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Regulatory Implications of Inadequately Designed Pimavanserin Drug Trials Published with Risk of Bias on Expedited Regulatory Approval Processes

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Abstract

The objective of this retrospective critical appraisal study was to determine if the trials submitted to the Food and Drug Administration for the expedited approval of pimavanserin was of sufficient methodological quality to ascertain its safety and efficacy. After the general metrics of the trials were assessed, the Risk of Bias 2 tool and the PRagmatic Explanatory Continuum Indicator Summary tool were employed to evaluate the risk of bias and the design suitability of the trials. This study suggests that the decision to approve pimavanserin for the treatment of Parkinson's Disease Psychosis failed to meet the threshold of evidence normally required for FDA drug applications. It also revealed serious risks of bias with the pivotal trial that was foundational to pimavanserin's delineation as a breakthrough drug, and that the safety studies were also questionably designed. These findings highlight the need to continue monitoring pimavanserin and re-examine expedited drug approval processes.

Keywords

pimavanserin, Parkinson's Disease, Risk of Bias, Clinical Trials, FDA, Breakthrough Therapy.

Summary for Lay Audience

Clinical trials provide the foundational evidence used by the Food and Drug Administration (FDA) and other regulators to assess a drug's safety and efficacy before being approved for public use. Trials that are poorly designed may lead to a biased or overly favorable interpretation of a drug's safety and efficacy and may make it difficult for regulators to determine whether a new drug is safe to be used by patients. One of these new drugs, pimavanserin, was recently approved by the FDA for the treatment of Parkinson's Disease Psychosis. It was approved under a special program that allowed it to be approved more quickly than normal, and its application also received ongoing support from the FDA. These special programs are reserved for promising drugs that are meant to treat serious conditions. Shortly after, however, serious concerns were raised by clinicians and the broader academic community about the FDA's decision to approve pimavanserin. These concerns revolved around the higher rates of drug side effects, suggesting a potential risk to patients. The goal of this study was to conduct an assessment to determine if pimavanserin's trials were of sufficient quality, and to determine if there were any potential biases that may have compromised the FDA's initial assessment. Ultimately, this assessment revealed that the trials were of insufficient length and quality based on the FDA's own standards, and that the main clinical trial that formed the basis for approval was at risk of bias. In the context of clinical trials, a risk of bias means that the clinical data may present the drug optimistically, usually as more effective, or safer than it is. This is potentially dangerous because it means that clinicians may prescribe the drug without a true understanding of its effects, and this could harm patients. These issues with pimavanserin's clinical trials suggest that there could be a risk to patients, and that it

should continue to be monitored. This project also suggests that the FDA should consider changing how their special expedited programs assess and interpret the quality of clinical trials.

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List of Abbreviations

ADL: Activities of Daily Living
ANDA: Abbreviated New Drug Application
BBW: Black Box Warnings
CGI: Clinical Global Impressions Scale
CGI-I: Clinical Global Impressions - Improvement Scale
CGI-S: Clinical Global Impressions - Severity Scale
CMAJ: Canadian Medical Association Journal
EQ-5D-5L: EuroQol-5-Dimensions-5 Levels
FAERS: FDA Adverse Event Reporting System
FDA: Food and Drug Administration
FDAAA: Food and Drug Administration Amendments Act
FDAMA: Food and Drug Administration Modernization Act of 1997
FDASIA: Food and Drug Administration Safety and Innovation Act
GAO: US Government Accountability Office
IND: Investigational New Drug
IRR: Incidence Rate Ratio
ISMP: Institute for Safe Medication Practices
MDS: Movement Disorder Society
MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale
mFSQ: Modified Functional Status Questionnaire
NDA: New Drug Application
PD: Parkinson's Disease
PDAC: Psychopharmacologic Drugs Advisory Committee
PDP: Parkinson's Disease Psychosis
PDUFA: Prescription Drug User Fee Act
PREICS-2: PRagmatic Explanatory Continuum Indicator Summary
PRO: Patient Reported Outcomes
RCT: Randomized control trial
RoB 2: Risk of Bias 2 Tool
SAPS: Scale for the Assessment of Positive Symptoms
sDNA: Supplemental New Drug Application
SCOPA-Sleep: Scales for Outcomes in Parkinson's Disease - Sleep
SCOPA-DS: Scale for outcomes in Parkinson's Disease Sleep Scale - Daytime Sleepiness
SCOPA-NS: Scale for outcomes in Parkinson's Disease Sleep Scale - Nighttime Sleep
UPDRS: Unified Parkinson's Disease Rating Scale

Chapter 1

1 Introduction

Parkinson's Disease (PD) is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra. The pathophysiological mechanisms of the disease have been extensively documented in the academic literature (Lang & Lozano, 1998). Common motor symptoms include tremors, bradykinesia, rigidity, balance, and posture impediments (Reich & Savitt, 2019). Additionally, there are non-motor symptoms such as cognitive decline (most notably related to memory and cognitive speed), speech problems (related to volume, pitch, and articulation), and psychosocial symptoms, including psychosis (Reich & Savitt, 2019). Parkinson's disease psychosis (PDP) poses a particular challenge as it can take a toll on both patients and care partners (Hermanowics & Edwards, 2015). PDP encompasses a wide variety of symptoms, including hallucinations that are usually visual in nature but that can involve other sensory domains, and delusions (Chen, 2017). While PDP may occur as a natural progression of PD, it is also a common side effect of levodopa, the primary drug intervention prescribed to manage PD (Moskovitz, Moses & Klawans, 1978), with approximately 50% of patients who take levodopa eventually developing PDP as a side effect (Hermanowics & Edwards, 2015). Although levodopa is not the sole cause of PDP, and it can manifest naturally over the disease course, research has indicated that levodopa substantially worsens PDP after one year of therapy (Friedman, 2010). Given its high prevalence, the management of PDP is important to PD patients, care partners, clinicians, and other stakeholders.

Traditional antipsychotics have been widely used to manage PDP, but their use has been linked to the progression of PD, rendering them counterproductive for symptom management (Chen, 2017). In 2016, pimavanserin tartrate (i.e., ACP-103), a selective inverse agonist of the 5-HT2A receptor marketed by Acadia Pharmaceuticals under the brand name Nuplazid, was approved by the United States Food and Drug Administration (FDA) for the management of PDP (Acadia Pharmaceuticals, 2016b).

The process by which industry-sponsored pharmaceuticals are authorized and made available to patients in the United States is a lengthy and complex process. This research and development process includes multiple pre-clinical and clinical trials with the goal of generating sufficient data to allow national regulatory authorities (e.g., FDA) to assess the safety and efficacy of the drug.

Sponsors (i.e., pharmaceutical companies) can pursue one of two submission pathways with the FDA in order to license their drug for use: standard or priority review, which relate to how long the FDA approval will take (Food and Drug Administration, 2018b). In addition to priority review, drugs may also be awarded Fast-Track, Breakthrough Therapy, and Accelerated Approval designations, which relate to the amount of support, communication, or trial design concessions that are offered by the FDA (Food and Drug Administration, 2018b). Pimavanserin's submission was approved with a Breakthrough Therapy designation within the Priority Review pathway because it is the first drug indicated specifically for the treatment of PDP (Acadia Pharmaceuticals, 2014; Acadia Pharmaceuticals, 2015).

Drug safety is less of a binary question (i.e., determining whether a drug is safe or unsafe), and more of a relative exercise in which the drug's potential therapeutic benefit is weighed with an established safety and adverse events profile. With a standard review, drugs usually go through a lengthy and extensive review by the FDA, after which they receive conditional approval for market authorization, or alternatively, are rejected. However, with the alternative and expedited regulatory review streams introduced in 1992, 1997, and 2012 by the FDA, sponsors can receive early market authorization with limited data. This means that if there are adequate justifications, sponsors can receive market authorization without comprehensive stage three clinical trials or with the use of less rigorous surrogate outcomes, amongst other concessions (Kepplinger, 2015). Such justifications are usually grounded in the view that a drug will address an unmet need, treat serious conditions, or demonstrate promising benefit over existing lines of therapy (Food and Drug Administration, 2018b; Kepplinger, 2015). There are well warranted concerns with these deviations from traditional approval mechanisms, as this means that drugs may be approved without the regularly applied checks and balances, contrary to the FDA's public messaging (Frakt, 2018; Redberg, 2015; Kim & Prasad, 2015). Determining which drugs are approved in this way depends upon interpretations of these justifications by sponsors and by the FDA.

Shortly after pimavanserin received expedited market authorization by the FDA through the Breakthrough Therapy designation and Priority Review pathway, the Institute for Safe Medicines Practices (ISMP) published concerning findings based on adverse events posted in the FDA Adverse Event Reporting System (FAERS) (Institute for Safe Medication Practices, 2017). The FAERS system aggregates adverse drug events reported

by consumers and clinicians after a drug has been approved for use (Food and Drug Administration, 2021b). Based on their preliminary investigation, the ISMP uncovered that there was a limited body of evidence to support pimavanserin's approval. They also cited emerging evidence pointing to concerning side effects not previously reported, including hallucinations, confusion, and death (Institute for Safe Medication Practices, 2017).

As of April 2021, the FDA has rejected the sponsor's (i.e., Acadia Pharmaceuticals) request to expand pimavanserin for use in dementia-related psychosis (Acadia Pharmaceuticals, 2021). Although the sponsor has stated that they stand behind Nuplazid's "robustly positive results", there is growing concern regarding pimavanserin's safety and efficacy (Acadia Pharmaceuticals, 2022a; Acadia Pharmaceuticals, 2022b Hwang et al., 2021).

This study presents a randomized control trial (RCT) critical appraisal aimed at examining: 1) the quality of the clinical trials design based on the degree of bias as determined by the RoB 2 tool; and 2) the overall body of clinical trial evidence supporting pimavanserin's approval. Doing so can help to 1) better interpret the results of pimavanserin's drug trials; 2) inform American and other regulatory decisions; and 3) improve future expedited approval practices. As it is conceptually unfeasible to provide an absolutely "objective" interpretation of trial design and data, the results of this study will be supported with validated assessment tools and will be considered in relation to the FDA's own regulatory decision. In this way, this study aims to provide a better understanding of whether there should have been other considerations, such as the

potential risk of bias in the clinical trials, when approving this potentially contentious pharmacotherapy.

The structure of this paper will first proceed with an introduction of the burden of disease for PDP and pimavanserin's research and development timeline. A description of the FDA's regulatory approval process, including the four different expedited pathways and their associated issues, will then be provided to give readers a foundational understanding of how the FDA operates. Following this introduction of the FDA, the issues associated with pimavanserin, and its approval will then be discussed. All this information will cumulate into Chapter 3, which will introduce the research question and describe the rationale of the study by emphasizing the importance of clinical trials design and rigor. The methods, and the justification for their employment, will then be described in Chapter 4. The results and their interpretation will be described in Chapter 5 and 6, respectively.

Chapter 2

2 Background

The purpose of this chapter is to provide readers with an understanding of the prevalence of PD and PDP, as well as illustrate the unmet need that pimavanserin was advertised to meet. This chapter will also provide readers with an understanding of pimavanserin's research and development timeline leading up to their regulatory approval. This will be followed by a review of the FDA's regulatory approval process, their expedited pathways, and the associated issues. Finally, pimavanserin's safety concerns which underly the need for this study, will be discussed.

2.1 Burden of Disease Surrounding Parkinson's Disease and Psychosis

PD is a debilitating neurodegenerative disease, primarily characterized by the death of dopaminergic neurons in the substantia nigra, leading to clinical symptoms including tremors, rigidity, and akinesia (Lang & Lozano, 1998). Discussions surrounding the specific pathophysiological mechanisms of PD are beyond the scope of this project, and these mechanisms have already been well documented in the literature by landmark articles like Lang & Lozano (1998). Of importance, however, is the increasing financial and healthcare burden that PD poses to patients, care partners, and clinicians. This is

important because the growing burden, if left unaddressed, may mean that the patients do not receive the appropriate treatment options.

The incidence and prevalence of PD is on the rise. Based on a 2016 systematic review and meta-analysis, the global incidence and prevalence of PD is increasing for both males and females (Hirsch et al., 2016). A separate 2016 systematic review of epidemiological data confirmed that from 1990 to 2016, Canada reported a 43.0% (95% CI: 16.5% to 67.0%) increase in the prevalence of PD and 44.5% (95% CI: 15.1% to 69%) increase in the burden of PD, measured in disability-adjusted life-years (Dorsey et al., 2018).

This increase is primarily caused by the growing aging population of Canada. Based on the Population Health Model, a series of microsimulations performed by Statistics Canada and the Public Health Agency of Canada, Canada's demographic distribution of adults 65+ will shift from 15% in 2011 to approximately 23% in 2031, substantially increasing the incidence rate of PD (Neurological Health Charities Canada et al., 2014). Combined with data from the Public Health Agency of Canada shown in *Figure 1* there is, and will continue to be, a growing impact of PD on our Canadian healthcare system as our population ages.

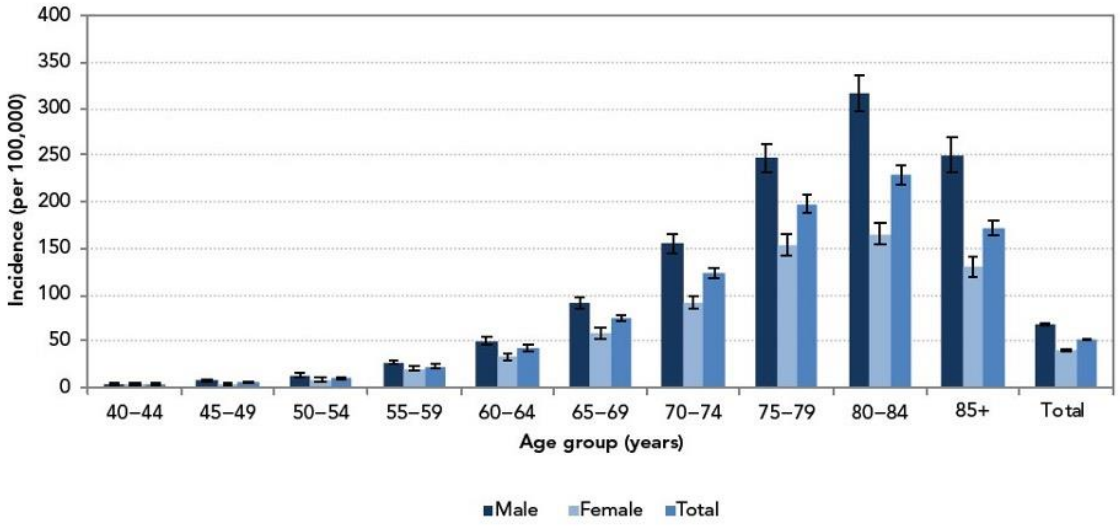

Figure 1: Incidence (per 100,000) of diagnosed parkinsonism, including PD, by sex and age group, Canada, 2013-2014 form the Public Health Agency of Canada (Neurological Health Charities Canada et al., 2014).

The burden of disease for patients, their care partners, and on the healthcare system cannot be understated. The management of PD is arduous, and involves substantial financial, emotional, and physical resources.

The most recent aggregated data from a 2007 Canadian Institute for Health Information report detailed that between 2000 and 2001, the total direct and indirect costs related to PD totaled $201.9 million and $244.9 million, respectively (Canadian Institute for Health Information, 2007). When compared to other neurological conditions, PD is the third most economically intensive neurological condition, ranking only behind epilepsy and dementias in healthcare spending (Canadian Institute for Health Information, 2007). As well, researchers from the British Columbia Administrative Data Project discovered that patients with PD have the highest prescription use (i.e., highest per capita dispensed prescription days), when compared to other neurological conditions such as

Alzheimer's Disease and Huntington's Disease, amongst others (Neurological Health Charities Canada et al., 2014). The costly prescription drug regimen used to address the symptoms of PD presents an ongoing challenge because multiple concurrent lines of therapy are often implemented to help manage both motor and non-motor symptoms.

One of the most taxing non-motor symptoms for patients and care partners is PDP, which occurs in 50% of patients over the course of their disease experience (Hermanowics & Edwards, 2015). PDP is a symptom that presents secondary to treatment with levodopa, the first-line treatment for PD, and is often used as an indicator for a diagnosis of PD (Grimes et al., 2019). However, it should also be noted that PDP can on rare occasion present without treatment with levodopa, but research has indicated that levodopa substantially worsens PDP after one year of therapy (Friedman, 2010). PDP may also cause secondary incidents such as falls, infections, and other concerns that put the patient at increased risk for hospitalization, in-home care, or permanent placement within a long-term care home (Kalilani et al., 2016).

Given the prolonged demands of care associated with PDP, there is a negative impact on care partner stress, depression, and quality of life (Schrag et al., 2006). As a result, the management of PD and PDP is sometimes concurrently supplemented with traditional antipsychotics, which are defined as drugs that primarily act on the dopaminergic system. Unfortunately, the use of these first-generation antipsychotics (i.e., dopamine receptor antagonists) may lead to the worsening of PD motor symptoms, making it counterproductive to the overall management of PD symptoms (Chen, 2017). As such, there is a strong clinical need for atypical antipsychotics (i.e., higher affinity for

serotoninergic receptors than dopaminergic receptors) that can minimize the presentation of PDP without hastening the progression of PD.

