



Delays in Confirmatory Trials for Drug Applications Granted FDA’s Accelerated Approval Raise Concerns

Background

The Food and Drug Administration’s (FDA) 2021 approval of aducanumab (Aduhelm), a drug intended to treat Alzheimer’s disease raised concerns about FDA’s accelerated approval pathway.¹ Subsequently, the Office of Inspector General (OIG) announced plans to conduct evaluations of the accelerated approval pathway. This data snapshot focuses on confirmatory trials, given ongoing concerns that sponsors of drug applications granted accelerated approval fail to complete their statutorily required confirmatory trials on schedule, and concerns that FDA’s oversight of the trials is lax.²

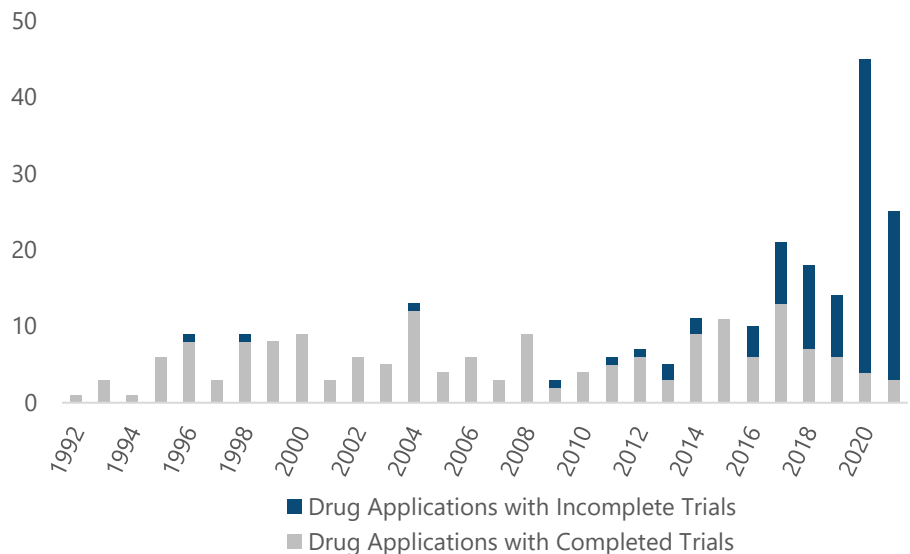
Key Takeaway
 More than one-third of accelerated approval drug applications with incomplete confirmatory trials are past their trials’ original planned completion dates, including four that are more than 5 years past those dates.

The accelerated approval pathway allows FDA to approve certain drugs that treat serious or life-threatening diseases and offer meaningful therapeutic benefit to patients over existing treatments before confirmatory trials are completed.³ To gain approval in this pathway, drug sponsors must meet the same FDA standards for safety and efficacy as traditionally approved drugs. However, they may rely on a surrogate or intermediate endpoint and do not need to show clinical benefit before approval, rather that the predicted clinical benefit is reasonably likely.⁴ Federal law grants FDA the authority to require sponsors to conduct confirmatory trials after approval to verify that the drugs provide the predicted clinical benefit.⁵ Typically, sponsors conduct such trials while these drugs are available to the public on a timeline agreed to by FDA and the sponsor.⁶

Results

Accelerated approvals have increased over time, and more than one-third of drug applications (104 of all 278) have incomplete confirmatory trials

Since the accelerated approval pathway began in 1992, drug applications granted accelerated approval by FDA’s Center for Drug Evaluation and Research (CDER) have steadily increased—with 278 approved between 1992 and December 31, 2021. One-quarter of these approvals (70 of 278) occurred in 2020 and 2021. Of all 278 drug applications granted accelerated approval from the start of this approval pathway, 104 have incomplete confirmatory trials. The 139 applications with completed trials took on average 48 months from when FDA granted them accelerated approval to when FDA deemed their trials to be completed.

