

Industry Presentation

Salix Pharmaceuticals, Inc.

Relistor[®]

Methylnaltrexone Bromide

Subcutaneous Injection

Supplemental NDA

**Anesthetic and Analgesic Drug Products
Advisory Committee**



Introduction

Bill Forbes, PharmD

Executive Vice President, Medical and R&D
Chief Development Officer
Salix Pharmaceuticals

Salix Pharmaceuticals, Inc.

- **Focus on gastrointestinal diseases**
- **Collaborative history with FDA**
 - Pediatric ulcerative colitis treatment
 - New treatment for prevention of hepatic encephalopathy
 - Novel treatment of diarrhea in patients with HIV infection on antiretroviral therapy
 - Innovative study designs and endpoints for IBS and IBD clinical development programs

Unmet Medical Need of OIC

- **Most common adverse effect of opioids**
- **Tolerance rarely develops**
- **Straining, debilitating abdominal pain, nausea, bloating, and vomiting**
- **Current treatments often inadequate**
- **May interfere with optimal pain management**

Class Issues for Discussion at this Meeting

Potential CV Signal Leading to Concern

- GSK014 (alvimopan): imbalance in MI

Generalizability

- Generalizability of GSK014 to all PAMORAs

Plausibility

- Potential mechanism(s) of CV signal, including opioid withdrawal

Future Evaluation

- Need, type, and timing of CV risk assessment

RELISTOR

Methylnaltrexone Bromide

- **Current Indication (April 24, 2008)**
 - Treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient
 - 1 SC injection every other day, as needed
 - Dose: 8 mg (38-62kg); 12 mg (62-114kg)
- **Available in 31 countries**
- **Prescribed in >800,000 patients worldwide**



Key Properties of Relistor

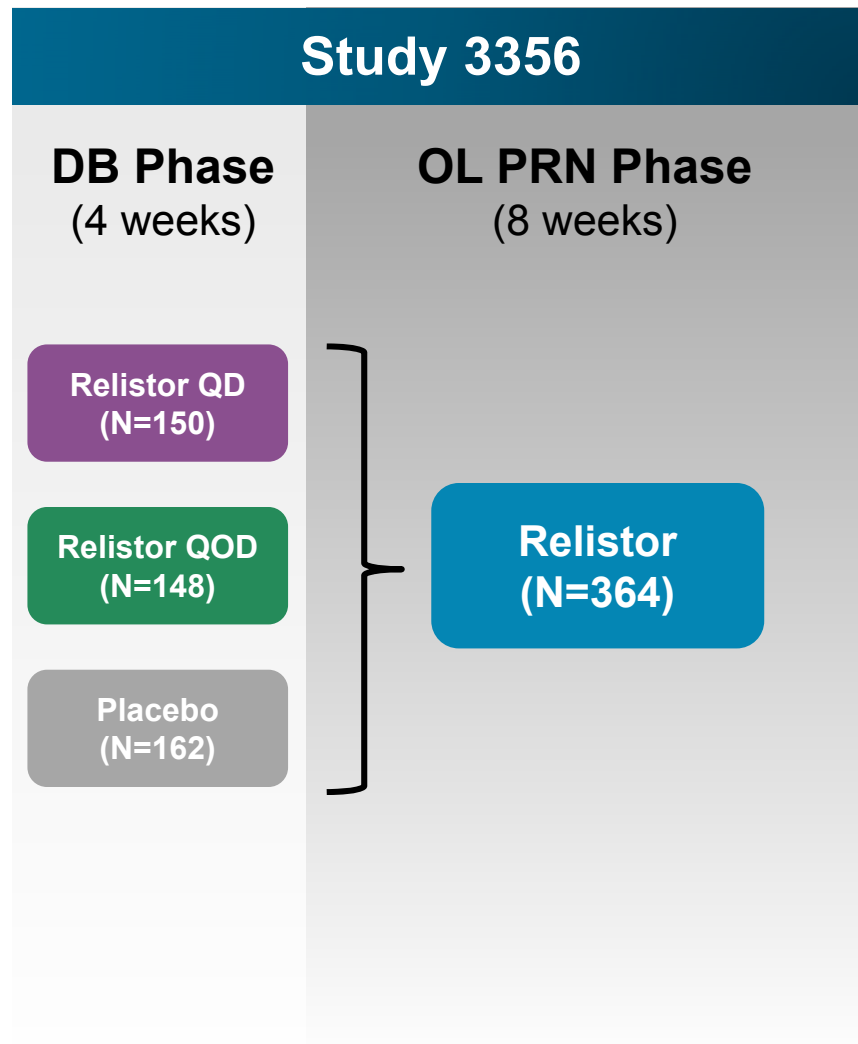
- **Peripheral therapeutic effect**
 - Targets mu-opioid receptor
 - Restricted penetration across blood-brain barrier
- **Rapid and predictable efficacy**
 - $\text{NNT} = 2.5 - 5.0$
- **Dosing and administration**
 - Subcutaneous dose, once every other day as needed
 - No drug accumulation
- **No known drug-drug interactions**

Relistor Development Program

	Population	Number of Studies	N	Route	Dosage
Non-clinical	In vitro/ In vivo	>150	NA	in vitro, PO, SC	0-1000 µM Mouse: 30-200/400mg/kg Rat: 30 – 300 mg/kg Dog: 1 – 250 mg/kg
Phase 1	Healthy Methadone U of Chicago	25 7 13	>1304	IV, SC, PO	IV: 0.3 mg/kg, 24 mg SC: 0.075-0.6 mg/kg, 12 mg PO: 75 – 900 mg
Phase 2	OIC	6	600	SC/PO	12 mg QD 4-7 days 10 to 600 mg QD 4 wks 1 to 20 mg QD or QOD 4 weeks 0.05-0.3 mg/kg QOD 12 weeks
	POI	1	65	IV	0.3 mg/kg q6 for ≤ 7 days
Phase 3	POI	3	1421	IV	12 or 24 mg q6h up to 10 days
	OIC in AI	5	337	SC	0.15 or 0.30 mg/kg QD up to 4 weeks
	OIC in NCP	2	1385	SC	12 mg QD or PRN up to 48 weeks
	OIC in NCP	1	804	PO	150, 300, or 450 mg QD for 28 days; PRN for 58 days
Phase 4	OIC	2	255	SC	8 or 12 mg QOD; 0.1-0.3 mg/kg

OIC = opioid induced constipation, AI = Advanced Illness,

Relistor Study 3356

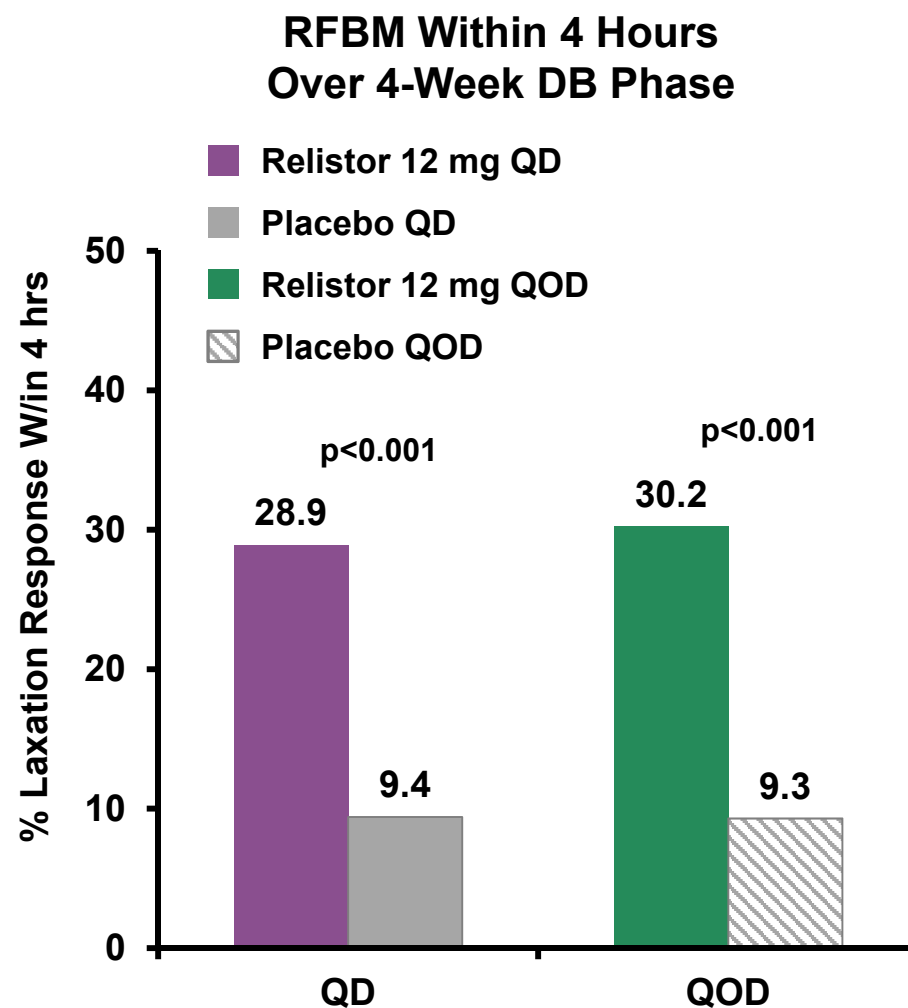
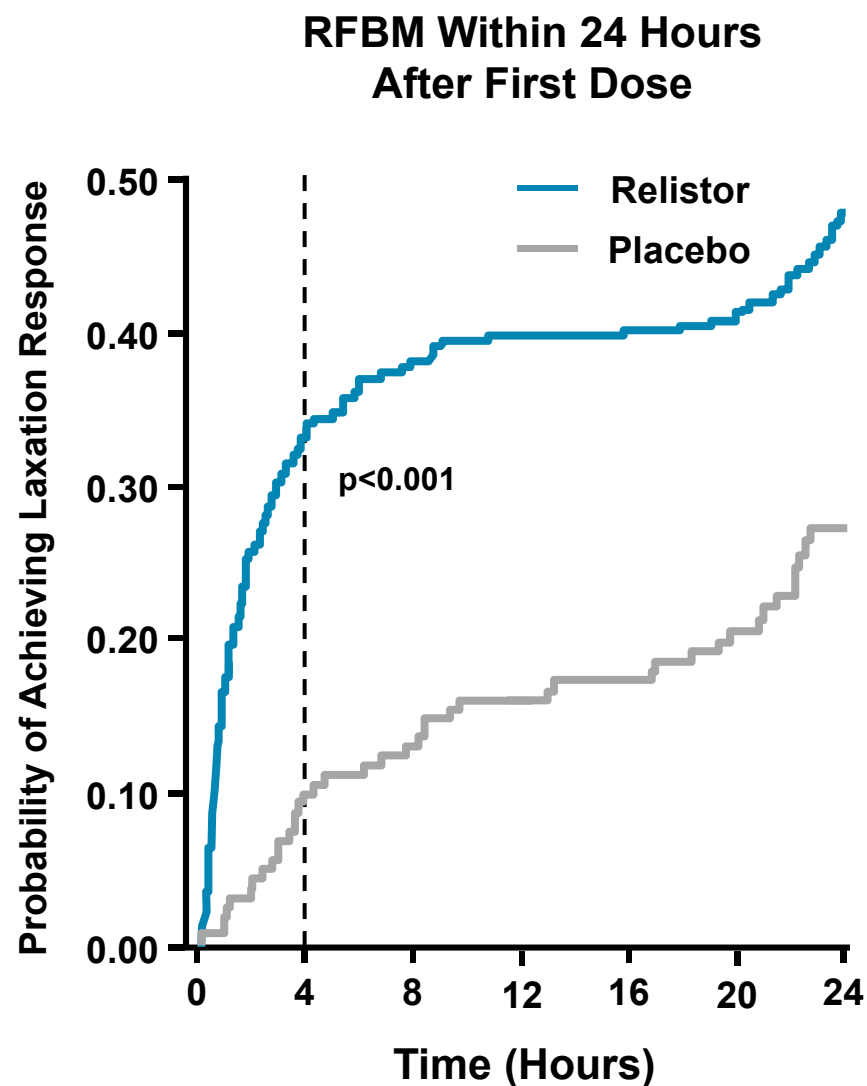


- ## Co-primary Endpoints
- **Proportion of subjects having a RFBM* within 4 hours of the first dose**
 - **Percentage of active injections resulting in a RFBM within 4 hours**