2.2 Pimavanserin A Novel Anti-Psychotic Medication

2.2.1 An Unmet Need within Existing Therapy Options

In 2016, pimavanserin tartrate (i.e., ACP-103), a selective serotonin inverse agonist of the 5-HT2A receptor marketed under the brand name Nuplazid, was approved by the FDA (Acadia Pharmaceuticals, 2016b). There are other treatment options that are currently employed by clinicians, but they are not specifically approved for use on patients with PDP (i.e., used off-label). At the time of this project, pimavanserin remains the only medication specifically approved for the treatment of PDP in the United States.

The management of PDP continues to be severely challenging. As demonstrated in a 2021 study of PD patients in the United States, the rates of initial and overall discontinuation for antipsychotics were at 38.6% and 61.4%, respectively (Pham Nguyen et al., 2021). These figures were more pronounced in patients using traditional antipsychotics with dopamine receptor blocking activity, including quetiapine, aripiprazole, risperidone, and olanzapine (Pham Nguyen et al., 2021). This discontinuation can be attributed to the worsening of parkinsonism caused by interactions with dopaminergic receptors, supporting the notion that there is a clinically unmet need for this indication (Pham Nguyen et al., 2021).

Prior to pimavanserin, clozapine was also suggested as a viable alternative for the management of PDP (Thomas & Friedman, 2010). As a non-dopaminergic antipsychotic,

clozapine demonstrated promising short-term and long-term efficacy in a limited number of published samples (Parkinson Study Group, 1999; Pollak et al., 2004). However, it is rarely used because of logistical barriers, most notably the stringent monitoring requirements that are in place because of the increased risk this medication poses for agranulocytosis, cardiovascular and respiratory events, and other adverse events (Fernandez et al., 2004).

As the first medication in the United States approved for the management of PDP advertised to be without many of the drawbacks from other first-generation antipsychotics (i.e., having dopaminergic effects), pimavanserin received interest from clinicians as it was seen as potentially serving an unmet need within existing lines of therapy (Grimes et al., 2019).

2.2.2 Research and Development Timeline

Because mandatory reporting of clinical trials was not in effect prior to September 27, 2007 (National Library of Medicine, 2020), the most complete sourcing of pimavanserin's development timeline before 2007 is contained within Acadia Pharmaceuticals' patent filing to the World Intellectual Property Organization, filed in November 2008 (Vanover et al., 2008). Within the patent filing, there is mention of two studies, one Phase 1 and one Phase 2 study to investigate the pharmacokinetic properties of pimavanserin, along with dose-response studies with fasted and fed healthy human subjects without PDP (Vanover et al., 2008).

In addition to these two studies, a variety of Phase 2 and 3 studies were conducted between March 2004 to March 2008 before the patent was filed in November 2008. These

were made public in the clinicaltrials.gov database. These studies include a Phase 2 open label safety study, a Phase 2 interventional study, a Phase 3 safety and tolerability study, and two additional Phase 3 safety and efficacy studies. An aggregated list of Acadia Pharmaceutical initiated or adjacent trials for pimavanserin, spanning 2004 to 2024, has been included in *Table 1*.

Study Identifier (NCT /ACP)	**Study Title**	**Phase**	**N**	**Start**	**Completed**	**Results Posted**	**Completed**
NCT01518309 ACP-103-010	An Open-label Safety Study of Pimavanserin in Parkinson's Disease Patients	Phase 2	39	November 17, 2004	May 2, 2013	November 23, 2020	Yes
NCT00087542 ACP-103-006	Treatment of Hallucinosis/ Psychosis in Parkinson's Disease by an Investigational Drug	Phase 2	60	March 2004	December 2005	N/A	Yes
NCT03482882 ACP-103-048	Safety and Efficacy of Pimavanserin in Adults With Parkinson's Disease and Depression	Phase 2	47	March 9 2018	July 9, 2019	August 31, 2020	Yes
NCT00550238 ACP-103-015	A Study of the Safety and Tolerability of Pimavanserin (ACP-103) in Patients With Parkinson's Disease Psychosis	Phase 3	459	July 2007	May 30, 2018	June 24, 2019	Yes
NCT01174004 ACP-103-020	Study of the Safety and Efficacy of Pimavanserin in Patients With Parkinson's Disease Psychosis	Phase 3	199	July 2010	November 2012	March 26, 2014	Yes
NCT00477672 ACP-103-012	A Study of the Safety and Efficacy of Pimavanserin (ACP-103) in Patients With Parkinson's Disease Psychosis	Phase 3	298	June 2007	June 2009	March 26, 2014	Yes

NCT00658567 ACP-103-014	A Study of Safety and Efficacy of Pimavanserin (ACP-103) in Patients With Parkinson's Disease Psychosis	Phase 3	123	March 2008	December 2009	September 9, 2014	Yes
NCT04292223 ACP-103-063	Open-Label Study With Pimavanserin on Activities of Daily Living in Subjects With Parkinson's Disease Psychosis	Phase 4	29	February 10, 2020	April 26, 2022	N/A	Yes
Terminated / No Updates							
NCT02762591 ACP-103-036	Expanded Access of Pimavanserin for Patients With PD Psychosis					N/A	Approved for Marketing
NCT03152292 ACP-NIS-001	The INSYTE (Management of Parkinson's Disease Psychosis in Actual Practice) Study		764	March 30, 2017	March 8, 2021	N/A	Terminated

Table 1: Full list of Acadia Pharmaceuticals initiated or adjacent trials for pimavanserin from the U.S. National Library of Medicine database.

In September 2014, the sponsor Acadia Pharmaceuticals received a Breakthrough Therapy designation for pimavanserin, allowing for special expedited review and preferential access to FDA supports (Acadia Pharmaceuticals, 2014). The following year, in September 2015, Acadia Pharmaceuticals submitted a New Drug Application (NDA) to the FDA, in which they sought regulatory approval under the Priority Review pathway (Acadia Pharmaceuticals, 2015). In November 2015, the FDA approved pimavanserin for the priority review pathway, shortening the expected review time by 40%, from 10 months to 6 months (Acadia Pharmaceuticals, 2015).

During the FDA's internal review process, Paul Andreason, a member of the FDA's Division of Psychiatry Products and the designated medical reviewer for the pimavanserin submission, completed his extensive 173-page review of pimavanserin, where he explicitly provided a strong "do-not-approve" recommendation, citing "unacceptably increased, drug- related, safety risk of mortality and serious morbidity" (Andreason, 2016). Despite his review, which was released internally in February 2016, the FDA's Psychopharmacologic Drugs Advisory Committee (PDAC) voted 12 to 2 in support of pimavanserin's efficacy and safety profile, leading to pimavanserin's regulatory approval in April 2016 (Acadia Pharmaceuticals, 2016a). Pimavanserin was approved based primarily on efficacy data from one clinical study (NCT01174004, ACP-103-020) that had a sample size of 199, along with sparse safety data from previous and concurrent trials (Food and Drug Administration, 2016). The decision to approve pimavanserin caused internal division amongst key reviewers within the FDA (Mathis et al., 2017), and sparked a broader public investigation and conversation about pimavanserin's safety (Ellis & Hicken, 2018).

2.2.3 Expansion into Additional Indications

Acadia Pharmaceuticals is currently (as of 17 April 2023) advocating for expanded regulatory approval of pimavanserin for dementia-related psychosis and Alzheimer's disease psychosis (Acadia Pharmaceuticals, 2022c; Soogrim et al., 2021). In September 2019, Acadia Pharmaceuticals stopped their pivotal HARMONY trial for the management of dementia-related psychosis, citing that they had achieved the primary endpoint for the treatment of dementia-related psychosis (Tariot et al., 2021). In June 2022, the FDA's PDAC committee voted 9 to 3 against pimavanesrin's efficacy and safety profile for the treatment of Alzheimer's disease psychosis (Acadia Pharmaceuticals, 2022a). In August 2022, the FDA rejected Acadia Pharmaceutical's Supplemental New Drug Application (sNDA) for the treatment of Alzheimer's disease psychosis (Acadia Pharmaceuticals, 2022b). Although this is not specifically related to PDP, these evolving updates may provide contextual insight into FDA's changing attitude towards pimavanserin. Without additional insight into the FDA's specific reasoning, it is difficult to pinpoint the exact reason behind this changing attitude towards pimavanserin as a Breakthrough Therapy product. It may be caused by a combination of factors, including response to negative press, a more careful examination of the clinical data, or other variables that have not yet been made public.

Figure 2 presents a timeline that illustrates pimavanserin's development and eventual market approval by the FDA. The data was amalgamated from a variety of sources, including US Library of Medicine clinical trials database and patent filings (U.S. National Library of Medicine, 2005; U.S. National Library of Medicine, 2014; U.S. National Library of Medicine, 2017a; U.S. National Library of Medicine, 2017b; U.S.

National Library of Medicine, 2019; U.S. National Library of Medicine, 2020a; U.S. National Library of Medicine, 2022; Vanover et al., 2008).

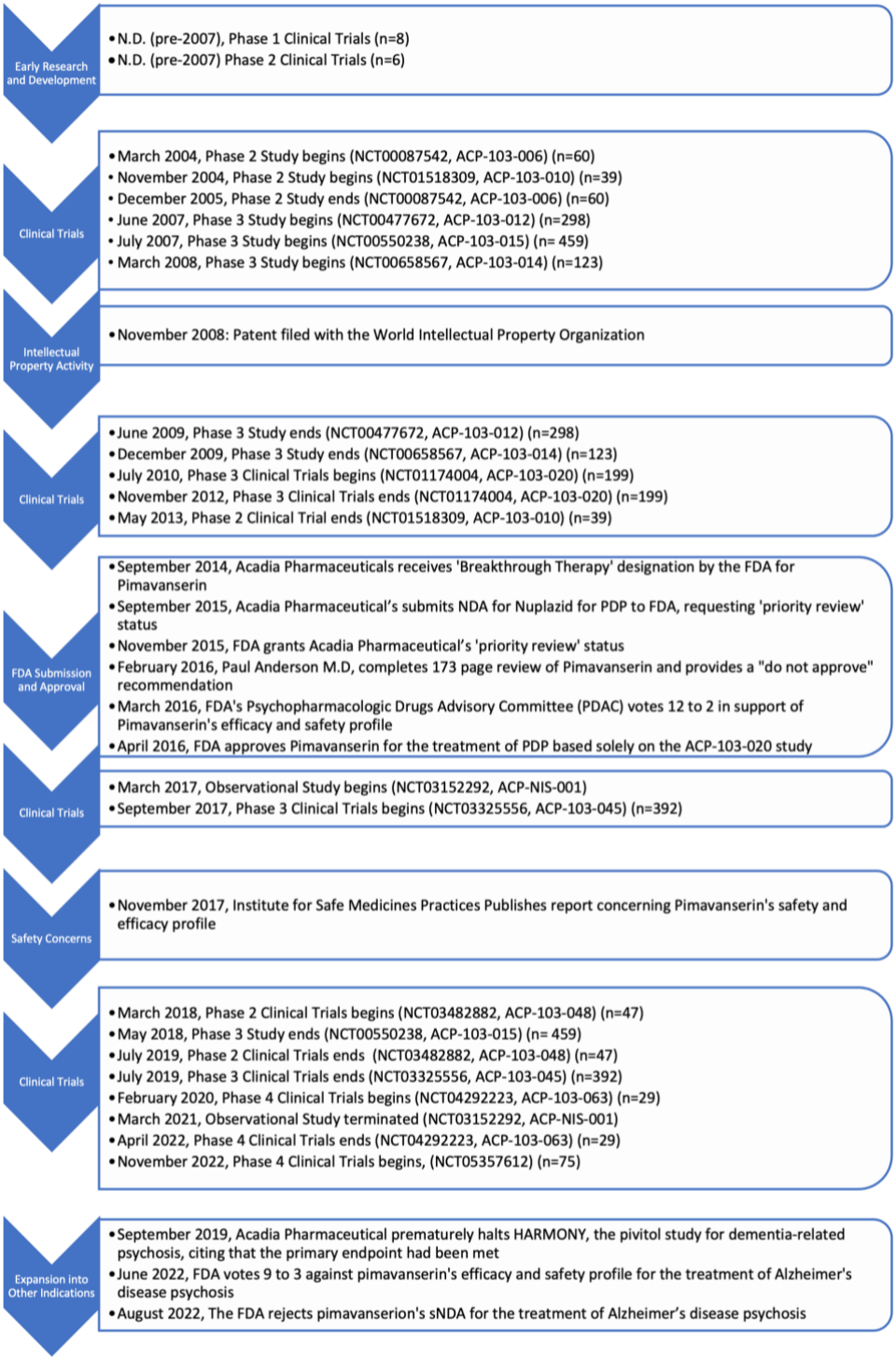

Figure 2: Timeline of pimavanserin's research, development, and regulatory approval.

2.3 FDA Regulation, Expedited Approvals, and Associated Ethical Concerns

2.3.1 Regulatory Landscape, Investigational New Drug Applications, and New Drug Applications

The drug approval process is lengthy, born out of numerous safety incidents that prompted the US government to act on threats to consumer and patient safety. Most notably, the Elixir Sulfanilamide incident of 1937 and the Thalidomide incident of the 1950s and 1960s, amongst other tragedies, prompted regulatory and policy changes (Food and Drug Administration, 2019). A timeline of these developments has been included as *Figure 3*.

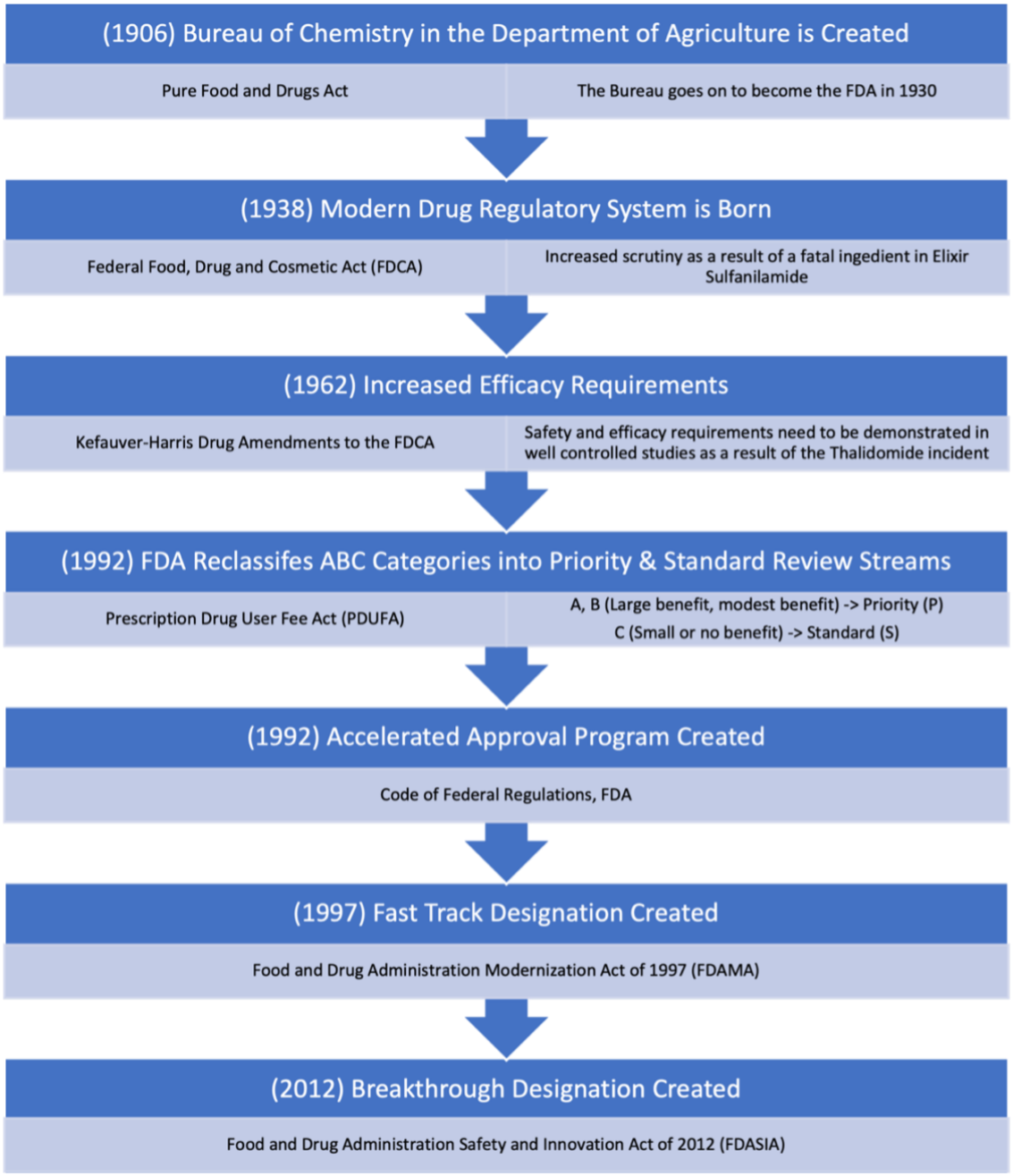

Figure 3: Brief history of FDA regulatory and policy changes.

For a drug to obtain regulatory approval in the United States, investigators must first conduct in-vitro or computational studies for potential new compounds. When a promising compound is identified, sponsors submit an Investigational New Drug (IND) application to the FDA to seek approval for shipping novel drug compounds across state lines for clinical trials (Food and Drug Administration, 2022d). Once sponsors believe they have sufficient evidence from Phase 1-3 clinical trials to undergo the FDA's review process, they submit an NDA (Food and Drug Administration, 2022b). Upon approval, drugs can be marketed in the United States.