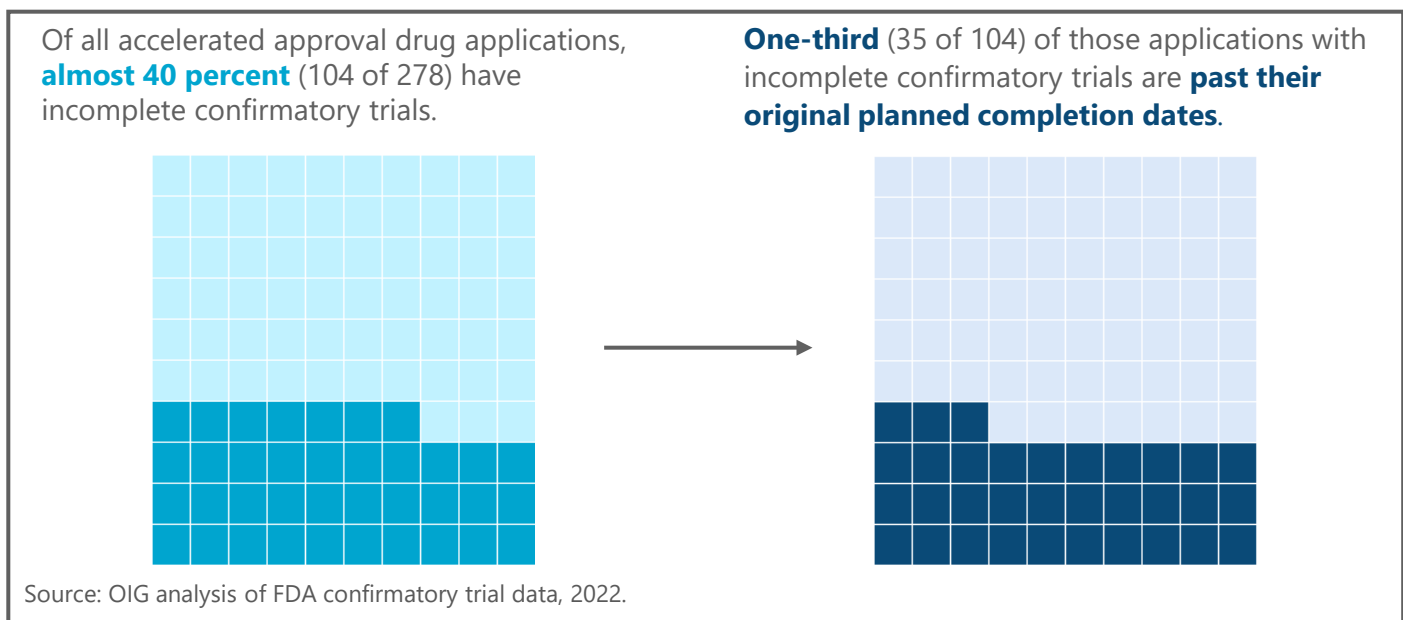


Source: OIG analysis of FDA accelerated approval data, 2022.

Thirty-four percent of accelerated approval drug applications with incomplete confirmatory trials (35 of 104) have at least one trial past its original planned completion date

Of the 104 drug applications with incomplete confirmatory trials, 34 percent of them—or 35 drug applications—are past their original planned completion dates. For these 35 drug applications, sponsors have not met the original planned completion date for 37 confirmatory trials as of May 5, 2022. On average, the 37 trials are about 20 months, or about 1.5 years, past their original planned completion dates. FDA may require multiple confirmatory trials for an application to verify the predicted clinical benefit. For example, FDA required two confirmatory trials for the application for ibrutinib (Imbruvica), which treats blood cancers. Of the 37 confirmatory trials past their original planned completion dates, 14 are delayed more than 1 year and 23 are delayed less than 1 year past their original completion dates.

Accelerated approval drug applications with incomplete confirmatory trials



Sponsors must submit annual status reports to FDA for their confirmatory trials; these reports may include information about why trials are past their original completion dates.⁷ If a sponsor changes a trial's planned dates, it must submit a revised schedule to FDA and reasons for the revision. However, FDA uses the original schedule to determine whether it considers a trial to be delayed.⁸

As a requirement of granting accelerated approval, FDA requires sponsors to commit to complete confirmatory trials with due diligence, meaning the trials must be conducted promptly.⁹ Per FDA's guidance, FDA and sponsors should agree on the design and conduct of trials, including their timelines.¹⁰ FDA staff reported that, although not a requirement, the agency generally reaches an agreement with sponsors on timelines. FDA specifies these timelines in the drug application approval letters it sends to sponsors.

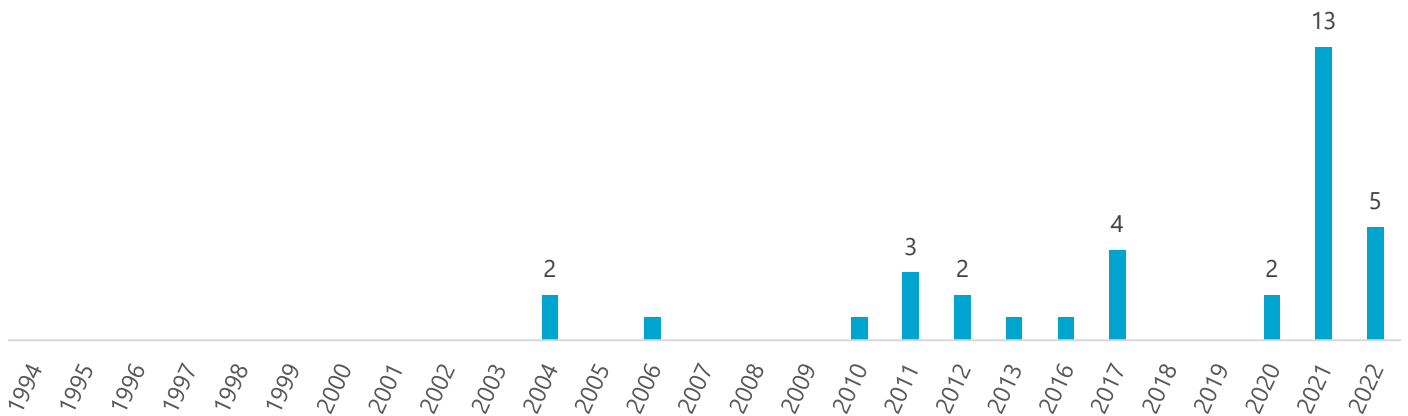
FDA and sponsors withdrew 13 percent of all accelerated approval drug applications, half of which were withdrawn since January 2021

Under certain conditions, FDA can withdraw its accelerated approval of a drug application. Those conditions include, for example, if a confirmatory trial fails to verify the predicted clinical benefit of a drug or if a sponsor does not conduct the trial promptly.¹¹ Alternatively, sponsors could request that a drug application be withdrawn or voluntarily withdraw a drug from the market.^{12, 13} Since the inception of the pathway in 1992 through May 2022, 35 of the 278 drug applications (13 percent) granted accelerated

approval have been withdrawn. Slightly more than half of these withdrawals (18) have come since January 2021.

