FDA Opening Remarks

Psychopharmacologic Drugs Advisory Committee Meeting
June 17, 2022

Pimavanserin (Nuplazid) for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis

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Today's Discussion

- Application under review is a resubmission after Complete Response
- The Applicant is now seeking a narrower indication than the prior submission
- No new studies; however, the Agency has agreed to review new analyses of existing data
- The Agency's presentations will briefly describe the regulatory history, including relevant aspects of the Complete Response decision and post-action discussions with the Applicant, followed by our evaluation of the current application.

Alzheimer’s Disease Psychosis

- Alzheimer’s disease is the most common form of dementia in the United States, with an estimated prevalence of 6.5 million individuals (2022)
- The pathological hallmarks of Alzheimer's disease include extracellular deposits of amyloid beta (plaques) and intracellular aggregates of hyperphosphorylated tau (neurofibrillary tangles)
- Although cognitive decline is the predominant symptom, neuropsychiatric symptoms, including hallucinations and delusions, are common
- Neuropsychiatric symptoms cause distress and are associated with a higher risk of rapid progression to severe dementia, death, and out-of-home placement

Alzheimer's Disease Psychosis

- No currently approved pharmacologic treatments for hallucinations and delusions associated with Alzheimer's disease psychosis
- Per the 2016 American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia, the benefits of antipsychotic medications are small at best

Pimavanserin (Nuplazid)

- Serotonin-selective inverse agonist that preferentially targets the 5-HT2A receptor subtype
- Indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP)
- Proposed indication: treatment of hallucinations and delusions associated with Alzheimer's disease psychosis (ADP)

Sources of Evidence

- Prior approval of pimavanserin for the treatment of hallucinations and delusions associated with PDP
- Study ACP-103-019 (Study 019)
  - Phase 2, 12-week, double-blind
  - Alzheimer's disease psychosis
  - Change from baseline to Day 43 on the Neuropsychiatric Inventory – Nursing Home Version Psychosis Score
  - Positive results on prespecified primary endpoint
- Study ACP-103-045 (Study 045)
  - Phase 3, relapse prevention, 12-week open-label period followed by 26-week randomized withdrawal double-blind period
  - Multiple subtypes of dementia including large Alzheimer's disease subgroup
  - Time from randomization to relapse in the double-blind period
  - Positive results on prespecified primary endpoint

Study ACP-103-020 (Study 020)

- Basis for prior approval of pimavanserin for the treatment of hallucinations and delusions associated with PDP
- Phase 3, double-blind, 6-week
- Parkinson's disease psychosis
  - Subset with Parkinson's disease dementia
- Change from baseline to Day 43 on the Scale for the Assessment of Positive Symptoms-Parkinson's Disease (SAPS-PD) total score
- Positive results on the prespecified primary endpoint

Applicant's Resubmission

- Study ACP-103-019 (Study 019) – primary evidence
  - Applicant is asking the Agency to consider this study adequate and well-controlled
  - Applicant has addressed concerns related to study design and conduct raised in the Complete Response letter
  - Study is positive on primary endpoint at Day 43
  - Current concerns relate to interpretation and clinical meaningfulness of change on the primary endpoint and overall strength of the data

Applicant's Resubmission

- Study ACP-103-045 (Study 045) – supportive evidence
  - Positive study in a population consisting of subjects with several dementia subtypes
  - Subgroup analyses suggest that the positive results on the primary endpoint were driven by the response in subjects with Parkinson's disease dementia (PDD)
  - Applicant has conducted a series of post-hoc analyses intended to show that pimavanserin's effect in the ADP subgroup is consistent with that in the PDD subgroup

Applicant's Resubmission

- Prior approval for hallucinations and delusions in PDP (i.e., Study 020)
  - Applicant asserts that ADP and PDP should be considered closely related conditions
  - Design of Study 045 based on a priori assumption that this approach was reasonable (Agency agreed with approach)
    - Although there are differences in pathophysiology of Alzheimer's (amyloid plaques, tau tangles) and Parkinson's (loss of dopaminergic cells in substantia nigra), psychotic symptoms are present in both
    - Pathophysiological underpinnings of psychosis in each condition is unknown
  - On face, results of Study 045 suggest differences in treatment response
  - Applicant's post-hoc analyses of Study 045 data intended to demonstrate similarities in response and support position that diseases are closely-related

Applicant's Resubmission

- Safety not a focus of this discussion
  - Findings from supplemental New Drug Application development program largely consistent with known safety profile of pimavanserin

Charge to the Committee

- Discuss the evidence supporting the effectiveness of pimavanserin for the treatment of hallucinations and delusions in the ADP population, including strengths, limitations, and potential contribution of:
  - Study 019
  - Study 045
  - The prior approval of pimavanserin for the treatment of hallucinations and delusions associated with PDP
- Voting question: Does the available evidence support a conclusion that pimavanserin is effective for the treatment of hallucinations and delusions in the ADP population?