Several NDA variations exist based on the type of drug and their stage in marketing. For drugs that are already approved, sponsors may submit a sNDA to expand the number of indications, labelling, ingredients, or packaging, as with pimavanserin's attempted expansion into dementia-related psychosis (Food and Drug Administration, 2017). With generic drugs, sponsors submit an abbreviated NDA (ANDA) to the FDA without the need for animal or human clinical studies (Food and Drug Administration, 2022a). For biologic products, sponsors are required to submit a Biologic License Application as per the regulations stated in the Public Health Service Act (Food and Drug Administration, 2020).

Once drug approval applications are submitted, the application undergoes review by the FDA's review team. This process includes individual assessments by each member of the review committee, who possess technical and clinical expertise (Food and Drug Administration, 2018a). This initial review will also include routine visits to the clinical sites by FDA inspectors to look for "evidence of fabrication, manipulation, or withholding of data" (Food and Drug Administration, 2018a). Additional review support

can be provided by expert review committees, as with the PDAC in pimavanserin's regulatory submission (Food and Drug Administration, 2018a). Once each member of the FDA's review committee has completed their assessment, an aggregated recommendation is issued by the division director based on a risk-benefit assessment. However, there are no specific documents outlining the exact process that guide this risk-benefit assessment and may depend on the individual expertise of the director in charge of that disease space.

Critics have also cited that these decision-making processes are not transparent enough, especially when it comes to drugs that are denied for market authorization (Sharfstein et al., 2017). In cases where drugs are denied for regulatory approval, information is often withheld from the public because much of the clinical data is considered proprietary (Sharfstein et al., 2017). As such, the clinical data and specific reasoning within the appraisal process is often kept private between the FDA and the sponsor. These criticism and proposed recommendations for increased transparency within FDA processes has been extensively explored by Sharfstein et al. (2017) and should be referenced. *Figure 4* has been included from the FDA's Center for Drug Evaluation and Research to illustrate an example of a drug's progression through the different regulatory approval stages.

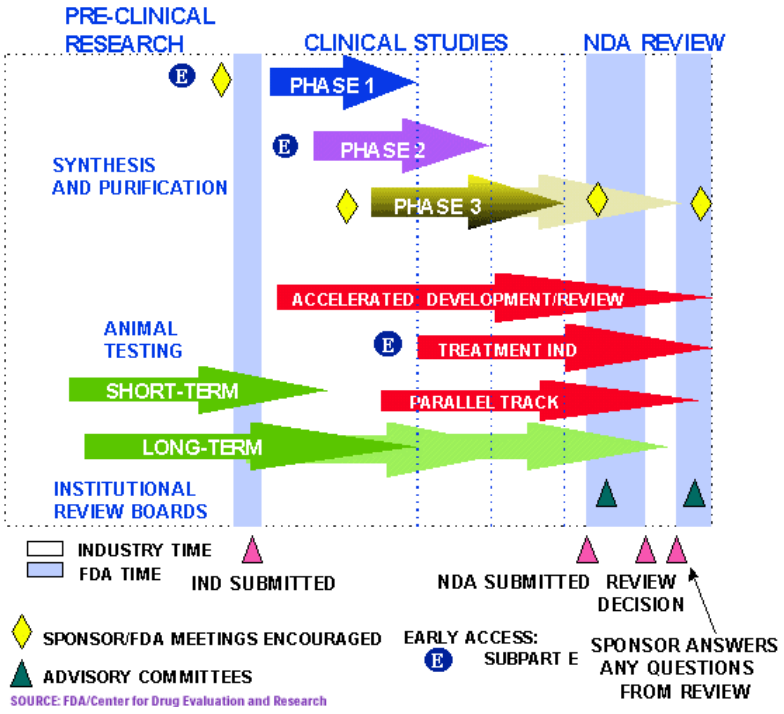

Figure 4: Illustration the regulatory approval process (Food and Drug Administration, 2022c).

2.3.2 Expedited Approvals

For drugs that treat a serious condition, satisfy an unmet need, or demonstrate superiority over existing treatment options, the FDA created four expedited pathways as part of ongoing policy changes to bring promising therapies more quickly to patients. These four are the Priority Review pathway, the Breakthrough Therapy designation, the Fast Track designation, and the Accelerated Approval designation (Food and Drug Administration, 2018b). These changes were originally born out of the need to expedite the regulatory process to better manage the novel AIDS/HIV pandemic of the 1980s (Kepplinger, 2015).

2.3.2.1 Priority Review Designation

Prior to the 1992 changes, drugs were prioritized for review under the A, B, and C potential therapeutic effect classifications, which denoted important, modest, or limited therapeutic benefit, respectively (Kepplinger, 2015). This classification system would be revised as part of the Prescription Drug User Fee Act (PDUFA), which re-classified the A and B classifications into Priority Review (P), and C designation into Standard Review (Kepplinger, 2015). The original top priority (AA), and subpar drug (E) were retained from earlier policy changes (Kepplinger, 2015). The PDUFA allowed the FDA to levy new fees as part of sponsor submissions to hire new staff to meet the shortened review periods (Kepplinger, 2015).

With these new changes, standard reviews were now conducted in 10 months and priority reviews conducted in only 6 months (Food and Drug Administration, 2018a). Priority reviews are granted if, in the view of the FDA, the candidate drug provides superior treatment, diagnostic, or prevention capabilities (Food and Drug Administration, 2018a). This can be demonstrated by evidence of increased efficacy, demonstration of reduction in adverse reactions, improved compliance rates amongst patients, or improved safety and efficacy within new subpopulations (Food and Drug Administration, 2018a).

2.3.2.2 Accelerated Approval Designation

As part of ongoing changes during this time, the Code of Federal Regulations pertaining to the FDA were also amended (Kepplinger, 2015). These new changes allowed drugs that were indicated for the treatment of serious conditions with an existing

unmet need to submit an NDA using unvalidated or novel surrogate endpoints, yielding immature data in lieu of more mature data (Food and Drug Administration, 2018a). The definition of ‘unmet need’ is only formally defined by the FDA within the Fast-Track designation and not the Accelerated Approval designation. The formal definition of unmet need is introduced under 2.3.2.3.

2.3.2.3 Fast-Track Designation

In 1997, as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), the Fast-Track designation was created (Kepplinger, 2015). Drugs that demonstrate an unmet need and are meant to treat serious conditions, especially those conditions that would deteriorate if left untreated, would be eligible for this designation (Food and Drug Administration, 2018a). Serious conditions are a matter of judgement and not formally defined by the FDA (Food and Drug Administration, 2018a). Unmet need is defined as a drug that shows superior effectiveness, avoids serious side effects, improves diagnosis leading to improved outcomes, decreases toxicity that would otherwise lead to treatment discontinuation, or addresses an emerging or anticipated public health need (Food and Drug Administration, 2018a).

As part of this Fast-Track designation, sponsors are eligible for more frequent meetings with FDA regulators who would aid with their submissions, and also makes them eligible for the Priority Review pathway and Accelerated Approval designation, as well as a rolling review, which enables partial NDA submissions in lieu of a complete NDA submission (Food and Drug Administration, 2018a). One of the most notable drugs to receive the fast-track designation was Vioxx, a selective nonsteroidal anti-

inflammatory drug that would go on to be recalled, but not before it caused substantial harm to patients, in the form of 88,000-140,000 additional cases of serious coronary heart disease in the United States (CMAJ, 2005; Graham et al., 2005). Subpoenaed documents later revealed that the sponsor (Merck) was aware of these risks during drug development and marketing (Whitstock, 2017).

2.3.2.4 Breakthrough Designation

In 2012, through the Food and Drug Administration Safety and Innovation Act (FDASIA) passed by Congress, the Breakthrough Therapy designation was created in part from pressure exerted by the Brookings Institute and Friends of Cancer Research; think tanks that are both partially funded by pharmaceutical companies (Brookings Institute, 2021; Friends of Cancer Research, 2020). The designation, as defined by the FDA,

> "… is intended to facilitate and expedite the development of those drugs that receive designation and involves a resource commitment from FDA to provide early and frequent advice, conduct multidisciplinary meetings involving senior managers, and when appropriate, expedite the review of resultant marketing applications" (U.S. Department of Health and Human Service et al., 2022).

Once granted approval through this new designation, drugs are conferred all the benefits of the Fast-Track designation, in addition to intensive guidance from the FDA, and designated support from senior FDA managers (Food and Drug Administration, 2018a). After receiving this designation, sponsors try to leverage these benefits and seek regulatory approval. Pimavanserin indicated for the treatment of both PDP and dementia-

related psychosis was supported through this designation, concurrent with the Priority Review pathway.

2.3.3 Summary of the Four Expedited Mechanisms

Although the requirements to engage the four mechanisms are similar in that they all need to satisfy an unmet need or a serious medical condition, they are four distinct mechanisms with tiered benefits, with the Breakthrough Therapy designation conferring the most support from the FDA, as illustrated in *Figure 5*. A table summarizing the key requirements and features has also been included below as *Table 2*. An in-depth analysis of these pathways is beyond the scope of this project, but the work of Kepplinger (2015) and Cox et al. (2020) can be referenced for further details.

Figure 5: Hierarchy of benefits for the expedited review mechanisms.

Mechanism (Year Introduced)	**FDA Definition**	**Origin of Request /Stage of Request**	**Requirements**	**Features**
Priority Review Pathway (1992)	"A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications" (Food and Drug Administration, 2018a).	-Determined by the FDA after receiving NDA from sponsor -Post-NDA	-Evidence under review should *demonstrate significant safety and efficacy* compared to existing treatment, diagnosis, or prevention options	- Reduces the review period by 40%, from 10 to 6 months
Accelerated Approval Designation (1992)	"…in 1992 FDA instituted the Accelerated Approval regulations. These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. Using a surrogate endpoint enabled the FDA to approve these drugs faster" (Food and Drug Administration, 2018a).	-Discussed in advance between the FDA and the sponsor -Prior to clinical studies	-Drug must demonstrate an effect on the surrogate or intermediate outcome -Sponsor must demonstrate that the surrogate or intermediate outcome can predict the primary clinical outcome -Post-market confirmatory Stage 4 trials must be conducted	-Allows for the use of a surrogate or intermediate endpoint instead of a primary clinical endpoint

Fast-Track Designation (1997)	"Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions" (Food and Drug Administration, 2018a).	-Requested by the sponsor -Pre-IND and anytime thereafter	-Early-stage application: Demonstrate benefit using nonclinical mechanism or early pharmacological data -Late-stage application: Clinical data supporting *potential for improvement* over existing lines of therapy	-More frequent meetings with the FDA -More frequent communications with the FDA
Breakthrough Therapy Designation (2012)	"Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)" (Food and Drug Administration, 2018a).	-Requested by the sponsor -Pre-IND and anytime thereafter	-Early clinical evidence demonstrates *substantial* improvement on a *clinical endpoint*	-All "fast-track" features -Support from senior FDA managers -Intensive drug development guidance early in the development process

Table 2: Summary of the four expedited approval mechanisms, their official definition, origin of request, requirements, and benefits.

2.3.4 Existing Issues and Past Recalls with Expedited Approvals

These mechanisms were created with the express purpose of hastening the drug approval process. Despite the FDA's prescribed messaging that expedited drugs undergo the same rigorous review process as standard reviews, the evidence from the literature presented in the following sections challenges this view.

It should be noted that the purpose of highlighting the shortfalls of expedited approvals is not an attack on regulatory processes as a whole. It would be unfeasible to develop a regulatory system where 100% of drugs are completely safe. So, although regulatory processes are not without their faults, the issues being illustrated here are specifically with expedited approvals, and the regulatory concessions granted by the FDA, that pose an additional level of risk that may not be warranted for patients. While patients and clinicians might accept a greater risk to bring a novel therapy more quickly to market, reasonable disagreement exists as to how much risk should be tolerated.

As mentioned previously, Vioxx is a landmark example of a drug that was approved using these pathways, which has caused substantial harm to patients, their families, communities, and for healthcare systems. Vioxx, amongst other examples, were approved with inadequate clinical trial data and inaccurate marketing strategies, leading to inadequately studied products being tested on the public (CMAJ, 2005).

Several issues have been uncovered while conducting the background research for this project. These issues within the literature concerning these four expedited approval mechanisms include: 1) the lack of confirmatory trials leading to high rates of market

withdrawal (Mahase, 2021); 2) the increased risk of black box warnings (Liang, 2002); and 3) the poor reliance on surrogate outcomes (Lenzer & Brownlee, 2021).

2.3.4.1 Lack of Confirmatory Trials and Untimely Market Withdrawal

When drugs receive expedited approval, sponsors are expected to conduct Phase 4 confirmatory post-market studies to study the real-world consequences for patients. A review conducted by Mahase (2021), however, found that of the 253 drugs approved by the accelerated streams over a 28-year period since 1992, 112 (44.27%) expedited drugs were not confirmed as clinically effective using Phase 4 studies. Mahase (2021) further notes that of those 112 drugs, many remained on the market despite poor effectiveness, with only 16 having been withdrawn, and one ineffective drug remaining on the market for as long as 12 years. More than two thirds of the drugs that had been on the market for over five years had not conducted confirmatory trials. As well, many of the sponsors failed to provide a response upon investigation by the authors of that review as to why confirmatory trials had not been conducted (Mahase, 2021).

Additional research with expedited oncology drugs has discovered that long-term studies after receiving market authorization are only performed in two thirds of cases and are usually delayed by an average of four years after market authorization (Johnson et al., 2011). In essence, this means that sponsors are not upholding their duty to conduct confirmatory trials in a timely manner; ineffective and possibly dangerous drugs are remaining on the market for years, putting patients at risk.

Both Mahase (2021) and Johnson et al. (2011) echoed an earlier 2015 study conducted by the US Government Accountability Office (GAO), which found that sponsors were submitting and receiving approval from the FDA for a large number of applications under the Fast-Track and Breakthrough Therapy designations (US Government Accountability Office, 2015). For the Fast-Track designation applications submitted between 2006 and 2014, 525 of 772 (68.00%) requests were approved. For the Breakthrough Therapy designation applications submitted between 2012 and 2014, 71 of 225 (31.56%) requests were approved (US Government Accountability Office, 2015). Despite a large volume of expedited approvals, the GAO report concluded that "[t]he FDA lacks reliable, readily accessible data on tracked safety issues and post-market studies needed to meet certain post-market safety reporting responsibilities and to conduct systematic oversight" (US Government Accountability Office, 2015). Combined with the apparent unwillingness of sponsors to fulfill their post-market obligations, this lack of systemic oversight could put patients at risk.

While the FDA and sponsors share responsibility for these issues, it is important to recognize that the lack of adequate post-market surveillance is particularly dangerous because it shifts the onus of drug safety from a pre-regulatory approval setting (i.e., clinical trials) to a post-market surveillance setting (i.e., on the market).

Ultimately, Mahase (2021), Johnson et al. (2011), and the report from the U.S Government Accountability Office illustrate the first of many problems, which is that the FDA has fostered a regulatory environment that approves an increasing volume of drugs under expedited pathways without ensuring proper post-market surveillance mechanisms

are in place to monitor safety. The remaining problems will be discussed in section 2.3.4.2 and section 2.3.4.3.

2.3.4.2 Increased Utilization of Black Box Warnings, Withdrawals, and Safety Communications

Black box warnings (BBW) are the most serious warning that can be prescribed by the FDA (Liang, 2002). These warnings, if assigned by the FDA, mandate sponsors to provide restrictions and warning of serious injury or death on all advertising, labelling, and promotional products associated with the drug product (Liang, 2002). Drugs that are part of accelerated approvals and indicated for psychiatric conditions were more likely to have BBWs, risk of safety events, product withdrawals, and safety communications (Downing et al., 2017). The increased risk of post-market safety events is quantifiable with accelerated approvals having an Incidence Rate Ratio (IRR) = 2.20 (95% CI, 1.15-4.21; P = .02), and psychiatric indications having an IRR = 3.78; (95% CI, 1.77-8.06; P < .001) (Downing et al., 2017).

Although these labels should be meant to alert prescribers of the potential risks, research has suggested that compliance with boxed warnings have mixed effects on prescribing patterns (Wagner et al., 2006), and in certain patient cases, no impact at all (Soumerai et al., 1987).

In a 2006 retrospective study of 929,958 health plan members in the United States, it was discovered that 41.7% of patients received a drug with a BBW that applied to their specific population (Wagner et al., 2006). Half of the compliance infractions were

caused by inadequate monitoring, meaning that even though monitoring requirements are required by the BBW, clinicians are often non-compliant because they do not conduct or follow-up with the necessary monitoring tests (Wagner et al., 2006). Poor compliance was also found to be more pronounced amongst older adult populations (Wagner et al., 2006). Although there could be many valid reasons to explain the high number of BBW prescriptions and poor compliance, Wagner et al. (2006) ultimately suggests that the efficacy and potential impact of BBW on patients is debatable.

A study examining drug approvals between 2001 and 2010 found that drugs approved through the accelerated approval pathways and indicated for psychiatric conditions were at increased risk of post-market safety events, including withdrawals and the release of safety information (Downing et al., 2017). However, the authors did not find risk associated with the priority review stream (Downing et al., 2017). It should also be noted that the Breakthrough Therapy designation and Fast-Track designation were not assessed in this study; only the Priority Review pathway and Accelerated Approval designation were examined (Downing et al., 2017).

