AXELOPRAN (TD-1211) BRIEFING DOCUMENT

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE

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TABLE OF CONTENTS

PAGE

TABLES

FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
APD	action potential duration
AUC	area under the curve
C_{max}	maximum concentration
CNS	central nervous system
COWS	clinical opiate withdrawal scale
CSF	cerebrospinal fluid
DAMGO	D-Ala2-MePhe4-Glyol5 enkephalin
DPDPE	D-penicillamine2-D-penicillamine5-enkephalin
ECG	electrocardiogram
ED_{50}	median effective dose
GLP	Good Laboratory Practice as described in Food and Drug Administration (FDA) Title 21 of the U.S. Code of Federal Regulations Part 58 or the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice ENV/MC/CHEM
hERG	human ether-à-go-go-related gene
IC_{50}	half maximal inhibitory concentration
INN	international nonproprietary name
IV	intravenous
NOEL	no-observed-effect level
OIC	opioid induced constipation
PAMORA	peripherally acting mu opioid receptor antagonist
P-gp	P-glycoprotein
pK_b	negative logarithm to base 10 of the equilibrium dissociation constant K_b
pK_d	negative logarithm to base 10 of the equilibrium dissociation constant K_d
pK_i	negative logarithm to base 10 of the equilibrium dissociation constant K_i
QWBA	quantitative whole body autoradiography
SAE	serious adverse event
USAN	United States Adopted Name

1 INTRODUCTION

Opioid receptor agonists such as morphine continue to play a critical role in the control of chronic malignant and nonmalignant pain {1}. In addition to their effectiveness, however, opioid analgesics have significant side effects, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression, and opioid induced constipation (OIC) {2}. Opioid induced constipation is extremely common, affecting up to 80% of patients receiving chronic opioid treatment, {3, 4, 5} and unlike the majority of opioid-related side effects, OIC is not prone to tolerance. Encompassing constipation, delayed gastric emptying, abdominal discomfort, and nausea, OIC can be extremely debilitating {4, 6, 7}. The phenomenon of OIC results from an interaction of the opioid agonist with receptors on enteric neurons in the myenteric and submucosal plexus and smooth muscle that inhibits coordinated rhythmic contractions associated with gastrointestinal transit and reduces secretion {6}.

Of the three principal opioid receptors (i.e., μ, κ, and δ), μ receptor activation of neurons on the myenteric and submucosal plexus of the gastrointestinal tract results in an increase in non-productive smooth muscle contractility that disrupts propagating activity, which delays gastric emptying, and reduces small and large intestinal transit {6, 8, 9, 10, 11, 12}. Inhibition of enteric acetylcholine and non-adrenergic non-cholinergic neurotransmitter release also acts as an important mechanism underlying opioid agonist-induced reductions in motility {13, 14}. In addition, reduced intestinal motility increases fluid absorption directly by inhibition of secretomotor neuron function.

Antagonism of μ opioid receptors in the (peripheral) gastrointestinal tract, but not in the central nervous system (CNS), should alleviate OIC without impairing analgesia. To optimize the clinical utility of a peripherally acting μ opioid receptor antagonist (PAMORA), a high degree of peripheral selectivity is essential; if suboptimal, impaired pain control and a behavioral opioid withdrawal syndrome could result.

Theravance, Inc. is developing axelopran (US Adopted Name [USAN] and recommended international nonproprietary name [INN] for TD-1211), a peripherally selective μ opioid receptor antagonist for the treatment of OIC. Axelopran was designed to counter the negative effect of opioids on the peripheral gastrointestinal tract while preserving analgesia by limiting CNS distribution. Axelopran's peripheral selectivity is derived from its physicochemical properties that specifically target ranges to optimize peripheral restriction