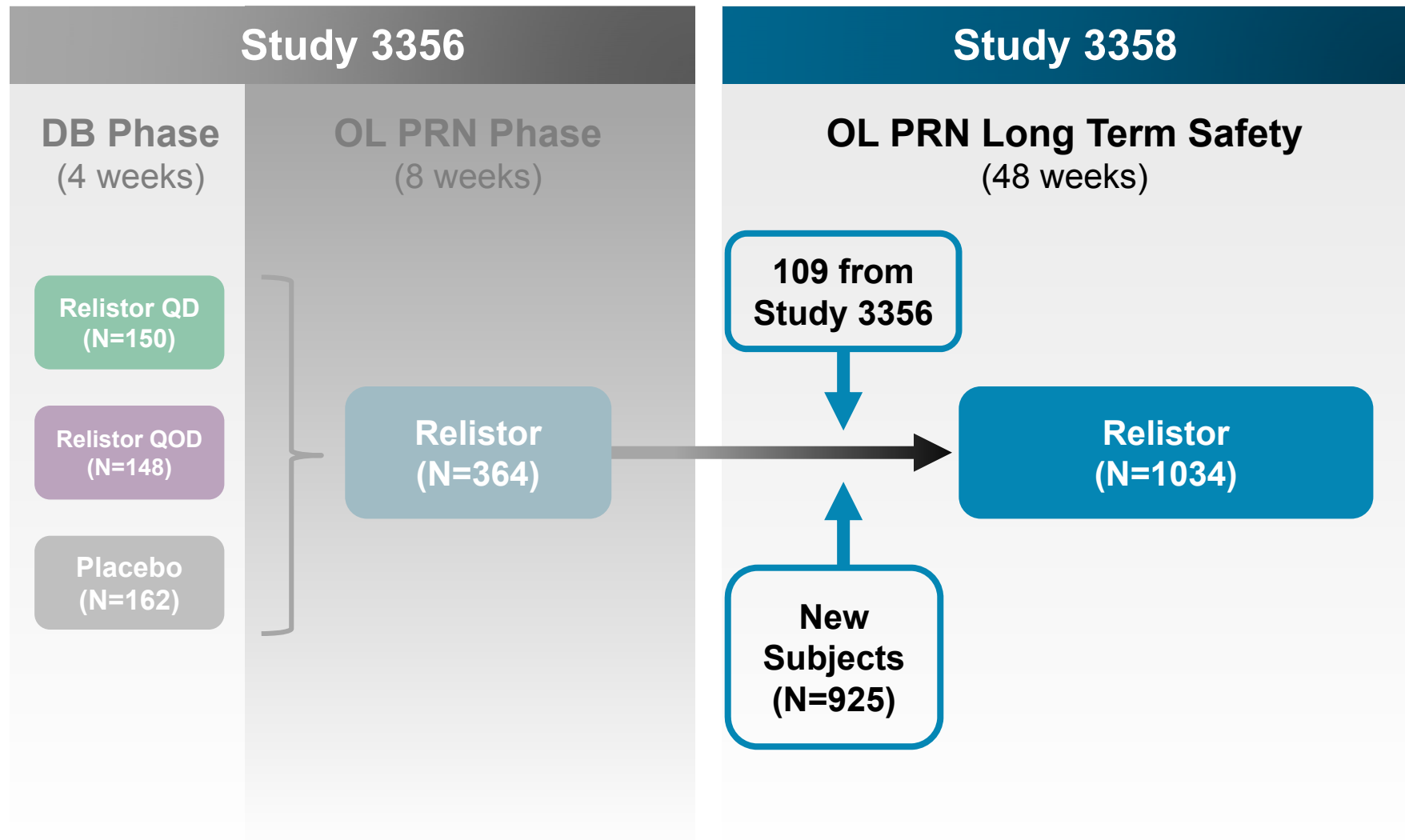
* RFBM = Rescue-free bowel movement

Rapid and Durable Efficacy of Relistor

Study 3356

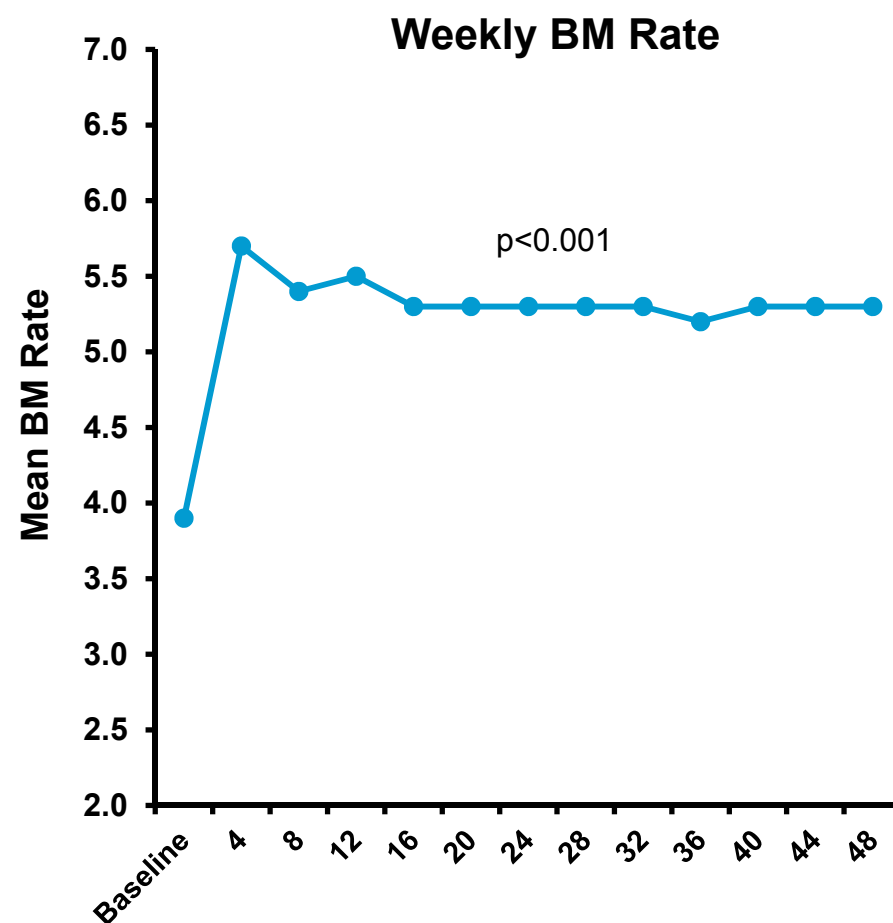
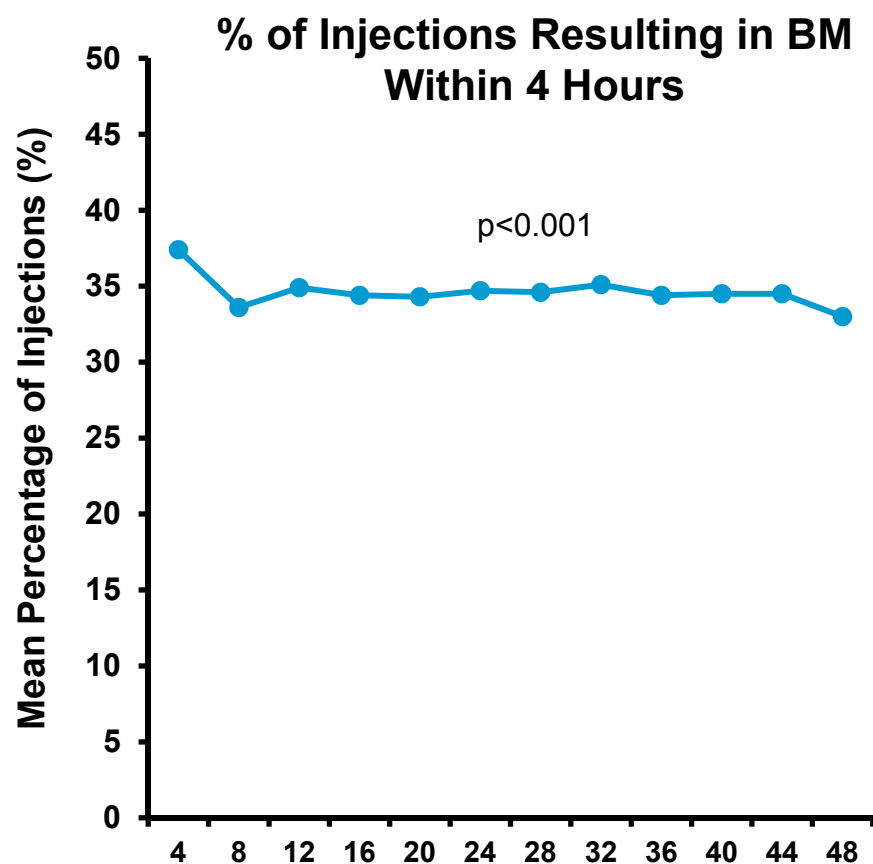


Relistor Study 3358



Sustainable Rapid and Durable Efficacy

Study 3358

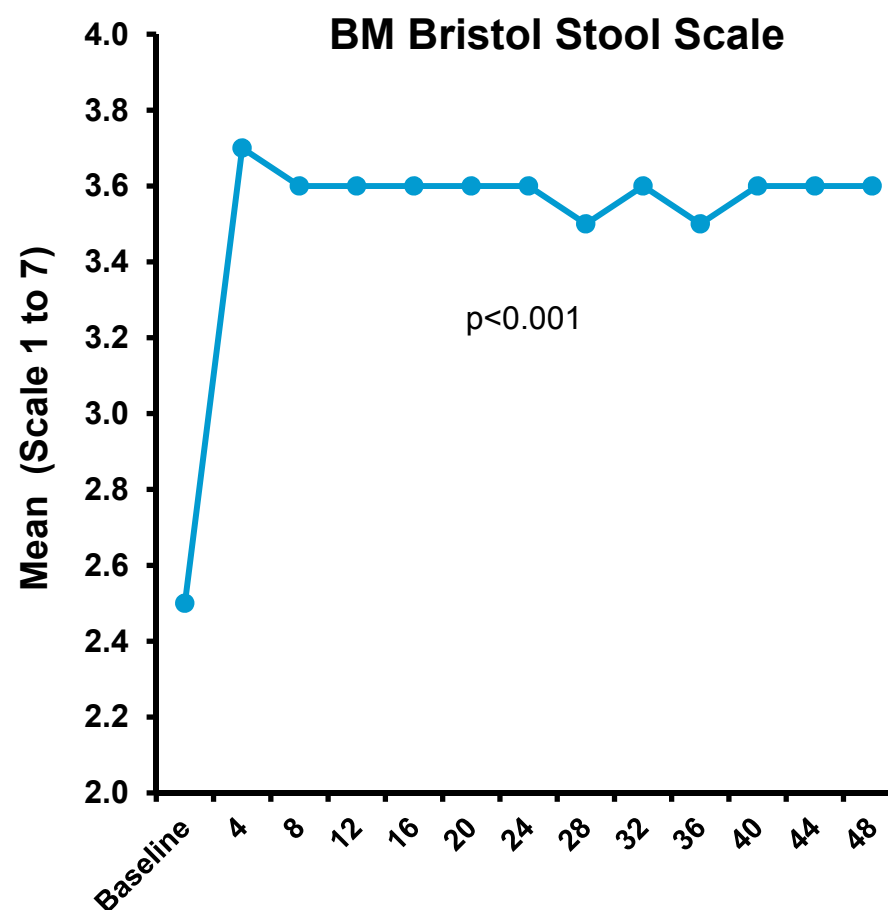
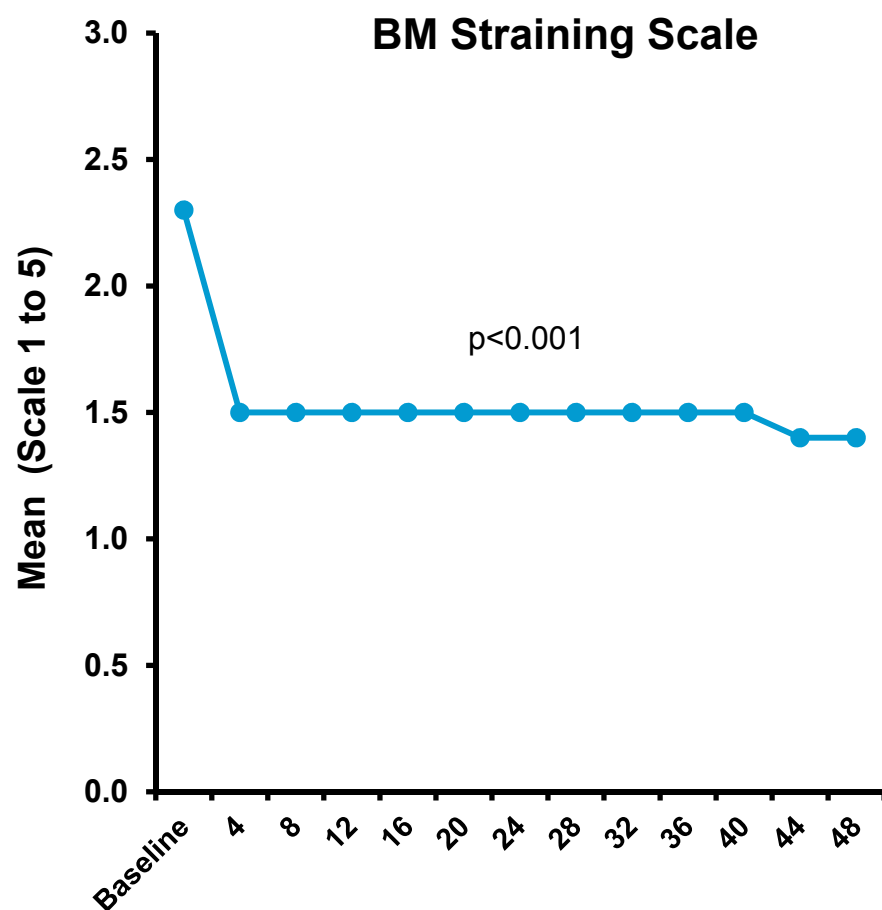