2.3.4.3 Poor Implementation Surrounding Surrogate Outcomes

The use of surrogate outcomes is approved under the Accelerated Approval designation, as described in Table 2. Surrogate outcomes, such as reduced tumor size, are substitute metrics that reduce the cost and length of clinical trials by reliably predicting clinical outcomes such as death (Fleming & DeMets, 1996). Kemp and Prasad (2017) however, has cited issues regarding its applications, specifically that surrogate outcomes are used without adequate statistical correlation to clinical endpoints, psychometric

validation, and that they are overused by sponsors to reduce the research and development timeline, yielding cost savings. Again, as stated previously, the use of surrogate endpoints is predicated on the expectation that confirmatory trials will be conducted after market launch to validate the surrogate endpoints, which as stated previously, do not always happen (Mahase, 2021).

A recent paper by Lenzer and Brownlee (2021) criticized the FDA for defending the Accelerated Approval pathway by citing rare success cases using surrogate outcomes but ignoring the unreliable nature and potential impact from an efficacy and health economic perspective. Lenzer and Brownlee (2021) identified four main issues with surrogate markers: 1) noncausal associations; 2) multiple casual pathways; 3) insensitivity; and 4) unintended outcomes.

Of the drugs that were approved through the Accelerated Approval pathway between 1992 to 2017, only 39 studies conducted completed confirmatory trials, of which 19 used the same surrogate outcomes as their initial trials (Gyawali et al., 2019). The authors uncovered cases where the same surrogate outcome was used to validate the drug in subsequent trials, which only increases temporal stability (by prioritizing test-retest reliability) and not the construct validity of the original surrogate outcome (Gyawali et al., 2019).

Although there are valid arguments to justify the use of surrogate outcomes, the system has been fraught with perverse incentives, including allowing for manufactures to gain larger initial market share (Kemp & Prasad, 2017). This has resulted in the burden of evidence to be transferred from clinical trials and onto patient populations, which has

resulted in ineffective, possible unsafe medications being tested on patients (Kemp & Prasad, 2017). A paper that outlines both the case for and against the use of surrogate endpoints is Ciani et al. (2017). Given the demonstrated inappropriate use of surrogate outcomes, there are concerns surrounding the proper application of these pathways, and it is often equivocal as to whether drugs meet the threshold of unmet need that justifies expedited market authorization.

2.4 Safety Concerns with Pimavanserin

Despite pimavanserin being advertised as a novel therapy meeting an unmet need, problems emerged during and shortly after its FDA approval. These primarily come from three sources: 1) the PDAC's dissenting opinions of pimavanserin (Food and Drug Administration, 2016); 2) the ISMP's quarterly report citing concerns (Institute for Safe Medication Practices, 2017); and 3) research stemming from commercial databases and the FAERS. From these sources, two serious concerns have emerged: 1) poor clinical evidence to support its regulatory approval; and 2) increased risk of death, adverse events, and serious adverse events.

2.4.1 Poor Clinical Evidence to Support Regulatory Approvals

Part of the dissenting opinion from PDAC was that pimavanserin received approval relying on one clinical trial (NCT01174004, ACP-103-020) that had a sample size of 199 patients. This decision goes against the guidelines that the FDA set for sponsors back in 1998, which state:

> "with regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness…reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible" (Food and Drug Administration, 1998).

At the time of the FDA's decision to approve pimavanserin's use for patients, two other Phase 3 studies had already been completed on pimavanserin: NCT00477672 / ACP-103-012 (n=298) and NCT00658567 / ACP-103-014 (n=123) by June 2009 and December 2009, respectively. Despite this evidence, these two trials were not considered heavily in the FDA's regulatory decision due to the role of NCT01174004 as the pivotal trial. Based on the aforementioned quote, this decision to primarily consider NCT01174004 / ACP-103-020 also inadvertently and incorrectly categorizes pimavanserin as a drug in which it would be "ethically or practically impossible" to conduct a second trial. This deviation from past FDA guidance raises questions as to the legitimacy and validity of pimavanserin's expedited approval designations.

The reason that the NCT01174004 / ACP-103-020 was heavily weighted in the consideration process is because it is considered the pivotal trial. The FDA does not provide any official guidance documents for the regulatory assessment of these pivotal trials, but an interview from Lexchin et al. (2021) with the FDA yielded this interpretation regarding pivotal trials.

> "The term 'pivotal' does not show up in regulations, but its general meaning to people is clear enough: It is the trial or trials that will be, or could be, the basis for our reaching a conclusion that there is 'substantial evidence of effectiveness,' the statutory and regulatory standard for approving a drug. That would also mean that the FDA considers it (or them) an 'adequate and well-controlled investigations,' which is the only basis for accepting a study as supporting effectiveness. A pivotal trial presents the most important data used by FDA to decide whether to approve a drug" (Lexchin et al., 2021).

In the context of pimavanserin's regulatory approval, NCT01174004 / ACP-103-020 acted as the most importance source of data in the FDA's regulatory decision, despite other existing trials suggesting varying degrees of efficacy.

2.4.2 Increased Risk of Death, Adverse Events, and Serious Adverse Events

Given the limited evidence submitted to the FDA as part of the review process, the PDAC expressed their concerns surrounding pimavanserin's risk profile (Food and Drug Administration, 2016). As the sample size was quite small, it would have been hard to ascertain with reasonable certainty whether the deaths, adverse events, and serious adverse events were statistically significant, or if they could be explained by an underlying pathophysiological mechanism.

In November 2017, the ISMP, a non-profit watchdog organization based in the United States dedicated to monitoring drug safety signals, published a quarterly report

citing concerning safety signals and adverse reports (Institute for Safe Medication Practices, 2020). These included hallucinations (21.8%; 487/2336), drug ineffectiveness (14.9%; 333/2236), confused state (11.5%; 258/2236), and death (10.9%; 244/2236) (Institute for Safe Medication Practice, 2017).

More recent follow-up studies conducted in 2021 and 2022 using the FAERS as well as commercial insurance databases have indicated that although a safety signal exists, there are no statistically significant differences when compared to existing treatment alternatives like clozapine and quetiapine (Brown et al., 2021; Nguyen et al., 2022). Other research has contested these findings, citing an increased risk of hospitalization at 180 days of utilization and an increased risk of mortality at 90 days, 180 days and 1 year of pimavanserin utilization relative to non-users (Hwang et al., 2021).

Although patients with PD are often older, frail, and have an extensive history of polypharmacy, which could confound potential safety signals, there remain concerns regarding the FDA review process and the clinical trials that led to the pimavanserin's market approval (Hwang et al., 2021). These concerns emerging from both trial data and real-world patient data are potentially problematic because patients could be at increased risk and the onus to protect these patients falls upon the FDA's review processes, which is the focus of this study.

2.5 Relevance to Canadians with Parkinson's Disease

The rigor of pimavanserin's trials should be examined not only to better understand the potential limitations of the FDA's approval processes, but also to inform

other markets, such as Canada, where it has not yet been approved. This is timely as patient groups and regulatory agencies are beginning to discuss and track pimavanserin's utilization and pricing in the United States market (Canadian Agency for Drugs and Technologies in Health, 2020; Patented Medicine Prices Review Board, 2018).

In addition, there is also mention of pimavanserin in the official Canadian PD guidelines published in the Canadian Medical Association Journal (CMAJ; Grimes et al., 2019). These guidelines are important documents that help to inform physicians on the most pertinent treatment protocols, scientific evidence, and best practices. The guideline utilized a literature review approach to aggregate evidence in the form of existing guidelines, systematic reviews, and RCTs. The PD guideline specifically mentions pimavanserin as a potential therapeutic of interest, assigning it a "Grade B" recommendation (Grimes et al., 2019). A Grade B recommendation denotes therapies with "a body of evidence including studies rated Level 2++, directly applicable to the target population and demonstrating overall constituency of results" (Grimes et al., 2019). "Level 2++" evidence denotes "High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal" (Grimes et al., 2019). Despite this recommendation, and the growing interest from Canadian stakeholders, the literature appears to suggest that there is still a high degree of uncertainty with pimavanserin's safety and efficacy. Pimavanserin has not yet received market authorization in Canada.

As such, this study aims to critically appraise pimavanserin's clinical trials, and assess the risk of bias and methodological design of the studies. This will ultimately add to the body of evidence that can be used to better ascertain pimavanserin's safety and

efficacy profile for patients in markets where pimavanserin has not yet been authorized for use.

Chapter 3

3 Research Questions and Objectives

The chapter will first introduce readers to the importance of methodologically rigorous clinical trials design, after which the research question and objectives will be communicated. This will transition into a justification as to why third-party research reviews like this project, acting independently of the FDA, are warranted. Specifically, Aduhelm, a controversial drug from the manufacture Biogen, will be discussed as an example to support the case for a review of pimavanserin's trials.

3.1 Objective: The Importance of Clinical Trials Design

Clinical trials are critical in determining whether pharmacotherapies are safe and efficacious enough to be prescribed to the public. Poorly executed trials with a high risk of bias may reduce the interpretability of the drug's efficacy, and can potentially omit adverse events, serious adverse events, and mortality risks to regulators. Several pertinent concerns include poor trial design, substandard outcome measurement, inadequate statistical methodology, and missing data (Lexchin, 2011; Little et al., 2012).

As such, this project will be a retrospective study with the research question "was there enough quality evidence and suitably designed trials to warrant an accurate safety and efficacy assessment?" with the primary objective of informing regulatory decision-making regarding the use of pimavanserin for the treatment of PDP. By conducting this extensive trial assessment in relation to the standards established by the FDA, the

academic and medical community can be better informed about pimavanserin's safety and efficacy profile as an alternative to traditional antipsychotics for the management of PDP.

3.2 Case Example: Biogen & Aduhelm (aducanumab-avwa)

A potential criticism of conducting independent third-party reviews is that the FDA is more qualified to scrutinize trial data and drug applications. While it is true that the FDA is better equipped with more resources to evaluate RCT data, there have been many cases where the FDA has approved new drugs through expedited pathways that should not have been approved. A recent example of this is Biogen's drug Aduhelm, which was indicated for the treatment of Alzheimer's disease, and approved by the FDA on June 7th, 2021, through both the Accelerated Approval and Fast-Track designations. These two designations awarded Biogen the ability to utilize a surrogate outcome and receive FDA support in their application, contingent on demonstrating benefit using nonclinical mechanisms or early pharmacological data.

Despite 10 of the 11 members on the FDA's own Peripheral and Central Nervous System Drugs Advisory Committee voting against Aduhelm, coupled with a lack of scientific support for their surrogate outcome, the FDA approved the drug (Biogen, 2020; Food and Drug Administration, 2021). An independent investigation by STAT news uncovered that the FDA's Director of the Office of Neuroscience, Billy Dunn, allegedly met with Biogen executives in unsanctioned meetings against FDA internal policies, to help push what was otherwise a questionable drug to the forefront of approval (Feuerstein et al., 2022). This is reminiscent of Curtis Wright IV, acting director of the FDA's

Division of Anesthetic, Critical Care, and Addiction of Drug Products from 1996 to 1997, who also held unsanctioned meetings with representatives from Purdue Pharma to help push for Oxycontin's approval (U.S. Department of Justice, 2006).

As a reaction to the alleged oversight by the FDA, several retrospective critical appraisals have since been conducted to examine the regulatory processes and clinical evidence that led to Aduhelm's approval. Although each varying in their scope, notable studies include a narrative review by Haddad et al. (2022), a critical appraisal of statistical methods by Knopman et al. (2020), and a critical appraisal of trial design and outcomes by Tampi et al. (2021). The narrative review conducted by Haddad et al. (2022) found that the controversy surrounding Aduhelm was multifaceted and included issues with the FDA's narrow interpretation of the clinical evidence, as well as the lack of statistical significance in some clinical studies, amongst other factors. Upon conducting a critical appraisal of Aduhelm's clinical trials, Both Knopman et al. (2020) and Tamp et al. (2012) reaffirmed the need for additional data by conducting another clinical trial. As a result, it is not uncommon, and arguably of significant value, for independent researchers to conduct retrospective critical appraisals of clinical trials independently of national regulatory authorities, especially in the case of controversial approvals, as each review adds to the body of evidence that can help other regulatory bodies better understand the safety and efficacy of a drug.

Chapter 4

4 Methodology

This study is a retrospective critical appraisal of pimavanserin's published clinical trials, using the Risk of Bias 2 (RoB 2) tool and the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2). The research consisted of two main stages: 1) collection of clinical trials data; and 2) evaluation using the RoB 2 and PRECIS-2, followed by a discussion that will be situated in the context of the FDA's own decision regarding the licensure of pimavanserin, alongside other extant independent reviews.

4.1 Stage One: Data Collection

The project began by gathering all pertinent clinical trials data from the Clinical Trials database of the US National Library of Medicine from 2007 onward. 2007 was chosen specifically because pimavanserin's approval from the FDA through the Breakthrough Therapy designation was in 2016. A decade prior to FDA approval is sufficient to capture all possible Phase 2 clinical data that Acadia Pharmaceuticals, or another organization, may have reported to the FDA. The two studies uncovered in pimavanserin's patent, both predating 2007, will not be evaluated because they did not contain sufficient information nor a substantial sample size to warrant a critical review of their trials.

There are two classes of clinical trials data specified within this study: the data of 'terminated', 'withdrawn', or 'unknown' status studies; and the data from 'completed'

status studies. The clinical data for both groups was systematically logged using an Excel spreadsheet, recording 1) the trial design type; 2) pimavanserin's dosage or drug delivery mechanism; 3) primary and secondary outcomes; 5) participants' data and/or missing data characteristics; and 6) study conclusions.

4.2 Stage Two: Evaluation Using the RoB 2 and PRECIS-2 Tools

The clinical trials were then evaluated using both the RoB 2 and PRECIS-2 tool. These two tools were used in conjunction because each assesses different aspects of a clinical trial's internal and external validity, resulting in the need for multiple tools, a concern realized by Moher et al. (1995). Both the RoB 2 and the PRECIS-2 tools were chosen because they have been widely used in clinical trials critical appraisals and have been shown to have good reliability and validity (Minozzi et al., 2022; Loudon et al., 2017). By using multiple tools, we were able to adequately capture areas of interest such as statistical methods, prognostic data, internal and external validity, trial design, and overall risk of bias.

It is important to consider that despite checklists and frameworks, there are no definitive means to determine if an RCT is "sound". Even amongst expert statisticians and epidemiologists, there are points of contention as to how the data and trial design should be interpreted and valued; although RCT features like blinding are core tenets, features like prognostic imbalances and sample size may be variably interpreted based on the nature of certain diseases. These competing values often need to be considered in light of existing treatment options, or lack thereof, and patient need. However, just because it is

difficult to achieve a resolutely perfect evaluative tool does not mean that the results should be rendered invalid. Likewise, no clinical trial is perfectly designed. Yet, this does not mean that the results of a clinical trial has no interpretative value. Rather, as long as the trial has a robust methodology, it can still build upon the body of clinical evidence. Therein lies the value of the RoB 2, the PRECIS-2, and this study. The results of this study, even if limited in scope, will add to the volume of literature examining the safety and efficacy of pimavanserin, and the robustness of the trials that contribute to its regulatory approval.

4.2.1 Risk of Bias 2 Tool

The Risk of Bias 2 (RoB 2) tool was originally released in 2008 by Cochrane, a not-for-profit organization located in the United Kingdom that aims to support the generation of quality evidence to better inform health decision-making (Cochrane, n.d.). Specifically, the tool is used to assess the methodological quality of randomized clinical trials, and to determine whether a risk of bias could skew the interpretation in favor of the experimental drug. Since the launch of RoB, an updated version called the RoB 2 was released in 2019, which incorporated user feedback and suggestions from the original RoB and has since been applied in a variety of studies (Sterne et al., 2019). The tool being applied to pimavanserin's clinical trials is the updated RoB 2.

The RoB 2 contains five primary domains: 1) bias from the randomization process; 2) bias arising from deviations from the intended intervention; 3) bias from missing outcome data; 4) bias in the outcome measurement; and 5) bias in the reported results. Altogether, the risk of bias from each of the five domains contribute to one of

three overall risk of bias scores: 1) low risk of bias; 2) some concerns; or 3) high risk of bias. An overall "low risk of bias" score is achieved only when each of the five domains have a "low risk of bias" score. An overall "some concerns" score is achieved if at least one of the five domains has a "some concerns" score, but no "high risk of bias" score for any domain. An overall "high risk of bias" score is achieved if any one of the five domains has a "high risk of bias" score, or if multiple domains have a "some concerns" score.