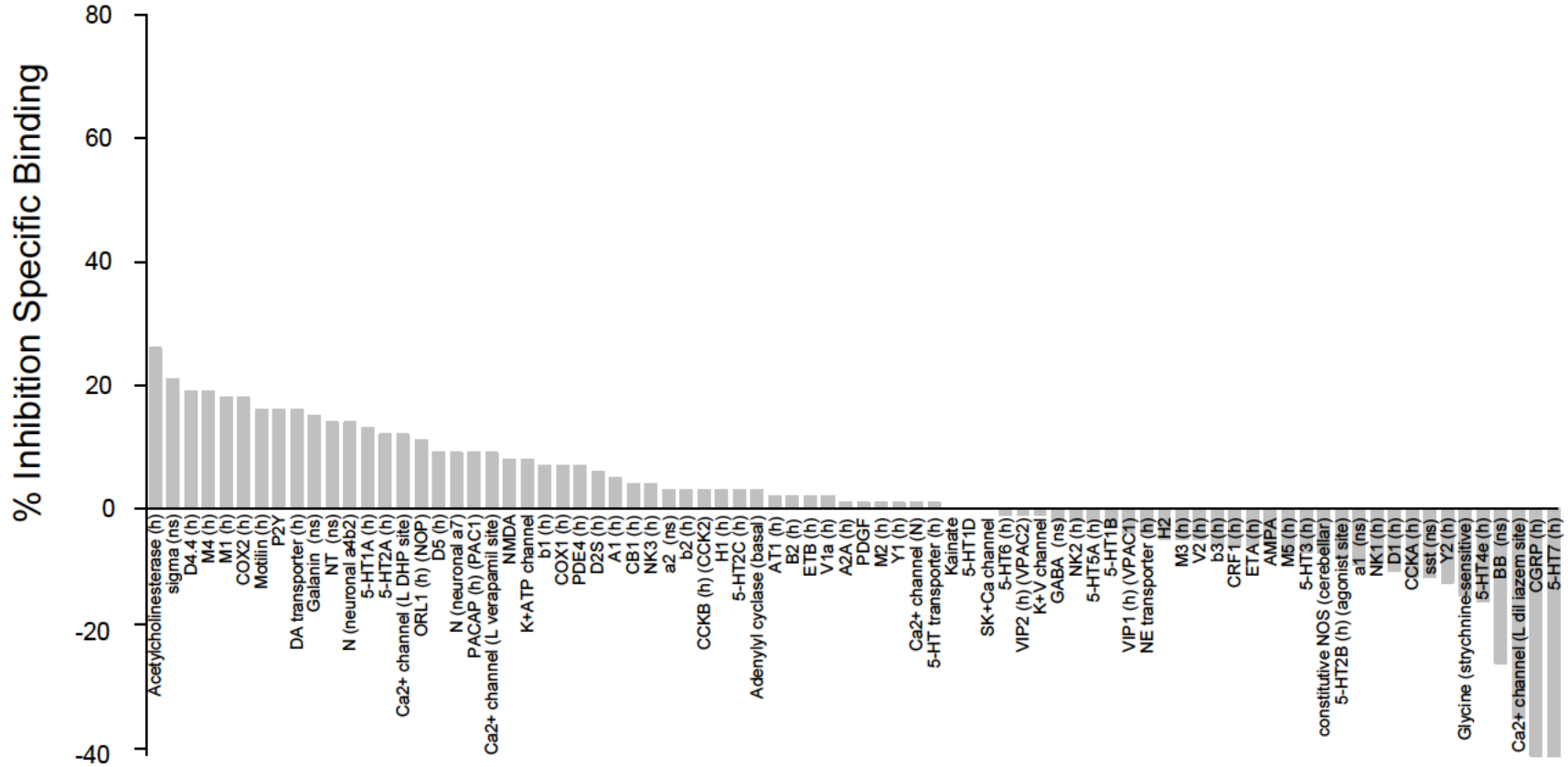
(i.e., a polar surface area of 107 Å, the presence of three hydrogen bond donors, and a calculated partition coefficient [clogD] of 0.47 at pH 7.4). Peripheral selectivity of axelopran results from a combination of physicochemical factors, which results in poor membrane permeation and P-glycoprotein (P-gp) mediated efflux at the blood-brain barrier.