Time (Weeks)

CI-12

Durable Improvements in Straining and Stool Consistency

Study 3358



Time (Weeks)

Relistor CV Risk Assessments

Assessment	Nonclinical	Clinical
Hemodynamics	BP, HR, LVP, LVEDP, cardiac output (anesthetized dogs)	BP and HR (supine, seated, standing) Acute/chronic administration
Electrophysiology	hERG assessment Purkinje fibers (rabbit, dog) ECG in dogs (IV, SC and PO), guinea pigs (IV)	ECG Thorough QTc studies (IV, SC)
Lipoproteins	TG, TC (rats, dogs)	TC, TG, HDL, LDL
Clinical Chemistry	Rats and dogs (chronic dosing)	Acute/chronic
Coagulation	PT, PTT (rats, dogs; chronic dosing)	PT, PTT, INR <i>Ex vivo</i> platelet aggregation

Agenda

Clinical Pharmacology

Pam Golden, PhD

*Associate Vice President, Nonclinical &
Clinical Pharmacology, Medical & R&D*
Salix Pharmaceuticals

Clinical Review of Safety

Craig Paterson, MD, MSc

*Vice President, Medical & Clinical
Development, Medical & R&D*
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Summary

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Clinical Pharmacology

Pamela L. Golden, PhD

Associate Vice President

Nonclinical and Clinical Pharmacology

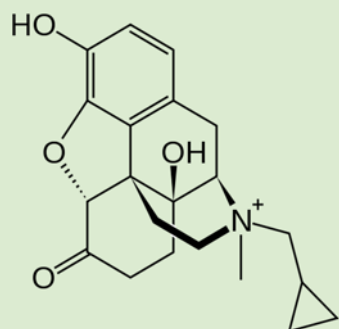
Salix Pharmaceuticals, Inc.

Relistor CV Risk Assessments

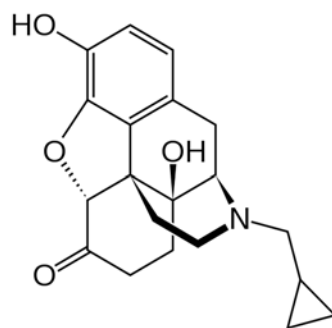
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Relistor is a 4,5 α -Epoxymorphinan

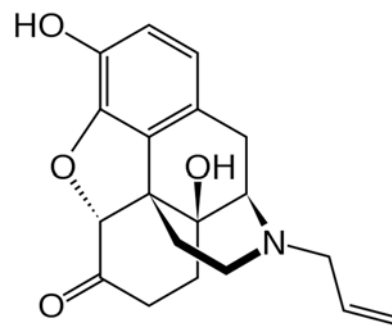
Structurally Related to Morphine



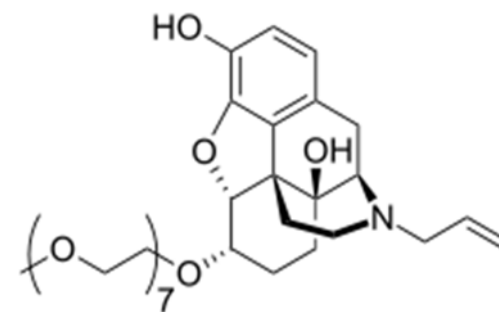
Methylnaltrexone



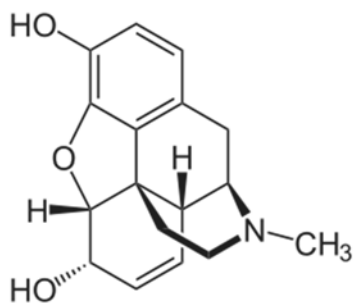
Naltrexone



Naloxone

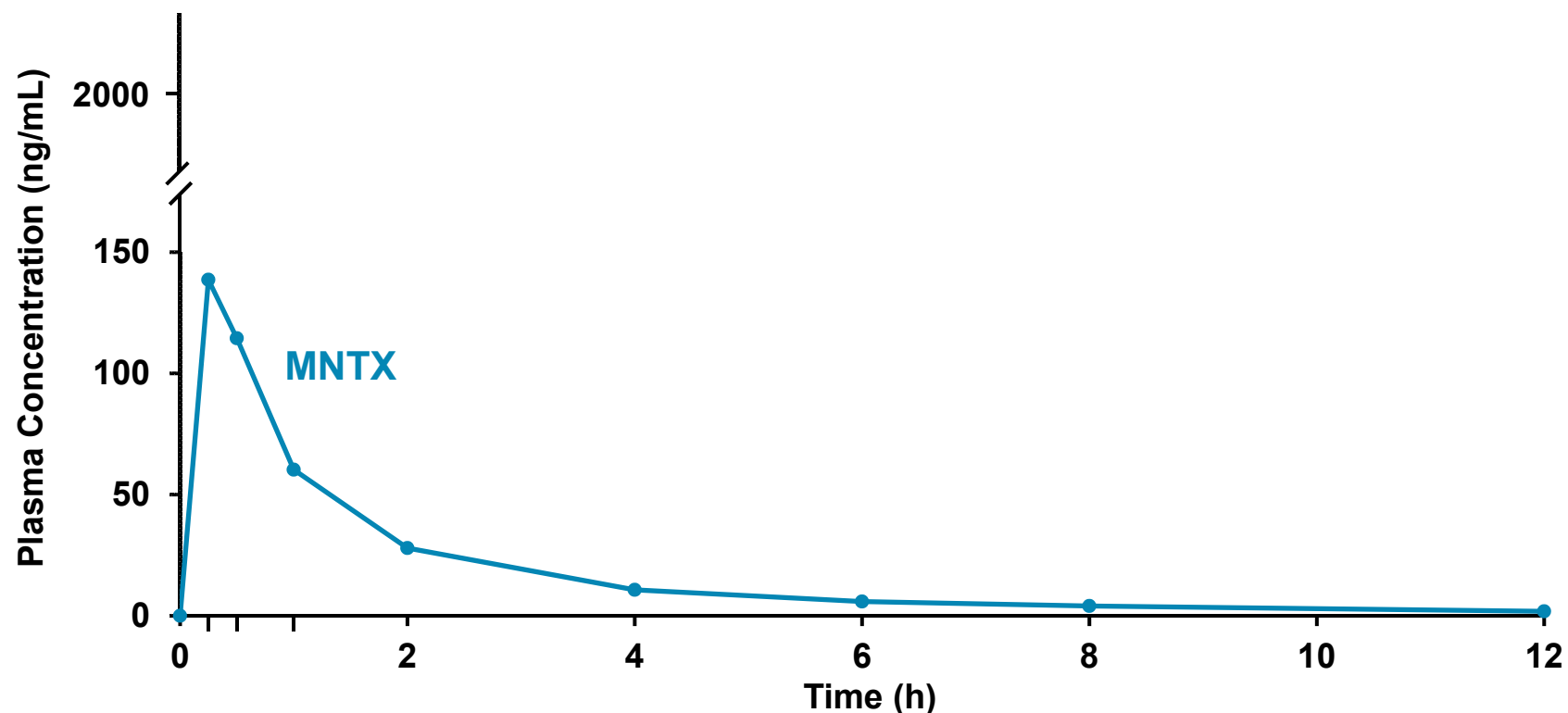


Naloxegol



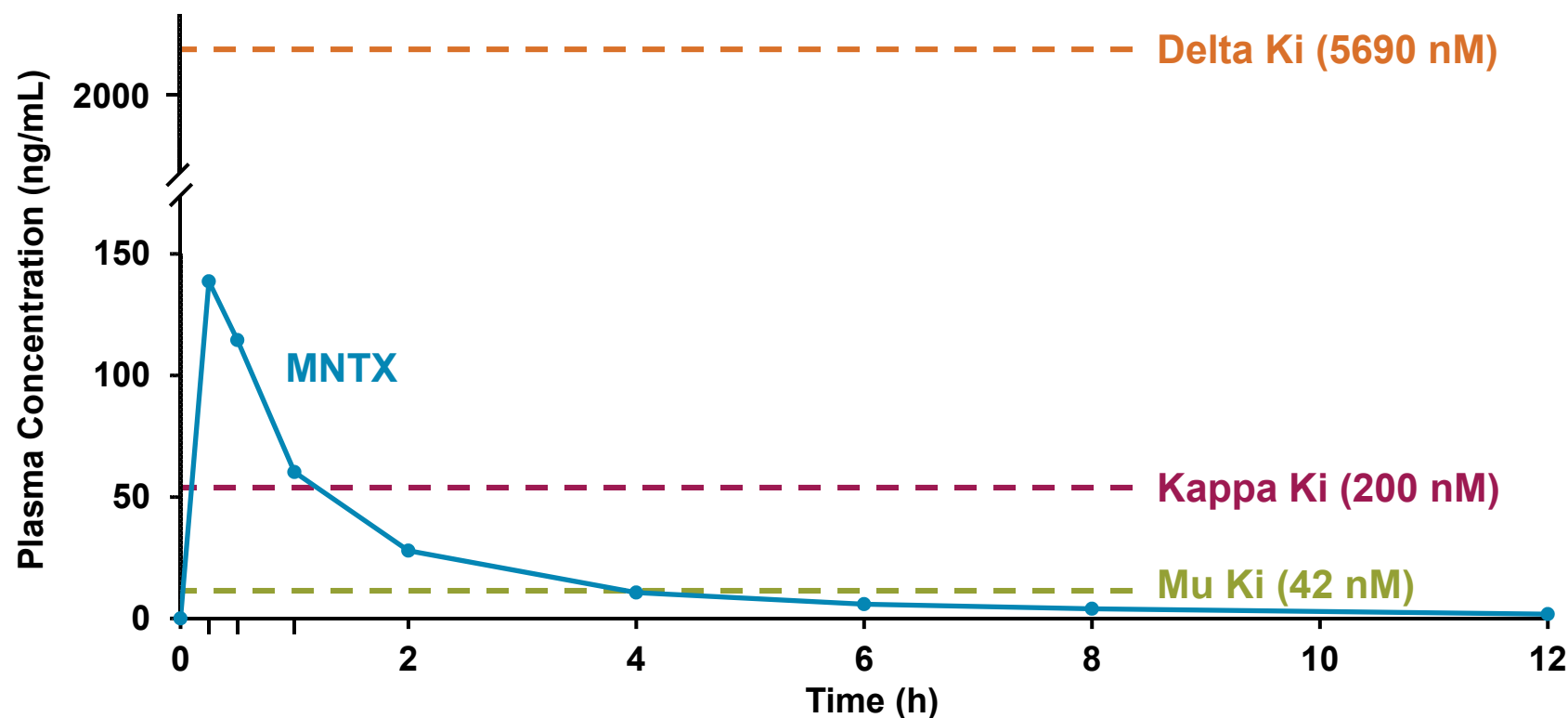
Morphine

Relistor ADME and Pharmacology



- **Pharmacokinetics and metabolism**
 - Rapid onset and short duration of effect, allowing PRN administration
 - Minimal metabolism; metabolites do not contribute to efficacy
 - No known drug-drug interactions

Relistor ADME and Pharmacology



- **Pharmacology**

- Limited time above mu or kappa opioid receptor K_i
- Partial agonist activity at the mu receptor
- Low multiple (0.06) of the delta opioid receptor K_i at C_{max}