The RoB 2 tool can be applied in one of two ways, either manually or autonomically using a macro-enabled Excel tool. For the first option, users apply the prescribed algorithms based on a set of domain-specific signaling questions created and validated by Cochrane to determine the domain-specific risk of bias. An algorithm in this tool refers to the set of rules and pathways processes that determine the risk of bias rating. An example algorithm from domain 1 (bias) from the randomization process has been included as *Figure 6* to illustrate its application. Alternatively, a user can employ an

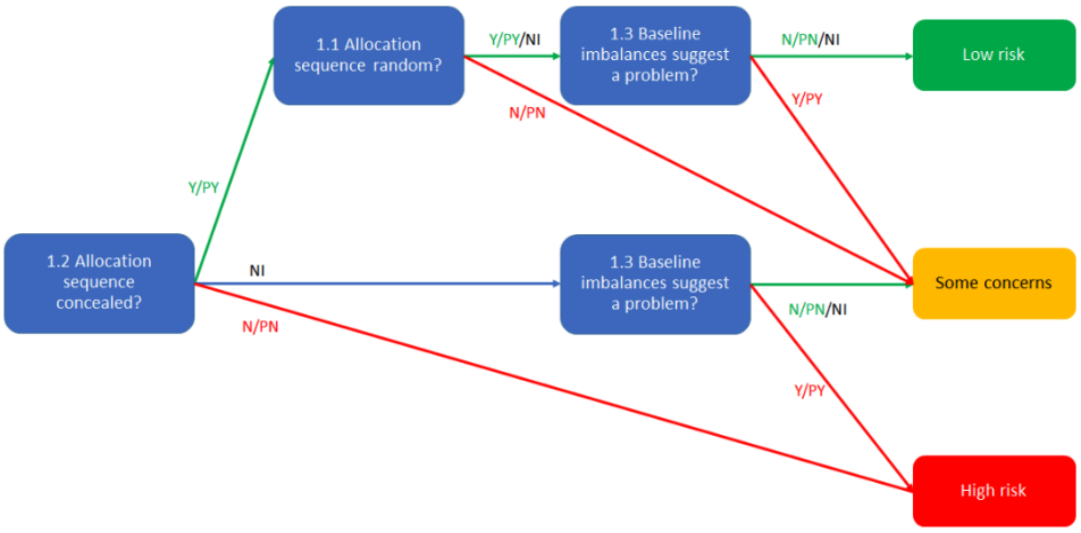

Figure 6: Algorithm for suggested judgement of risk of bias arising from the randomization process (Sterne et al., 2019).

Excel document with macros enabled which automatically apply the algorithms based on user-provided answers to the signaling questions. A complete list of the signaling questions from each of the given domains have been included in *Table 3.* To reduce the potential for misinterpretation and to streamline the process, the macro-enabled Excel tool was used in this step of the study.

Domain	**Signaling Question**
1. Risk of Bias Arising from the Randomization Process	-Was the allocation sequence random? -Was the allocation sequence concealed until participants were enrolled and assigned to interventions? -Did baseline differences between intervention group suggest a problem with the randomization process?
2. Risk of Bias Due to Deviations from the Intended Interventions	-Were participants aware of their assigned intervention during the trial? -Were carers and people delivering the intervention aware of participants' assigned intervention during the trial? -Were there deviations from the intended that arose because of the trial context? -Were these deviations likely to have affected the outcome? -Were these deviations from intended intervention balanced between groups? -Was an appropriate analysis used to estimate the effect of assignment to intervention? -Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?
3. Risk of Bias Due to Missing Outcome Data	-Were data for this outcome available for all, or nearly all, participants randomized? -Is there evidence that the result was not biased by missing outcome data? -Could missingness in the outcome depend on its true value? -Is it likely that missingness in the outcome depended on its true value?
4. Risk of Bias in Measurement of Outcome	-Was the method of measuring the outcome inappropriate? -Could measurement or ascertainment of the outcome have differed between intervention groups?

	-Were outcome assessors aware of the intervention received by study participants? -Could assessment of the outcome have been influenced by knowledge of intervention received? -Is it likely that assessment of the outcome was influenced by knowledge of intervention received?
5. Risk of Bias in Selection of the Reported Result	-Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? -Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? -Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?

Table 3: Complete list of signaling questions from the RoB 2 tool.

It should be noted only four of eight studies gathered were randomized and blinded trials. Three of the four remaining studies were single arm open-label studies. One of the four remaining studies was an open-label extension study of another RCT. The descriptive breakdown of the studies, their phases, and trials designs, are detailed under the ‘Results’ section.

Even though the RoB 2 tool is meant to be applied to randomized trials, the three single arm assignment trials were also assessed with the RoB 2 because certain signaling questions within domain 3 (missing data), domain 4 (measurement of the outcome), and domain 5 (selection of the report results) can still be applied. The domains that are applicable to the single arm studies, along with their limitations, are discussed further under the ‘Results’ and ‘Discussion’ sections. It should also be acknowledged that single arm studies have an important role and add value to clinical trials but should be considered in light of their risk of bias and statistical limitations (Cucherat et al., 2020). At the moment, there are no widely validated tools for the assessment of bias for single arm studies, so the RoB 2 was employed on all of the studies, RCT or otherwise.

Using the RoB 2 tool on single arm studies is not a completely novel approach. Checcucci et al. (2021) employed the original RoB tool, which is also designed for randomized trials, to review single arm studies investigating ultra-minimally invasive surgical treatments on perioperative and functional outcomes. As well, Gupta et al. (2016) employed the RoB tool to evaluate single arm studies investigating the effects of positive airway pressure on depression in patients with obstructive sleep apnea. As such, employing the RoB 2 tool in this study in the absence of a validated tool meant for single arm trials, is a similar approach adopted by other investigators.

4.2.2 PRECIS-2 Tool

The PRagmatic Explanatory Continuum Indicatory Summary (PRECIS) is a tool that can be used to evaluate whether a clinical trial is more pragmatic or explanatory in nature (Loudon et al., 2015). Originally developed from 2005-2008, the tool can be applied prospectively by clinical trialists to design a trial suitable for their needs or, as with this study, applied retrospectively to examine whether a clinical trial is "fit for purpose" (Loudon et al., 2015). Since its release, it has been updated based on user feedback to include a better scoring system, reduce redundant domains, amongst other improvements, to yield the improved PRECIS-2. The tool being applied to pimavanserin's clinical trials is the updated PRECIS-2 tool.

The purpose of this tool is to provide insight into nine domains, which include: 1) eligibility; 2) recruitment; 3) setting of the trial; 4) organization of trial resources; 5) flexibility with the intervention delivery; 6) flexibility with intervention adherence; 7) the degree of participant follow-up; 8) relevance of the primary outcome; and 9) the comprehensiveness of the primary analysis (Loudon et al., 2015). Each domain is rated from one, representing very explanatory, to five, representing very pragmatic. Domains that are not applicable are not ranked.

A highly pragmatic study is one that is designed to emulate real world conditions with the usual standard of care, and with heterogenous patient adherence levels, amongst other factors (Treweek & Zwarenstein, 2009). A highly explanatory trial is one that is designed and carried out to confirm a casual hypothesis between a therapeutic intervention and a physiological outcome under stringent testing conditions on a specific

population (Treweek & Zwarenstein, 2009). It is important to keep in mind that a study does not need to be completely pragmatic or explanatory, as these classifications exist on a continuum rather than on a binary scale (Loudon et al., 2015). A PRECIS-2 has been included as *Figure 7* to illustrate how a completed exampled would be presented. This example illustrates a highly pragmatic trial. Even within the nine different domains, certain design features may be more pragmatic, while others are more explanatory, as illustrated by the example in *Figure* 7.

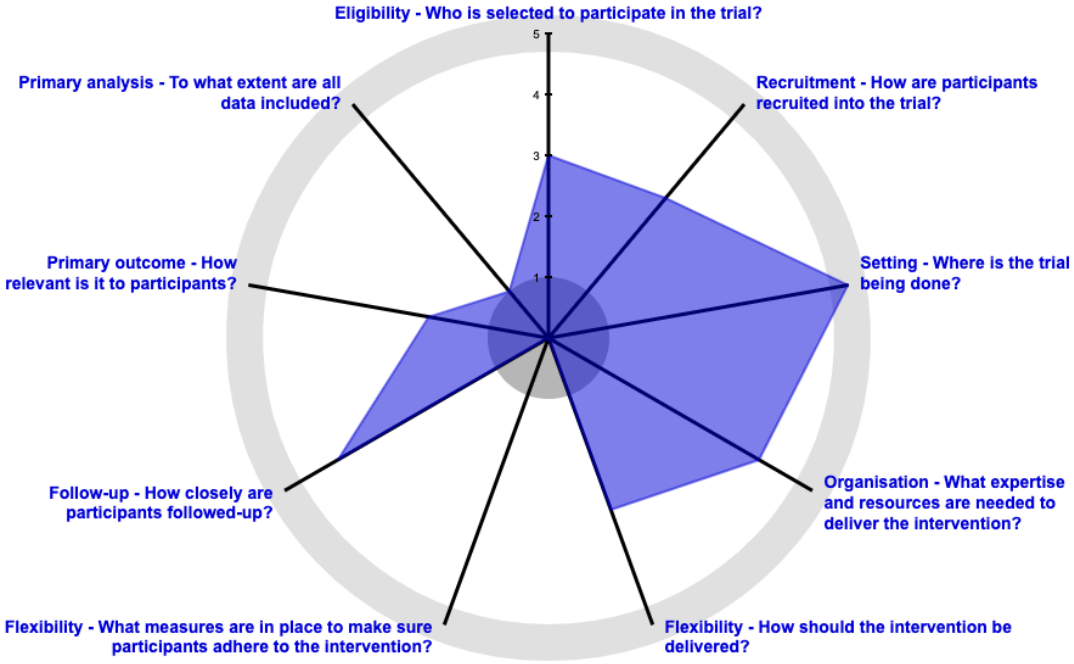

Figure 7: Example of a completed PRECIS-2 tool (Aronson et al., 2008).

Neither pragmatic study designs nor explanatory trial designs are inherently 'better' than the other; each have their own respective applications and should be judged for suitability based on the objectives of the study. In the context of pimavanserin's drug trials or trials for other psychiatric drugs, an explanatory study might be best suited for determining the efficacy of the drug, while a pragmatic trial might be more applicable for

a study investigating its safety profile (e.g., mortality risk, adverse events), especially with concerns surrounding polypharmacy in this patient population (McLean et al., 2017). The application of the PRECIS-2 on the aggregated pimavanserin trials will help to illustrate the interpretability of the trial data in the context of its primary outcome, whether it is efficacy or drug safety.

Chapter 5

5 Results

The results will be presented to first illustrate findings from the data collection process. This will be followed by a description of the eligible studies, including their study designs, length of trials, amongst other descriptive parameters. Finally, the specific primary and secondary endpoints, along with their suitability, will be presented.

The results of the Risk of Bias 2 (RoB 2) tool will then be presented. High-level summary figures will be presented to illustrate the areas that present the greatest risk of bias. This will be followed by a presentation of the most prominent risk of bias that were uncovered using the RoB 2 tool. The presentation of these results will be grouped based on their respective study designs, either as an RCT, a safety study, or a single arm study. This is because each type of study serves a different purpose in determining the safety and efficacy of the drug, and because certain study designs (i.e., RCTs), should be weighed more heavily than other study designs (e.g., single arm studies).

Finally, the results of the PRECIS-2 tool for each will be presented in a graphical format to illustrate whether designs were more explanatory or pragmatic. Similar to the results of the RoB 2 tools, the studies evaluated with the PRECIS-2 tool will be presented based on their respective study designs, either as an RCT, a safety study, or a single arm study.

5.1 Description of the Collected Studies

5.1.1 Eligible Studies

A total of 14 studies were identified through the clinicaltrials.gov search An adapted PRISMA flow chart has been included as *Figure 8* (Page et al., 2021). Inclusion criteria included studies that were sponsored by Acadia Pharmaceuticals, were investigating patients with PD, and had relevant endpoints related to psychosis or general psychiatric functioning. Of those 14 studies, two studies were excluded because their results had not been reported at the time of the FDA decision. As such, these two studies would not provide any pertinent information about the FDA's original decision to approve pimavanserin. Of the remaining 12 clinical studies initiated by the sponsor, three were excluded because the study had been terminated, their status was unknown, or they were still recruiting. One other study was removed because it was part of the sponsor's application for dementia-related psychosis and not part of the PD patient population. As such, these studies did not contribute any data to the regulatory decision-making process.

One study (NCT03482882), titled an "An Open-Label, 8-Week Study of Safety and Efficacy of Pimavanserin Treatment in Adults with Parkinson's Disease and Depression" was included despite not being specifically meant for PDP. It was included because it was conducted on patients with PD and had relevant secondary endpoints, including the Clinical Global Impression-Improvement (CGI-I) at week 8 and Clinical Global Impression-Severity (CGI-S) at week 8. Both secondary endpoints are global psychiatric functioning measures used to assess overall patient health.

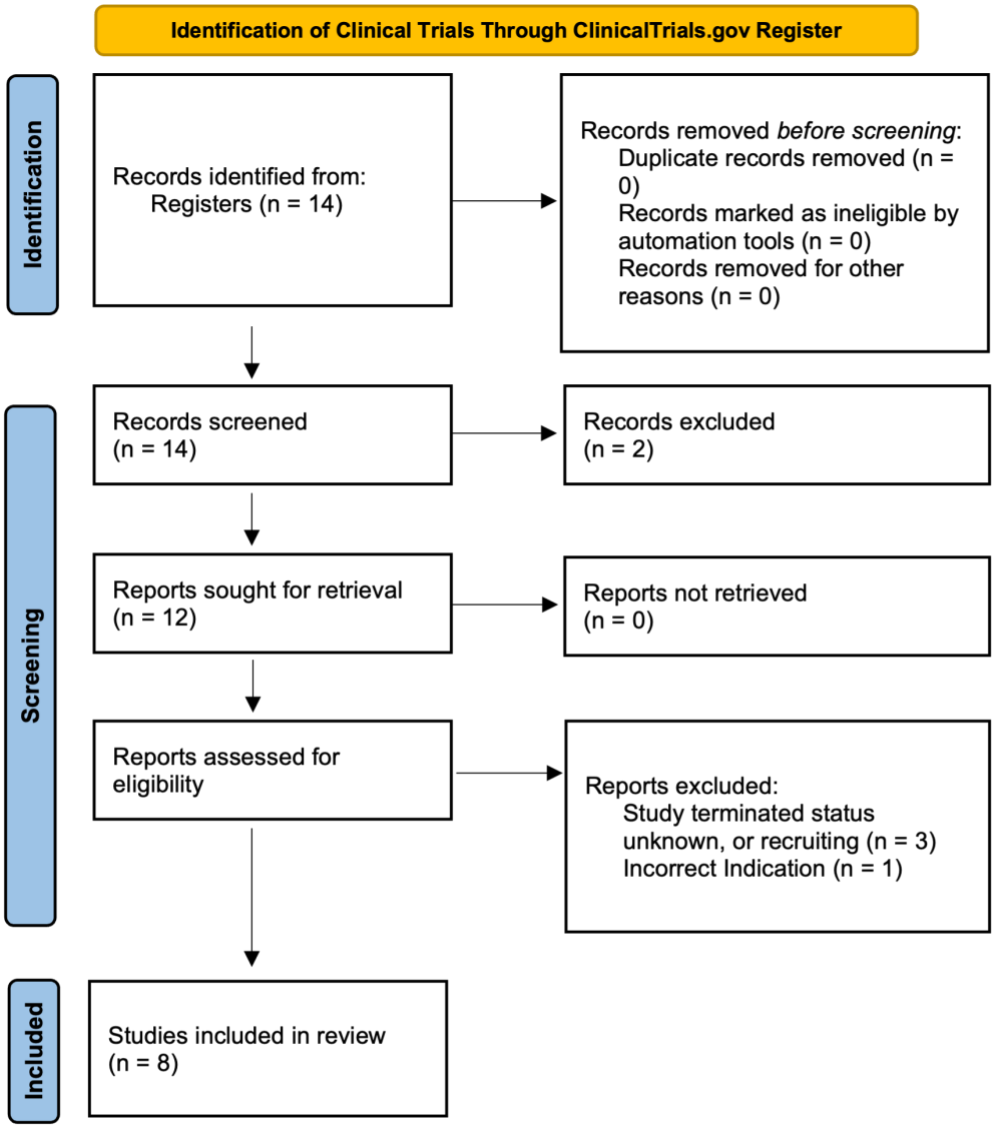

Figure 8: An adapted PRISMA diagram of eligible studies.

5.1.2 Description of the Eligible Studies

Of the eight studies that were completed and funded by Acadia Pharmaceuticals, there were three Phase 2, four Phase 3, and one Phase 4 study. Four of the studies were parallel assignment RCTs (i.e., they have a comparator group), while three were single group assignment studies with no control arm.

One of the eight studies (NCT00550238) was a prospective cohort study where participants were selected by investigators from completed pimavanserin RCTs. These participants were selectively chosen because the investigators believed they would benefit from further treatment with pimavanserin. These study participants were categorized as either receiving concomitant antipsychotic medications which was mainly quetiapine and clozapine, or not receiving concomitant antipsychotic medications. Although all participants from each group received pimavanserin, the concurrent antipsychotic medications were prescribed by clinicians outside the investigation team and were considered as the 'exposure'. As such, this study can be best described as a prospective cohort study, where the outcomes are mortality, serious adverse events, and adverse events, and the exposure being other atypical antipsychotics.

Five of the eight trials had intervention periods between 6-8 weeks, inclusive of follow-up time. The sole Phase 4 open-label trial had a primary endpoint of 16 weeks. Two of the open-label safety studies investigating mortality, serious adverse events, and adverse events, had indefinite endpoints. This meant that patients were considered enrolled in the study until patients ceased treatment because of an adverse event, death,

irremediable disease progression, voluntary withdrawal by subject, physician decision, poor efficacy, patient non-compliance, lost to follow-up, or withdrawn by the sponsor.