The clinical development program for axelopran is ongoing. Data describing the safety of the investigational product are available for 363 subjects with OIC who were treated with varying doses for durations ranging from 2 to 5 weeks. These data suggest that axelopran is pharmacologically active and generally well tolerated. Evidence of CNS penetration, measured as a reversal of morphine-mediated decreases in pupil diameter, was not observed.

2 NONCLINICAL PHARMACOLOGY PROFILE

Axelopran is a high affinity, potent, peripherally restricted μ opioid receptor antagonist (Table 1). In radioligand competition binding studies, axelopran exhibits high and equivalent binding affinity for the human recombinant μ and guinea pig κ opioid receptors (pK_i values of 9.8 and 9.9, respectively), and lower affinity at the human δ opioid receptor (pK_i = 8.8) {15}. In addition, [^{3}H]axelopran binds with high affinity to μ and κ opioid receptors in membranes prepared from the human caudate (pK_d = 9.5) and hypothalamus (pK_d = 9.2), respectively {16}. Axelopran (1 μM, i.e., a concentration 6,300-fold higher than its human recombinant μ opioid receptor K_i value) has no significant affinity for any of the non-opioid receptors, enzymes, transporters, or ion channels at which it has been tested (n= 80) {17}. These data measuring off-target pharmacologic activity are shown in Figure 1.

Figure 1: Binding Affinity of Axelopran at Non-Opioid Targets



Axelopran is a potent antagonist of DAMGO-mediated [^{35}S]GTPγS binding in Chinese hamster ovary (CHO)-K1 cells heterologously expressing cloned human μ opioid receptors, with a pK_b value (i.e., the negative log of the molar concentration of antagonist which at equilibrium would occupy 50% of the receptors in the absence of agonist) of 9.6 {18}. Axelopran has no significant μ intrinsic activity (-3%, relative to that of the full agonist, DAMGO [100%]) {19}. Axelopran is a potent antagonist (pK_b = 8.8) of DPDPE mediated [^{35}S]GTPγS binding in CHO-K1 cells heterologously expressing cloned human δ opioid receptors {18}. Axelopran is a potent antagonist of U69593-mediated [^{35}S]GTPγS binding in CHO-K1 cells heterologously expressing cloned guinea pig κ opioid receptors, with a pK_b value of 9.5 {18}. In the guinea pig isolated ileum, axelopran produces a concentration dependent antagonism of endomorphin-1 (a μ-selective opioid receptor agonist) and U69593 (a κ-selective opioid receptor agonist)-mediated inhibition of electrically-evoked contractions (pA_2 and pK_b values of 10.1 and 8.8, respectively) {20}. In the hamster vas deferens, axelopran antagonizes DPDPE (a δ-selective opioid receptor agonist)-induced inhibition of electrically-evoked contractions (pK_b = 8.4) {21}. With respect to its functional antagonism in tissue, axelopran has a μ opioid receptor selectivity of 20 and 50, respectively, over the κ and δ receptor subtypes.

Axelopran has potent μ opioid receptor antagonist activity in the gastrointestinal tract in vivo. Thus, axelopran produces a dose-dependent inhibition of opioid receptor agonist-induced (loperamide or morphine) delays in gastric emptying in mice and rats following subcutaneous (ED_{50} values of 0.01 and 0.024 mg/kg, respectively) and oral (ED_{50} values of 0.09 and 0.26 mg/kg, respectively) dosing {22, 23}. Axelopran is associated with a dose-dependent inhibition of morphine-induced reductions in small intestinal transit in mice and rats following subcutaneous (ED_{50} values of 0.026 and 0.093 mg/kg) and oral (ED_{50} values of TD-1211 are 0.34 and 1.25 mg/kg, respectively) dosing {24, 25}. Also, axelopran attenuates loperamide-induced anti-diarrheal and constipating activity in rats (ED_{50} values of 10 μg/kg following subcutaneous and oral dosing) {26}. Finally, oral dosing of axelopran (0.03, 0.3, and 3 mg/kg) produces a dose-dependent inhibition of loperamide induced contractility of the circular muscle of the antrum, duodenum, and jejunum of conscious dogs {27}.

