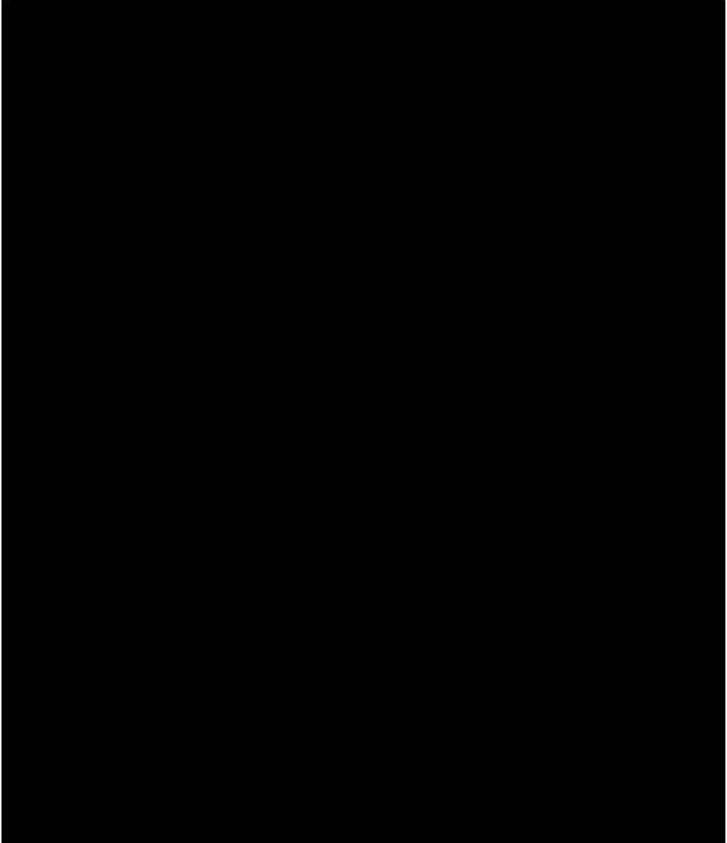
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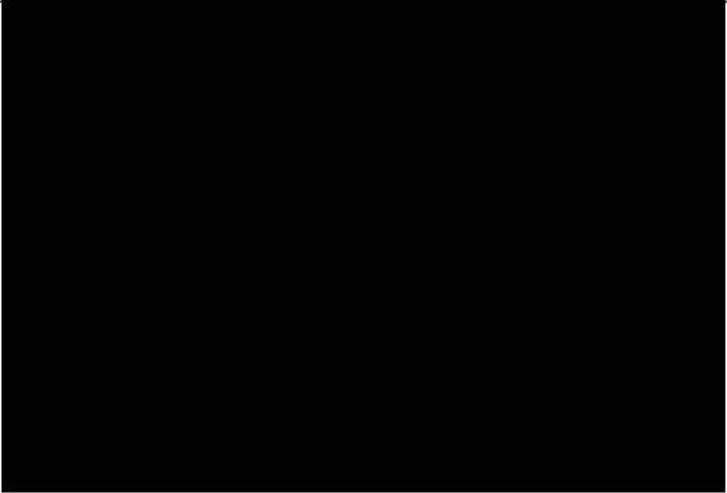
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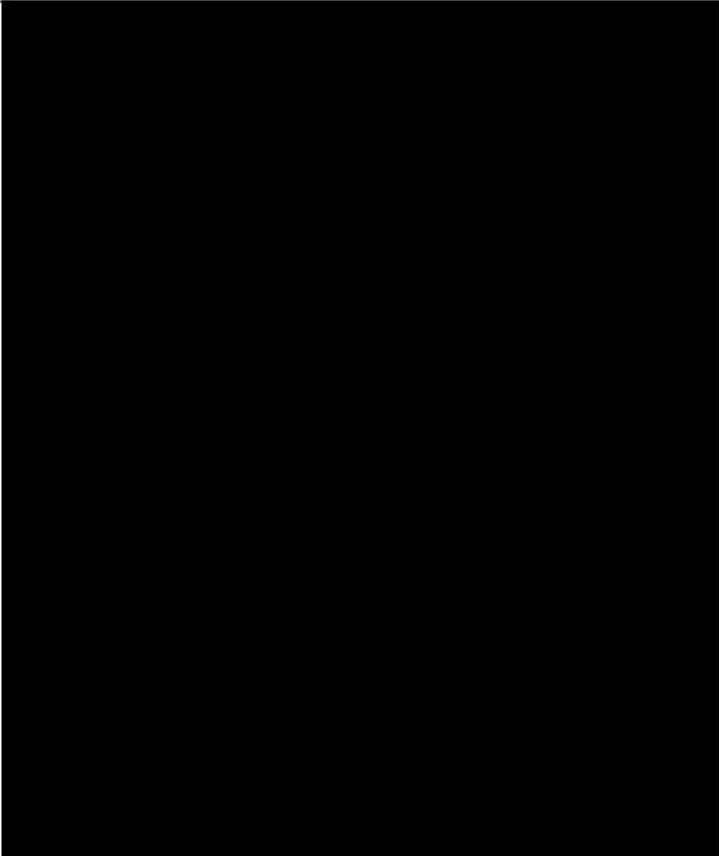
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[REDACTED]	<p>The company has benefited from two types of Federal Financial Support in the form of two separate tax credits related to R&D expenses for Imbruvica – the R&D credit and the Orphan Drug Credit.</p> <p>[REDACTED]</p>	OTH	VA Salt Lake City System	<p>This is CRADA between AbbVie/Pharmacyclics and the VA Salt Lake City for research in Waldenstrom Macroglobulinemia and Lymphoplasmatic Lymphoma in Veterans with non-Hodgkins Lymphoma.</p> <p>[REDACTED]</p>

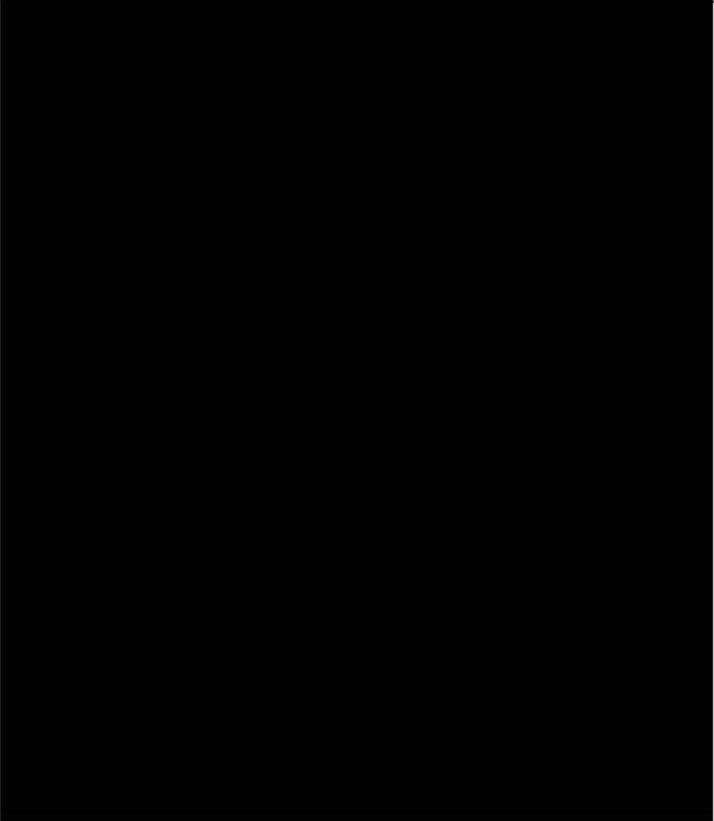
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Explanations: This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics's business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.

AbbVie/Pharmacyclics submits this information under CMS's assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42).

AbbVie/Pharmacyclics's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics's rights to confidential treatment and predisclosure notification.

F. Patents, Exclusivities, and Approvals

Patents (Expired and Non-Expired) and Patent Applications

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This table lists each patent that is related to the selected drug, as well as each application for a patent related to the selected drug that is pending with the USPTO.

Patent #	Date Filed	Patent Expiry Date	Drug Product Patent	Drug Substance Patent	Drug Method of Use Patent	Patent Application Pending	Patent Type	Listed in FDA Orange Book / Purple Book
10828259	2020-04-10	2036-03-03	Y	N	N	N	UTL	Y
10213386	2018-05-03	2036-03-03	Y	N	N	N	UTL	Y
10010507	2018-03-01	2036-03-03	Y	N	N	N	UTL	Y
9655857	2016-03-03	2036-03-03	Y	N	N	N	UTL	Y
9545407	2015-08-07	2035-08-07	Y	N	N	N	UTL	N
10695350	2019-09-25	2034-10-24	N	N	Y	N	UTL	Y
10463668	2017-05-03	2034-10-24	N	N	Y	N	UTL	Y
9795604	2014-10-24	2034-10-24	N	N	Y	N	UTL	Y
9296753	2013-06-03	2033-10-30	Y	Y	N	N	UTL	Y
9540382	2013-06-03	2033-08-18	N	N	Y	N	UTL	Y

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10961251	2020-11-18	2033-06-03	Y	N	N	N	UTL	Y
10752634	2020-04-01	2033-06-03	Y	N	N	N	UTL	Y
10294231	2018-08-23	2033-06-03	Y	N	N	N	UTL	Y
10294232	2018-08-23	2033-06-03	Y	N	N	N	UTL	Y
10125140	2018-07-16	2033-06-03	Y	Y	N	N	UTL	Y
10266540	2018-07-13	2033-06-03	N	Y	N	N	UTL	N
10065968	2018-02-21	2033-06-03	Y	Y	N	N	UTL	N
10106548	2018-02-20	2033-06-03	Y	Y	N	N	UTL	Y
9828383	2017-08-17	2033-06-03	N	N	N	N	UTL	N
9725455	2017-04-26	2033-06-03	N	Y	N	N	UTL	Y
9713617	2016-12-21	2033-06-03	Y	N	N	N	UTL	Y
11672803	2020-07-10	2031-06-03	N	N	Y	N	UTL	Y
10751342	2020-01-21	2031-06-03	N	N	Y	N	UTL	Y
10478439	2018-04-27	2031-06-03	N	N	Y	N	UTL	Y
10016435	2017-09-26	2031-06-03	N	N	Y	N	UTL	Y

F. Patents, Exclusivities, and Approvals

Patents (Expired and Non-Expired) and Patent Applications

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This table lists each patent that is related to the selected drug, as well as each application for a patent related to the selected drug that is pending with the USPTO.

Patent #	Date Filed	Patent Expiry Date	Drug Product Patent	Drug Substance Patent	Drug Method of Use Patent	Patent Application Pending	Patent Type	Listed in FDA Orange Book / Purple Book
10004746	2017-07-26	2031-06-03	N	N	Y	N	UTL	Y
9814721	2016-03-10	2031-06-03	N	N	Y	N	UTL	N
9801883	2016-02-26	2031-06-03	N	N	Y	N	UTL	Y
9125889	2014-07-31	2031-06-03	N	N	Y	N	UTL	Y
9801881	2013-11-26	2031-06-03	N	N	Y	N	UTL	Y
8999999	2013-01-22	2031-06-03	N	N	Y	N	UTL	Y
8754090	2011-12-29	2031-06-03	N	N	Y	N	UTL	N
8008309	2009-07-07	2027-11-13	Y	Y	N	N	UTL	Y
8563563	2012-01-30	2027-04-26	N	N	Y	N	UTL	Y
9266893	2014-01-10	2026-12-28	Y	N	N	N	UTL	N
9181257	2013-11-14	2026-12-28	Y	Y	N	N	UTL	Y
8759516	2013-07-26	2026-12-28	N	N	N	N	UTL	N
8957079	2012-10-17	2026-12-28	Y	Y	N	N	UTL	Y
8754091	2012-07-05	2026-12-28	Y	N	N	N	UTL	Y
8703780	2012-06-18	2026-12-28	N	N	Y	N	UTL	Y
8697711	2012-05-23	2026-12-28	Y	Y	N	N	UTL	Y
8476284	2011-12-16	2026-12-28	N	N	Y	N	UTL	Y
8497277	2011-12-06	2026-12-28	N	N	Y	N	UTL	Y

F. Patents, Exclusivities, and Approvals

Patents (Expired and Non-Expired) and Patent Applications

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This table lists each patent that is related to the selected drug, as well as each application for a patent related to the selected drug that is pending with the USPTO.

Patent #	Date Filed	Patent Expiry Date	Drug Product Patent	Drug Substance Patent	Drug Method of Use Patent	Patent Application Pending	Patent Type	Listed in FDA Orange Book / Purple Book
8735403	2011-09-29	2026-12-28	Y	Y	N	N	UTL	Y
8158786	2011-06-15	2026-12-28	N	N	N	N	UTL	N
8952015	2010-10-19	2026-12-28	N	N	Y	N	UTL	Y
7514444	2006-12-28	2026-12-28	Y	Y	N	N	UTL	Y
10653696	2019-08-08	2031-06-03	N	N	Y	N	UTL	N

Explanations: This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics's business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials. AbbVie/Pharmacyclics submits this information under CMS's assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42). AbbVie/Pharmacyclics's future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics's rights to confidential treatment and predisclosure notification.

Imbruvica's revolutionary therapeutic advancements are reflected in the Imbruvica patents. Those patents embody the result of years of extensive research and development by Pharmacyclics (prior to its acquisition by AbbVie/Pharmacyclics), and further R&D development by AbbVie/Pharmacyclics. These efforts include the creation of a new molecule with exceptional efficacy and tolerability; crystalline forms with beneficial characteristics; formulations enabling patients to take daily oral doses; and an extensive clinical trial program. Trailblazing work on Imbruvica, and investment in its development program and product improvements, transformed the treatment landscape for patients with

certain intractable B-cell cancers and cGVHD, thereby filling many unmet therapeutic needs. These innovations and others are encompassed by the Imbruvica patents.

The first critical invention in Imbruvica's development was the creation of its novel active ingredient, ibrutinib. Ibrutinib is a ground-breaking new chemical entity that covalently binds to the Bruton's tyrosine kinase (BTK) protein, thereby irreversibly inhibiting BTK's activity. Abnormalities in the BTK signaling pathway can cause cancers of the blood and bone marrow. The decision to pursue an irreversible inhibitor in the face of significant industry skepticism was truly innovative. As the first FDA-approved BTK inhibitor, Imbruvica opened the door to a new class of drugs. Several companies have developed follow-on BTK inhibitors.

Clinical research on Imbruvica includes over 150 clinical trials and has resulted in FDA-approvals for diseases including Waldenström's macroglobulinemia (WM), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), chronic lymphocytic leukemia/small lymphocytic lymphoma with 17p deletion (CLL/SLL 17pdel), and chronic graft-versus-host-disease (cGVHD). The patents relating to Imbruvica reflect these indications. Dosing for Imbruvica was developed using an innovative dose escalation study that measured the occupancy and inhibition of BTK instead of trying to determine the maximum tolerated dose. The dosing regimen for Imbruvica that was achieved through this new pharmacodynamic approach contributes to its remarkable tolerability. Imbruvica's impressive clinical results resulted in the FDA granting Breakthrough Therapy Designations (BTDs) for CLL/SLL with 17p deletion and WM. The United States Patent and Trademark Office (USPTO) also acknowledged ibrutinib's superior results over existing therapies in granting several patents claiming methods of treatment using the approved dosages of Imbruvica for the treatment of CLL/SLL, CLL/SLL with 17p deletion, and WM.

Imbruvica is the first FDA-approved treatment for cGVHD, after failure of one or more lines of systemic therapy. Chronic GVHD is a rare, life-threatening condition, affecting subjects who survive past the first 100 days after allogeneic hematopoietic cell transplant, a standard therapy for some hematologic malignancies. Treatment of cGVHD with Imbruvica achieved a remarkable and sustained response rate. Recognizing these results, the FDA awarded a BTD for Imbruvica for the treatment of cGVHD. This innovation is also encompassed in the patent covering Imbruvica's use in treating cGVHD. The strength of this patent was demonstrated when a generic manufacturer lost its challenge on the cGVHD patent before the USPTO in an inter partes review proceeding, confirming the validity of several claims of the patent.

The Imbruvica patent portfolio further reflects its important achievements in its Imbruvica capsule and tablet formulations. Formulating the compound presented several challenges, particularly because ibrutinib was a first-in-class compound with poor solubility, low oral bioavailability, and low bulk density. Scientists overcame these challenges to first invent a novel 140 mg capsule formulation and later an innovative high-load tablet formulation allowing patients to take a single 420 mg daily oral dosage form, rather than multiple capsules per day. These innovations were captured in patents directed to capsule and tablet formulations, respectively.

Patents also reflect the invention of several ibrutinib crystalline forms (polymorphs), including an ibrutinib crystalline form ideal for pharmaceutical formulations. Thus, ibrutinib can be manufactured and stored as an oral dosage form while maintaining its therapeutic

properties. This development work produced an active ingredient that has excellent stability and critically can be formulated into a high-load tablet. Patents have been granted on ibrutinib polymorphs as well, recognizing the innovation in these important inventions.

The strength of these patents has been shown again and again. Nine generic companies have challenged one or more Imbruvica patents in court. None have succeeded. In the only case to reach a final court decision, the court found that all of the asserted patents were valid and infringed. In doing so, the court acknowledged multiple unique features and benefits of Imbruvica’s active ingredient and tablet formulation. The court also recognized that Imbruvica is well-tolerated, safer than standard chemotherapy treatments, and has a low incidence of side effects. The court also acknowledged Imbruvica’s novel dosing regimen, and the pioneering clinical study design. The court also noted the excellent stability and handling characteristics of the Imbruvica crystalline form. As a result, no generic tablet entry is expected before 2036. Settlement agreements and licenses with generic companies seeking approval for ibrutinib capsules permit generic entry on March 30, 2032.

AbbVie’s patents covering its specific inventions have not shielded it from competition from other innovators. Imbruvica competes with other innovator BTK inhibitor drugs, as well as other biologic and small molecule drugs, as the field of competitors has only expanded over time.

Imbruvica was a transformative innovation. Its patent teachings represent major scientific contributions that have already spurred others to build upon its inventions.

F. Patents, Exclusivities, and Approvals				
Regulatory Exclusivity Periods				
Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.				
Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
CIE	2017-02-12	205552	57962-0140	None
CIE	2017-07-28	205552	57962-0140	None
CIE	2018-01-29	205552	57962-0140	None

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
CEE	2018-11-13	205552	57962-0070, 57962-0140	None
CIE	2019-03-04	205552	57962-0140	None
CIE	2019-05-06	205552	57962-0140	None
CIE	2019-05-06	205552	57962-0140	None
CIE	2019-05-06	205552	57962-0140	None
CIE	2020-01-18	205552	57962-0140	None
CIE	2020-08-02	205552	57962-0140	None
ODE	2020-11-13	205552	57962-0140	None
ODE	2021-02-12	205552	57962-0140	None
ODE	2021-07-28	205552	57962-0140	None
CIE	2021-08-24	205552	57962-0070, 57962-0140	None
CIE	2022-01-25	205552	57962-0070, 57962-0140	None
ODE	2022-01-29	205552	57962-0140	None
ODE	2023-03-04	205552	57962-0070, 57962-0140	None
ODE	2023-05-06	205552	57962-0070, 57962-0140	None
ODE	2023-05-18	205552	57962-0070, 57962-0140	Original expiration date 01/18/2024; ended upon removal of indication.
PED	2023-05-18	205552	57962-0070, 57962-0140	Pediatric exclusivity extension of ODE with original expiration date 01/18/2024. Original

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
				expiration date of pediatric extension 07/18/2024; ended upon removal of indication.
ODE	2024-08-02	205552	57962-0070, 57962-0140	None
PED	2025-02-02	205552	57962-0140	Pediatric exclusivity extension of ODE with expiration date 08/02/2024
CIE	2025-08-24	205552	57962-0070, 57962-0140	None
PED	2026-02-24	205552	57962-0070, 57962-0140	Pediatric exclusivity extension of NCI exclusivity with expiration date 08/24/2025
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 7,514,444
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,476,284
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,497,277
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,697,711
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,703,780
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,735,403

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

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Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,754,091
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,952,015
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,957,079
PED	2027-06-28	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,181,257
PED	2027-10-26	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,563,563
PED	2028-05-13	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,008,309
ODE	2029-08-24	205552	57962-0070, 57962-0140	None
PED	2030-02-24	205552	57962-0070, 57962-0140	Pediatric exclusivity extension of ODE with expiration date 08/24/2029
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,754,090
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,999,999
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,125,889

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

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Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,801,881
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,801,883
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,814,721
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,004,746
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,016,435
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,478,439
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,653,696
PED	2031-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,751,342
PED	2033-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,713,617
PED	2033-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,725,455

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2033-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,106,548
PED	2033-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,125,140
PED	2033-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,294,231
PED	2033-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,294,232
PED	2033-12-03	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,961,251
PED	2033-12-03	205552	57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,752,634
PED	2034-02-18	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,540,382
PED	2034-04-30	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,296,753
PED	2035-04-24	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,795,604
PED	2035-04-24	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,463,668

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

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Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2035-04-24	205552	57962-0070, 57962-0140	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,695,350
CIE	2025-08-24	217003	57962-0007	None
PED	2026-02-24	217003	57962-0007	Pediatric exclusivity extension of NCI exclusivity with expiration date 08/24/2025
PED	2027-06-28	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 7,514,444
PED	2027-06-28	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,497,277
PED	2027-06-28	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,697,711
PED	2027-06-28	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,735,403
PED	2027-06-28	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,754,091
PED	2027-06-28	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,957,079
PED	2027-06-28	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,181,257
PED	2028-05-13	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,008,309

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
ODE	2029-08-24	217003	57962-0007	None
PED	2030-02-24	217003	57962-0007	Pediatric exclusivity extension of ODE with expiration date 08/24/2029
PED	2031-12-03	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,478,439
PED	2033-12-03	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,725,455
PED	2033-12-03	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,106,548
PED	2033-12-03	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,125,140
PED	2033-12-03	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,961,251
PED	2034-04-30	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,296,753
PED	2035-04-24	217003	57962-0007	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,795,604
CEE	2018-11-13	210563	57962-0014, 57962-0280, 57962-0420	None
CIE	2021-08-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	None

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

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Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
CIE	2022-01-25	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	None
ODE	2023-03-04	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	None
ODE	2023-05-06	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	None
ODE	2023-05-18	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Original expiration date 01/18/2024; ended upon removal of indication.
PED	2023-05-18	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric exclusivity extension of ODE with original expiration date 01/18/2024. Original expiration date of pediatric extension 07/18/2024; ended upon removal of indication.
ODE	2024-08-02	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	None
PED	2025-02-02	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric exclusivity extension of ODE with expiration date 08/02/2024
CIE	2025-08-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	None
PED	2026-02-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric exclusivity extension of NCI exclusivity with expiration date 08/24/2025

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 7,514,444
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,476,284
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,497,277
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,697,711
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,703,780
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,735,403
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,754,091
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,952,015
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,957,079
PED	2027-06-28	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,181,257

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2027-10-26	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,563,563
PED	2028-05-13	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,008,309
ODE	2029-08-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	None
PED	2030-02-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric exclusivity extension of ODE with expiration date 08/24/2029
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,004,746
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,016,435
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,478,439
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,653,696
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,751,342
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,754,090

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 8,999,999
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,125,889
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,801,881
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,801,883
PED	2031-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,814,721
PED	2033-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,106,548
PED	2033-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,125,140
PED	2033-12-03	210563	57962-0014	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,752,634
PED	2033-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,961,251
PED	2033-12-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,725,455

F. Patents, Exclusivities, and Approvals

Regulatory Exclusivity Periods

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. Manufacturers reported all regulatory exclusivity periods under the FD&C Act or the PHS Act that are listed in the Orange Book or the Purple Book and in effect or have expired for the selected drug.

Type of Exclusivity	Exclusivity Expiration Date	Application (NDA/BLA) Number	NDC-9s Covered by Exclusivity	Comments
PED	2034-04-30	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,296,753
PED	2035-04-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,463,668
PED	2035-04-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,695,350
PED	2035-04-24	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,795,604
PED	2036-09-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,010,507
PED	2036-09-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,213,386
PED	2036-09-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 10,828,259
PED	2036-09-03	210563	57962-0014, 57962-0280, 57962-0420, 57962-0560	Pediatric extension of patent-based exclusivity associated with U.S. Pat. No. 9,655,857

Explanations: None.

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
210563	NDA	3	2018-02-16	Treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion, Waldenström's macroglobulinemia (WM), and chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.	Tablets, 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
210563	NDA	10	2018-02-16	Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, and	Tablets, 140 mg, 280 mg, 420 mg, and 560	Pharmacyclics LLC	APP	MCL and MZL were later withdrawn under application #205552

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.	mg.			
210563	NDA	4	2018-08-24	Updates to USPI for IMBRUVICA® (ibrutinib) with new efficacy and safety data for the treatment of adult patients with Waldenström's Macroglobulinemia, including new data on ibrutinib in combination with rituximab. The revisions to the USPI include section 2 Dosage and Administration, Section 5 Warnings and Precautions, Section 6 Adverse Reactions, and	Capsules, 70 mg and 140 mg and tablets, 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				Section 14 Clinical Studies.				
210563	NDA	4	2019-01-25	Updates to Section 6 Adverse Reactions and Section 14 Clinical Studies of the Imbruvica United States Prescribing Information to include: · Efficacy and safety data from the iLLUMINATE study in patients with treatment naïve chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) treated with Imbruvica in combination with obinutuzumab or chlorambucil in combination with obinutuzumab. · Additional follow-up data in the CLL/SLL population	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				from the RESONATE and RESONATE-2 studies.				
210563	NDA	10	2019-07-15	Updates to the United States Prescribing Information, Section 5.1 Hemorrhage based on the results from PMR 2060-4, entitled "Enhanced Pharmacovigilance to Evaluate the Risks of Hemorrhage with the Administration of IMBRUVICA (ibrutinib)".	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
210563	NDA	10	2019-11-21	Updates to the United States Prescribing Information Adverse Reactions section with long-term safety data from the final report for PMR 3038-01, entitled "Assessment of Safety Risks with Long-term use	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				of IMBRUVICA® (Ibrutinib): A Post Marketing Requirement.”	mg.			
210563	NDA	4	2020-04-21	Labeling updates to add efficacy and safety data from the E1912 study (A Randomized Phase III Study of Ibrutinib based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab [FCR] Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia [CLL]) to expand ibrutinib in combination with rituximab for adult patients with chronic lymphocytic leukemia or small lymphocytic	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				lymphoma (SLL).				
210563	NDA	10	2020-08-07	Revisions to the Full Prescribing Information (FPI) Section 6 Adverse Reactions: Sub Section 6.1 Clinical Trial Experience to add ischemic cerebrovascular events to the subsection Cardiovascular Events, and for revisions to Sub Section 6.2 Post Marketing Experience to add neutrophilic dermatoses.	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
210563	NDA	10	2020-12-18	Updates to the United States Prescribing Information (USPI) sections 6.1 Adverse Reactions Clinical Trial Experience and 14.3 Clinical Studies	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg,	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				Waldenstrom's Macroglobulinemia to include long-term follow-up data on ibrutinib in combination with rituximab in subjects with Waldenstrom's macroglobulinemia.	420 mg, and 560 mg.			
210563	NDA	10	2020-12-22	Updates to USPI including revisions to Section 5 Warnings and Precautions subsection 5.1 Hemorrhage to modify the information on bleeding events and for revisions to subsection 5.4 Cardiac Arrhythmias and Cardiac Failure, Section 6 Adverse Reactions subsection 6.1 Clinical Trials Experience, Section 17 Patient Counseling Information of	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				the Full Prescribing Information (FPI) to add cardiac failure with corresponding changes to the Patient Package Insert (PPI). In addition, Highlights of Prescribing Information was updated to reflect revisions made to the FPI and minor formatting edits were made throughout the FPI and PPI.				
210563	NDA	10	2022-05-11	Updates to the USPI regarding cardiac toxicity, including the following changes: • Warnings and Precautions, Section 5.3 regarding cardiac toxicity – added information on the risk of sudden death, cardiac death and grade 3	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				or higher tachyarrhythmias using an expanded pooled safety population; renamed from "Cardiac Arrhythmias and Cardiac Failure" to "Cardiac Arrhythmias, Cardiac Failure, and Sudden Death" and repositioned from fourth to third Warning and Precaution. • Dosage and Administration, Section 2.2 (Dosage Modifications for Adverse Reactions) – added new dosage modification guidelines for cardiac toxicity; added instruction to evaluate the benefit-risk before resuming treatment for grade 2 cardiac failure,	mg.			

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				grade 3 cardiac arrhythmias, and grade 4 non-hematological toxicities. • Warnings and Precautions, Section 5.4 (Hypertension) – added instruction to initiate or adjust anti-hypertensive medication.				
210563	NDA	10	2022-08-24	Indication of the treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. Also, corresponding updates were made to the USPI based on Study PCYC-1146-IM (iMAGINE).	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
210563	NDA	10	2022-08-24	Updates to the USPI in	Capsules:	Pharmacyclics	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				Section 14 for chronic graft versus host disease (cGVHD) in adult patients based on Study PCYC-1129-CA in addition to editorial and formatting changes throughout the USPI.	70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	LLC		
210563	NDA	10	2022-08-24	Updates to the USPI section 8.4 Pediatric Use based on Study 54179060LYM3003 (SPARKLE), entitled "A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma."	Capsules: 70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
210563	NDA	10	2023-05-18	For revisions to the USPI	Capsules:	Pharmacyclics	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				to voluntarily remove the following indications, previously approved under accelerated approval: • treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy • treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy NDA 210563/S-017 also provides for removal of the 560 mg ibrutinib tablet	70 mg and 140 mg, and tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	LLC		
205552	NDA	1	2013-11-13	Mantle Cell Lymphome (MCL)	Capsules, 140mg.	Pharmacyclics LLC	APP	None
205552	NDA	10	2014-02-12	Chronic Lymphocytic	Capsules,	Pharmacyclics	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				Leukemia (CLL) who have received at least one prior therapy.	140mg.	LLC		
205552	NDA	10	2014-07-28	• Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy • Chronic lymphocytic leukemia with 17p deletion.	Capsules, 140mg.	Pharmacyclics LLC	APP	None
205552	NDA	10	2015-01-29	New indication for the treatment of patients with Waldenström's macroglobulinemia (WM) and fulfillment of the postmarketing requirement trial, PMR 2060-5, "An Open-Label, Multicenter, Pharmacokinetic, Study of PCI-3265in Subjects with Varying Degrees of Hepatic Impairment".	Capsules /140mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
205552	NDA	10	2016-03-04	Frontline indication of IMBRUVICA® (ibrutinib) for the treatment of Chronic Lymphocytic Leukemia.	Capsules /140mg.	Pharmacyclics LLC	APP	None
205552	NDA	4	2016-05-06	Revised indication for the use of IMBRUVICA® (ibrutinib) in the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and dosing of IMBRUVICA® (ibrutinib) with bendamustine and rituximab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma.	Capsules /140mg.	Pharmacyclics LLC	APP	None
205552	NDA	10	2016-06-28	Updates to the package insert with addition of interstitial lung disease in	Capsules /140mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				Section 6.2 Postmarketing Experience and QT information in Section 12.2 Pharmacodynamics.				
205552	NDA	10	2016-05-06	A revised indication for the use of IMBRUVICA® (ibrutinib) in the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.	Capsules /140mg.	Pharmacyclics LLC	APP	None
205552	NDA	10	2017-01-18	Provides for the addition of a new indication for treatment of patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.	Capsules /140mg.	Pharmacyclics LLC	APP	None
205552	NDA	10	2017-08-02	Chronic graft versus host disease (cGVHD) after	Capsules, 140 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				failure of one or more lines of systemic therapy				
205552	NDA	5	2017-12-20	For adding a 70 mg capsule to allow for dose reductions in patients with moderate hepatic impairment, updated dose modifications for ibrutinib when co-administered with CYP3A inhibitors (Section 2.4 of the USPI) and updates to Section 5.4 in the Warnings and Precautions of the USPI.	Capsules, 70 mg and 140 mg.	Pharmacyclics LLC	APP	None
205552	NDA	4	2018-08-24	updates to the USPI for IMBRUVICA® (ibrutinib) with new efficacy and safety data for the treatment of adult patients with Waldenström's Macroglobulinemia,	Capsules, 70 mg and 140 mg and tablets, 140 mg, 280 mg, 420 mg,	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				including new data on ibrutinib in combination with rituximab. The revisions to the USPI include section 2 Dosage and Administration, Section 5 Warnings and Precautions, Section 6 Adverse Reactions, and Section 14 Clinical Studies.	and 560 mg.			
205552	NDA	10	2018-08-24	Updates to the US Prescribing Information (USPI), subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility, with carcinogenicity information.	Capsules, 70 mg and 140 mg.	Pharmacyclics LLC	APP	None
205552	NDA	4	2019-01-25	Updates to Section 6 Adverse Reactions and Section 14 Clinical Studies of the Imbruvica United	Capsules: 70 mg ,140 mg; Tablets:	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				States Prescribing Information to include: · Efficacy and safety data from the iLLUMINATE study in patients with treatment naïve chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) treated with Imbruvica in combination with obinutuzumab or chlorambucil in combination with obinutuzumab. · Additional follow-up data in the CLL/SLL population from the RESONATE and RESONATE-2 studies.	140 mg, 280 mg, 420 mg, and 560 mg.			
205552	NDA	10	2019-07-15	Updates to the United States Prescribing Information, Section 5.1	Capsules: 70 mg ,140 mg;	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				Hemorrhage based on the results from PMR 2060-4, entitled "Enhanced Pharmacovigilance to Evaluate the Risks of Hemorrhage with the Administration of IMBRUVICA (ibrutinib)".	Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.			
205552	NDA	10	2019-11-21	Updates to the United States Prescribing Information Adverse Reactions section with long-term safety data from the final report for PMR 3038-01, entitled "Assessment of Safety Risks with Long-term use of IMBRUVICA® (Ibrutinib): A Post Marketing Requirement."	Capsules: 70 mg, 140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
205552	NDA	4	2020-04-21	Labeling updates to add efficacy and safety data	Capsules: 70 mg	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				from the E1912 study (A Randomized Phase III Study of Ibrutinib based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab [FCR] Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia [CLL]) to expand ibrutinib in combination with rituximab for adult patients with CLL or SLL.	,140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.			
205552	NDA	10	2020-08-07	Revisions to the Full Prescribing Information (FPI) Section 6 Adverse Reactions: Sub Section 6.1 Clinical Trial Experience to add ischemic cerebrovascular events to	Capsules: 70 mg ,140 mg; Tablets: 140 mg, 280 mg, 420 mg,	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				the subsection Cardiovascular Events, and for revisions to Sub Section 6.2 Post Marketing Experience to add neutrophilic dermatoses.	and 560 mg.			
205552	NDA	10	2020-12-18	Updates to the United States Prescribing Information (USPI) sections 6.1 Adverse Reactions Clinical Trial Experience and 14.3 Clinical Studies Waldenstrom's Macroglobulinemia to include long-term follow-up data on ibrutinib in combination with rituximab in subjects with Waldenstrom's macroglobulinemia.	Capsules: 70 mg ,140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
205552	NDA	10	2020-12-22	Updates to the United States Prescribing Information (USPI) including revisions to Section 5 Warnings and Precautions subsection 5.1 Hemorrhage to modify the information on bleeding events and for revisions to subsection 5.4 Cardiac Arrhythmias and Cardiac Failure, Section 6 Adverse Reactions subsection 6.1 Clinical Trials Experience, Section 17 Patient Counseling Information of the Full Prescribing Information (FPI) to add cardiac failure with corresponding changes to the Patient Package Insert (PPI). In	Capsules: 70 mg, 140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				addition, Highlights of Prescribing Information was updated to reflect revisions made to the FPI and minor formatting edits were made throughout the FPI and PPI.				
205552	NDA	10	2022-05-11	Updates to the US Prescribing Information (USPI) regarding cardiac toxicity, including the following changes: • Warnings and Precautions, Section 5.3 regarding cardiac toxicity – added information on the risk of sudden death, cardiac death and grade 3 or higher tachyarrhythmias using an expanded pooled safety	Capsules: 70 mg, 140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				population; renamed from "Cardiac Arrhythmias and Cardiac Failure" to "Cardiac Arrhythmias, Cardiac Failure, and Sudden Death" and repositioned from fourth to third Warning and Precaution. • Dosage and Administration, Section 2.2 (Dosage Modifications for Adverse Reactions) – added new dosage modification guidelines for cardiac toxicity; added instruction to evaluate the benefit-risk before resuming treatment for grade 2 cardiac failure, grade 3 cardiac arrhythmias, and grade 4 non-hematological				

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				toxicities. • Warnings and Precautions, Section 5.4 (Hypertension) – added instruction to initiate or adjust anti-hypertensive medication.				
205552	NDA	10	2022-08-24	Provide for the indication of the treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. Also, corresponding updates were made to the United States Prescribing Information (USPI) based on Study PCYC-1146-IM (iMAGINE).	Capsules: 70 mg ,140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
205552	NDA	10	2022-08-24	Updates to the USPI in Section 14 for chronic	Capsules: 70 mg	Pharmacyclics LLC	APP	None

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				graft versus host disease (cGVHD) in adult patients based on Study PCYC-1129-CA in addition to editorial and formatting changes throughout the USPI.	,140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.			
205552	NDA	10	2022-08-24	Updates to the USPI section 8.4 Pediatric Use based on Study 54179060LYM3003 (SPARKLE), entitled "A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma."	Capsules: 70 mg ,140 mg; Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.	Pharmacyclics LLC	APP	None
205552	NDA	10	2023-05-18	USPI-voluntary removal for MCL and MZL indications and removal of	Capsules: 70 mg ,140 mg;	Pharmacyclics LLC	APP	MZL and MCL indications were withdrawn under

F. Patents, Exclusivities, and Approvals

All Active and Pending FDA Applications and Approvals

Description: Section F focuses on capturing data on the selected drug related to pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act or section 351(a) of the Public Health Service (PHS) Act. This list contains all active and pending FDA applications and approvals for the selected drug under section 505(c) of the FD&C Act and 351(a) of the PHS Act.

Application (NDA / BLA) Number	Application Type (NDA; BLA)	Class Code	Approval Date	Indication	Dosage Form and Strength	Sponsor	Application Status	Comments
				560 mg tablet from NDA 210563	Tablets: 140 mg, 280 mg, 420 mg, and 560 mg.			this application.
217003	NDA	5	2022-08-24	Treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.	Oral suspension: 70mg/ml	Pharmacyclics LLC	APP	None



Explanations: None.

