Psychopharmacologic Drugs Advisory Committee Meeting

Pimavanserin for the Treatment of Psychosis Associated with Parkinson's Disease

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U.S. Food and Drug Administration Clinical Review of Pimavanserin for the Treatment of Psychosis Associated with Parkinson's Disease

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Topics to be Covered

- Overview of Clinical Program
- Brief Summary of Efficacy
- Presentation of Number Needed to Treat (NNT)
- Focus on the Serious Adverse Events Including Death
- Presentation of Number Needed to Harm (NNH)
  - (Harm Defined as Serious Adverse Events and Death)
- Presentation and Analysis of NNH/NNT
  - (Benefit to Harm Comparison)

Psychosis Associated with Parkinson's Disease (PDP)

- Parkinson's Disease Foundation estimates that 7 to 10 million people worldwide are living with Parkinson's disease (PD)
- The incidence of PD increases with age. Only an estimated four percent of people with PD are diagnosed before the age of 50.
- Men are one and a half times more likely to have PD than women.
- PDP was identified as a treatment target in 1999. Prior to that it was widely thought of as an adverse effect from PD drug-treatment.
- PDP is common. In a retrospective study of 445 PD patients, 50% had a history of PDP symptoms (Williams and Lees, Lancet Neurol, 4:10; 605; 2005).

Standard of Evidence

- In April 2013, in the face of three failed trials, ACADIA Pharmaceuticals Inc. met with FDA and gained agreement that an NDA would be accepted for filing on the basis of **data from a single, strongly positive study (Study-020) with supportive safety and efficacy data from earlier trials.**
- Designation of PDP as a serious unmet medical need was a key consideration in these discussions. The Agency granted Breakthrough Designation to pimavanserin for the treatment of PDP.

1 positive of 4 Studies

-020	**Double Blind, Placebo Controlled, Fixed Dose, Randomized 1:1**	**PIM 34 mg PBO PO Daily**	**SAPS-PD (Primary)**	**6-week Duration /Assessed on Days 15, 29, 43**	**199**	**Parkinson's disease with psychosis 116 Male 69 Female Age mean 72.0 years (Range 53-90 years)**	**54 sites US: 52 Canada: 2**
-012	Double Blind, Placebo Controlled, Fixed Dose, Randomized 1:1	PIM 8.5 mg PIM 34 mg PBO PO Daily	SAPS H+D (Primary)	6-week Duration /Assessed Days 8, 15, 29, 42	287	Parkinson's Disease with Psychosis 181 Male 106 Female Mean Age 70.0 years (Range 40-87 years)	73 Sites US:34 Europe: 26 India: 13
-014	Double Blind, Placebo Controlled Fixed Dose, Randomized 1:1 (Terminated Early)	PIM 8.5 mg PIM 17 mg PBO PO Daily	SAPS H+D (Primary)	6-week Duration /Assessed Days 8, 15, 29, 42	123	Parkinson's disease with psychosis 74 Males/43 Females Mean Age 72.0 years (Range 53-90 years)	39 Sites US 18 Europe 21
-006	Placebo-controlled, dose-escalation exploratory efficacy and safety in PDP	17-34-51mg (Flexible) PBO PO Daily	SAPS-H+D, SAPS-H, -D, CGI-S, CGI-I	Days 8, 15, 28 (SAPS on D28 only)	60	Parkinson's disease with psychosis 45 Male/14 Female Mean Age 70.0 years (Range 46-90 years)	US 15 Sites

Clinical Review of Pimavanserin for the Treatment of PDP

- Efficacy: One positive controlled clinical study:
  - Study-020 (6-week, placebo-controlled)
  - *FDA exploratory analysis: Parkinson's Disease Psychosis-6-week controlled trial pooled data (PDP-6) Studies -020, 014, and 012*
- Safety: All pimavanserin exposures with particular focus on comparative analysis of:
  - PDP6 pooled safety data
  - Study -020 alone

Efficacy Evaluation-Study-020

- 6-week, out patient, multi-center, double-blind, randomized, placebo-controlled trial
- Two treatment groups randomized 1:1
  - Pimavanserin 34 mg PO daily (n=105)
  - Placebo (n=94)
- Overall completion rate was 88%
- Placebo 87/94 (93%); PIM 89/105 (85%)

Efficacy Evaluation-Study-020 -Endpoints

- Primary Endpoint:
  - SAPS-PD: 9 items of the 20-item Schedule for the Assessment of Positive Symptoms [of schizophrenia] (SAPS) (Andreasen, University of Iowa,1984). SAPS-PD scores from 0-45. Each item is scored from 0-5. Evaluation by a central rater.
- Secondary Endpoint:
  - Clinical Global Impression (CGI) was rated by the local clinician.

Psychoses Symptoms Assessed by SAPS-PD

- H1 Auditory Hallucinations
- H3 Voices Conversing
- H4 Somatic or Tactile Hallucinations
- H6 Visual Hallucinations
- H7 Global Rating of Severity of Hallucinations
- D1 Persecutory Delusions
- D2 Delusions of Jealousy
- D7 Ideas and Delusions of Reference
- D13 Global Rating of Severity of Delusions

At the baseline visit, subject must have had a SAPS Hallucinations or Delusions global item (H7 or D13) score ≥3 AND a score ≥3 on at least one other non-global item using the 9-item SAPS Hallucinations and Delusions domains. (minimum score of 6/45).