Pharmacodynamic data have confirmed that axelopran has a high degree of peripheral selectivity; much higher doses of axelopran than those active in the gastrointestinal assays are required to antagonize opioid receptor agonist activity in the CNS. Axelopran produces

an inhibition of morphine-mediated analgesia in mice and rats, but with ED_{50} values of 14.6 and >60 mg/kg, respectively, following oral dosing {28, 29} which are 43 to 162, and >48 to >230-fold higher than the ED_{50} values in mice and rats, respectively, for activity in the gastric emptying or intestinal transit assays. Axelopran (0.01 to 10 mg/kg subcutaneously and 0.01 to 30 mg/kg orally) fails to produce a CNS withdrawal response in morphine-dependent mice {30}. Axelopran (3 mg/kg orally) has no effect on morphine-induced analgesia or sedation in dogs {31}.

Table 1: Summary of Axelopran's In Vitro Opioid Receptor Binding Affinities and Antagonist Potencies

	Binding Affinity	Antagonist Potency
Human recombinant μ receptor	9.8 (pK_i)	9.6 (pK_b)
Human recombinant δ receptor	8.8 (pK_i)	8.8 (pK_b)
Guinea pig recombinant κ receptor	9.9 (pK_i)	9.7 (pK_b)
Human caudate μ receptor	9.5 (pK_d)	NT
Human hypothalamus κ receptor	9.2 (pK_d)	NT
Guinea pig ileum μ receptor	NT	10.1 (pA_2)
Guinea pig ileum κ receptor	NT	8.8 (pK_b)
Hamster vas deferens δ receptor	NT	8.4 (pK_b)

NT = not tested

3 BIOAVAILABILITY AND ORGAN DISTRIBUTION

The single-dose pharmacokinetics and oral bioavailability of axelopran were determined in male mice, in male and female rats and dogs, and in male cynomolgus monkeys following single IV or oral dose administration {32, 33, 34, 35}. Axelopran has moderate oral bioavailability in rats (13% to 26%), dogs (29% to 45%), and monkeys (13%). Sex-related differences in plasma pharmacokinetics have not been observed in rats or dogs. Absorption is approximately dose proportional in rats up to 20 mg/kg. Oral bioavailability was not determined in mice.

Tissue distribution in rats was studied using quantitative whole-body autoradiography (QWBA) {36}. [^{14}C]Axelopran was distributed widely into the tissues of partially pigmented rats after single oral administration (5 mg equiv./kg). High concentrations of radioactivity were observed in nearly all peripheral tissues 1.5 hours after dosing and radioactivity was

eliminated rapidly from the majority of the tissues examined 24 hours after oral administration.

[^{14}C]Axelopran exhibits poor penetration into the CNS. [^{14}C]Axelopran concentrations in CNS tissues protected by the blood-brain barrier (cerebellum, cerebrum, medulla, olfactory lobe, and spinal cord) were not quantifiable at any sampling time (Table 2).

Table 2: Distribution of Radioactivity in Selected Tissues Following a Single Oral Administration of ^{14}C-Axelopran to Male and Female Partially Pigmented Rats at a Dose of 5 mg equiv./kg

Tissue	Tissue Concentration (µg equiv./g)							
	Bile	Blood	Large Intestine	Liver	Cerebellum	Cerebrum	Medulla	Spinal Cord
Male	15.2	0.159	1.24	10.1	BLQ	BLQ	BLQ	BLQ
Female	9.27	0.107	0.636	5.05	BLQ	BLQ	BLQ	BLQ

BLQ: Below the limit of quantitation.