G. Market Data and Revenue and Sales Volume Data				
Wholesale Acquisition Cost Unit Price				
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.				
National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0140-09	2018-Q3	\$135.33	EA	
57962-0140-12	2018-Q3	\$135.33	EA	
57962-0070-28	2018-Q3	\$406.00	EA	
57962-0014-28	2018-Q3	\$406.00	EA	
57962-0280-28	2018-Q3	\$406.00	EA	
57962-0420-28	2018-Q3	\$406.00	EA	
57962-0560-28	2018-Q3	\$406.00	EA	
57962-0007-12	2018-Q3		ML	
57962-0140-09	2018-Q4	\$135.33	EA	
57962-0140-12	2018-Q4	\$135.33	EA	
57962-0070-28	2018-Q4	\$406.00	EA	
57962-0014-28	2018-Q4	\$406.00	EA	
57962-0280-28	2018-Q4	\$406.00	EA	
57962-0420-28	2018-Q4	\$406.00	EA	
57962-0560-28	2018-Q4	\$406.00	EA	
57962-0007-12	2018-Q4		ML	
57962-0140-09	2019-Q1	\$143.72	EA	
57962-0140-12	2019-Q1	\$143.72	EA	
57962-0070-28	2019-Q1	\$431.17	EA	

57962-0014-28	2019-Q1	\$431.17	EA	
57962-0280-28	2019-Q1	\$431.17	EA	
57962-0420-28	2019-Q1	\$431.17	EA	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0560-28	2019-Q1	\$431.17	EA	
57962-0007-12	2019-Q1		ML	
57962-0140-09	2019-Q2	\$143.72	EA	
57962-0140-12	2019-Q2	\$143.72	EA	
57962-0070-28	2019-Q2	\$431.17	EA	
57962-0014-28	2019-Q2	\$431.17	EA	
57962-0280-28	2019-Q2	\$431.17	EA	
57962-0420-28	2019-Q2	\$431.17	EA	
57962-0560-28	2019-Q2	\$431.17	EA	
57962-0007-12	2019-Q2		ML	
57962-0140-09	2019-Q3	\$143.72	EA	
57962-0140-12	2019-Q3	\$143.72	EA	
57962-0070-28	2019-Q3	\$431.17	EA	
57962-0014-28	2019-Q3	\$431.17	EA	
57962-0280-28	2019-Q3	\$431.17	EA	
57962-0420-28	2019-Q3	\$431.17	EA	
57962-0560-28	2019-Q3	\$431.17	EA	
57962-0007-12	2019-Q3		ML	
57962-0140-09	2019-Q4	\$143.72	EA	
57962-0140-12	2019-Q4	\$143.72	EA	
57962-0070-28	2019-Q4	\$431.17	EA	
57962-0014-28	2019-Q4	\$431.17	EA	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0280-28	2019-Q4	\$431.17	EA	
57962-0420-28	2019-Q4	\$431.17	EA	
57962-0560-28	2019-Q4	\$431.17	EA	
57962-0007-12	2019-Q4		ML	
57962-0140-09	2020-Q1	\$154.36	EA	
57962-0140-12	2020-Q1	\$154.36	EA	
57962-0070-28	2020-Q1	\$463.08	EA	
57962-0014-28	2020-Q1	\$463.08	EA	
57962-0280-28	2020-Q1	\$463.08	EA	
57962-0420-28	2020-Q1	\$463.08	EA	
57962-0560-28	2020-Q1	\$463.08	EA	
57962-0007-12	2020-Q1		ML	
57962-0140-09	2020-Q2	\$154.36	EA	
57962-0140-12	2020-Q2	\$154.36	EA	
57962-0070-28	2020-Q2	\$463.08	EA	
57962-0014-28	2020-Q2	\$463.08	EA	
57962-0280-28	2020-Q2	\$463.08	EA	
57962-0420-28	2020-Q2	\$463.08	EA	
57962-0560-28	2020-Q2	\$463.08	EA	
57962-0007-12	2020-Q2		ML	
57962-0140-09	2020-Q3	\$154.36	EA	
57962-0140-12	2020-Q3	\$154.36	EA	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0070-28	2020-Q3	\$463.08	EA	[REDACTED]
57962-0014-28	2020-Q3	\$463.08	EA	
57962-0280-28	2020-Q3	\$463.08	EA	
57962-0420-28	2020-Q3	\$463.08	EA	
57962-0560-28	2020-Q3	\$463.08	EA	
57962-0007-12	2020-Q3		ML	
57962-0140-09	2020-Q4	\$154.36	EA	
57962-0140-12	2020-Q4	\$154.36	EA	
57962-0070-28	2020-Q4	\$463.08	EA	
57962-0014-28	2020-Q4	\$463.08	EA	
57962-0280-28	2020-Q4	\$463.08	EA	
57962-0420-28	2020-Q4	\$463.08	EA	
57962-0560-28	2020-Q4	\$463.08	EA	
57962-0007-12	2020-Q4		ML	
57962-0140-09	2021-Q1	\$165.78	EA	
57962-0140-12	2021-Q1	\$165.78	EA	
57962-0070-28	2021-Q1	\$497.34	EA	
57962-0014-28	2021-Q1	\$497.34	EA	
57962-0280-28	2021-Q1	\$497.34	EA	
57962-0420-28	2021-Q1	\$497.34	EA	
57962-0560-28	2021-Q1	\$497.34	EA	
57962-0007-12	2021-Q1		ML	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0140-09	2021-Q2	\$165.78	EA	[REDACTED]
57962-0140-12	2021-Q2	\$165.78	EA	
57962-0070-28	2021-Q2	\$497.34	EA	
57962-0014-28	2021-Q2	\$497.34	EA	
57962-0280-28	2021-Q2	\$497.34	EA	
57962-0420-28	2021-Q2	\$497.34	EA	
57962-0560-28	2021-Q2	\$497.34	EA	
57962-0007-12	2021-Q2		ML	
57962-0140-09	2021-Q3	\$165.78	EA	
57962-0140-12	2021-Q3	\$165.78	EA	
57962-0070-28	2021-Q3	\$497.34	EA	
57962-0014-28	2021-Q3	\$497.34	EA	
57962-0280-28	2021-Q3	\$497.34	EA	
57962-0420-28	2021-Q3	\$497.34	EA	
57962-0560-28	2021-Q3	\$497.34	EA	
57962-0007-12	2021-Q3		ML	
57962-0140-09	2021-Q4	\$165.78	EA	
57962-0140-12	2021-Q4	\$165.78	EA	
57962-0070-28	2021-Q4	\$497.34	EA	
57962-0014-28	2021-Q4	\$497.34	EA	
57962-0280-28	2021-Q4	\$497.34	EA	
57962-0420-28	2021-Q4	\$497.34	EA	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0560-28	2021-Q4	\$497.34	EA	
57962-0007-12	2021-Q4		ML	
57962-0140-09	2022-Q1	\$176.44	EA	
57962-0140-12	2022-Q1	\$176.44	EA	
57962-0070-28	2022-Q1	\$529.33	EA	
57962-0014-28	2022-Q1	\$529.33	EA	
57962-0280-28	2022-Q1	\$529.33	EA	
57962-0420-28	2022-Q1	\$529.33	EA	
57962-0560-28	2022-Q1	\$529.33	EA	
57962-0007-12	2022-Q1		ML	
57962-0140-09	2022-Q2	\$178.05	EA	
57962-0140-12	2022-Q2	\$178.05	EA	
57962-0070-28	2022-Q2	\$534.15	EA	
57962-0014-28	2022-Q2	\$534.15	EA	
57962-0280-28	2022-Q2	\$534.15	EA	
57962-0420-28	2022-Q2	\$534.15	EA	
57962-0560-28	2022-Q2	\$534.15	EA	
57962-0007-12	2022-Q2		ML	
57962-0140-09	2022-Q3	\$178.05	EA	
57962-0140-12	2022-Q3	\$178.05	EA	
57962-0070-28	2022-Q3	\$534.15	EA	
57962-0014-28	2022-Q3	\$534.15	EA	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0280-28	2022-Q3	\$534.15	EA	
57962-0420-28	2022-Q3	\$534.15	EA	
57962-0560-28	2022-Q3	\$534.15	EA	
57962-0007-12	2022-Q3	\$89.02	ML	
57962-0140-09	2022-Q4	\$178.05	EA	
57962-0140-12	2022-Q4	\$178.05	EA	
57962-0070-28	2022-Q4	\$534.15	EA	
57962-0014-28	2022-Q4	\$534.15	EA	
57962-0280-28	2022-Q4	\$534.15	EA	
57962-0420-28	2022-Q4	\$534.15	EA	
57962-0560-28	2022-Q4	\$534.15	EA	
57962-0007-12	2022-Q4	\$89.02	ML	
57962-0140-09	2023-Q1	\$189.09	EA	
57962-0140-12	2023-Q1	\$189.09	EA	
57962-0070-28	2023-Q1	\$567.26	EA	
57962-0014-28	2023-Q1	\$567.26	EA	
57962-0280-28	2023-Q1	\$567.26	EA	
57962-0420-28	2023-Q1	\$567.26	EA	
57962-0560-28	2023-Q1	\$567.26	EA	
57962-0007-12	2023-Q1	\$94.54	ML	
57962-0140-09	2023-Q2	\$189.09	EA	
57962-0140-12	2023-Q2	\$189.09	EA	

G. Market Data and Revenue and Sales Volume Data

Wholesale Acquisition Cost Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Wholesale Acquisition Cost (WAC) unit price of the selected drug.

National Drug Code (NDC-11)	Quarter	WAC	Unit type (each, ML, GM)	Total Unit Volume
57962-0070-28	2023-Q2	\$567.26	EA	
57962-0014-28	2023-Q2	\$567.26	EA	
57962-0280-28	2023-Q2	\$567.26	EA	
57962-0420-28	2023-Q2	\$567.26	EA	
57962-0560-28	2023-Q2	\$567.26	EA	
57962-0007-12	2023-Q2	\$94.54	ML	

Explanations: This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.

AbbVie/Pharmacyclics submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisdisclosure notification is required (45 C.F.R. 5.42).

AbbVie/Pharmacyclics’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics’s rights to confidential treatment and predisdisclosure notification.

For Q1 2022, a price change occurred on a date other than the first date of the quarter. AbbVie/Pharmacyclics determined a weighted average WAC price based on the number of units sold at each WAC price. As a result, the WAC unit price for Q1 2022 reported in Question 16 differs from the WAC unit price as reported in wholesale price guides or other publications.

Two NDCs, 57962042071 and 57962056071, are included in Section A as NDC’s that were registered and active earlier in the Imbruvica lifecycle. The NDCs were active from February of 2019 to December of 2020. However, these NDC’s were never commercially saleable units: they were

only distributed as free samples. No WAC was ever established or reported for these NDCs. As such, these NDCs are excluded from the submitted market and sales data responses (Section G).

G. Market Data and Revenue and Sales Volume Data					
Medicaid Best Price					
<p>Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.</p>					
Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0140	2018-Q3		EA	
Y	57962-0070	2018-Q3		EA	
Y	57962-0014	2018-Q3		EA	
Y	57962-0280	2018-Q3		EA	
Y	57962-0420	2018-Q3		EA	
Y	57962-0560	2018-Q3		EA	
Y	57962-0007	2018-Q3		ML	
Y	57962-0140	2018-Q4		EA	
Y	57962-0070	2018-Q4		EA	
Y	57962-0014	2018-Q4		EA	
Y	57962-0280	2018-Q4		EA	
Y	57962-0420	2018-Q4		EA	
Y	57962-0560	2018-Q4		EA	
Y	57962-0007	2018-Q4		ML	
Y	57962-0140	2019-Q1		EA	
Y	57962-0070	2019-Q1		EA	
Y	57962-0014	2019-Q1		EA	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0280	2019-Q1		EA	
Y	57962-0420	2019-Q1		EA	
Y	57962-0560	2019-Q1		EA	
Y	57962-0007	2019-Q1		ML	
Y	57962-0140	2019-Q2		EA	
Y	57962-0070	2019-Q2		EA	
Y	57962-0014	2019-Q2		EA	
Y	57962-0280	2019-Q2		EA	
Y	57962-0420	2019-Q2		EA	
Y	57962-0560	2019-Q2		EA	
Y	57962-0007	2019-Q2		ML	
Y	57962-0140	2019-Q3		EA	
Y	57962-0070	2019-Q3		EA	
Y	57962-0014	2019-Q3		EA	
Y	57962-0280	2019-Q3		EA	
Y	57962-0420	2019-Q3		EA	
Y	57962-0560	2019-Q3		EA	
Y	57962-0007	2019-Q3		ML	
Y	57962-0140	2019-Q4		EA	
Y	57962-0070	2019-Q4		EA	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0014	2019-Q4		EA	
Y	57962-0280	2019-Q4		EA	
Y	57962-0420	2019-Q4		EA	
Y	57962-0560	2019-Q4		EA	
Y	57962-0007	2019-Q4		ML	
Y	57962-0140	2020-Q1		EA	
Y	57962-0070	2020-Q1		EA	
Y	57962-0014	2020-Q1		EA	
Y	57962-0280	2020-Q1		EA	
Y	57962-0420	2020-Q1		EA	
Y	57962-0560	2020-Q1		EA	
Y	57962-0007	2020-Q1		ML	
Y	57962-0140	2020-Q2		EA	
Y	57962-0070	2020-Q2		EA	
Y	57962-0014	2020-Q2		EA	
Y	57962-0280	2020-Q2		EA	
Y	57962-0420	2020-Q2		EA	
Y	57962-0560	2020-Q2		EA	
Y	57962-0007	2020-Q2		ML	
Y	57962-0140	2020-Q3		EA	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0070	2020-Q3		EA	
Y	57962-0014	2020-Q3		EA	
Y	57962-0280	2020-Q3		EA	
Y	57962-0420	2020-Q3		EA	
Y	57962-0560	2020-Q3		EA	
Y	57962-0007	2020-Q3		ML	
Y	57962-0140	2020-Q4		EA	
Y	57962-0070	2020-Q4		EA	
Y	57962-0014	2020-Q4		EA	
Y	57962-0280	2020-Q4		EA	
Y	57962-0420	2020-Q4		EA	
Y	57962-0560	2020-Q4		EA	
Y	57962-0007	2020-Q4		ML	
Y	57962-0140	2021-Q1		EA	
Y	57962-0070	2021-Q1		EA	
Y	57962-0014	2021-Q1		EA	
Y	57962-0280	2021-Q1		EA	
Y	57962-0420	2021-Q1		EA	
Y	57962-0560	2021-Q1		EA	
Y	57962-0007	2021-Q1		ML	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0140	2021-Q2		EA	
Y	57962-0070	2021-Q2		EA	
Y	57962-0014	2021-Q2		EA	
Y	57962-0280	2021-Q2		EA	
Y	57962-0420	2021-Q2		EA	
Y	57962-0560	2021-Q2		EA	
Y	57962-0007	2021-Q2		ML	
Y	57962-0140	2021-Q3		EA	
Y	57962-0070	2021-Q3		EA	
Y	57962-0014	2021-Q3		EA	
Y	57962-0280	2021-Q3		EA	
Y	57962-0420	2021-Q3		EA	
Y	57962-0560	2021-Q3		EA	
Y	57962-0007	2021-Q3		ML	
Y	57962-0140	2021-Q4		EA	
Y	57962-0070	2021-Q4		EA	
Y	57962-0014	2021-Q4		EA	
Y	57962-0280	2021-Q4		EA	
Y	57962-0420	2021-Q4		EA	
Y	57962-0560	2021-Q4		EA	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0007	2021-Q4		ML	
Y	57962-0140	2022-Q1		EA	
Y	57962-0070	2022-Q1		EA	
Y	57962-0014	2022-Q1		EA	
Y	57962-0280	2022-Q1		EA	
Y	57962-0420	2022-Q1		EA	
Y	57962-0560	2022-Q1		EA	
Y	57962-0007	2022-Q1		ML	
Y	57962-0140	2022-Q2		EA	
Y	57962-0070	2022-Q2		EA	
Y	57962-0014	2022-Q2		EA	
Y	57962-0280	2022-Q2		EA	
Y	57962-0420	2022-Q2		EA	
Y	57962-0560	2022-Q2		EA	
Y	57962-0007	2022-Q2		ML	
Y	57962-0140	2022-Q3		EA	
Y	57962-0070	2022-Q3		EA	
Y	57962-0014	2022-Q3		EA	
Y	57962-0280	2022-Q3		EA	
Y	57962-0420	2022-Q3		EA	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0560	2022-Q3		EA	
Y	57962-0007	2022-Q3		ML	
Y	57962-0140	2022-Q4		EA	
Y	57962-0070	2022-Q4		EA	
Y	57962-0014	2022-Q4		EA	
Y	57962-0280	2022-Q4		EA	
Y	57962-0420	2022-Q4		EA	
Y	57962-0560	2022-Q4		EA	
Y	57962-0007	2022-Q4		ML	
Y	57962-0140	2023-Q1		EA	
Y	57962-0070	2023-Q1		EA	
Y	57962-0014	2023-Q1		EA	
Y	57962-0280	2023-Q1		EA	
Y	57962-0420	2023-Q1		EA	
Y	57962-0560	2023-Q1		EA	
Y	57962-0007	2023-Q1		ML	
Y	57962-0140	2023-Q2		EA	
Y	57962-0070	2023-Q2		EA	
Y	57962-0014	2023-Q2		EA	
Y	57962-0280	2023-Q2		EA	

G. Market Data and Revenue and Sales Volume Data

Medicaid Best Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Medicaid best price of the selected drug. The Medicaid best price information reflects what was submitted to Medicaid under the MDRP in accordance with the Medicaid National Drug Rebate Agreement and as described in section 42 C.F.R. § 447.505 – determination of best price.

Medicaid Best Price	National Drug Code (NDC-9)	Quarter	Medicaid Best Price	Unit Type	Total Unit Volume
Y	57962-0420	2023-Q2	[REDACTED]	EA	[REDACTED]
Y	57962-0560	2023-Q2	[REDACTED]	EA	[REDACTED]
Y	57962-0007	2023-Q2	[REDACTED]	ML	[REDACTED]

Explanations: This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.

AbbVie/Pharmacyclics submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42).

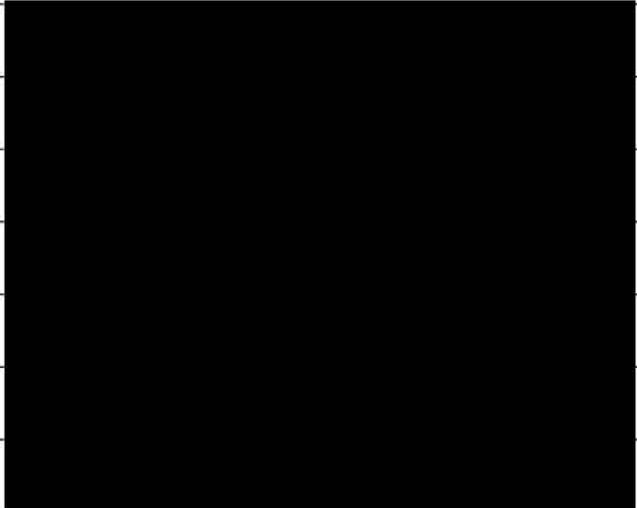
AbbVie/Pharmacyclics’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics’s rights to confidential treatment and predisclosure notification.

[REDACTED]

The unit type used to report AMP and Medicaid Best Price for the following NDCs is capsules: 57962-0140, 57962-0070.

The unit type used to report AMP and Medicaid Best Price for the following NDCs is tablets: 57962-0014, 57962-0280, 57962-0420, 57962-0560.

The unit type used to report AMP and Medicaid Best Price for the following NDC is mL: 57962-0007.

G. Market Data and Revenue and Sales Volume Data					
Federal Supply Schedule Price					
<p>Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.</p>					
Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0007-12	2023-01-01 - 2023-06-30	\$78.74	ML	
Y	57962-0014-28	2018-07-01 - 2019-12-31	\$393.76	EA	
Y	57962-0014-28	2020-01-01 - 2020-12-31	\$400.49	EA	
Y	57962-0014-28	2021-01-01 - 2021-12-31	\$405.98	EA	
Y	57962-0014-28	2022-01-01 - 2022-12-31	\$427.86	EA	
Y	57962-0014-28	2023-01-01 - 2023-06-30	\$440.20	EA	
Y	57962-0070-28	2018-07-01 - 2019-12-31	\$393.76	EA	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

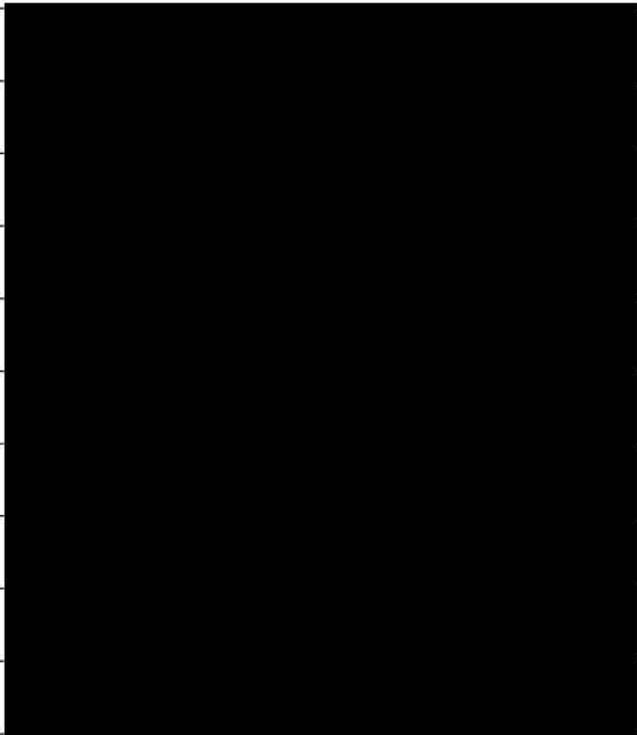
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0070-28	2020-01-01 - 2020-12-31	\$400.49	EA	
Y	57962-0070-28	2021-01-01 - 2021-12-31	\$405.98	EA	
Y	57962-0070-28	2022-01-01 - 2022-12-31	\$427.86	EA	
Y	57962-0070-28	2023-01-01 - 2023-06-30	\$440.20	EA	
Y	57962-0140-09	2018-07-01 - 2018-12-31	\$83.84	EA	
Y	57962-0140-09	2019-01-01 - 2019-12-31	\$128.34	EA	
Y	57962-0140-09	2020-01-01 - 2020-12-31	\$130.54	EA	
Y	57962-0140-09	2021-01-01 - 2021-12-31	\$128.34	EA	
Y	57962-0140-09	2022-01-01 - 2022-12-31	\$139.46	EA	
Y	57962-0140-09	2023-01-01 - 2023-06-30	\$146.73	EA	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0140-12	2018-07-01 - 2018-12-31	\$83.45	EA	
Y	57962-0140-12	2019-01-01 - 2019-12-31	\$128.34	EA	
Y	57962-0140-12	2020-01-01 - 2020-12-31	\$130.54	EA	
Y	57962-0140-12	2021-01-01 - 2021-12-31	\$132.33	EA	
Y	57962-0140-12	2022-01-01 - 2022-12-31	\$139.46	EA	
Y	57962-0140-12	2023-01-01 - 2023-06-30	\$146.73	EA	
Y	57962-0280-28	2018-07-01 - 2019-12-31	\$393.76	EA	
Y	57962-0280-28	2020-01-01 - 2020-12-31	\$400.49	EA	
Y	57962-0280-28	2021-01-01 - 2021-12-31	\$405.98	EA	
Y	57962-0280-28	2022-01-01 - 2022-12-31	\$427.86	EA	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0280-28	2023-01-01 - 2023-06-30	\$440.20	EA	
Y	57962-0420-28	2018-07-01 - 2019-12-31	\$393.76	EA	
Y	57962-0420-28	2020-01-01 - 2020-12-31	\$400.49	EA	
Y	57962-0420-28	2021-01-01 - 2021-12-31	\$405.98	EA	
Y	57962-0420-28	2022-01-01 - 2022-12-31	\$427.86	EA	
Y	57962-0420-28	2023-01-01 - 2023-06-30	\$440.20	EA	
Y	57962-0560-28	2018-07-01 - 2019-12-31	\$393.76	EA	
Y	57962-0560-28	2020-01-01 - 2020-12-31	\$400.49	EA	
Y	57962-0560-28	2021-01-01 - 2021-12-31	\$405.98	EA	
Y	57962-0560-28	2022-01-01 - 2022-12-31	\$427.86	EA	

G. Market Data and Revenue and Sales Volume Data

Federal Supply Schedule Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. Manufacturers reported any federal supply schedule (FSS) price for the selected drug made available during the most recent five years. The FSS price information reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Federal Supply Schedule Price	National Drug Code (NDC-11)	Price Start Date to End Date	Federal Supply Schedule Service Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0560-28	2023-01-01 - 2023-06-30	\$440.20	EA	[REDACTED]

Explanations: This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.

AbbVie/Pharmacyclics submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42).

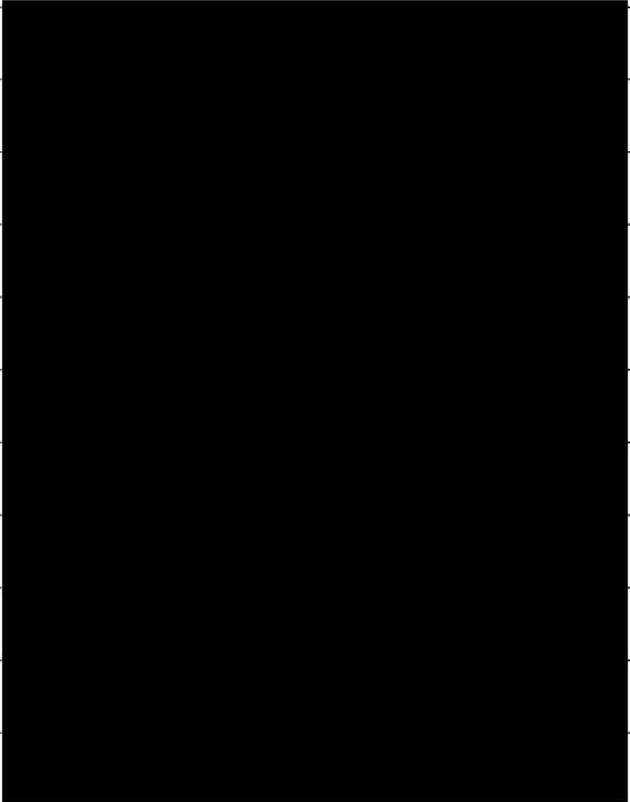
AbbVie/Pharmacyclics’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics’s rights to confidential treatment and predisclosure notification.

The FSS contract for Imbruvica is a dual price contract. The FSS price listed is inclusive of the 0.5% industrial funding fee (IFF). The volume represents sales sold directly to other government agency (“OGA”) federal purchasers at the FSS OGA price. Please note that, consistent with the ICR instructions, the FSS price reflects what can be found online in the pharmaceutical pricing data for all VA National Acquisition Centers [REDACTED]

G. Market Data and Revenue and Sales Volume Data

Big Four Price

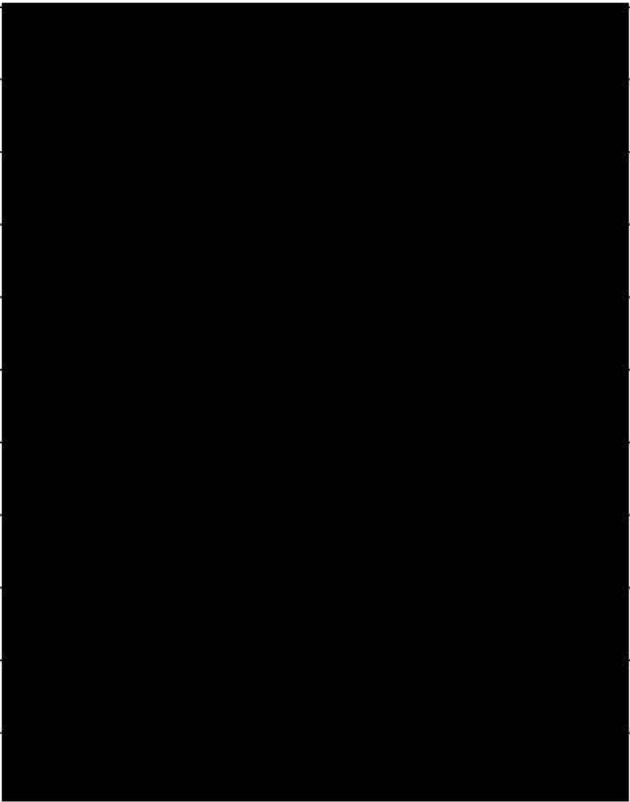
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0007-12	2023-01-01 - 2023-06-30	\$66.61	ML	
Y	57962-0014-28	2018-07-01 - 2018-09-28	\$303.91	EA	
Y	57962-0014-28	2018-09-29 - 2018-12-31	\$299.01	EA	
Y	57962-0014-28	2020-01-01 - 2020-12-31	\$298.73	EA	
Y	57962-0014-28	2021-01-01 - 2021-12-31	\$309.43	EA	
Y	57962-0014-28	2022-01-01 - 2022-12-31	\$346.46	EA	
Y	57962-0014-28	2023-01-01 - 2023-06-30	\$356.08	EA	
Y	57962-0014-28	2019-01-01 - 2019-12-31	\$298.54	EA	
Y	57962-0070-28	2018-07-01 - 2018-09-28	\$303.91	EA	
Y	57962-0070-28	2018-09-29 - 2018-12-31	\$301.79	EA	
Y	57962-0070-28	2019-01-01 - 2019-12-31	\$300.10	EA	

G. Market Data and Revenue and Sales Volume Data

Big Four Price

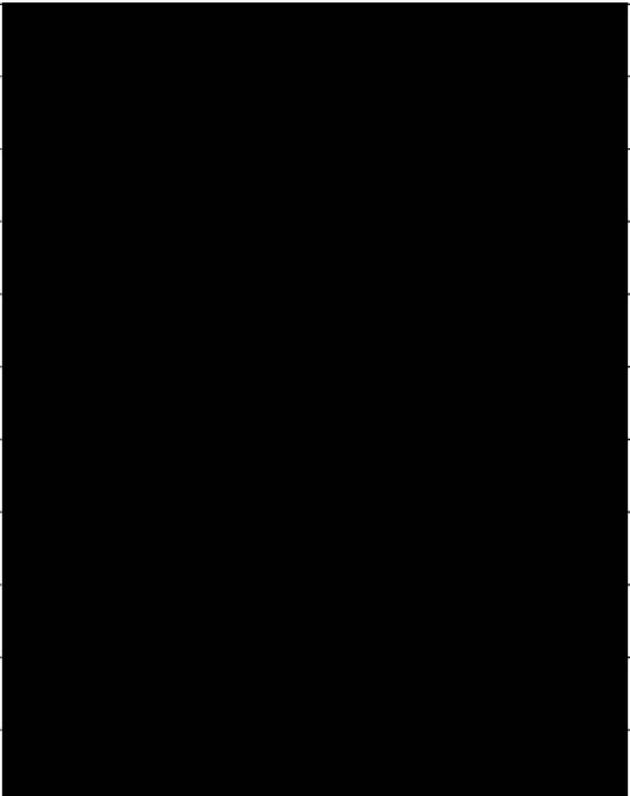
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0070-28	2020-01-01 - 2020-12-31	\$300.62	EA	
Y	57962-0070-28	2021-01-01 - 2021-12-31	\$313.06	EA	
Y	57962-0070-28	2022-01-01 - 2022-12-31	\$342.93	EA	
Y	57962-0070-28	2023-01-01 - 2023-06-30	\$356.99	EA	
Y	57962-0140-09	2018-07-01 - 2018-12-31	\$83.84	EA	
Y	57962-0140-09	2019-01-01 - 2019-12-31	\$87.81	EA	
Y	57962-0140-09	2020-01-01 - 2020-12-31	\$98.24	EA	
Y	57962-0140-09	2021-01-01 - 2021-12-31	\$103.42	EA	
Y	57962-0140-09	2022-01-01 - 2022-12-31	\$114.21	EA	
Y	57962-0140-09	2023-01-01 - 2023-06-30	\$120.89	EA	
Y	57962-0140-12	2018-07-01 - 2018-12-31	\$83.45	EA	

G. Market Data and Revenue and Sales Volume Data

Big Four Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0140-12	2019-01-01 - 2019-12-31	\$88.06	EA	
Y	57962-0140-12	2020-01-01 - 2020-12-31	\$98.19	EA	
Y	57962-0140-12	2021-01-01 - 2021-12-31	\$104.64	EA	
Y	57962-0140-12	2022-01-01 - 2022-12-31	\$113.98	EA	
Y	57962-0140-12	2023-01-01 - 2023-06-30	\$129.36	EA	
Y	57962-0280-28	2018-07-01 - 2018-09-28	\$303.91	EA	
Y	57962-0280-28	2018-09-29 - 2018-12-31	\$299.21	EA	
Y	57962-0280-28	2019-01-01 - 2019-12-31	\$298.48	EA	
Y	57962-0280-28	2020-01-01 - 2020-12-31	\$297.52	EA	
Y	57962-0280-28	2021-01-01 - 2021-12-31	\$310.49	EA	
Y	57962-0280-28	2022-01-01 - 2022-12-31	\$343.94	EA	

G. Market Data and Revenue and Sales Volume Data

Big Four Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0280-28	2023-01-01 - 2023-06-30	\$349.74	EA	
Y	57962-0420-28	2018-07-01 - 2018-09-28	\$303.91	EA	
Y	57962-0420-28	2018-09-29 - 2018-12-31	\$298.83	EA	
Y	57962-0420-28	2019-01-01 - 2019-12-31	\$298.31	EA	
Y	57962-0420-28	2020-01-01 - 2020-12-31	\$297.21	EA	
Y	57962-0420-28	2021-01-01 - 2021-12-31	\$310.48	EA	
Y	57962-0420-28	2022-01-01 - 2022-12-31	\$343.28	EA	
Y	57962-0420-28	2023-01-01 - 2023-06-30	\$349.03	EA	
Y	57962-0560-28	2018-07-01 - 2018-09-28	\$303.91	EA	
Y	57962-0560-28	2018-09-29 - 2018-12-31	\$299.51	EA	
Y	57962-0560-28	2019-01-01 - 2019-12-31	\$298.56	EA	

G. Market Data and Revenue and Sales Volume Data

Big Four Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides responses about the Big Four price of the selected drug. The Big Four price information reflects the information that can be found online in the pharmaceutical pricing data for all VA National Acquisition Center programs.

Big Four Price	National Drug Code (NDC-11)	Price Start Date to End Date	Big Four Price	Unit Type (EA, ML, GM)	Total Unit Volume
Y	57962-0560-28	2020-01-01 - 2020-12-31	\$297.35	EA	
Y	57962-0560-28	2021-01-01 - 2021-12-31	\$311.24	EA	
Y	57962-0560-28	2022-01-01 - 2022-12-31	\$343.24	EA	
Y	57962-0560-28	2023-01-01 - 2023-06-30	\$358.86	EA	

Explanations: This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.

AbbVie/Pharmacyclics submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42).

AbbVie/Pharmacyclics’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics’s rights to confidential treatment and predisclosure notification.

The Big Four price represents the lower of the FSS price and Federal Ceiling Price (FCP). For all quarters during the reported period, the FCP was lower, and therefore the Big Four price reflects the statutory FCP. Please note that, consistent with the ICR instructions, the Big Four price reflects

what can be found online in the pharmaceutical pricing data for all VA National Acquisition Centers

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0140-09	2018-Q3				EA	
57962-0140-12	2018-Q3				EA	
57962-0070-28	2018-Q3				EA	
57962-0014-28	2018-Q3				EA	
57962-0280-28	2018-Q3				EA	
57962-0420-28	2018-Q3				EA	
57962-0560-28	2018-Q3				EA	
57962-0007-12	2018-Q3				ML	
57962-0140-09	2018-Q4				EA	
57962-0140-12	2018-Q4				EA	
57962-0070-28	2018-Q4				EA	
57962-0014-28	2018-Q4				EA	
57962-0280-28	2018-Q4				EA	
57962-0420-28	2018-Q4				EA	
57962-0560-28	2018-Q4				EA	
57962-0007-12	2018-Q4				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0140-09	2019-Q1				EA	
57962-0140-12	2019-Q1				EA	
57962-0070-28	2019-Q1				EA	
57962-0014-28	2019-Q1				EA	
57962-0280-28	2019-Q1				EA	
57962-0420-28	2019-Q1				EA	
57962-0560-28	2019-Q1				EA	
57962-0007-12	2019-Q1				ML	
57962-0140-09	2019-Q2				EA	
57962-0140-12	2019-Q2				EA	
57962-0070-28	2019-Q2				EA	
57962-0014-28	2019-Q2				EA	
57962-0280-28	2019-Q2				EA	
57962-0420-28	2019-Q2				EA	
57962-0560-28	2019-Q2				EA	
57962-0007-12	2019-Q2				ML	
57962-0140-09	2019-Q3				EA	
57962-0140-12	2019-Q3				EA	
57962-0070-28	2019-Q3				EA	
57962-0014-28	2019-Q3				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0280-28	2019-Q3				EA	
57962-0420-28	2019-Q3				EA	
57962-0560-28	2019-Q3				EA	
57962-0007-12	2019-Q3				ML	
57962-0140-09	2019-Q4				EA	
57962-0140-12	2019-Q4				EA	
57962-0070-28	2019-Q4				EA	
57962-0014-28	2019-Q4				EA	
57962-0280-28	2019-Q4				EA	
57962-0420-28	2019-Q4				EA	
57962-0560-28	2019-Q4				EA	
57962-0007-12	2019-Q4				ML	
57962-0140-09	2020-Q1				EA	
57962-0140-12	2020-Q1				EA	
57962-0070-28	2020-Q1				EA	
57962-0014-28	2020-Q1				EA	
57962-0280-28	2020-Q1				EA	
57962-0420-28	2020-Q1				EA	
57962-0560-28	2020-Q1				EA	
57962-0007-12	2020-Q1				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0140-09	2020-Q2				EA	
57962-0140-12	2020-Q2				EA	
57962-0070-28	2020-Q2				EA	
57962-0014-28	2020-Q2				EA	
57962-0280-28	2020-Q2				EA	
57962-0420-28	2020-Q2				EA	
57962-0560-28	2020-Q2				EA	
57962-0007-12	2020-Q2				ML	
57962-0140-09	2020-Q3				EA	
57962-0140-12	2020-Q3				EA	
57962-0070-28	2020-Q3				EA	
57962-0014-28	2020-Q3				EA	
57962-0280-28	2020-Q3				EA	
57962-0420-28	2020-Q3				EA	
57962-0560-28	2020-Q3				EA	
57962-0007-12	2020-Q3				ML	
57962-0140-09	2020-Q4				EA	
57962-0140-12	2020-Q4				EA	
57962-0070-28	2020-Q4				EA	
57962-0014-28	2020-Q4				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0280-28	2020-Q4				EA	
57962-0420-28	2020-Q4				EA	
57962-0560-28	2020-Q4				EA	
57962-0007-12	2020-Q4				ML	
57962-0140-09	2021-Q1				EA	
57962-0140-12	2021-Q1				EA	
57962-0070-28	2021-Q1				EA	
57962-0014-28	2021-Q1				EA	
57962-0280-28	2021-Q1				EA	
57962-0420-28	2021-Q1				EA	
57962-0560-28	2021-Q1				EA	
57962-0007-12	2021-Q1				ML	
57962-0140-09	2021-Q2				EA	
57962-0140-12	2021-Q2				EA	
57962-0070-28	2021-Q2				EA	
57962-0014-28	2021-Q2				EA	
57962-0280-28	2021-Q2				EA	
57962-0420-28	2021-Q2				EA	
57962-0560-28	2021-Q2				EA	
57962-0007-12	2021-Q2				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0140-09	2021-Q3				EA	
57962-0140-12	2021-Q3				EA	
57962-0070-28	2021-Q3				EA	
57962-0014-28	2021-Q3				EA	
57962-0280-28	2021-Q3				EA	
57962-0420-28	2021-Q3				EA	
57962-0560-28	2021-Q3				EA	
57962-0007-12	2021-Q3				ML	
57962-0140-09	2021-Q4				EA	
57962-0140-12	2021-Q4				EA	
57962-0070-28	2021-Q4				EA	
57962-0014-28	2021-Q4				EA	
57962-0280-28	2021-Q4				EA	
57962-0420-28	2021-Q4				EA	
57962-0560-28	2021-Q4				EA	
57962-0007-12	2021-Q4				ML	
57962-0140-09	2022-Q1				EA	
57962-0140-12	2022-Q1				EA	
57962-0070-28	2022-Q1				EA	
57962-0014-28	2022-Q1				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0280-28	2022-Q1				EA	
57962-0420-28	2022-Q1				EA	
57962-0560-28	2022-Q1				EA	
57962-0007-12	2022-Q1				ML	
57962-0140-09	2022-Q2				EA	
57962-0140-12	2022-Q2				EA	
57962-0070-28	2022-Q2				EA	
57962-0014-28	2022-Q2				EA	
57962-0280-28	2022-Q2				EA	
57962-0420-28	2022-Q2				EA	
57962-0560-28	2022-Q2				EA	
57962-0007-12	2022-Q2				ML	
57962-0140-09	2022-Q3				EA	
57962-0140-12	2022-Q3				EA	
57962-0070-28	2022-Q3				EA	
57962-0014-28	2022-Q3				EA	
57962-0280-28	2022-Q3				EA	
57962-0420-28	2022-Q3				EA	
57962-0560-28	2022-Q3				EA	
57962-0007-12	2022-Q3				ML	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0140-09	2022-Q4				EA	
57962-0140-12	2022-Q4				EA	
57962-0070-28	2022-Q4				EA	
57962-0014-28	2022-Q4				EA	
57962-0280-28	2022-Q4				EA	
57962-0420-28	2022-Q4				EA	
57962-0560-28	2022-Q4				EA	
57962-0007-12	2022-Q4				ML	
57962-0140-09	2023-Q1				EA	
57962-0140-12	2023-Q1				EA	
57962-0070-28	2023-Q1				EA	
57962-0014-28	2023-Q1				EA	
57962-0280-28	2023-Q1				EA	
57962-0420-28	2023-Q1				EA	
57962-0560-28	2023-Q1				EA	
57962-0007-12	2023-Q1				ML	
57962-0140-09	2023-Q2				EA	
57962-0140-12	2023-Q2				EA	
57962-0070-28	2023-Q2				EA	
57962-0014-28	2023-Q2				EA	

G. Market Data and Revenue and Sales Volume Data

U.S. Commercial Average Net Unit Price

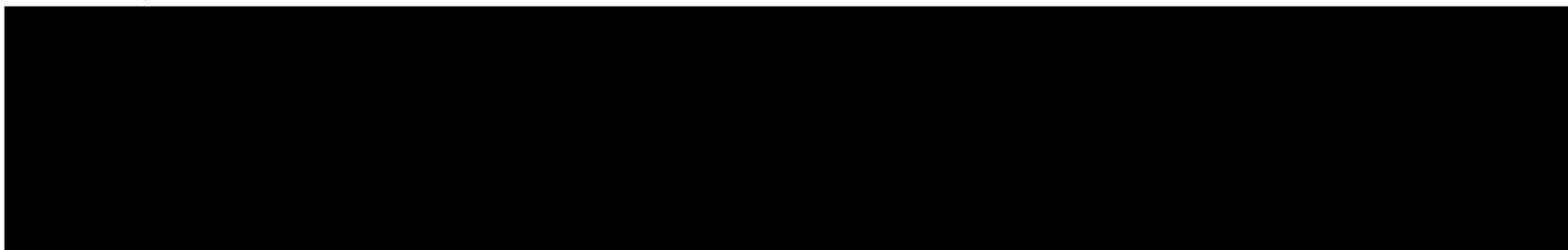
Description: The purpose of this section is to collect the market data, revenue and sales volume data described in section 1194(e)(1)(E) of the Act. The following table provides the U.S. commercial average net unit price, including group and individual commercial plans on- and off-exchange of the selected drug.