FDA has stated that the process to withdraw a drug's approval can be cumbersome, and can take months to years, particularly if the sponsor does not voluntarily withdraw the drug from the market. For example, in December 2010, FDA announced that it would seek to remove an indication for bevacizumab (Avastin), for which it granted accelerated approval in 2008 to treat breast cancer.¹⁴ In November 2011, FDA finalized the withdrawal.¹⁵ The process to withdraw a drug application involves numerous steps, including FDA detailing the reasons for withdrawal, a withdrawal hearing if requested by the sponsor, presentation of evidence and questioning by FDA and the sponsor, and a decision by the FDA Commissioner.¹⁶ The sponsor may then petition a court to review the Commissioner's decision and request an order to stay the action pending review.¹⁷

Half of all withdrawals of accelerated approval drug applications have occurred since January 2021.

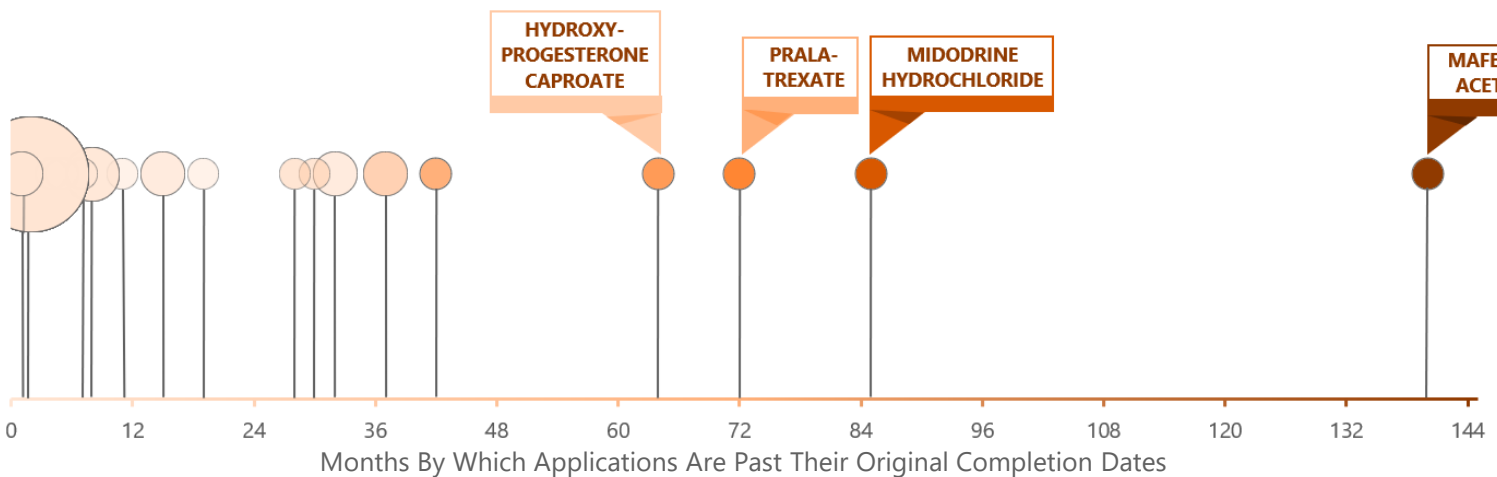


Source: OIG analysis of FDA accelerated approval data, 2022.

Four drug applications have confirmatory trials that are significantly late—ranging from more than 5 years to nearly 12 years past their original planned completion dates

Four drug applications granted accelerated approval each have confirmatory trials significantly past their original planned completion dates, overdue by at least 64 months or about 5 years. One trial for mafenide acetate (Sulfamylon) is overdue by 140 months, or nearly 12 years. Trials for two other drug applications, midodrine hydrochloride (Proamatine) and pralatrexate (Folotyn), are 85 months and 72 months late, respectively. One trial for hydroxyprogesterone caproate (Makena) is 64 months late.¹⁸

Four drug applications' trials are **more than 5 years** past their original planned completion dates.



Note: Each data point's size proportionally reflects how many drug applications are delayed by the number of months shown.
Source: OIG analysis of FDA accelerated approval data, 2022.

FDA staff cited two common challenges that affect sponsors' abilities to complete confirmatory trials promptly. These challenges also apply to three of the four drug applications with significantly late trials.



Advances in Standard of Care

Advances in the standard of care for a particular condition can improve patient outcomes, making it difficult for a drug's confirmatory trial to detect those improvements attributable to the drug.



Ownership of Drug Applications

Changes in ownership of a drug application can slow its progress. With each change in ownership, FDA must establish a working relationship with the new sponsor. The new sponsor is responsible for completing confirmatory trials and the FDA-negotiated timelines, and the transfer of ownership can cause delays in ongoing trials.

FDA is addressing, and has been for years in some cases, drug applications with the longest-delayed confirmatory trials, including by withdrawing one application

FDA staff provided details on each of the four drug applications furthest past their completion dates.