Tissue distribution studies were also conducted after single oral administrations of [^{14}C]axelopran in dogs (3 mg equiv./kg) {37}. Highest concentrations of radioactivity were found in bile, gall bladder, and liver at 24 hours after dosing. [^{14}C]Axelopran concentrations in the brain, cerebrospinal fluid (CSF), and spinal cord were low (≤0.01 µg equiv./g) indicating poor CNS penetration or retention of [^{14}C]axelopran.

The CNS penetration of axelopran was evaluated in Sprague-Dawley rats after single oral administrations (20 mg/kg) {38}. Axelopran exhibits poor penetration into the CNS in rats (Table 3). After oral administration, CSF to plasma and brain to plasma ratios were 0.0134 and 0.0666 (based on AUC). Degree of CNS penetration is best expressed as a ratio of the brain, $_{free}$ or CSF exposure versus the plasma, $_{free}$ exposure. Central nervous system exposure was highly limited in these models with ratios of CNS penetration less than 0.02 (< 2% CNS penetrant) based on free brain and plasma exposure. Unrestricted penetration into the CNS would result in a ratio of 1.0. These data suggest axelopran is highly restricted to the peripheral plasma compartment in rats.

Table 3: Ratios of Axelopran CNS to Plasma Exposure in Sprague-Dawley Rats

	Brain/Plasma	Brain, $_{free}$/Plasma, $_{free}$*	CSF/Plasma	CSF/Plasma, $_{free}$
Axelopran	0.0666	0.0122	0.0134	0.0181

* In vitro experiments were conducted to evaluate binding to rat whole brain homogenate and rat plasma protein binding. TD-1211 was 13.6% unbound in rat brain homogenate and 74.2% unbound in rat plasma.

P-glycoprotein (P-gp) is expressed at the blood-brain barrier and limits penetration of P-gp substrates into the CNS. Axelopran was assessed as a substrate of P-gp in bi-directional transport studies in Caco-2 and MDR1-MDCK cells {39, 40}. Efflux ratios of 10 (Caco-2) and 24 (MDR1-MDCK) were observed in these studies.

Axelopran is a substrate of P-gp, therefore P-gp may limit its penetration into the CNS. Central nervous system penetration was assessed in wild-type and P-gp deficient (Mdr1a/1b-knockout) mice {41}. The P-gp deficient mice exhibited significantly higher amounts (~6.25-fold) of axelopran in mouse brain relative to wild-type mice, indicating that P-gp restricts the CNS penetration of axelopran in mice.

4 NONCLINICAL CARDIOVASCULAR SAFETY STUDIES

To assess potential cardiovascular effects, axelopran was evaluated for its ability to inhibit human ether-à-go-go-related gene (hERG) potassium channel currents, alter action potentials in isolated canine Purkinje cells, alter heart rate and blood pressure in rats, and alter electrocardiographic parameters and blood pressure in conscious, instrumented dogs. In addition, electrocardiograms (ECGs) from dogs in the repeated-dose toxicity studies of 29-days, 13-weeks, and 39-weeks duration were examined. To evaluate the potential of identified metabolites of axelopran to cause altered cardiac function, an exploratory (non-GLP) study was conducted to evaluate the potential of the three metabolites (THRX-157412, THRX-254018, and THRX-308069) to affect hERG potassium channel currents. A fourth metabolite, THRX-892364, was evaluated in a GLP hERG study.