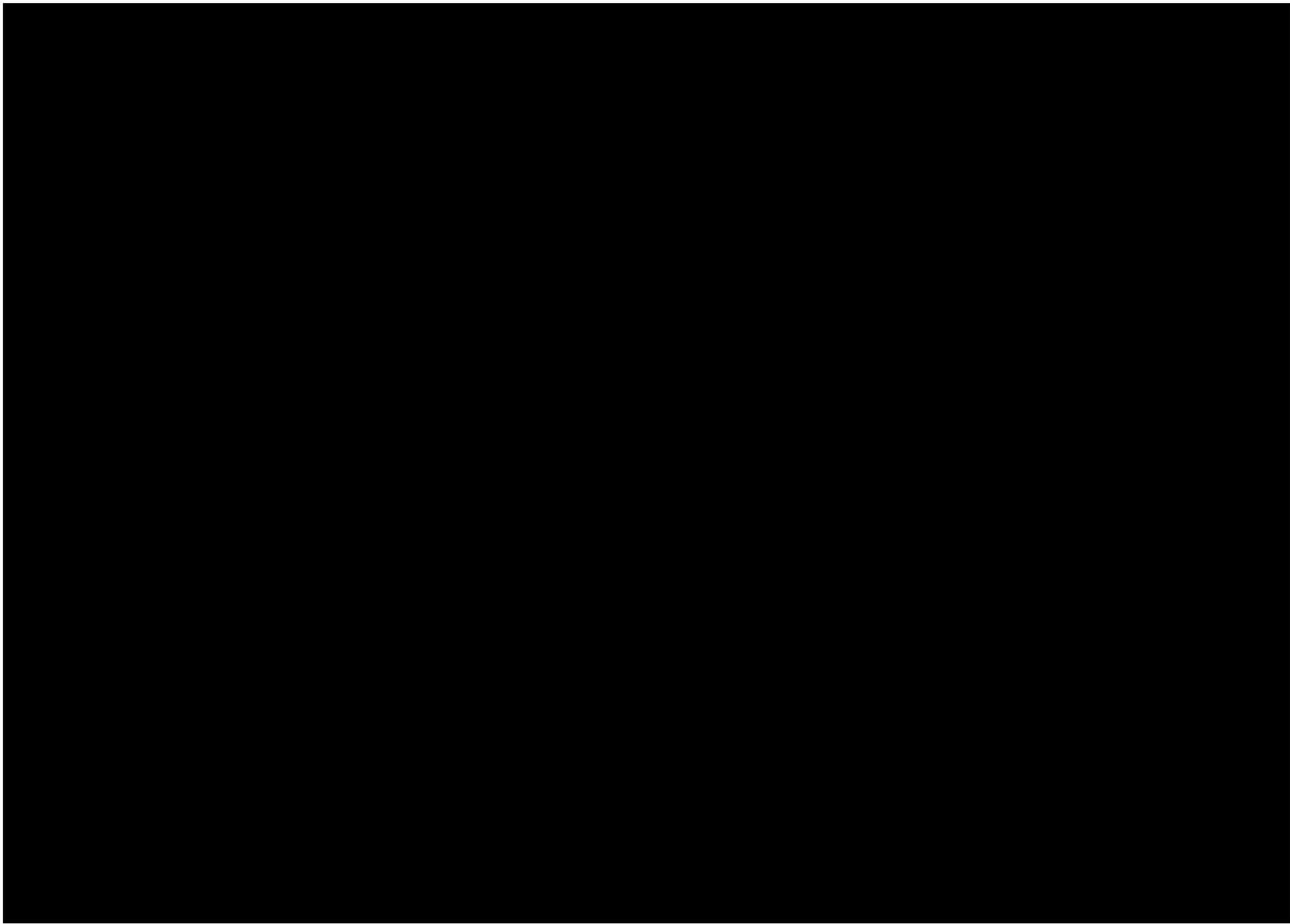
National Drug Code (NDC-11)	Quarter	U.S. Commercial Average Unit Net Price	U.S. Commercial Average Net Unit Price - Without Patient Assistance Programs	U.S. Commercial Average Net Unit Price- Best	Unit type (EA, ML, GM)	Total Unit Volume
57962-0280-28	2023-Q2				EA	
57962-0420-28	2023-Q2				EA	
57962-0560-28	2023-Q2				EA	
57962-0007-12	2023-Q2				ML	

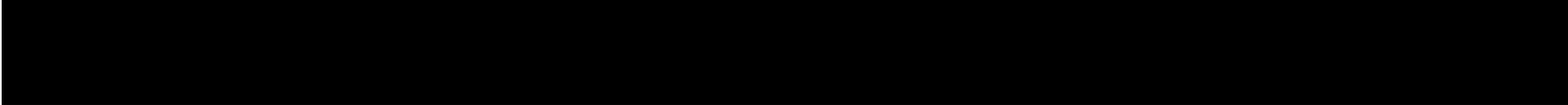
Explanations: This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.

AbbVie/Pharmacyclics submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42).

AbbVie/Pharmacyclics’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics’s rights to confidential treatment and predisclosure notification.





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- Two NDC's, 57962042071 and 57962056071, are included in Section A as NDC's that were registered and active earlier in the Imbruvica lifecycle. The NDC's were active from February of 2019 to December of 2020. However, these NDC's were never commercially saleable units: they were only distributed as free samples. As such, these NDCs are excluded from submitted market and sales data.

Manufacturer E2 Submission - AbbVie



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Respondent Name	Martha Skup
	Organization Name (if applicable)	AbbVie
	Respondent Email	martha.skup@abbvie.com
	Who is completing this form?	
Question 27: Prescribing Information	Prescribing Information	<p>**Disclaimer**: This information exchange is intended only for the use by CMS for clinical & value discussion as part of the Medicare Drug Price Negotiation Program. Information is being provided solely to support the required data submission and pricing process under the Inflation Reduction Act.</p> <p>IMBRUVICA (Ibrutinib) significantly transformed the standard of care and treatment paradigm since its approval, 2014, for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and other B-cell malignancies [see footnote A]. Ibrutinib is a first-in-class small molecule inhibitor of Bruton's tyrosine kinase (BTKi), a critical signaling molecule of the B-cell receptor (BCR) and cytokine receptor pathways. Extensive clinical studies have demonstrated Ibrutinib's significant clinical benefits for numerous patients with B-cell malignancies, including those who are elderly or terminally ill and in both the first-line (1L) and relapsed/refractory (R/R) settings (Imbruvica US package insert).</p> <p>The below section summarizes the Food and Drug Administration (FDA)-approved indications for Ibrutinib (presented in order of indication prevalence) and the corresponding therapeutic alternatives, which were identified based on 1) FDA APPROVAL WITHIN THE INDICATION OF INTEREST AND 2) NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES, AVAILABLE AT WWW.NCCN.ORG). The therapeutic alternatives were further categorized as Primary and Other, based on 1) SIMILARITY OF CHEMICAL CLASS, THERAPEUTIC CLASS, AND MECHANISM OF ACTION TO IBRUTINIB, 2) REAL-WORLD UTILIZATION PATTERNS AND 3) UTILIZATION WITHIN MEDICARE POPULATIONS.</p> <p>**Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)**:</p> <ul style="list-style-type: none"> • ADULT PATIENTS WITH CLL/SLL (2014 approval, NDA 205552/2016 approval, NDA 205552) <ul style="list-style-type: none"> - PRIMARY THERAPEUTIC ALTERNATIVE(S): BTK INHIBITORS: ACALABRUTINIB (2019 approval), ZANUBRUTINIB (2023 approval) - Other Therapeutic Alternative(s): BCL-2 Inhibitors: Venetoclax ± Obinutuzumab; Chemoimmunotherapy



Question	Sub-Question	Response
		<p>(CIT):</p> <p>Chlorambucil, Obinutuzumab, Obinutuzumab + chlorambucil (GC), bendamustine + rituximab (BR)</p> <ul style="list-style-type: none"> • ADULT PATIENTS WITH CLL/SLL WITH 17P DELETION (2014 approval, NDA 205552) <ul style="list-style-type: none"> - PRIMARY THERAPEUTIC ALTERNATIVE(S): BTK INHIBITORS: ACALABRUTINIB (2019 approval), ZANUBRUTINIB (2023 approval) - Other Therapeutic Alternative(s): BCL-2 Inhibitors: Venetoclax ± Obinutuzumab <p>**Waldenström’s macroglobulinemia (WM)**:</p> <ul style="list-style-type: none"> • ADULT PATIENTS WITH WM (2015 approval, NDA 205552) <ul style="list-style-type: none"> - PRIMARY THERAPEUTIC ALTERNATIVE(S): BTK INHIBITORS: ZANUBRUTINIB (2021 approval) - Other Therapeutic Alternative(s): Chemoimmunotherapy (CIT): Bendamustine/rituximab (BR), bortezomib/dexamethasone/rituximab <p>**Chronic graft-versus-host disease (cGVHD)**:</p> <ul style="list-style-type: none"> • ADULT AND PEDIATRIC PATIENTS AGE 1 YEAR AND OLDER WITH cGVHD AFTER FAILURE OF ONE OR MORE LINES OF SYSTEMIC THERAPY (adult: 2017 approval, NDA 205552; pediatric: 2022 approval, NDA 217003) <ul style="list-style-type: none"> - PRIMARY THERAPEUTIC ALTERNATIVE(S): JAK inhibitor: Ruxolitinib; Kinase inhibitor: Belumosudil <p>Real-world studies examining 1L CLL/SLL treatment patterns indicate that following the approval of Ibrutinib and other subsequent BTKis, the usage of BTKis has grown continuously leading to a decrease in CIT, BTKis are now the most commonly used 1L CLL/SLL treatment [1], [2], [3]. Evidence shows the proportion of 1L patients treated with BTKis increased from 40% in 2016 to 65% in 2020, further demonstrating this change in standard of care [1]. These observed treatment patterns in the United States align with the NCCN Guidelines, which are available at www.nccn.org (see also [4]).</p> <div style="background-color: black; height: 20px; width: 100%; margin: 10px 0;"></div> <p>**SUMMARY**:</p> <p>OVERALL, BASED ON THE SIMILARITY TO IBRUTINIB OF CHEMICAL CLASS/THERAPEUTIC CLASS/MECHANISM OF ACTION, THE OVERLAP OF INDICATIONS IN THE POPULATIONS WITH MAJORITY OF USE, NCCN TREATMENT GUIDELINES, MEDICARE UTILIZATION PATTERNS AND THE PUBLISHED EVIDENCE IN CLL/SLL AND WM TREATMENT PATTERNS, BTKIS ARE CONSIDERED AS THE PRIMARY THERAPEUTIC ALTERNATIVES TO IBRUTINIB. THUS, COMPARATIVE EFFECTIVENESS ASSESSMENT PRESENTED IN QUESTIONS 28-29 ARE ANCHORED TO THESE PRIMARY THERAPEUTIC ALTERNATIVES AND FOCUS MAINLY ON THE CLL/SLL INDICATION, GIVEN THIS ACCOUNTS FOR THE MAJORITY OF IBRUTINIB USE.</p>



Question	Sub-Question	Response
		<p>**Footnotes**: A: B-cell malignancies refer to a group of cancers that affect the immune system.</p> <p>**Citations**:</p> <ol style="list-style-type: none"> 1. Smith TW, Owusu HF, Wormser D, Woo J. Real-world evaluation of the treatment landscape for chronic lymphocytic leukemia. Blood. 2021;138(Suppl 1): 1559. 2. Mato AR, Ravelo R, To TM, Schuldt R, Biondo JML. Real-world treatment patterns and outcomes of patients with chronic lymphocytic leukemia (CLL) receiving first-line (1L) therapy in the United States (US). Blood. 2021;138(Suppl 1):4086. 3. Shadman M, Manzoor BS, Sail K, Tuncer HH, Allan JN, Ujjani C, Emechebe N, Kamalakar R, Coombs CC, Leslie L, Barr PM, Brown JR, Eyre TA, Rampotas A, Schuh A, Lamanna N, Skarbnik A, Roeker LE, Bannerji R, Eichhorst B, Fleury I, Davids MS, Alhasani H, Jiang D, Hill BT, Schuster SJ, Brander DM, Pivneva I, Burne R, Guerin A, Mato AR. Treatment discontinuation patterns for patients with chronic lymphocytic leukemia in real-world settings: Results from a multi-center international study. Clin Lymphoma Myeloma Leuk. 2023a Jul;23(7):515-526. 4. Stephens DM. NCCN Guidelines update: Chronic lymphocytic leukemia/small lymphocytic lymphoma. J Natl Compr Cancer Netw. 2023 May;21(5.5):563-6.
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>**Disclaimer**: This information exchange is intended only for the use by CMS for clinical & value discussion as part of the Medicare Drug Price Negotiation Program. Information is being provided solely to support the required data submission and pricing process under the Inflation Reduction Act.</p> <p>This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.</p> <p>AbbVie/Pharmacyclics submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45</p>



Question	Sub-Question	Response
		<p>C.F.R. 5.42).</p> <p>AbbVie/Pharmacyclics’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics’s rights to confidential treatment and predisclosure notification.</p> <p>[REDACTED]</p> <p>Published clinical and real-world studies, ranging from 2014-2023, are summarized below. These data provide evidence differentiating Ibrutinib from CIT, establishing BTKis as standard of care while demonstrating parity within class, and confirming benefit of Ibrutinib in special populations and those of unmet need. Findings of comparative effectiveness research (both clinical and economic) with Ibrutinib versus the primary therapeutic alternatives (i.e., other BTKis) are summarized below.</p> <p>**Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)**</p> <p>**Clinical and Real-World Efficacy/Effectiveness of Ibrutinib Versus Primary Therapeutic Alternatives**:</p> <ul style="list-style-type: none"> • FIRSTLINE (1L) CLL/SLL <p>No head-to-head trials have compared Ibrutinib to other BTKis in 1L CLL/SLL. However, a matching-adjusted indirect comparison (MAIC) (PFS: HR=0.92; 95% CI [0.44-1.95]) along with multiple real-world evidence (RWE) studies have demonstrated parity in real-world effectiveness outcomes [time to next treatment (TTNT) and persistence] between Ibrutinib and Acalabrutinib in 1L CLL [2], [3] [4], [5]. Consistent PFS outcomes were reported for Ibrutinib versus Acalabrutinib across RESONATE-2 and ELEVATE-TN trials implementing a MAIC analysis [6]. An RWE study conducted in patients with treatment naïve CLL/SLL reported significantly higher early adherence at 3 months post-index in the subgroup of patients with atrial fibrillation (AF) in the Ibrutinib cohort compared to the Acalabrutinib (odds ratio [OR]=3.13; 95% CI, 1.04-9.09; P=0.042) [2]. Also, parity in early treatment persistence (OR=0.79; 95% CI [0.52-1.20]) and adherence (OR=0.90; 95% CI [0.57-1.41]) was observed between Ibrutinib and Acalabrutinib in patients with CLL/SLL in the 1L setting. Additional real-world data showed TTNT benefit with Ibrutinib over Acalabrutinib in patients with previously untreated CLL [5]. At median follow-up of 18.1 months for Ibrutinib and 11.9 months for Acalabrutinib, 5.9% of Ibrutinib-treated patients and 7.5% of Acalabrutinib patients initiated a next or additional treatment. Acalabrutinib-treated patients were 89% more likely to start a next or additional treatment compared to Ibrutinib-treated patients (HR, 1.89 [95% CI, 1.12-3.13]; P=0.016).</p> <p>In summary, based on MAIC and RWE, recently approved BTKIs are at parity with Ibrutinib on efficacy/effectiveness</p>



Question	Sub-Question	Response
		<p>outcomes.</p> <ul style="list-style-type: none"> • RELAPSED/REFRACTORY (R/R) CLL/SLL <p>Acalabrutinib and Zanubrutinib have been compared with Ibrutinib in head-to-head trials in R/R CLL/SLL.</p> <p>In the phase 3 ELEVATE-RR study, Acalabrutinib demonstrated non-inferior PFS to Ibrutinib, with median PFS of 38.4 months in both arms [7]. Overall survival (OS) was not reached, and discontinuation rates were similar between Acalabrutinib (53.4%) and Ibrutinib (58.6%). Median TTNT was 51.7 months for Ibrutinib and 47.1 months for Acalabrutinib.</p> <p>In the phase 3 ALPINE trial, the primary endpoint of IRC-assessed ORR was 86.2% (95% CI, 82.0 to 89.8) for Zanubrutinib versus 75.5% (95% CI, 70.7 to 80.3) [8]. At median follow-up of 29.6 months, the median PFS was not reached with Zanubrutinib versus 34.2 months with Ibrutinib. However, some key considerations related to the trial design and outcome assessment need to be considered when interpreting these results: a) The ORR assessment excluded partial response with lymphocytosis (PR-L), which may have led to underestimation of Ibrutinib's response rate (including PR-L diminished the difference in response rates between the two drugs) b) the trial was not designed for statistically significant interim analysis of PFS and investigator-assessed response data are immature and inconclusive, requiring longer follow-up. Additionally, there were differences in patient characteristics between the two arms of ALPINE; the Ibrutinib arm included more heavily pre-treated and high-risk patients compared to the Zanubrutinib arm [9]. These differences may have resulted in underperformance in efficacy outcomes for Ibrutinib control arm in the ALPINE study.</p> <p>OVERALL, FINDINGS FROM MULTIPLE CLINICAL AND REAL-WORLD PUBLICATIONS INDICATE CLINICAL/RW EFFICACY/EFFECTIVENESS ARE SIMILAR ACROSS IBRUTINIB AND BTKI PRIMARY THERAPEUTIC ALTERNATIVES IN TREATMENT NAÏVE AND R/R SETTING.</p> <p>**Comparative Cost Analysis of Ibrutinib Versus Primary Therapeutic Alternatives**:</p> <p>The economic impact of Ibrutinib treatment compared with the Primary Therapeutic alternatives was assessed using a semi-Markov economic model. To inform this economic model, published efficacy and safety data from BTKi pivotal clinical trials (A. 1L CLL: RESONATE-2, ELEVATE-TN, and SEQUOIA; B. R/R CLL: RESONATE, ELEVATE-RR, and ALPINE, <see Model Table 1> for more details) and data from each drug prescribing information were used as model inputs. The semi-Markov model was created with three health states (PFS, progressive disease (PD), and death) and included key clinical and cost inputs among patients with frontline CLL/SLL and R/R CLL/SLL <see Model Table 1 & Model Table 2>. Each simulated comparator cohort was assumed treated with monotherapy. Key outcomes</p>



Question	Sub-Question	Response
		<p>generated by the model for each cohort include: time spent in either living health state, PD or PFS, as well as total cost SCALED PER PATIENT PER MONTH (PPPM) AND PER PATIENT PER YEAR (PPPY). [REDACTED]</p> <ul style="list-style-type: none"> • Model Parameters and Attributes <p>Among modeled patients with 1L CLL/SLL, 24-month PFS and 24-month OS as reported from key publications on pivotal published BTKi clinical trials were used to inform model transition probabilities <see Model Table 1>. For modeled patients with R/R CLL/SLL, median reported PFS and 24-month OS were used for Acalabrutinib modeled patients, 36-month PFS and 24-month OS were used for Ibrutinib modeled patients, and 24-month PFS and OS were used for Zanubrutinib patients. Transition probabilities were calculated assuming constant hazard ratios using time-based point estimate of key progression or survival event rates. Adverse event (AE) rates for each treatment as reported in prescribing information (where available) for pivotal clinical trials were used to populate the model <see Model Table 1>. In instances where a specific AE rate was not available from the trial-specific prescribing information, key publications on pivotal trials were used to abstract AE rates (LIST OF GRADE 3+ AES AND CORRESPONDING RATES SUMMARIZED IN <MODEL TABLE 2>). Costs included aggregate drug acquisition costs, administration costs, treatment-related costs, costs associated with progressed disease, medical costs as defined by costs related to disease management, and AE costs. AE costs were calculated as the product of the treatment specific AE incidence and its respective unit cost. Further specific cost references are included in <Model Table 3>. Outcomes were evaluated at 1-year.</p> <ul style="list-style-type: none"> • Key Model Results • 1L CLL/SLL: [REDACTED] • R/R CLL/SLL: [REDACTED]



Question	Sub-Question	Response
		<p>[REDACTED]</p> <p>[REDACTED]</p> <ul style="list-style-type: none"> • Sensitivity Analysis and Conclusion <p>To understand the impact of these assumptions, one-way sensitivity analyses (OWSA) were conducted. 95% confidence intervals were used to inform OWSA where published estimates were available. Where unavailable, confidence intervals were assumed to be +/- 20% from base case parameter estimates. OWSA of 1L CLL modeled patient outputs indicate that drug acquisition costs for each therapy are key drivers of modeled costs outcomes. Adverse event (AE) rates and clinical efficacy had a much lower impact on incremental costs of Ibrutinib relative to Acalabrutinib and Zanubrutinib. Annual medical costs and subsequent treatment costs had minimal impact. Among RR CLL modeled patients, acquisition cost of Ibrutinib and the comparator has the largest impact on base case results. Parameters associated with efficacy and safety also had an impact, although considerably less than acquisition costs. One limitation worth noting is that there may exist some differences in pivotal study patient populations, used to populate parameters included in this model. For the purposes of this evaluation, base case estimates were assumed to be those published in the clinical studies. Future explorations should consider these patient population differences as a potential sensitivity or scenario analysis.</p> <p>[REDACTED]</p> <p>**Waldenstrom’s macroglobulinemia (WM) **</p> <p>**Clinical Evidence Versus Primary Therapeutic Alternatives**:</p> <p>Studies selected for this section include a published clinical trial program (ASPEN). To date, there are no RWE available for Ibrutinib versus follow-on BTKis.</p> <ul style="list-style-type: none"> • 1L and R/R WM <p>A phase 3 study (ASPEN; NCT03053440) compared Ibrutinib and Zanubrutinib for treating patients with WM and</p>



Question	Sub-Question	Response
		<p>MYD88L265P mutation [27], [28]. At the interim analysis (median follow up of 19.4 months), the IRC-assessed primary endpoint (complete response [CR] +very good partial response [VGPR] rates) was not significantly different between arms: 19% for Ibrutinib and 28% for Zanubrutinib and no patient achieved a CR (P=0.09) [27]. Thus, the ASPEN trial did not meet its primary endpoint of demonstrating superiority of deep response (CR or VGPR) for Zanubrutinib vs Ibrutinib in WM and this is noted in the Zanubrutinib USPI. The overall response rates were similar, 78% for Ibrutinib and 77% for Zanubrutinib. The trial was not powered to detect differences in PFS and OS, thus conclusions or trends implying superiority in PFS or OS would be inappropriate. Furthermore, there is no available information that demonstrates CR + VGPR can be a surrogate for PFS. At median follow-up of 44.4 months, the investigator-assessed CR + VGPR rate was 22% for Ibrutinib and 36% for Zanubrutinib (P=0.02) [28]. No further data were presented on the primary endpoint of IRC-assessed CR + VGPR rate.</p> <p>**SUMMARY**: IBRUTINIB HAS CONSISTENTLY EXHIBITED COMPARABLE CLINICAL EFFICACY AND REAL-WORLD EFFECTIVENESS WHEN COMPARED TO THE PRIMARY THERAPEUTIC ALTERNATIVES, ALONG WITH DEMONSTRATING SUPERIORITY OVER CONVENTIONAL CIT IN CLL/SLL PATIENTS ACROSS MULTIPLE RIGOROUS STUDIES. NOTABLY, IBRUTINIB STANDS AS THE ONLY BTKI WITH A ROBUST DATASET DEMONSTRATING ITS EFFICACY AND SAFETY OVER AN EXTENDED PERIOD (10+ YEARS), WHILE THE DATA FOR OTHER BTKIS CONTINUES TO EVOLVE, WITH LONGER FOLLOW-UP NEEDED. AS OUR UNDERSTANDING OF ZANUBRUTINIB'S UTILITY IN CLL/SLL AND WM MATURES, RWE CAN PLAY A PIVOTAL ROLE IN FURTHER ASSESSING THE COMPARATIVE EFFECTIVENESS OF IBRUTINIB VERSUS ZANUBRUTINIB.</p> <p>[REDACTED]</p> <ul style="list-style-type: none"> • Please provide information on the risks, harms, or side effects, and any unique scenarios or considerations related to clinical benefit, safety, and patient experience related to the selected drug and its therapeutic alternative(s) for each indication, as applicable. Please describe any differences in the safety profile of the selected drug and its therapeutic alternative(s) for each indication, as applicable <p>**Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)**</p> <p>**Clinical Safety of Ibrutinib Versus other Primary Therapeutic Alternatives**:</p> <p>In the ELEVATE-RR trial, Acalabrutinib and Ibrutinib showed similar overall rates of AEs at approximately 97.7% and 97.3%, respectively [7]. Grade 1 or 2 AEs (28.9% Acalabrutinib vs 22.4% Ibrutinib) and Grade 3 or higher AEs (68.8% Acalabrutinib vs. 74.9% Ibrutinib) were comparable in both arms. The ELEVATE-RR trial also reported all-grade AF</p>



Question	Sub-Question	Response
		<p>rates of 9.4% and 16.0% in the Acalabrutinib and Ibrutinib arms (P=0.023), respectively. However, Grade 3+ AF rates were 4.5% in the Acalabrutinib arm and 3.4% in the Ibrutinib arm, consistent with Ibrutinib USPI, indicating that Acalabrutinib adverse event profile continues to mature.</p> <p>The prevalence of AF rates over time with Ibrutinib has remained relatively consistent with up to 8 years of follow-up [29], [30]. A pooled analysis of Ibrutinib randomized controlled registration trials reported that the onset of AF was highest in the first 6 months of treatment and then decreased over time [31]. AF has been observed with both Acalabrutinib and Ibrutinib in clinical studies and the prescribing information for both agents recommend monitoring for this AE [15], [17]. These data demonstrate that AF is an AE shared by multiple BTKis, suggesting a class effect. Appropriate monitoring and dose management strategies could be effective in AE management.</p> <p>Zanubrutinib has limited and immature safety data compared to the long-term follow-up and experience of Ibrutinib. Zanubrutinib and Ibrutinib related hypertension rates reported in Zanubrutinib USPI safety section are as follows: Grade 3+: 13% vs 13%, All Grade: 19% vs 20%. There have also been updates to the cardiac arrhythmias Warnings and Precautions (W&P) (addition of Grade 3+ ventricular arrhythmias [0.2%], increase in All Grade/Grade3+ [3.2->3.7%/1.1->1.7%] AF and flutter rates, and updated guidance for cardiac monitoring and risk/benefit assessment) [16].</p> <p>Ibrutinib has a well-established and predictable long-term safety profile which has been further established during the nearly 10 years since its first conditional approval, resulting in an updated label to help with better patient management [15]. For example, a recent Ibrutinib label update suggests that dose management can be an effective strategy to mitigate AE burden without compromising efficacy, permitting patients to remain on therapy. In the phase 3 RESONATE-2 trial, dose reductions were used to manage AEs in 16/79 (20%) patients who were on long-term Ibrutinib treatment (≥5 years) [32]. Following dose reductions, 13/16 (81%) patients had resolution of the initial AE and AEs did not recur or recurred at a lower grade for 12/16 patients (75%). Subsequent real-world data have helped confirm the dose management benefits of Ibrutinib in CLL/SLL and WM. A study compared the TTNT following the first incidence AE between patients with CLL/SLL who did and did not have a dose reduction of 1L Ibrutinib [33]. In the adjusted analyses, patients with dose reduction after an AE had a longer TTNT than patients without a dose reduction (HR=0.62; P=0.017) thus validating the clinical findings from the RESONATE-2 analysis.</p> <p>**Waldenstrom’s Macroglobulinemia (WM) **</p> <p>**Clinical Safety of Ibrutinib Versus other Primary Therapeutic Alternatives**:</p> <p>The ASPEN trial was not powered to determine statistical differences in AE rates between Ibrutinib and Zanubrutinib</p>



Question	Sub-Question	Response
		<p>[27]. Since the primary endpoint (IRC-assessed CR + VGPR rate) was not met, secondary endpoints including safety were not tested for statistical significance. The reported rates of Grade 3+ AEs were similar for Zanubrutinib and Ibrutinib respectively (58% vs. 63%). AF did not lead to discontinuation in either arm. AF has been observed with both agents in clinical studies and both package inserts including cardiac arrhythmias as a W&P [15], [16]. Appropriate monitoring and dose management should be exercised when treating patients with cardiovascular risk. Moreover, the W&P section for Zanubrutinib was updated with increased rates for hemorrhage, infections, second primary malignancies, and AF/flutter with the additional clinical studies included for the WM approval. These revised rates are similar to those found in the Ibrutinib W&P. Furthermore, this highlights the immaturity of the safety profile for Zanubrutinib and demonstrates the need for further follow-up to fully characterize its evolving AE profile.</p> <p>**SUMMARY**: OVERALL, THE IBRUTINIB LABEL HAS EVOLVED OVER THE YEARS BASED ON CLINICAL AND RW EXPERIENCES, AND CURRENTLY OFFERS DOSING FLEXIBILITY TO MANAGE AES WITH NO IMPACT ON EFFICACY/EFFECTIVENESS. OTHER BTKIS ARE LIMITED IN LONG-TERM DATASETS DUE TO TIME ON MARKET.</p> <ul style="list-style-type: none"> • Please provide current costs of such existing therapeutic alternatives (if known). <p>WAC prices as of 2023 for other primary therapeutic alternatives are listed below. Prices reflect the cost for the dose and formulation shown.</p> <ul style="list-style-type: none"> o Acalabrutinib 100 mg tablets (CLL/SLL, WM): \$14,920 o Zanubrutinib 80 mg capsules (CLL/SLL, WM): \$14,487
	<p>Hyperlink to Citation - Additional Materials for Question 28</p>	<p>[REDACTED]</p>
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p>	<p>[REDACTED]</p>



Question	Sub-Question	Response
	Evidence Submitted include a cost-effectiveness measure?	Y
	What type of Evidence is shown?	N
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	<p>**Disclaimer**: This information exchange is intended only for the use by CMS for clinical & value discussion as part of the Medicare Drug Price Negotiation Program. Information is being provided solely to support the required data submission and pricing process under the Inflation Reduction Act.</p> <p>This response contains trade secret and confidential commercial and financial information that AbbVie/Pharmacyclics customarily and actually treats as private. Disclosure of this information would result in harm to AbbVie/Pharmacyclics’s business interests, including because disclosure of any individual piece(s) of information could result in public identification of confidential materials.</p> <p>AbbVie/Pharmacyclics submits this information under CMS’s assurances of confidentiality (Guidance § 40.2.1 (citing id. § 40.2.2; 5 U.S.C. § 552(b)(3), (4); 18 U.S.C. § 1905)) and designates this submission as confidential and exempt from disclosure under Exemption 4 of the FOIA (45 C.F.R. 5.41). As such, predisclosure notification is required (45 C.F.R. 5.42).</p> <p>AbbVie/Pharmacyclics’s future disclosure of any piece of the information contained herein and designated as confidential does not alter the status of the remaining information as exempt from disclosure nor otherwise waive or forfeit AbbVie/Pharmacyclics’s rights to confidential treatment and predisclosure notification.</p> <p>Ibrutinib has been evaluated across several sub-populations in clinical and real-world settings including age, gender, mutational status, IgM levels, ECOG performance status, etc. The current section summarizes comparative effectiveness in CLL/SLL and WM across the following three sub-populations: A) ELDERLY PATIENTS, B) HIGH-RISK PATIENT SUB-GROUPS, AND C) UNDERSERVED RACE/ETHNIC GROUPS. Available published literature was selected from published clinical and RWE studies ranging in date from 2018 to 2023.</p> <p>**Clinical and Real-World Evidence of Ibrutinib Versus Primary Therapeutic Alternatives Across CLL/SLL and WM**</p> <p>1. ELDERLY PATIENTS</p>



Question	Sub-Question	Response
		<p>CLL and various other B-cell malignancies are diseases of the elderly (age ≥65 years) who often have involvement of multiple comorbidities and reduced organ function that impact daily activities and quality of life [1]. Treatments such as CIT further increase burden in these elderly patients such as the need to travel to infusion centers and increased toxicity, and provide limited efficacy compared with novel treatments like Ibrutinib. Ibrutinib was one of the first oral therapies in CLL that offered one-pill, once-daily, oral dosing, with superior efficacy versus CIT, and improved quality of life. Several clinical and RWE studies have demonstrated efficacy/effectiveness of Ibrutinib versus the Primary and Other Therapeutic Alternatives in CLL/SLL and WM [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12].</p> <p>**Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) **</p> <ul style="list-style-type: none"> • EVIDENCE VS. PRIMARY THERAPEUTIC ALTERNATIVE: There are no head-to-head data between Ibrutinib and primary therapeutic alternatives in the 1L setting. The median age of R/R CLL/SLL Ibrutinib treated patients in the ALPINE and ELEVATE-RR trial was 68 and 66 years, respectively [6], [7]. In the ELEVATE-RR trial, overall, across age subgroups, no significant difference in PFS outcomes were observed in the Ibrutinib cohort compared to Acalabrutinib: <65 years (HR=1.09; 95% CI [0.79 -1.52]); >65 to <75 years (HR=0.98; 95% CI [0.66 -1.47]); >75 years (HR=0.69; 95% CI [0.37 -1.28]) [6]. In the ALPINE trial, for ≥65 years age subgroup, no significant differences in investigator-assessed PFS outcomes were observed in the Ibrutinib cohort compared to Zanubrutinib: <65 years (HR=0.53; 95% CI [0.32 - 0.86]); ≥65 years (HR=0.72; 95% CI [0.52 - 1.01]) [7]. • EVIDENCE VS. OTHER THERAPEUTIC ALTERNATIVE: The median age of R/R CLL/SLL patients in the RESONATE trial was 67 years [2]. Subgroup analyses demonstrated that Ibrutinib had better PFS outcomes compared to chlorambucil in both <70 years (HR=0.120; 95% CI [0.084 -0.172]) and ≥70 years (HR=0.219; 95% CI [0.146 - 0.328]) age subgroups. A RW study compared adherence for the subgroup of patients with baseline AF in the Ibrutinib versus Acalabrutinib cohort [10]. The study reported a median age of 75 years across both the cohorts. Significantly higher early adherence was observed at 3 months post-index in the subgroup of patients with AF in the Ibrutinib compared with the Acalabrutinib (OR: 3.13; 95% CI, 1.04-9.09; P=0.042), and no significant difference in the early adherence and persistence rates was observed for the general study population. <p>**Waldenstrom’s Macroglobulinemia (WM)**</p> <ul style="list-style-type: none"> • EVIDENCE VS. PRIMARY THERAPEUTIC ALTERNATIVE: The median age of TN and R/R WM patients in the ASPEN trial was 70 years [13]. Overall, across age subgroups, no significant difference in response rates were observed compared to Zanubrutinib: <65 years (Rate Difference=12.0; 95% CI [-7.5 - 31.6]); >65 years (Rate Difference =7.9; 95% CI [-6.8 - 22.5]) at interim analysis. • EVIDENCE VS. OTHER THERAPEUTIC ALTERNATIVE: The median age of TN and R/R WM patients in the INNOVATE