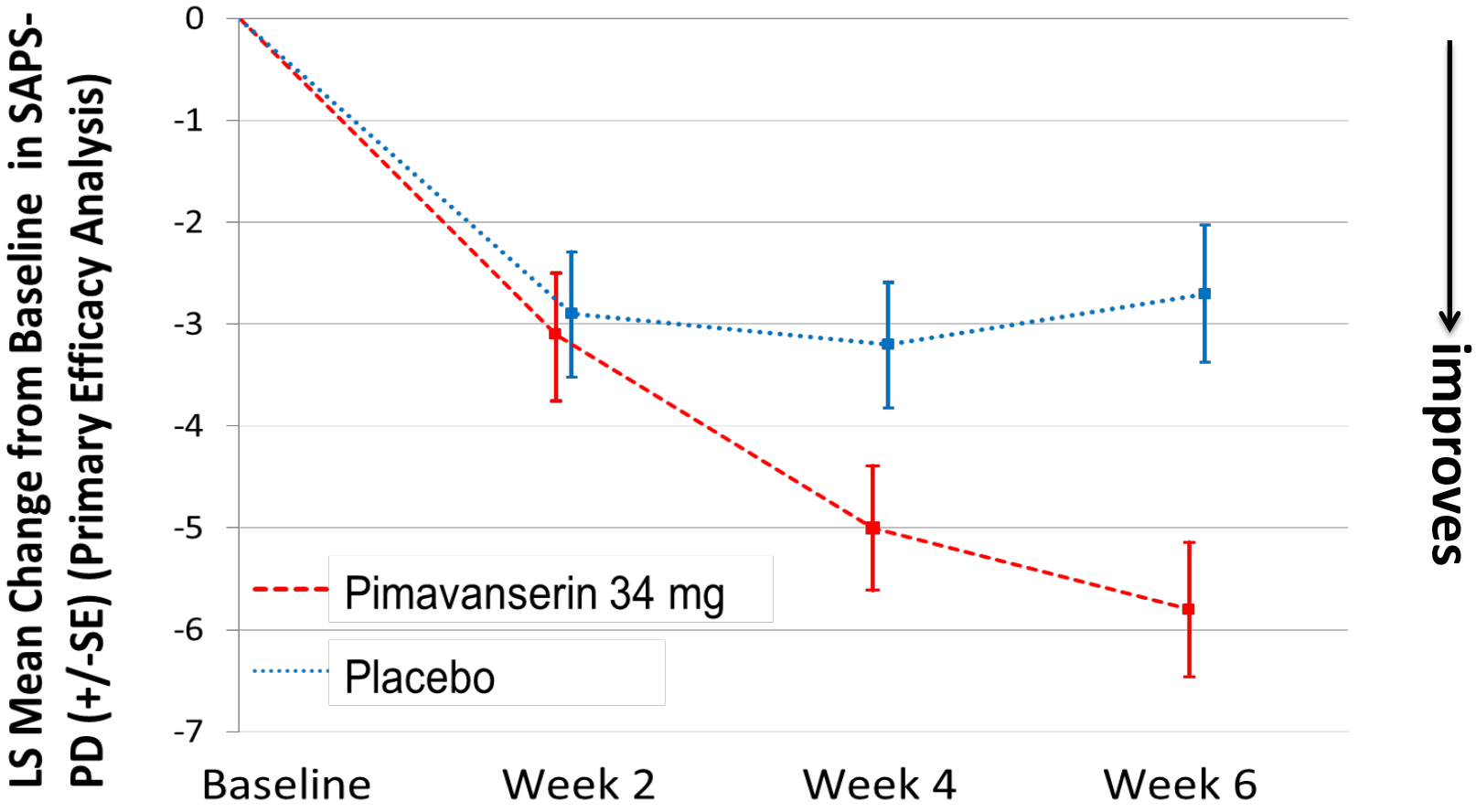
Efficacy Results

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)
SAPS-PD	**Pimavanserin**	15.9 (6.12)	-5.79 (0.66)	-3.06 (-4.91, -1.20)
	Placebo	14.7 (5.55)	-2.73 (0.67)	
CGI-I	**Pimavanserin**	NA	3.45 (0.14)	-0.67 (-1.06, -0.27)
	Placebo	NA	2.78 (0.14)	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval. (Source: FDA statistical review)

Improvement in SAPS-PD Over Time (Study-020; N=185)

Source: FDA statistical reviewer Eiji Ishida



Safety Evaluation-Program Population

- Integrated safety database -1592 subjects from 18 trials.
  - 1096 were exposed to pimavanserin alone or in combination with adjunctive therapy, of these,
  - 625 had PD/PDP total patients
  - 177 had schizophrenia
  - 294 were healthy volunteers.
- 764 exposures to 34 mg,
- >34 mg- 42.5 mg (n-10); 57mg (n-54); 68mg (n-72); 85mg (n-40); 102 mg (n=8); 127.5 mg (n=6); 136 mg (n=8); 170 mg (n=4); and 255 mg (n=4).

Safety Evaluation-PDP Controlled Trials

Parkinson's disease controlled trial database

- 498 total patients with PDP were exposed to pimavanserin .
- 202 patients with PDP were exposed to the 34mg daily dose in the 6-week controlled trial population (PDP6)
- 231 patients with PDP were randomized to placebo in studies of 6-weeks' duration

Safety Evaluation: Death in Open-label Population

Open-label, PDP Population pimavanserin exposure

- 459 Patients received long-term open label pimavanserin treatment
- 51 Deaths in open label treatment (11.1%)
- Causes of death and descriptions SAEs were not entities that are associated with drug development (e.g. liver failure, Toxic epidermal necrolysis, agranulocytosis)
- Death and serious medical complications are common in the PDP population (Stebbins et al, Neurology 1995;45:669; Levy et al, Neurology 2002;59:1708).

Open label adverse experiences cannot qualitatively be linked to pimavanserin

Safety Focus

6-week controlled trial PDP treatment (Studies -012, -014, and-020)

- Deaths
- Serious adverse events-including deaths (SAE)
- Severe adverse events

Safety-Controlled Trials

In the review of serious adverse events (including deaths) the estimated odds ratio, stratified by study, for serious adverse events is

2.0 (95% CI 0.9 to 4.5, p=0.10) for all drug vs. placebo

2.4 (95% CI 1.0 to 5.7, p=0.05) for 34 mg vs. placebo (PDP6 population)

1.4 (95% CI 0.5 to 3.8, p=0.46) for less than 34 mg vs. placebo

Class Effect

- The deaths and serious adverse events observed with pimavanserin development did not have a readily apparent unifying mechanism
- This is consistent with what we observe with the use of conventional and new generation antipsychotics in the demented elderly population.
- FDA has not approved antipsychotic drugs with this safety signal for use in the agitated or psychotic demented elderly populations.