Pimavanserin (Nuplazid) for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis

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Outline

- Relevant Regulatory History
- Study ACP-103-019 (Study 019)
  - Design and results
  - Resubmission
- Study ACP-103-045 (Study 045)
  - Design and results
  - Resubmission analyses

Relevant Regulatory History

- Approved in 2016 for treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP)
- At 2008 pre-IND meeting, Applicant outlined plan for Study 019, a phase 2, randomized, double-blind, placebo-controlled study of pimavanserin in subjects with Alzheimer's disease psychosis (ADP) as part of multi-study approach to support dementia-related psychosis indication

Relevant Regulatory History

- At 2017 End-Of-Phase 2 meeting, Agency agreed treatment of hallucinations and delusions associated with dementia-related psychosis potentially approvable indication
- Agency expressed concerns about basing regulatory decision on proposed single, randomized withdrawal study (Study 045), but agreed
  - Subjects needed to be stratified by dementia subtype
  - Potential labeling would reflect subtype composition and response of subjects
- Applicant submitted application June 2020 supported by primary Study 045 with Study 019 and resubmitted data from Study ACP-103-020 (Study 020) — phase 3 study in subjects with PDP, a subset of whom had dementia

Relevant Regulatory History: Complete Response

- Complete Response (CR) April 2021 concluded application did not provide substantial evidence of effectiveness for dementia-related psychosis
- Although Study 045 not powered for subgroup efficacy demonstration, subgroup observations included:
  - Results for Parkinson's disease dementia (PDD) subgroup were highly nominally statistically significant, appearing to drive overall results despite smaller size (n=35)
  - Results for Alzheimer's disease (AD) subgroup not nominally statistically significant despite largest subgroup (n=123)
  - Too few subjects with dementia with Lewy bodies (n=10) or frontotemporal dementia (n=3) to adequately represent those subgroup responses
  - No difference on time-to-relapse for vascular dementia (n=25)

Relevant Regulatory History: Complete Response

- Agency noted that Study 045 results:
  - Essentially demonstrated what was already accepted – that pimavanserin was effective in the treatment of PDP
  - Suggested differential response across dementia subtypes, calling into question whether dementia-related psychosis is useful construct for potential indication
- Agency did not consider Study 019 to be an adequate and well-controlled trial, highlighting concerns related to trial design and conduct

Relevant Regulatory History: Resubmission

- Applicant discussed resubmission plans with Agency at post-CR meetings, including intention to change proposed indication to treatment of hallucinations and delusions associated with ADP
- Agency agreed to consider Applicant's points in a resubmission but advised that an additional adequate and well-controlled study in subjects with ADP would likely provide strongest data in support of resubmission

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Study 019

Overview of Design

- Phase 2, randomized, double-blind, placebo-controlled study of pimavanserin tartrate 40 mg once daily versus placebo
- Conducted at network of 133 nursing homes in United Kingdom under the supervision of a single principal investigator
- 12-week treatment period
- 3-week screening period included antipsychotic washout (if necessary) and brief psychosocial therapy

Design and Population

- Enrolled 181 nursing home residents ≥ 50 years-old who met criteria for AD, with psychosis, with baseline Mini-Mental Status Examination (MMSE) score ≥ 1 and ≤ 22
- Excluded for psychotic symptoms caused by other reason
- Antidementia drugs, antidepressants, and anxiolytics permitted if stable before and during study
- Randomization 1:1 stratified by baseline MMSE and Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) Psychosis Score (NPI-NH PS)

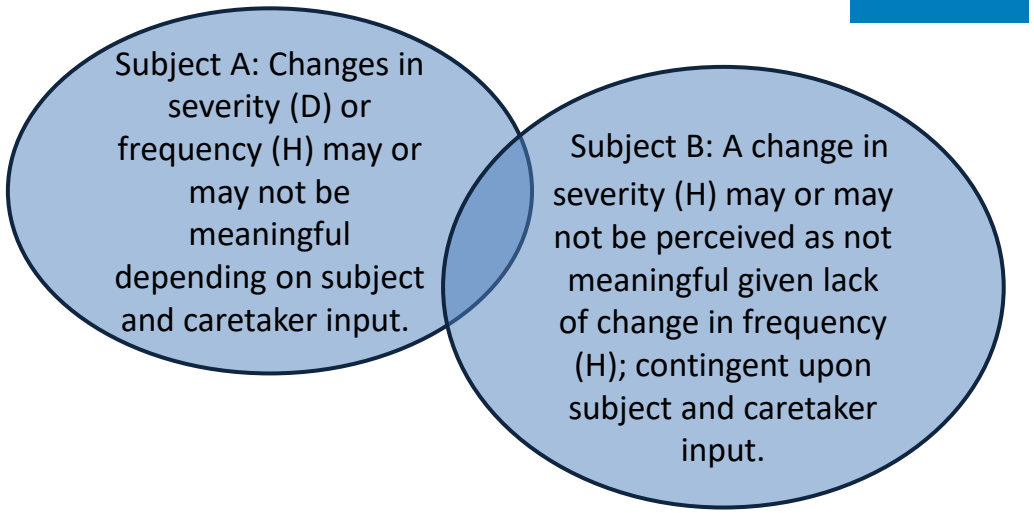
Primary Endpoint

- Mean change from baseline to Day 43 on the NPI-NH PS
- NPI evaluates 12 domains common in dementia, PS includes Delusions domain + Hallucinations domain
- Score of each item is product of frequency (range 1 to 4) and severity (range 1 to 3) for maximum 12 on each domain, 24 total (higher = worse)
- Although adequate for exploratory purposes:
  - Concerns regarding scoring and interpretation of group and individual differences
  - Supported by limited evidence of content validity for context of use

NPI-NH Scoring Interpretation Challenges

Possible Score Values

Severity	Frequency: Rarely	Sometimes	Often	Very Often
Mild	1	2	3	4
Moderate	2	4	6	8
Severe	3	6	9	12