The comprehensiveness of the data varied among the studies, meaning that some studies only published their data results on clinicaltrials.gov, whereas other studies also published their protocols and analysis in journal articles. Optimally, every study would publish their results on clinicaltrials.gov, as well as their protocol, statical analysis plan, and a journal article. Unfortunately, this poor reporting of potentially negative results, termed 'positive publication bias', is a chronic issue within the scientific community (Mlinarić et al., 2017). The degree to which data results, journal articles, and protocols were reported was an important factor to capture the scope of each study, and substandard reporting of these sources can make it difficult to capture the risk of bias as well as ascertain the drug's safety and efficacy profile.

Most of the trials (n=6) posted their study results on clinicaltrials.gov, as required by the FDA Amendments Act (FDAAA) of 2007. Two studies (NCT00087542, NCT04292223) that had recently concluded were within the 12-month grace period allowed by the FDAAA, meaning they were not yet required to post their results publicly as of the conclusion of this project. Three clinical trials were posted with journal articles and two were also posted with the statistical analysis plan and study protocol. Three trials were posted with only their study results on clinicaltrials.gov. A summary of these study components has been included in *Table 4* and a detailed summary of the studies can be found in *Supplementary File A.*

Study Design		**Percentage of Total Studies**
RCT (Parallel Assignment)	4	50%
Uncontrolled Single Group Assignment	3	37.5%
Prospective Cohort Study	1	12.5%
Length of Trial		
6-8 Weeks	5	62.5%
16 Weeks	1	12.5%
Indefinite	2	25%
Comprehensiveness of Data Results		
1) Trial with a Study Results Posted	6	75%
2) Trials with a Journal Publication	3	37.5%
3) Trials with a Posted Statistical Analysis Plan	2	25%
4) Trials with a Posted Study Protocol	2	25%
Trials with 1), 2), 3), and 4)	2	25%
Studies with only 1)	3	37.5%

Table 4: Summary of study components.

5.1.3 Primary and Secondary Outcomes and Scales Utilized

Due to the multifaceted nature of PDP and its associated management, there were a variety of primary and secondary outcomes and tools employed within the clinical trials. They can be broadly categorized into five groups based on their relation to a patient's care: 1) psychosis specific endpoints; 2) general psychiatric endpoints; 3) other PD endpoints (e.g., motor function, sleep); 4) care partner endpoints; and 5) safety endpoints. They are summarized in *Table 5*.

Type of Endpoint	**Name of Endpoint / Tool**	**Number of Times Used (n)**
Psychosis Specific Endpoint	SAPS-PD (Scale for the Assessment of Positive Symptoms)	3
General Psychiatric	CGI-I (Clinical Global Impression-Improvement)	3
	CGI-S (Clinical Global Impression-Severity)	3
	PGI-I (Patient Global Impression of Improvement)	1
Other PD Endpoints	UPDRS-2 & 3 (Activities of Daily Living, Motor Impairment)	3
	MDS-UPDRS Part 1 and 2 (Movement Disorders Society - Unified PD Rating Scale - Caregiver and Patient Version)	1
	Schwab and England ADL Scale (Caregiver and Patient Version)	1
	SCOPA-SLEEP (Scale for Outcomes in PD-Sleep Scale)	2
	mFSQ (Modified Functional Status Questionnaire)	2
	EQ-5D	1
Caregiver Related	(CBS) Zarit 22 Item Caregiver Burden scale	1
Safety Endpoints	Mortality, Serious Adverse Events, Adverse Events	2

Table 5: different endpoints used in the clinical trials, along with their frequency of use.

The primary tool used to assess symptoms of psychosis was a modified version of the Scale for the Assessment of Positive Symptoms (SAPS), which is administered using a formal clinical interview between a clinician and a patient (Fernandez et al., 2008). The PD-specific version, the SAPS-PD, is a shortened version of the original SAPS that includes only the subsections assessing hallucinations and delusions and was used three times throughout the trials (Voss et al., 2012). The original SAPS was a recommended tool by the Movement Disorder Society Task Force of the International Parkinson and Movement Disorder Society (Fernandez et al., 2008). Although the SAPS-PD shows strong validity and reliability, it should be noted that research validating the SAPS-PD was conducted by investigators from Acadia Pharmaceuticals, the drug company behind pimavanserin (Voss et al., 2013).

Another psychiatric scale, the Clinical Global Impressions Scale (CGI), which is not psychosis specific, was also employed within the clinical studies. Within the CGI are two individual scales, the severity scale (CGI-S) and the improvement scale (CGI-I), each with only one signaling question. The former assesses the severity of the mental illness based on the patient's function, symptoms, and behaviors while the latter is used to assess the patient's improvement after initiating a new therapy (Busner & Targum, 2007). Both can be used to assess a patient's disease course over time and are commonly used in clinical trials that are part of FDA submissions (Busner & Targum, 2007). The CGI-I and CGI-S were each employed three times throughout the trials.

The Unified Parkinson's Disease Rating Scale (UPDRS), developed in 1987, was a prominent assessment tool for patients with PD. It contains four scales: 1) mentation, behavior, and mood; 2) activities of daily living (ADL); 3) motor; and 4) complications.

In 2008, the Movement Disorder Society (MDS) conducted revisions to improve the UPDRS to yield the MDS-UPDRS (Goetz et al., 2008). The revised tool can be completed by either the physician, the patient, or a combination of the two, and contains four scales: 1) non-motor experiences of daily living; 2) motor experiences of daily living; 3) motor examination; and 4) motor complications (Goetz et al., 2008). Although the UPDRS and MDS-UPDRS both assess hallucinations and delusion to some degree, their focus is on PD as a whole, and as such, were not categorized as a psychosis specific or as a general psychiatric tool. The Schwab and England Activities of Daily Living Scale was another tool that was used by the clinical trials to assess a patient's degree of independence and capacity for completing their ADLs.

Other tools used to assess non-psychiatric aspects of PD included the Scale for Outcomes in PD Sleep Scale (SCOPA-SLEEP), the Modified Functional Status Questionnaire (mFSQ), and the EuroQol-5-Dimensions-5 Levels (EQ-5D-5L). The SCOPA-SLEEP is a patient-administered tool that facilitates a clinician's understanding of their nighttime sleep and daytime sleepiness (Marinus et al., 2003). This is of particular interest because the etiology of sleep issues experienced by PD patients are often poorly understood and, as a result, inadequately managed (Adler & Thorpy, 2005). The mFSQ is a general patient-administered assessment tool that captures aspects of the patient's physical function as it related to ADL, psychological function, role function, social function, and other performance measures (e.g., work, sexual relationships, etc.) (Jette et al., 1986). The EQ-5D-5L is a quality-of-life tool which contains five domains: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; and 5) anxiety/depression

(Williams, 1990). The ‘5L’ refers to the five levels that patients can rate the severity of their problems (Williams, 1990).

Another important aspect of PD’s management that was assessed was the wellbeing of care partners. Caring for someone with PD is usually taxing for care partners, who are commonly close family and loved ones, and caregiver burden is often worsened by psychiatric symptoms, falls, and the patient’s own decreasing quality of life (Schrag et al., 2006). In turn, care partners themselves experience worsening depression and dissatisfaction with their marriage, social, and sexual life (Schrag et al., 2006). The only relevant tool employed in pimavanserin’s clinical trials was the Zarit 22 Item Caregiver Burden Scale. Originally developed in 1980 by Zarit et al.. The version used in the clinical trials is a reduced 22 item version that aims to elicit care partner perspectives surrounding the dependence of the individual with PD, as well as their own feelings of burnout, frustration and anger, the strain on their own lives, and other dimensions (Zarit et al., 1980).

Finally, for the two safety studies, the outcomes measures were counts of mortality, adverse events, and serious adverse events.

5.2 Risk of Bias 2 (RoB 2)

The RoB 2 was applied to all eight of the reviewed clinical trials. As mentioned previously, there are five domains that together yield the overall risk of bias for each study. These domains are as follows: 1) Randomization process; 2) Deviations from the Intended Interventions; 3) Missing Outcome Data; 4) Measurement of the Outcome; and 5) Selection of the Reported Result. *Figure 9* illustrates the domain-specific risk of bias and overall risk of bias for each study.

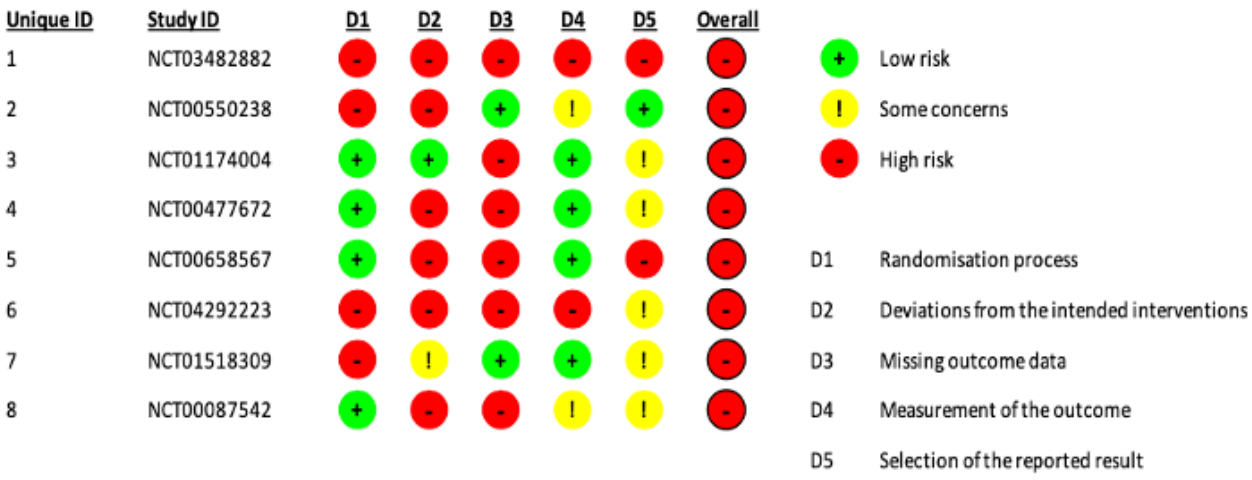

Figure 9: RoB 2 summary table.

Overall, there were methodological concerns with every study conducted by the sponsor. The most prominent issue that was uncovered was the poor management of missing data, with six of eight studies indicating major risk of bias from this issue. Another prominent issue was deviations from the intended intervention, with six of eight studies indicating major risk of bias. *Figure 10* has been included to illustrate the risk of bias as a percentage of the total studies, and the domains that produced the greatest risk of

bias within these studies. *Supplementary File B*, the RoB 2 Excel document with the original ratings and rationales, has also been included.

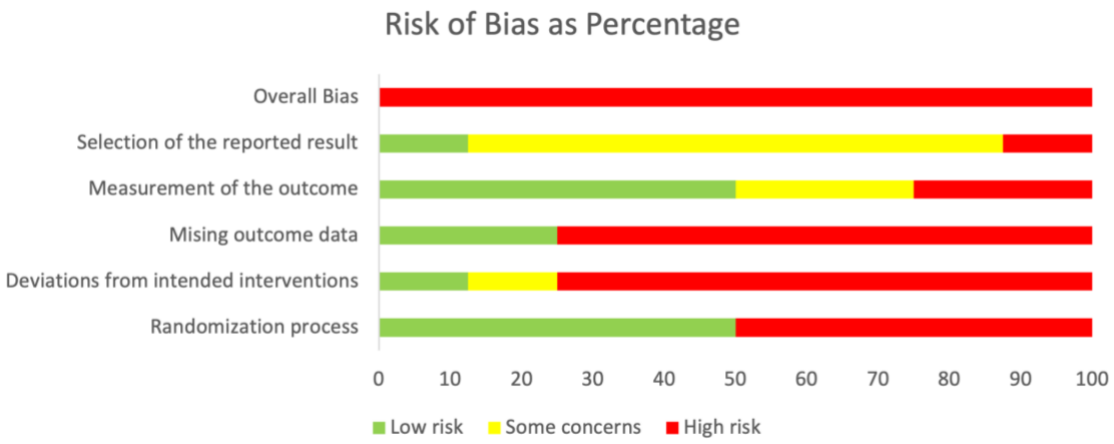

Figure 10: Risk of bias as a percentage of total bias.

As previously mentioned, the following sub-sections present the methodological concerns identified for each type of clinical trial, whether they were an RCT, a safety study, or a single arm study. The reason the results are presented in this manner is because the RoB 2 is best applied to RCTs, and as such, should be presented separately from the other types of study designs for which only certain parts of the RoB 2 are applicable. As well, each study design has their own methodological concerns, and should be presented and discussed separately. The results in the following paragraphs will also be presented with contextual information gathered from their respective journal articles, statistical analysis protocols, study protocols, amongst other applicable resources.

5.2.1 Randomized Control Trials

5.2.1.1 Randomization

There were a total of four RCTs (NCT00087542, NCT01174004, NCT00477672, and NCT00658567). One of those trials (NCT00087542) did not have any results posted as it was completed in 2005 before mandatory reporting was in effect, so it was impossible to ascertain issues with randomization, deviations from the intended intervention, or issues with the reporting of the results.

However, amongst the remaining three RCTs, the randomization process contributed to a low risk of bias as there were robust methodologies in place. For example, NCT01174004 used a pre-programmed kit randomization schedule generated by PharamaNet, ensuring robust randomization and allocation blinding. The other studies, however, did not publish their specific protocols, but can reasonably be assumed to have randomization as per Cochrane's user protocol (i.e., cribsheet), and as a result, were rated as having a low risk of bias.

5.2.1.2 Missing Outcome Data

A major source of bias that contributed to poor RoB 2 ratings within the RCTs was unexplained or poorly explained missing outcome data. In NCT01174004, the landmark RCT that formed the basis of pimavanserin's approval, 23 out of 199 participants (11.56%) withdrew from the study and data was not reported on them: 7 out of 94 from the placebo arm and 16 out of 105 from the experimental arm. The reasons cited were vague and broadly categorized as either removal due to an adverse event,

withdrawal by subject, sponsor's discretion, protocol violation, or physician decision. Missing data stemming from adverse events may indicate safety issues, and of even greater concern are participants withdrawn due to sponsor's discretion and physician decision, which may point to questionable management of efficacy data. No statistical compensatory methods were employed. Resulting from the sponsor's poor explanation as to the nature of the absence of the data besides broad generalizations, and due to their poor statistical methods for handling missing data, this study was rated as having a high risk of bias, which may have contributed to the positive efficacy conclusion drawn by Acadia Pharmaceuticals. *Table 6* illustrates the specific breakdown of missing outcome data from each RCT.

The issue of poorly explained missing data is not unique to NCT01174004, as both NCT00477672 and NCT00658567 presented with a similar issue. With NCT00477672, consent was withdrawn by 15 patients across the 10mg (total n = 101) and 40mg (total n = 99) treatment arms, the reasons for which have not been provided by the sponsor. Since there were no issues with prognostic baseline imbalances and the treatment arms were similar in size, there may be reason to believe that the patients who withdrew consent from participation in the treatment arm points to greater safety risk that has not yet been acknowledged by the sponsor.

Study (NCT01174004)	**Control Arm**	**Pimavanserin Arm**	
Total n	94	105	
Missing n	7	16	
Percentage of Drop-Out	7.45%	15.24%	
Adverse event	2	10	
Withdrawal by Subject	2	3	
Sponsor Discretion	2	2	
Protocol Violation	0	1	
Physician Decision	1	0	
Study (NCT00477672)	**Control**	**Pimavanserin Arm 40mg**	**Pimavanserin Arm 10mg**
Total n	98	101	99
Missing n	7	16	16
Percentage of Drop-Out	7.14%	15.84%	16.16%
Adverse Event	3	6	5
Death	0	0	1
Disease Progression	0	0	1
Physician Decision	1	0	0
Protocol Noncompliance	0	0	2

Consent Withdrawn	2	10	5
Sponsor Discretion	1	0	2
Study (NCT00658567)	**Control**	**Pimavanserin Arm 20mg**	**Pimavanserin Arm 10mg**
Total n	40	42	41
Missing n	8	6	4
Percentage of Drop-Out	20%	14.29%	9.76%
Adverse Event	5	3	2
Consent Withdrawn	2	2	0
Physician Decision	0	0	1
Sponsor Discretion	1	1	1

Table 6: Breakdown of missing data from each treatment arm.

5.2.1.3 Deviations from Intended Intervention and Selection of the Reported Result

Building upon the issue of missing data, there were major deviations from the intended intervention in the RCTs. For NCT00658567, the study was prematurely arrested and the statistical analysis for the 10mg was not conducted. The sponsor did not provide a reason for this deviation. As a result, this failure to implement the intervention led to missing data for both the primary and secondary outcomes in this treatment arm. This also led to selective reporting and analysis of the primary and secondary endpoint data for the only remaining 40mg treatment arm.

5.2.1.4 Measurement of the Outcome

Of the four RCTs, three received a low risk of bias rating and one received a moderate risk of bias rating for this domain. In addition, the studies were blinded and randomized, so patients were less likely to provide biased outcome data. These precautions also helped to minimize the risk of bias arising from a clinician's assessment of the outcome. As well, the endpoints and tools that were previously discussed as being used to measure the outcome were appropriate for the scope and objective of the trials. This is because the RCTs employed a validated psychosis specific tool (i.e., the SAPS-PD) alongside other well-established PD and quality of life tools. As such, there were limited concerns regarding the measurement of the outcome across the RCTs.