Treatment-emergent Adverse Event Summary for PDP6 Population

n (%)	Placebo (N=231)	PIM 8.5mg (N=140)	PIM 17mg (N=41)	PIM 34mg (N=202)
Death	1 (0.4)	1 (0.7)	0	3 (1.5)
SAE	8 (3.5)	8 (5.7)	1 (2.4)	16 (7.9)
Adverse Dropout	10 (4.3)	9 (6.4)	3 (7.3)	16 (7.9)
Severe AE	11 (4.8)	8 (5.7)	3 (7.3)	20 (9.9)
Any Adverse Event	141 (61)	79 (56.4)	21 (51.2)	124 (61.4)

Source: Table PDP6 2-1 and Page 155 of ISS NDA 207-318

Pimavanserin 16 Treatment Emergent SAEs in Analysis

- Mental status changes
- Headache (hospitalized with delirium-died 74 days later-not counted among deaths)
- Confusional state-Hallucination
- Hallucination
- Fall-Mental status changes
- Psychotic disorder -Multi-organ failure-Septic shock (fatal)
- Sepsis-Psychotic disorder (fatal)
- Bronchitis followed by Septic shock
- Urinary tract infection (3)
- Syncope -Respiratory distress (fatal)
- Atrial fibrillation
- Hemorrhoids (GI Bleed; hospital evaluation)
- Parkinson's disease
- Breast cancer

Placebo SAE 8 Cases

- Mental status changes
- Gastroenteritis-Delirium
- Bronchitis
- Urinary tract infection
- Arrhythmia-Cardio-respiratory arrest-Transient ischemic attack (fatal)
- Anemia-Gastrointestinal ulcer hemorrhage
- Spinal fracture
- Decubitus ulcer

SAE-Cases in PDP6 Population

	Placebo	Pimavanserin
Mental Status Change	2	5
Infection	2	6**
Cardiovascular	1*	2*
Gastrointestinal Bleeding	1	1
Other	2 (Fracture and Decubitus ulcer)	2 (Cancer and worsened Parkinson's disease)
Each * denotes one death		

Exploration of Clinically Meaningful Response

- Efficacy is established via statistical testing of the primary efficacy variable. This accounts for patients who both improve, have no change or worsen. Is a mean change of 3 points meaningful? Is that the right (only) question to ask?
- What different levels of response occur?
- How many people will achieve such a response that can be attributed to the treatment.
- How do the benefits justify any potential safety risks
- How can potential risks be minimized?

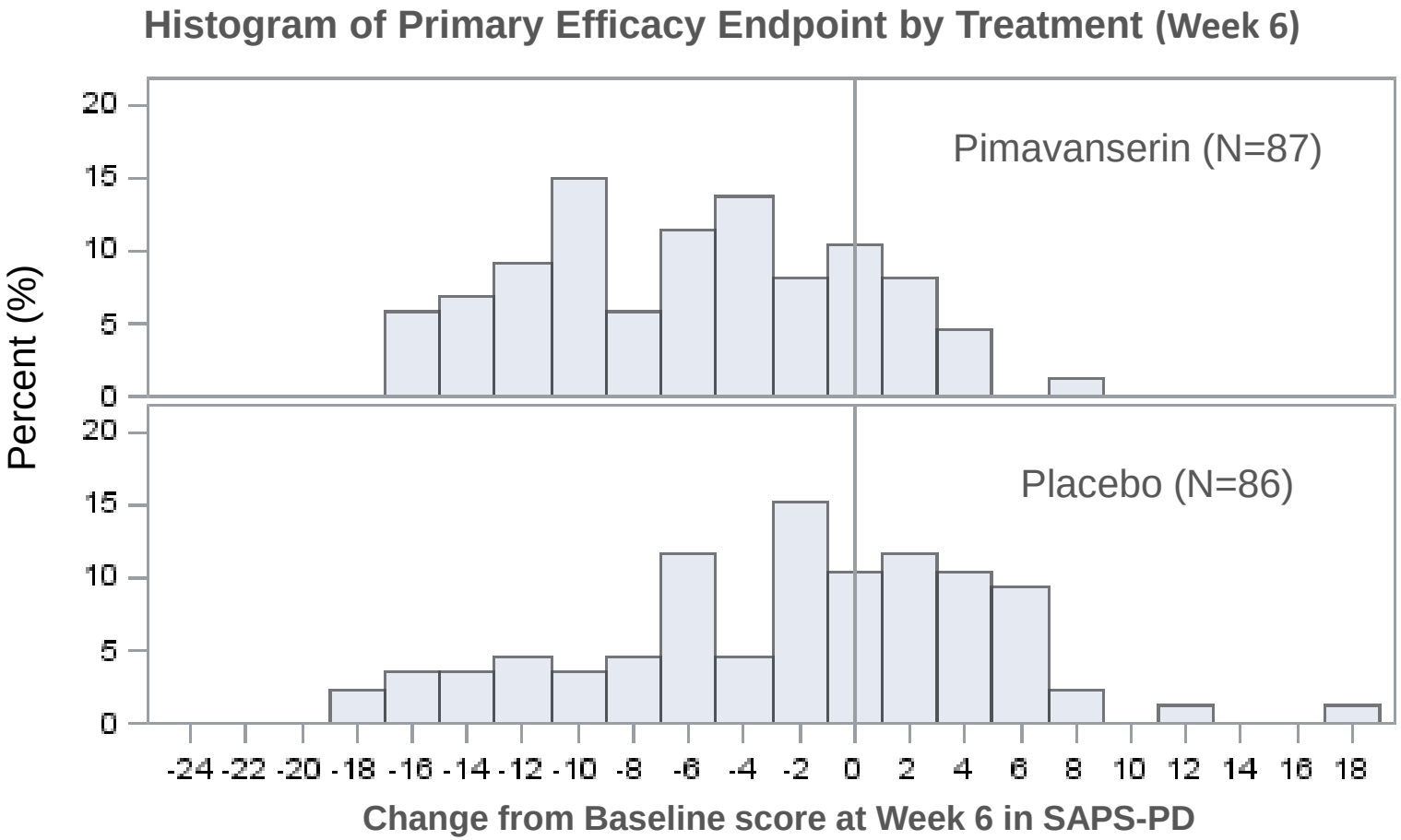
SAPS-PD Complete Response, and CGI-I at Week 6 (Study 020, mITT)