Subject – NPI-NH PS domain	Baseline Severity (S)		Baseline Frequency (F)		Baseline S x F Score	End of Study Severity (S)		End of Study Frequency (F)		End of Study S x F Score	S x F Score Delta
Subject A – Delusions (D)	Moderate	2	Very Often	4	8	Mild	1	Very often	4	4	-4
Subject A – Hallucinations (H)	Severe	3	Very Often	4	12	Severe	3	Often	3	9	-3
Subject A – Combined Score					20					13	-7
Subject B – Delusions (D)	Mild	1	Sometimes	2	2	None	0	None	0	0	-2
Subject B – Hallucinations (H)	Severe	3	Often	3	9	Moderate	2	Often	3	6	-3
Subject B – Combined Score					11					6	-5

NPI-NH Content Validity

- Missing evidence:
  - Research within the development program to provide evidence of content validity of the NPI-NH PS
  - Comprehensive review of the literature with a summary focused on how the items measure the targeted concept of interest (i.e., delusions and hallucinations)
  - Overall gaps in psychometric evidence from the literature
- Missing concepts on NPI-NH PS can result in a potentially incomplete picture of psychosis in subjects with ADP (capture of activity, severity, frequency)

Secondary Endpoints

- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) at Day 43
- Change from baseline to Day 43 on:
  - NPI-NH domains: Agitation/Aggression, Sleep and Nighttime Behavior Disorders
  - Cohen-Mansfield Agitation Inventory-Short Form (CMAI-SF) total score
    - 14 items assessing frequency of behaviors in past 2 weeks
    - Each rated 1 to 5 for maximum 70 (higher = worse)
  - CMAI-SF subdomains: Aggressive Behavior, Physically Nonaggressive Behavior, Verbally Agitated Behavior

Relevant Exploratory Endpoints

- Analysis of primary and secondary endpoints at other time points
  - Including NPI-NH PS durability of response from Day 43 to Day 85
- Primary endpoint by subgroups
  - Including by baseline NPI-NH PS scores < 12 versus ≥ 12 and baseline MMSE < 6 versus ≥ 6
- Change from baseline to Day 43 on Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) total score
  - Exploratory functional endpoint

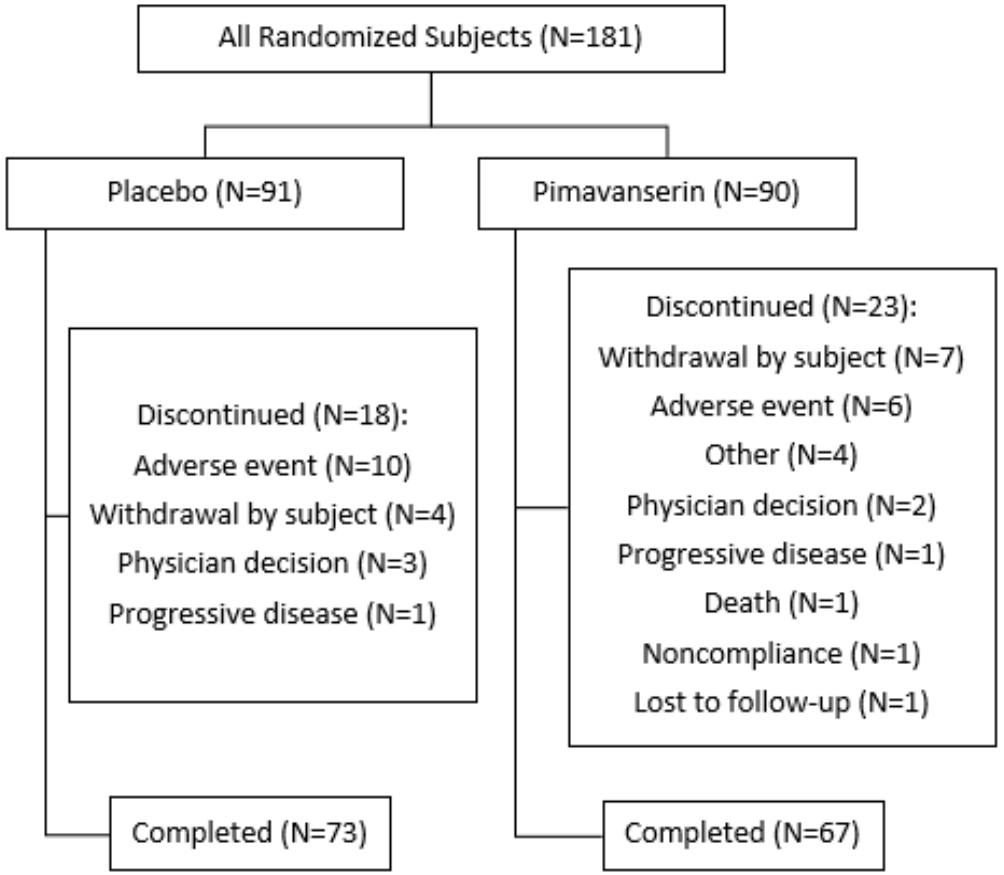
Statistical Design

- Primary endpoint analysis: mixed-effect model repeated measures (MMRM)
- Fixed effects
  - Baseline MMSE category (< 6 and ≥ 6)
  - Baseline NPI-NH PS
  - Treatment (placebo or pimavanserin 40 mg)
  - Visit (Days 15, 29, 43, 64, and 85)
  - Treatment-by-visit interaction
- No multiplicity adjustment for secondary endpoints

Analysis Set

- All randomized subjects (N=181)
  - N=91 placebo
  - N=90 pimavanserin
- Full Analysis Set (FAS) (N=178) included randomized subjects with both Baseline and at least one post-Baseline NPI-NH PS
  - N=91 placebo
  - N=87 pimavanserin

Subject Disposition



Source: Clinical reviewer-created from Study 019 Clinical Study Report, Figure 10-1, p. 68.