Mafenide acetate (Sulfamylon, topical antimicrobial treatment for burns, approved in 1998, trial is 140 months past the original planned date)



FDA approved the drug application through the accelerated approval pathway in the 1990s, before FDA and sponsors agreed on trial milestones and timelines. FDA staff acknowledged that the lack of trial milestones undermined their ability to hold the sponsor accountable for completing the trials promptly. Furthermore, advances in standards of care likely created challenges for the sponsor. According to FDA's Postmarketing Commitments Database, the agency is having ongoing discussions with the sponsor regarding the trial design.

Midodrine hydrochloride (Proamatine, treatment for postural hypotension, approved in 1996, trial is 85 months past the original planned date)



FDA attempted to withdraw this drug application in 2010. Media reports stated that professional organizations, health care professionals, and patients appealed to the FDA directly to keep the drug on the market.^{19, 20} Additionally, Proamatine has numerous generic alternatives, which increases market competition and may decrease the original sponsor's incentive to complete confirmatory trials with due diligence.²¹ In fact, the sponsor of Proamatine has discontinued the drug and does not currently market it.²¹ Finally, in the time since its approval, ownership of the drug application moved among three different sponsors, slowing the pace of confirmatory trials.

Pralatrexate (Folotyn, treatment for T-cell lymphoma, approved in 2009, trial is 72 months past the original planned date)



This drug application faced several common challenges since it was granted accelerated approval. Specifically, changes in the standard of care for T-cell lymphoma rendered the original planned confirmatory trial infeasible. In response, FDA and the sponsor agreed on two new trials in which the sponsor would incorporate the new standard of care. The sponsor completed the first trial in 2021 after a delay, and it submitted to FDA its protocol for the second trial, which was dependent on results from the first trial, in early 2022. Additionally, the drug application changed ownership several times, which further delayed the trials.

Hydroxyprogesterone caproate (Makena, to reduce risk of preterm birth, approved in 2011, trial is 64 months past the original planned date)



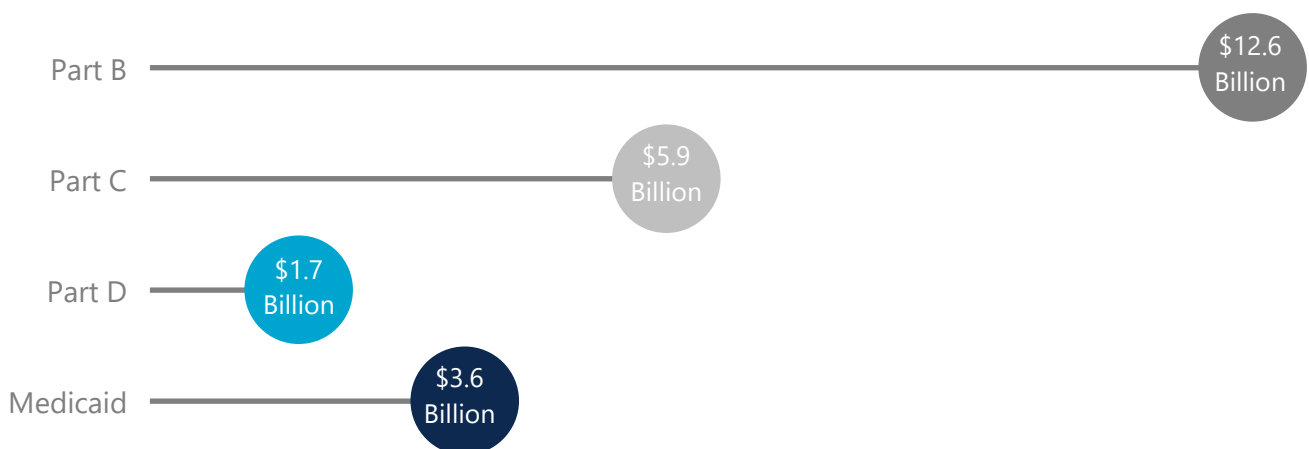
In 2020 FDA began the process of withdrawing this drug application's approval after the sponsor's 2018 trial failed to demonstrate a clinical benefit. The sponsor disagreed with CDER's action, explaining that the drug is effective in certain patient subgroups. FDA staff cited this case as an example of how lengthy and burdensome the withdrawal process may be when a sponsor disagrees with FDA's decision to withdraw a drug's approval. The sponsor has requested a hearing to discuss CDER's proposal to withdraw the approval. The current docket for the case includes numerous exchanges between CDER and the sponsor, including sponsor requests to extend deadlines, communications between CDER and the sponsor regarding technical and legal aspects of the hearing, and letters from patient advocates and physicians. A hearing is scheduled for October 2022.

Medicare and Medicaid spent more than \$18 billion from 2018 to 2021 for accelerated approval drugs with incomplete confirmatory trials past their original planned completion dates

We estimated Medicare and Medicaid spending from 2018 to 2021 for the 18 drugs that correspond to the 35 drug applications granted accelerated approval with incomplete confirmatory trials past their original planned completion dates as of May 5, 2022. We estimated that Medicare Part B and Part D spent more than \$14 billion.²² We also estimated that Medicare Part C spent nearly \$6 billion on these drugs.²³ Finally, we estimated that Medicaid spending—for both fee-for-service and managed care—for these drugs was nearly \$3.6 billion.