The IC_{50} value for inhibition of hERG tail currents was 8.8 µM, a concentration that exceeds the binding affinity of the molecule towards the human µ-opioid receptor by more than 55,000-fold and exceeds the human exposure at a clinical dose of 15 mg once daily by greater than 1100-fold {42}. None of the four axelopran metabolites (THRX-157412, THRX-254018, THRX-308069, THRX-892364) tested at a concentration of 3 µM in CHO-K1

cells had an effect on hERG potassium tail currents {43, 44}. The major metabolite (THRX-892364) was also tested at concentrations up to 30 µM and did not exhibit any inhibition of hERG currents.

In a study of the potential effects on action potential duration (APD) in canine Purkinje fibers, axelopran increased the APD_{60} and APD_{90} to values between 9% and 16% at a concentration of 3 µM, with concentration-related increases at higher concentrations {45}. These results are consistent with the results of the hERG assay, which demonstrated an IC_{50} of 8.8 µM.

In an exploratory cardiovascular study in rats, axelopran had no effect on mean arterial blood pressure or heart rate up to the highest dose tested, 30 mg/kg {46}.

In the cardiovascular safety study in dogs, axelopran had no effect on the arterial blood pressure (mean, diastolic or systolic) or heart rate during the 24-hour period following administration of oral doses up to 10 mg/kg {47}. Axelopran had no effect on the duration of the PR and RR intervals, or of the QRS complex, suggesting that axelopran is devoid of potentially deleterious effect on either the atrioventricular and intraventricular conduction velocities. Axelopran had no biologically relevant effect on the duration of the QT and QTc intervals, irrespective of the formula used for correction (Van de Water's or Fridericia's) consistent with an absence of effects on ventricular repolarization. Based on the toxicokinetic evaluations, the C_{max} at 10 mg/kg is approximately 322-fold the C_{max} in patients receiving a dose of 15 mg once daily (Table 4).

Additional experience was gained from the 29-day, 13-week, and 39-week studies in dogs, studies in which ECGs were evaluated on Day 1 of dosing and periodically during the dosing period {48, 49, 50}. In these studies, the highest doses (up to 100 mg/kg/day) exceeded the highest dose evaluated in the cardiovascular safety studies. The no-observed effect level (NOEL) for electrocardiographic changes in each of these studies was 10 mg/kg/day, the same as for the cardiovascular safety study. At 30 mg/kg/day (13-week and 39-week studies) and 100 mg/kg/day (29-day study) increases in the duration of QTc (Fridericia's correction) were observed. Based on plasma concentrations at these dose levels, these findings are consistent with the results of the hERG assay. At 100 mg/kg/day in dogs, for instance, the C_{max} was approximately 23 µM or about 2- to 3-fold the IC_{50} for inhibition of hERG potassium channel currents.

Table 4: Ratio of Concentrations of Axelopran Associated with hERG Prolongation and Adverse Effects to Concentrations in Subjects Receiving a Daily Dose of 15 mg

	Fold Increase Over Human C_{max} at 15 mg [a]
hERG IC_{50}	1177[b]
NOEL for QTc increases in dogs (10 mg/kg/day)[c]	322

[a] Human exposure at 15 mg: C_{max} = 4.32 ng/mL; AUC_{0-24} = 35 ng·hr/mL

[b] Human C_{max} corrected for protein binding in human plasma

[c] Exposure data for dogs is the mean of male and female exposures at 10 mg/kg/day on Day 272 of the 39-Week study

Given the large margins for these effects compared to the maximum plasma concentrations in humans, these effects on hERG potassium channel currents and QTc in dogs are not considered to represent a significant risk of cardiac arrhythmias at the recommended clinical dose of 15 mg, once daily as shown in Table 4.

5 CLINICAL SAFETY SUMMARY

5.1 Phase 1 Studies

Axelopran has been evaluated in multiple Phase 1 studies and has been administered to healthy subjects as single doses (0.1, 0.5, 1, 2, 5, 10, 20, 40, 60, and 100 mg), and multiple doses for up to 1 week (2, 10, 20, or 30 mg). In healthy subjects axelopran was generally well tolerated with adverse events (AEs) similar to placebo. No safety signals were apparent from assessment of adverse events, clinical laboratory measurements, vital signs, physical exams, and ECG results. In the Phase 1 studies, over 5,000 ECGs were recorded and evaluated. No effect on cardiac conduction and rhythm was detected.