Major Protocol Deviations

Major Protocol Deviation	Placebo (N=91) n (%)	Pimavanserin (N=90) n (%)
Study procedures	60 (65.9%)	51 (56.7%)
Informed consent	46 (50.5%)	39 (43.3%)
Eligibility	39 (42.9%)	44 (48.9%)
Exclusionary medication use or change at time of randomization or within randomization window	20 (22.0%)	25 (27.8%)
Unable to confirm ADP onset after AD diagnosis	19 (20.1%)	20 (22.2%)
Investigational product compliance	8 (8.8%)	9 (10.0%)
Visit schedule	4 (4.4%)	8 (8.9%)
Concomitant medication	1 (1.1%)	4 (4.4%)
Serious adverse event reporting	1 (1.1%)	0
Other	1 (1.1%)	0

Source: Clinical reviewer-created from Study 019 Clinical Study Report, Table 10-2, and Study 019 ADDV dataset

AD = Alzheimer's disease, ADP = Alzheimer's disease psychosis

Note: Subjects may have had multiple protocol deviations within each category and are counted once within each. Subjects with eligibility deviations in both listed subcategories appear in both subcategories and not all eligibility deviation subcategories are listed; subcategories do not add up to the eligibility deviations total.

Demographics and Baseline Characteristics

- Mean age ~86 years
- ~80% female
- Race
  - Placebo: 98% White
  - Pimavanserin: 93% White
- Ethnicity 100% not Hispanic or Latino
- Median duration of AD ~57 months
- Median duration of ADP ~16 months
- Median NPI-NH PS = 8
- Median CMAI-SF = 27

Primary Endpoint Results

	Placebo (N=91)	Pimavanserin (N=87)
Mean NPI-NH PS score at Baseline (SD)	10.00 (5.584)	9.52 (4.839)
Mean NPI-NH PS score at Day 43 (SD)	7.88 (6.187)	6.14 (5.445)
LSM[1] Change from Baseline (SE)	-1.93 (0.634)	-3.76 (0.653)
Placebo-subtracted difference (95% CI)		**-1.84 (-3.64, -0.04)**
P-value (two-sided)		**0.045**

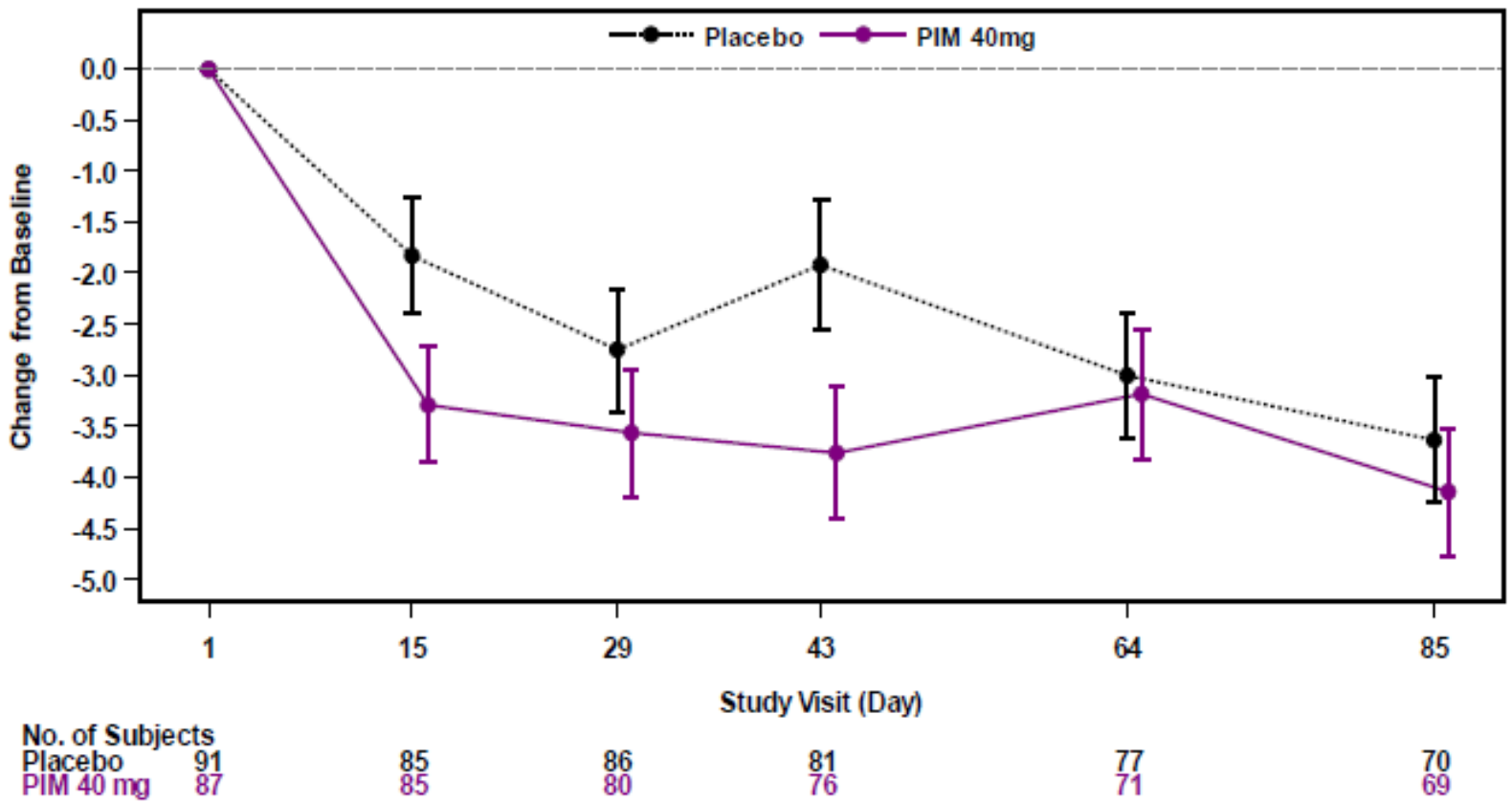
Source: Study 019 Clinical Study Report, Table 11-5, p. 84