Due to data limitations, these estimates are conservative, and they should be understood to be the best available estimates, not exact amounts. These estimates demonstrate that Medicare and Medicaid are spending billions of dollars on drugs that have yet to verify a clinical benefit.

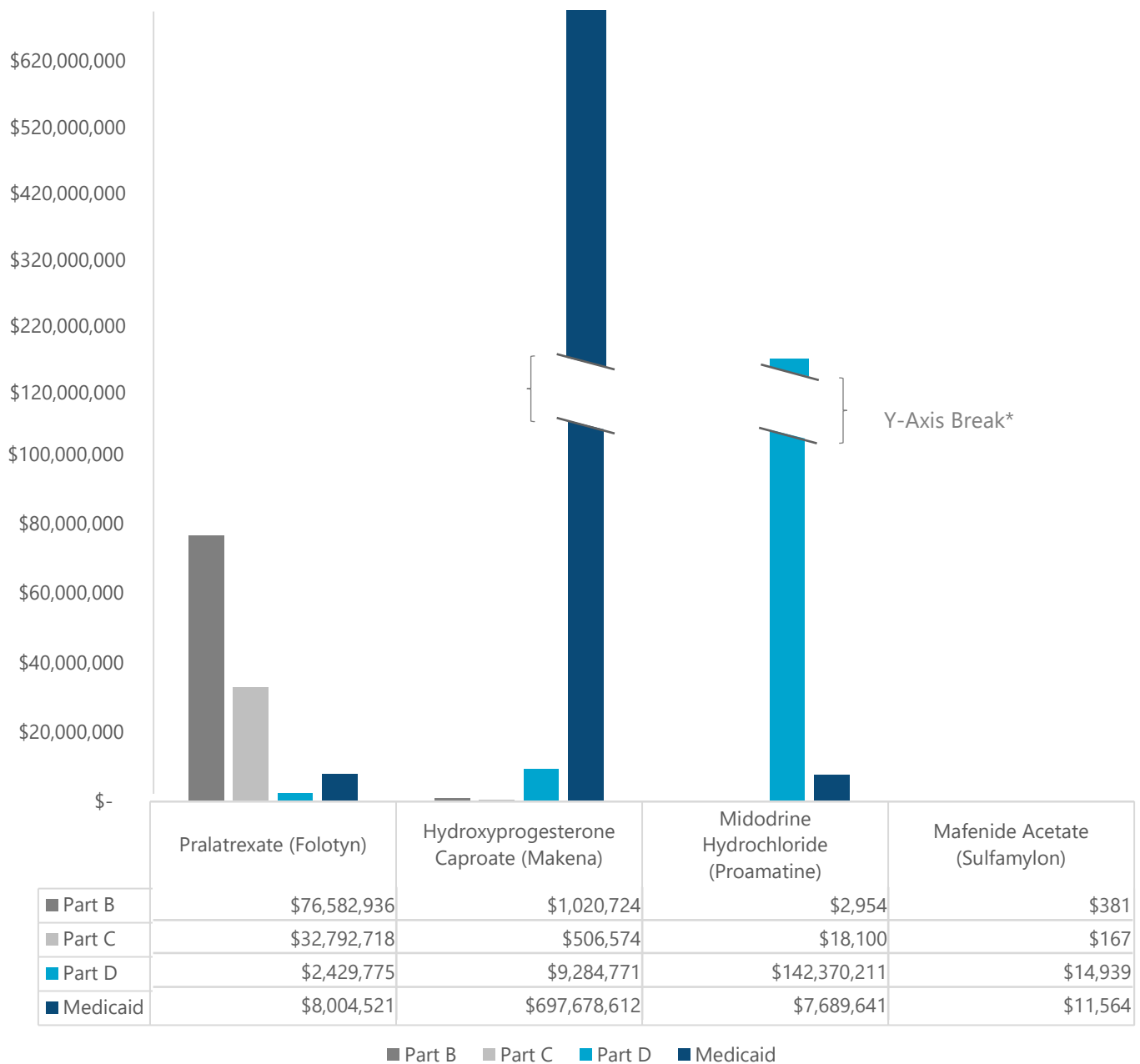
Medicare and Medicaid spent billions of dollars on drugs that have yet to verify clinical benefit.



Note: Estimated spending calculations are limited to only indications associated with accelerated approval.
Source: OIG analysis of Medicare claims and Medicaid T-MSIS data, 2022.

Of the four drugs with confirmatory trials furthest past their original planned completion dates, midodrine hydrochloride (Proamatine) had the highest Medicare Part D estimated spending at \$142 million and hydroxyprogesterone caproate (Makena) had the highest estimated Medicaid spending, nearly \$700 million.

Medicare and Medicaid spending from 2018 to 2021 for the four drugs with the most delayed confirmatory trials.



*Y-axis break utilized to display total spending for Makena and Proamatine.

Note: Estimated spending calculations are limited to only indications associated with accelerated approval.
 Source: OIG analysis of Medicare and Medicaid prescriptions filled during 2022.

Why This Matters

The accelerated approval pathway holds promise for patients who face serious illnesses where adequate treatments are lacking. In the best-case scenarios, sponsors complete confirmatory trials promptly and provide evidence to verify the drugs’ clinical benefits. In those cases, FDA enables patients to access drugs that can help them and Medicare and Medicaid to pay for effective treatments.