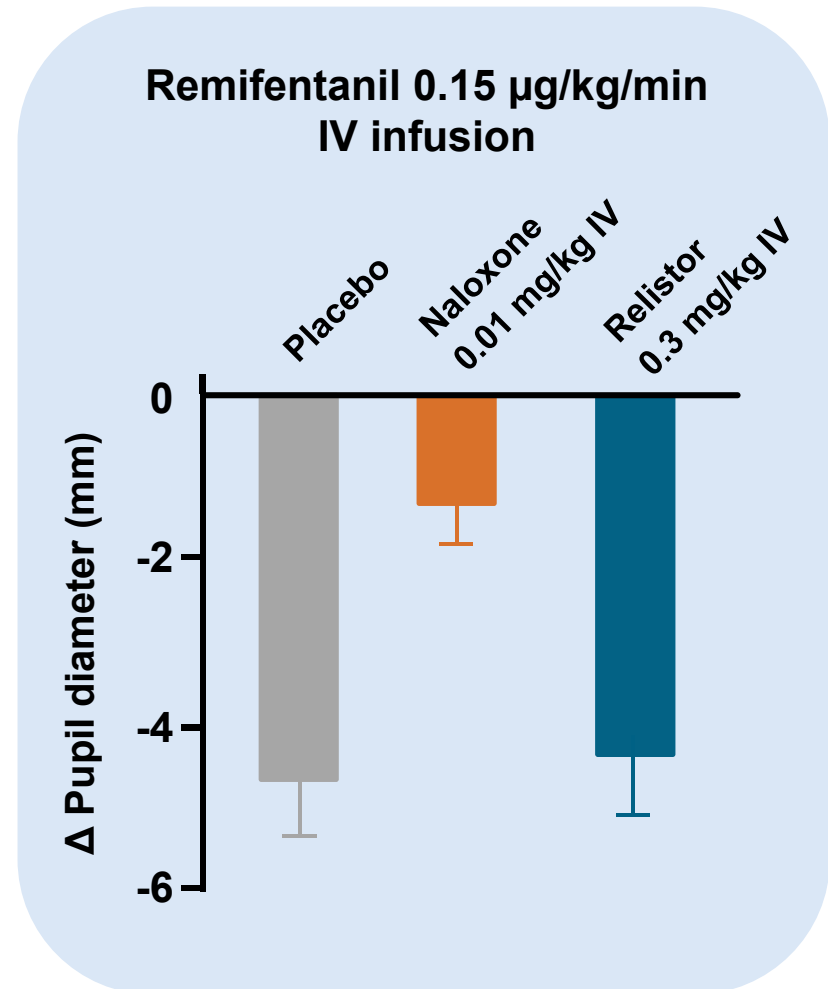
MNTX Distribution

- **Humans**

- No reversal of opioid-induced pupillary miosis after Relistor 0.3 mg/kg IV

- **Rats**

- MNTX (up to 60 mg/kg, 580 mg HED)
 - Reversed morphine effects on GI transit but not antinociception
- ³H-MNTX (5 mg/kg IV, 48 mg HED)
 - Brain-to-plasma ratio < 0.03



Hemodynamic Changes Across Species

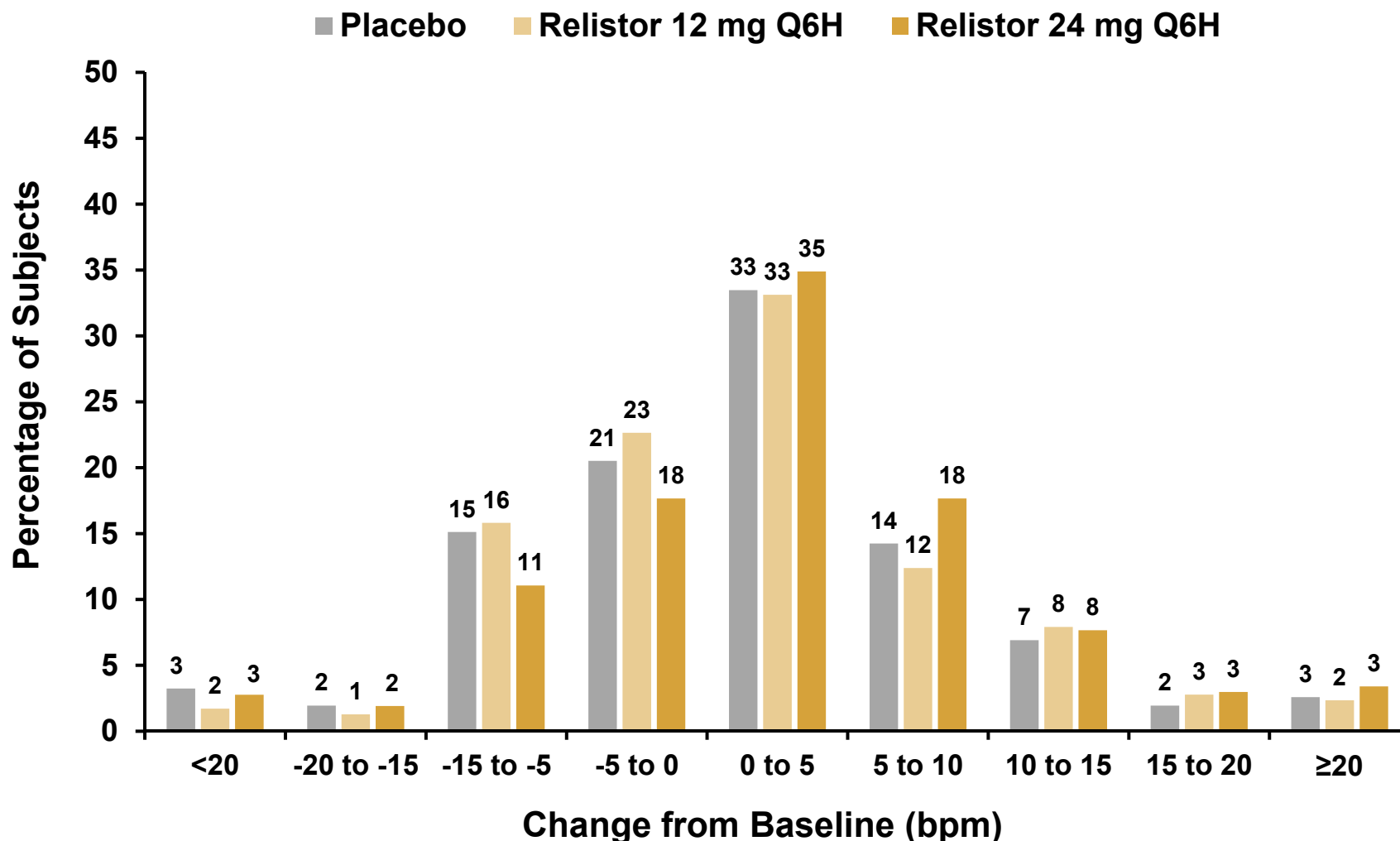
- **Nonclinical Species**

- **Anesthetized dogs:** Dose-dependent, transient HR decreases at doses up to 25 mg/kg IV (HED 833 mg)
- **Conscious dogs:** Dose-dependent, transient decreases in arterial pressure and systolic BP at doses up to 20 mg/kg IV (HED 667 mg)

- **Humans**

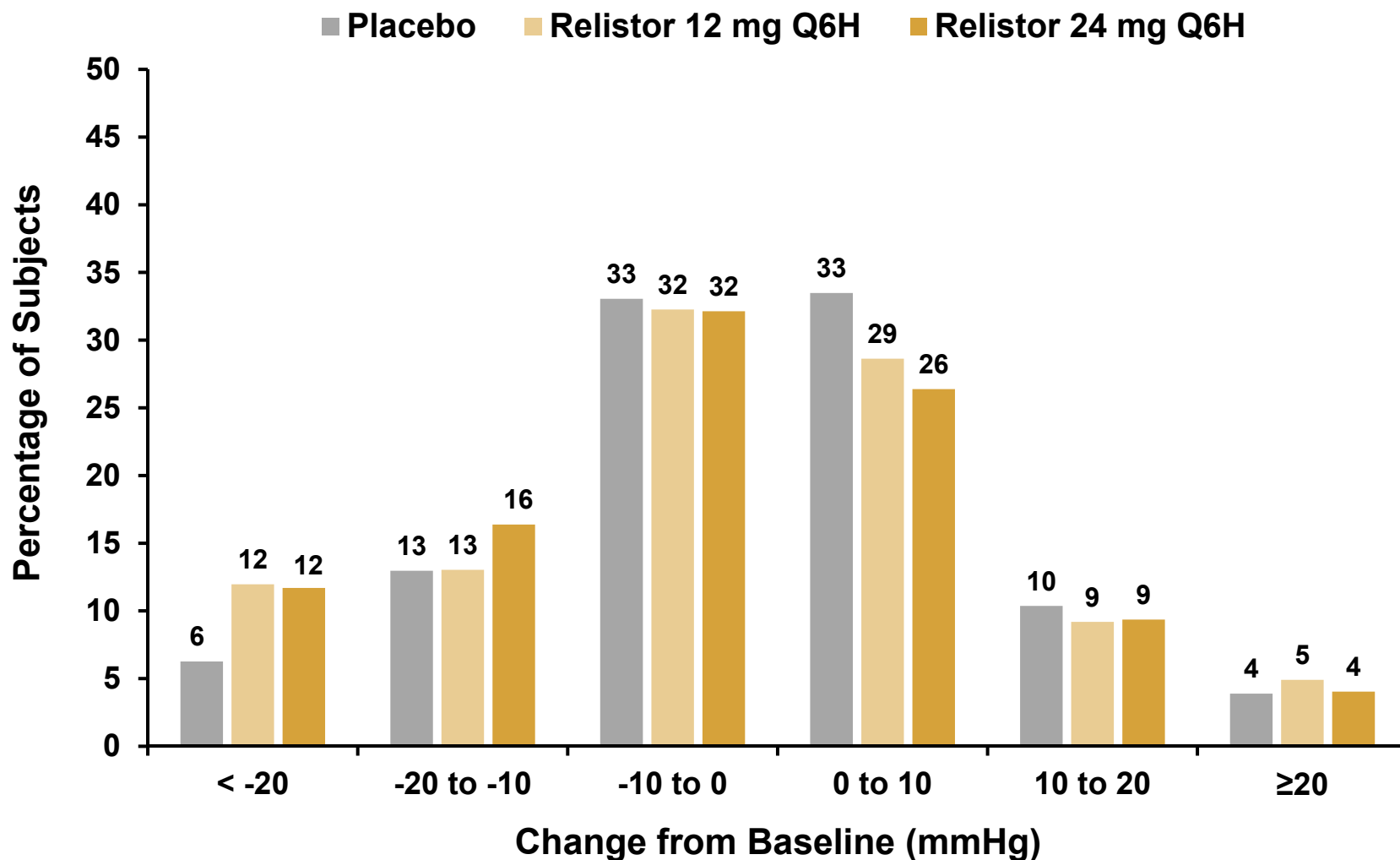
- No apparent dose-dependent effects on pulse or BP
 - SC doses up to 12 mg QOD - QD
 - IV doses up to 24 mg every 6 hours