Human Model of Peripheral Restriction

The selectivity of axelopran (central vs. peripheral) was examined in a pupillometry study in eight healthy subjects. Reversal of morphine-mediated pupillary constriction was used as a measure of CNS penetration following administration of 30 mg of immediate-release morphine by mouth (PO). Multiple assessments of pupil diameter were performed before and after study drug administration to assess the change in pupil diameter for each individual subject: 1 hour after study drug administration to assess the acute effects of

axelopran 20 mg on morphine-mediated miosis, and at steady-state dosing to assess miotic changes occurring following multiple doses. There were no changes in averaged pupil diameter from time-matched measurements from the morphine-only baseline to Day 1 (after the first daily oral dose of axelopran 20 mg or placebo) or on Day 7 at steady state. Results from this pupillometry study indicate that axelopran should not interfere with opioid analgesia.

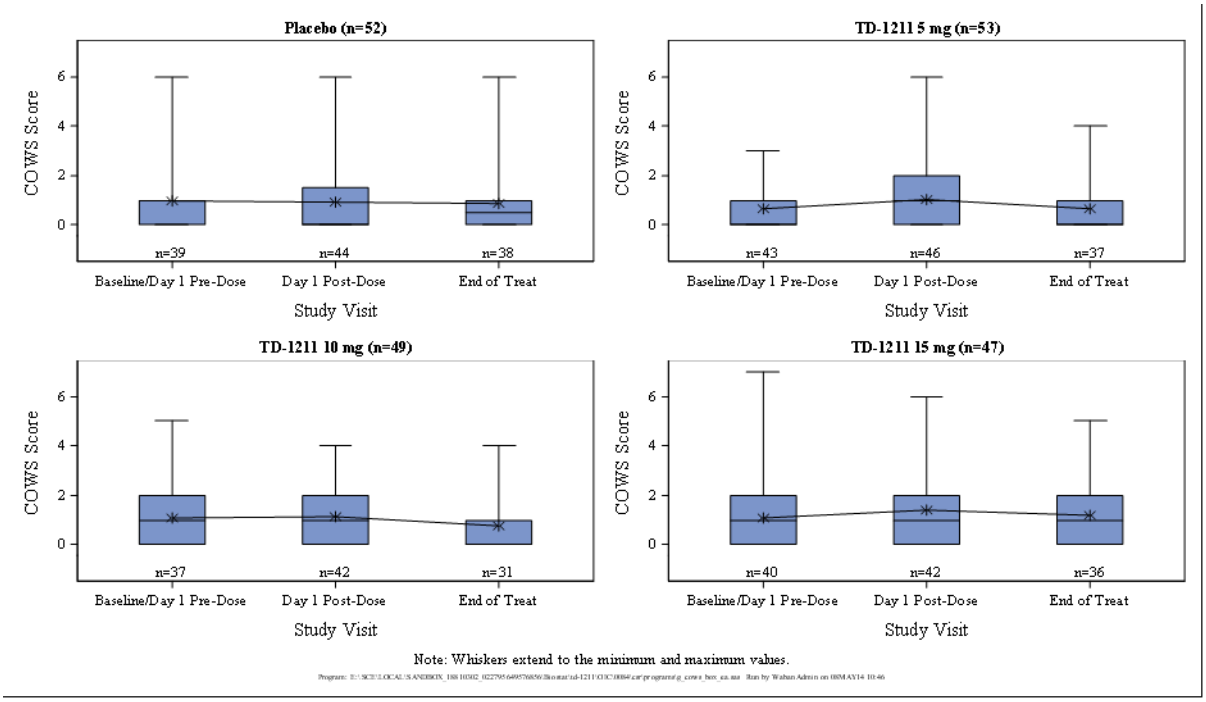
5.2 Phase 2 Studies

Four Phase 2 studies have been conducted to date. These studies were designed to assess safety and tolerability of axelopran as well as the effect on constipation in subjects having OIC. A total of 363 subjects received at least one dose of axelopran, ranging from 2 to 15 mg, for periods of 2 to 5 weeks. Subjects treated with axelopran exhibited no evidence of organ toxicity assessed by AEs, physical exam, clinical chemistry, and vital sign measurements. Cardiovascular monitoring, including over 1,500 ECGs recorded and analyzed, found no effects of axelopran on cardiac conduction and rhythm. The most commonly reported adverse events for axelopran were GI-related and included abdominal pain and cramping, diarrhea, nausea and vomiting. No deaths have occurred in the axelopran clinical studies. Eight treatment-emergent serious adverse events (SAEs) have been reported for axelopran across the four Phase 2 studies; all eight SAEs were assessed by the investigators as not related to study drug.

One of the Phase 2 studies, Study 0084, utilized a randomized, double-blind, placebo-controlled, parallel group design and randomized 217 subjects with OIC into 4 treatment groups: placebo; 5, 10, and 15 mg axelopran daily {51}. Subjects received an initial dose of 5 mg axelopran, or matching placebo, for four days. On Day 5, subjects randomized to axelopran remained on 5 mg or their dose increased to 10 or 15 mg; placebo subjects remained on placebo for the duration of the study.