NPI-NH PS = Neuropsychiatric Inventory-Nursing Home Version Psychosis Score, SD = standard deviation, SE = standard error, LSM = least squares mean, CI = confidence interval.

Secondary and Exploratory Endpoint Results

- No between-group comparisons met nominal significance, and demonstrated no notable numerical separation (including the ADCS-CGIC, CMAI-SF total score, or ADCS-ADL total score)
- No nominal separation from placebo at Days 64 or 85

NPI-NH PS Change From Baseline By Visit



Source: Study 019 Clinical Study Report, Figure 1.1, p. 85

Treatment effect appeared largest at Day 43 but diminished afterwards.
Placebo response at Day 43 appeared to increase the treatment difference.

Resubmission

- Applicant has responded to CR letter concerns regarding study design and conduct
- Agency has concluded study design could allow it be considered an adequate and well-controlled study suitable for regulatory decision making
  - For NPI-NH, questions remain regarding if methods of assessment of subjects' response are well-defined and reliable

Resubmission

- Office of Scientific Investigations (OSI) inspected Applicant during initial supplement submission (not UK site due to COVID-19)
- Data reliability concerns given protocol deviations
  - Subjects lacking clear documentation that psychotic symptoms developed after AD diagnosis
  - Subjects who received exclusionary medications at baseline

Resubmission

- Applicant noted proportion of subjects with deviations balanced across arms
- Applicant noted challenges establishing date of diagnosis, but other eligibility criteria excluded psychosis caused by other conditions
- Applicant re-presented per-protocol analysis results to demonstrate impact of protocol deviations

Primary Endpoint: Per-Protocol vs. non-Per-Protocol Analysis Set

	Per-Protocol Analysis Set*		Non-Per-Protocol Analysis Set**	
	Placebo (N=50)	Pimavanserin (N=45)	Placebo (N=41)	Pimavanserin (N=45)
Mean NPI-NH PS score at Baseline (SD)	9.70 (6.02)	10.31 (5.5)	10.37 (5.05)	8.73 (3.91)
Mean NPI-NH PS score at Day 43 (SD)	7.85 (6.41)	4.82 (4.57)	7.91 (5.98)	7.47 (5.96)
LSM[1] Change from Baseline (SE)	-2.27 (0.79)	-5.57 (0.87)	-1.42 (1.01)	-2.07 (0.98)
Placebo-subtracted difference (95% CI)	**-3.31 (-5.66, -0.96)**		**-0.65 (-2.17, 3.46)**	
P-value	**0.006**		**0.648**	

Source: Results for Per-Protocol analysis set: Applicant's Study 019 CSR, Table 5-2, p. 14. Results for non-Per-Protocol analysis set: FDA statistical reviewer
LSM = least squares mean, CI = confidence interval
* per-protocol analysis set: All randomized subjects who had no protocol deviations pre-defined by the Applicant.
** non-per-protocol analysis set: all randomized subjects who were not on the per-protocol analysis set.
Note: Both Per-Protocol analysis and Non-Per-Protocol analysis are based on MMRM analysis.

Primary Endpoint: Per-Protocol vs. non-Per-Protocol Analysis Set

- Almost 47% of subjects were excluded in per-protocol analysis
- Such a large number of randomized subjects excluded from the analysis could lead to selection bias and exaggeration of treatment effect and the results of this subgroup may not be generalizable to the intended population
- The full analysis set should be used to assess treatment effect rather than the per-protocol set

Resubmission

- Overall, the Agency anticipates that we will be able to rely upon the data from Study 019 for regulatory decision making based on:
  - Balanced distribution of the protocol deviations between arms
  - Examination of the nature of the deviations
  - Mitigating factors, such as other eligibility criteria

Study 019: Summary

- Statistically significant result on primary endpoint change from baseline to Day 43 on the NPI-NH PS
  - Endpoint appears to have face validity for phase 2 exploratory study, but limited support for use in registration trial for indication
  - Clinical meaningfulness of treatment difference unclear
- Lack of notable separation from placebo (nominal statistical significance or numerical) on secondary and exploratory endpoints
- Lack of discernable differences on primary outcome measure after Day 43 raises questions of whether difference at Day 43 is a chance finding or about the durability of effect