Categorical Changes in Pulse One Hour Post Dose on Day 1 – IV Pool



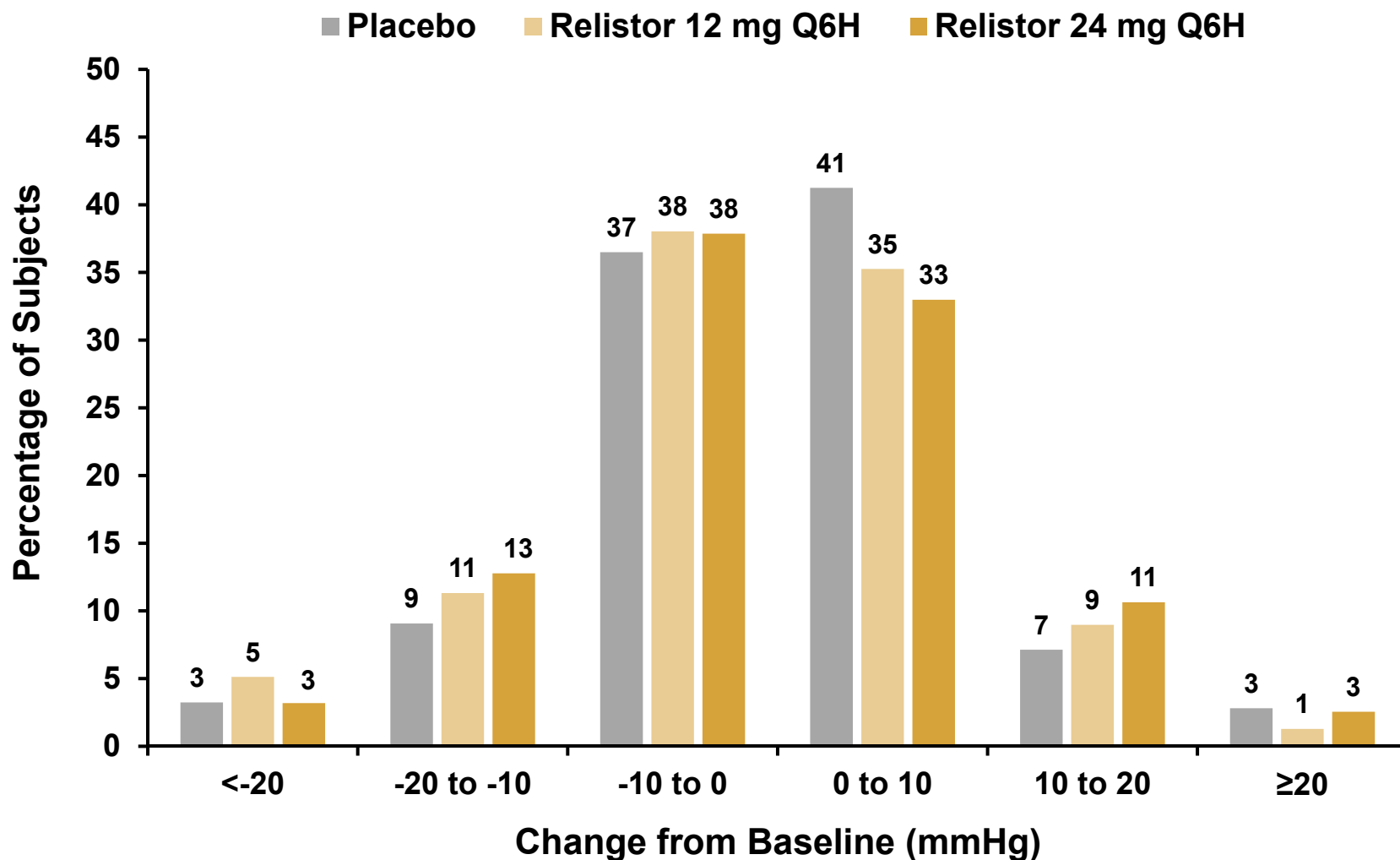
Categories include the lower limit of the interval (eg. 0 to 10 means ≥ 0 to <10). Studies MNTX 3301, 300, 301-IV

Categorical Changes in Systolic Blood Pressure One Hour Post Dose on Day 1 – IV Pool



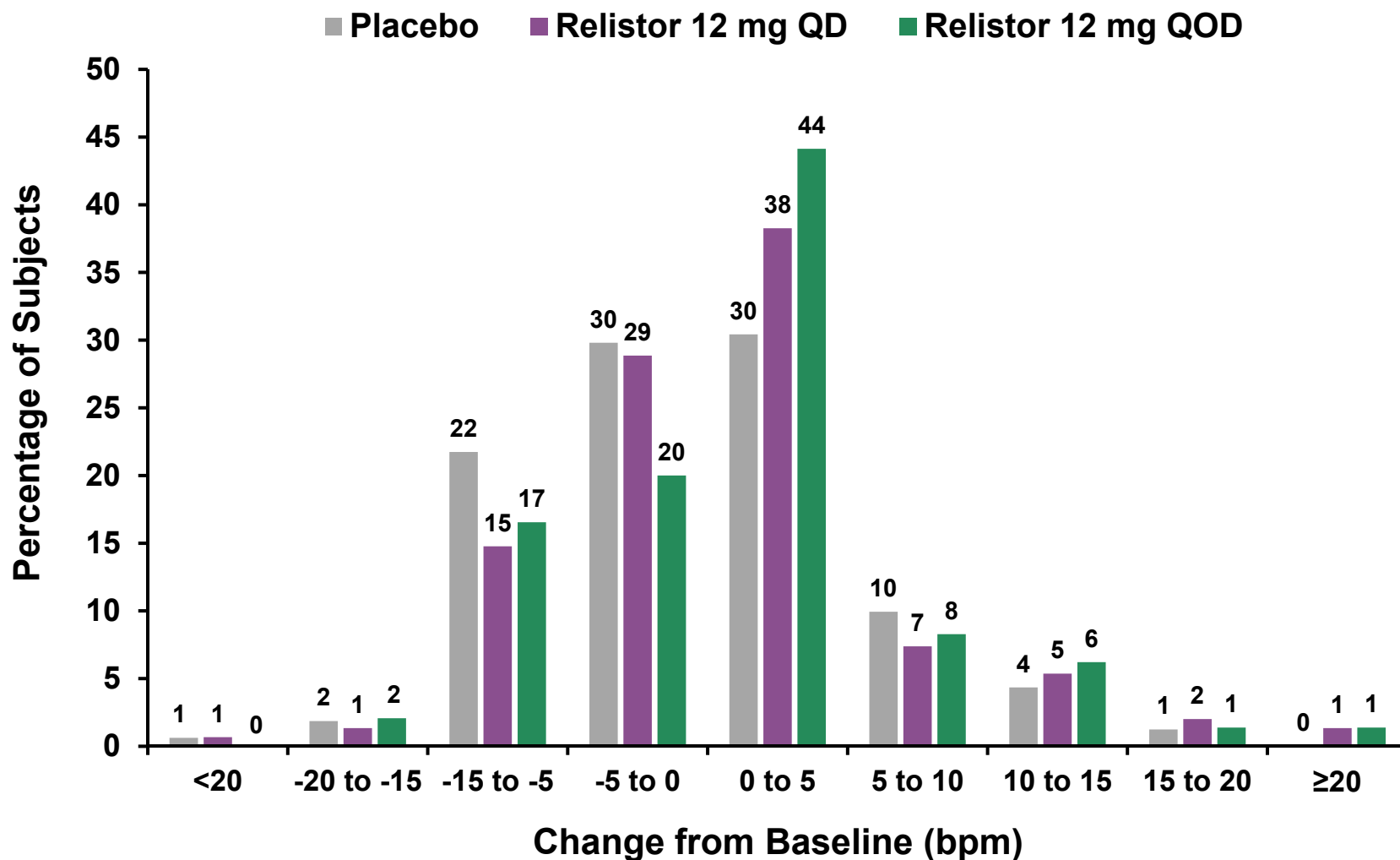
Categories include the lower limit of the interval (eg. 0 to 10 means ≥ 0 to <10). Studies MNTX 3301, 300, 301-IV

Categorical Changes in Diastolic Blood Pressure One Hour Post Dose on Day 1 – IV Pool



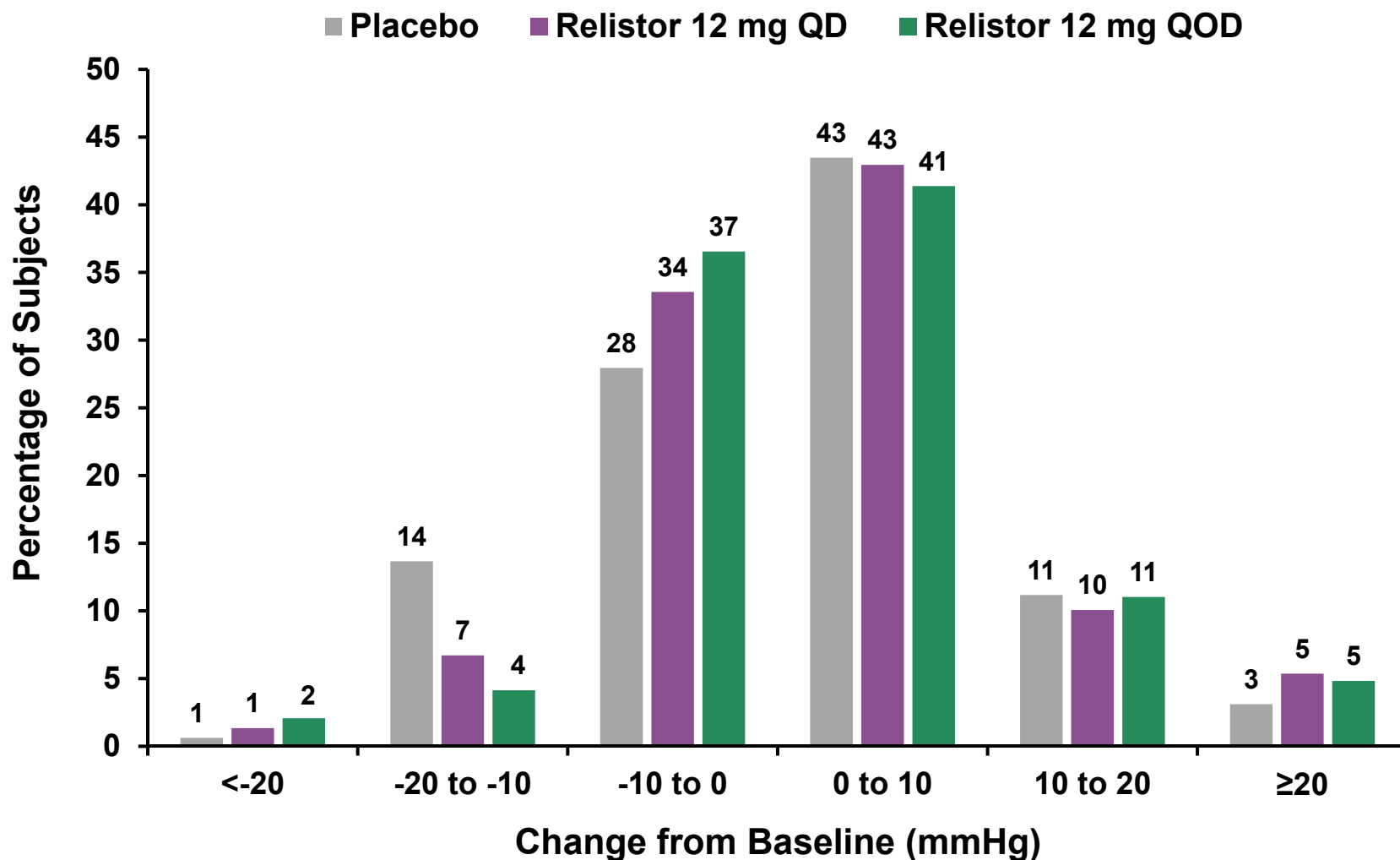
Categories include the lower limit of the interval (eg. 0 to 10 means ≥ 0 to <10). Studies MNTX 3301, 300, 301-IV

Categorical Changes in Pulse One Hour Post Dose on Day 1 – Study 3356



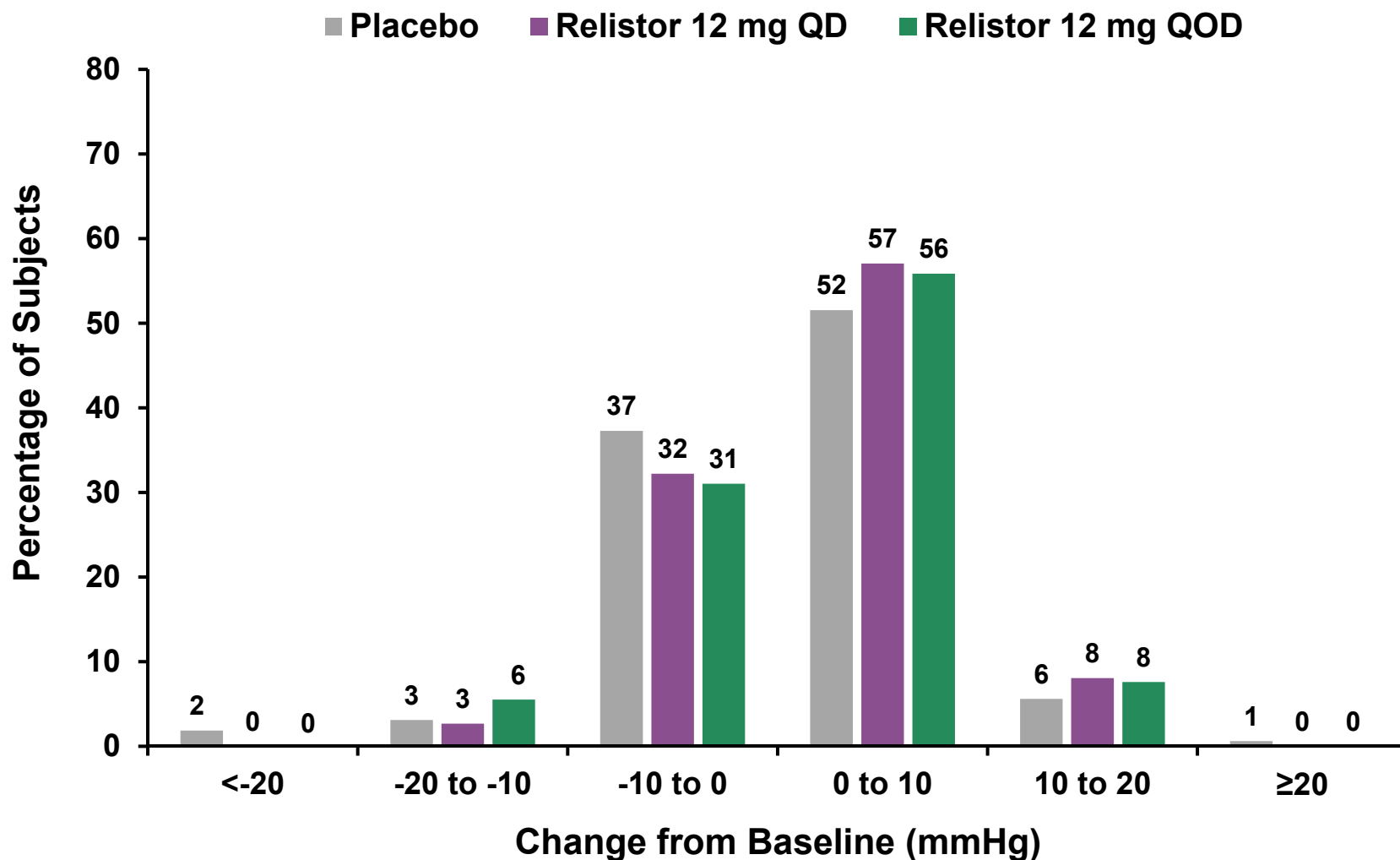
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Categorical Changes in Systolic Blood Pressure One Hour Post Dose on Day 1 – Study 3356