Why This Matters, continued

However, for a variety of reasons, sponsors do not always complete trials promptly. In fact, more than one-third of accelerated approval drug applications with incomplete confirmatory trials are past their original planned completion dates, including four that are more than 5 years past those dates. In addition, sponsors may have little incentive to complete trials promptly once they can market a drug under accelerated approval.²⁴ Likewise, patients may have little incentive to enroll in a confirmatory trial when the therapeutic treatment is already available.²⁵ Finally, FDA's process to withdraw a drug approved through the accelerated approval pathway can be lengthy and contentious. These challenges can result in drugs staying on the market—and being administered to patients—for years without the predicted clinical benefit being verified. Also, insurers—including Medicare and Medicaid—could end up paying billions of dollars for treatments that are not verified to have clinical benefit.

This data snapshot offers insights into FDA's ability to hold sponsors to their original completion schedules and to withdraw drugs with unverified clinical benefit, as well as the challenges FDA faces in doing so, even as it has approved greater numbers of drugs through the accelerated pathway in recent years. Ensuring that FDA has the tools to effectively administer the accelerated approval pathway is crucial to FDA's mission to protect the public health by ensuring the safety, efficacy, and security of human drugs and biologics.

Methodology

Assessing Confirmatory Trial Status

Our review included all accelerated approval drug applications approved by FDA's CDER, from the pathway's inception in 1992 through December 2021. We first created a subset of drug applications for which sponsors had not yet completed their required confirmatory trials, using FDA's publicly available list of accelerated approval drug applications. For those drug applications, we identified the statuses of their incomplete trials, using data from FDA's Postmarketing Commitments Database. We used the most recent publicly available data as of May 2022, following FDA's quarterly update of the database. We conducted followup with FDA to obtain missing data for six drug applications, and additional data on six other drug applications. We then calculated the length of time a trial was past its original planned completion date. We conducted structured interviews with FDA staff about four drug applications with confirmatory trials that are long overdue and discussed reasons for the delays. Additionally, for drugs with completed confirmatory trials, we calculated the elapsed time it took to complete the trials.

Estimating Medicare and Medicaid Spending

We used claims data to calculate how much Medicare Parts B, C, and D spent in 2018 through 2021 for accelerated approval drugs whose trials failed to meet their original planned completion dates. For each drug, we identified all corresponding National Drug Codes and ICD-10 diagnosis codes associated with an accelerated approval drug's indication. To limit our spending calculations to only accelerated approval indications, we reviewed prescriptions in Medicare Parts A, B, and C claims and then went back 365 days to identify diagnosis codes associated with those claims. If a drug indication involved more than just the diagnosis (e.g., specifics of treatment history or remission/relapse events), we could not identify and separate claims based on these additional elements beyond the diagnosis.

We conducted a parallel analysis using the Transformed Medicaid Statistical Information System (T-MSIS) data to calculate total Medicaid spending on accelerated approval drugs whose trials failed to meet their original planned completion dates.

Methodology, continued

Because we did not conduct a medical record review, this analysis relied on the accuracy of Parts A and B claims, Part C encounter data, Part D prescription drug event records, and T-MSIS data for drug utilization and diagnosis information. We did not determine whether all required Part C encounter records were submitted or were accurate. We also did not account for manufacturer rebates in Part D data. We did not determine whether T-MSIS data are complete or accurate. Finally, we could not identify and separate claims for off-label use.

We included spending for therapeutically equivalent generic drugs that were approved based on FDA granting accelerated approval to the original drug. Our results include claims billed during the COVID-19 pandemic and therefore may not reflect typical utilization and spending.

Limitations

We did not assess the scientific appropriateness of FDA's clinical judgment regarding any of the drugs under review. We also did not independently verify information we analyzed in FDA's Postmarketing Commitments Database, including original completion dates. Our spending calculations are estimates due to limitations with the data.

Standards

We conducted this study in accordance with the Quality Standards for Inspection and Evaluation issued by the Council of the Inspectors General on Integrity and Efficiency.

Acknowledgments

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This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston Regional Office, and Kenneth Price, Deputy Regional Inspector General.

Endnotes

¹ We refer to pharmaceutical drug products and biological products as "drugs."

² Institute for Clinical and Economic Review, *Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, And Costs*, April 2021. Accessed online at <https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway--ICER-White-Paper--April-2021.pdf> on June 23, 2022.

³ Federal Food, Drug, and Cosmetic Act (FD&C Act) § 506(c)(1)(A) and 21 CFR § 314.500.

⁴ FD&C Act § 507(e)(9) and FDA, *Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics*, May 2014. A surrogate endpoint is a marker, such as a laboratory measurement or physical sign, that is either known to predict clinical benefit or is reasonably likely to predict clinical benefit. For example, FDA may grant accelerated approval to a drug based on evidence that the drug shrinks tumors, because

Endnotes, continued

tumor shrinkage in some cancers is considered a surrogate endpoint reasonably likely to predict clinical benefit (i.e., overall survival). Similarly, an intermediate endpoint is a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit (see FD&C Act § 506(c)(1)(A)).

⁵ FD&C Act § 506(c)(2).

⁶ FDA, What Are the Different Types of Clinical Research? Accessed online at <https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-types-clinical-research> on June 23, 2022, and FDA, *Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics*, May 2014.

⁷ 21 CFR § 314.81(b)(2)(vii).