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Study 045

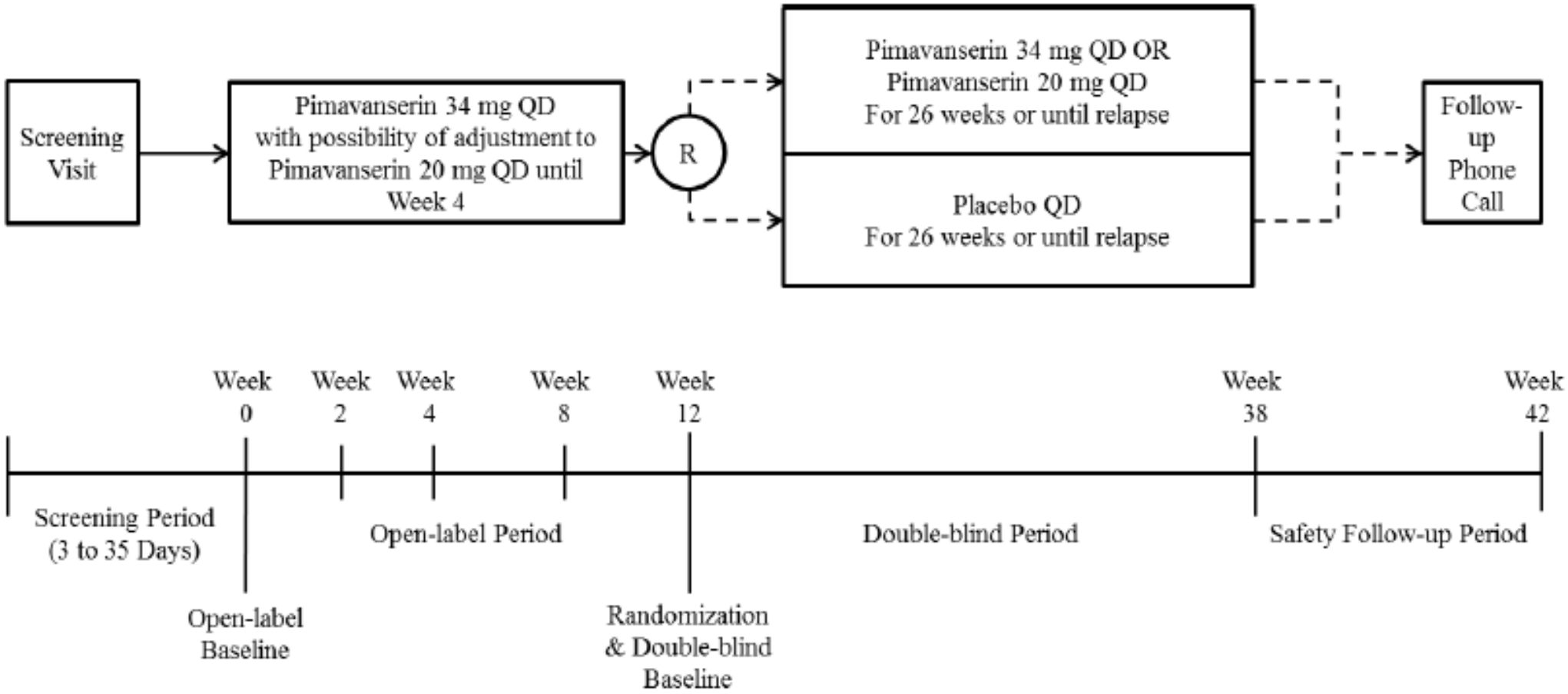
Overview of Design

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, randomized withdrawal study of pimavanserin 34 mg once daily versus placebo (dose adjustment to 20 mg permitted during open-label period)
- Screened across 101 international sites (27 in United States)
- 3- to 35-day screening period included brief psychosocial therapy and antipsychotic washout if necessary
- 12-week open-label (OL) period followed by up to 26-week double-blind (DB) period

Population

- Subjects ages ≥ 50 to ≤ 90 years-old with all-cause dementia, meeting clinical criteria for a dementia subtype, with baseline MMSE ≥ 6 and ≤ 24, and with psychosis x2+ months
- Screening and baseline:
  - Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions (SAPS-H+D) ≥ 10
  - CGI-S ≥ 4
  - SAPS-H+D global items ≥ 4
- Excluded for psychotic symptoms caused by other reason
- Antidementia drugs, antidepressants, and anxiolytics permitted if stable before and during study

Design Schema



Source: Study ACP-103-045 Clinical Study Report, Figure 9-1, p. 49; Abbreviations: QD = once daily, R = randomization

Randomization and Relapse Criteria

- OL subjects randomized 1:1 to DB period for (at Weeks 8 and 12):
  - ≥ 30% improvement on SAPS-H+D and
  - Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2
- Randomization stratified by dementia subtype and region
- DB subjects considered relapse if (compared to DB baseline):
  - ≥ 30% worsening on SAPS-H+D and CGI-I score of 6 or 7
  - Treated with other antipsychotic for dementia-related psychosis
  - Stopped drug or withdrew for lack of efficacy
  - Hospitalized for worsening psychosis

Endpoints

- Primary: time from randomization to relapse in the DB period
- Secondary: time from randomization to discontinuation from the DB period for any reason
- Relevant exploratory: SAPS-H+D total and domain scores

Statistical Design

- The total number of relapse events required at the final analysis is 75
- Sample size calculation based on:
  - Placebo relapse rate 60% over 26 weeks
  - Pimavanserin relapse rate 35% over 26 weeks (hazard ratio (HR) = 0.47)
  - Dropout rate 25% over 26 weeks
  - Overall two-sided alpha 0.05
  - One-sided O'Brien-Fleming stopping boundary (0.0033) for interim analysis when half of total planned relapse events occurred
- Primary endpoint analyzed with Cox regression model
  - Covariates for treatment group, dementia subtype, and region