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Categorical Changes in Diastolic Blood Pressure One Hour Post Dose on Day 1 – Study 3356



Categories include the lower limit of the interval (eg. 0 to 10 means ≥ 0 to <10).

No Evidence of Coagulation or ECG Effects

- **Coagulation**

- No induction of platelet aggregation in *ex vivo* assays
- No effects on PT, PTT, or INR in OIC patients

- **ECG**

- **Humans:** No evidence of QT prolongation in thorough QT studies
- ***In vitro*:** hERG IC₅₀ not achieved up to 1000 µM (356,000 ng/mL)
- **Telemeterized dogs:** No clinically significant QT effects at doses up to 20 mg/kg (667 mg HED)

No Substantive Changes in Metabolic Parameters

Study 3358

Parameter	Study Week	N	Mean (SD)	Mean Change (SE)
Glucose (mmol/L)	24	337	5.76 (1.96)	0.16 (0.11)
	48	183	5.74 (1.93)	0.05 (0.14)
Cholesterol (mmol/L)	24	336	5.09 (1.15)	-0.07 (0.05)
	48	184	5.11 (1.36)	-0.23 (0.09)
Triglycerides (mmol/L)	24	336	1.83 (1.02)	0.10 (0.06)
	48	184	2.09 (5.04)	-0.28 (0.36)

Conclusions

- **Rapid onset of effect and no accumulation**
- **PK not altered by any known drug-drug interactions**
- **Limited CNS penetration**
- **Available data do not suggest a signal predicting increased CV risk or a mechanism that would mediate CV risk**

Agenda

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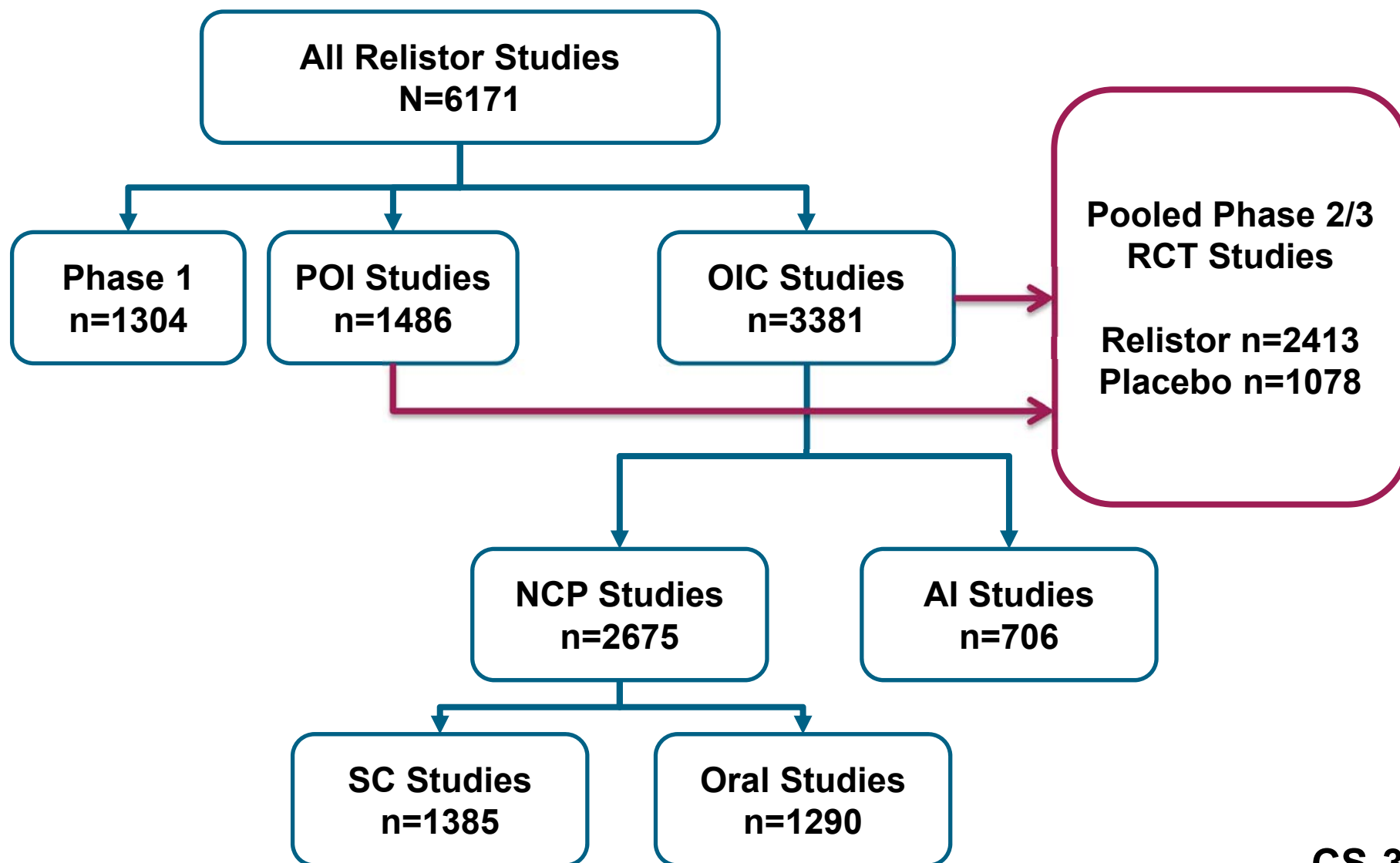
Craig Paterson, MD, MSc

VP, Medical and Clinical Development
Salix Pharmaceuticals

Outline

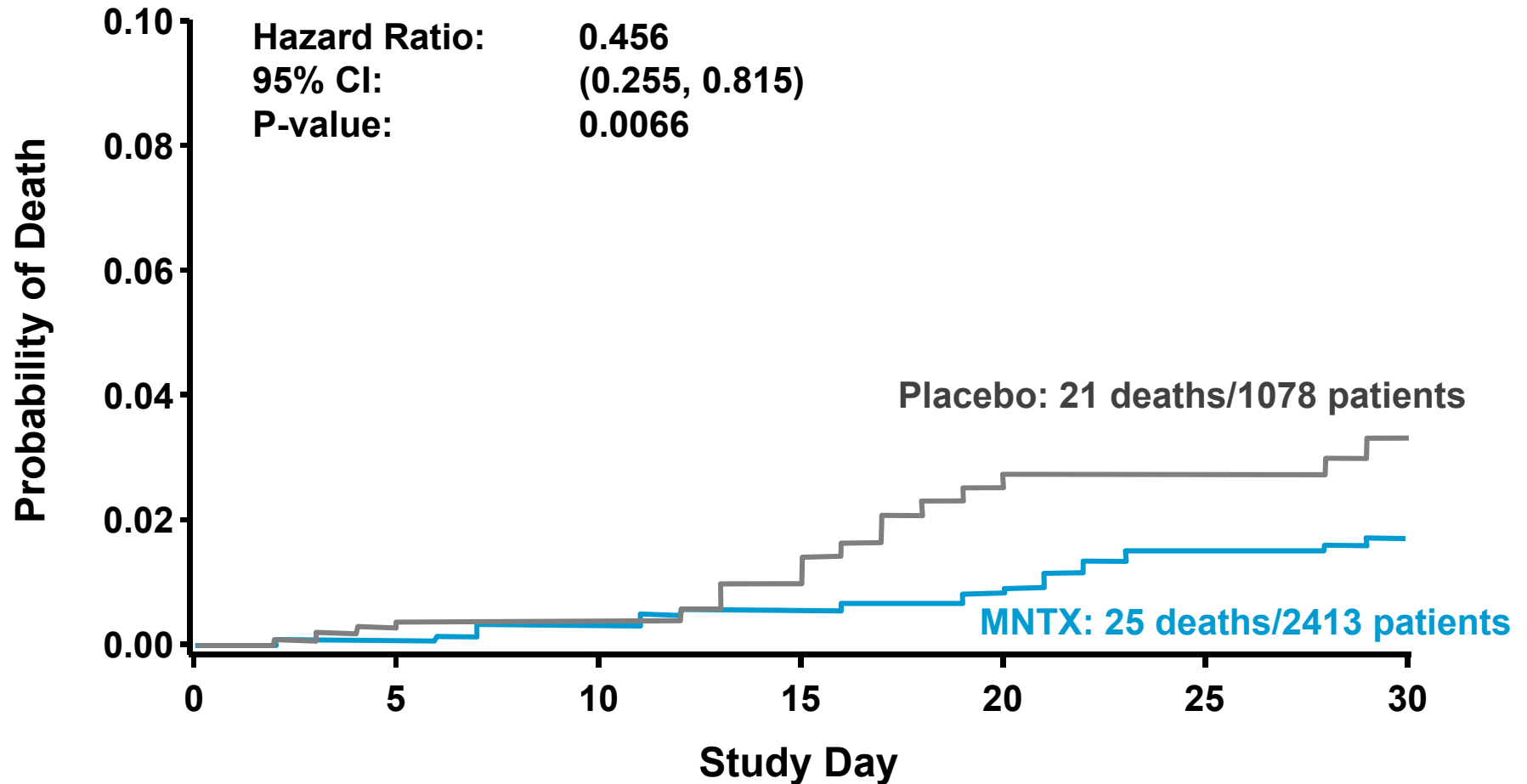
- **CV safety overview**
- **CV events of interest**
- **Interpretability of CV event rates**
- **Potential withdrawal symptoms**
- **Post-marketing surveillance**
- **Safety summary**

Disposition of Relistor Clinical Development Studies



No Increase in All-cause Mortality

Relistor Phase 2/3 Trials - Placebo Controlled Data



Population included the double-blind, placebo-controlled periods of studies in the advanced illness population, non-cancer pain population, and POI population. These studies included Relistor doses using IV, SC and oral routes of administration.