⁸ 21 CFR § 314.81(b)(2)(vii)(a)(9) and FDA, *Guidance for Industry, Reports on the Status of Postmarketing Study Commitments—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*, February 2006.

⁹ FD&C Act § 506(c)(3)(A) and FDA, *Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics*, May 2014.

¹⁰ FDA, *Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics*, May 2014.

¹¹ 21 CFR § 314.530.

¹² 21 CFR § 314.150(c).

¹³ For example, see: Fierce Pharma, “FDA: Pfizer Voluntarily Withdraws Cancer Treatment Mylotarg from U.S. Market,” June 21, 2010. Accessed online at <https://www.fiercepharma.com/pharma/fda-pfizer-voluntarily-withdraws-cancer-treatment-mylotarg-from-u-s-market> on June 23, 2022.

¹⁴ FDA, Avastin (bevacizumab) Information. Accessed online at <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/avastin-bevacizumab-information> on July 21, 2022.

¹⁵ Shari Roan, “FDA Withdraws Approval of Avastin to Treat Breast Cancer,” *Los Angeles Times*, November 18, 2011. Accessed online at <https://www.latimes.com/nation/la-xpm-2011-nov-18-la-he-avastin-breast-cancer-20111119-story.html> on July 25, 2022.

¹⁶ 21 CFR § 314.530.

¹⁷ 21 CFR § 314.530(f).

¹⁸ Although results of the confirmatory trial for hydroxyprogesterone caproate (Makena) were submitted to FDA, FDA’s assessment of the trial and CDER’s proposal to withdraw the drug’s approval will be discussed in a hearing scheduled for October 17–19, 2022.

¹⁹ Gardiner Harris, “F.D.A. Backtracks and Returns Drug to Market,” *The New York Times*, September 3, 2010. Accessed at <https://www.nytimes.com/2010/09/04/health/policy/04fda.html> on July 6, 2022.

²⁰ Sanket S. Dhruva, MD, and Rita F. Redberg, MD, MSc, “Accelerated Approval and Possible Withdrawal of Midodrine,” *JAMA*, Vol. 304, No. 19, November 17, 2010, pp. 2172-2173.

²¹ FDA, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*.

Endnotes, continued

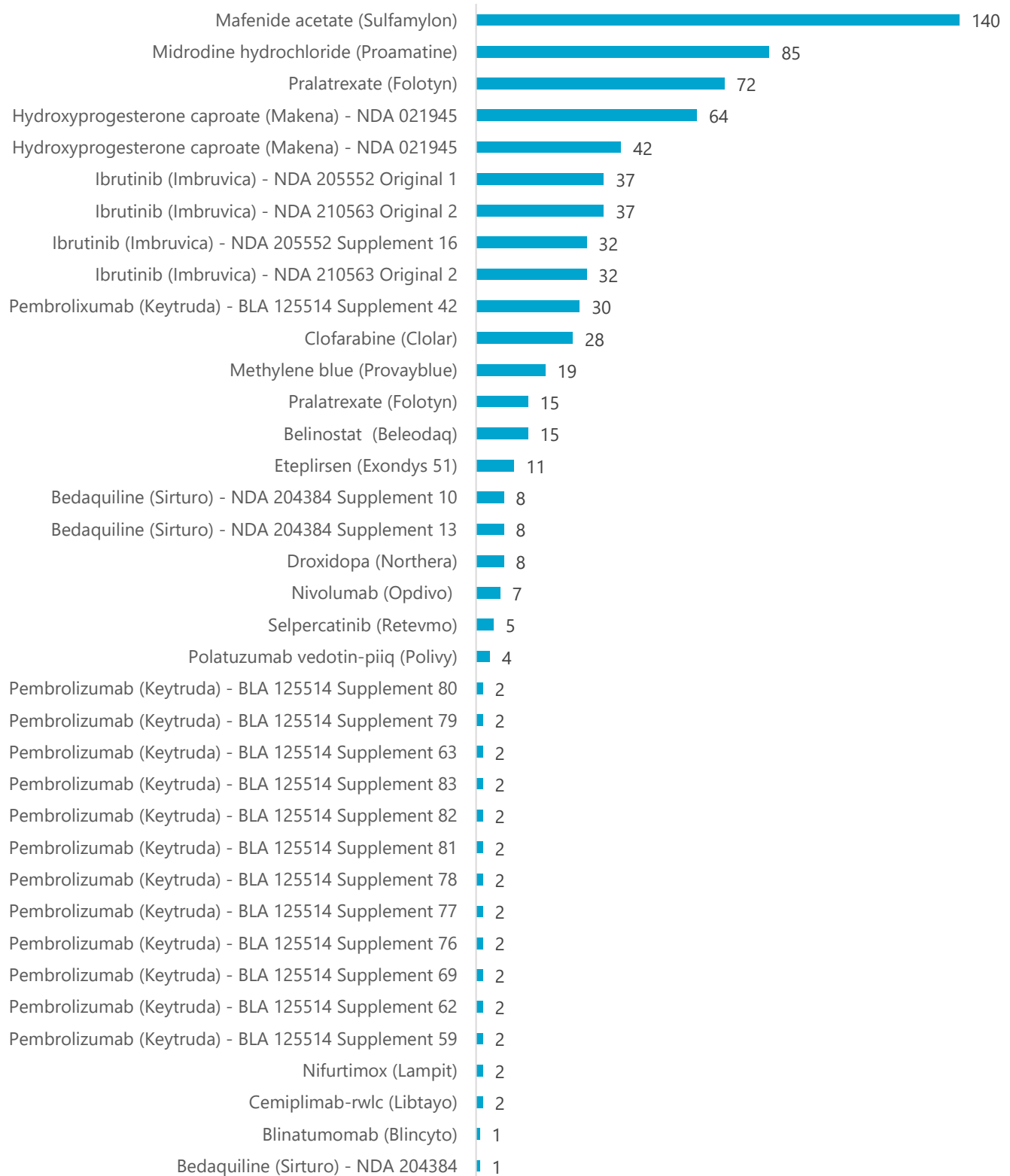
²² Drug sponsors typically submit separate applications for FDA approval of different treatment indications for the same drug. For example, FDA granted accelerated approval to numerous separate applications for pembrolizumab (Keytruda) to treat different conditions, including renal cell cancer, non-small cell lung cancer, and endometrial cancer, among others.