Subject Disposition

- Of 392 subjects enrolled in OL period:
  - 351 subjects discontinued or completed OL period
  - 41 ongoing in OL period at time of study discontinuation following interim analysis
- 217/351 subjects (62%) met response criteria to enter DB
- Common early terminations:
  - Lack of response (20%)
  - Discontinuation for adverse events (8%)

Subject Disposition: Open-Label Responses

	Sustained Response* % (n/N)	Complete Response+ % (n/N)
Overall	61.8 (217/351)	20.8 (73/351)
Alzheimer's disease	59.8 (137/229)	19.2 (44/229)
Parkinson's disease dementia	71.2 (42/59)	27.1 (16/59)
Other	60.3 (38/63)	20.6 (13/63)

Source: Study 045 Clinical Study Report - Addendum Table 6-1.

*Sustained response is defined as ≥30% SAPS-H+D improvement and CGI-I very much or much improved at both Weeks 8 and 12. includes subjects in the OL phase who were randomized into the DB phase. Note that 2 subjects achieved sustained response but terminated from study before randomization.

+Complete response is defined as 100% Symptom Reduction in SAPS-H+D and CGI-I=1 or 2

Excluded 41 subjects who were ongoing in the OL period at the time of study discontinuation.

Demographics and Baseline Characteristics

- Across the OL period and both DB arms, approximately:
  - 60% female
  - Mean age 74 years-old
  - Race almost entirely White
  - Ethnicity 76% not Hispanic or Latino
- DB dementia subtypes approximately:
  - 63% AD
  - 19% PDD
- DB mean baseline MMSE scores approximately 18
- Mean baseline SAPS-H+D: 24.4
  - OL baseline: 24
  - DB baseline: approximately 5 across arms

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Study 045 Efficacy Results & Resubmission Analyses

Primary Endpoint Results

	Placebo (N=99)	Pimavanserin (N=95)
Number of subjects having a relapse event, n (%)	28 (28.3)	12 (12.6)
Number of subjects censored, n (%)	71 (71.7)	83 (87.4)
Hazard Ratio[1] (pimavanserin/placebo) (95% CI)[2]		0.353 (0.172, 0.727)
One-sided p-value (vs placebo)		0.0023
O'Brien-Fleming stopping boundary (one-sided p-value scale)		0.0033

Source: Applicant's Analysis, Study 045 Clinical Study Report, Table 11-10, p. 125.
Time from randomization to relapse in the Double-Blind Period determined by the independent adjudication committee, interim analysis (Intention-To-Treat Analysis Set)
[1] The Cox regression model included treatment, designated dementia subtype, and region.
[2] 95% CI = 95% confidence interval without adjusting for multiple looks

Primary Endpoint Results: Subgroup Analysis

Subgroup	Subjects with a Relapse Event		Cox Regression Analysis[1]
	Placebo n/N (%)	Pimavanserin n/N (%)	Hazard Ratio (Pimavanserin/Placebo) (95% CI)[2]
Designated dementia subtype			
AD or FTD-spectrum disorders	14/64 (21.9)	9/62 (14.5)	0.690 (0.295, 1.611)
PDD or DLB	12/23 (52.2)	1/21 (4.8)	0.034 (0.010, 0.116)
VaD	2/12 (16.7)	2/12 (16.7)	1.065 (0.159, 7.122)
Dementia subtype			
AD	14/62 (22.6)	8/61 (13.1)	0.618 (0.257, 1.487)
DLB	2/3 (66.7)	0/6	--
FTD-spectrum disorders	0/2	1/1 (100.0)	--
PDD	10/20 (50.0)	1/15 (6.7)	0.054 (0.017, 0.175)
VaD	2/12 (16.7)	2/12 (16.7)	1.065 (0.159, 7.122)

Source: Adapted from Applicant's analysis, Study 045 Clinical Study Report, Table 11–13, p. 130.

AD = Alzheimer's disease,
DLB = dementia with Lewy bodies,
FTD = frontotemporal dementia,
PDD = Parkinson's disease dementia,
VaD = vascular dementia

Time from randomization to relapse as determined by the independent adjudication committee

[1] The Cox regression model included treatment, designated dementia subtype, and region.
[2] 95% CI = 95% confidence interval without adjusting for multiple looks

Primary Endpoint Results: Exploratory Analysis

Analysis Type	Placebo n/N (%)	Pimavanserin n/N (%)	Cox Regression Analysis[1]		
			Hazard Ratio (Pimavanserin /Placebo)	95% CI[2]	One-Sided P-Value
Primary: determined by the IAC interim analysis	28/99 (28.3)	12/95 (12.6)	0.353	0.172, 0.727	0.0023
Excluding subjects with PDD	18/79 (22.8)	11/80 (13.8)	0.600	0.281, 1.281	0.0935
Excluding subjects with PDD or DLB	16/76 (21.1)	11/74 (14.9)	0.719	0.333, 1.554	0.2008

Source: FDA Statistical reviewer.

DLB = dementia with Lewy bodies, PDD = Parkinson's disease dementia

Time from randomization to relapse as determined by the independent adjudication committee

[1] The Cox regression model included treatment, designated dementia subtype, and region.

[2] 95% CI = 95% confidence interval without adjusting for multiple looks

Note: The one-sided p-values from the interim analysis were compared with the O'Brien-Fleming stopping boundary 0.0033.