Response Criteria	PIM 34 mg (N=95)	Placebo (N=90)	Nominal p-value
100% SAPS-PD Responder (score of 0 post-baseline)	13 (13.7%)	1 (1.1%)	<0.05
CGI-I Much or Very Much Improved	43 (45.3%)	22 (24.4%)	<0.05
Source: FDA analysis based on mITT population (N=185) of Study-020; Reference: Acadia Advisory Committee Briefing Document Table 8–14, Page 70/71			

SAPS-PD Complete Response, and CGI-I All patients from 6-week studies (Pimavanserin 34 mg or Placebo)

Response Criteria	PIM 34 mg (N=202)	Placebo (N=231)	Nominal p-value
100% SAPS-PD Responder (score of 0 post-baseline)	28 (13.9%)	17 (7.4%)	<0.05
CGI-I Much or Very Much Improved	80 (39.6%)	67 (29.0%)	<0.05
Source: FDA Analysis based on 433 subjects obtained from Sponsor-defined *PDP6 Population* (ISS report, Page 153/155). The 433 patients were specified by the following criteria: Pimavanserin 34 mg or Placebo; and Studies 012, 014 or 020.			

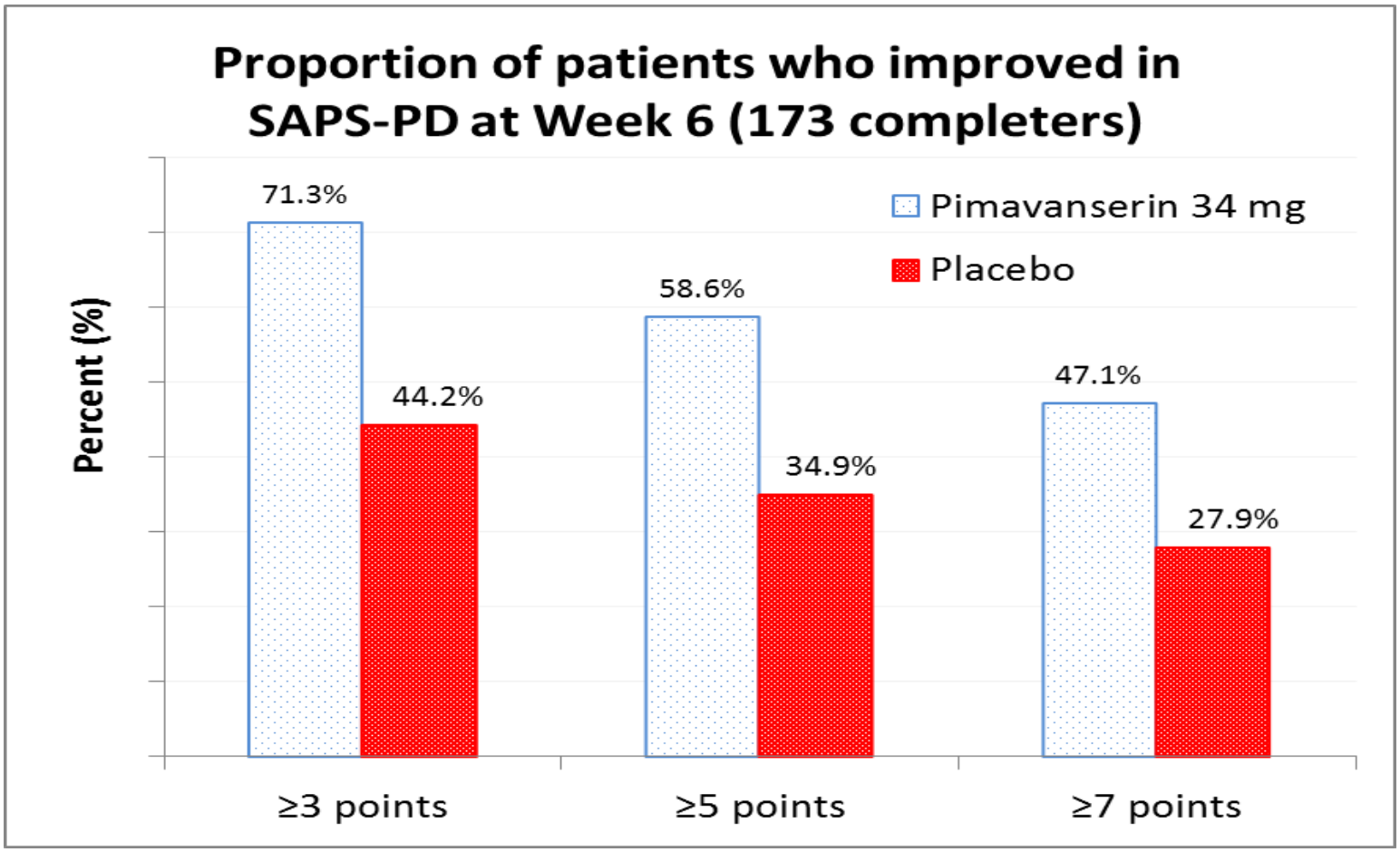
Empirical Distribution of Change from Baseline to Week 6 in SAPS-PD (for 173 Completers)