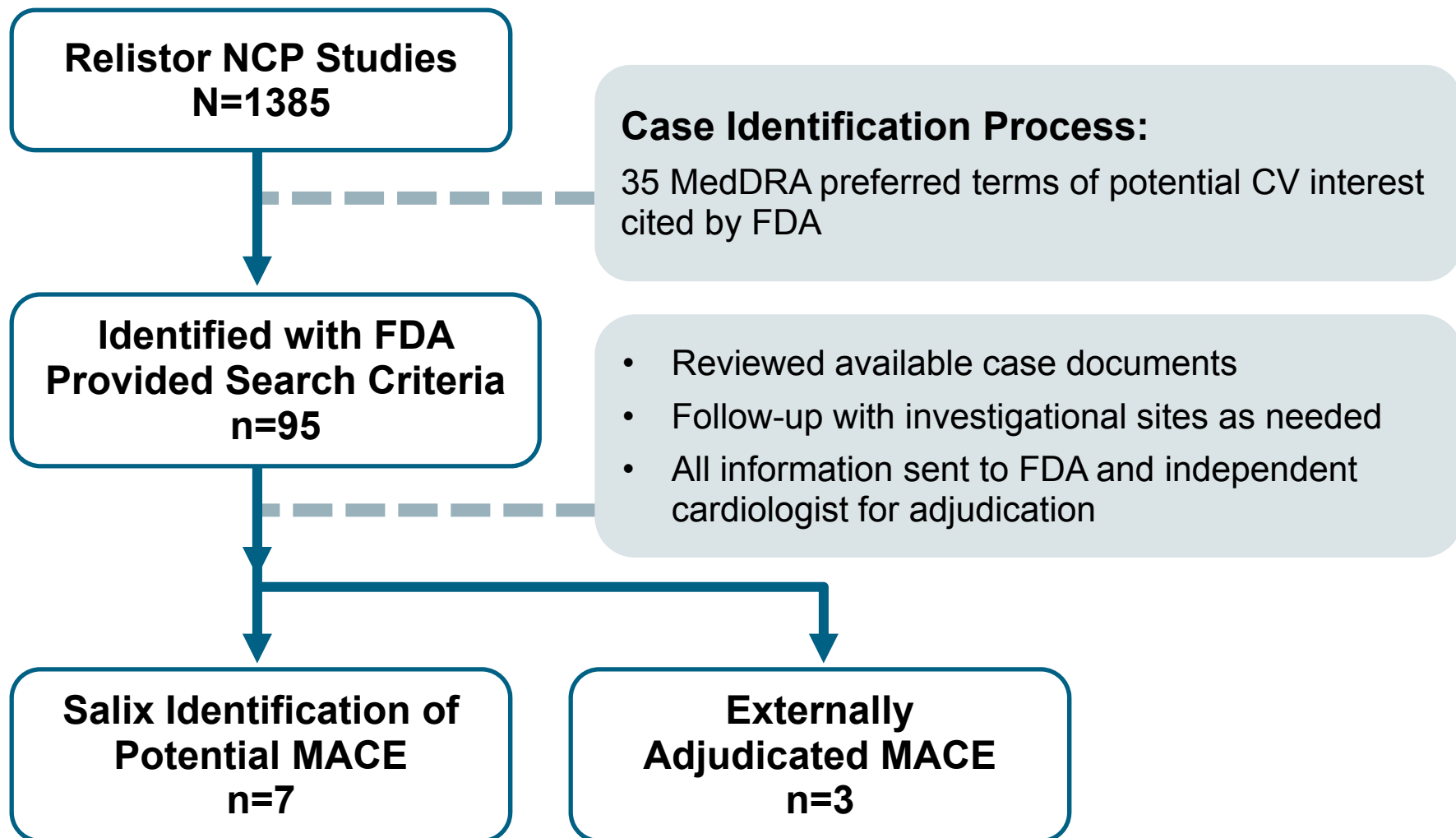
Cardiac Treatment-Emergent SAEs

	Placebo (N=1078) (PY=66.9) n, [AE Rate]	DB Relistor (N=2413) (PY=182.0) n, [AE Rate]	OL Study 3358 (N=1034) (PY=598.7) n, [AE Rate]
Cardiac disorders (SOC)	11 [16.5]	11 [6.0]	9 [1.5]
Acute MI/MI	1 [1.5]	1 [0.5]	4 [0.7]
Cardiac arrest/Cardiorespiratory arrest	1 [1.5]	1 [0.5]	1 [0.2]
Cardiac failure congestive	2 [3.0]	2 [1.1]	1 [0.2]
Cardiovascular disorder	0	1 [0.5]	0
Coronary artery disease	0	1 [0.5]	2 [0.3]
Cyanosis	1 [1.5]	0	0
Ischemic coronary artery disorders	0	1 [0.5]	3 [0.5]
Rate and rhythm disorders	1 [1.5]	3 [1.6]	0
Supraventricular arrhythmias	5 [7.5]	1 [0.5]	0

Note: The AE Rate is calculated as events per 100 patient years of exposure.

PY = patient years of exposure

Identification of Potential MACE in NCP Studies



MACE defined as non-fatal stroke, non-fatal MI, or CV death

Potential MACE in NCP Studies

Pivotal (Study 3356) & Open-Label Safety (Study 3358)

Event	Age	# Doses Prior to SAE	Study Day of SAE	Days Off Drug Prior to SAE	Study Drug Restarted	Outcome
MI	57	291	306	2	Yes	Completed study
Death (MI)	57	248	278	13	N/A	Death
MI	81	140	238	5	Yes	Completed study
CVA	45	210	211	0	N/A	Death
Cardiac arrest	67	57	63	6	N/A	Death
Sudden death	46	238	257	7	N/A	Death
MI	59	6	6	0	Yes	Completed through Day 274

None of these events occurred in Study 3356

*Highlighted events represent external blinded post-hoc adjudication as MACE

Patient 095-082943

SAE: Myocardial Infarction

Event Summary	57 yo female with CAD and multiple cardiac risk factors had MI on study day 306 (2 days after last dose of study drug) Resumed study medication following stent placement (LAD & RCA) and hospital discharge and with no further documented issues
Risk Factors	BMI=23.3, CAD, hyperlipidemia, smoker, COPD, pre-existing stenosis of both right and LAD coronary arteries
Con Meds	Percocet, amitriptyline, carisoprodol, neurontin, duloxetine, alprazolam, and bisacodyl
Evaluations	ECG normal at study Screening; No changes in blood pressure or heart rate over study
Assessment	Well-documented MI in a patient with high CV risk

Post hoc external adjudication as MACE

Patient 200-083696

SAE: Presumed Myocardial Infarction (Fatal)

Event Summary	57 yo male with extensive cardiac hx found dead at home on study day 278, 13 days after last dose of study drug. Cause of death presumed to be MI or cardiac failure (no autopsy)
Risk Factors	BMI=29, angina pectoris, dyslipidemia, myocardial infarction, stent placement x2, hypercholesterolemia, hypertension, tobacco (80 pack-years), orthostatic hypotension
Con Meds	diltiazem, metoprolol, atorvastatin, acetylsalicylic acid, ramipril, transdermal fentanyl, hydromorphone, docusate sodium , tamsulosin, domperidone, lansoprazole, diazepam, gabapentin, dihydroergotamine, amitriptyline, indomethacin, ciclopirox olamine, cortisone acetate, and ketoconazole
Assessment	Characterized as CV death in high risk patient with known CAD. No evidence of an MI

Post hoc external adjudication as MACE

Patient 198-083617

SAEs: Small Bowel Obstruction, Myocardial Infarction

Event Summary	MI in an 81 yo female with pre-existing angina and CV risk factors occurring 5 days after hospitalization for partial SBO and 5 days after last dose of Relistor
Risk Factors	BMI=32, angina pectoris, hyperlipidemia, carotid endarterectomy, and CVA
Con Meds	Diltiazem, atorvastatin, clopidogrel, hydromorphone, acetaminophen/codeine, didrocal, esomeprazole, temazepam, citalopram, methylprednisolone, minocycline, mirapex, ferrous sulfate, and docusate sodium
Evaluations	<p>Study Day 238 troponins 0.07 and 0.1 twelve hours later. T wave inversion in central pre-cordial leads</p> <p>Cardiac catheterization LVEDP = 30 mm Hg; “results consistent with a recent anterior myocardial infarction.” Left ventricular angiogram - anteroapical akinesia with EF 39%. Coronary angiography: LAD minor proximal and distal disease only</p>
Assessment	Event may be a complication of the SBO but no evidence of actual MI

Post hoc external adjudication as not MACE

Patient 008-080235

SAE: Cerebrovascular Accident (Fatal)

Event Summary	45 yo female with long-standing history of poorly controlled hypertension expired on study day 211. Cause of death listed as stroke with hypertension as the contributing factor. No autopsy or imaging. Last dose of study drug on day of event.
Risk Factors	BMI=46, hypertension, sinus bradycardia (diagnosed at study screening)
Con Meds	lisinopril, oxycodone, alprazolam, simethicone, ibuprofen, albuterol, cetirizine, phenylpropanolamine, aspirin, calcium carbonate, bismuth subsalicylate, and bisacodyl
Assessment	No confirmatory evidence of CVA. Potential etiologies include drug abuse (PPA), arrhythmia or cardiomyopathy.

Post hoc external adjudication as not MACE

Patient 020-080651

SAE: Cardiac Arrest

Event Summary	<p>68 yo female with cardiac risk factors progressively obtunded after urgent care visit and unresponsive after being left in car overnight (asystole in ER). Seen at urgent care facility night before event for pain medication (reported being out of pain medication for 5 days).</p> <p>Drug screen only identified acetaminophen (15.3 ug/mL, normal range 10-50 ug/mL). Last dose of study drug 6 days prior to event.</p>
Risk Factors	BMI=46.5, hypertension, past tobacco use, past history of paroxysmal supraventricular tachycardia
Con Meds	hydrochlorothiazide, benzapril, codeine, and nitroglycerin?
Assessment	Sudden death of unknown etiology. No post-mortem exam.

Post hoc external adjudication as not MACE

Patient 073-081899

SAE: Sudden Death

Event Summary	46 yo male with ALS and low oxygen saturation died suddenly on Study Day 257, 7 days after last dose of study drug. Autopsy results were not available
Risk Factors	Seizures, Amyotrophic Lateral Sclerosis (2006), asthma, low oxygen saturation, smoker (1 pack per day)
Con Meds	morphine, oxycodone, carisoprodol, escitalopram, Azmacort, Combivent, Singulair, baclofen, tamsulosin, and gabapentin
Assessment	Patient likely died as a result of ALS.

Post hoc external adjudication as not MACE

CS-45

Patient 198-083624

SAEs: CAD, Myocardial Infarction, CHF, Worsening HTN

Event Summary	59 yo male with cardiac risk factors with MI (study day 6), CHF (study day 43), and worsening HTN (study day 57). Underwent CABG and was maintained on study drug through day 274 with no further issues
Risk Factors	BMI=33, CAD, longstanding tobacco use, uncontrolled HTN, dyslipidemia, ↑ blood sugar, brother had MI at age 57, atypical non-cardiac chest pain, rheumatic fever
Con Meds	Methadone (1,125 mg METDD), acetaminophen, lidocaine injections, dimenhydrinate, and docusate sodium
Evaluations	Screening ECG - sinus bradycardia and QTcB borderline prolonged; BP 170/84 mmHg and HR = 64 Study Day 1: BP 160/75 and HR 62 (pre-dose) and BP 162/74 and HR 60 (post dose). Cardiac Cath: Total occlusion of LAD after first diagonal, with 90% narrowing of first diagonal, and 70-80% narrowing of RCA.
Assessment	MI diagnosed post event based on imaging and symptom recall in a patient with high CV risk

Post hoc external adjudication as MACE

Patient 198-083624 (Cont'd)

- **Chest heaviness at study entry**
- **Last Relistor dose on Day 5 (7:30 pm)**
- **Woke at 2:00 am with chest pain on Day 6**
- **Further chest pain while walking slowly**
 - Associated symptoms: nausea and cold sweating
- **MI diagnosed retrospectively – Study Day 57**
- **Restarted on Relistor by physicians during hospitalization**
 - “It would be a greater strain on his heart if he had to strain and push”

Hemodynamic Effects With First Relistor Dose in Patients with MACE

Patient Age	Event	Systolic BP (mmHg)		Diastolic BP (mmHg)		Pulse (bpm)	
		Pre-dose	1 Hour Post-dose	Pre-dose	1 Hour Post-dose	Pre-dose	1 Hour Post-dose
57	MI	138	127	88	93	76	80
57	Death (MI)	106	106	67	67	57	57
81	MI	134	138	68	64	72	70
45	CVA	129	126	83	80	84	83
67	Cardiac arrest	135	133	86	85	81	85
46	Sudden death	132	130	88	86	76	72
59	MI	160	162	75	74	62	60

Patient 053-002484

SAE: Extrasystoles

Event Summary	50 yo female with a reported SAE of extrasystoles on study day 1 (following first dose)
Risk Factors & Past Med Hx.	Hypertension, generalized anxiety disorder, panic attacks, Prinzmetal angina, COPD, mitral valve prolapse and 1 PPD smoker
Con Meds	methadone 50 mg daily, clonazepam, clonidine, metoprolol, cyclobenzaprine, and lisinopril/HCTZ
Evaluations	Screening (study day -14): 126/93 (standing), 152/97 (supine) Study day 1 (pre-dose): 132/106 (standing), 162/102 (supine) Study day 1 (post-dose): 178/138 (standing), 209/109 (supine) Early withdrawal: 156/110 (standing), 157/111 (supine) ECG (post-dose): Bigeminy; Troponin: 0.01 ng/mL (normal <0.04)
Assessment	Patient had opioid withdrawal <u>prior</u> to first dose of Relistor

Claims-Based Analysis of CV Risk in Chronic Opioid Users

MI Events by Cohort	Person Years	Events	IR*	Lower 95% CI	Upper 95% CI	Standardized IR†	Lower 95% CI	Upper 95% CI
Opioids	176,732	1,067	6.04	5.68	6.41	5.93	5.58	6.30
General	174,906	276	1.58	1.40	1.78	1.58	1.40	1.78

Patients with baseline history of MI or coronary revascularization procedure were excluded

CI, confidence interval; IR, incidence rate

*Incidence rates expressed as events per 1000 person-years; total computed using weighted average; 95% exact confidence intervals

†The standardized rate is the overall incidence rate that would be expected if this cohort had the age-gender distribution of the general population cohort that was age-gender frequency matched to the chronic opioid users' cohort.