Question	Sub-Question	Response
		<p>trial was 69 years [14]. Subgroup analyses demonstrated that Ibrutinib + rituximab (IR) had significantly better PFS outcomes compared to placebo + rituximab in both <65 (HR=0.29; 95% CI [0.11 -0.76]) and >65 (HR=0.17; 95% CI [0.07 -0.39]) age subgroups at primary analysis.</p> <p>2. HIGH-RISK PATIENTS</p> <p>CLL and WM are variable with some patients burdened with high-risk cytogenetic anomalies (del11q, del17p, TP53, IGHV, MYD88L265P) while testing rates in the clinical practice setting are low (~11 to 30%). These patients are more refractory to treatment with high relapse rates. Ibrutinib has consistently demonstrated sustained effectiveness (PFS) in high-risk patients with established economic benefit [2], [3], [4], [11], [15].</p> <p>**Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)**</p> <p>The iwCLL guidelines note that patients with del(17p) or TP53 mutations have poorer outcomes and do not respond well to CIT, and they emphasize the prognostic value of IGHV mutational status testing [16]. However, studies have revealed that testing for chromosomal abnormalities by FISH, TP53 mutation, or IGHV mutation status occurs infrequently among patients (31%, 11%, and 11%, respectively); and approximately one third of high-risk patients (del17p and TP53) received CIT [17], [18].</p> <p>Ibrutinib has demonstrated consistent long-term disease control and PFS benefit in patients with high-risk CLL/SLL where benefits with CIT are limited [2], [3], [4], [15], [19], [20].</p> <p>EVIDENCE AGAINST PRIMARY THERAPEUTIC ALTERNATIVE: In the ELEVATE-RR trial, the study population was patients with previously treated CLL with centrally confirmed del(17)(p13.1) or del(11)(q22.3) [6]. In the Ibrutinib treated arm, 89.4% also had unmutated IGHV, and 42.3% also had mutated TP53. Overall, Acalabrutinib demonstrated noninferior PFS with Ibrutinib. Similarly, no significant difference in PFS outcomes were seen in high-risk sub-groups for Ibrutinib vs Acalabrutinib arms: unmutated IGHV (HR=1.09; 95% CI [0.85 -1.40]); mutated TP53 (HR=.95; 95% CI [0.68 -1.33]). Similar results were seen in the ALPINE trial; Ibrutinib demonstrated no differences compared to Zanubrutinib in PFS outcomes for unmutated IGHV (HR=0.60; 95% CI [0.44 -0.82]); significant differences in PFS outcomes were seen for del(17)/TP53 (HR=0.53; 95% CI [0.31 -0.88]) [7].</p> <p>EVIDENCE AGAINST OTHER THERAPEUTIC ALTERNATIVE: Among Ibrutinib-treated patients in the RESONATE-2 trial, 53% (143 of 269) had 1 or more high-risk genomic features (TP53 mutation, del(11q) and/or unmutated IGHV), 22%</p>



Question	Sub-Question	Response
		<p>(54 of 251) had del(11q) mutation, and 58% (118 of 204) had unmutated IGHV [3]. Ibrutinib demonstrated significantly improved PFS compared to chlorambucil in this high-risk patient sub-group: with TP53 mutation, del11q, and/or unmutated IGHV (HR=0.098; 95% CI, [0.060-0.161) and with unmutated IGHV (HR=0.13; 95% CI [0.06 -0.31]). Patients with these high-risk genomic features had notably better 7-year PFS rates with Ibrutinib. Similar results were seen in the iLLUMINATE trial (Ibrutinib with obinutuzumab versus chlorambucil with obinutuzumab) [4] and E1912 study (Ibrutinib+rituximab versus CIT) [15].</p> <p>Multiple real-world studies have also demonstrated improved treatment outcomes in high-risk patients treated with Ibrutinib vs. CIT, thus complementing clinical trial findings [21], [22], [23].</p> <p>**Waldenstrom’s Macroglobulinemia (WM)** Ibrutinib-based treatments are effective for WM patients with the MYD88L265P mutation, which is common in over 90% of cases [11], [14], [24], [25], [26].</p> <p>EVIDENCE AGAINST PRIMARY THERAPEUTIC ALTERNATIVE: In the ASPEN trial cohort 1, all patients had MYD88 mutations and 20% and 32% had CXCR4 mutations in the Ibrutinib and Zanubrutinib arms, respectively [12]. In the final analysis, among patients with CXCR4 mutations, higher major response rates were observed with Zanubrutinib versus Ibrutinib.</p> <p>EVIDENCE AGAINST OTHER THERAPEUTIC ALTERNATIVE: In the iNNOVATE trial, baseline mutational data was available for 136 of 150 patients [14]. MYD88 L265P and CXCR4WHIM genotypes were found in 85% and 36%, respectively. At median follow-up of 26.5 months, subgroup analyses demonstrated that IR had significantly better PFS outcomes compared to placebo + rituximab across all genotype sub-groups: MYD88 L265P/CXCR4 WT (HR=0.17; 95% CI [0.06 -0.49]); MYD88 L265P/CXCR4 WHIM (HR=0.24; 95% CI [0.09 -0.66]) and MYD88 WT/CXCR4 WT (HR=0.21; 95% CI [0.04 -1.08]). This benefit persisted up to 5 years. The study's final analysis confirmed these findings; at median follow-up of 50 months, PFS benefit was maintained with IR regardless of genotype [11].</p> <p>3. UNDERSERVED RACE/ETHNIC PATIENT POPULATIONS</p> <p>Studies confirm consistent efficacy of Ibrutinib across racial groups. A retrospective cohort analysis was the first to identify a potential health disparity with respect to the use of novel agents (Ibrutinib, venetoclax, or idelalisib) among Black and White patients with CLL treated in the Department of Veterans Affairs (VA) [27]. Overall, Black patients were significantly less likely to receive novel agents than White patients (14% vs 26%; P=0.02). A recent study found long-term benefits independent of race/ethnicity; 36-month OS rates were 97% for Black and 85% for White Ibrutinib-treated patients [28]. These studies suggest that Ibrutinib's efficacy is not dependent on a patient's</p>



Question	Sub-Question	Response
		<p>race or ethnicity, making it a valuable treatment option for diverse patient populations.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>**SUMMARY**: IBRUTINIB HAS TRANSFORMED THE TREATMENT LANDSCAPE IN THE BROADER CLL/SLL, WM AND SUB-POPULATIONS SUCH AS ELDERLY AND HIGH-RISK PATIENTS, AND ADDITIONALLY, FOR UNDERSERVED RACE/ETHNIC SUBGROUPS WHO PREVIOUSLY DID NOT HAVE MANY TREATMENT OPTIONS WITH OPTIMAL EFFICACY AND SAFETY. THE ABOVE HIGHLIGHTED STUDIES UNDERSCORE THAT IBRUTINIB'S EFFICACY IS NOT DEPENDENT ON A PATIENT'S RACE OR ETHNICITY, MAKING IT A VALUABLE TREATMENT OPTION FOR DIVERSE PATIENT POPULATIONS.</p>
	Hyperlink to Citation - Additional Materials for Question 29	<p>[REDACTED]</p>



Question	Sub-Question	Response
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	[REDACTED]
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	<p>**Disclaimer**: This information exchange is intended only for the use by CMS for clinical & value discussion as part of the Medicare Drug Price Negotiation Program. Information is being provided solely to support the required data submission and pricing process under the Inflation Reduction Act.</p> <p>**Ibrutinib has been a revolutionary therapy for patients with B-cell malignancies and addresses unmet need across 5 key areas**:</p> <p>1. IBRUTINIB TRANSFORMED STANDARD OF CARE AWAY FROM CIT AND CONTINUES TO BE ONE OF THE MOST EFFECTIVE ORAL TREATMENTS IN CLL/SLL AND WM:</p> <p>Prior to 2014, CIT was the standard of care for patients with CLL/SLL and WM. However, CIT had extensive limitations, including myelosuppressive side effects, limited efficacy in high-risk cytogenetics, and necessary administration at infusion centers [1]. Due to CIT toxicity, elderly patients (≥65 years of age) were commonly treated with rituximab monotherapy despite suboptimal efficacy [2]. There was a historical unmet need in this population.</p> <p>Approval of Ibrutinib transformed the treatment landscape. Ibrutinib is a first-in-class oral small molecule BTKi demonstrating significant clinical benefit and tolerability vs. CIT in multiple clinical studies of patients with CLL/SLL and WM [3], [4], [5], [6], including the elderly and/or terminally ill [7]. Ibrutinib has also exhibited superior patient-reported outcomes [8], [9], [10].</p> <p>Ibrutinib was extensively studied across multiple B-cell malignancies in clinical and real-world settings with 15+</p>



Question	Sub-Question	Response
		<p>years of ongoing clinical development, 18+ phase 3 studies (CLL/SLL, mantle cell lymphoma [MCL], MZL, WN, cGVHD, follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL]), 8+ years of long-term data in CLL/SLL, and >190 investigator-initiated and collaborative research studies. Recent data indicates survival in Ibrutinib-treated patients with CLL/SLL is similar to the age-matched general population, further supporting Ibrutinib’s transformative contribution to changing standard of care <see Figure 1> [5]. Ibrutinib paved the way for follow-on BTKis; however, these agents have less evidence across B-cell malignancies and limited long-term follow-up. Follow-on BTKis are now recognized as the appropriate therapeutic alternatives to Ibrutinib, as supported by evidence, clinical guidelines, and their growing utilization. Over the past decade, BTKis, namely Ibrutinib (2014), Acalabrutinib (2019), and Zanubrutinib (2023), have received FDA approval for CLL/SLL (Ibrutinib, Acalabrutinib, and Zanubrutinib) and WM (Ibrutinib and Zanubrutinib), demonstrating superiority vs CIT [11], [12], [13], [14], [15], [16], [17], and establishing BTKis as the standard of care.</p> <p>2. IBRUTINIB PROVIDES DOSING FLEXIBILITY</p> <p>Ibrutinib distinctly addresses significant unmet need through dosing flexibility. Ibrutinib is the sole BTKi whose prescribing information provides guidance for dose reductions to manage AEs. Dose adjustment schedule has effectively alleviated common AEs in around 95% of cases. This strategy extends the duration of time on therapy while maintaining PFS benefit.</p> <p>An analysis of CLL/SLL patients receiving long-term 1L Ibrutinib in the RESONATE-2 study showed no significant difference in median PFS between patients with Ibrutinib dose reduction (n=31) and those without (n=104): 87.7 months (95% CI, 56.9–NE) vs NR (95% CI, 81.9–NE) (HR 0.96 [95% CI, 0.50–1.84]; P=0.9011) [18]. A retrospective analysis in WM showed patients with Ibrutinib dose reduction had superior 4-year PFS compared to those without: 85% (95% CI, 74-92) vs 75% (95% CI, 68-81), respectively (P=0.03) [19]. These findings were confirmed in another RW study [20].</p> <p>3. IBRUTINIB IS THE ONLY BTKI WITH FDA-APPROVED FORMULATION OPTIONALITY ALLOWING FOR PERSONALIZATION OF THERAPIES AND OFFERS CONVENIENT ONE PILL ONCE DAILY ADMINISTRATION</p> <p>Ibrutinib is the sole BTKi available in multiple formulations (tablets, capsules, oral suspension), personalizing treatment.. Oral suspension formulation is especially useful for elderly patients with difficulties swallowing pills. The iMAGINE study demonstrated safe and effective utilization of Ibrutinib in oral suspension in patients aged <12 years, investigators reporting benefits to patients of all ages with dysphagia secondary to cGVHD [21].</p> <p>Ibrutinib's unique once daily oral regimen decreases pill burden, reduces the potential for mis-dosing, assisting with</p>



Question	Sub-Question	Response
		<p>adherence among the elderly population. Real-world evidence vs Acalabrutinib has demonstrated parity in effectiveness outcomes [TTNT and adherence] in 1L CLL [22] or improved outcomes with Ibrutinib [23], [24].</p> <p>4. IBRUTINIB SERVES AS THE ONLY APPROVED BTKI IN ADULT AND PEDIATRIC PATIENTS WITH cGVHD</p> <p>Ibrutinib is the only BTKi with demonstrated efficacy and approval in adult and pediatric patients (aged >1 year) with cGVHD. A significant proportion of patients with cGVHD fail to receive benefit from 1L therapy and become steroid-dependent or steroid-refractory [25]. The efficacy of treatment options for these patients is inconsistent, of limited duration, and associated with significant toxicities. There is a need for steroid-sparing therapies with better efficacy and tolerability.</p> <p>The phase 1b/2, multicenter study (PCYC-1129) of Ibrutinib in adult patients with cGVHD with treatment failure after ≥1 prior line of systemic therapy showed after a median follow-up of 26 months, the ORR was 69% and 55% of responders had a sustained response at ≥44 weeks [25]. Additionally, 64% patients achieved corticosteroid doses <0.15 mg/kg/day for ≥1 week and 28% of responders were able to completely discontinue all corticosteroid treatment.</p> <p>In the phase 1/2 iMAGINE study (PCYC-1146) of pediatric patients aged ≥1 to <22 years with 1L or R/R moderate/severe cGVHD showed Ibrutinib treated younger and older children achieved plasma concentration-time profiles consistent with those observed in adults [21]. At median follow-up of 20.4 months, the ORR was 78%. Similar results were seen in another study of Ibrutinib in pediatric patients with cGVHD [26].</p> <p>5. OTHER B-CELL MALIGNANCIES</p> <p>Ibrutinib has a large body of clinical evidence in other B-cell malignancies, including MCL and MZL [27], [28], [29], [30], [31], [32], [33], [34], [35]. Ibrutinib has been utilized successfully in CLL/SLL in non-approved combinations, such as with venetoclax [36], [37], [38].</p> <p>**SUMMARY**: IBRUTINIB IS AN ESTABLISHED CORNERSTONE OF CLL AND WM TREATMENT. ITS DEVELOPMENT HAS LED TO NOTABLE ADVANCEMENTS IN PATIENT OUTCOMES, INCLUDING ELDERLY AND FRAILER POPULATIONS. IBRUTINIB'S UNIQUE ONCE DAILY PILL REGIMEN HELPS ADDRESS ADHERENCE CHALLENGES COMMON AMONG ELDERLY PATIENTS. THE AVAILABILITY OF MULTIPLE FORMULATIONS, INCLUDING ORAL SUSPENSION, ENHANCES IBRUTINIB'S VERSATILITY AND PATIENT-CENTRIC APPROACH. IBRUTINIB HAS DEMONSTRATED EFFICACY IN MULTIPLE OTHER B-CELL MALIGNANCIES. IBRUTINIB'S UTILITY EXTENDS TO ADULT AND PEDIATRIC PATIENTS WITH cGVHD, OFFERING A DESPERATE ALTERNATIVE FOR THIS CHALLENGING SYSTEMIC DISORDER.</p>



Question	Sub-Question	Response
	Hyperlink to Citation - Additional Materials for Question 30	[REDACTED]
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	[REDACTED]
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>**Disclaimer**: This information exchange is intended only for the use by CMS for clinical & value discussion as part of the Medicare Drug Price Negotiation Program. Information is being provided solely to support the required data submission and pricing process under the Inflation Reduction Act.</p> <p>CLL is an incurable blood cancer that affects approximately 207,000 patients in the United States, mostly elderly; 68% of new cases occur among patients ≥65 years of age. It causes serious complications and heightened risk of other cancers and death that confer significant medical and cost burden, especially among minorities. The approval of IMBRUVICA (Ibrutinib), a first-in-class BTKi, transformed the treatment landscape for CLL/SLL and other B-cell</p>



Question	Sub-Question	Response
		<p>malignancies away from broad systemic agents to safe and effective targeted oral treatments. Cytotoxic chemotherapy, the prior treatment cornerstone, resulted in remission for some patients but also short- and long-term treatment-related adverse effects, including myelosuppression. For patients with high-risk disease, remissions were short lived, requiring follow-on therapies. It is largely due to the advancement in therapy demonstrated by Ibrutinib that patients with CLL/SLL no longer die from the illness and have an average life expectancy similar to the age matched general population, as demonstrated by recent data indicating survival in Ibrutinib-treated patients with CLL/SLL is similar to the age-matched general population. In addition, Ibrutinib's and follow-on BTKi's oral dosing flexibility compared to in-office CIT Ibrutinib has resulted in reduced patient/caregiver burden.</p> <p>It is important to note that Ibrutinib is an extensively studied targeted therapy across B-cell malignancies, including 15+ years of ongoing clinical development, 18+ phase 3 studies across multiple B-cell malignancies. Numerous phase 3 and real-world studies have confirmed the PFS and OS benefit for Ibrutinib versus previous standard of care in CLL/SLL and WM. Ibrutinib is approved for use in CLL/SLL, WM, and adult and pediatric cGVHD, with ~80% of its use in CLL.</p> <p>In addition, Ibrutinib paved the way for the development of follow-on BTKis, including Calquence (Acalabrutinib) and Brukinsa (Zanubrutinib). These follow-on BTKis entered the marketplace over 5 years after Ibrutinib and are similar in mechanism of action. These follow-on BTKis have limited clinical evidence across B-cell malignancies compared with Ibrutinib, and less real-world experience.</p> <p>Follow-on BTKis (Acalabrutinib and Zanubrutinib) are recognized as the appropriate therapeutic alternatives for Ibrutinib based on similarity of mechanism of action/treatment class, published evidence, clinical guidelines, and utilization. The BTKi class has demonstrated superiority versus CIT across multiple 1L and R/R clinical trials. United States and European Union physician-driven treatment guidelines continue to recommend BTKis as one of the preferred 1L treatments in CLL/SLL and WM. The BTKi class is now considered standard of care in CLL/SLL and WM (these indications comprise ~90% of Ibrutinib use in Medicare).</p> <p>[REDACTED]</p> <p>Based on available evidence, BTKis are considered largely similar in efficacy and safety profile in CLL/SLL and WM with some distinctions. No randomized controlled trials in 1L CLL are available. Few head-to-head 2L clinical studies versus Ibrutinib were designed to show comparable efficacy to Ibrutinib, with some tradeoffs in AEs and uniquely in the R/R population. Long-term effectiveness, safety and clinical experience for recently approved follow-on BTKis continue to evolve over time. [REDACTED]</p>



Question	Sub-Question	Response
		<p>[REDACTED]</p> <p>Even with the recent approval of follow-on BTKis, Ibrutinib continues to meet a distinctive unmet need versus other BTKis. Ibrutinib offers flexibility in therapy for patients needing an alternate dosing regimen and/or formulation. As CLL/SLL and WM are diseases of the elderly (≥ 65 years), patients are generally fragile with multiple serious comorbidities, predisposing them to AEs. Ibrutinib's established dose modification guidelines have demonstrated value to clinicians and patients by largely resolving common AEs (~95%) while allowing patients to remain on therapy over the long term without compromising efficacy. Only Ibrutinib is available in multiple dosage forms to support personalization in therapy, including an oral suspension formulation for patients who may have trouble swallowing and/or require alternate delivery options. Ibrutinib offers unique benefits versus other BTKis in multiple distinct patient populations. Ibrutinib consistently demonstrated superior and sustained effectiveness (OS, PFS) along with established economic benefit in patients with high-risk cytogenetic abnormalities. Ibrutinib is the only BTKi with demonstrated safety and efficacy in adult and pediatric cGVHD. Ibrutinib has also shown consistent safety and efficacy in fragile, vulnerable patient populations and across diverse racial and ethnic populations as well as veterans. Only Ibrutinib has been investigated and demonstrated efficacy in other B-cell malignancies and more aggressive cancers.</p> <p>Ibrutinib has made a substantial impact in patients' lives and is the only BTKi with demonstrated OS benefit in the 1L setting. In addition to Ibrutinib's unsurpassed long-term survival evidence, it has proven value compared to follow-on BTKis (therapeutic alternative) due to the strength of its long-term RWE, once-daily dosing, and unique indications. [REDACTED]</p> <p>[REDACTED]</p>

MODEL TABLE 1. Model Parameter Details

ATTRIBUTE	FEATURES
Model Type	Semi-Markov
Time Horizon	1-year
Cycle Length	1 week
Perspective	Medicare Payer
Currency	US Dollar (2023)
Effectiveness	Overall Survival, Progression Free Survival
Cost Outcomes	Per Patient Per Month Cost, Per Patient Per Year Cost
Direct Medical Cost Definition	Costs related to disease management, beyond drug-related acquisition costs, PD costs or AE costs.
Costs Definition	Aggregate of drug acquisition, administration, treatment-related, costs related to AE's, costs associated with progressed disease, and direct medical costs
Discount Rate	3%
Population	Treatment Naïve and Relapsed & Refractory CLL/SLL patients
Data Sources	Published Literature, Validated Clinical Assumptions

US = United States, PD = Progressed Disease, AE = Adverse Events, CLL/SLL= Chronic Lymphocytic Leukemia

MODEL TABLE 2. Key Clinical Parameter Inputs

CLINICAL PARAMETERS	1L CLL					
	IBRUTINIB		ACALABRUTINIB		ZANUBRUTINIB	
	ESTIMATE	SOURCE	ESTIMATE	SOURCE	ESTIMATE	SOURCE [†]
Efficacy (at 2-years)						
OS	98%	[12]	95.0%	[13]	94.3%	[14]
PFS	86.9%*	[12]	87.0%	[13]	85.5%	[14]
AE Rates						
Hypertension	4.0%	[15]	2.2%	[13]	6.6%	[16]
Anemia	5.9%	[12]	10.0%	[17]	0.3%	[16]
Neutropenia	10.0%	[12]	13.0%	[17]	12.5%	[14]
Headache	1.0%	[15]	1.1%	[17]	0.6%	[16]
Diarrhea	4.0%	[15]	0.6%	[17]	0.9%	[16]
Pneumonia	8.0%	[15]	4.5%	[17]	6.0%	[16]
Thrombocytopenia	2.2%	[12]	3.4%	[17]	1.4%	[14]
Atrial Fibrillation	1.5%	[12]	0.0%	[13]	2.0%	[14]
Infection	9.6%	[12]	9.5%	[13]	9.7%	[14]
Fatigue	1.0%	[15]	1.1%	[17]	1.1%	[16]
Rash	4.0%	[15]	0.6%	[17]	0.9%	[16]
Hemorrhage	3.7%	[12]	1.7%	[17]	4.3%	[16]
Arthralgia	1.0%	[15]	0.6%	[17]	0.9%	[14]
Nausea	1.0%	[15]	0.0%	[17]	0.0%	[16]
Sepsis	0.0%	NR	0.0%	[13]	0.9%	[14]
	RELAPSED & REFRACTORY CLL					
	IBRUTINIB		ACALABRUTINIB		ZANUBRUTINIB	
	ESTIMATE	SOURCE	ESTIMATE	SOURCE	ESTIMATE	SOURCE
Efficacy (at 2-years)						
OS	83.5%	[18]	85.8%	[7]	89.1%	[19]
PFS	70.3%	[18]	64.8%	[7]	78.4%	[19]
AE Rates						
Hypertension	8.0%	[18]	2.0%	[20]	13.0%	[16]
Anemia	5.0%	[21]	15.0%	[17]	2.2%	[19]
Neutropenia	16.0%	[21]	23.0%	[17]	16.0%	[19]
Headache	1.0%	[15]	0.6%	[17]	0.0%	NR
Diarrhea	4.0%	[15]	1.3%	[17]	1.5%	[16]
Pneumonia	12.0%	[15]	5.0%	[20]	9.0%	[16]
Thrombocytopenia	6.0%	[21]	6.0%	[17]	2.8%	[19]

Atrial Fibrillation	3.0%	[21]	1.9%	[20]	1.9%	[19]
Infection	16.0%	[21]	8.5%	[17]	8.3%	[22]
Fatigue	2.0%	[21]	1.9%	[17]	0.9%	[16]
Rash	3.0%	[15]	0.0%	[20]	1.2%	[16]
Hemorrhage	1.0%	[21]	1.3%	[17]	2.5%	[16]
Arthralgia	1.0%	[15]	1.3%	[17]	0.6%	[16]
Nausea	2.0%	[15]	0.0%	[20]	0.0%	NR
Sepsis	1.0%	[21]	1.5%	Assumption based on [7]	0.5%	[22]

**The 2-yr PFS values were based on 18-month PFS according to independent assessment taken from [12].*

† Both Zanubrutinib monotherapy treatment arms were pooled from the SEQUOIA trial.

NR=Not Reported; PI=Prescribing Information; 1L=Treatment naïve

In this analysis, we use the best available data as available in the public domain. However, due to limited data a few key assumptions were made based on our literature review and expert opinion. AE rates that were taken from the PI are based on trial-specific data for the indicated population. For Acalabrutinib, the PI reported AEs for 1L patients in the ELEVATE-TN trial and RR CLL in the ASCEND trial.

MODEL TABLE 3. Key Cost Parameter Inputs

COST PARAMETERS	COST (\$)	SOURCE
Annual Drug Acquisition Costs (30 day supply)		
Ibrutinib	\$17,018	[10]
Acalabrutinib	\$14,920	[10]
Zanubrutinib	\$14,487	[10]
Annual Medical Costs		
Frontline CLL/SLL		
PFS	\$510	[23]
PD	\$2,994	[23]
R/R CLL/SLL		
PFS	\$1,000	[24]
PD	\$2,520	[24]
Adverse Event Costs		
Hypertension	\$5,417	[23]
Anemia	\$8,800	[23]
Neutropenia	\$14,529	[23]
Headache	\$0	Assumption
Diarrhea	\$8,576	[23]
Pneumonia	\$9,427	[25]
Thrombocytopenia	\$14,529	[23]
Atrial Fibrillation	\$11,894	[23]
Infection	\$10,801	[23]
Fatigue	\$744	[23]
Rash	\$5,891	[23]
Hemorrhage	\$27,071	[23]
Arthralgia	\$6,871	[26]
Nausea	\$7,962	[26]
Sepsis	\$20,851	[25]

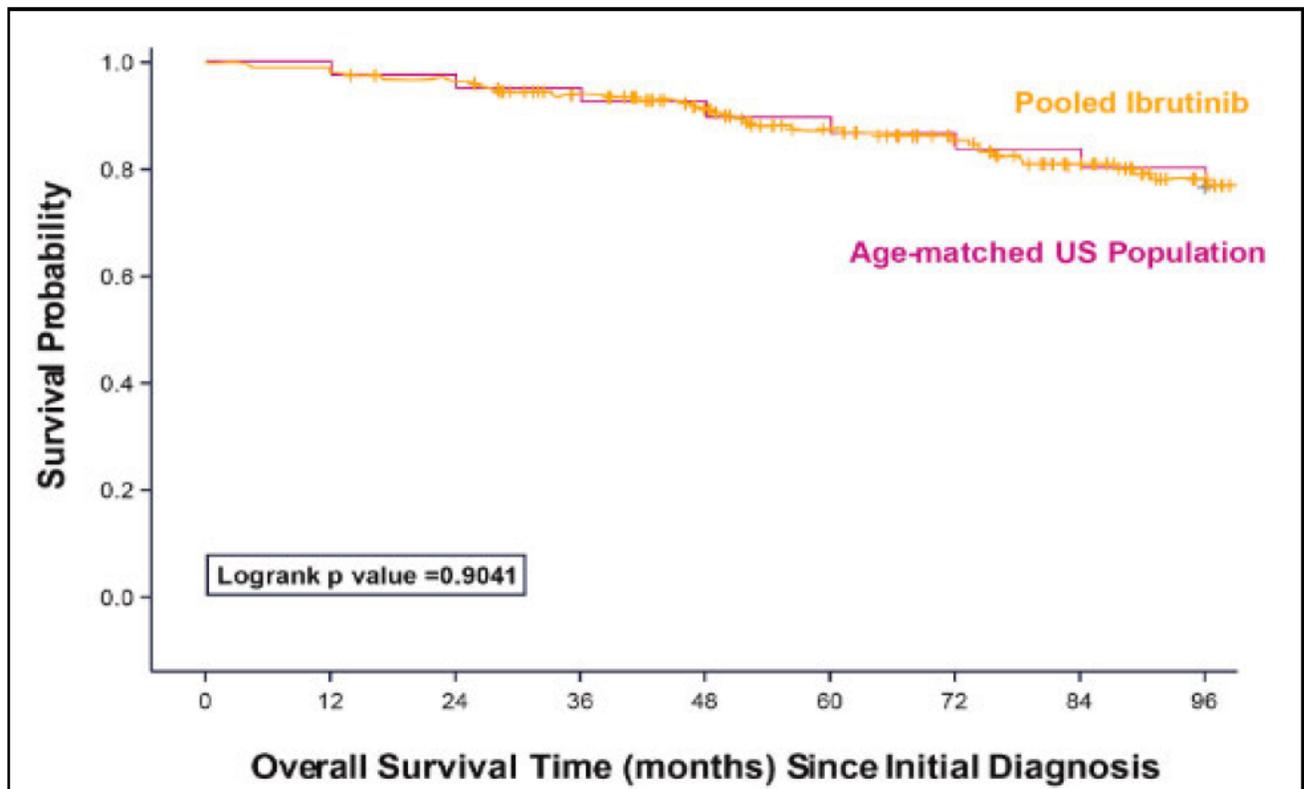
** Among the headache patients, approximately 1% may have to discontinue due to severity, thus costs are accounted for in disease progression and treatment discontinuation.*

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FIGURE 1: Similar OS for pooled 1L Ibrutinib for ≥ 65 years patients (N=201) vs age-matched general population (N=201) [5]



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Public E2 Submission

IPAY: 2026



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	AARP
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	PAT
	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure?	
Question 28: Therapeutic Impact and Comparative Effectiveness	What type of Evidence is shown?	
	Therapeutic Impact and Comparative Effectiveness	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
	Response to Question 29	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	
	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	

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Question Sub-Question

Question 31:
Patient and
Caregiver
Experience

Response to Question 31

Response

AARP, which advocates for the more than 100 million Americans age 50 and over, is pleased to submit the following comments in response to the Centers for Medicare and Medicaid Services' (CMS) Medicare Drug Price Negotiation Program Patient-Focused Listening Sessions. AARP commends CMS for soliciting feedback from the public and appreciates its efforts to ensure that patients, caregivers, and health care providers have a voice in the negotiation process. ..Data shows that brand-name drug prices have increased dramatically faster than inflation for decades. List prices for the 25 brand-name drugs with the highest total Medicare Part D spending in 2021 have increased by an average of 226% - or more than tripled - since they first entered the market. Data also shows that all but one of the top 25 drugs' lifetime price increases greatly exceeded the corresponding annual rate of general inflation (Consumer Price Index All Urban Consumers for All Items; CPI-U) over the period that each product has been on the market (i.e., product launch date until May 2023). For example, the price of Enbrel (Etanercept), used to treat rheumatoid arthritis and psoriatic arthritis, has increased by 701% since coming to market in 1998, and the price of Januvia (Sitagliptin), used to treat diabetes, has increased by 275% since entering the market in 2006. Further, the median price of a new brand-name prescription drug is now approximately \$200,000 per year, so even relatively small percentage price increases can translate into thousands of dollars and put life-saving medications out of reach of the patients who need them...High prescription drug prices can negatively affect older adults' health and financial security. [REDACTED], a Medicare enrollee from [REDACTED], is living with a health condition and takes Imbruvica to treat the condition. "The Imbruvica is doing what it's supposed to do. My CLL is in remission. But it's a drug that you take forever unless you can't tolerate it for one reason or another." [REDACTED]'s annual out-of-pocket costs for Imbruvica have increased year after year, paying \$8,500 in 2016 to \$11,768 in 2020. "The Imbruvica in 2020 was 13% of our gross income. ... If you have one prescription [that] costs you 13% of your GROSS income, that's obscene. My husband's question to me when we were paying these outrageous amounts was, 'What do you do if you can't afford it? You just die.' It shouldn't go up every year after it's been approved and there's no more research and development." ..AARP fiercely believes that the needs of Medicare beneficiaries should remain paramount as the agency implements the Negotiation Program. In 2022, about 1 in 5 adults ages 65 and up either skipped, delayed, took less medication than was prescribed, or took someone else's medication last year because of concerns about cost. It is not fair or right to ask patients and taxpayers to continue paying for high prescription drug prices that are the result of broken markets. ..Successful implementation of the new federal law will help reduce prescription drug prices and costs and ensure that millions of older Americans are better able to access the prescription drugs they need at a price they can afford. The Medicare drug price negotiation process will also finally allow CMS to push back on indiscriminately escalating drug prices and ensure that taxpayer funds are paying for value – all while saving billions for Medicare and its beneficiaries. The CBO estimates that the Negotiation Program will save Medicare and the American taxpayers nearly \$98.5 billion over 10 years, reduce the budget deficit by \$25 billion in 2031, and save Medicare Part D enrollees \$7 billion in 2031 due to lower out-of-pocket costs and premiums. ..This is about real people whose lives are on the line. For decades, older Americans have paid the highest prices in the world for prescription drugs - often three

Public E2 Submission

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Question	Sub-Question	Response
		<p>times higher than people in other countries. Now is the time to change that. Effective implementation of this Program will represent a major victory for older Americans and their families across the country who are struggling to afford their prescriptions. It will also help encourage and appropriately reward the development of truly innovative products. AARP stands ready to assist in any way with these and other efforts to bring down drug prices and help older Americans afford the medications and treatments they need. If you have any questions, please do not hesitate to contact me or Gidget Benitez at gbenitez@aarp.org...Sincerely, ..Nancy LeaMond.Executive Vice President and Chief Advocacy & Engagement Officer</p>
Question 32: Executive Summary	Response to Question 32	



October 2, 2023

Meena Seshamani, M.D., Ph.D.
Director, Center for Medicare
Centers for Medicare & Medicaid Services
U.S. Department of Health and Human Services

Dear Dr. Seshamani:

AARP, which advocates for the more than 100 million Americans age 50 and over, is pleased to submit the following comments in response to the Centers for Medicare and Medicaid Services' (CMS) Medicare Drug Price Negotiation Program Patient-Focused Listening Sessions. AARP commends CMS for soliciting feedback from the public and appreciates its efforts to ensure that patients, caregivers, and health care providers have a voice in the negotiation process.

Data shows that brand-name drug prices have increased dramatically faster than inflation for decades. List prices for the 25 brand-name drugs with the highest total Medicare Part D spending in 2021 have increased by an average of 226%—or more than tripled—since they first entered the market.¹ Data also shows that all but one of the top 25 drugs' lifetime price increases greatly exceeded the corresponding annual rate of general inflation (Consumer Price Index All Urban Consumers for All Items; CPI-U) over the period that each product has been on the market (i.e., product launch date until May 2023).² For example, the price of Enbrel (Etanercept), used to treat rheumatoid arthritis and psoriatic arthritis, has increased by 701% since coming to market in 1998, and the price of Januvia (Sitagliptin), used to treat diabetes, has increased by 275% since entering the market in 2006.³ Further, the median price of a new brand-name prescription drug is now approximately \$200,000 per year,⁴ so even relatively small percentage price increases can translate into thousands of dollars and put life-saving medications out of reach of the patients who need them.

High prescription drug prices can negatively affect older adults' health and financial security. ██████, a Medicare enrollee from ██████, is living with a health condition and takes Imbruvica to treat the condition. "The Imbruvica is doing what it's supposed to do. My CLL is in remission. But it's a drug that you take forever unless you can't tolerate it for one reason or another." ██████'s annual out-of-pocket costs for Imbruvica have increased year after year, paying \$8,500 in 2016 to \$11,768 in 2020. "The Imbruvica in 2020 was 13% of our gross income. ... If you have one prescription [that] costs you 13% of your GROSS income, that's

¹ Leigh Purvis, "Prices for Top Medicare Part D Drugs Have More Than Tripled Since Entering the Market." Washington, DC: AARP Public Policy Institute, August 10, 2023. <https://doi.org/10.26419/ppi.00202.001>.

² *Id.*

³ *Id.*

⁴ Benjamin N. Rome, Alexander C. Egilman, and Aaron S. Kesselheim, "Trends in Prescription Drug Launch Prices, 2008–2021," *Journal of the American Medical Association* 327, no. 21 (2022): 2145–47, <https://jamanetwork.com/journals/jama/fullarticle/2792986>; Deena Beasley, "U.S. New Drug Price Exceeds \$200,000 Median in 2022," Reuters, January 5, 2023, <https://www.reuters.com/business/healthcare-pharmaceuticals/us-new-drug-price-exceeds-200000-median-2022-2023-01-05/>.

obscene. My husband’s question to me when we were paying these outrageous amounts was, ‘What do you do if you can’t afford it? You just die.’ It shouldn’t go up every year after it’s been approved and there’s no more research and development.”

AARP fiercely believes that the needs of Medicare beneficiaries should remain paramount as the agency implements the Negotiation Program. In 2022, about 1 in 5 adults ages 65 and up either skipped, delayed, took less medication than was prescribed, or took someone else’s medication last year because of concerns about cost.⁵ It is not fair or right to ask patients and taxpayers to continue paying for high prescription drug prices that are the result of broken markets.

Successful implementation of the new federal law will help reduce prescription drug prices and costs and ensure that millions of older Americans are better able to access the prescription drugs they need at a price they can afford. The Medicare drug price negotiation process will also finally allow CMS to push back on indiscriminately escalating drug prices and ensure that taxpayer funds are paying for value – all while saving billions for Medicare and its beneficiaries. The CBO estimates that the Negotiation Program will save Medicare and the American taxpayers nearly \$98.5 billion over 10 years,⁶ reduce the budget deficit by \$25 billion in 2031,⁷ and save Medicare Part D enrollees \$7 billion in 2031 due to lower out-of-pocket costs and premiums.⁸

This is about real people whose lives are on the line. For decades, older Americans have paid the highest prices in the world for prescription drugs - often three times higher than people in other countries. Now is the time to change that. Effective implementation of this Program will represent a major victory for older Americans and their families across the country who are struggling to afford their prescriptions. It will also help encourage and appropriately reward the development of truly innovative products. AARP stands ready to assist in any way with these and other efforts to bring down drug prices and help older Americans afford the medications and treatments they need. If you have any questions, please do not hesitate to contact me or Gidget Benitez at gbenitez@aarp.org.

Sincerely,



Nancy A. LeMond
Executive Vice President and
Chief Advocacy & Engagement Officer

⁵ Stacie B. Dusetzina et al., “Cost-Related Medication Nonadherence and Desire for Medication Cost Information Among Adults Aged 65 Years and Older in the US in 2022,” *JAMA Network Open* 6, no. 5 (2023): e2314211, <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2805012>.

⁶ Congressional Budget Office, “Estimated Budgetary Effects of Public Law 117-169, to Provide for Reconciliation Pursuant to Title II of S. Con. Res. 14.” https://www.cbo.gov/system/files/2022-09/PL117-169_9-7-22.pdf. Accessed September 27, 2023.

⁷ Congressional Budget Office, “How CBO Estimated the Budgetary Impact of Key Prescription Drug Provisions in the 2022 Reconciliation Act.” <https://www.cbo.gov/system/files/2023-02/58850-IRA-Drug-Provs.pdf>. Accessed September 27, 2023.