Source: Figure 5 of FDA Statistical Review (NDA207813)

Proportion of Patients who had SAPS-PD Score Improvement: Study-020

Source: FDA Office of Biostatistics



Clinical Meaningfulness

Number Needed to Treat

Laupacis A, Sackett DL, Roberts RS (1988). "An assessment of clinically useful measures of the consequences of treatment". N. Engl. J. Med. ***318*** *(26): 1728–33.*

Number Needed to Treat

- The **number needed to treat (NNT)** is an epidemiological measure used in communicating the effectiveness of a health-care intervention, typically a treatment with medication.
- The NNT is the average number of patients who need to be treated for one to benefit compared with a control in a clinical trial.
- It is defined as the reciprocal of the absolute risk reduction.

Number Needed to Treat Formula

- $\mathrm{NNT} = \frac{1}{(\mathrm{IMPact}/\mathrm{TOTact}) - (\mathrm{IMPcon}/\mathrm{TOTcon})}$
- IMPact = number of patients given active treatment achieving the target
- TOTact = total number of patients given the active treatment
- IMPcon = number of patients given a control treatment achieving the target
- TOTcon = total number of patients given the control treatment

Number Needed to Treat
CGI-I Much or Very Much Improved

(Study-020, mITT)

- Pimavanserin 43/95 (45.2%)
- Placebo 22 /90 (24.4%)

$$\text{NNT} = \frac{1}{(\text{IMPact}/\text{TOTact}) - (\text{IMPcon}/\text{TOTcon})}$$

- $1/(0.452\text{-}0.244)=1/0.208=4.8\approx5$
- One must treat 5 patients to obtain1 improved or much improved response due to the drug

NNT Summary

Efficacy Response	**$NNT_{Study-020}$**	**NNT_{PDP6}**
≥50% Reduction SAPS-PD	11	15
≥30% Reduction SAPS-PD	7	5
Full Response	8	13
CGI-Improved/Much Improved	5	8
Source: FDA statistical reviewer Eiji Ishida		

Number Needed to Harm: Pooled Data

- Harm= Serious Adverse Event -Including Death (SAE)
- PDP 6-Week Controlled Trial Population
  - Pimavanserin SAEs=16/202 7.9%
  - Placebo SAEs= 8/231 3.5%

$$\text{NNH} = \frac{1}{(\text{IMPact}/\text{TOTact}) - (\text{IMPcon}/\text{TOTcon})}$$

  - $1/(0.079-0.035)=1/0.044=22.7\approx 23$
  - NNH=23

In treating 23 patients, 1 SAE will occur that is due to the drug

Number Needed to Harm-Pooled Data

- Harm= Death PDP 6-Week Controlled Trial Population

– Pimavanserin	SAEs=3/202	1.5%
– Placebo	SAEs=1/231	0.4%

$$\text{NNH}= \frac{1}{(\text{IMPact/TOTact}) - (\text{IMPcon/TOTcon})}$$

- 1/(0.015-0.004)=1/0.011=90.9≈91
- NNH=91

In treating 91 patients, 1 death will occur that is due to the drug

Number Needed to Harm: Study-020

- Harm= Death
- Study-020
  - Pimavanserin Deaths=2/95 2.1%
  - Placebo SAEs= 1/90 1.1%

$$\text{NNH} = \frac{1}{(\text{IMPact}/\text{TOTact}) - (\text{IMPcon}/\text{TOTcon})}$$

  - 1/(0.021-0.011)=1/0.01=100
  - NNH=100

In treating 100 patients, 1 Death will occur that is due to the drug

Number Needed to Harm: Study-020

- Harm= Serious Adverse Event -Including Death (SAE)
- Study-020
  - Pimavanserin SAEs=11/94 11.7%
  - Placebo SAEs= 4/90 4.4%

$$\text{NNH} = \frac{1}{(\text{IMPact}/\text{TOTact}) - (\text{IMPcon}/\text{TOTcon})}$$

  - $1/(0.117-0.044)=1/0.073=13.7\approx14$
  - NNH=14

In treating 14 patients, 1 SAE will occur that is due to the drug

Benefit to Risk-NNH/NNT

- Example1: If NNH/NNT is 100/ 2 the ratio is 50:1
  - for every 100 patients who receive any given benefit because of the drug, 1 patient dies or experiences a SAE because of the drug

- Example 2: If NNH/NNT is 100/10 the ratio is 10:1
  - for every 10 patients who receive any given benefit because of the drug, another patient dies or experiences a SAE that because of the drug

Benefit to Harm Comparison

- The NNH/NNT ratio provides a numerical calculation of benefit to harm
- Harm=
  - 1) Death
  - 2) Any Serious Adverse Event Including Death
- Calculated for multiple levels of clinical response
- The ratio provides the number of patients who shall receive any given treatment response due to the drug and at the same time the number of patients experiencing death or a SAE that is due to the drug (compared to placebo).