Pharmacoepidemiology and Drug Safety, 2011; 20: 754-762

Comparison of MI Event Rates

	Number of Events	Patient Years of Exposure	Event Rate per 100 PY (95% CI)
NCP + Chronic opioid (Carman et al.)	1067	176,732	0.60 (0.57-0.64)
NCP + Chronic Opioid + Relistor (Study 3356 & 3358)	4	668.1	0.60 (0.16-1.53)

NCP + Chronic Opioid + alvimopan (GSK014 Study)	7	350.9	2.0 (0.80-4.08)
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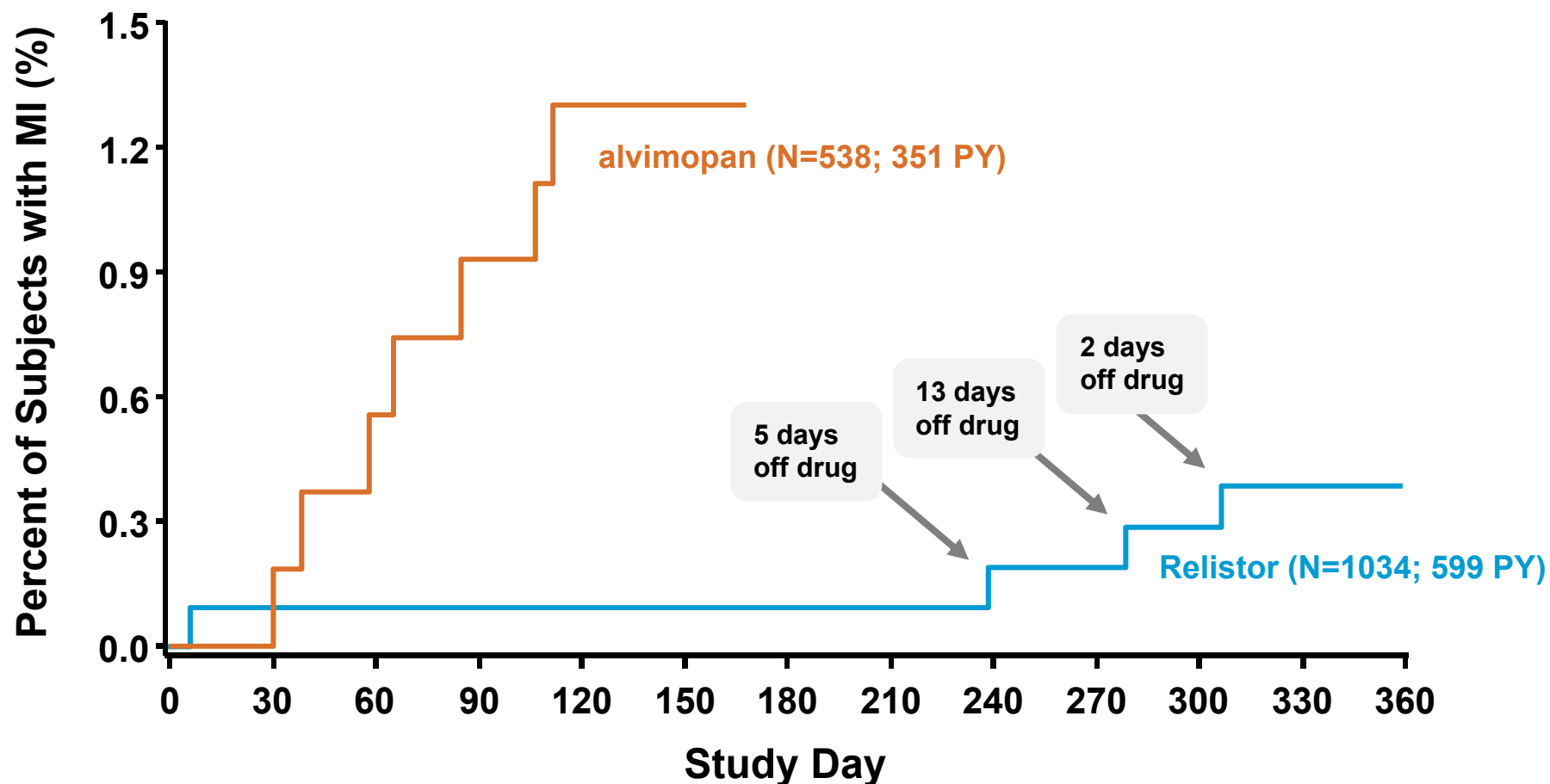
Based on rate in GSK014 study, 13 MIs would have been predicted in Relistor NCP studies

NCP = noncancer pain, PY = patient years of exposure

CS-51

Time to Event for Myocardial Infarctions

Relistor Study 3358 vs Alvimopan Study GSK014



Note: GSK 014 data reproduced from 6-month interim analysis reported in FDA medical review of Entereg®.
Study 3358 is a 48-week, open-label study. PY = patient years of exposure

Comparison of MACE Event Rates

	Number of Events	Patient Years of Exposure	Event Rate per 100 PY (95% CI)
NCP + Chronic Opioid + Relistor (Study 3356 & 3358)	7	668.1	1.05 (0.42-2.15)
NCP + Chronic Opioid + alvimopan (GSK014 Study)	8	350.9	2.3 (0.99-4.46)

Based on rate in GSK014 study, 15 MACE would have been predicted in Relistor NCP studies

NCP = noncancer pain, PY = patient years of exposure

CS-53

Incidence of Potential Withdrawal Symptoms

Comparison with Extended Release Opioids

Adverse Event	Relistor		Extended Release Opioids ¹⁻⁶ (%)
	8-wk Open-label Phase 3356 N=364 (%)	48-wk Open-label Study 3358 N=1,034 (%)	
Drug withdrawal syndrome	0	<0.4	0-10
Anxiety	0.3	3.4	0-10
Hot flush	1.4	4.7	0-10
Hyperhidrosis	2.2	9.0	1-10
Piloerection	0	0.5	<1
Tremor	0.8	1.6	0-10

1. Exalgo Prescribing Information (2012).
2. Oxycontin CR Prescribing Information (2012).
3. Opana ER Prescribing Information (2012).
4. Avinza Prescribing Information (2008).
5. Embeda Prescribing Information (2009).
6. Nucynta ER Prescribing Information (2012).

Assessment for Opioid Withdrawal

All Relistor Phase 2/3 DB Data vs OL 3358

	All Phase 2/3 DB Phase		OL 3358
	Placebo N=1078 PY=66.9 n, [AE Rate]	Relistor N=2413 PY=182.0 n, [AE Rate]	Relistor N=1034 PY=598.7 n, [AE Rate]
Drug withdrawal syndrome- Investigator Reported	0	3 [1.7]	4 [0.7]
Potential OW based on DSM-V Criteria	9 [13.5]	20 [11.0]	26 [4.4]
Potential OW based on DSM-V Criteria without GI	2 [3.0]	0	4 [0.7]
Potential OW from either Investigator Reports or DSM-V Criteria	9 [13.5]	23 [12.7]	30 [5.1]
Potential OW from either Investigator Reports or DSM-V Criteria without GI	2 [3.0]	3 [1.7]	8 [1.3]

OW = opioid withdrawal, PY = patient years of exposure

CS-55

Assessment for Opioid Withdrawal

Relistor DB NCP Data vs OL 3358

	3356 DB Phase		OL 3358
	Placebo N=162 PY=12.1 n, [AE Rate]	Relistor N=298 PY=20.7 n, [AE Rate]	Relistor N=1034 PY=598.7 n, [AE Rate]
Drug withdrawal syndrome- Investigator Reported	0	0	4 [0.7]
Potential OW based on DSM-V Criteria	1 [8.3]	3 [14.5]	26 [4.4]
Potential OW based on DSM-V Criteria without GI	0	0	4 [0.7]
Potential OW from either Investigator Reports or DSM-V Criteria	1 [8.3]	3 [14.5]	30 [5.1]
Potential OW from either Investigator Reports or DSM-V Criteria without GI	0	0	8 [1.3]

OW = opioid withdrawal, PY = patient years of exposure

Assessment for Opioid Withdrawal

All 95 Patients With a Potential CV MedDRA Term

Patient	Treatment	Potential CV Event(s) Reported MedDRA Term	DSM-V for OW Any Time Prior to Event	DSM-V for OW on Date of Event
053-2484	DB MNTX	Extrasystoles, palpitations	No	Yes
019-080605	OL MNTX	Vision blurred	No	Yes
073-081914	OL MNTX	Dyspnea exertional	Yes	No
198-083618	OL MNTX	Vision blurred	Yes	Yes
198-083624	OL MNTX	Myocardial infarction, coronary artery disease	Yes	Yes

DSM-V post hoc analysis of 95 FDA IR patients based on reported AE terms

Assessment for Opioid Withdrawal

All 95 Patients With a Potential CV MedDRA Term

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198-083624	OL MNTX	Myocardial infarction, coronary artery disease	Yes	Yes

DSM-V post hoc analysis of 95 FDA IR patients based on reported AE terms

Relistor Worldwide Post-marketing Surveillance

- **Over 800,000 patients exposed with >15,000 patient years of exposure**
- **PMS database includes:**
 - 16 reports including term “withdrawal” or “reversal”
 - 1 MI (non-fatal)
 - 35 total deaths
 - 32 deaths attributed to progression of malignancy, sepsis, GI hemorrhage, unknown cause, etc.
 - 3 deaths (CVA, cardiac arrest, cardio-respiratory arrest)

Relistor Safety Conclusions

- **MI event rates consistent with patients under study:**
 - Epidemiologic studies
 - Data from other sponsors
- **Little evidence to support a relationship between withdrawal symptoms and CV events**
- **No apparent signal in clinical or post-marketing safety data**

Summary

Bill Forbes, PharmD

Executive Vice President, Medical and R&D
Chief Development Officer
Salix Pharmaceuticals

Relistor CV Risk Summary

- **Data available do not suggest a “class” signal of increased CV risk**
- **Low absolute CV event rate**
 - Event rate consistent with other data
 - 5/7 MACE off drug ≥ 2 days
 - All-cause mortality
- **Low incidence of withdrawal symptoms**
 - Unable to link to CV events
- **MACE index case**

Challenges in Conducting Long-term Controlled Studies in OIC

- **Bias**
 - Blind compromised due to rapid onset/offset of laxation
- **Attrition**
 - High patient dropout rates
- **Interpretability**
 - Timing of events relative to study drug exposure
 - Low intrinsic CV event rate
 - Informative censoring

Relistor: Positive Benefit/Risk Assessment in NCP

- **Addresses a significant unmet need**
- **Clinically meaningful efficacy**
- **‘As-needed’ (PRN) dosing**
- **Low CV event rate consistent with epidemiological studies**
- **Available evidence supports labeling**

Relistor[®]
Methylnaltrexone Bromide
Subcutaneous Injection
Supplemental NDA

**Anesthetic and Analgesic Drug Products
Advisory Committee**



Backup Slides

Salix Pharmaceuticals, Inc.

Summary of Pain Intensity Scale

Study 3358

	N	Mean (SD)	Mean Change from Baseline (SD)
Baseline	1029	6.1 (1.9)	-0.1 (1.8)
Week 4	898	6.0 (2.0)	0.0 (2.0)
Week 8	789	6.0 (2.1)	0.1 (1.9)
Week 12	733	6.1 (2.1)	0.0 (2.0)
Week 16	689	6.1 (2.2)	0.0 (2.0)
Week 24	626	6.1 (2.2)	0.0 (2.0)
Week 32	582	6.1 (2.1)	0.0 (2.0)
Week 40	521	6.1 (2.1)	0.0 (2.0)
Week 48	435	6.1 (2.1)	0.0 (2.1)
Follow-up	286	6.2 (2.2)	0.1 (2.0)