⁸ *Id.*

Public E2 Submission

IPAY: 2026



Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	ACS CAN
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	
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	Response to Question 29	Please see attached file

Public E2 Submission

IPAY: 2026



Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
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Public E2 Submission

IPAY: 2026



Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	Please see attached letter



October 2, 2023

Chiquita Brooks-LaSure Administrator
Centers for Medicare and Medicaid
Services 200 Independence Avenue
S.W. Washington, D.C., 20201

Re: Medicare Drug Price Negotiation Program: Considerations for Selected Oncology Drugs

Dear Administrator LaSure:

On behalf of the American Cancer Society Cancer Action Network (ACS CAN) and the undersigned patient advocacy organizations, we appreciate the opportunity to offer input on how the Agency should consider pharmaceutical therapeutic alternative(s) to selected oncology drugs for Initial Price Applicability Year 2026.

Our organizations represent millions of cancer patients. We encourage CMS to implement the negotiation of selected drugs in a way that encompasses the many unique oncology considerations. In determining therapeutic alternatives to negotiate a Maximum Fair Price (MFP), we recommend CMS consider the following for selected oncology products:

- Prioritize evidence from, and validate identified therapeutic alternative(s) with, experts in cancer treatments and oncology-specific features;
- Account for health equity considerations to address cancer disparities;
- Consider the potential consequence of plan “steering” on beneficiary health outcomes; and
- Ensure that the initial offer based on the therapeutic alternative price, and the eventual MFP, do not discourage future innovation in cancer therapies.

We urge CMS to prioritize evidence from, and validate identified therapeutic alternative(s) with, experts in cancer treatments

We appreciate the Agency’s solicitation of public input on therapeutic alternatives and understand CMS will use this input, as well as its research, to identify a selected drug’s therapeutic alternatives to generate an initial offer price. As therapeutic alternatives are considered for selected oncology drugs, we recommend CMS give credence to input from organizations with expertise in cancer treatments, to include the patient perspective.

We support comparative effectiveness research because it provides clinicians with information regarding the relative clinical effectiveness of a given intervention and potential differences in side effects, but at the same time recognize that in oncology, there are very few drugs that are truly equivalent with respect to the FDA approved label indication and the scientific evidence supporting the efficacy of a given drug.

The National Comprehensive Cancer Network’s Drug and Biologics Compendium and treatment guidelines are examples of science-based resources from which CMS can gain information on the comparative effectiveness of selected oncology drugs and their therapeutic alternatives. We also support CMS considering health

outcomes such as cure, survival, progression-free survival, or improved morbidity when comparing a selected drug to therapeutic alternatives.

Importantly, drugs may also have multiple indications and the therapeutic alternatives may vary greatly from indication to indication. This is quite common in oncology, and CMS should clarify how it intends to address the issue of multiple indications with widely varying alternatives.

In addition to provider-focused evidence, we also encourage CMS to use both patient-reported outcomes and patient experience data. Patients have first-hand knowledge of the effectiveness of a treatment, as well as the impact on their quality of life. It is particularly important for cancer patients that CMS considers whether a selected drug fills an unmet medical need through its on- or off-label use, such as treating a disease or condition in cases where extremely limited or no other treatment options exist. Evidence-based off-label use of oncology drugs is not only common, but it is supported by statutory requirements for CMS coverage as well.

To increase transparency and bolster support from the cancer community, we recommend that CMS engage provider and patient experts to validate the identified therapeutic alternatives throughout the negotiation process and beyond the limited public submission and patient-focused listening session opportunities.

CMS should account for health equity considerations to address cancer disparities

Disparities persist despite efforts to address equity in cancer diagnosis and treatment. We appreciate CMS's solicitation of input on how the effectiveness and safety of a selected drug or its therapeutic alternatives may vary across different populations. We strongly support a negotiation approach that does not assess a drug's benefit for the average person without considering its benefit for specific populations. We offer the following oncology-specific considerations:

Oral selected drugs should have oral therapeutic alternatives

Small-molecule oral oncology drugs are particularly important tools in the treatment of cancer. These therapies can be taken by patients at home, which can reduce patient time and transportation burdens. Accordingly, it may be more difficult for certain populations to receive physician-administered infusions, including, but not limited to, individuals with disabilities, the elderly, individuals who are terminally ill, lower-income individuals, individuals without transportation, working individuals, and individuals who live in rural areas. For this reason, we urge CMS to identify oral therapeutic alternatives for oral selected drugs in oncology.

Safety and effectiveness of selected drugs and their therapeutic alternatives should be stratified by race/ethnicity

CMS identified individuals with disabilities, the elderly, individuals who are terminally ill, and children as specific populations for which there may be challenges or advantages to access, differences in clinical or other outcomes, or differences in disease or condition symptoms, and asks if there are other specific populations not noted that could be considered. Racial disparities are observed in many different cancer measures, including screening and diagnosis rates, incidence and prevalence, and overall outcomes including survival and mortality.¹ For this reason, we recommend the comparative effectiveness of selected

¹ National Cancer Institute, Cancer Disparities, 2022. <https://www.cancer.gov/about-cancer/understanding/disparities>

oncology drugs and their therapeutic alternatives be evaluated with respect to non-white populations. To the extent that a selected drug or its therapeutic alternatives represents a therapeutic advantage for a specific race or ethnicity, that value should be reflected in the negotiation process.

Cancer is a specific population that requires special consideration

As CMS looks at the comparative effectiveness on specific populations, it should also consider people living with cancer as a patient population that requires special consideration, given the chronic, progressive nature and high mortality.

Cancer is not just one disease; it is hundreds of diseases. For example, lung cancer is subdivided into small cell lung cancer and non-small-cell lung cancer, which is further defined by up to ten distinct biomarker driven subtypes. Each cancer patient and his or her disease is distinct and requires a tailored treatment approach.

The benefit of a cancer drug can vary across conditions, being curative in some and palliative in others. We reiterate our suggestions that CMS consider real-world evidence and patient experience data to determine the comparative effectiveness, and further recommend that comparative effectiveness reviews be determined for each on- and off-label use of a selected drug, with consideration being given to any use that represents an unmet need.

CMS should consider the potential consequence of plan “steering” on beneficiary health outcomes

As CMS negotiates selected drugs with the aim to achieve “the lowest maximum fair price for each selected drug,” we want to ensure that beneficiaries are not steered towards a particular drug.

As Part D plans will bear more risk under the IRA’s Part D benefit redesign, plans have a financial incentive to steer beneficiaries toward a drug with the lowest price the plan is able to negotiate. While it is possible that negotiated drugs would represent the lowest price, non-negotiated drugs may cost less due to rebate dynamics. It is possible that Part D plans could steer beneficiaries toward negotiated drugs or non-negotiated drugs and may impose barriers (such as more rigorous prior authorization or step therapy requirements) on others in the class.

Cancer patients should have uninhibited access to the full range of treatment options available to best address their specific needs. For cancer patients who have found a specific drug that works for treating their cancer, and for patients who may benefit from a novel therapy, being steered towards another – potentially less effective drug – could be detrimental.

CMS should bear these dynamics in mind when determining the MFP for oncology products, and monitor plan formularies to determine the extent to which plans are using more utilization management tools that can hinder access to the medications initially prescribed by an oncologist.

Ensure that the initial offer based on the therapeutic alternative price, and the eventual MFP, do not hinder innovation in cancer therapies

The U.S. cancer death rate has declined 33 percent since 1991 due in large part to access to new drug therapies.² There has been a remarkable increase in the number of new cancer drug therapies in recent years, with 10 out of the 37 new drug therapies approved by the Food and Drug Administration (FDA) in 2022 for the treatment of cancer.³ We urge CMS to carefully balance the need to lower the cost of drugs offered through Medicare with the need to incentivize the development of new treatments and cures.

Implementation of the negotiation process is expected to have a downstream impact on research and development. While the overall cancer mortality rate continues to decline, there is still an enormous unmet need for the development of therapies to treat cancer, and we encourage CMS to approach the MFP negotiation process in a way that does not impede future innovation in cancer drugs.

A growing number of manufacturers have announced decisions to deprioritize small molecule drug development due to the shorter period before IRA negotiation eligibility compared to biologics. For example, several oncology drug manufacturers have noted strong disincentives to pursue small molecule drugs (e.g., [Alkermes](#), [Eli Lilly](#), [Novartis](#), [Pfizer/Seagen](#)) and smaller indications (e.g., [Astellas](#), [AstraZeneca](#), [Genentech](#), [Merck](#), [Mirati](#), [Seagen](#)), while others have announced discontinued pursuits of cancer treatments ([Alkermes](#), [BMS](#), [Eli Lilly](#)).

Many oncology medicines approved a decade ago also received approvals for additional indications in later years, and most of those were seven or more years after initial FDA approval. These indications are often for earlier-stage cancers when cancer is more treatable, and many expanded indications are for rare cancers.

We want to ensure that overall investment in small molecule cancer drug development and the pursuit of follow-on indications is not put at risk. To mitigate this potential unintended consequence of government negotiation, we request the following:

- CMS should work with the FDA to monitor and report the implications of the negotiation program, including:
 - The submission of applications for new indications of existing therapies; and
 - Trends in the number of new cancer therapies brought to market.
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² ACS Journals, Cancer statistics, 2023, <https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21763>

³ U.S Food and Drug Administration, New Drug Therapy Approvals 2022, <https://www.fda.gov/drugs/new-drugs-fda-cdersnew-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2022>.

Conclusion

We appreciate the opportunity to provide input on the negotiation process for the Initial Price Applicability Year 2026 selected drugs. If you have any questions or need additional information, please feel free to contact Kirsten Sloan, Managing Director, Public Policy at Kirsten.Sloan@cancer.org.

Sincerely,

ACS CAN

Association of Community Cancer Centers

Brem Foundation to Defeat Breast Cancer

Cancer Help Desk

CancerCare

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CLL Society

Colon Cancer Coalition

Color of Crohn's and Chronic Illness

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Sincerely,

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Public E2 Submission

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Public E2 Submission

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Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	



September 28, 2023

Chiquita Brooks-LaSure
Administrator
U.S. Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: IRA Patient Listening Sessions

Dear Administrator Brooks-LaSure:

Aimed Alliance is a not-for-profit health policy organization that seeks to protect and enhance the rights of health care consumers and providers. We are writing to express our concerns with the Inflation Reduction Act's (IRA) Medicare Drug Price Negotiation Program Patient-Focused Listening Sessions.

While we support efforts aimed at making prescription drugs more affordable for Medicare Part D beneficiaries, Aimed Alliance strongly urges the Centers for Medicare & Medicaid Services (CMS) to ensure the patient voice and perspective is valued in a genuine, long-term, and sustainable manner.

I. Background

In August 2022, Congress passed the IRA, which provided CMS the authority to directly negotiate the prices of certain prescription drugs with drug manufacturers.¹ The negotiations are limited to single source drugs, without generic or biosimilar alternatives, that have been on the market for at least 7 years, or 11 years for biologics.² On August 29, 2023, CMS published a list of 10 prescription drugs that are subject to the Medicare negotiation process. These drugs cover treatments for cardiovascular diseases, diabetes, chronic kidney disease, psoriasis, rheumatoid arthritis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.³ CMS stated these drugs were identified as the ten most expensive covered Part D drugs.

In determining the negotiated price CMS will impose, CMS stated it will consider various factors, including comparative effectiveness and impact on specific populations, such as individuals with disabilities, the elderly, terminally ill patients, children, and others; and the extent to which the drug and its alternatives address an unmet medical need.⁴ Aimed Alliance urges CMS to ensure patient and provider lived experiences are adequately valued when considering these factors and throughout this process.

¹ CMS, *Fact Sheet: Key Information on the Process for the First Round of Negotiations for the Medicare Drug Price Negotiation Program*, <https://www.cms.gov/files/document/fact-sheet-negotiation-process-flow.pdf>

² *Id.*; CMS, *Medicare Drug Price Negotiation Program: Selected Drugs for Initial Price Applicability Year 2026*, <https://www.cms.gov/files/document/fact-sheet-medicare-selected-drug-negotiation-list-ipay-2026.pdf>

³ *Id.*

⁴ <https://www.cms.gov/files/document/fact-sheet-medicare-selected-drug-negotiation-list-ipay-2026.pdf>

II. Appropriately Value Patient and Provider Lived Experiences

Aimed Alliance applauds CMS for incorporating patient and provider lived experiences in the drug negotiation process. However, we urge CMS to expand the current process to ensure a wider network of patients and providers can participate, and to guarantee patient and provider voices are genuinely valued.

Internationally, several countries employ mechanisms that allow governments to negotiate drug prices with manufacturers. For example, France and Sweden base drug pricing on factors such as therapeutic value, the price of comparable treatments, and the contributions of the drug's sales to the national economy.⁵ Sweden further incorporates ethical considerations, prioritizing those with the greatest health care needs and ensuring the process upholds and respects individual human dignity.⁶ By valuing the needs of patients and providers, Sweden maintains an overall high health care satisfaction rate.⁷ In contrast, the United Kingdom, which also implements a government negotiation program, has seen reports of patients being unable to access innovative treatments that may improve their condition and quality of life due to non-patient-centered valuations.⁸ As a result of failing to appropriately value patient-perspectives on the benefits of treatments, patients in the United Kingdom also experience reduced uptake of new cancer treatments.⁹

Ultimately, while various systems have provided means to center patient-perspectives and lived experiences, not all systems genuinely value these insights in determining drug prices, ultimately impacting treatment accessibility. Aimed Alliance urges CMS to properly value the lived experiences of patients, providers, and caregivers, and recognize the benefits these treatments provide to consumer's health and quality of life.

III. Expand the Number of Listening Sessions to Ensure Diverse Representation

Under the current framework, CMS offers only one listening session for each selected prescription drug, with each session lasting less than two hours and accommodating only 20 in-person speakers. Members of the public who are not selected to speak also have the option to submit written comments.¹⁰ Aimed Alliance urges CMS to expand the number of listening

⁵ David J. Gross, Jonathan Ratner, James Perez & Sarah Glavin, *International Pharmaceutical Controls: France, Germany, Sweden, and the United Kingdom*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4193451/#:~:text=New%20product%20prices%20emerge%20from,sales%20to%20the%20national%20economy>.

⁶ Global Legal Rights, *Pricing & Reimbursement Laws and Regulations 2023*,

<https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/sweden>

⁷ Roosa Tikkanen, et al., *Sweden Scorecard*, <https://www.commonwealthfund.org/international-health-policy-center/countries/sweden>; Ketevan Kandelaki, *Patient-centeredness as a quality domain in Swedish healthcare: results from the first national surveys in difference Swedish health care setting*, <https://bmjopen.bmj.com/content/6/1/e009056>.

⁸ Houses of Parliament: Parliamentary Office of Science & Technology, *Drug Pricing*, https://www.parliament.uk/globalassets/documents/post/postpn_364_Drug_Pricing.pdf

⁹ *Id.*

¹⁰ CMS, *Medicare Drug Price Negotiations Program Patient-Focused Listening Sessions*, <https://www.cms.gov/inflation-reduction-act-and-medicare/medicare-drug-price-negotiation-program-patient-focused-listening-sessions>

sessions to ensure patients, organizations, and caregivers have the opportunity to speak on behalf of their communities.

The 20 speakers selected to participate in each session are requested to address patients' day-to-day experiences living with their condition and under their treatment; the benefits and side effects of the treatments; patient access, adherence, and affordability; and any additional information the speaker considers significant.¹¹ While Aamed Alliance believes this information is crucial for appropriately determining the negotiated prices, we are concerned that relying on 20 randomly selected speakers will not provide CMS with a comprehensive perspective on these medications and their benefits to patients, providers, and caregivers. We are also concerned that this random selection process could unintentionally exclude speakers who shed light on health equity, minority health, and other access issues.¹² Therefore, we urge CMS to expand the number of listening sessions to ensure CMS appropriately considers the broad implications and health equity considerations of these treatments; and how these price negotiations could impact access for diverse communities.

Lastly, we strongly encourage CMS to value and give due consideration to both written and spoken comments provided by patient advocacy organizations. Individuals with chronic illnesses such as multiple sclerosis and inflammatory bowel disease (IBD) frequently experience social stigma, rejection, and workplace discrimination resulting from their condition.¹³ For instance, one study found that out of 105 patients with IBD, 84 percent reported experiencing stigma associated with their condition.¹⁴ Consequently, it is critical to recognize that some individuals with chronic conditions may not feel comfortable discussing their health, treatments, and challenges openly. As a result, they often rely on advocacy organizations to share their stories, perspectives, and experiences.

IV. Conclusion

In conclusion, we sincerely appreciate the opportunity to provide feedback on the IRA process and CMS's efforts to ensure the voices of patients, providers, and caregivers are at the forefront of this process. Please contact us at policy@aimedalliance.org if you have any additional questions.

Sincerely,
Ashira Vantrees
Counsel

¹¹ *Id.*

¹² Khiara Bridges, *Implicit Bias and Racial Disparities in Health Care*, https://www.americanbar.org/groups/crsj/publications/human_rights_magazine_home/the-state-of-healthcare-in-the-united-states/racial-disparities-in-health-care/

¹³ Valerie A Earnshaw, Diane M. Quinn & Crystall L. Park, *Anticipated stigma and quality of life among people living with chronic illnesses*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3644808/>

¹⁴ Marco Vinezco Lenti, et al., *Stigmatization and resilience in inflammatory bowel disease patients at one-year follow up*, <https://www.frontiersin.org/articles/10.3389/fgstr.2022.1063325/full>

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Chronic Care Policy Alliance
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	<p>The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public. ..As CMS weighs information on how this product is prescribed and factors that information into the negotiation process, CMS should ensure that the negotiated price continues to support the patients using the product and their current usage. Patients using the product off-label or in different doses than the label should continue to have the same access after the negotiation process. Additionally, ensuring that the negotiation does not spur greater restrictions to access or utilization management, is also important to patients.</p>
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	N
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public...As CMS weighs information on the therapeutic impact and comparative effectiveness of this product, it is paramount that CMS recognize that individual patients may experience substantial benefit from a product that may not be apparent in aggregated data. Because of this, as CMS considers how this area factors into the overall price negotiation, CMS should ensure a negotiated price reflects the value the product provides to each unique patient. CCPA believes it is important that the incentives to continue developing treatments for chronic diseases be preserved, and it is important to reward the value treatments bring to patients.</p>

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Question	Sub-Question	Response
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>N</p>
<p>Question 29: Comparative Effectiveness on Specific Populations</p>	<p>Response to Question 29</p> <p>Hyperlink to Citation - Additional Materials for Question 29</p> <p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p>Evidence Submitted include a cost-effectiveness measure?</p>	<p>The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public...Patients with chronic diseases all have their own unique experiences – in considering comparative effectiveness, CMS should weigh equally the experiences of individuals the same as measurements of experiences of specific populations – in a way that elevates all voices, instead of letting larger voices outweigh single patients. CCPA also encourages CMS to take into account populations that may be uniquely adversely affected by negotiation, such as specific patient populations that may face new utilization or formulary restrictions. In this way, CMS can ensure that it pursues a patient-centered approach.</p> <p>N</p>

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Question	Sub-Question	Response
	What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	The Chronic Care Policy Alliance (CCPA) is a network of advocates focused on issues affecting patients living with chronic conditions. While we will let other disease-specific organizations offer their detailed perspectives on this drug, CCPA wishes to convey its views on how CMS should use the information gathered from the public...CMS should ensure that its negotiation process on this product does not disadvantage any patient with an unmet medical need. Specifically, CMS should guard against the results of negotiations undercutting research into the product that may meet other unmet medical needs or may negatively impact the development of other products focused on unmet medical needs.
	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	CLL Society
	Respondent Email Who is completing this form?	PAO
Question 27: Prescribing Information	Prescribing Information	<p>A. Selected Drug - IMBRUVICA® is a Bruton's tyrosine kinase (BTK) inhibitor indicated [1] for the treatment of: Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)..Dose: 420 mg taken orally once daily. Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion..Dose: 420 mg taken orally once daily. Adult patients with Waldenström's macroglobulinemia (WM)..Dose: 420 mg taken orally once daily. Adult and pediatric patients aged 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy..Dose: Patients 12 years and older: 420 mg taken orally once daily; Patients between 1 and 12 years of age: 240 mg/m2 taken orally once daily (up to a dose of 420 mg)..Recommended dosage modifications (CLL/SLL) of IMBRUVICA for Grade 3 or 4 non-hematological toxicities, Grade 3 or 4 neutropenia with infection or fever and Grade 4 hematological toxicities as well as Grade 2 cardiac failure is to restart at 280 mg daily for first occurrence, at 140 mg daily for second occurrence, and discontinue at third occurrence. Recommended dosage modification for concurrent use of a moderate CYP3A inhibitor is to reduce dose to 280 mg daily. IMBRUVICA should not be co-administered with a strong CYP3A inhibitor. .B. Therapeutic Alternatives.1. Indication: Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)..a. CALQUENCE® (acalabrutinib) [2].Dose: 100 mg orally approximately every 12 hours.Recommended dosage modifications of CALQUENCE for Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days are to interrupt treatment until toxicity has resolved to Grade 1 and then resume at 100 mg every 12 hours for first and second occurrence. For the third occurrence, once toxicity has resolved to Grade 1 following interruption, treatment can be resumed at reduced frequency of 100 mg once daily. CALQUENCE should be discontinued if there is a fourth occurrence. .Use of CALQUENCE with strong CYP3A inhibitors should be avoided. CALQUENCE dose should be reduced to 100 mg once daily if used with a moderate CYP3A inhibitor. CALQUENCE should not be used with a strong CYP3A inducer, but if use cannot be avoided, CALQUENCE dose should be increased to 200 mg twice daily. .b. BRUKINSA® (zanubrutinib) [3].Dose: 160 mg taken orally twice daily, or 320 mg taken orally once daily until disease progression or unacceptable toxicity..Recommended dosage modifications of</p>

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Question Sub-Question

Response

BRUKINSA for Grade 3 or higher adverse reactions in CLL/SLL are to interrupt treatment until AE has resolved to Grade 1 and then resume at 160 mg twice daily or 320 mg once daily for first occurrence; 80 mg twice daily or 160 mg once daily for second occurrence; 80 mg once daily for third occurrence. Treatment should be discontinued at the fourth occurrence of a Grade 3 or higher AE..Recommended dosage modifications of BRUKINSA for use with strong or moderate CYP3A inhibitors is 80 mg once daily. Concomitant use with moderate CYP3A inducers should be avoided, but if the inducer cannot be avoided, BRUKINSA dose should be increased to 320 mg twice daily. .2. Indication: Adult patients with Waldenström's macroglobulinemia (WM)..a. BRUKINSA® (zanubrutinib) [3].Dose and dosage modifications are the same as those for CLL/SLL..b. CALQUENCE® (acalabrutinib) [2].CALQUENCE® (acalabrutinib) is used off-label to treat WM..3. Indication: Adult and pediatric patients aged 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy..The selected drug, IMBRUVICA® is the only BTK inhibitor approved for treating cGVHD. It is the only FDA approved treatment for cGVHD in children under 12 years of age. .Currently, there are three FDA approvals for treatment of chronic GVHD:

- The selected drug, IMBRUVICA® (ibrutinib), was the first drug approved for chronic GVHD in both adults and children under 12 years of age after failure of one or more lines of systemic therapy (August 2, 2017, adults; August 24, 2022, pediatric) [1]
- REZUROCK® (belumosudil), is an oral selective inhibitor of ROCK2 approved for patients 12 years of age and older (July 16, 2021) with chronic GVHD who received at least two prior lines of treatment. The recommended dose of REZUROCK is 200 mg given orally once a day until progression of chronic GVHD that requires new systemic therapy. [4]
- JAKAFI® (ruxolitinib) is approved for chronic graft-versus-host disease in adult and pediatric patients 12 years and older after failure of one or two lines of systemic therapy. Ruxolitinib is administered at 5 mg twice daily and can be increased to 10 mg twice daily after 3 days without toxicity (September 22, 2021).
- Prior to Jakafi treatment, patients should have a complete blood count
- During treatment with Jakafi, patients should have a complete blood count every 2 to 4 weeks until doses are stabilized and have lipid parameters assessed every 8-12 weeks after Jakafi initiation. [5]

Please provide information about how the selected drug and its therapeutic alternative(s) are used in the course of care for the condition or disease treated by each indication. .CLL/SLL is a chronic blood cancer of the white blood cells known as B-lymphocytes where there is a progressive accumulation of too many mature B-lymphocytes. CLL is the most common type of adult leukemia in the United States, with around 21,000 cases diagnosed annually. It is classified as both a type of leukemia and a type of non-Hodgkin's lymphoma (NHL). SLL is simply a different manifestation of the same disease and is best understood as a stage of CLL where there are not yet a significant number of cancer cells located in the bloodstream. We refer to the disease state collectively as CLL. ..CLL is extremely heterogeneous, meaning each person's disease course and progression can vary considerably. Some patients have an aggressive form of the disease, experience rapid deterioration,

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Response

and survive for as little as two years. Others have a less aggressive form of the disease, may never need treatment, and can expect to have a normal life expectancy. For most patients, CLL is indolent and incurable. Since patients with advanced CLL are not cured with conventional therapy, the goals of therapy are to improve quality of life and prolong overall survival (OS). [6] Today, the median OS from start of front-line therapy is 5 to 15 years, depending on disease features, individual patient factors, and treatment choices. Patients requiring front-line and even second-line therapy to help control the disease have better treatment options than patients had a decade ago. ..Targeted therapies such as BTK inhibitors and the BCL2 inhibitor known as venetoclax offer substantial efficacy against CLL and have transformed care for our patient community. Patients now have more treatment options compared to just years ago when the standard of care was chemoimmunotherapy. They can take continuous daily oral therapy with a BTK inhibitor (with or without the addition of a monoclonal antibody) until their disease progresses. Alternatively, patients can choose a short-term time-limited treatment approach that combines venetoclax and a monoclonal antibody or IMBRUVICA. The latter approach allows for drug discontinuation until active monitoring reveals that another treatment is needed...The selected drug, IMBRUVICA® (ibrutinib) was heralded as offering a sea change in the treatment of CLL as it was the first targeted oral small molecule therapy with large, randomized studies showing improved outcomes compared to the standard of care (SOC) existing at the time. Like ibrutinib, the more recently approved BTK inhibitors (acalabrutinib and zanubrutinib) are effective in treating CLL subtypes that are refractory to the former SOC..The NCCN Guidelines for CLL emphasize that the most appropriate treatment plan for a particular patient depends on multiple factors, including the patient's IGHV status, del(17p)/TP53 mutation status, age, and comorbidities. Subsequent therapies are selected based on the prior therapy received, patient comorbidities, resistant mutations, and other factors. In choosing subsequent therapy, prior therapy, comorbidities, and resistance mutations should be considered. [7] ..While chemoimmunotherapy had been the SOC for the treatment of CLL, targeted therapies are now the preferred option in all patients with CLL since chemoimmunotherapy is not appropriate for patients with del(17p) and/or TP53 mutation and is less effective in all patients. For most patients, front-line treatment could consist of:

- Continuous therapy with a BTK inhibitor. This is a better option than venetoclax plus obinutuzumab in patients with kidney impairment.
- Fixed duration venetoclax plus obinutuzumab, administered over one year. This option may be preferred over BTK inhibitors in patients with cardiovascular disorders, uncontrolled hypertension, and/or a high risk for bleeding (e.g., patients receiving anticoagulation medication, especially warfarin).
- Fixed duration ibrutinib plus venetoclax, administered over 15 months. Although patients with certain cardiovascular disorders may not be able to tolerate a BTK inhibitor, this option is important for patients wishing to avoid continuous therapy. [7]

If the selected drug is used off-label to treat a certain disease or condition, please indicate this and provide evidence from nationally recognized, evidence-based guidelines and recognized by CMS-approved Part D compendia, as applicable..The manufacturer for the selected drug announced earlier this year that they were

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Response

withdrawing the accelerated approvals of IMBRUVICA for mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL) based on phase 3 trials. [8]

- Hairy Cell Leukemia (HCL) [9] – HCL is a rare B-cell malignancy with an unmet need in patients failing to benefit from purine nucleoside analogs (PNA). A recent phase 2 study of IMBRUVICA showed promising results. “The durable PFS in this difficult to treat population makes ibrutinib an effective therapy for select patients with HCL who are not expected to benefit from a PNA.” [10]
- Primary CNS lymphoma (PCNSL). PCNSL is a rare form of lymphoma in the central nervous system without evidence of systemic involvement. It comprises approximately 2% of all primary brain tumors. [11] Approximately 80-90% of PCNSL cases are diffuse-large B-cell lymphomas (DLBCL). Several studies have investigated the use of ibrutinib alone and in combination with chemotherapy as an option for treating PCNSL. These studies have shown high (and durable) treatment response and tolerability despite a high rate of Aspergillus infections.

References

1. Dosing & Administration - CLL/SLL | IMBRUVICA® (ibrutinib) HCP (imbruvicahcp.com)
2. Calquence Full Prescribing Information (den8dhaj6zs0e.cloudfront.net)
3. prescribing-information.pdf (brukinsa.com)
4. (REZUROCK) label (fda.gov)
5. prescribing-information.pdf (jakafi.com)
6. Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia/small lymphocytic lymphoma – UpToDate
7. NCCN Guidelines Update: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in: Journal of the National Comprehensive Cancer Network Volume 21 Issue 5.5 (2023) (jnccn.org)
8. Update on IMBRUVICA® (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications | AbbVie News Center
9. Update on IMBRUVICA® (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications | AbbVie News Center
10. Kerry A. Rogers, Eric McLaughlin, Lai Wei, Mirela Iulia Anghelina, Mir Khader Ali, Leslie A. Andritsos, Evgeny Arons, James S. Blachly, Timothy G. Call, S. Percy Ivy, Lacey James-Echenique, Jeffrey A. Jones, Robert J. Kreitman, Gerard Lozanski, Farhad Ravandi, Charles A. Schiffer, William E. Carson, Michael R. Grever; Extended Follow up of a Phase 2 Study of Ibrutinib in Hairy Cell Leukemia. Blood 2022; 140 (Supplement 1): 6494-6495. doi: <https://doi.org/10.1182/blood-2022-165795>

Evidence Submitted include a cost-effectiveness measure?

N

What type of Evidence is shown?



Question Sub-Question

Question 28:
Therapeutic
Impact and
Comparative
Effectiveness

Therapeutic Impact and
Comparative Effectiveness

Response

CLL Society wishes to emphasize that the high variability among CLL patients (age, preferences, aggressiveness of disease, comorbidities, and other factors) not only makes clinical studies particularly difficult but inject a great deal of uncertainty into any discussion on comparative effectiveness. Taken together, the factors outlined above (heterogeneity, indolence, response to previous therapies) make overall survival a poor endpoint in clinical trials and comparative effectiveness analyses for CLL, particularly in early lines of therapy. The selected drug, IMBRUVICA® (ibrutinib) was heralded as offering a sea change in the treatment of CLL as it was the first targeted oral small molecule therapy with large, randomized studies showing improved outcomes compared to the standard of care (SOC) existing at the time. Like ibrutinib, the more recently approved BTK inhibitors (acalabrutinib and zanubrutinib) are effective in treating CLL subtypes that are refractory to the former SOC...The NCCN Guidelines for CLL emphasize that the most appropriate treatment plan for a particular patient depends on multiple factors, including the patient's IGHV status, del(17p)/TP53 mutation status, age, and comorbidities. Subsequent therapies are selected based on the prior therapy received, patient comorbidities, resistant mutations, and other factors. In choosing subsequent therapy, prior therapy, comorbidities, and resistance mutations should be considered. [1] ..While chemoimmunotherapy had been the SOC for the treatment of CLL, targeted therapies are now the preferred option in all patients with CLL since chemoimmunotherapy is not appropriate for patients with del(17p) and/or TP53 mutation and is less effective in all patients. For most patients, front-line treatment could consist of:

- Continuous therapy with a BTK inhibitor. This is a better option than venetoclax plus obinutuzumab in patients with kidney impairment.
- Fixed duration venetoclax plus obinutuzumab, administered over one year. This option may be preferred over BTK inhibitors in patients with cardiovascular disorders, uncontrolled hypertension, and/or a high risk for bleeding (e.g., patients receiving anticoagulation medication, especially warfarin).
- Fixed duration ibrutinib plus venetoclax, administered over 15 months. Although patients with certain cardiovascular disorders may not be able to tolerate a BTK inhibitor, this option is important for patients wishing to avoid continuous therapy. [1]

As noted above, BTK inhibitors offer considerable improvements in care for our patients but can result in drug intolerance requiring interruption, dose reduction, and even treatment discontinuation. The relatively recent approval of second generation BTK inhibitors makes it difficult to undertake a comparative effectiveness analysis beyond chronic use of these products as monotherapy. The NCCN guidelines and uptodate.com treatment algorithm discussed above cited head-to-head monotherapy studies of zanubrutinib vs. ibrutinib and acalabrutinib vs. ibrutinib indicating that the next-generation BTK inhibitors have superior safety and efficacy in studied populations. There are, however, no studies directly comparing acalabrutinib to zanubrutinib. Zanubrutinib has demonstrated fewer cases of atrial fibrillation than ibrutinib and no cardiac-related deaths. CLL patients taking zanubrutinib also appear to have a higher response rate and improved PFS (progression free survival).. The reduced side effect profile for both acalabrutinib and zanubrutinib will likely enable more patients to remain on treatment longer. But once their disease progresses, they cannot simply

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Question	Sub-Question	Response
	<p data-bbox="262 1112 619 1356">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p> <p data-bbox="262 1250 619 1356">Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 1396 619 1461">What type of Evidence is shown?</p>	<p data-bbox="619 251 1953 1104">switch to one of the other irreversibly binding BTK inhibitors that are approved for CLL and expect a response. This is because once a drug within that same BTK inhibitor drug class has failed the patient, all drugs within that same class will also likely fail. ..In addition, it is important to recognize that BTK inhibitors are a relatively new class of drugs targeting rare cancers and, as expected, new market entrants focus on improved response, greater tolerability, or both. Although the selected drug does not have generic competition, the emergence of next generation BTK inhibitors have created a highly competitive landscape in a relatively small disease population. Although clinical guidelines and recommendations recognize that newer BTK inhibitors have greater tolerability that would tend to improve outcomes, there is still much to learn about the various BTK inhibitors through real world data generated over time. For patients, it is vital that payers, including Part D plans, include all available treatment options in their formularies so that clinicians and patients are able to make treatment decisions based on what will enable the patient to achieve a durable treatment response while maintaining their quality of life. ..For now, patients with a CLL diagnosis can expect to live the rest of their lives with cancer. This means that endpoints demonstrating the potential for patients to live treatment-free for months, years, or longer can be particularly meaningful. Measurable residual disease (MRD) is not useful in evaluating chronic BTK inhibitor use as monotherapy and has not yet been included as an endpoint toward gaining approval of these treatments in combination with other agents in treating CLL. While not definitive, existing data suggests that MRD is predictive of overall survival. [2]..A recent review on the use of MRD in CLL concluded that, “[m]easurable residual disease (MRD) status in chronic lymphocytic leukemia (CLL), assessed on and after treatment, correlates with increased progression-free and overall survival benefit.” Use of MRD as a surrogate endpoint would not only improve the breadth of data available to FDA and CMS but could significantly improve patient and clinician understanding of the treatment effects of emerging CLL product candidates. Future research on use of MRD in evaluating comparative effectiveness of ibrutinib and the next-generation BTK inhibitors in combination with venetoclax (or other agents) could be particularly helpful in guiding treatment for patients preferring a fixed-duration option over continuous therapy. [2]</p> <p data-bbox="619 1323 661 1356">N</p>

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	<p>Patient comorbidities, combined with expected toxicities, can impact patient outcomes with specific treatment options. .A recent article focused on selecting the right BTK inhibitor emphasized that patient-specific factors should guide treatment choice. “Now that ibrutinib is no longer the sole BTK inhibitor on the market for the treatment of CLL, clinicians are faced with the challenge of selecting the most appropriate BTK inhibitor and weighing the advantages and disadvantages of each. Selection of the appropriate BTK inhibitor is multifactorial and depends on side effect profile, comorbidities of the patient, concomitant medications, and potential drug-drug interactions, cost, ease of administration, and desired outcomes of therapy.” [1].Ibrutinib is the least selective of the BTK inhibitors, with off-target effects leading to increased incidence of adverse events, particular cardiovascular adverse events. .Certain disease-related factors may influence the choice of a BTK inhibitor. In the ELEVATE-TN and ELEVATE-RR studies, patients with significant cardiovascular disease and those taking vitamin K antagonists were excluded. [2] The SEQUOIA trial included patients with cardiovascular disease and those receiving anticoagulation. [3] Zanubrutinib could be considered for those at risk for major bleeds, such as patients on concomitant anticoagulation or antiplatelet therapy, as the SEQUOIA trial demonstrated safety in this population, but it has not been studied head-to-head against acalabrutinib..All three available BTK inhibitors are associated with drug-to-drug interactions that can complicate treatment. The selected drug, ibrutinib, however, has the most tablet or capsule strengths available and its label includes manufacturer-recommended dose modifications for those taking moderate or strong CYP3A inhibitors. Clinicians and patients may be more comfortable with the dose adjustments associated with ibrutinib in some patient populations despite clinical guidelines that increasingly prefer the second generation BTK inhibitors..Disease-related factors may also impact BTK inhibitor selection. [4-6] An analysis of 89 newly diagnosed patients with TP53 aberrations treated with ibrutinib or the combination of ibrutinib with an anti-CD20 monoclonal antibody showed a 4-year PFS rate of 79%. In comparison, a trial evaluating venetoclax combined with obinutuzumab revealed a 4-year PFS rate of 53% in patients with TP53 mutations. [7] Zanubrutinib has demonstrated robust responses in patients with del17p. [8]</p> <p>Al-Sawaf O, Zhang C, Robrecht S, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 4-year follow-up analysis of the randomized CLL14 study. <i>Hematol Oncol</i> 2021; 39: S146.</p> <p>Visentin A, Mauro FR, Cibien F, et al. Continuous treatment with Ibrutinib in 100 untreated patients with TP53 disrupted chronic lymphocytic leukemia: a real-life campus CLL study. <i>Am J Hematol</i> 2022; 97: E95-E99.</p> <p>Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. <i>Haematologica</i> 2020; 106: 2354-2363.</p> <p>Lovell AR, Jammal N, Bose P. Selecting the optimal BTK inhibitor therapy in CLL: rationale and practical considerations. <i>Therapeutic Advances in Hematology</i>. 2022;13. doi:10.1177/20406207221116577</p> <p>Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. <i>Blood</i> 2019; 133: 2031-2042.</p> <p>Sivina M, Kim E, Wierda WG, et al. Ibrutinib induces durable remissions in treatment-naïve patients with CLL and 17p deletion and/or TP53 mutations. <i>Blood</i> 2021; 138: 2589-2592.</p>