²³ We report Medicare Part C spending estimates separately from Parts B and D because payment fields in Part C encounter data are not always complete or accurate.

²⁴ Institute for Clinical and Economic Review, *Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, and Costs*, April 2021. Accessed online at <https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway--ICER-White-Paper--April-2021.pdf> on June 23, 2022.

²⁵ Ibid.

Appendix A: Delay of drug applications' confirmatory trials by months



Note: Sponsors may submit multiple drug applications (via either New Drug Applications/Biologic License Applications or supplemental applications) for the same drug for different indications or routes of administration. Also, FDA can require some sponsors to conduct more than one confirmatory trial for a single drug application.

Source: OIG analysis of FDA's Postmarketing Commitments Database, 2022.

Appendix B: Medicare and Medicaid utilization and spending for drugs with trials past original planned completion dates (2018–2021)

Drug Names	Utilization					Spending				
	Medicare			Medicaid		Medicare			Medicaid	
	Part B	Part C	Part D	Fee for Service	Managed Care	Part B	Part C	Part D	Fee for Service	Managed Care
Bedaquiline (Sirturo)	0	0	89	5	146	\$0	\$0	\$347,759	\$19,199	\$553,799
Belinostat (Beleodaq)	6,132	1,961	18	199	792	\$27,387,420	\$10,000,837	\$574,294	\$498,256	\$2,170,709
Blinatumomab (Blincyto)	9,647	3,477	175	2,858	5,084	\$90,554,863	\$36,347,641	\$4,003,180	\$22,200,250	\$64,954,075
Cemiplimab-rwlc (Libtayo)	17,281	6,729	173	394	598	\$162,223,766	\$60,583,482	\$1,659,843	\$1,513,769	\$3,358,076
Clofarabine (Clolar)	43	15	0	58	33	\$162,212	\$69,654	\$0	\$79,568	\$312,660
Droxidopa (Northera)	0	0	68,769	759	2,128	\$0	\$0	\$643,604,481	\$4,872,887	\$15,905,566
Eteplirsen (Exondys 51)	101	26	745	11,114	13,855	\$2,499,449	\$657,455	\$47,031,620	\$297,063,447	\$327,001,302
Hydroxyprogesterone caproate (Makena)	2,279	993	3,172	92,674	313,903	\$1,020,724	\$506,574	\$9,284,771	\$138,868,573	\$558,406,017
Ibrutinib (Imbruvica)	0	0	51,944	784	2,281	\$0	\$0	\$668,882,920	\$10,146,083	\$28,167,563
Mafenide acetate (Sulfamylon)	2	1	10	8	12	\$381	\$167	\$14,939	\$2,534	\$9,031
Methylene blue (Provayblue)	13	6	0	4	18	\$8,551	\$1,697	\$0	\$642	\$11,214
Midodrine hydrochloride (Proamatine)	419	675	1,633,413	38,496	105,359	\$2,954	\$18,100	\$142,370,211	\$1,908,508	\$5,841,505
Nifurtimox (Lampit)	0	0	0	5	0	\$0	\$0	\$0	\$1,497	\$0
Nivolumab (Opdivo)	55,531	24,640	916	4,786	7,686	\$375,526,078	\$175,786,606	\$10,196,369	\$18,250,499	\$51,054,768
Pembrolizumab (Keytruda)	1,273,846	596,626	17,186	128,707	172,510	\$11,726,796,104	\$5,494,073,858	\$174,755,065	\$561,231,656	\$1,438,827,176
Polatuzumab vedotin-piiq (Polivy)	8,637	3,886	34	386	611	\$98,101,874	\$47,172,402	\$676,965	\$2,581,187	\$6,773,639
Pralatrexate (Folotyn)	10,487	4,067	45	857	694	\$76,582,936	\$32,792,718	\$2,429,775	\$2,552,513	\$5,452,008
Selpercatinib (Retevmo)	0	0	1,282	109	373	\$0	\$0	\$22,633,101	\$1,714,196	\$6,199,495

Note: Utilization is the number of prescriptions for Medicare Part D and Medicaid prescriptions or claim line items for Medicare Parts B and C and for other Medicaid claims. Estimated spending calculations are limited to only indications associated with accelerated approval.

Source: OIG analysis of Medicare and Medicaid prescriptions filled during 2022.