5.2.2 Safety Studies

There were two safety studies (NCT01518309 and NCT00550238) and both were open-labelled extension studies. Since the RoB 2 is intended for RCTs, the following paragraphs will present methodological issues from select domains that apply to these studies. These domains were chosen because of their potential risk of bias, and because of their relevance to the interpretation of pimavanserin's safety profile. As well, methodological issues that are not adequately captured by the RoB 2 signaling questions will also be presented alongside their most relevant domain.

5.2.2.1 Randomization Process and Participant Selection

As these were non-randomized studies, there is a risk of bias that could confound the results of the study. The lack of randomization is not, however, the primary concern as non-randomized trials are not unusual (Singh & Loke, 2012). Rather, the concern is how patients were initially recruited. Patients for both safety trials originated from existing pimavanserin RCTs and were selected to participate by the investigators based on their perceived benefit with the continued use of pimavanserin. For NCT01518309, the sponsor selected patients "who had completed study ACP-103-006 (PD psychosis [PDP]) or study ACP-103-004 (PD with dyskinesias) and would benefit from continued pimavanserin treatment, as judged by the investigator" (U.S. National Library of Medicine, 2020b). For NCT00550238, the sponsor selected patients that "were adult males or females with Parkinson's Disease Psychosis who had completed a prior double-blind study with pimavanserin and were determined by the treating physician (i.e. the

investigator) to benefit from continued treatment" (U.S. National Library of Medicine, 2019).

This choice of participant selection presents a large risk of bias as it may allow patients who are benefiting from pimavanserin or are experiencing few or no adverse events to selectively participate in the study.

5.2.2.2 Measurement of the Outcome

The design of the studies also poses a risk of bias. For NCT01518309, the statistical analysis of mortality, adverse events, and serious adverse events was calculated for the single group exposed to varying doses of pimavanserin, ranging from 20mg to 60mg. The results for risk were not calculated with consideration for the level of exposure different patients had experienced. As such, patients who were treated with 20mg were analyzed together with patients treated with 40mg or even 60mg of pimavanserin. Without stratification for dosage in the analysis, if a risk were to exist at higher doses, it may be averaged out by participant data from lower dosages. Alternatively, if a risk were to exist at a lower dose, it may be averaged out by participant data from higher doses.

For NCT00550238, the IRR for mortality, adverse events, and serious adverse events were calculated separately for two groups: one group for patients who were treated with pimavanserin 40mg concurrently with other antipsychotics and the other group for patients treated with only pimavanserin 40mg. The most pressing issue with NCT00550238 is that the study did not actually ascertain the standalone risk of pimavanserin, but rather ascertained the risk of concurrent atypical antipsychotic use, which lends limited insight into the safety of pimavanserin.

For both safety studies, a better methodological design would be to have two treatment arms, one for the treatment with pimavanserin and the other with either placebo or existing atypical antipsychotics. In the FDA's own guidance document for sponsors, the instructions for the design of safety studies should include a suitable comparator. Specifically, "the ability of a comparative trial to detect a difference between treatments when one exists needs to be established because a trial incapable of distinguishing between treatments that are in fact different cannot provide useful comparative information" (Food and Drug Administration, 2001).

Employing an appropriate comparator group, either placebo or another atypical antipsychotic would have allowed the risk profile of pimavanserin to be more accurately compared and understood.

5.2.3 Single Arm Studies

There were two single arm studies (NCT03482882 and NCT04292223). Again, as the RoB 2 was not designed to evaluate single-arm studies, only applicable methodological issues in select domains will be presented. Only the results for NCT03482882 will be discussed as the results of NCT04292223 were not posted on clinicaltrials.gov because it was only recently completed and still falls within the 1-year grace period of mandatory reporting.

5.2.3.1 Deviations from the Intended Intervention and Measurement of the Outcome

As with the safety studies, there is a substantial risk of bias associated with an unblinded, non-placebo-controlled study. This design may have resulted in both the investigators and study participants being influenced throughout the delivery of the intervention and may have also introduced bias in the measurement of the endpoints. For NCT03482882 specifically, the clinician investigator may have been biased when assessing the severity and clinical improvement of the patient while administering the CGI-S and CGI-I. These issues contributed to the "high risk of bias" ratings for both domain 2 (deviations from intended intervention) and domain 3 (measurement of the outcome).

5.2.3.2 Missing Outcome Data

For NCT03482882, there was an issue with missing data, which may have been a source of bias. From a total participant size of 47, seven participants (14.89%) did not complete the trial, resulting in a concerning degree of missing data. As with the previously discussed RCTs, there was an inadequate explanation as to the source of the patient attrition, beyond vague and broad categories. These have been illustrated in *Table 7.*

Study (NCT03482882)	**Pimavanserin 34mg (n=7)**
Total n	47
Percentage of Drop-Out	14.89%
Adverse Event	3
Lost to Follow-Up	1
Protocol Violation	2
No Further Specifications	1

Table 7: Breakdown of missing data from NCT03482882.

There was a statistical analysis protocol that explained how missing data were handled and the compensatory methods employed. The investigators utilized different compensatory methods based on the endpoints being valued. For the CGI-S, CGI-I and EQ-5D-5L, missing values were not inputted. For SCOPA-DS and SCOPA-NS, mean imputation was used to compensate for missing values. Overall, due to serious shortcoming in the description regarding the categorization of the missing data, the domain was rated as being at a “high risk of bias”.

5.3 PRECIS-2

The PRECIS-2 was applied to all eight trials. The detailed ratings and rationales can be found in *Supplementary File C.* It should be noted that due to the limited availability of published journal articles (n=3), study protocols (n=2), and statistical

analysis plans (n=2) for some studies, certain domains for the PRECIS-2 are necessarily rated as “not applicable”.

5.3.1 Randomized Control Trials

For the four RCTs, their study design was mainly explanatory in nature. Across all the domains, the average score amongst the RCTs was 2.139, with the greatest explanatory domains being follow-up (score 1.00), eligibility (score 1.75), and primary analysis (score 2.00). The specific domain scores can be found in *Supplementary File C* and the PRECIS-2 graphs can be found below if *Figure 11*.

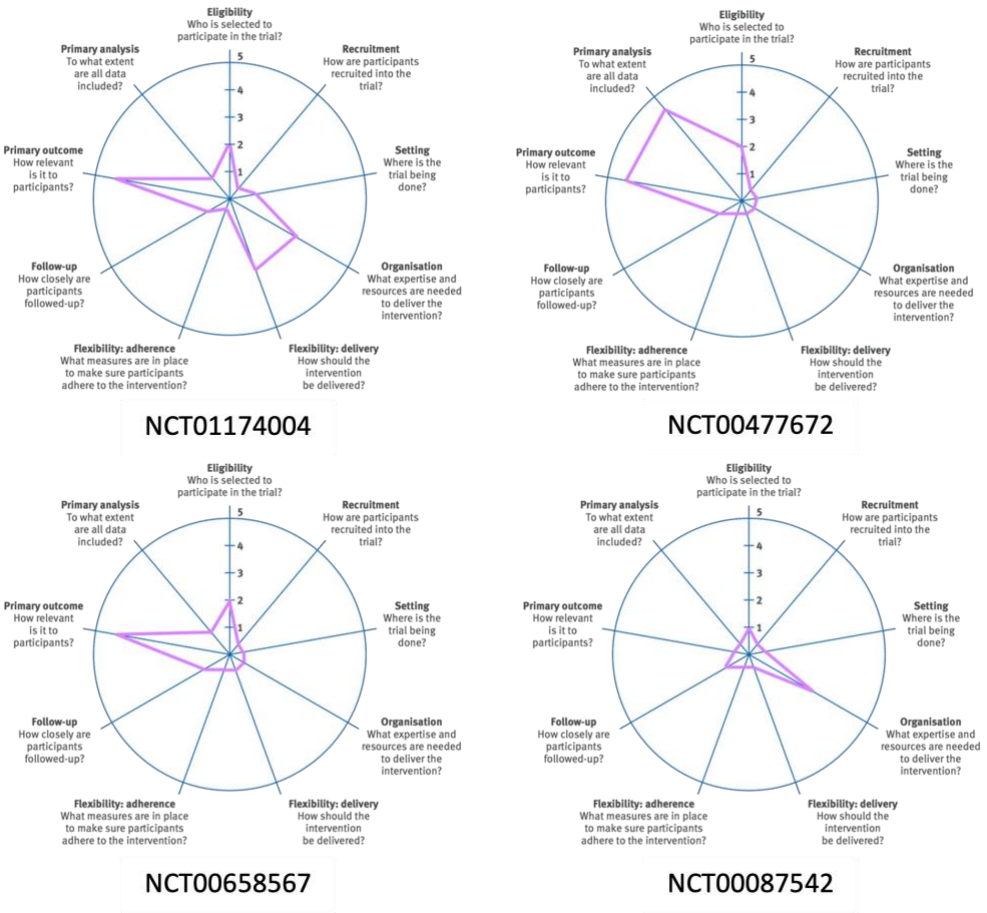

Figure 11: PRECIS-2 chart for RCTs.

5.3.1.1 Follow-Up

The follow-up was rated as being highly explanatory because there were frequent check-ins for measurement of the primary and secondary endpoints. This intensity of check-ins is much greater than that of usual care, leading to a low rating. Another contributor to the explanatory rating was that the overall follow up period was quite short, between 6-8 weeks, and does not represent the longitudinal nature of PDP, which can be experienced by patients for years (Friedman, 2010). As such, the initial intensity of visits and the subsequent limited follow-up period caused this domain to be assessed as highly explanatory.

5.3.1.2 Eligibility

The eligibility criteria for the RCTs were explanatory, with strict inclusion and exclusion criteria for participants. The inclusion criteria for the studies required the patients have at least three cardinal features of PD (e.g., rest tremor, rigidity, bradykinesia), psychosis (e.g., visual and/or auditory hallucinations) lasting four weeks or longer, clinical validated psychosis, be on stable doses of PD medication, a reliable caretaker, amongst other stringent inclusionary criteria. Exclusionary criteria included people who were pregnant or breastfeeding, had systematic factors that could contribute to psychosis, history of significant pre-morbid psychiatric conditions (e.g., depression, etc.), dementia precluding accurate assessment, use of depot neuroleptic in the past year, prior exposure to non-depot neuroleptic except for quetiapine or clozapine, amongst other highly stringent exclusionary factors.

5.3.1.3 Primary Analysis

Another contributor to the explanatory nature of the RCTs was how the primary analysis was conducted with regards to missing data. One of the studies (NCT01174004) simply did not impute any of the data, which is a highly explanatory means to handle missing data. Two of the studies (NCT00477672 and NCT00658567) employed a last observation carried forward (LOCF) method, which imputes missing data using the last collected data value and is a more pragmatic approach to missing data than simply not imputing the data. However, for NCT00658567, an entire arm was terminated prematurely with no reason cited, even though data were collected, which led to a highly explanatory rating. For NCT00087542, no statistical analysis plan was provided, so no rating for primary analysis could be provided.

5.3.2 Safety Studies

The two safety studies (NCT01518309 and NCT00550238) were mainly pragmatic in nature. Their PRECIS-2 diagrams can be found below as *Figure 12* and detailed rationales and ratings can be found in *Supplementary File C.* The average PRECIS-2 score across all domains were 4.032. The greatest contributors to this highly explanatory score were eligibility (score 4.00), setting (score 5.00), follow-up (score 5.00), and primary outcome (score 5.00).

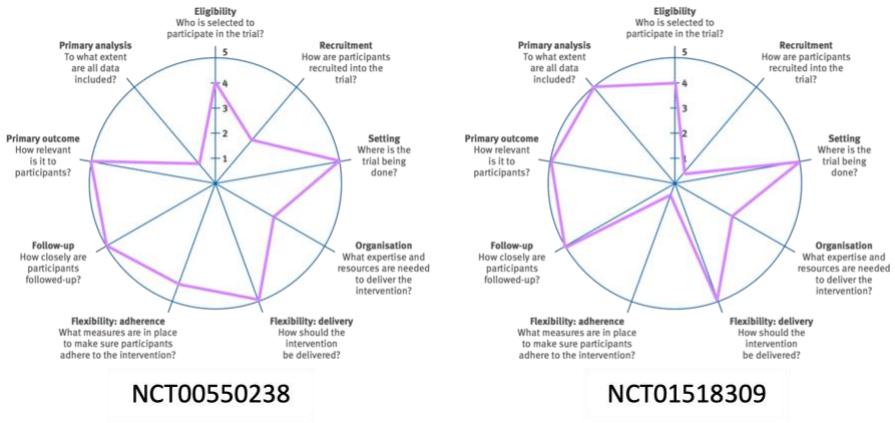

Figure 12: PRECIS-2 chart for safety studies.

5.3.2.1 Eligibility

In both studies, patients were selected from patients participating in existing RCTs based on a physician's determination that they would benefit from continued treatment with pimavanserin. Although the RCTs from which the patients were drawn had strict eligibility criteria and could lead to the studies being assessed as more explanatory in nature, the fact that there was a clinical decision applied for patient eligibility led to a pragmatic score. This is because in usual care, a physician would make a similar clinical decision where only patients deemed to likely benefit from a drug would be prescribed that drug.

5.3.2.2 Setting

The setting for these studies was in an outpatient setting. This means that patients were not in a highly controlled clinical environment for the duration of the study, and could continue their treatment with other PD medications, and in the case of NCT00550238, other concurrent atypical antipsychotics. This study design feature is

congruent with how long-term safety studies are normally conducted, and emulated real-world interactions that patients may be in. As a result, this domain for safety studies was highly pragmatic in nature.

5.3.2.3 Follow-Up

As a result of the outpatient setting, patients were observed until they encountered an adverse event, a serious adverse event, or death. This length of follow-up varied and in NCT00550238, patients on concurrent atypical antipsychotics were followed for an average of 172 days while patients not on concurrent atypical antipsychotics were followed on average for 421 days. This domain of the study design was highly pragmatic in nature due to the extensive length of follow-up.

5.3.2.4 Primary Outcome

The primary outcomes for the safety studies were adverse events, serious adverse events, or mortality. These outcomes are of obvious importance to patients, unlike more explanatory outcomes such as surrogate or physiological outcomes. As a result, the primary outcome domain for the two safety studies were rated as highly pragmatic.

5.3.3 Single Arm Studies

The two single-arm studies (NCT04292223 and NCT03482882) had an average score of 2.7, leaning more towards pragmatic than explanatory. The results of these domains will not be extensively discussed because of limited information stemming from the lack of published protocols and statistical analysis plans. For both studies, four of the nine domains did not have sufficient information to rate their domains. Their PRECIS-2 diagrams can be found below as *Figure 13* and their detailed rationales and ratings can be found as *Supplementary File C.*

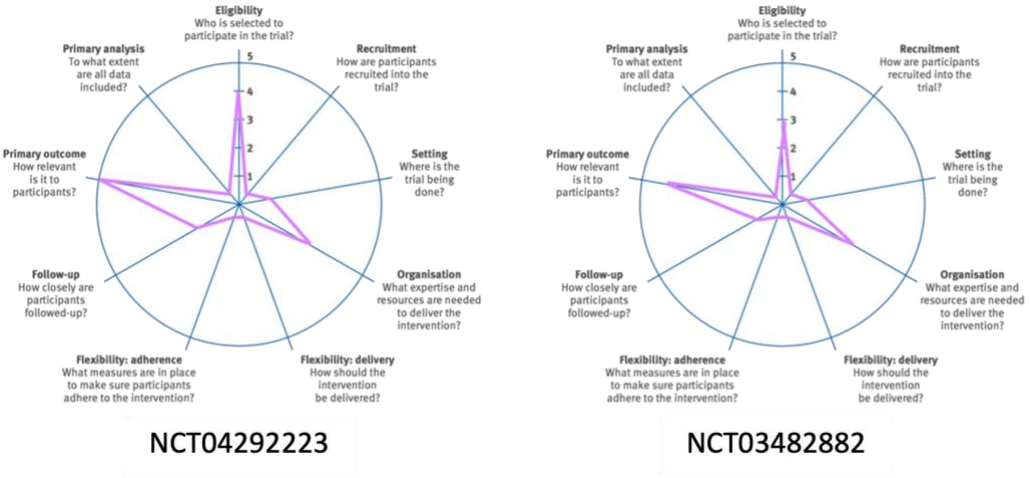

Figure 13: PRECIS-2 chart for single-arm studies.

5.3.3.1 Eligibility

The inclusion and exclusion criteria for both studies were quite extensive but less stringent than the RCTs. For both, patients had to be diagnosed with PD and had psychotic symptoms that developed after the onset of PD, along with being stable on PD medication.

5.3.3.2 Primary Outcome

Both primary outcomes were global performance scales that are highly applicable to patients, and as a result, were more pragmatic. For NCT03482882, the outcomes used were the CGI-S and the CGI-I, which gauge the patients' disease severity and degree of improvement after initiating treatment. Both endpoints are pragmatic because they relate directly to a patient's day-to-day health and can be applied in routine care (Loudon et al., 2015). This contrasts with explanatory outcomes, which are more esoteric in nature, and may not be of obvious importance to a patient. Examples of explanatory outcomes can include surrogate endpoints and physiological outcomes (Loudon et al., 2015). For NCT04292223, the primary outcome was the mSFQ, which assessed ADL, psychological function and mental health, and social function (e.g., work, social activity, quality interaction, sexual life, etc.), which led to a pragmatic rating.