Hyperlink to Citation -
Additional Materials for
Question 29

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Question	Sub-Question	Response
	<p data-bbox="262 519 619 657">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p data-bbox="262 706 619 812">Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 836 619 909">What type of Evidence is shown?</p>	<p data-bbox="619 251 1974 357">Allan JN, Shanafelt T, Wiestner A, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukemia in patients with TP53 aberrations: a pooled analysis from four clinical trials. Br J Haematol 2022; 196: 947-953.</p> <p data-bbox="619 787 661 820">N</p>
<p data-bbox="63 1136 262 1315">Question 30: Addressing Unmet Medical Needs</p>	<p data-bbox="262 1209 619 1242">Response to Question 30</p>	<ul data-bbox="672 925 1974 1526" style="list-style-type: none"><li data-bbox="672 925 1974 1031">• BTK inhibitors have changed the landscape of CLL treatment in a way that not only improves survival but improves quality of life. Introduction of an oral treatment is extremely important as patients have expressed a preference for long term oral medications over infused chemoimmunotherapy. [1].<ul data-bbox="672 1031 1974 1421" style="list-style-type: none"><li data-bbox="672 1031 1974 1136">- As one CLL patient reported, “After failing a bone marrow transplant for aggressive CLL, I was out of options that offered any probability of success based on the genetics of my CLL. I entered a phase 1 trial of PCI-32765, that later was known as ibrutinib and enjoyed a 7-year remission.”<li data-bbox="672 1136 1974 1274">- “My health was severely compromised with problems with massive internal bleeding due to low platelets, massive splenomegaly, massively enlarged and painful lymph nodes in the neck, axillae, and groin, overwhelming fatigue, and general malaise. All of those improved dramatically soon after starting therapy.”<li data-bbox="672 1274 1974 1421">- “I did have significant side effects that limited my ability to work, sleep, and enjoy life. They included GI issues and severe muscle pains, rashes, and other symptoms. I still have hypertension induced by the therapy. Fortunately, I did not develop any of the serious cardiac arrhythmias and obviously I was not part of the 1-2% that suffered sudden death.”<li data-bbox="672 1421 1974 1526">• CLL Society has significant concerns, however, that innovation to address unmet needs could be if manufacturers find that increasing competition within a small disease population is riskier now than it was before enactment of the Inflation Reduction Act's drug negotiation program. There is, therefore, a

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Question	Sub-Question	Response
	<p data-bbox="262 755 556 852">Hyperlink to Citation - Additional Materials for Question 30</p> <p data-bbox="262 901 556 1031">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30</p> <p data-bbox="262 1071 598 1169">Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="262 1242 567 1307">What type of Evidence is shown?</p>	<p data-bbox="724 251 1921 349">significant unmet need for new treatments and treatment combinations that improve the depth and duration of response, and/or are better tolerated, so that fewer of our patients experiencing serial relapses are without an approved therapeutic option.</p> <ul data-bbox="672 365 1953 714" style="list-style-type: none"><li data-bbox="672 365 1953 535">• Richter's syndrome (RS) is an aggressive histologic transformation of CLL, most often into diffuse large B-cell lymphoma (DLBCL). These patients have poor outcomes, with CR rates of approximately 20% and long-term survival below 20% with chemoimmunotherapy. Several studies have demonstrated activity for PD-1 inhibitors, especially in combination with ibrutinib, with ibrutinib-naïve patients having high response rates. [2]<li data-bbox="672 544 1953 714">• Further studies on combination therapy regimens including ibrutinib and other BTK inhibitors are crucial to enabling patients to maximize the full potential benefits of this class of cancer drugs. Unfortunately, the feasibility of continued industry-sponsored studies may depend on whether sponsors can make a business case for added investment in these products for the CLL patient population. <p data-bbox="630 722 1911 893">NCCN Guidelines Update: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in: Journal of the National Comprehensive Cancer Network Volume 21 Issue 5.5 (2023) (jnccn.org) Fisher A, Goradia H, Martinez-Calle N, Patten P, Munir T. The evolving use of measurable residual disease in chronic lymphocytic leukemia clinical trials. Front Oncol. 2023 Feb 22;13:1130617. doi: 10.3389/fonc.2023.1130617. PMID: 36910619; PMCID: PMC99927</p>
Question 31: Patient and Caregiver Experience	Response to Question 31	N

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Question Sub-Question

Question 32:
Executive
Summary

Response to Question 32

Response

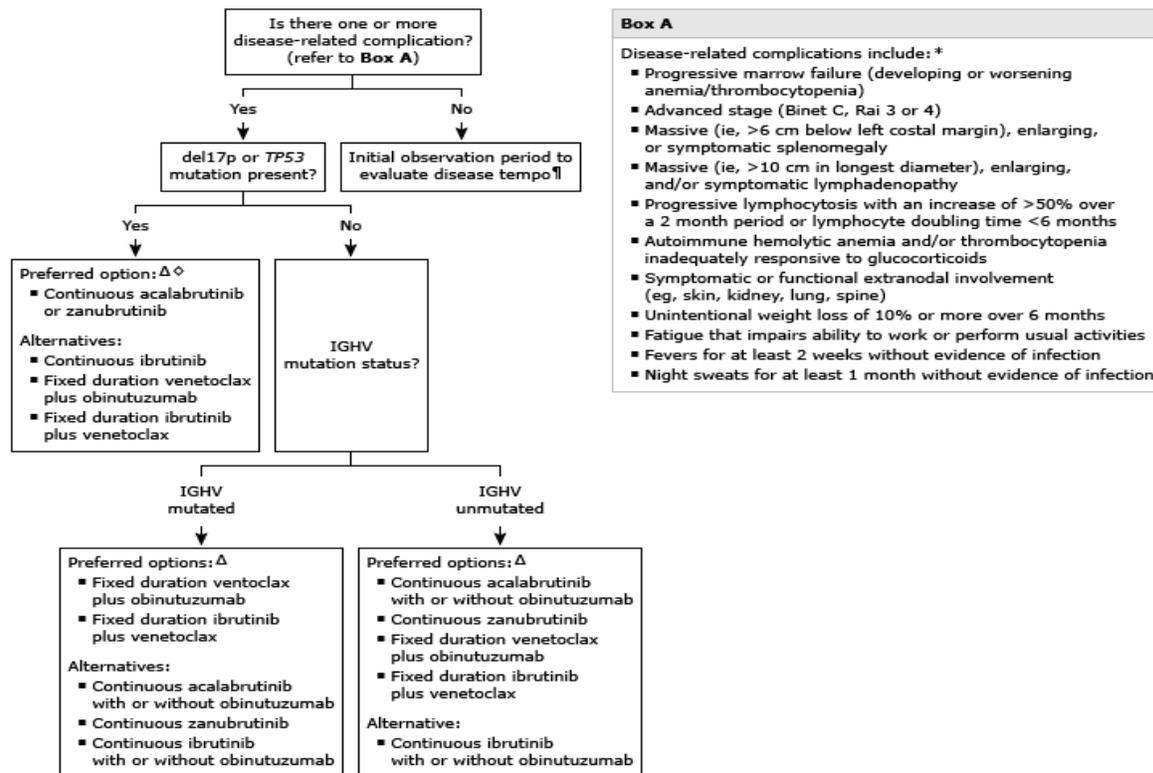
While the drug price negotiation program may have a marginal impact on healthcare costs for patients with relatively common conditions, as well as CLL patients who are not currently receiving active treatment, it will have no impact on out-of-pocket costs for patients requiring active therapy. There is little doubt that the decisions CMS makes now on the price negotiation program will become part of the complex calculations researchers, investors, and drug manufacturers make when deciding whether to pursue a particular drug candidate for a specific indication. We fear that without a proactive intent to preserve the fragile cost/benefit balance in small population diseases, CMS will inadvertently tip the scales away from innovation in CLL and other related blood cancers. We are concerned that if ibrutinib is priced in a way that encourages health plans to insist on it as a first step, more patients will be forced to experience potentially dangerous serious adverse events and discontinue treatment. It is essential that Medicare beneficiaries have access to all medications used to treat CLL because these medications are generally used as continuous therapy and:

- Individuals initially started on and responding to ibrutinib will need to stay on ibrutinib until they are unable to tolerate the treatment or their disease progresses.
- NCCN guidelines now recommend that clinicians select the next-generation BTK inhibitors (acalabrutinib or zanubrutinib) over ibrutinib when starting a patient on a BTK inhibitor.
- Requiring a step through ibrutinib or implementing burdensome prior authorization requirements would be contrary to clinical guidelines.
- It is not sufficient to include ibrutinib plus one of the next-generation BTK inhibitors within a plan formulary. Patients cannot simply switch from a BTK inhibitor that has worked for them to another as there is little, if any, data on the impact of switching treatments after six months, one year, five years, or longer on a BTK inhibitor.

The pre-IRA reimbursement landscape facilitated a level of confidence among researchers and investors sufficient to drive innovation in treating CLL. Medicare beneficiaries with CLL currently have access to all FDA-approved BTK inhibitors. We are hopeful that research will continue with the next generation of “reversible” BTK inhibitors so that patients progressing on the currently approved drugs have an additional line of life-extending therapy. CLL Society strongly urges CMS to:

- ensure that our patients retain access to all therapeutic options
- recognize, monitor, and address the potential chilling effect that the drug price negotiation program might have on innovation in life-threatening rare conditions that, like CLL, disproportionately impact the Medicare population. New cancer treatments are costly, and the virtual certainty that a new CLL treatment would become a selected drug as soon as it is eligible could
- drive resources away from CLL completely,
- deter investment in small molecules due to the longer timeline to selection eligibility for biologics, and
- reshape product development strategies from initial programs in, for example, mantle cell lymphoma, to a single-orphan designation in CLL. This will increase both the cost and time required to complete product development through an initial FDA approval.

Initial management of chronic lymphocytic leukemia



IGHV: immunoglobulin heavy chain variable region; BTK: Bruton tyrosine kinase.

* Lymphocytosis itself, even if extreme, is not a strict indication for treatment. Likewise, treatment is not indicated solely on the basis of hypogammaglobulinemia or the presence of a monoclonal or oligoclonal paraproteinemia.

¶ Treatment is indicated if the patient develops significant disease-related complications at any time. During observation, we perform blood counts at 3-month intervals along with a clinical examination. At the end of 12 months, these evaluations can determine disease aggressiveness. The interval of examination may be lengthened for those with clinically stable disease.

Δ The choice among targeted agents is strongly dependent upon patient comorbidities and preferences. Fixed duration therapy is more intensive and logistically complicated but offers a treatment-free interval. Continuous therapy is given until progression or unacceptable toxicity. When selecting among the BTK inhibitors, we prefer acalabrutinib or zanubrutinib rather than ibrutinib as acalabrutinib and zanubrutinib appear to be at least as effective and better tolerated than ibrutinib. If the goal is best efficacy with acceptable tolerability, we offer zanubrutinib. If the goal is best tolerability with good efficacy, we offer acalabrutinib. The addition of obinutuzumab to acalabrutinib or ibrutinib increases efficacy and increases toxicity with higher rates of cytopenias and infections. Further details on the impact of comorbidities and drug interactions is provided in related UpToDate content.

◇ In patients with del17p or TP53 mutation, continuous acalabrutinib or zanubrutinib may be preferred over fixed duration venetoclax plus obinutuzumab based on cross-trial comparisons that suggest decreased efficacy of the latter in this population.

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
	Response to Question 29	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	
	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	I have been taking this drug for 7 years. It has completely alleviated my CLL symptoms, thereby improving my overall health and my quality of life. I have experienced some side effects; skin cancers, hypertension, bruising, coughing. I am a clinical trial participant. The trial provides me with the drug, so I have no access issues.
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email	
	Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
	Response to Question 29	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	
	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	<p>I have been taking ibrutinib since January 2014. Before that, my Waldenstrom's Macroglobulinemia was treated with different IV chemotherapy regimens that were also used to treat other blood cancers, as there was no specific treatment for my disease. All these were largely ineffective, and some had very unpleasant side effects. In addition, they required many hours sitting in an infusion chair with a needle stuck in my veins. Since the first few months of taking ibrutinib, I have had a very deep response, and my disease is under good control. Side effects include skin issues (bruising and some thinning) and nail thinning. They are a small price to pay for keeping me healthy and alive for 20 years when I was given a prognosis of 3-5 years of survival.</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	At the time of my first prescription of Ibrutinib, there were NO therapeutic alternatives available to treat my Chronic Lymphocytic Leukemia. I had already failed 3 different approved chemotherapy treatments and there were NO alternatives for me to try. I was fortunate enough to be in the Registration Trial (Resonate) for Ibrutinib. Without a doubt, this drug saved my life, and there were no more options available to me. I was able to continue taking this drug for over 9 1/2 years and it effectively kept my Chronic Lymphocytic Leukemia under control for most of that time.
	Evidence Submitted include a cost-effectiveness measure?	Y
	What type of Evidence is shown?	Y
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	It has been obvious thru patient analysis over the years that chemotherapy based treatment (FCR & BR, as well as others) for Chronic Lymphocytic Leukemia works in providing a long term remission in only a very SMALL number of patients. There is also evidence that chemotherapy damages DNA, that is permanent in many patients. Providing a non chemotherapy regime for CLL patients created a whole new model for physicians to treat this disease. It has none of the side effects that are associated with chemotherapy. This is not to say that there are still adverse events that can occur with this new class of drug (BTK Inhibitors). It is well documented that this treatment can cause atrial fibrillation, bleeding, joint pain, GI issues. Most of these adverse events can be managed and still leave the drug to be well tolerated as well as effective.

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Question	Sub-Question	Response
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
Question 29: Comparative Effectiveness on Specific Populations	Response to Question 29	Even though there are now newer generations of Ibrutinib on the market, making this drug more cost effective would allow certain populations to gain better access to this class of drug. This drug could be a starting point for therapy and if the adverse events become to much the patient would have the opportunity to switch to another drug in this class. By appropriate screening and monitoring I feel like this could be easily managed. It is not always the case to jump to the NEXT BEST Thing when the overall treatment has not really been shown to be that much more effective.
	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
Question 30: Addressing Unmet	Response to Question 30	
	Hyperlink to Citation - Additional Materials for Question 30	

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Question	Sub-Question	Response
Medical Needs	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	I took Ibrutinib for almost 9 1/2 years. The effect was noticeable almost immediately and then slowly over time all of my blood work came into NORMAL range. All of the symptoms that I had before I started Ibrutinib resolved very quickly. Early on I experienced the documented side effects, but over time most of them went away. The one major side affect I had was GI issues, specifically diarrhea. This could be controlled when it happened and became more of a nuisance than anything. After dealing with Chronic Lymphocytic Leukemia for over 12 years, I finally felt like I was beginning to get my life back. Because I was on two different Clinical Trials for IBRUTINIB, the drug was paid for my the pharmaceutical company
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	None
	Respondent Email Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	I was diagnosed in 2000 with CLL, I had chemotherapy in 2004 which left me with breathing issues that I continue to have. In 2012 when I needed treatment again, I was fortunate to get into the NIH trial for Ibrutinib and I truly believe that this drug saved my life as my only alternative then was more chemotherapy. I had minimal side effects, Ibrutinib was the first pill form of treatment for CLL. I continued on the drug until May of this year and expect to have a long remission until the next time I need to have treatment. This drug is a lifesaver and I was so pleased that it was designated as one of the first drugs given this special designation. My life has changed for the better since I was on Ibrutinib because I no longer feel as though I have a black cloud hanging over my head waiting for the next shoe to drop. I have been able to watch my grandchildren grow up and if it wasn't for being immunocompromised and Covid , it would be ideal. CLL is a chronic disease with no cure and more than 16,000 people a year are diagnosed with it. Ibrutinib was the first light at the end of a very long tunnel for CLL patients to have hope that we could live a long time with this disease.
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	Ibrutinib was the catalyst for other drugs to help CLL patients. CLL is a very complex disease. Someone stated that we are like crayons in a box with each of us having different variations of the disease so all that was available previously was chemotherapy which was not beneficial to some of types of CLL. Additionally chemotherapy had many side effects including my 20+ years with breathing problems that no Doctor has been able to figure out. My minor side effects from my years on Ibrutinib were mouth sores, body cramps neither of which caused me to stop the drug. The benefits have been immense, life is better than I expected after living with CLL for 23 years. Additionally, I have familial CLL so I am no longer concerned if my children or grandchildren get CLL.

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Question	Sub-Question	Response
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	
Question 29: Comparative Effectiveness on Specific Populations	<p>Response to Question 29</p> <p>Hyperlink to Citation - Additional Materials for Question 29</p> <p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>Ibrutinib works on all varieties of CLL where chemotherapy was not recommended for certain types of deletions for CLL patients. The drug gives people no matter their type of CLL a chance of remission and until it stops working effectively when more treatment options are and will be available.</p>
	Response to Question 30	

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Question	Sub-Question	Response
Question 30: Addressing Unmet Medical Needs	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	I was on Ibrutinib from March of 2012 until May of this year. I was extremely fortunate to get into a trial at NIH. Fortunately, I never had to pay for the drug because the cost probably would have bankrupted us based on how long I was on it. CLL patients are very scared about the high cost of treatment and how they are going to afford the medication. I do a lot of counseling with new CLL patients through my being a first connection volunteer with the Leukemia and Lymphoma Society and an Facebook CLL group, and that is one of their biggest concerns.
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	PAT
	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
	Response to Question 29	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	
	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	<p>I take Ibrutinib, 420mg daily, to treat Waldenström's Macroglobulinemia. I have been taking this treatment since 2016. My doctor gave me a choice in 2016 of trying Ibrutinib vs. a mix of other treatment approaches. I decided to try Ibrutinib. It's proven effective, overall. I tolerate it well, with a few side effects. Re effectiveness, I get related bloodwork testing two to three times a year and Ibrutinib is controlling the cancer from increasing or spreading. Side effects include some dealing with heart palpitations and slight bruising, elbows to hands, leg cramps, and fatigue. A cardiologist is treating and monitoring the palpitations. If the palpitations increase or other heart issues evolve, my doctor may transition me to an alternative treatment. .With Ibrutinib, I have an easy to follow treatment to manage this disease while allowing me to continue my life -- and I feel very fortunate to have this med..While I get some cost benefits from my secondary health insurance and a grant from a patient care organization, substantial price increase may prove prohibitive in the future and force me to consider alternative treatments.</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	
	Respondent Email Who is completing this form?	PAT
Question 27: Prescribing Information	Prescribing Information	<p>My oncologist from [REDACTED] prescribed Ibrutinib to me in April, 2020. I was concerned to start taking it as we were in the middle of a pandemic. My concerns were: what if I have side effects and need to go to an emergency room? I was feeling bad (tired, achey, headaches, swollen glands throughout my head and neck and scared). My husband and I discussed the pros and cons of taking this new medicine during the pandemic. The outcome was to take it and worry about side effects later. Looking back in retrospect, our decision was the correct one. Within two weeks, I felt exceptionally well. Today, I am happy to report that my quality of life is excellent. I am monitored closely at [REDACTED]. My bloodwork numbers are excellent. I am so grateful that this targeted cancer medicine was available for me.</p>
	Evidence Submitted include a cost-effectiveness measure?	N
	What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	<p>Therapeutic Impact and Comparative Effectiveness</p> <p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p>	<p>Ibrutinib is a once a day targeted medicine. If I did not have this medicine, I would be receiving infusions at my oncologist. The side effects of Ibrutinib are minor: some nosebleeds, increased sinus drainage, some nail and skin issues, minor headaches. I am now 78 years old. My grandmother also had CLL in the 1950's and died in her early 60's. Not only do I have an increased life expectancy, I also have an excellent quality of life. I am able to volunteer in my local schools and senior center so I feel that I am able to contribute to society, because of Ibrutinib...My insurance plus my Side-by-Side ambassador has lowered the cost of this expensive drug</p>

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Question	Sub-Question	Response
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
	Response to Question 29	I can not answer these questions as I do not have this information
	Hyperlink to Citation - Additional Materials for Question 29	
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
	Response to Question 30	I am unsure of how to answer these questions
Question 30: Addressing Unmet Medical Needs	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	

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Question	Sub-Question	Response
	<p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	
Question 31: Patient and Caregiver Experience	Response to Question 31	<p>This medicine is easy to take orally at the same time daily with a full glass of water. The medicine comes in a packet for easy to read and remember what day has been taken. When I travel, I take the entire packet with me, choosing not to separate it from its original container. ..My oncologist's office has taken care of the difficulties of being accepted for this medicine. I personally do not have any problems renewing my prescriptions (every 28 days) and receiving the orders.</p>
Question 32: Executive Summary	Response to Question 32	

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Knowledge Ecology International
	Respondent Email Who is completing this form?	NAR
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	The attached files address the funding of R&D on Imbruvica
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
	Response to Question 29	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	
	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>The Orphan Drug provided a significant subsidy for the development of the Imbruvica. The FDA granted 14 Orphan designations for Imbruvica including eight indications that have received FDA approval. The credit was equal to 50 percent of qualifying expenditures through the end of 2017 and 25 percent thereafter...The 2009 Affordable Care Act (ACA) requires most health plans to pay routine care costs for patients who participate in clinical trials to prevent, detect or treat cancer and other life-threatening conditions. ..The NIH ClinicalTrials.Gov database lists companies owned by AbbVie or J&J as the sponsor and funder of 21 percent of all trials involving Imbruvica. The NIH is identified as one of the funders of Imbruvica trials 17 percent of the time. The largest funder of trials for Imbruvica is “other.”</p>

KEI Notes on the Clinical Studies for Imbruvica/Ibrutinib

October 2, 2023

James Love

Brandname: Imbruvica
INN: Ibrutinib
Marketed through a joint venture between AbbVie and J&J
Originally named PCI-32765.

Introduction	1
The Orphan Drug Tax Credit	2
Orphan Drug Designations and Approvals for Imbruvica	3
Table 1: Imbruvica Orphan Designations and Approvals	3
Affordable Care Act Requirements on Health Plans to cover routine care in clinical trials	4
Funders of trials listed in ClinicalTrials.Gov	5
Table 2: Funders of trials in ClinicalTrials.Gov	7
Pediatric studies requested by FDA to extend the Imbruvica patent and regulatory exclusivities	7

Introduction

In a separate note, Arianna Schouten has examined the research that led to the development of Ibrutinib, marketed by AbbVie and J&J as Imbruvica, and reached this conclusion:¹

The preclinical research that led to the development and FDA approval of Imbruvica/Ibrutinib benefited from studies and research by companies now owned by the drug sponsors (AbbVie and J&J), as well as independent research funded by the US National Institutes of Health (NIH), the German government, the European Union, the Cancer Prevention and Research Institute of Texas, the CLL Global Research Foundation, the Leukemia & Lymphoma Society, the Howard Hughes Medical Institute, and the D Warren Brown Foundation.

This note looks at the clinical studies used for initial registration and subsequent modifications of the FDA marketing approvals, the pediatric studies requested by FDA to extend the Imbruvica patent and regulatory exclusivities, the subsidies provided by the U.S. Orphan Drug Act and the funders of all studies listed in the NIH database ClinicalTrials.Gov, through September 30, 2023.

¹ Arianna Schouten, Notes on the preclinical development Imbruvica (Ibrutinib), knowledge Ecology International, October 2, 2023

Among the findings:

- The Orphan Drug provided a significant subsidy for the development of the Imbruvica. The FDA granted 14 Orphan designations for Imbruvica including eight indications that have received FDA approval. The credit was equal to 50 percent of qualifying expenditures through the end of 2017 and 25 percent thereafter.
- The 2009 Affordable Care Act (ACA) requires most health plans to pay routine care costs for patients who participate in clinical trials to prevent, detect or treat cancer and other life-threatening conditions.
- The NIH ClinicalTrials.gov database lists companies owned by AbbVie or J&J as the sponsor and funder of 21 percent of all trials involving Imbruvica. The NIH is identified as one of the funders of Imbruvica trials 17 percent of the time. The largest funder of trials for Imbruvica is “other.”

The Orphan Drug Tax Credit

The ODTTC is a significant public subsidy designed to lower the cost of clinical trials used to evaluate the safety and efficacy of drugs for qualifying diseases.

The statute providing the tax credit is [26 U.S. Code § 45C](#) - Clinical testing expenses for certain drugs for rare diseases or conditions.

A qualifying “rare disease or condition” means any disease or condition which:

(A) affects less than 200,000 persons in the United States, or

(B) affects more than 200,000 persons in the United States but for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.

A disease can be defined narrower, and a single product can qualify for several different orphan indications.

The credit is used to directly offset a taxpayer's federal income tax liability. Until 2018, the credit was equal to 50 percent of qualifying expenditures on a clinical for a qualifying orphan disease or condition. Beginning in 2018, the credit was reduced to 25 percent of expenditures on the trial.

The IRS form 8820 is used to calculate the amount of the credit and provides an explanation for taxpayers. The form has been [revised several times](#) to reflect changes in the statutes.

Among the nuances in the Act are those concerning the timing for qualifying expenditures. The credit only applies after the date the drug is designated and before the date on which an application for the drug is approved. Trials conducted outside the United States only qualify for the credit if there is an insufficient U.S. testing population, a condition that will be met for some indications but not others.

The credit can be carried back one year, or forward 20 years and can be used by a company that acquires the unprofitable company.

Orphan Drug Designations and Approvals for Imbruvica

Between 2012 and 2018, the drug sponsors received 14 Orphan Drug designations for Imbruvica. To date, eight of the 14 designations have received FDA approval. One designation was later withdrawn or revoked.

Table 1: Imbruvica Orphan Designations and Approvals

Orphan Designation	Designation	Approval	Designation Status
Treatment of chronic lymphocytic leukemia (CLL).	03/27/2012		Designation Withdrawn or Revoked
Treatment of chronic lymphocytic leukemia (CLL)	04/06/2012	02/12/2014, 07/28/2014, 03/04/2016	Designated/Approved
Treatment of mantle cell lymphoma	12/03/2012	11/13/2013	Designated/Approved
Treatment of multiple myeloma	05/16/2013		Designated
Treatment of small lymphocytic lymphoma	05/30/2013	05/06/2016	Designated/Approved
Treatment of Waldenstrom's macroglobulinemia	10/15/2013	01/29/2015	Designated/Approved
Treatment of diffuse large B-cell lymphoma	10/23/2013		Designated
Treatment of follicular lymphoma	09/08/2014		Designated
Treatment of splenic marginal zone lymphoma	02/05/2015	01/18/2017	Designated/Approved
Treatment of nodal marginal zone lymphoma	02/05/2015	01/18/2017	Designated/Approved
Treatment of patients with extranodal marginal zone lymphoma (mucosa associated lymphoid tissue [MALT type] lymphoma)	02/02/2016	01/18/2017	Designated/Approved
Treatment of chronic Graft versus Host disease	06/23/2016	08/02/2017 08/24/2022	Designated/Approved
Treatment of pancreatic cancer	06/12/2017		Designated

Treatment of gastric cancer, including gastroesophageal junction adenocarcinoma	02/01/2018		Designated
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Some of the trials for Imbruvica began before receiving an FDA designated indication, or extended after an FDA approval, and the credit would only apply to part of the trial outlays.

Thirteen of the first fourteen trials only included U.S. patients, but subsequent trials were frequently more international in character.

The amount of the credit is not currently transparent. In 2017, the Senate Finance Committee proposed to disclose the recipient, amount, drug and the disease or condition, but the transparency provision was later eliminated in the final bill after lobbying from drug companies. This is the original transparency proposal

SEC. 13401. MODIFICATION OF ORPHAN DRUG CREDIT.

(b) DISCLOSURE OF CREDITS.—Section 45C is amended by adding at the end the following new subsection:

“(e) DISCLOSURE OF CREDITS.—The Secretary shall publicly disclose the identity of any taxpayer (in the case of a pass-thru entity, the name of the entity) to whom a credit is allowed under this section, as well as the amount of such credit, the drug with respect to which the qualified clinical testing expenses were taken into account under this section, and the rare disease or condition for which such drug was being tested.”.

Affordable Care Act Requirements on Health Plans to cover routine care in clinical trials

The Patient Protection and Affordable Care Act (ACA) added Section 2709 to the Public Health Service Act, requiring private insurers to cover routine patient costs for individuals participating in clinical trials for the prevention, detection, and treatment of cancer or other life-threatening diseases or conditions.

The obligation is set out in [42 U.S.C. §300gg–8](#). Coverage for individuals participating in approved clinical trials. Routine patient costs are defined as “all items and services consistent with the coverage provided in the plan (or coverage) that is typically covered for a qualified individual who is not enrolled in a clinical trial.”

The trials covered include any study or investigation that is approved or funded (including funding through in-kind contributions) by a large set of federal agencies, or is conducted under an investigational new drug application reviewed by the Food and Drug Administration, or if the study or investigation is a drug trial that is exempt from having such an investigational new drug application.

Excluded from the reimbursement obligation are:

- (i) the investigational item, device, or service, itself;
- (ii) items and services that are provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient; or
- (iii) a service that is clearly inconsistent with widely accepted and established standards of care for a particular diagnosis.

This obligation requires the broader public to bear significant costs for clinical trials. For example, consider the trial [NCT01578707](#), “A Phase 3 Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (RESONATE™),” a trial pivotal in the FDA’s 2014 expanded approval of Imbruvica for the treatment of CLL. The trial contained two arms, one with 195 patients treated with Imbruvica and one with 191 patients treated with Ofatumumab. Some of the costs associated with the Imbruvica treatment would have been covered, but all of the treatment related expenses for Ofatumumab would have been covered, because it was a current standard of care for CLL.

Little is known about the extent that clinical trials are financed through the obligations on health plans to cover routine care, but the contributions are significant.

Funders of trials listed in ClinicalTrials.Gov

A September 29, 2023 search of the NIH ClinicalTrials.Gov database using the search term “ibrutinib” for Intervention/Treatment returned 396 trials.

The ClinicalTrials.Gov database has a number of data fields, including fields listing the funders and sponsors of trials. There are four main funder types:

- NIH
- Other U.S. federal agency
- Industry
- All others (individuals, universities, organizations)

Some trials have multiple funders. In the past, downloaded data from a query of the database listed additional categories for multiple funder types, such as NIH|Other or Industry|NIH|Other.

The query on September 30, 2023 provided one set of numbers in interactive mode, but different numbers when the data is downloaded. The interactive mode appears to report funding for a category when there is any funding of a trial. In this mode, more funders are reported than trials. The downloaded data only provides one funder type for a trial, and is probably either the sole or the primary funder. Given the interest in knowing the role of different funders of clinical trials, the NIH should improve the reporting of this data field.

Table 2 provides the statistics from ClinicalTrials.Gov on funders of trials. The first three columns are from the data downloaded, which only assigns one funder type to each trial. 138 of the 396 trials have industry as the funder type. Of the 138 industry funded trials, 83 have an AbbVie or J&J owned company as the sponsor of the trial. There are 55 trials funded by industry competitors. The NIH is listed as the funder for 31 trials, or 8 percent of the total. The biggest category is “other,” which accounts for 218, or more than half of all trials.

The last three columns in Table 2 report statistics displayed in the Interactive query of ClinicalTrials.Gov, which reports more funder types than trials. The number of trials with industry funding is 244, or 62 percent of all trials, but it is not possible to determine how many of these trials involved AbbVie or J&J companies as compared to their competitors. The number of trials with NIH funding is 68, or 17 percent of all trials. The number of trials with “All other” funders is 233, or 59 percent of the total.

Table 2: Funders of trials in ClinicalTrials.Gov

<i>Downloaded data</i>			<i>Interactive data</i>		
Sole or Primary Funder	Number of trials		Among Funders	Number of trials	
Industry	138	35%	Industry	244	62%
Industry (sponsor is AbbVie or J&J owned company)	83	21%			
NIH	31	8%	NIH	68	17%
OTHER_GOV	3	1%	Other US Federal		
Other	218	55%	All other	233	59%
NETWORK	5	1%			
UNKNOWN	1	0%			
	396	100%		545	138%

Pediatric studies requested by FDA to extend the Imbruvica patent and regulatory exclusivities

On August 8, 2022, the FDA make a request to Pharmacyclics LLC, a company now owned by AbbVie, to undertake three small studies of ibrutinib on pediatric populations. The request was

made under 21 U.S. Code § 355a - Pediatric studies of drugs, and grants a six month extension of the Imbruvica patent and regulatory exclusivities, imposing significant costs on the public. The requested enrollment for the studies were at least 35 patients across both Studies 1 and 2, and at least 65 patients in Study 3, or just 100 patients.

The cost to the public for the three studies with as few as 100 patients is expected to be massive. The 2021 Medicare and Medicaid outlays on Imbruvica were \$3.2 billion and the U.S. expenditures on the drug by other payers was also substantial.

Notes on the preclinical development of Imbruvica (Ibrutinib)

October 2, 2023

Arianna Schouten, Knowledge Ecology International

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Introduction and findings

The preclinical research that led to the development and FDA approval of Imbruvica/Ibrutinib benefited from studies and research by companies now owned by the drug sponsors (AbbVie and Johnson&Johnson), as well as independent research funded by the US National Institutes of Health (NIH), the German government, the European Union, the Cancer Prevention and Research Institute of Texas, the CLL Global Research Foundation, the Leukemia & Lymphoma Society, the Howard Hughes Medical Institute, and the D Warren Brown Foundation.

Background

Standard therapy for patients with chronic lymphocytic leukemia (CLL) has included chemotherapy and, more recently, chemoimmunotherapy regimens. Despite this, none of the

chemoimmunotherapy regimens are curative and carry many toxicities, which provides a strong motivation for developing effective and better tolerable agents.¹

Imbruvica is an oral inhibitor of Bruton's tyrosine kinase (BTK). BTK is a key protein of the B-cell receptor pathway and BTK plays an important role in the functioning of certain immune cells (such as B lymphocytes). Imbruvica inhibits the B-cell receptor pathway, leading to several effects on malignant B lymphocytes, such as:

- Directly causing some of the malignant B lymphocytes to self-destruct (apoptosis);
- Stopping B lymphocytes from growing and dividing (proliferation); and
- Changing how lymphocytes move around in the body. When the lymphocytes leave their 'protective environment' they become more vulnerable and can lead to more cell death (egress lymphocytes).

1991: The founding of Pharmacyclics

Ronald Levy co-founded IDEC with his Stanford colleague Richard Miller. IDEC delivered rituximab, the first monoclonal antibody approved by the FDA for cancer. Miller then left IDEC and co-founded Pharmacyclics in 1991. Initially, Pharmacyclics focused on a class of molecules called texaphryns, but after unsuccessful clinical trials, they needed to think of another avenue of focus.

1998 - 2001: Celera Genomics

Celera Genomics emerged in 1998 and began working towards the same goal as the Human Genome Project: to generate the first sequence of the human genome. Celera was headed by geneticist and businessman Craig Venter, a former NIH scientist, initially to compete with the publicly funded Human Genome Project, in part with the prospect of gaining control over potential patents.² Celera's stock later plummeted in reaction to President Bill Clinton and Prime Minister Tony Blair stating that genetic information should be made public.³

As the business model of selling access to sequence data was not successful, Celera changed gears, and in 2001 acquired Axys Pharmaceuticals for \$174 million.⁴ With this purchase, Celera intended to tie together its database and begin the development of small molecule compounds, and in 2002, Venter left Celera, "a casualty of the company's bid to transform itself from a force

¹ Davids MS, Brown JR. Ibrutinib: a first in class covalent inhibitor of Bruton's tyrosine kinase. *Future Oncol.* 2014 May;10(6):957-67. doi: 10.2217/fon.14.51. PMID: 24941982; PMCID: PMC4632638. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632638/>

² See: Georgina Ferry and John Sulston, *The Common Thread: A Story of Science, Politics, Ethics and the Human Genome*, Joseph Henry Press, 2002.

³ Kristen Philpkoski, Investors Sue Celera: A class action lawsuit was filed against Celera for making misleading statements in SEC documents, *Wired*, May 18, 2000.

<https://www.wired.com/2000/05/investors-sue-celera/>.

⁴ <https://money.cnn.com/2001/06/13/deals/celera/index.htm>; Andrew Pollack, Technology; Genome Research Pioneer to Buy Drug Maker, *The New York Times*, June 14, 2001.

<https://www.nytimes.com/2001/06/14/business/technology-genome-research-pioneer-to-buy-drug-maker.html>

in genetic decoding to a discoverer and producer of new medicines,” according to the Wall Street Journal.⁵

2006: Initial preclinical work and the sale of some Celera assets to Pharmacyclics

In a study published in 2006, researchers from Celera reported the discovery of selective irreversible inhibitors for BTK. They had conducted a number of experiments and screenings to identify compounds that could selectively and irreversibly inhibit BTK activity. Their study resulted in the discovery of potential inhibitors that could serve as the basis for further drug development.⁶

Table 1: Pan et al. Celera funded

Study	Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. <i>ChemMedChem</i> . 2007;2(1):58-61
Summary	Pivotal study where researchers identified a set of compounds that effectively inhibit BTK activity.
Funding	Celera

The same year, Celera announced the sale of their therapeutic programs to Pharmacyclics. Under the terms of the agreement, Pharmacyclics acquired Celera technology and intellectual property relating to drugs that target histone deacetylase (HDAC) enzymes, selective HDAC enzymes, angiogenesis molecules and B-cell tyrosine kinases.⁷

The deal was focused on Celera's Phase 1 HDAC assets, however, the co-founder of Pharmacyclics noted that he was keen for the BTK inhibitor program to be included in the acquisition as well. This was an easy task since the perceived value of the BTK program was close to zero.⁸

⁵ Scott Hensley, Craig Venter Leaves Celera as Firm Seeks New Direction. *Wall Street Journal*, January 23, 2002. <https://www.wsj.com/articles/SB1011714052194210440>

⁶ Pan, Z., Scheerens, H., Li, S.J., Schultz, B.E., Sprengeler, P.A., Burrill, L.C., Mendonca, R.V., Sweeney, M.D., Scott, K.C., Grothaus, P.G. and Jeffery, D.A., 2007. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. *ChemMedChem: Chemistry Enabling Drug Discovery*, 2(1), pp.58-61.

⁷ Celera Genomics Announces Sale Of Therapeutic Programs To Pharmacyclics, Press Release. April 10, 2006.

<https://www.sec.gov/Archives/edgar/data/949699/000094969906000018/exh99-1.pdf>

⁸ David Shaywitz, The Wild Story Behind A Promising Experimental Cancer. *Forbes*, April 5, 2013. <https://www.forbes.com/sites/davidshaywitz/2013/04/05/the-wild-story-behind-a-promising-experimental-cancer-drug/?sh=4695d6db5857>

The transaction included an upfront cash payment of \$2 million and an equity payment of between five hundred thousand and one million shares of Pharmacyclics common stock. If the programs met certain milestone events and resulted in drugs that became approved and commercialized, they would generate potential future milestone payments to Celera of up to \$144 million. In addition, Celera would be entitled to royalty payments in the mid-to high single digits based on annual sales of any drugs commercialized from the three programs.⁹

2007: Publicly-funded study shows positive conclusions

During this time, the results of a significant preclinical study came to positive conclusions about the role of B-cell receptors (BCR) for B-cell development (see Table 1). This study had promising implications for the understanding of B-cell development and immune responses. By modulating BCR signaling, the immune system can regulate the activation and survival of B-cells.