NNH/NNT Comparison: Given Efficacy Response/Death: Study-020

Efficacy Response	**NNT_{20}**	**NNH_{20}/NNT_{20}**	
≥50% Reduction SAPS-PD	11	100/11=9.1	≈9 responses: 1 Death
≥30% Reduction SAPS-PD	7	100/7=14.3	≈14 responses: 1 Death
Full Response	8	100/8=12.5	≈13 responses: 1 Death
CGI-Improved/Much Improved	5	100/5=20	≈20 responses: 1 Death

NNH/NNT: Given Efficacy Response/SAE Study-020

Efficacy Response	**NNT_{20}**	**NNH_{20}/NNT_{20}**	
≥50% Reduction SAPS-PD	11	16/11=1.5	≈3 responses: 2 SAE
≥30% Reduction SAPS-PD	7	16/7=2.3	≈5 responses: 2 SAE
Full Response	8	16/8=2	≈2 responses: 1 SAE
CGI-Improved/Much Improved	5	16/5=3.2	≈3 responses: 1 SAE

NNH/NNT Ratios: Given Efficacy Response/Death PDP6 Population

Efficacy Response	**NNT_{PDP6}**	**NNH_{PDP6}/NNT_{PDP6}**	
≥50% Reduction SAPS-PD	15	91/15=6.1	≈6 responses: 1 Death
≥30% Reduction SAPS-PD	5	91/5=18.2	≈18 responses: 1 Death
Full Response	13	91/13=7	≈7 responses: 1 Death
CGI-Improved/Much Improved	9	91/9=10.1	≈10 responses: 1 Death

NNH/NNT Ratios: SAE/Given Efficacy Response: PDP6-Population

Efficacy Response	**NNT_{PDP6}**	**NNH_{PDP6}/NNT_{PDP6}**	
≥50% Reduction SAPS-PD	15	23/15=1.5	≈3 responses: 2 SAE
≥30% Reduction SAPS-PD	5	23/5=4.6	≈9 responses: 2 SAE
Full Response	13	23/13=1.77	≈7 responses: 4 SAE
CGI-Improved/Much Improved	9	23/9=2.6	≈5 responses: 2 SAE

Benefit and Harm: Based on NNH/NNT_{PDP6} Ratios

Treat-91 **NNT x Responses**	**Responses**	**SAEs (Including Death)**	**Death**
Full Response	7	5	1
CGI Improved/ Much Improved	10	4	1
PDP6 Data			

Questions?

Thank you

Mortality and Antipsychotic Drug Use in Dementia

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Boxed Warning

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. [*Antipsychotic*] is not approved for the treatment of patients with dementia-related psychosis.

Studies Reviewed

17 Randomized Placebo-controlled Trials

- Aripiprazole (3)
- Haloperidol (2)
- Olanzapine (5)
- Quetiapine (2)
- Risperidone (7)
- Ziprasidone (1)

Five studies were fixed-dose

Studies Reviewed

- 5377 Subjects (3611 drug, 1766 placebo)
- Average Age 81
  - Range 44 – 105
  - Approximately 95% between 66 and 96

Deaths Within 30 Days Beyond Intended Treatment Period

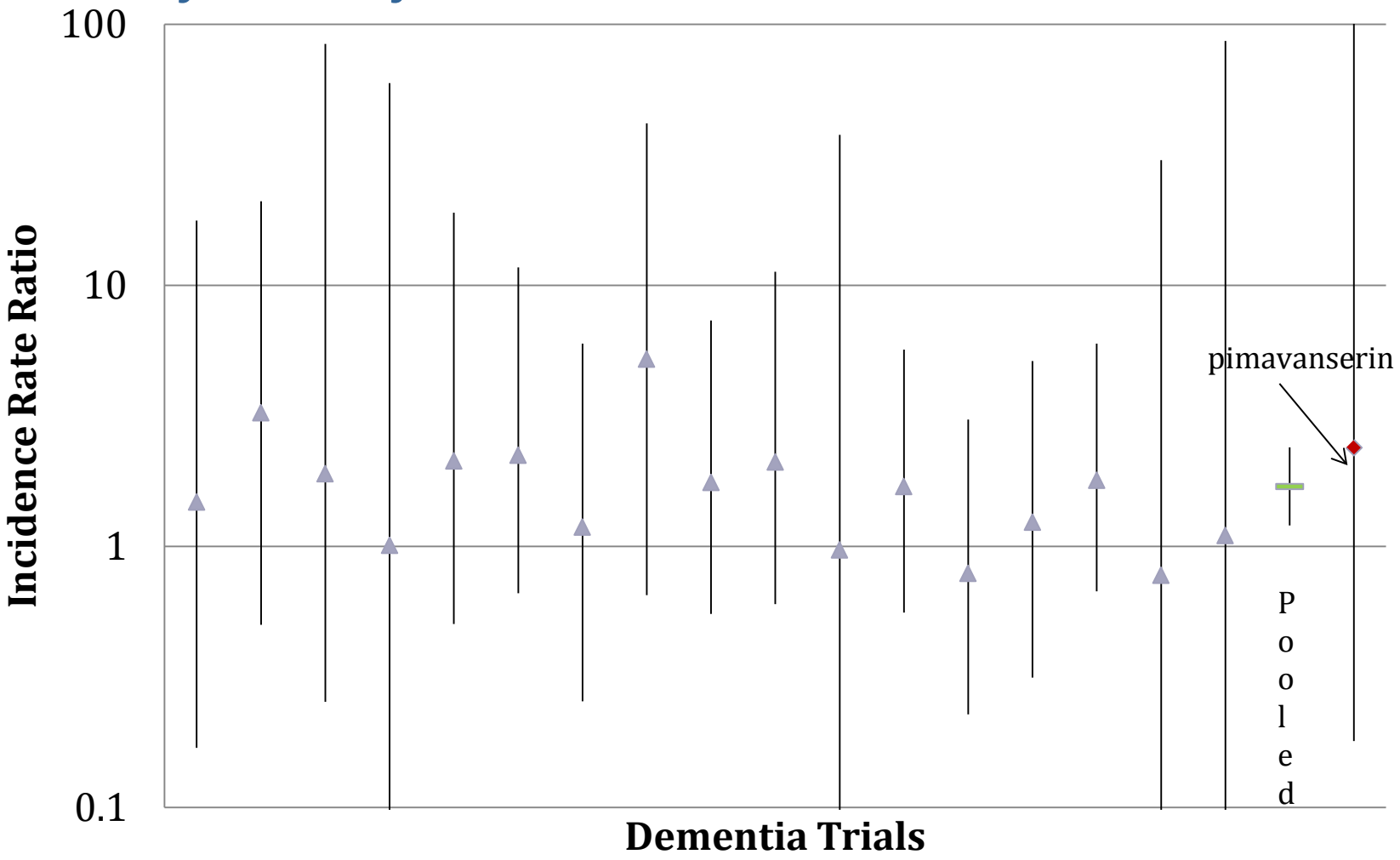
- 30 randomized comparisons of drug and placebo
  - Mortality higher with drug in 28/30 ($p<10^{-6}$)