Resubmission Analyses

- Applicant asserts consistency of response across subgroups
- Hypothesizes that PDD subgroup's smaller HR is caused by dopaminergic therapy for PD, which may have contributed to more rapid rate of relapse for subjects switched to placebo
- Re-analyses of primary and exploratory efficacy endpoints in AD subgroup
- Exposure-response analyses

Comparison Across Dementia Subgroups

- Applicant conducted a test for a qualitative (or cross-over) interaction and concluded that treatment effects are directionally consistent
- However, there is apparent variation in the magnitude, but not the direction, of the treatment effect across subgroups
- Strong evidence of a quantitative interaction (p=0.0036 for the interaction of treatment by designated dementia subgroup) suggests differential treatment effects across subgroups

Post-hoc Analyses

Potential Confounding by Dopaminergic Therapy Use

- Differential results by dementia subgroup include notable difference in placebo response across subgroups
- However, dopaminergic medication use almost completely confounded with dementia subtype (most in PDD subgroup)
  - Not possible to adjust to dopaminergic effect for PDD subjects on placebo
- Unclear whether effect of dopaminergic medication on risk of relapse is the only explanation for possible difference in treatment effect between PDD and AD subgroups

Post-hoc Analyses of Primary Endpoint for AD Subgroup

- Pre-specified primary analysis model
  - Included treatment, designated dementia subtype, and region as factors
- Applicant re-analyzed primary endpoint data for AD subgroup
  - Included a set of post-hoc covariates: treatment, baseline severity of psychosis, baseline dementia severity, prior antipsychotic treatment and concomitant antidementia medications, and excluded pre-specified region factor

	HR	95% CI	p-value
Pre-specified Primary Cox Model	0.62	(0.26, 1.49)	0.28
Applicant's Modified Cox Model	0.48	(0.19, 1.16)	0.10

Source: Study 045 Clinical Study Report - Addendum Table 7–11, Figure 7–9.
CI = confidence interval, HR = hazard ratio
Time from randomization to relapse in the double-blind period for Alzheimer's disease subgroup

Caveats of Post-hoc Analyses of Primary Endpoint for AD Subgroup

- Choice of covariates should be prespecified, post hoc data-driven analyses difficult to interpret
- OL baseline SAPS-H+D score used as covariate for baseline severity of psychosis – but why not DB baseline score
- Stratified region variable excluded without explanation

Post-hoc Analyses of Primary Endpoint for AD Subgroup

- Reviewer's analysis using DB baseline SAPS-H+D score and stratified region covariate yielded similar results to those from pre-specified primary model

	HR	95% CI	p-value
Pre-specified Primary Cox Model	0.62	(0.26, 1.49)	0.28
Applicant's Modified Cox Model	0.48	(0.19, 1.16)	0.10
Reviewer's Modified Cox Model	0.64	(0.27, 1.52)	0.31

Source: Study 045 Clinical Study Report - Addendum Table 7–11, Figure 7–9, statistical reviewer.

CI = confidence interval
HR = hazard ratio

Time from randomization to relapse in the double-blind period for Alzheimer's disease subgroup

- None of the p-values reach nominal statistical significance. Inference on treatment effect should be based on primary Cox model

Post-hoc Analyses of Exploratory Endpoints

- Most relevant: change from DB baseline in SAPS-H+D score
- Van Elteren test based on ranking scores
  - Applicant assigned same best or second-best rank to over half of subjects whose scores never worsened, yielding nominal p = 0.0375
  - But differences in terms of how much SAPS-H+D score changed, and relapses may be considered the worst outcomes
  - Reviewer assigned worse ranks to subjects who ever relapsed based on time to relapse and better ranks to those who never relapsed based on their maximum change of SAPS-H+D score, yielding nominal p = 0.1355
- Results of the exploratory endpoint of SAPS-H+D score did not provide additional support for efficacy

Post-hoc Exposure-Response Analysis

- Applicant conducted exposure-response analysis to assess whether efficacy difference between AD and PDD associated with plasma concentration and its variability
- However, does not appear that differences in subgroup efficacy related to pharmacokinetic exposure differences, as exposures were similar between the AD and PDD subgroups
- Higher pharmacokinetic exposures were associated with higher relapse-free probability for both subgroups, but drug effect lower for AD than PDD

Study 045: Summary

- Statistically significant result on primary endpoint time to relapse in the DB period
- Overall results appear driven by PDD subgroup, suggesting a possible differential response to pimavanserin across dementia subtypes
- Unclear whether effect of dopaminergic medication on risk of relapse is only explanation for possible difference in treatment effect between PDD and AD subgroups, and use confounded by dementia subtype
- Post hoc analyses demonstrated mixed results and are subject to inherent limitations

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Overall Summary: Evidence and Uncertainties

Overall Summary: Evidence

- Study 019
  - Primary endpoint NPI-NH PS change from baseline to Day 43 statistically significant
- Study 045
  - Primary endpoint time from randomization to relapse statistically significant

Overall Summary: Uncertainties

- Study 019
  - Clinical meaningfulness of primary endpoint treatment difference unclear
  - No separation on secondary and relevant exploratory endpoints
  - Lack of NPI-NH PS separation after Day 43 raises possibility of chance finding on Day 43 or lack of durable effect
- Study 045
  - Primary endpoint results appear driven by PDD subgroup
  - Unclear if dopaminergic medication use only explanation for difference
  - Post hoc analyses mixed results and inherent limitations


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