Table 2: The Waisman et al. Celera study

Study	Waisman, A., Kraus, M., Seagal, J., Ghosh, S., Melamed, D., Song, J., Sasaki, Y., Classen, S., Lutz, C., Brombacher, F. and Nitschke, L., 2007. IgG1 B cell receptor signaling is inhibited by CD22 and promotes the development of B cells whose survival is less dependent on Igα/β. The Journal of experimental medicine, 204(4), pp.747-758.
Summary	Examined the signaling pathways and factors that influence the survival of B-cells. Study concluded that the CD22 protein has an inhibitory effect of the specific B-cell receptors (so the protein can put brakes on certain signals within B-cells). While not explicit at the time, the findings have implications on therapies targeting B-cells.
Funding	This work was supported by the FP6 Marie Curie Research Training Network (grant MRTN-CT-2004-005632 to A. Waisman), the Deutsche Forschungsgemeinschaft (grant SFB 243 to K. Rajewsky, grant SFB 490 to A. Waisman, and grant SFB 466 to L. Nitschke), and the National Institutes of Health (grant 1 R37 AI054636-01).

2008: Leadership change at Pharmacyclics

In 2008, Miller (the co-founder of Pharmacyclics) was forced out of Pharmacyclics by Robert Duggan, who is a member of and one of biggest donors to the Church of Scientology. Miller had

⁹ Celera Genomics Announces Sale Of Therapeutic Programs To Pharmacyclics, Press Release. April 10, 2006.

<https://www.sec.gov/Archives/edgar/data/949699/000094969906000018/exh99-1.pdf>

played a pivotal role in the company's early stages. Duggan had invested in Pharmacyclics when its shares were worth 1-3\$ per share. He acted as CEO and Chairman of Pharmacyclics from 2008 until 2015.

2008 - 2010: Preclinical studies supporting PCI-32765

Pharmacyclics was eager to explore the potential of BTK inhibitors with B-cell cancers. They contributed to the following preclinical studies, which had early promising results (see Table 3). In addition to the industry funded preclinical work, at the same time, there was research published in *Nature* which showed that PCI-32765 showed the promotion of some of the malignant B lymphocytes to self-destruct (see Table 4). Together, these preclinical studies provided critical support for the development of PCI-32764 as a therapeutic agent for the treatment of CLL and other diseases. These studies set the stage for the subsequent phases of development and clinical trials.

Table 3: Honigberg et al. Pharmacyclics study

Study	Honigberg, L.A., Smith, A.M., Sirisawad, M., Verner, E., Louny, D., Chang, B., Li, S., Pan, Z., Thamm, D.H., Miller, R.A. and Buggy, J.J., 2010. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. <i>Proceedings of the National Academy of Sciences</i> , 107(29), pp.13075-13080.
Summary	Studied the ability of PCI-32765 to inhibit the activation of B-cells. The study found that it blocked the activation of B-cells, indicating that it would be a promising drug candidate.
Funding	Industry

Table 4: Davis et al. publicly-funded study

Study	Davis, R., Ngo, V., Lenz, G. et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. <i>Nature</i> 463, 88–92 (2010).
Summary	BTK was identified as an essential kinase for survival in a subset of diffuse large cell lymphomas driven by activated BCR where an irreversible BTK inhibitor (PCI-32765) showed the promotion of apoptosis.
Funding disclosure	This research was supported by the Intramural Research Program of the National Institutes of Health, the National Cancer Institute, the Center for Cancer Research, the National Institute of Allergy and Infectious Disease, and the National Human Genome Research Institute. P.B.R. was a Howard Hughes Medical Institute-National Institutes of Health

	Research Scholar.
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2011: Co-development agreement with Janssen

Beginning in 2010, Phase I and Phase II trials were launched involving PCI-32765, the drug later named Ibrutinib. Johnson and Johnson, through its Janssen subsidiary, entered into an agreement with Pharmacylics to co-develop the drug, using the brand name Imbruvica. Janssen paid Pharmacylics \$150 million upfront and up to \$825 in milestone payments. The companies entered into a worldwide 50/50 profit-loss agreement, sharing development and commercialization activities,¹⁰ with each company leading the development of specific indications with a cost share of 40/60 (Pharmacylics/Janssen).

2011 - 2012: Further studies

The following three studies, published before the first FDA approval, provided further support for the use of Ibrutinib in the treatment of chronic lymphocytic leukemia (CLL) and received various funding sources.

Table 5: de Rooij et al. Pharmacylics funded

Study	de Rooij, M. F., Kuil, A., Geest, C. R., Eldering, E., Chang, B. Y., Buggy, J. J., ... & Spaargaren, M. (2012). The clinically active BTK inhibitor PCI-32765 targets B-cell receptor–and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. <i>Blood, The Journal of the American Society of Hematology</i> , 119(11), 2590-2594.
Summary	In this study, the authors evaluated PCI-32765 and found that it effectively targeted and inhibited BTK, which was significant because it disrupted the signaling pathways that promote the growth and survival of CLL cells.
Funding disclosure	Pharmacylics

¹⁰ Janssen Biotech, Inc. Announces Collaborative Development And Worldwide License Agreement For Investigational Anti-Cancer Drug, PCI-32765, Press Release. December 8, 2011. <https://www.jnj.com/media-center/press-releases/janssen-biotech-inc-announces-collaborative-development-and-worldwide-license-agreement-for-investigational-anti-cancer-drug-pci-32765>

Table 6: Herman et al. charitable and publicly funded study

Study	Herman, S. E., Gordon, A. L., Hertlein, E., Ramanunni, A., Zhang, X., Jaglowski, S., ... & Byrd, J. C. (2011). Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. <i>Blood, The Journal of the American Society of Hematology</i> , 117(23), 6287-6296
Summary	In this study, the authors evaluated PCI-32765 and found that it effectively targeted and inhibited BTK, which was significant because it disrupted the signaling pathways that promote the growth and survival of CLL cells.
Funding disclosure	This work was supported by the Leukemia & Lymphoma Society, the NIH (P50-CA140158, PO1-CA95426, PO1 CA81534, 1K12 CA133250), and The D. Warren Brown Foundation. A.J.J. is a Paul Calabresi Scholar.

Table 7: Ponader et al. Pharmacyclics and charity funded study

Study	Ponader, S., Chen, S. S., Buggy, J. J., Balakrishnan, K., Gandhi, V., Wierda, W. G., ... & Burger, J. A. (2012). The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. <i>Blood, The Journal of the American Society of Hematology</i> , 119(5), 1182-1189.
Summary	This study aimed to assess the potential of PCI-32765 as a treatment for CLL. The study included in vitro and in vivo experiments and found that the drug inhibited BTK, thus impeding the survival and growth of CLL cells. This was observed in both in vitro and in vivo. The findings of the research suggest that PCI-32765 had the potential to be a valuable therapeutic option of CLL.
Funding disclosure	The study was supported by CLL Global Research Foundation grants (W.G.W., V.G., and J.A.B.), by Pharmacyclics Inc, and by a Cancer Prevention and Research Institute of Texas (CPRIT) grant (J.A.B.).

Summary Table: Selected published studies essential for Ibrutinib development prior to FDA approval and funders cited in papers

Year published	Published paper describing study	Funders cited in paper
2007	Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. <i>ChemMedChem</i> . 2007;2(1):58-61. doi: 10.1002/cmdc.200600221	Celera
2007	Waisman A, Kraus M, Seagal J, et al. IgG1 B cell receptor signaling is inhibited by CD22 and promotes the development of B cells whose survival is less dependent on Ig alpha/beta. <i>J Exp Med</i> . 2007;204(4):747-758. doi: 10.1084/jem.20062024	FP6 Marie Curie Training Network (grant MRTN-CT-2004-005632, the European Commission)
		Deutsche Forschungsgemeinschaft (grant SFB 243, German government funded research foundation)
		Deutsche Forschungsgemeinschaft (grant SFB 466, German government funded research foundation)
		NIH (1 R37 AI054636-01)
2010	Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. <i>Proc Natl Acad Sci U S A</i> . 2010;107(29):13075-13080. doi: 10.1073/pnas.1004594107	Pharmacyclics
2010	Davis, R., Ngo, V., Lenz, G. et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. <i>Nature</i> 463, 88–92 (2010). https://doi.org/10.1038/nature08638	Howard Hughes Medical Institute (Author PBR was a research scholar)
		NIH (NIH0011349228)
		NIH (NIH0011349228)
2011	de Rooij, M. F., Kuil, A., Geest, C. R., Eldering, E., Chang, B. Y., Buggy, J. J., ... & Spaargaren, M. (2012). The clinically active BTK inhibitor PCI-32765 targets B-cell receptor—and	Pharmacyclics

Year published	Published paper describing study	Funders cited in paper
	chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. <i>Blood</i> , The Journal of the American Society of Hematology, 119(11), 2590-2594. https://doi.org/10.1182/blood-2011-11-390989	
2011	Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. <i>Blood</i> . 2011;117(23):6287-6296. doi: 10.1182/blood-2011-01-328484	Leukemia & Lymphoma Society NIH (P50-CA140158) NIH (PO1-CA95426) NIH (PO1 CA81534) NIH (1K12 CA133250) D Warren Brown Foundation
2012	Sabine Ponader, Shih-Shih Chen, Joseph J. Buggy, Kumudha Balakrishnan, Varsha Gandhi, William G. Wierda, Michael J. Keating, Susan O'Brien, Nicholas Chiorazzi, Jan A. Burger, The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. <i>Blood</i> (2012) 119 (5): 1182–1189. https://doi.org/10.1182/blood-2011-10-386417	Pharmacyclics Cancer Prevention and Research Institute of Texas (State of Texas) CLL Global Research Foundation Grant

Public E2 Submission

IPAY: 2026



Question	Sub-Question	Response																																			
Question 26: Respondent Information	Selected Drug	IBRUTINIB																																			
	Q26 - Respondent Name																																				
	Q26 - Organization Name (if applicable)	The Leukemia & Lymphoma Society																																			
	Respondent Email Who is completing this form?	PAO																																			
Question 27: Prescribing Information	Prescribing Information	<p>Ibrutinib (Imbruvica) is approved by the FDA for adult patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (with or without 17p deletion), adults with Waldenström's macroglobulinemia, and Adult and pediatric patients age 1 year and older with chronic graft versus host disease after failure of one or more lines of systemic therapy. Accelerated approval indications for mantle cell lymphoma and marginal zone lymphoma were removed by the FDA in May 2023. ..Zanubrutinib (Brukinsa) is approved by the FDA for adult patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, adults with Waldenström's macroglobulinemia, adults with mantle cell lymphoma under accelerated approval, and relapsed or refractory marginal zone lymphoma who have received at least one anti-CD20-based regimen under accelerated approval. ..Acalabrutinib (Calquence) is approved by the FDA for adult patients with chronic lymphocytic leukemia/small lymphocytic lymphoma and adult mantle cell lymphoma patients who have received at least one prior therapy under accelerated approval. ..Pirtobrutinib (Jaypirca) is approved by the FDA for adult patients with relapse or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a BTK inhibitor. This is an accelerated approval indication.</p> <table border="1" data-bbox="619 1136 1959 1331"> <thead> <tr> <th></th> <th>CLL/SLL</th> <th>CLL/SLL 17P</th> <th>WM</th> <th>GvH</th> <th>MCL</th> <th>MZL</th> </tr> </thead> <tbody> <tr> <td>Ibrutinib</td> <td>X</td> <td>X</td> <td></td> <td>X</td> <td></td> <td>X</td> </tr> <tr> <td>Zanubrutinib</td> <td>X</td> <td></td> <td>X</td> <td></td> <td></td> <td>X</td> </tr> <tr> <td>Acalabrutinib</td> <td>X</td> <td></td> <td></td> <td></td> <td></td> <td>X</td> </tr> <tr> <td>Pirtobrutinib</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>X</td> </tr> </tbody> </table>		CLL/SLL	CLL/SLL 17P	WM	GvH	MCL	MZL	Ibrutinib	X	X		X		X	Zanubrutinib	X		X			X	Acalabrutinib	X					X	Pirtobrutinib						X
			CLL/SLL	CLL/SLL 17P	WM	GvH	MCL	MZL																													
Ibrutinib	X	X		X		X																															
Zanubrutinib	X		X			X																															
Acalabrutinib	X					X																															
Pirtobrutinib						X																															
<p>Each of these drugs is a Bruton tyrosine kinase (BTK) inhibitor that is used similarly in clinical settings. BTK inhibition blocks different downstream cell signaling pathways related to the development of B-cell malignancies, halting or reducing abnormal B-cell development. [1] BTK inhibitors are used both as monotherapy for as long as treatment is tolerated or as a fixed-dose treatment plan in combination with venetoclax (a BCL-2 inhibitor) and obinutuzimab (a CD-20 antibody). [2] Ibrutinib is currently a standard treatment for patients in first-line or relapsed patients who have not yet tried a BTK inhibitor. However, with</p>																																					

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Question	Sub-Question	Response
	<p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>the exception of Pirtobrutinib, BTK inhibitors work in a similar manner: by binding to the BTK enzyme irreversibly. [1] This means that if a patient does not succeed on ibrutinib, they will not succeed on other irreversible BTK inhibitors. ..[1] Brullo C, Villa C, Tasso B, Russo E, Spallarossa A. Btk Inhibitors: A Medicinal Chemistry and Drug Delivery Perspective. Int J Mol Sci. 2021 Jul 16;22(14):7641. doi: 10.3390/ijms22147641. PMID: 34299259; PMCID: PMC8303217..[2] Wierda WG, Brown J, Abramson JS, et al. NCCN Guidelines insights: chronic lymphocytic leukemia/small lymphocytic lymphoma, version 3.2022. J Natl Compr Canc Netw 2022;20:622-634.</p> <p>N</p>
<p>Question 28: Therapeutic Impact and Comparative Effectiveness</p>	<p>Therapeutic Impact and Comparative Effectiveness</p>	<p>While effective, ibrutinib is associated with potentially treatment-limiting cardiotoxicity, including hypertension and arrhythmia. [1] ..Comparing ibrutinib with zanubrutinib in relapsed and refractory patients with CLL/SLL shows that zanubrutinib has a significantly higher overall response rate, improved progression-free survival, lower atrial fibrillation rates, and a superior cardiac safety profile, while overall survival appears similar. [2][3] ..Comparing ibrutinib with acalabrutinib in relapsed and refractory patients with CLL/SLL shows that acalabrutinib has a favorable benefit-risk profile, including lower incidence of cardiovascular-related toxicities. [4] ..Pirtobrutinib is a first-in-class reversible BTK inhibitor, with demonstrated durable efficacy after prior BTK inhibitor therapy in heavily pretreated R/R mantle cell lymphoma. [5] Several other reversible BTK inhibitors are currently being studied for therapeutic use, including CLL/SLL patients previously treated with an irreversible BTK inhibitor. [6] [7]..Thus, while ibrutinib continues to have important uses, such as for high-risk CLL patients with 17p deletion, the class of BTK inhibitors appears to have advanced to more effective therapies both in terms of better outcomes and fewer side effects. ..[1] Dickerson T, Wiczer T, Waller A, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. Blood. 2019 Nov 28;134(22):1919-1928. doi: 10.1182/blood.2019000840. PMID: 31582362; PMCID: PMC6887116..[2] Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023;388(4):319-32. [3] Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. J Clin Oncol. 2023 Feb 10;41(5):1035-1045. doi: 10.1200/JCO.22.00510. Epub 2022 Nov 17. PMID: 36395435; PMCID: PMC9928683..[4] Seymour JF, Byrd JC, Ghia P, et al. Detailed safety profile of acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. Blood. 2023 Aug 24;142(8):687-699. doi: 10.1182/blood.2022018818. PMID: 37390310..[5] Wang ML, Jurczak W, Zinzani PL, et al. Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma. J Clin Oncol. 2023 Aug 20;41(24):3988-3997. doi: 10.1200/JCO.23.00562. Epub 2023 May 16. PMID: 37192437; PMCID: PMC10461952..[6] Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a covalent BTK inhibitor in</p>

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Question	Sub-Question	Response
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>chronic lymphocytic leukemia. N Engl J Med 2023;389:33-44..[7] Brullo C, Villa C, Tasso B, Russo E, Spallarossa A. Btk Inhibitors: A Medicinal Chemistry and Drug Delivery Perspective. Int J Mol Sci. 2021 Jul 16;22(14):7641. doi: 10.3390/ijms22147641. PMID: 34299259; PMCID: PMC8303217.</p>
<p>Question 29: Comparative Effectiveness on Specific Populations</p>	<p>Response to Question 29</p> <p>Hyperlink to Citation - Additional Materials for Question 29</p> <p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	
	<p>Response to Question 30</p>	

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Question	Sub-Question	Response
Question 30: Addressing Unmet Medical Needs	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	While ibrutinib has important therapeutic uses, its therapeutic alternatives may offer more favorable risk-benefit profiles. However, there are some patients for whom ibrutinib continues to be the only FDA-approved indication: CLL/SLL patients with 17 p deletion and patients with chronic graft versus host disease after failure of one or more lines of systemic therapy.

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Patients for Affordable Drugs
	Respondent Email	
Question 27: Prescribing Information	Who is completing this form?	OTH
	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure?	
Question 28: Therapeutic Impact and Comparative Effectiveness	What type of Evidence is shown?	
	Therapeutic Impact and Comparative Effectiveness	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28	
	Evidence Submitted include a cost-effectiveness measure?	
	What type of Evidence is shown?	
	Response to Question 29	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 30: Addressing Unmet Medical Needs	Response to Question 30	Imbruvica is a targeted therapy; albeit non cytotoxic systemically as chemotherapy is. Imbruvica is in a class of drugs called BTK inhibitors.
	Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	

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Question	Sub-Question	Response
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	<p>Ibrutinib was the first drug of its kind to be FDA approved to treat CLL (2007). At a cost of \$17,000 per month it has incurred an annual increase in price since approximately 2013. This is not affordable to many seniors on Medicare. However, now with Medicare negotiations it is possible to cut the price by 50% as it is in the rest of the world. It is difficult to be part of the population just over the threshold for financial help. Please make healthcare affordable for all including seniors living on a fixed income.</p>

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	Pharmaceutical Care Management Association (PCMA)
	Respondent Email Who is completing this form?	TRD
Question 27: Prescribing Information	Prescribing Information	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 28: Therapeutic Impact and Comparative Effectiveness	Therapeutic Impact and Comparative Effectiveness	<p>The Pharmaceutical Care Management Association (PCMA) appreciates the opportunity to submit comments regarding the therapeutic alternatives for Ibrutinib. Our members help administer the Part D prescription drug benefit on behalf of many Part D plan sponsors, and a central component of that function is the identification of therapeutic alternatives to develop comprehensive prescription drug formularies consistent with applicable statutory, regulatory, and clinical requirements, including ensuring formularies are not discriminatory...In general, while we understand that CMS cannot disclose the specifics of their negotiations with manufacturers of selected drugs, we believe the public is best served by CMS disclosing as much about this process as possible, and otherwise aligning its methodology for selecting therapeutic alternatives with how Part D plans select therapeutic alternatives. Our comments focus on emphasizing the differences between identifying therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program, and the role that the identification of therapeutic alternatives plays under the Medicare Part D program's formulary standards and enrollee communication requirements. PCMA has three main points...1. As a general principle, CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for the Part D program. ...2. CMS should clarify in an HPMS memo to Part D plans that CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program will not impact the agency's existing approach towards evaluating Part D formulary design for compliance with Part D formulary requirements...3. CMS</p>

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Question Sub-Question

Response

should clarify in an HPMS memo that Part D plans retain discretion on how to communicate therapeutic alternatives to enrollees, and that CMS's identification of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program will not affect these enrollee communications...We discuss these issues in more detail below...I. CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for their formulary submissions. ..Currently, Part D plan sponsors consider a variety of factors when identifying therapeutic alternatives for their formulary submissions, including but not limited to (i) clinical effectiveness, (ii) safety, (iii) price, (iv) availability, and (v) patient preferences. Importantly, these factors are considered within a regulatory framework that imposes certain overarching formulary requirements. ..First, Part D plans must ensure that their formulary designs are nondiscriminatory. CMS considers several criteria when assessing whether a formulary is nondiscriminatory. CMS may presumptively approve formulary designs which align with the United States Pharmacopoeia's (USP) Medicare Model Guidelines (MMGs) based on the view that the MMGs reflect a scientifically and-clinically-based taxonomy developed by an independent expert body without a vested financial interest in the Part D program. The MMGs are also important because they provide a guiding framework for Part D plans to use when determining therapeutic alternatives. The MMGs group drugs into categories and classes. These categories and classes generally encompass the universe of potential therapeutic alternatives for a given medical condition. This means that Part D plans can use the MMGs to identify the range of therapeutic alternatives to consider when developing their formularies...Second, Part D plans must provide an adequate formulary, which among other things, means including at least two Part D drugs within a particular category or class of Part D drugs. This minimum formulary standard helps ensure a wide range of treatment options for enrollees, even if they have complex or rare medical conditions. Additionally, this requirement promotes patient choice and competition among drug manufacturers because the ability for patients to access alternative treatments incentivizes drug manufacturers to lower prices and innovate. The requirement to include at least two drugs per category or class helps to ensure that patients with a given medical condition have at least two formulary treatment options available to them, even if there are few therapeutic alternatives. This requirement is important because it prevents Part D plans from excluding entire categories or classes of drugs from their formularies...Third, Part D plans must consider cost sharing in the development of formularies. For example, CMS could raise concerns about formularies that place drugs on high cost-sharing tiers without placing therapeutic alternatives in preferable positions. CMS has also expressed concerns about "adverse tiering" where a plan sponsor assigns most or all drugs in the same therapeutic class needed to treat a specific chronic, high-cost medical condition to a high cost-sharing tier. In short, Part D plans must consider the enrollee's share of costs for a particular drug when considering therapeutic alternatives...PCMA encourages CMS to identify therapeutic alternatives for the Medicare Drug Price Negotiation Program in the same way that Part D plans do for their formularies. This would ensure consistency in process across two closely related programs and avoid introducing multiple, confusing standards for the same underlying definitional term. At the very least, aligning

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the selection of therapeutic alternatives under the Medicare Drug Price Negotiation Program with Part D formulary submissions would give Part D plans some assurance that CMS's assessment of their formulary submissions will not be affected by CMS's own process of selecting therapeutic alternatives...II. CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program should not compromise the agency's evaluation of the adequacy of Part D plan formulary design, ensuring that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs...PCMA acknowledges that CMS's identification of therapeutic alternatives under the Medicare Drug Price Negotiation Program is required by law and essential for successful drug pricing negotiations. As stated above, we urge CMS to attempt to align its selection of therapeutic alternatives with how Part D plans select therapeutic alternatives...That being said, it is important to recognize that the exercise of selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program and the Part D program, while overlapping in some areas, are ultimately distinct. Selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program requires unique considerations that are not fully applicable to how Part D plans identify and leverage therapeutic alternatives for formulary development. Accordingly, we do not expect CMS to perfectly align itself with Part D plan sponsor methodologies for selecting therapeutic alternatives.. .First, therapeutic alternatives are a statutory feature of the Medicare Drug Price Negotiation Program. CMS selects therapeutic alternatives when negotiating pricing for selected drugs because the statute requires the agency to do so. Even if the statute did not require CMS to identify therapeutic alternatives, CMS would likely need to do so because it supports the agency in carrying out its statutory mandate to negotiate a "maximum fair price" (MFP) with manufacturers. Importantly, the MFP applies in a vacuum without regards to affordability and relative competitiveness with other drugs that a beneficiary may access...By contrast, while Part D plans are required to select therapeutic alternatives for formulary submissions, Part D plans select therapeutic alternatives based on a delicate balance between clinical comparability, cost-effectiveness, and beneficiary access. Unlike CMS, which is required to focus on a single drug in isolation when assessing therapeutic alternatives, Part D plans, PBMs, and their pharmacy and therapeutics (P&T) committees are tasked with developing comprehensive formularies that holistically meet the complex needs of their enrollees. Part D plans must, already, cover selected drugs on their formularies under the statute, and CMS's interpretation worryingly suggests that such coverage may also involve a preferred status designation. Additional indirect restrictions on formulary design stemming from CMS's evaluation criteria under the Medicare Drug Price Negotiation Program could significantly hamper Part D plans' ability to offer competitive plan designs. In light of the comprehensive considerations that Part D plans must consider in developing formularies, CMS must ensure plans retain flexibility to adequately weigh all of these factors when developing formularies, including identifying therapeutic alternatives...Second, CMS's selection of therapeutic alternatives is a one-time event, done solely to determine the MFP for a selected drug. Once the MFP is determined, the drug's therapeutic alternatives play no further role in how Medicare beneficiaries access the selected drug...In contrast, a Part D plan sponsor's selection of therapeutic alternatives is used in multiple ways, including formulary design, coverage

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determination, tiering exceptions, and Part D appeals. This means that Part D plans must carefully consider all potential scenarios in which their selection of therapeutic alternatives may be challenged...Third, CMS's identification of therapeutic alternatives for purposes of the Drug Price Negotiation Program is nonpublic. CMS indicates in the Revised Guidance for the Medicare Drug Price Negotiation Program that the agency will not unilaterally disclose any information pertaining to its negotiations with manufacturers, including the therapeutic alternatives identified for such negotiations. As a result, Part D plans do not have access to the therapeutic alternatives that CMS identifies for selected drugs. It would be unfair and arbitrary for CMS to evaluate Part D plan formulary submissions, including the identification of therapeutic alternatives contained in the submission, on a criteria that CMS never releases to the public. Formulary guidelines like the USP Medicare Model Guidelines provide a more predictable basis for administering a prescription drug benefit than nonpublic information. ..In short, while we urge CMS to align its methodology for selecting therapeutic alternatives as much as possible with Part D plans, we also request that CMS clarify that the therapeutic alternatives considered in the Medicare Drug Price Negotiation Program are distinct from the therapeutic alternatives that Part D plans must identify for purposes of formulary submissions and the overall administration of the prescription drug benefit. This will help ensure that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs. CMS can do this via an HPMS memo to Part D plans...III. Part D plans may continue to identify therapeutic alternatives in enrollee communications consistent with existing practices, regardless of CMS's identification of therapeutic alternatives for Medicare Drug Price Negotiation Program. ..Apart from formulary development, the issue of a drug's therapeutic alternatives also has implications on communications Part D sponsors are required to provide to enrollees. The Annual Notice of Change (ANOC) describes any changes to the plan's benefits, formularies, and costs for the upcoming year. The Evidence of Coverage (EOC) document describes the plan's benefits, coverage, and exclusions. Real-time benefit tools (RTBT) provide prescribers with information at the point-of-care on formulary and benefit information (including cost, formulary alternatives, and utilization management requirements). The monthly Explanation of Benefits (EOB) must include lower cost alternatives. ..While Part D plans are not required to include information about therapeutic alternatives in the ANOC or EOC, many voluntarily do so to help enrollees make informed decisions about their prescription drug coverage. This information is especially valuable for enrollees and prospective enrollees to fully understand the different treatment options available to them based on their unique circumstances. This transparency also promotes competition among Part D plans, as enrollees can better assess which plans are best for them. ..The RTBT and EOB rules have granted plans latitude in selecting which therapeutic alternatives would be displayed. CMS has stated that the "purpose of the beneficiary RTBT is to better inform beneficiaries about alternative medications," and thus, CMS allows "part D sponsors flexibility in implementing this requirement." For the EOB, CMS requires Part D sponsors to include lower-cost therapeutic alternatives but does not impose any specific requirements on plans on how they should identify those therapeutic alternatives...In summary, while Part D plans are required to communicate certain information to enrollees about therapeutic alternatives, CMS

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Question	Sub-Question	Response
	<p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>provides plans with significant flexibility in the selection of those therapeutic alternatives. As such, CMS should explicitly clarify that the information on therapeutic alternatives that Part D plans choose to communicate to enrollees in required enrollee communications to beneficiaries and other regulatory requirements is not affected by CMS's selection of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program.</p>
<p>Question 29: Comparative Effectiveness on Specific Populations</p>	<p>Response to Question 29</p> <p>Hyperlink to Citation - Additional Materials for Question 29</p> <p>Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29</p> <p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	

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Question	Sub-Question	Response
Question 30: Addressing Unmet Medical Needs	Response to Question 30 Hyperlink to Citation - Additional Materials for Question 30 Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30 Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	

Answers to Question #28 for Public Submission

The Pharmaceutical Care Management Association (PCMA) appreciates the opportunity to submit comments regarding the therapeutic alternatives for Ibrutinib. Our members help administer the Part D prescription drug benefit on behalf of many Part D plan sponsors, and a central component of that function is the identification of therapeutic alternatives to develop comprehensive prescription drug formularies consistent with applicable statutory, regulatory, and clinical requirements, including ensuring formularies are not discriminatory.

In general, while we understand that CMS cannot disclose the specifics of their negotiations with manufacturers of selected drugs, we believe the public is best served by CMS disclosing as much about this process as possible, and otherwise aligning its methodology for selecting therapeutic alternatives with how Part D plans select therapeutic alternatives. Our comments focus on emphasizing the differences between identifying therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program, and the role that the identification of therapeutic alternatives plays under the Medicare Part D program's formulary standards and enrollee communication requirements. PCMA has three main points:

1. As a general principle, CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for the Part D program.
2. CMS should clarify in an HPMS memo to Part D plans that CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program will not impact the agency's existing approach towards evaluating Part D formulary design for compliance with Part D formulary requirements.
3. CMS should clarify in an HPMS memo that Part D plans retain discretion on how to communicate therapeutic alternatives to enrollees, and that CMS's identification of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program will not affect these enrollee communications.

We discuss these issues in more detail below.

I. CMS should identify therapeutic alternatives under the Medicare Drug Price Negotiation Program consistent with the guardrails that apply to Part D plan sponsors when identifying therapeutic alternatives for their formulary submissions.

Currently, Part D plan sponsors consider a variety of factors when identifying therapeutic alternatives for their formulary submissions, including but not limited to (i) clinical effectiveness, (ii) safety, (iii) price, (iv) availability, and (v) patient preferences. Importantly, these factors are considered within a regulatory framework that imposes certain overarching formulary requirements.

First, Part D plans must ensure that their formulary designs are nondiscriminatory.¹ CMS considers several criteria when assessing whether a formulary is nondiscriminatory. CMS may presumptively approve formulary designs which align with the United States Pharmacopoeia's (USP) Medicare Model Guidelines (MMGs) based on the view that the MMGs reflect a

¹ See 42 C.F.R. § 423.272(b)(2).

scientifically and-clinically-based taxonomy developed by an independent expert body without a vested financial interest in the Part D program. The MMGs are also important because they provide a guiding framework for Part D plans to use when determining therapeutic alternatives. The MMGs group drugs into categories and classes. These categories and classes generally encompass the universe of potential therapeutic alternatives for a given medical condition. This means that Part D plans can use the MMGs to identify the range of therapeutic alternatives to consider when developing their formularies.

Second, Part D plans must provide an adequate formulary, which among other things, means including at least two Part D drugs within a particular category or class of Part D drugs.² This minimum formulary standard helps ensure a wide range of treatment options for enrollees, even if they have complex or rare medical conditions. Additionally, this requirement promotes patient choice and competition among drug manufacturers because the ability for patients to access alternative treatments incentivizes drug manufacturers to lower prices and innovate. The requirement to include at least two drugs per category or class helps to ensure that patients with a given medical condition have at least two formulary treatment options available to them, even if there are few therapeutic alternatives. This requirement is important because it prevents Part D plans from excluding entire categories or classes of drugs from their formularies.

Third, Part D plans must consider cost sharing in the development of formularies. For example, CMS could raise concerns about formularies that place drugs on high cost-sharing tiers without placing therapeutic alternatives in preferable positions.³ CMS has also expressed concerns about "adverse tiering" where a plan sponsor assigns most or all drugs in the same therapeutic class needed to treat a specific chronic, high-cost medical condition to a high cost-sharing tier.⁴ In short, Part D plans must consider the enrollee's share of costs for a particular drug when considering therapeutic alternatives.

PCMA encourages CMS to identify therapeutic alternatives for the Medicare Drug Price Negotiation Program in the same way that Part D plans do for their formularies. This would ensure consistency in process across two closely related programs and avoid introducing multiple, confusing standards for the same underlying definitional term. At the very least, aligning the selection of therapeutic alternatives under the Medicare Drug Price Negotiation Program with Part D formulary submissions would give Part D plans some assurance that CMS's assessment of their formulary submissions will not be affected by CMS's own process of selecting therapeutic alternatives.

II. CMS's identification of therapeutic alternatives for the Medicare Drug Price Negotiation Program should not compromise the agency's evaluation of the adequacy of Part D plan formulary design, ensuring that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs.

PCMA acknowledges that CMS's identification of therapeutic alternatives under the Medicare Drug Price Negotiation Program is required by law and essential for successful drug pricing

² *Id.* at §

³ § 30.2.7, Chapter 6, Medicare Prescription Drug Manual ("The CMS review will focus on identifying drug categories that may substantially discourage enrollment of certain beneficiaries by placing drugs in non-preferred tiers in the absence of commonly used therapeutically similar drugs in more preferred positions.").

⁴ 87 Fed. Reg. 27208, 27303 (May 6, 2022).

negotiations. As stated above, we urge CMS to attempt to align its selection of therapeutic alternatives with how Part D plans select therapeutic alternatives.

That being said, it is important to recognize that the exercise of selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program and the Part D program, while overlapping in some areas, are ultimately distinct. Selecting therapeutic alternatives for the Medicare Drug Price Negotiation Program requires unique considerations that are not fully applicable to how Part D plans identify and leverage therapeutic alternatives for formulary development.⁵ Accordingly, we do not expect CMS to perfectly align itself with Part D plan sponsor methodologies for selecting therapeutic alternatives.

First, therapeutic alternatives are a statutory feature of the Medicare Drug Price Negotiation Program. CMS selects therapeutic alternatives when negotiating pricing for selected drugs because the statute *requires* the agency to do so. Even if the statute did not require CMS to identify therapeutic alternatives, CMS would likely need to do so because it supports the agency in carrying out its statutory mandate to negotiate a "maximum fair price" (MFP) with manufacturers. Importantly, the MFP applies in a vacuum without regards to affordability and relative competitiveness with other drugs that a beneficiary may access.

By contrast, while Part D plans are required to select therapeutic alternatives for formulary submissions, Part D plans select therapeutic alternatives based on a delicate balance between clinical comparability, cost-effectiveness, and beneficiary access. Unlike CMS, which is required to focus on a single drug in isolation when assessing therapeutic alternatives, Part D plans, PBMs, and their pharmacy and therapeutics (P&T) committees are tasked with developing comprehensive formularies that holistically meet the complex needs of their enrollees. Part D plans must, already, cover selected drugs on their formularies under the statute,⁶ and CMS's interpretation worryingly suggests that such coverage may also involve a preferred status designation.⁷ Additional indirect restrictions on formulary design stemming from CMS's evaluation criteria under the Medicare Drug Price Negotiation Program could significantly hamper Part D plans' ability to offer competitive plan designs. In light of the comprehensive considerations that Part D plans must consider in developing formularies, CMS must ensure plans retain flexibility to adequately weigh all of these factors when developing formularies, including identifying therapeutic alternatives.

Second, CMS's selection of therapeutic alternatives is a one-time event, done solely to determine the MFP for a selected drug. Once the MFP is determined, the drug's therapeutic alternatives play no further role in how Medicare beneficiaries access the selected drug.

In contrast, a Part D plan sponsor's selection of therapeutic alternatives is used in multiple ways, including formulary design, coverage determination, tiering exceptions, and Part D appeals. This means that Part D plans must carefully consider all potential scenarios in which their selection of therapeutic alternatives may be challenged.

Third, CMS's identification of therapeutic alternatives for purposes of the Drug Price Negotiation Program is nonpublic. CMS indicates in the Revised Guidance for the Medicare Drug Price

⁵ See 42 C.F.R. § 423.128(d)(4)(ii).

⁶ Social Security Act § 1860D-4(b)(3)(I).

⁷ See § 110, Medicare Drug Price Negotiation Program: Revised Guidance (June 30, 2023), <https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf>.

Negotiation Program that the agency will not unilaterally disclose any information pertaining to its negotiations with manufacturers, including the therapeutic alternatives identified for such negotiations. As a result, Part D plans do not have access to the therapeutic alternatives that CMS identifies for selected drugs. It would be unfair and arbitrary for CMS to evaluate Part D plan formulary submissions, including the identification of therapeutic alternatives contained in the submission, on a criteria that CMS never releases to the public. Formulary guidelines like the USP Medicare Model Guidelines provide a more predictable basis for administering a prescription drug benefit than nonpublic information.

In short, while we urge CMS to align its methodology for selecting therapeutic alternatives as much as possible with Part D plans, we also request that CMS clarify that the therapeutic alternatives considered in the Medicare Drug Price Negotiation Program are distinct from the therapeutic alternatives that Part D plans must identify for purposes of formulary submissions and the overall administration of the prescription drug benefit. This will help ensure that Medicare beneficiaries continue to have access to a broad range of affordable prescription drugs. CMS can do this via an HPMS memo to Part D plans.

III. Part D plans may continue to identify therapeutic alternatives in enrollee communications consistent with existing practices, regardless of CMS's identification of therapeutic alternatives for Medicare Drug Price Negotiation Program.

Apart from formulary development, the issue of a drug's therapeutic alternatives also has implications on communications Part D sponsors are required to provide to enrollees. The Annual Notice of Change (ANOC) describes any changes to the plan's benefits, formularies, and costs for the upcoming year. The Evidence of Coverage (EOC) document describes the plan's benefits, coverage, and exclusions. Real-time benefit tools (RTBT) provide prescribers with information at the point-of-care on formulary and benefit information (including cost, formulary alternatives, and utilization management requirements).⁸ The monthly Explanation of Benefits (EOB) must include lower cost alternatives.⁹

While Part D plans are not required to include information about therapeutic alternatives in the ANOC or EOC, many voluntarily do so to help enrollees make informed decisions about their prescription drug coverage. This information is especially valuable for enrollees and prospective enrollees to fully understand the different treatment options available to them based on their unique circumstances. This transparency also promotes competition among Part D plans, as enrollees can better assess which plans are best for them.

The RTBT and EOB rules have granted plans latitude in selecting which therapeutic alternatives would be displayed. CMS has stated that the "purpose of the beneficiary RTBT is to better inform beneficiaries about alternative medications," and thus, CMS allows "part D sponsors flexibility in implementing this requirement."¹⁰ For the EOB, CMS requires Part D sponsors to include lower-cost therapeutic alternatives but does not impose any specific requirements on plans on how they should identify those therapeutic alternatives.

⁸ § 119, Title I, Division CC, Consolidated Appropriations Act, 2021, Pub. L. No. 117-328 (amending section 1860D-4); *see also* 86 Fed. Reg. 5864, 5868 (Jan. 19, 2021).

⁹ 42 C.F.R. 423.138(e)(5).

¹⁰ 86 Fed. Reg. 5864, (May 6, 2022).

In summary, while Part D plans are required to communicate certain information to enrollees about therapeutic alternatives, CMS provides plans with significant flexibility in the selection of those therapeutic alternatives. As such, CMS should explicitly clarify that the information on therapeutic alternatives that Part D plans choose to communicate to enrollees in required enrollee communications to beneficiaries and other regulatory requirements is not affected by CMS's selection of therapeutic alternatives for purposes of the Medicare Drug Price Negotiation Program.

