Notes on Clinical Studies for Imbruvica/Ibrutinib

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

Introduction

In a separate note, Arianna Schouten has examined the research that led to the development of Ibrutinib, marked 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.

[1] Arianna Schouten, Notes on the preclinical development Imbruvica (Ibrutinib), Knowledge Ecology International, October 2, 2023.

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.

Among the findings:

- The Orphan Drug Act tax credit 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 ODTC 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
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> (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 trial for a qualifying orphan disease or condition. Beginning in 2018, the credit was reduced to 25 percent of qualifying 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

Some of the trials for Imbruvica began before receiving an FDA designated indication, or extended after an FDA approval, and in those cases 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 Kesimpta (Ofatumumab). Some of the costs associated with the Imbruvica treatment would have been covered, but all of the treatment related expenses for the Ofatumumab arm 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. Of the 396 trials, 138 have industry as the funder type. Of those 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

Downloaded data				*Interactive data*		
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 made a request to Pharmacyclics LLC (a company now owned by AbbVie), to undertake three small studies of Imbruvica 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 was at least 35 patients across Studies 1 and 2, and at least 65 patients in Study 3, or just 100 patients total.

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.