- Incidence Rate Ratio
  1.70
  (95% CI: 1.20 to 2.40, p=0.003)
  Random effects Poisson regression

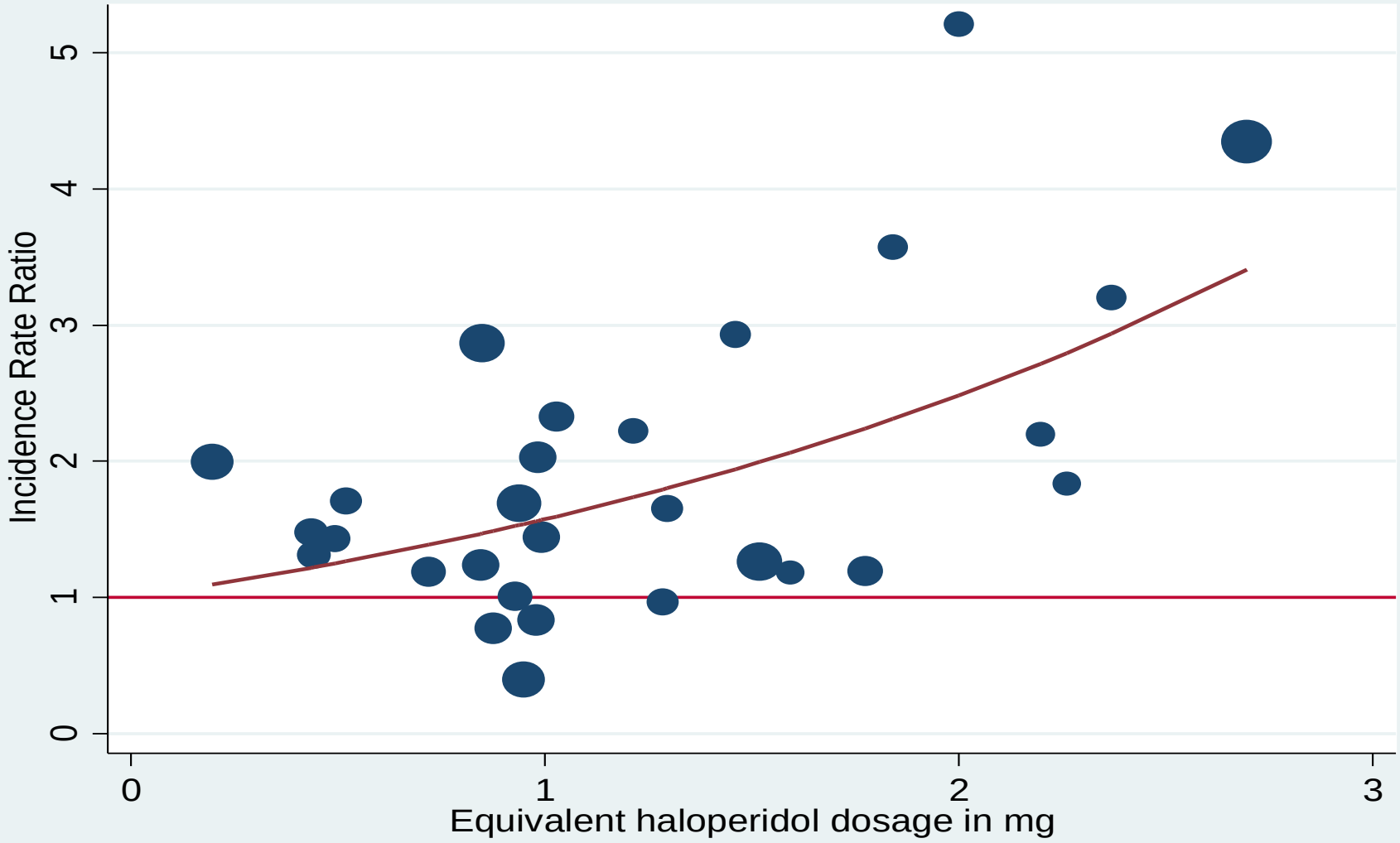
Mortality Rates

- Antipsychotic
  141 Deaths per 1000 patient-years (104 to 180)
- Placebo
  83 Deaths per 1000 patient-years (58 to 120)
- Difference
  58 Deaths per 1000 patient-years (22 to 95)