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Question	Sub-Question	Response
Question 26: Respondent Information	Selected Drug	IBRUTINIB
	Q26 - Respondent Name	
	Q26 - Organization Name (if applicable)	multiple: Cutaneous Lymphoma Foundation; Histiocytosis Association; CLL Society; International Cancer Advocacy Network; Biomarker Collaborative; Exon 20 Group; MET Crusaders; PD-L1 Amplifieds
	Respondent Email Who is completing this form?	OTH
Question 27: Prescribing Information	Prescribing Information	<p>OTH</p> <p>A. Selected Drug. The selected drug, IMBRUVICA (ibrutinib), is a Bruton's tyrosine kinase (BTK) inhibitor that initially received accelerated approval in 2013 for the treatment of mantle cell lymphoma (MCL) in patients who had received at least one prior therapy. In 2016, the U.S. Food and Drug Administration (FDA) approved the drug for treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma with 17p deletion. [1]. When FDA announced additional approval of IMBRUVICA to treat patients with Waldenström's macroglobulinemia (WM), Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research stated, "[t]oday's approval highlights the importance of development of drugs for supplemental indications. Continued research has discovered new uses of Imbruvica." WM is a rare form of non-Hodgkin lymphoma. [2]. In 2016, FDA expanded the IMBRUVICA label to include overall survival data in previously treated CLL patients [3], added new indications for small lymphocytic lymphoma [3], and for use in first-line treatment of CLL [4]. In its 2017 announcement that IMBRUVICA received an additional accelerated approval and became the first treatment specifically approved to treat marginal zone lymphoma (MZL), Darrin Beaupre, M.D., Ph.D., Head of Early Development and Immunotherapy at Pharmacyclics LLC, stated, "[t]his milestone marks the fifth patient population for whom Imbruvica is now approved and broadens the number of patients who may be treated with the medication. We continue to research Imbruvica across many disease areas, including but not limited to other B-cell malignancies." [5]. In addition to the lymphoma label expansions, IMBRUVICA was approved in 2017 for treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of one or more treatments. As was the case with the drug's approval in MZL, IMBRUVICA became the first FDA-approved therapy for the treatment of cGVHD. [6] Once again, FDA emphasized the benefit of researching new uses of existing treatments. "Patients with cGVHD who do not respond to other forms of therapy – typically corticosteroids to suppress their immune system – now have a treatment option specifically indicated to treat their condition. This approval highlights how a known treatment for cancer is finding a new use in treating a serious and life-threatening condition that may occur in patients with blood cancer who receive a stem cell transplant." Richard Pazdur, M.D., Director of the FDA's Oncology Center of Excellence and Acting director of the Office of Hematology and Oncology</p>



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Products in the FDA's Center for Drug Evaluation and Research. [7] .In 2022, the cGVHD indication was expanded to include pediatric patients over 1 year of age. [8].In May 2023, the accelerated approval indications in MCL and MZL were voluntarily withdrawn because the Phase 3 confirmatory studies were not sufficient for traditional approval. [9].The dosing for IMBRUVICA, according to the FDA approved label is:.420 mg taken orally once daily for:

- adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) [10]
- adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion [10]
- adult patients with Waldenström's macroglobulinemia (WM) [10]
- adult patients with chronic graft versus host disease (cGVHD) [10]

240 mg/m² taken orally once daily (up to a dose of 420 mg) for:

- pediatric patients age 1 year and older with cGVHD [10]

B. Therapeutic Alternatives

1. Indication: Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).

a. CALQUENCE® (acalabrutinib) 100 mg orally approximately every 12 hours [11]

b. BRUKINSA® (zanubrutinib) 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity [12].

2. Indication: Adult patients with Waldenström's macroglobulinemia (WM).

a. BRUKINSA® (zanubrutinib) 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity. [12]

b. CALQUENCE® (acalabrutinib) CALQUENCEÂ® (acalabrutinib) is used off-label to treat WM.

3. Indication: Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy..The selected drug, IMBRUVICAÂ® is the only BTK inhibitor approved for treating cGVHD and the only FDA approved treatment for children under 12 years of age with cGVHD. .Please provide information about how the selected drug and its therapeutic alternative(s) are used in the course of care for the condition or disease treated by each indication. .According to NCCN Guidelines, the most appropriate frontline treatment for CLL and SLL depends on patient-specific factors, including characteristics of the cancer and mutation status, age, and comorbidities. Subsequent lines of therapy of therapy are chosen based on the previous treatment as well as the factors outlined above. [13]

In WM, the BTK inhibitors, including IMBRUVICA, are often used as initial therapy in elderly patients and other individuals unable to tolerate systemic chemotherapy. There is divergence of opinion among experts on whether to reserve BTK inhibitors for relapsed or refractory disease in other patients or to incorporate their use in initial treatment. [15] IMBRUVICA can be used with or without coadministration of rituximab (375 mg/m²) once a week for weeks 1-4 and 17-20..If the selected drug is used off-label to treat a certain disease or



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condition, please indicate this and provide evidence from nationally recognized, evidence-based guidelines and recognized by CMS-approved Part D compendia, as applicable.

- Mantle Cell Lymphoma: In BTK inhibitor-naïve patients with a first relapse of MCL or primary refractory MCL, IMBRUVICA may be used if acalabrutinib and zanubrutinib are unavailable. [16]
- Hairy Cell Leukemia (HCL): HCL is a rare B-cell malignancy with an unmet need in patients failing to benefit from purine nucleoside analogs (PNA). A recent phase 2 study of IMBRUVICA showed promising results. [9]
- Primary CNS lymphoma (PCNSL): PCNSL is a rare form of lymphoma in the central nervous system without evidence of systemic involvement. It comprises approximately 2% of all primary brain tumors. [11] Approximately 80%–90% of PCNSL cases are diffuse-large B-cell lymphomas (DLBCL). Several studies have investigated the use of IMBRUVICA alone and in combination with chemotherapy as an option for treating PCNSL. These studies have shown high (and durable) treatment response and tolerability despite a high rate of Aspergillus infections.

It is important to note that the BTK inhibitors, including IMBRUVICA, are increasingly being studied in combination with other treatment options. The attached table sets forth industry-sponsored clinical studies listed on clinicaltrials.gov that are currently recruiting patients. The studies examine IMBRUVICA as a treatment for additional oncologic indications and in combination with other treatments. Other BTK inhibitors are currently studied for non-cancer uses, including in treating multiple sclerosis. We strongly urge CMS to actively monitor the impact that the drug negotiation program has on industry-sponsored studies of existing treatments. The cost/benefit balance for rare cancers is particularly fragile. For patients, competition is both meaningful and beneficial when it results in improved treatments as well as expanding knowledge of how existing treatments can be used – alone and with other therapies. The BTK inhibitor class is an example where we expect that, without pricing intervention, the set of available products and our understanding of their value would evolve over time to the benefit of patients.

References

1. de Claro RA, McGinn KM, Verdun N, Lee SL, Chiu HJ, Saber H, Brower ME, Chang CJ, Pfuma E, Habtemariam B, Bullock J, Wang Y, Nie L, Chen XH, Lu DR, Al-Hakim A, Kane RC, Kaminskas E, Justice R, Farrell AT, Pazdur R. FDA Approval: Ibrutinib for Patients with Previously Treated Mantle Cell Lymphoma and Previously Treated Chronic Lymphocytic Leukemia. *Clin Cancer Res*. 2015 Aug 15;21(16):3586-90. doi: 10.1158/1078-0432.CCR-14-2225. PMID: 26275952.
2. FDA Expands Approved Use of Imbruvica (ibrutinib) for Waldenström's Macroglobulinemia ([drugs.com](https://www.drugs.com))
3. U.S. FDA Expands Imbruvica (ibrutinib) Label to Include Overall Survival Data in Previously Untreated Chronic Lymphocytic Leukemia (CLL) and New Indication for Small Lymphocytic Lymphoma (SLL) Patients ([drugs.com](https://www.drugs.com))
4. FDA Approves Imbruvica (ibrutinib) for the First-Line Treatment of Chronic Lymphocytic Leukemia ([drugs.com](https://www.drugs.com))

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Question	Sub-Question	Response
	<p>Evidence Submitted include a cost-effectiveness measure?</p> <p>What type of Evidence is shown?</p>	<p>5. U.S. FDA Approves Imbruvica (ibrutinib) as First Treatment Specifically Indicated for Relapsed/Refractory Marginal Zone Lymphoma (MZL) (drugs.com)</p> <p>6. FDA Approves Imbruvica (ibrutinib) for Chronic Graft Versus Host Disease (drugs.com)</p> <p>7. FDA Approves Imbruvica (ibrutinib) for Chronic Graft Versus Host Disease (drugs.com)</p> <p>8. FDA Approves Imbruvica (ibrutinib) for Chronic Graft Versus Host Disease (drugs.com)</p> <p>9. Update on Imbruvica (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications - Drugs.com MedNews</p> <p>10. Dosing & Administration - CLL/SLL IMBRUVICA® (ibrutinib) HCP (imbruvicahcp.com)</p> <p>11. Calquence Full Prescribing Information (den8dhaj6zs0e.cloudfront.net)</p> <p>12. prescribing-information.pdf (brukinsa.com)</p> <p>13. Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia/small lymphocytic lymphoma – UpToDate</p> <p>14. NCCN Guidelines Update: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in: Journal of the National Comprehensive Cancer Network Volume 21 Issue 5.5 (2023) (jnccn.org)</p> <p>15. Treon SP. How I treat Waldenström macroglobulinemia. Blood 2015; 126:721.</p> <p>16. T Low J, B Peters K. Ibrutinib in primary central nervous system diffuse large B-cell lymphoma. CNS Oncol. 2020 Mar 1;9(1):CNS51. doi: 10.2217/cns-2019-0022. Epub 2020 Mar 6. PMID: 32141313; PMCID: PMC7163401.</p> <p>17. Ostrom QT, Gittleman H, De Blank PM. et al. American Brain Tumor Association adolescent and young adult primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro Oncol. 18(Suppl. 1), i1-i50 (2016).</p> <p>18. T Low J, B Peters K. Ibrutinib in primary central nervous system diffuse large B-cell lymphoma. CNS Oncol. 2020 Mar 1;9(1):CNS51. doi: 10.2217/cns-2019-0022. Epub 2020 Mar 6. PMID: 32141313; PMCID: PMC7163401.</p> <p>N</p>
<p>Question 28: Therapeutic Impact and Comparative Effectiveness</p>	<p>Therapeutic Impact and Comparative Effectiveness</p>	<p>Because BTK inhibitors are a relatively new class of drugs targeting rare cancers, we are concerned that the drug negotiation program could have an unintended impact on their further research and development. Unless a specific treatment has significant use over a long time period, it is unlikely that generic competition would provide a significant benefit to patients. In fact, the BTK inhibitor class demonstrates the potential for improved, next-generation treatments that create in-class competition based on quality and value to patients; this is of higher value to patients than entry of a generic competitor to the first generation therapy, IMBRUVICA. Ideally, a competitive landscape pressures innovators to continue studying treatments for new</p>

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Question	Sub-Question	Response
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 28 Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	<p>indications as well as their use alone and with other therapies to improve patient outcomes. Cancer patients have experienced improved survival and better quality of life due to expanded uses of treatments as well as expanded treatment offerings within new classes of therapies. We have significant concerns that the drug negotiation program could inject new considerations into both product development and manufacturer interest in label expansions. ..We strongly believe that there are insufficient head-to-head studies among the BTK inhibitors to conclusively determine that there is a superior treatment option for all patients. Although clinical guidelines and recommendations have recently recognized that newer BTK inhibitors offer fewer side effects and may enable patients to stay on treatment longer, the drug price negotiation program will, we fear, prioritize negotiated discounted price over therapeutic advantages. The lower the negotiated price, the more likely it will be that patients will have new step therapy protocols driving their treatment and, ultimately, their health outcomes. These utilization management strategies are particularly inappropriate when applied to cancer treatments generally and the BTK inhibitor class specifically. Resistance to subsequent covalent BTK inhibitors can arise through multiple mechanisms, including acquired mutations in BTK at the binding site of covalent BTK inhibitors. This means that a plan-driven decision to treat a patient with IMBRUVICA, or one of the other BTK inhibitors would, at some point in time, render another covalent BTK inhibitor ineffective. [19] Rare cancer patients generally have few treatment options and any external forces (including drug price) driving choice of therapy could result in patients exhausting all available treatments more quickly than they would if their cancer and overall health status drove treatment decisions. ..For patients, the bottom line is that all available treatment options should be listed on Part D plan formularies. In addition, CMS should carefully consider both the high-volume indications and the more rare uses of IMBRUVICA and other drugs selected for this initial year of the drug price negotiation program. ..Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. Haematologica 2020; 106: 2354-2363.</p>
	Response to Question 29	

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Question	Sub-Question	Response
Question 29: Comparative Effectiveness on Specific Populations	Hyperlink to Citation - Additional Materials for Question 29	
	Hyperlink to Table/Charts/Graphs - Additional Materials for Question 29	
	Evidence Submitted include a cost-effectiveness measure? What type of Evidence is shown?	N
Question 30: Addressing Unmet Medical Needs	Response to Question 30	<ul style="list-style-type: none">• BTK inhibitors have led to improved survival and quality of life for patients. This is, in part, due to the fact that these treatments offer patients the opportunity to avoid receiving their treatment in an infusion center. [1]• Richter's syndrome (RS) is a very rare and aggressive histologic transformation of CLL that results in a very poor prognosis. Further studies on combinations of BTK inhibitors with other treatments could confirm what small studies have found – that IMBRUVICA plus a PD-1 inhibitor can significantly improve outcomes for these patients. [2] <p>Attached, please see our table outlining rare cancer studies of IMBRUVICA and other BTK inhibitors and the unmet medical needs the studied treatment addresses.</p> <p>Lovell AR, Jammal N, Bose P. Selecting the optimal BTK inhibitor therapy in CLL: rationale and practical considerations. <i>Therapeutic Advances in Hematology</i>. 2022;13. doi:10.1177/20406207221116577</p> <p>Al-Sawaf O, Zhang C, Robrecht S, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 4-year follow-up analysis of the randomized CLL14 study. <i>Hematol Oncol</i> 2021; 39: S146.</p> <p>Wang, E.; Mi, X.; Thompson, M.C.; Montoya, S.; Notti, R.Q.; Afaghani, J.; Durham, B.H.; Penson, A.; Witkowski, M.T.; Lu, S.X.; et al. Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors. <i>N. Engl. J. Med.</i> 2022, 386, 735-743</p>
	Hyperlink to Citation - Additional Materials for Question 30	

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Question	Sub-Question	Response
	<p data-bbox="260 467 541 602">Hyperlink to Table/Charts/Graphs - Additional Materials for Question 30</p> <p data-bbox="260 643 604 740">Evidence Submitted include a cost-effectiveness measure?</p> <p data-bbox="260 813 569 878">What type of Evidence is shown?</p>	<p data-bbox="609 248 1953 464">Visentin A, Mauro FR, Cibien F, et al. Continuous treatment with Ibrutinib in 100 untreated patients with TP53 disrupted chronic lymphocytic leukemia: a real-life campus CLL study. <i>Am J Hematol</i> 2022; 97: E95-E99. Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. <i>Haematologica</i> 2020; 106: 2354-2363. Sivina M, Kim E, Wierda WG, et al. Ibrutinib induces durable remissions in treatment-naïve patients with CLL and 17p deletion and/or TP53 mutations. <i>Blood</i> 2021; 138: 2589-2592.</p> <p data-bbox="609 740 653 773">N</p>
Question 31: Patient and Caregiver Experience	Response to Question 31	
Question 32: Executive Summary	Response to Question 32	

Industry-Sponsored Studies of BTK Inhibitors that are Currently Recruiting Participants

Study Title	Primary Outcome Measures	Sponsor	Start Date
Acalabrutinib Plus RICE for Relapsed/Refractory DLBCL	Cohort A: Complete Response Rate, To estimate the confirmed complete response (CR) rate (RECIL 2017 criteria) prior to transplant in patients undergoing second-line therapy for relapsed/refractory DLBCL., 10 weeks Cohort B: Progression Free Survival	Swedish Medical Center	8/16/2019
HMPL-760 in Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma	Number of subjects with Dose Limiting Toxicities (DLTs) with relapsed/refractory B-cell non-Hodgkin's lymphoma	Hutchison Medipharma Limited	1/4/2022
Obinutuzumab and Ibrutinib as Front Line Therapy in Treating Patients With Indolent Non-Hodgkin's Lymphomas	Overall response rate in patients with newly diagnosed indolent lymphoma requiring treatment	Sidney Kimmel Cancer Center at Thomas Jefferson University	2/20/2018
Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Patients With Newly Diagnosed or Refractory/Recurrent Primary Central Nervous System Lymphoma (PCNSL) and Refractory/Recurrent Secondary Central Nervous System Lymphoma (SCNSL)	Maximum Tolerated Dose (MTD) of ibrutinib (phase I), A standard 3+3 design will be employed. Three dose levels of ibrutinib will be investigated.	Memorial Sloan Kettering Cancer Center	2014-12
Zanubrutinib, in Combination With Lenalidomide, With or Without Rituximab in Participants With Relapsed/Refractory Diffuse Large B-Cell Lymphoma	Part 1: Number of Participants Experiencing Adverse Events (AEs), Up to 48 months Part 1: Number of Participants Experiencing Severe Adverse Events (SAEs), Up to 48 months Part 2: Overall Response Rate (ORR), The proportion of participants who achieve either a partial response (PR) or complete response (CR), Up to 48 months	BeiGene	9/11/2020
Study of BTK Inhibitor LOXO-305 Versus Approved BTK Inhibitor Drugs in Patients With Mantle Cell Lymphoma (MCL)	To compare progression-free survival (PFS) of pirtobrutinib as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) in patients with previously treated mantle cell lymphoma (MCL), Assessed per Lugano criteria, Up to approximately 24 months	Loxo Oncology, Inc.	4/8/2021
Zanubrutinib and Venetoclax in CLL (ZANU-VEN)	Rate of undetectable minimal residual disease (uMRD), Assessed by flow cytometry (FC), At the end of cycle 15 (each cycle is 28 days)	Dana-Farber Cancer Institute	2/18/2022

Acalabrutinib for the Treatment of Chronic Graft Versus Host Disease	Best response (complete and partial response [CR + PR]), The composite outcome of CR and PR, calculated according to the proposed response definitions of the 2014 National Institutes of Health Consensus Conference.	Fred Hutchinson Cancer Center	12/12/2020
A Study of NX-5948 in Adults With Relapsed/Refractory B-cell Malignancies	Number of participants with protocol specified dose-limiting toxicities,	Nurix Therapeutics, Inc.	4/13/2022
Acalabrutinib and Obinutuzumab for the Treatment of Previously Untreated Follicular Lymphoma or Other Indolent Non-Hodgkin Lymphomas	Complete response (CR) rate	Emory University	9/3/2021
Acalabrutinib and Rituximab in Elderly Patients With Untreated Mantle Cell Lymphoma	Progression-free survival	Nordic Lymphoma Group	12/15/2021
Zanubrutinib (BGB-3111) in Participants With Previously Treated B-Cell Lymphoma Intolerant of Prior Bruton Tyrosine Kinase Inhibitor (BTKi) Treatment	Recurrence and change in severity of treatment-emergent Adverse Events (AEs) of interest.,	BeiGene	10/15/2019
A Study of NX-2127 in Adults With Relapsed/Refractory B-cell Malignancies	Number of Participants with Protocol Specified Dose-Limiting Toxicities	Nurix Therapeutics, Inc.	5/5/2021
Study to Evaluate the Efficacy and Safety of BGB-11417 in Participants With Waldenström's Macroglobulinemia	Major Response Rate (MRR) in Cohort 1, MRR is defined as the percentage of participants who achieved complete response (CR), very good partial response (VGPR), or partial response (PR), as assessed by the Independent Review Committee (IRC) up to approximately 4 years	BeiGene	2023-10
A Study of LP-168 in Participants With Relapse or Refractory Mantle Cell Lymphoma	Overall Response Rate	Guangzhou Lupeng Pharmaceutical Company LTD.	2/21/2023
Bruton's Tyrosine Kinase Inhibitor Ibrutinib as Maintenance Treatment in Elderly Patients With Primary CNS Lymphoma	PFS- progression free survival, Progression free survival, 3 years	Rabin Medical Center	2016-10
Study of LOXO-305 Versus Investigator's Choice (IdelaR or BR) in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)	To evaluate progression-free survival (PFS) of LOXO-305 monotherapy (Arm A) compared to investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B)	Loxo Oncology, Inc.	3/9/2021
Primary Progressive Multiple Sclerosis (PPMS) Study of Bruton's Tyrosine Kinase (BTK)	6 month Confirmed Disability Progression (CDP)	Sanofi	8/13/2020

Inhibitor Tolebrutinib (SAR442168)			
Study of Tirabrutinib (ONO-4059) in Patients With Primary Central Nervous System Lymphoma (PROSPECT Study)	Overall response rate (ORR) (Part A),	Ono Pharmaceutical Co. Ltd	12/29/2021
Obinutuzumab, Ibrutinib, and Venetoclax for the Treatment of Previously Untreated Stage II-IV Follicular Lymphoma	Complete response (CR) rate, Determined by positron emission tomography (PET)/computed tomography (CT) based on Cheson, Lugano classification 2014 as assessed by the investigator.	Joseph Tuscano	2/24/2021
Safety and Efficacy of KRT-232 in Combination With Acalabrutinib in Subjects With R/R DLBCL or R/R CLL	Primary Objective Phase 1b: To determine the KRT-232 maximum tolerated dose/ maximum administered dose (MTD/MAD) and recommended Phase 2 Dose (RP2D) in combination with acalabrutinib in subjects with R/R DLBCL or R/R CLL,	Kartos Therapeutics, Inc.	2/23/2021
A Study Of The Selective PKC- ζ^2 Inhibitor MS- 553	The primary objective of this study is to evaluate the safety of MS-553 in patients with CLL/SLL whose disease relapsed after or was refractory to at least one prior therapy. The primary endpoint of this study is the incidence rate of dose-limiting toxicities and treatment-emergent adverse events requiring study drug discontinuation,	MingSight Pharmaceuticals, Inc	5/25/2018
Study to Evaluate the Safety and Tolerability of TT-01488 in Patients With B-Cell Malignancies	Dose-Limiting Toxicity (DLT) of TT-01488, Safety and tolerability of TT-01488 as a single agent, Up to 28 days after first dose	TransThera Sciences (Nanjing), Inc.	2022-06
A Study to Evaluate the Efficacy and Safety of Orelabrutinib in Adult Patients With Immune Thrombocytopenia		Beijing InnoCare Pharma Tech Co., Ltd.	2/21/2022
A Study to Assess the Anti-Tumor Activity and Safety of Odronextamab in Patients With B-cell Non-Hodgkin Lymphoma That Have Been Previously Treated	ORR (FL grade 1-3a/MZL), For each of the 5 disease-specific cohorts according to the Lugano Classification of response in malignant lymphoma (Cheson, 2014) and as assessed by independent central review.	Regeneron Pharmaceuticals	11/13/2019
A Study of ICP-022 in Patients With R/R DLBCL	Overall response rate	Beijing InnoCare Pharma Tech Co., Ltd.	5/7/2020
A Study of CG-806 in Patients With Relapsed or Refractory AML or Higher-Risk MDS	Incidence of treatment-emergent adverse events of CG-806	Aptose Biosciences Inc.	10/6/2020
Bendamustine, Rituximab and Acalabrutinib in Waldenstrom's Macroglobulinemia	Best combined complete response (CR) and very good partial response (VGPR),	Sunnybrook Health Sciences Centre	3/2/2021
Acalabrutinib in Combination With Venetoclax for the	Rate of undetectable measurable residual disease (uMRD), MRD will be	Fred Hutchinson Cancer Center	5/31/2023

Treatment of Refractory or Recurrent Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma	assessed using multicolor flow cytometry (sensitivity 10^{-4}) (uMRD4) from peripheral blood (PB)., At the end of treatment (26 cycles, 1 cycle = 28 days)		
A Study of Zilovetamab Vedotin (MK-2140) as Monotherapy and in Combination in Participants With Aggressive and Indolent B-cell Malignancies (MK-2140-006)	Percentage of Participants with Adverse Event	Merck Sharp & Dohme LLC	7/21/2022
Ibrutinib and Blinatumomab in Treating Patients With Relapsed or Refractory B Acute Lymphoblastic Leukemia	Rate of CR, Up to 91 days	Brian Jonas	6/27/2017
Acalabrutinib Maintenance for the Treatment of Patients With Large B-cell Lymphoma	Permanent discontinuation of acalabrutinib, Tolerability will be determined by the number of patients who permanently discontinue acalabrutinib within 12 months from cellular therapy due to intolerance.	Jonsson Comprehensive Cancer Center	1/23/2023
Study to Evaluate the Safety and Preliminary Efficacy of Ibrutinib and Pembrolizumab in Patients With Chronic Lymphocytic Leukemia (CLL) or Mantle Cell Lymphoma (MCL)	Dose Limiting Toxicity (DLT)	Joshua Brody	7/14/2017
Zanubrutinib and Venetoclax as Initial Therapy for Chronic Lymphocytic Leukemia (CLL) With Response-based Obinutuzumab	Percentage of total patients that have achieved undetectable minimal residual disease (MRD) at cycle 16, as assessed via peripheral blood,	Weill Medical College of Cornell University	5/8/2023
Acalabrutinib and Anti-CD19 CAR T-cell Therapy for the Treatment of B-cell Lymphoma	Incidence of adverse events, Toxicity as defined by the following: grade ≥ 3 cytokine release syndrome, grade ≥ 3 neurotoxicity within 30 days of infusion of axicabtagene ciloleucel.	University of Washington	12/2/2020
An Extension Study of Long-term Efficacy, Safety and Tolerability of Remibrutinib in Chronic Spontaneous Urticaria Patients Who Completed Preceding Studies With Remibrutinib	Time to first composite event (i.e., relapse period (Epoch 1)	Novartis Pharmaceuticals	12/9/2022
A Study of Pirtobrutinib (LOXO-305) Versus Bendamustine Plus Rituximab (BR) in Untreated Patients With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)	To evaluate progression-free survival (PFS) of pirtobrutinib (Arm A) compared to bendamustine and rituximab (Arm B),	Loxo Oncology, Inc.	9/23/2021
Acalabrutinib in Combination With R-miniCHOP in Older Adults With Untreated Diffuse Large B-Cell Lymphoma	Progression-free survival (PFS)	Universität des Saarlandes	6/7/2023

A Study to Investigate the Efficacy and Safety of MS-553 in CLL/SLL	Incidence of dose limiting toxicities, 28 days	Shenzhen MingSight Relin Pharmaceuticals Co., Ltd.	4/28/2022
Study of a Triple Combination Therapy, DTRM-555, in Patients With R/R CLL or R/R Non-Hodgkin's Lymphomas	Complete Responses (CR) and Partial Responses (PR) with DTRM-555 in the five disease-specific cohorts	Zhejiang DTRM Biopharma	4/24/2020
Treatment of CD79B Mutant Relapsed/Refractory Diffuse Large B-Cell Lymphoma With Bruton Tyrosine Kinase Inhibitor Zanubrutinib	Overall response rate (ORR), Defined as the proportion of participants who achieved complete response (CR) or partial response (PR)	BeiGene	8/11/2021
A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1 Antihistamines	Change from baseline in UAS7	Novartis Pharmaceuticals	11/30/2021
Pirtobrutinib and Venetoclax in Waldenström Macroglobulinemia	Very Good Partial Response (VGPR) or Better Response Rate	Dana-Farber Cancer Institute	5/2/2023

Industry-Sponsored Studies of BTK Inhibitors that are Currently Recruiting Participants

Study Title	Primary Outcome Measures	Sponsor	Start Date
Acalabrutinib Plus RICE for Relapsed/Refractory DLBCL	Cohort A: Complete Response Rate, To estimate the confirmed complete response (CR) rate (RECIL 2017 criteria) prior to transplant in patients undergoing second-line therapy for relapsed/refractory DLBCL., 10 weeks Cohort B: Progression Free Survival	Swedish Medical Center	8/16/2019
HMPL-760 in Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma	Number of subjects with Dose Limiting Toxicities (DLTs) with relapsed/refractory B-cell non-Hodgkin's lymphoma	Hutchison Medipharma Limited	1/4/2022
Obinutuzumab and Ibrutinib as Front Line Therapy in Treating Patients With Indolent Non-Hodgkin's Lymphomas	Overall response rate in patients with newly diagnosed indolent lymphoma requiring treatment	Sidney Kimmel Cancer Center at Thomas Jefferson University	2/20/2018
Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Patients With Newly Diagnosed or Refractory/Recurrent Primary Central Nervous System Lymphoma (PCNSL) and Refractory/Recurrent Secondary Central Nervous System Lymphoma (SCNSL)	Maximum Tolerated Dose (MTD) of ibrutinib (phase I), A standard 3+3 design will be employed. Three dose levels of ibrutinib will be investigated.	Memorial Sloan Kettering Cancer Center	2014-12
Zanubrutinib, in Combination With Lenalidomide, With or Without Rituximab in Participants With Relapsed/Refractory Diffuse Large B-Cell Lymphoma	Part 1: Number of Participants Experiencing Adverse Events (AEs), Up to 48 months Part 1: Number of Participants Experiencing Severe Adverse Events (SAEs), Up to 48 months Part 2: Overall Response Rate (ORR), The proportion of participants who achieve either a partial response (PR) or complete response (CR), Up to 48 months	BeiGene	9/11/2020
Study of BTK Inhibitor LOXO-305 Versus Approved BTK Inhibitor Drugs in Patients With Mantle Cell Lymphoma (MCL)	To compare progression-free survival (PFS) of pirtobrutinib as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) in patients with previously treated mantle cell lymphoma (MCL), Assessed per Lugano criteria, Up to approximately 24 months	Loxo Oncology, Inc.	4/8/2021
Zanubrutinib and Venetoclax in CLL (ZANU-VEN)	Rate of undetectable minimal residual disease (uMRD), Assessed by flow cytometry (FC), At the end of cycle 15 (each cycle is 28 days)	Dana-Farber Cancer Institute	2/18/2022

Acalabrutinib for the Treatment of Chronic Graft Versus Host Disease	Best response (complete and partial response [CR + PR]), The composite outcome of CR and PR, calculated according to the proposed response definitions of the 2014 National Institutes of Health Consensus Conference.	Fred Hutchinson Cancer Center	12/12/2020
A Study of NX-5948 in Adults With Relapsed/Refractory B-cell Malignancies	Number of participants with protocol specified dose-limiting toxicities,	Nurix Therapeutics, Inc.	4/13/2022
Acalabrutinib and Obinutuzumab for the Treatment of Previously Untreated Follicular Lymphoma or Other Indolent Non-Hodgkin Lymphomas	Complete response (CR) rate	Emory University	9/3/2021
Acalabrutinib and Rituximab in Elderly Patients With Untreated Mantle Cell Lymphoma	Progression-free survival	Nordic Lymphoma Group	12/15/2021
Zanubrutinib (BGB-3111) in Participants With Previously Treated B-Cell Lymphoma Intolerant of Prior Bruton Tyrosine Kinase Inhibitor (BTKi) Treatment	Recurrence and change in severity of treatment-emergent Adverse Events (AEs) of interest.,	BeiGene	10/15/2019
A Study of NX-2127 in Adults With Relapsed/Refractory B-cell Malignancies	Number of Participants with Protocol Specified Dose-Limiting Toxicities	Nurix Therapeutics, Inc.	5/5/2021
Study to Evaluate the Efficacy and Safety of BGB-11417 in Participants With Waldenström's Macroglobulinemia	Major Response Rate (MRR) in Cohort 1, MRR is defined as the percentage of participants who achieved complete response (CR), very good partial response (VGPR), or partial response (PR), as assessed by the Independent Review Committee (IRC) up to approximately 4 years	BeiGene	2023-10
A Study of LP-168 in Participants With Relapse or Refractory Mantle Cell Lymphoma	Overall Response Rate	Guangzhou Lupeng Pharmaceutical Company LTD.	2/21/2023
Bruton's Tyrosine Kinase Inhibitor Ibrutinib as Maintenance Treatment in Elderly Patients With Primary CNS Lymphoma	PFS- progression free survival, Progression free survival, 3 years	Rabin Medical Center	2016-10
Study of LOXO-305 Versus Investigator's Choice (IdelaR or BR) in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)	To evaluate progression-free survival (PFS) of LOXO-305 monotherapy (Arm A) compared to investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B)	Loxo Oncology, Inc.	3/9/2021
Primary Progressive Multiple Sclerosis (PPMS) Study of Bruton's Tyrosine Kinase (BTK)	6 month Confirmed Disability Progression (CDP)	Sanofi	8/13/2020

Inhibitor Tolebrutinib (SAR442168)			
Study of Tirabrutinib (ONO-4059) in Patients With Primary Central Nervous System Lymphoma (PROSPECT Study)	Overall response rate (ORR) (Part A),	Ono Pharmaceutical Co. Ltd	12/29/2021
Obinutuzumab, Ibrutinib, and Venetoclax for the Treatment of Previously Untreated Stage II-IV Follicular Lymphoma	Complete response (CR) rate, Determined by positron emission tomography (PET)/computed tomography (CT) based on Cheson, Lugano classification 2014 as assessed by the investigator.	Joseph Tuscano	2/24/2021
Safety and Efficacy of KRT-232 in Combination With Acalabrutinib in Subjects With R/R DLBCL or R/R CLL	Primary Objective Phase 1b: To determine the KRT-232 maximum tolerated dose/ maximum administered dose (MTD/MAD) and recommended Phase 2 Dose (RP2D) in combination with acalabrutinib in subjects with R/R DLBCL or R/R CLL,	Kartos Therapeutics, Inc.	2/23/2021
A Study Of The Selective PKC- ζ^2 Inhibitor MS- 553	The primary objective of this study is to evaluate the safety of MS-553 in patients with CLL/SLL whose disease relapsed after or was refractory to at least one prior therapy. The primary endpoint of this study is the incidence rate of dose-limiting toxicities and treatment-emergent adverse events requiring study drug discontinuation,	MingSight Pharmaceuticals, Inc	5/25/2018
Study to Evaluate the Safety and Tolerability of TT-01488 in Patients With B-Cell Malignancies	Dose-Limiting Toxicity (DLT) of TT-01488, Safety and tolerability of TT-01488 as a single agent, Up to 28 days after first dose	TransThera Sciences (Nanjing), Inc.	2022-06
A Study to Evaluate the Efficacy and Safety of Orelabrutinib in Adult Patients With Immune Thrombocytopenia		Beijing InnoCare Pharma Tech Co., Ltd.	2/21/2022
A Study to Assess the Anti-Tumor Activity and Safety of Odronextamab in Patients With B-cell Non-Hodgkin Lymphoma That Have Been Previously Treated	ORR (FL grade 1-3a/MZL), For each of the 5 disease-specific cohorts according to the Lugano Classification of response in malignant lymphoma (Cheson, 2014) and as assessed by independent central review.	Regeneron Pharmaceuticals	11/13/2019
A Study of ICP-022 in Patients With R/R DLBCL	Overall response rate	Beijing InnoCare Pharma Tech Co., Ltd.	5/7/2020
A Study of CG-806 in Patients With Relapsed or Refractory AML or Higher-Risk MDS	Incidence of treatment-emergent adverse events of CG-806	Aptose Biosciences Inc.	10/6/2020
Bendamustine, Rituximab and Acalabrutinib in Waldenstrom's Macroglobulinemia	Best combined complete response (CR) and very good partial response (VGPR),	Sunnybrook Health Sciences Centre	3/2/2021
Acalabrutinib in Combination With Venetoclax for the	Rate of undetectable measurable residual disease (uMRD), MRD will be	Fred Hutchinson Cancer Center	5/31/2023

Treatment of Refractory or Recurrent Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma	assessed using multicolor flow cytometry (sensitivity 10^{-4}) (uMRD4) from peripheral blood (PB)., At the end of treatment (26 cycles, 1 cycle = 28 days)		
A Study of Zilovetamab Vedotin (MK-2140) as Monotherapy and in Combination in Participants With Aggressive and Indolent B-cell Malignancies (MK-2140-006)	Percentage of Participants with Adverse Event	Merck Sharp & Dohme LLC	7/21/2022
Ibrutinib and Blinatumomab in Treating Patients With Relapsed or Refractory B Acute Lymphoblastic Leukemia	Rate of CR, Up to 91 days	Brian Jonas	6/27/2017
Acalabrutinib Maintenance for the Treatment of Patients With Large B-cell Lymphoma	Permanent discontinuation of acalabrutinib, Tolerability will be determined by the number of patients who permanently discontinue acalabrutinib within 12 months from cellular therapy due to intolerance.	Jonsson Comprehensive Cancer Center	1/23/2023
Study to Evaluate the Safety and Preliminary Efficacy of Ibrutinib and Pembrolizumab in Patients With Chronic Lymphocytic Leukemia (CLL) or Mantle Cell Lymphoma (MCL)	Dose Limiting Toxicity (DLT)	Joshua Brody	7/14/2017
Zanubrutinib and Venetoclax as Initial Therapy for Chronic Lymphocytic Leukemia (CLL) With Response-based Obinutuzumab	Percentage of total patients that have achieved undetectable minimal residual disease (MRD) at cycle 16, as assessed via peripheral blood,	Weill Medical College of Cornell University	5/8/2023
Acalabrutinib and Anti-CD19 CAR T-cell Therapy for the Treatment of B-cell Lymphoma	Incidence of adverse events, Toxicity as defined by the following: grade ≥ 3 cytokine release syndrome, grade ≥ 3 neurotoxicity within 30 days of infusion of axicabtagene ciloleucel.	University of Washington	12/2/2020
An Extension Study of Long-term Efficacy, Safety and Tolerability of Remibrutinib in Chronic Spontaneous Urticaria Patients Who Completed Preceding Studies With Remibrutinib	Time to first composite event (i.e., relapse period (Epoch 1)	Novartis Pharmaceuticals	12/9/2022
A Study of Pirtobrutinib (LOXO-305) Versus Bendamustine Plus Rituximab (BR) in Untreated Patients With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)	To evaluate progression-free survival (PFS) of pirtobrutinib (Arm A) compared to bendamustine and rituximab (Arm B),	Loxo Oncology, Inc.	9/23/2021
Acalabrutinib in Combination With R-miniCHOP in Older Adults With Untreated Diffuse Large B-Cell Lymphoma	Progression-free survival (PFS)	Universität des Saarlandes	6/7/2023

A Study to Investigate the Efficacy and Safety of MS-553 in CLL/SLL	Incidence of dose limiting toxicities, 28 days	Shenzhen MingSight Relin Pharmaceuticals Co., Ltd.	4/28/2022
Study of a Triple Combination Therapy, DTRM-555, in Patients With R/R CLL or R/R Non-Hodgkin's Lymphomas	Complete Responses (CR) and Partial Responses (PR) with DTRM-555 in the five disease-specific cohorts	Zhejiang DTRM Biopharma	4/24/2020
Treatment of CD79B Mutant Relapsed/Refractory Diffuse Large B-Cell Lymphoma With Bruton Tyrosine Kinase Inhibitor Zanubrutinib	Overall response rate (ORR), Defined as the proportion of participants who achieved complete response (CR) or partial response (PR)	BeiGene	8/11/2021
A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1 Antihistamines	Change from baseline in UAS7	Novartis Pharmaceuticals	11/30/2021
Pirtobrutinib and Venetoclax in Waldenström Macroglobulinemia	Very Good Partial Response (VGPR) or Better Response Rate	Dana-Farber Cancer Institute	5/2/2023