Chapter 6

6 Discussion

In light of the breadth of information presented within the results, it needs to be reiterated and acknowledged that no discussion or assessment will be wholly ‘objective’. In the realm of drug safety and new pharmacotherapies, there is often a trade-off between the clinical benefit and the potential risk to patients. Therapies with a favorable efficacy profile and a low risk profile, or those with a poor efficacy profile and a high-risk profile, are not contentious. What is of contention are those therapies for which the efficacy is moderate or high, and the risk to the patient is equally great. In those cases, it is important to implement well-designed trials that can clearly communicate to regulators, clinicians and patients if such a risk exists, and to assess the interplay of these risks with the potential therapeutic benefit, leading to informed decision making.

As such, the scope of the discussion will focus on the interpretation of these results, specifically considering the FDA’s decision to expedite pimavanserin’s approval. The following discussion will be presented first with a preface highlighting the duties of different medical experts within the realm of pharmacovigilance, followed by major safety themes amongst the results, this project’s contribution to the literature, and limitations.

6.1 Duty of Medical Experts: A Preface

Amidst the discussion on trial design and regulatory policies, the most important stakeholder can sometimes be forgotten; the patient. The patient is a uniquely important stakeholder in clinical trials and their role should be highlighted. There is a dichotomy. On one hand, the patient is an expert of how they experience their condition and is in a unique position to exercise some degree of autonomy over their disease experience. They are also active agents in the development of new therapies, and clinical trials could not be conducted without their participation. On the other hand, patients are often themselves not a basic scientist, a health economist, a clinician, or a drug regulator. They are in a vulnerable position, having limited expertise required to properly exercise their autonomy. Therein lies the duty of medical experts.

The duty of a clinician is to guide the patient to make well-informed treatment decision for themselves, and to accept (or not) the therapy with the risk-benefit assessment that fits the patient's value system (Forte et al., 2018). Similarly, the duty of the regulator is as a legal authority, as an arbiter, and as a public advocate. Firstly, the regulator ensures that the information provided for the risk-benefit profile is clear enough such that the clinician can help guide the patient to make an informed treatment decision. This is done by setting the rules regarding how this efficacy and safety information is collected, presented, and analyzed. Secondly, they act as an arbiter, such that once a clear risk-benefit profile has been established, it can be analyzed and debated before being authorized to clinicians and to patients (Nelson et al., 2014). Finally, the third duty of a regulator is that of an advocate for the best interest of the public by "helping to speed

innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health" (Food and Drug Administration, 2018c).

By contrast, the duty of the drug manufacture is arguably primarily to its shareholders, which is achieved by maximizing corporate profitability of its medicines either through expanded indications or other means (Kitsis, 2011). Oftentimes, these different duties align with one another, and the patient and their family receive the appropriate care (Fleming et al., 2017). There are instances, however, when the different duties of each party are not aligned, which may result in harm to patients (Fleming et al., 2017). The role of the regulator is particularly important as their actions can impact the faith the public has towards the medical establishment.

Through this lens, the FDA as regulators in the case of pimavanserin had several responsibilities. On a systems level, the FDA needed to ensure that the drug and indication were suitable for the expedited pathways. On an approval decision level, the FDA needed to ensure there was enough quality efficacy and safety evidence presented through trials that were 'fit for purpose', such that their approval decision, if one were to be granted, was well informed. The former was not within the scope of this project, as many clinicians, patients, and their families will argue that PDP is a pressing indication with no current treatment alternatives that requires expedited treatment. What has been established through this study, however, is that there are serious methodological and risk of bias concerns.

6.2 Positive Trial Features

The most notable positive features of the RCTs were the choice of the endpoints and the perspectives from which those endpoints were elicited. The use of the SAPS-PD as the primary endpoint, along with other general psychiatric, motor, and quality of life metrics as secondary endpoints, allowed the RCTs to capture a more holistic understanding of pimavanserin's efficacy. This is especially important given that PDP is multifaceted disease, and that for pimavanserin to demonstrate superior clinical efficacy, it could not exert degenerative effects on motor functions like its dopaminergic predecessors. This was accomplished by the sponsors using the UPDRS and the MDS-UPDRS. In addition, using a broad range of secondary endpoints to capture a complex condition is especially important in late-stage trials that hold greater weight in clinical and policy decision-making, therefore requiring a more comprehensive understanding of the therapy's properties (McLeod et al., 2019).

As well, the use of patient reported outcomes (PROs) and care partner reported outcomes to capture features like ADLs and the potential impact on care partner burden is commendable. With the paradigm shift to patient-centered care and clinical trials design, incorporating metrics that report on both patients and care partners can be a means to help achieve that (Sharma, 2015). With PROs gaining prominence in the past two decades, their clinical, health economic, and regulatory benefits have also been recognized. These include: 1) helping to guide better treatment decisions; 2) enriching regulators' understanding of patients' lived experiences, especially with difficult to capture domains (e.g., pain and fatigue); 3) improving cost-effective analyses; and 4) supporting patient

advocacy (Mercieca-Bebber et al., 2018). With a condition like PDP, where the impact of treatment is felt by close family members, using these metrics to communicate varying disease experiences put the FDA in a better position to understand pimavanserin's efficacy and impact on different stakeholders.

6.3 Primary Concerns

There was a wide spectrum of concerns identified in this analysis, as highlighted by the RoB 2 and PRECIS-2. These concerns can most succinctly be understood and discussed through the lens of three main themes. These are 1) inadequate number and length of trials, 2) high risk of bias, and 3) poor trial design leading to a poorly understood safety profile.

6.3.1 Inadequate Number and Length of Trials

The most prominent concern identified in this study was the inadequate number and length of the RCTs that formed the basis for regulatory approval. As previously mentioned, the FDA's own threshold established in 1998 to require at least two adequate and well-controlled studies was not met. With this benchmark, while the sponsor technically had four RCTs, and had satisfied the requirement of two studies, there were two issues that arose from this.

Firstly, only one RCT (NCT01174004) formed the basis for the FDA's approval (Food and Drug Administration, 2016). Stemming from the Breakthrough Therapy designation, the standard of evidence for pimavanserin's approval as agreed between Acadia Pharmaceuticals and the FDA rested only on one strongly positive study

supported by data from other trials, rather than two studies which are each convincing on their own. This agreement can be referenced in the FDA's PDAC transcript, which is attached as *Supplementary File D* and can be referenced on page 150. Specifically, this study highlights concerns that under these expedited mechanisms, the criteria suitable for warranting approvals was not met.

Secondly, with regards to the term "adequate trials" and their impact on establishing a clinically meaningful effect, the RCTs with a trial length ranging from 6-8 weeks is arguably not long enough. The disease experience of PDP is long lasting and in in 60% of cases, leads to a patient's eventual institutionalization (Zahodne & Fernandez, 2008; Aarsland et al., 2000). As such, to paint a more comprehensive picture of pimavanserin's clinically meaningful effect, an adequate trial length extending past 6-8 weeks should have been established. While it is understandable that it is both logistically and financially unfeasible to require sponsors to implement trials that are several years in length, such trials for PDP exist. For example, the exploratory trials from the Parkinson Study Group (1999) and Pollak et al. (2004) using clozapine for the treatment of PDP had a total study period of 14 months and five months, respectively. Although these two study periods vary greatly, longer trials are clearly possible and would have improved the quality the data. it should be expected that the RCTs of therapies for the same indication be of a similar length. Even though pimavanserin was a Breakthrough Therapy designation product within the Priority Review pathway, it should not preclude the implementation of a sufficient trial period.

It is also concerning that the benefits conferred within the Breakthrough Therapy designation included intensive guidance from the FDA on the drug's development and

trial design, yet each of the four RCTs were of insufficient length. This may simply suggest that the guidance from the FDA did not include a discussion with the sponsor about adopting a suitable trial length. Alternatively, it may suggest that a sufficient trial length was not a prerequisite to gaining a Breakthrough Therapy designation, or that it was not a prerequisite to gaining final regulatory approval as an expedited product. The latter, if true, would be extremely concerning, as it would mean that the threshold for final regulatory approval is different for expedited products compared to non-expedited products, and would be contrary to the FDA's prescribed messaging that the approval standards are uniform for all regulatory approval applications. At the time of this manuscript's publication, no additional systematic review has been conducted comparing the trial lengths between expedited and non-expedited products. Additional research is recommended in this area to further investigate this concern.

6.3.2 High Risk of Bias: Missing Data

A secondary concern that emerged from the results was the high risk of bias observed using the RoB 2 amongst the RCTs. One of the most notable concerns stemmed from the poorly explained nature of the missing data (i.e., randomness). This alone was enough to cause the rating for the pivotal study (NCT01174004) to receive a high risk of bias rating as opposed to a moderate risk of bias rating. Although participant attrition in clinical trials is not unexpected, different rates of losses between the experimental and control group, as observed in pimavanserin's trials, can lead to attrition bias (Bankhead et al., 2017). A review of RCTs conducted by Akl et al. (2012) estimated that up to 33% of trial outcomes were no longer significant amongst trials where the missing data were disproportionately represented in the experimental group. This is particularly concerning

since the pivotal trial (NCT01174004), which formed the basis of pimavanserin's approval, did not employ any statistical compensatory techniques, and simply chose to not impute the data. With this review in mind, the systemic risk of bias originating from missing data could have negatively influenced the interpretation of pimavanserin's efficacy as a breakthrough product. As previously mentioned, an analysis of the PDAC's meeting transcript revealed that the FDA's approval of pimavanserin was primarily dependent on NCT01174004 and supported by data from earlier trials. Putting so much interpretive weight on a single trial at a high risk of bias could compromise the interpretability of pimavanserin's safety and efficacy profile.

6.3.3 Poor Trial Design and Poorly Understood Safety Profile

Another theme of concern that was uncovered by the RoB 2 and PRECIS -2 tool was the poor design of the safety studies. Although the safety studies were pragmatic in nature, as illustrated by the PRECIS-2 graphs, this was not the issue. In fact, pragmatic safety studies may be beneficial in that they allow study investigators to observe patients in a 'real-world' environment, where there may be interactions with other medications, co-morbid conditions and variable adherence regimens (Treweek & Zwarenstein, 2009). The main concern with these studies, rather, was that there was a selection bias in that participants were selected from pre-existing RCTs. As well, for NCT00550238, the comparison of mortality risk, serious adverse events, and adverse events, were made between patients on pimavanserin and concurrent atypical antipsychotics compared to patients only on pimavanserin. This made it difficult to ascertain the standalone risk of pimavanserin compared to placebo and confounds the understanding of its safety profile. Unfortunately, approving a drug with a poorly understood risk profile means that the onus

and risk of uncovering safety risks shifts from regulators to patients. This issue was echoed by members of the PDAC, who despite voting favorably on pimavanserin, brought up reservations about the unclear risk to patients.

With respect to being a Breakthrough Therapy designation product, it is concerning that a drug that was acknowledged to have a poorly understood safety profile was approved for market authorization. It raises questions as to whether the FDA is trading 'perceived benefit' for 'perceived risk', given that pimavanserin is the first therapy specifically indicated for PDP. If that is the case, then it raises even more questions as to whether the FDA ought to hold the authority to trade potential risk for potential benefit on behalf of patients. Again, this is not a point against the FDA approving drugs with a *known* harmful safety profile, as that decision would be understandable. For example, oncology drugs frequently have a toxic safety profile, yet they are still approved due to their known benefit. Rather, the concern is directed at the FDA approving drugs with an *inadequately studied* safety profile, in which the risk is not well understood, and this issue is compounded by polypharmacy within the patient demographic.

Therein also lies the issue with expedited approvals. As previously discussed, the FDA as a regulator has duties as a legal authority, an arbiter, and as a public advocate. By creating expedited pathways where drugs can be expeditiously reviewed and approved on limited safety data, potentially resulting in harm to patients, the FDA may be failing in their roles.

6.4 Contributions to the Literature

Several prominent pimavanserin safety studies have already been conducted. Some of these studies include a re-analysis conducted by the FDA using public and sponsor-provided data (Food and Drug Administration, 2018d), an independent retrospective cohort study of 2186 pimavanserin users from an administrative database (Hwang et al., 2021), and an ongoing independently conducted trial (VA Office of Research and Development, 2022). These post-hoc studies, although important, contribute narrowly to the literature by debating the nuances and statistical significance of safety signals.

This study, however, contributes to the literature by examining the very foundation of pimavanserin's approval, and raises questions regarding whether the quality of evidence, determined by the risk of bias and trial design, should have led to an FDA approval. To the knowledge of the author, this study is the first of its kind for pimavanserin.

Finally, this study contributes to the literature by highlighting the concerns of substandard trial design and risk of bias when expediting 'first-in-line' drugs. It highlights that despite stakeholder demand, there is still a duty on the part of the regulator to ensure quality evidence is being submitted and assessed. An expedited approval should not mean a compromise in quality and safety or "lowering the bar" *per se*. Rather, it should only mean that the sponsor is able to reach the threshold for generating quality efficacy and safety more quickly, with guidance and support from regulators.

6.5 Limitations

There are several limitations that should be considered when interpreting these results. Primarily, the scope of this study is limited to the FDA's approval of pimavanserin and to PDP, and may might not be generalizable to other disease divisions within the FDA or other drugs. With each new drug application, there may be other variables that may impact the design, feasibility of implementation, and integration of clinical trial data. As well, because pimavanserin was approved through the Breakthrough Therapy designation and Priority Review pathway, the results of this study may not be fully generalizable to the Fast-Track and Accelerated Approval designations. Future research to comprehensively assess the full scope of these expedited programs, and the robustness of their pivotal trials is recommended.

Another limitation of the study is the subjective nature of the RoB 2 and PRECIS-2 tools. No tool is perfect. As each tool requires interpretation from the individual rater using it, there is a degree of subjectivity within the reported results. This may be even more pronounced in the RoB 2 tool, as there have been concerns from users regarding its steep learning curve and poor interrater reliability (Minozzi et al., 2020). This stems from issues relating to the difficulty interpreting the signaling questions, new terminology, amongst other issues, which may hinder the application and interpretation of the tool's results (Minozzi et al., 2020). In an ideal research setting, this project would have been conducted with multiple raters with extensive expertise in clinical trials. However, practical implementation of such a project given the resources available to the research team would be untenable.

A final limitation of the study is the lack of available protocols and publications for some of the studies, in particular the single-armed studies. The lack of published information made it difficult to populate certain domains of the RoB 2 and PRECIS-2 tool, and as a result, limited the interpretation of certain domains to a degree. This is also the reason why the single-arm studies were included in the results but were not contextualized in the discussion, as the author was hesitant to make premature assumptions and instead focused the narrative on the RCTs and safety studies.

6.6 Next Steps

The next steps for the medical and research community should be to continue monitoring potential safety signals, as well as to conduct independent RCTs with the aim of validating the sponsor's original safety and efficacy claims. The reason that third party investigations should be conducted is because sponsor led RCTs may be at high risk of bias, as demonstrated by this study. Although this may burden the medical and academic community, the FDA could introduce a system where fees are levied as part of the regulatory submission process and be used towards conducting confirmatory trials. These confirmatory trials would not be conducted for every submission application but may be limited to submissions where the original trials were at a high risk of bias.

The next steps for the FDA and for the broader regulatory community is threefold. The FDA should not only continue to monitor pimavanserin for safety issues, but to more stringently evaluate Acadia Pharmaceuticals' future applications to expand pimavanserin's indications, with particular attention on their pivotal clinical trials. This

includes Acadia Pharmaceuticals' attempt to expand pimavanserin for the treatment of dementia-related psychosis and Alzheimer's disease psychosis.

Secondly, the FDA should re-examine the threshold for approving novel therapies through the expedited pathways, and to reconsider the potential harms posed to patients when drugs are approved on limited or biased clinical trial data. This would include standardizing the length of trials that should be expected for different indications or drugs classes. This would more easily convey the standards and expectations for study designs that the FDA have for sponsors. This would also benefit sponsors, as it means that there is less ambiguity when it comes to designing and conducting clinical trials, leading to a more transparent regulatory submission process.

Thirdly, future efforts should focus on incorporating tools to formally assess risk of bias and trial robustness into official regulatory processes. While the specific mechanisms to implement such tools are out of the scope of this paper, the RoB 2 can be highlighted as an example. Specifically, the RoB 2 could be used as a filter for drug applications. In this scenario, only drug applications with a low risk of bias would be allowed to be considered for regulatory approval, and those with some or high risk of bias would be rejected. Further research into the optimal implementation of the RoB 2 is recommended.

6.7 Conclusion

With pimavanserin, it was demonstrated that there exists a substantive risk of bias amongst the pivotal RCT and methodological design concerns with the safety studies.

Based on these findings, the conclusion to the research question is that there was not enough quality evidence and suitably designed trials to warrant an accurate safety and efficacy assessment. Specifically, an insufficient number and length of trials, poor handling of missing data, and substandard safety trials contributed to this conclusion. There is still much to be learned about the application of expedited trials, especially regarding the standards surrounding pivotal trials and the robustness of their designs. Future research should continue to monitor pimavanserin's safety, as well as provide actionable guidelines for the FDA to improve their regulatory processes moving forward to protect patients' best interests.

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