Mortality Risk by Trial

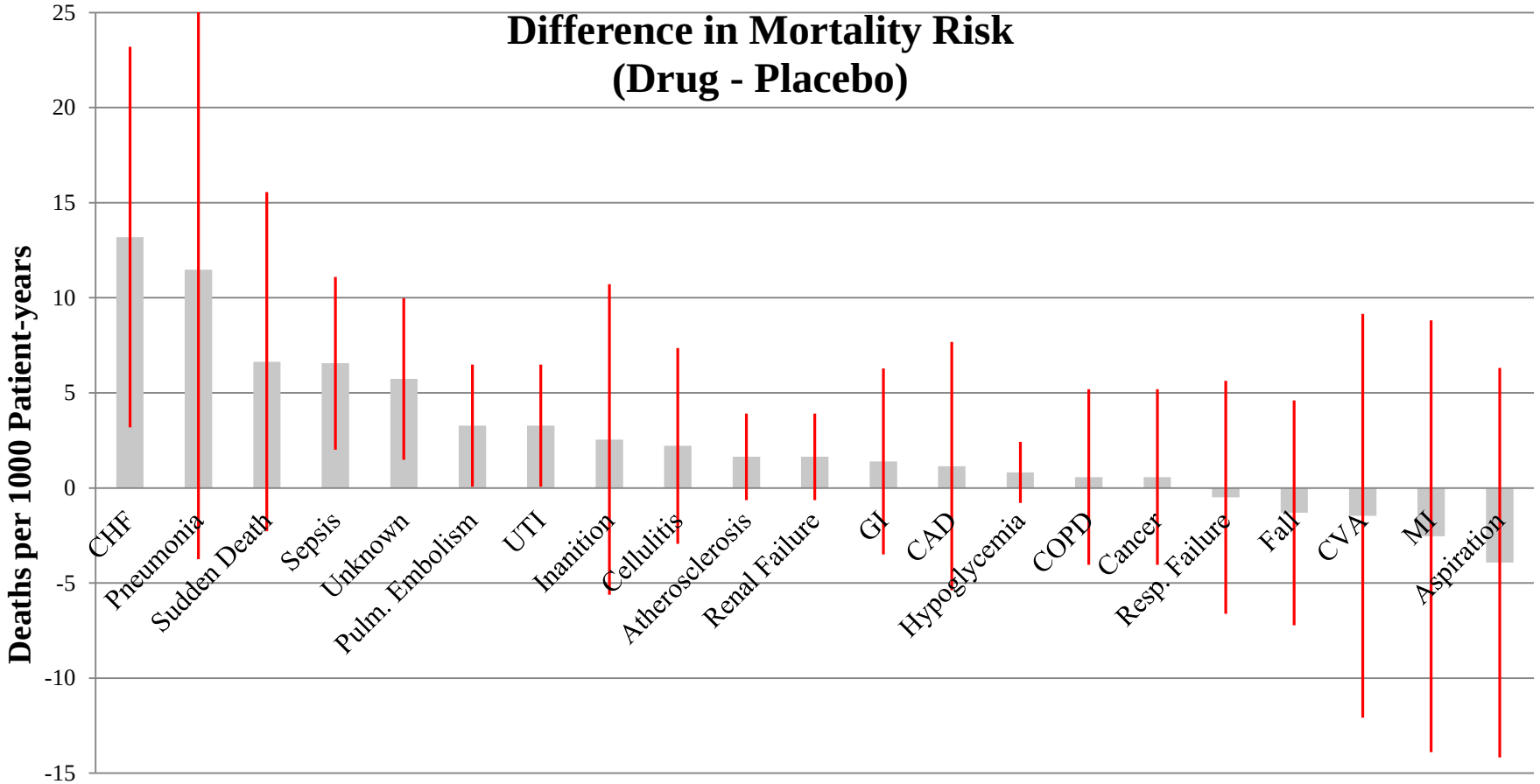


Dose Response



Causes of Death

Causes of Death



What is Driving Increased Mortality?

What is Driving Increased Mortality?

Physiological Process?

- *What physiological process would lead to such diversity of causes of death? (Contrast with Cox-2 drugs)*
- But is the diversity real?

  Better observation and data collection could show less diversity

What is Driving Increased Mortality?

Psychosomatic Process?

"Will to Live" in demented patients

- Manifested as behavioral problems
- Suppressed by antipsychotic drugs
- *How would you test this?*

What is Driving Increased Mortality?

Patient Care Process?

- Do "Squeaky Wheels" get more attention and better supportive care?
- Do chemical (or other) restraints facilitate neglect?

Questions?

Back-up Slides Shown

Clozapine and PDP (EU)

	Death	SAE		AE Dropout
Clozapine	0/32	4/32 (12.5%)		2/32
Placebo	0/27	7/28 (25.0%)		2/27

25/60 (41.6%) experienced complete remission with 12 weeks treatment in extension study

Pollak, P., F. Tison, O. Rascol, A. Destée, J. J. Péré, J. M. Senard, F. Durif, and I. Bourdeix, 2004, Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up: J Neurol Neurosurg Psychiatry, v. 75, p. 689-95. (4-week RCT followed by 12 –weeks treatment followed by withdrawal-19/25 relapsed within 1 month after withdrawal)

Table 2 Comparison of change scores in patients taking clozapine compared with the placebo group at the end of period II (PII)

	Clozapine (N = 32)			Placebo (N = 28)			
Scores	Baseline	End of PII	Δ End PII*	Baseline	End of PII	Δ End PII*	Between group comparison†
CGI	5.1 (0.8)	3.3 (1.5)	−1.8 (1.5); −2.3 to −1.3; p<0.0001	4.9 (0.9)	4.3 (1.5)	−0.6 (1.1); −1 to −0.2; p = 0.011	t = −3.45; df = 58; p = 0.001
Positive PANSS	17.8 (4.7)	12.3 (4.1)	−5.6 (3.9); −6.9 to −4.3; p<0.0001	15.3 (5.0)	14.5 (5.7)	−0.8 (2.8); −1.8 to 0.2; p = 0.127	t = −5.37; df = 58; p<0.0001

Values are mean (SD).
*95% confidence interval and p value for within group *t* test on change from baseline also shown; †t statistic, degrees of freedom (df), and p value for between group *t* test on change from baseline also shown.
CGI, clinical global impression scale; PANSS, positive and negative syndrome scale.

Clozapine and PDP (US)

	Death	Dropout	SAE * described in text	CGI-S decrease of 2 or greater
Clozapine	0/30	3/30	1/30 (3.3%)	15/30 (50%)
Placebo	0/30	3/30	2/30 (6.7%)	5/30 (16.7%)

1999, Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group: N Engl J Med, v. 340, p. 757-63.
4-week RCT followed by 12 week open-label.

NNT=1/0.50-0.167=1/0.33=3

*Presumed from descriptions of adverse dropouts
SAE Cloz: Myocardial Infarction
SAE Placebo: 2 Hospitalizations-Pneumonia, psychosis