The 48-point clinical opiate withdrawal scale (COWS) {52} was used to assess opioid withdrawal in Study 0084. Results from the COWS assessments are displayed in Figure 2. The maximum post-treatment score was 6 for five study subjects (two axelopran subjects and three placebo subjects). One patient in the 15 mg axelopran group had a score of 7 at baseline (prior to treatment).

Figure 2: Clinical Opiate Withdrawal Scale Total Scores by Treatment Group, Study 0084, Efficacy Analysis Population



Source: {53}

The Phase 2 clinical trials showed axelopran was well tolerated at the doses studied. The AEs in the Phase 2 studies were primarily GI-related and included abdominal pain and cramping, diarrhea, nausea and vomiting at a frequency similar to placebo, with the exception of diarrhea which occurred in axelopran-treated subjects only. Moreover, Study 0084 results support continued development of axelopran for the treatment of patients with OIC using a dosing regimen of a four-day initiation dose of 5 mg followed by dose-escalation to 15 mg.

6 SUMMARY

Axelopran is being developed as a potential treatment for OIC. Axelopran has high affinity for the human μ opioid receptor and demonstrates functional selectivity for μ over the κ and δ opioid receptors in preclinical models. In nonclinical pharmacokinetic studies, axelopran was found to be highly peripherally restricted having negligible central penetration in mice, rats, and dogs. Accordingly, preclinical pharmacodynamic studies demonstrated that axelopran selectively antagonizes the peripheral gastrointestinal effects of opioids at doses that do not inhibit opioid analgesia. Peripheral restriction of axelopran is further supported

by the lack of an effect observed in a pupillometry study conducted in healthy volunteers. Further, in the main Phase 2 study evaluating the efficacy, safety, and tolerability of axelopran , there was no clinically meaningful difference in the reported COWs scores assessed pre-and post-dose, and at end of treatment. In nonclinical safety studies, any cardiovascular effects, characterized by inhibition of hERG potassium channel currents and prolongation of QTc intervals in dogs at doses that provide plasma concentrations at or above the hERG IC_{50}, are orders of magnitude higher than the concentrations proposed for clinical evaluation. These data are supported by the axelopran clinical trials conducted to date in which over 6,500 ECGs were recorded and evaluated, and no effect on cardiac conduction and rhythm was detected. Data from the axelopran development program through Phase 2 have not identified evidence of CNS penetration or cardiovascular risk.

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