Axelopran Phase 2b Study Demonstrates a Sustained Increase in Bowel Movement Frequency in Patients Regardless of Duration of Opioid-Induced Constipation

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Introduction

- Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control.[1] Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression and bowel dysfunction.[2]
- Opioid-induced constipation (OIC) is common, affecting up to 80% of patients receiving opioids for chronic non-cancer pain.[3]
- Axelopran (formerly TD-1211) is an investigational, peripherally selective, multivalent mu-opioid receptor antagonist designed to alleviate gastrointestinal side effects of opioid therapy without affecting analgesia.
- Safety and efficacy results, including the primary and key secondary endpoints, from a 5-week, Phase 2b study in chronic non-cancer pain OIC patients have been previously reported.[4]
- Since OIC is not prone to tolerance and patients can experience OIC for the duration of opioid therapy, patients were divided into short and long duration of OIC groups (<5 and ≥5 years) to explore if OIC duration impacts axelopran treatment response.

Methods

- A 5-week, double-blind, randomized, multi-center, placebo-controlled, parallel-group study was conducted in chronic non-cancer pain patients with OIC, defined as ≤5 spontaneous bowel movements (SBMs) over a 2-week baseline period and at least one additional symptom of constipation in at least 25% of the bowel movements.
- For the first 4 days of dosing, patients randomized to axelopran received 5mg daily and on Day 5, remained at 5mg or were dose-escalated to 10mg or 15mg daily for the remainder of the treatment period. Patients randomized to placebo received placebo for all 5 weeks.
- For at least 14 days prior to Day 1, patients were on a stable chronic opioid regimen, with a total daily dose of ≥30mg morphine equivalent units (MEU).
- Patients were required to stop laxatives and bowel regimens, except protocol-permitted rescue bisacodyl use, throughout the study.
- Electronic diaries collected frequency, timing, and symptoms of bowel movements; use of laxatives and opioids; daily pain scores; and satisfaction/ quality of life metrics.
- Primary efficacy endpoint was the change from baseline in weekly average complete spontaneous bowel movements (CSBMs) over weeks 2-5 of treatment.
- Key secondary endpoint was the change from baseline in weekly average spontaneous bowel movements (SBMs) over the same period.
- Week 1 was excluded from the primary analysis in order to confirm the durability of response and predictability of longer term efficacy studies.
- Patients were divided into short and long duration of OIC groups (<5 and ≥5 years) and evaluated on the study's primary and key secondary endpoints.

Results

Patient baseline demographics

- As shown in Table 1, baseline characteristics were similar for all treatment groups in the overall population as well as the short and long duration of OIC groups.
- Subjects were on a representative spectrum of opioids.
- Daily opioid doses ranged from 30-1740 oral MEU.
- Back pain was the most commonly reported reason for chronic opioid use.
- Mean and range of OIC duration in the study were 6.0 years and 0.2 - 39.3 years, respectively.

Table 1: Patient Baseline Demographics by Duration of OIC

Overall Population	Placebo (N=54)	5 mg (N=55)	Axelopran 10 mg (N=53)	15 mg (N=53)
Mean Age (years)	47.6	48.3	49.2	48.9
Female Gender	28	37	32	30
BMI Mean (kg/m^2)	28.3	27.8	27.8	28.1
Duration of OIC (yrs)	5.5	6.4	6.7	5.3

Duration of OIC <5 years	Placebo (N=28)	5 mg (N=24)	Axelopran 10 mg (N=25)	15 mg (N=32)
Mean Age (years)	45.7	47.5	48.8	47.9
Female Gender	17	16	15	17
BMI Mean (kg/m^2)	27.9	27.4	27.8	28.3
Duration of OIC (yrs)	2.1	2.2	2.0	2.4

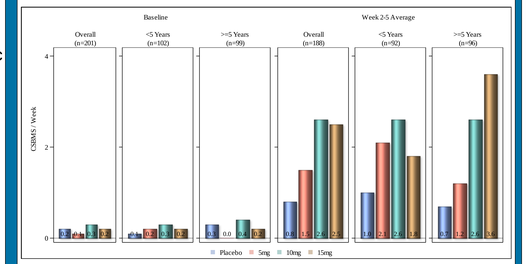
Duration of OIC ≥5 years	Placebo (N=26)	5 mg (N=31)	Axelopran 10 mg (N=28)	15 mg (N=21)
Mean Age (years)	49.7	48.9	50.3	49.5
Female Gender	11	21	17	13
BMI Mean (kg/m^2)	28.8	28.2	27.7	27.8
Duration of OIC (yrs)	9.2	9.7	10.9	9.9

Modified Intent to Treat Population

Efficacy Endpoints by Duration of OIC Group

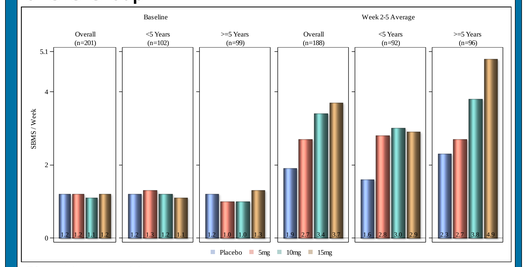
- The baseline frequency of CSBMs and SBMs was similar for short and long duration of OIC groups (Figs. 1-2).
- During weeks 2-5, all doses of axelopran resulted in higher average CSBMs and SBMs per week compared to placebo for the overall population & both OIC duration groups (Figs. 1-2).
- For the ≥5 year OIC duration group, there was a dose-response relationship in average CSBM and SBM frequency during weeks 2-5 and similarly in the overall population for SBM frequency (Figs. 1-2, Table 2).

Figure 1: Baseline and Weeks 2-5 Average Complete Spontaneous Bowel Movements (CSBMs) by Duration of OIC Group



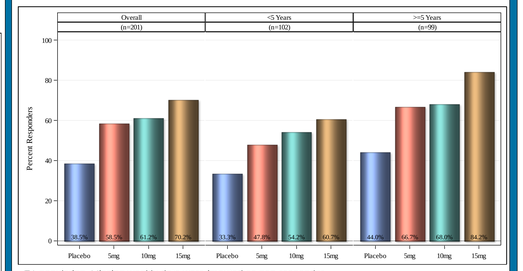
EA population; no imputation

Figure 2: Baseline and Weeks 2-5 Average Spontaneous Bowel Movements (SBMs) by Duration of OIC Group



EA population; no imputation

Figure 3: Pre-Specified SBM Responder Analysis by Duration of OIC Group



EA population. Missing weekly data were imputed as non-responder.

- Responder definition: ≥3 SBMs per week and an increase of ≥ 1 SBM per week from baseline for ≥3 weeks over Weeks 2-5

Table 2: Mean (SD) Change from Baseline in Weeks 2-5 Weekly Average CSBMs and SBMs by Baseline Opioid Use

	Mean (SD) Change from Baseline in Weekly Average CSBMs				Mean (SD) Change from Baseline in Weekly Average SBMs			
	Placebo	5mg Axelopran	10mg Axelopran	15mg Axelopran	Placebo	5mg Axelopran	10mg Axelopran	15mg Axelopran
Overall	0.8 (1.4) (n=50)	1.5 (2.2) (n=46) p=0.0413	2.6 (2.4) (n=47) p=0.0010	2.5 (3.3) (n=45) p=0.0003	1.9 (1.8) (n=50)	2.7 (2.2) (n=46) p=0.0739	3.4 (2.7) (n=47) p=0.0038	3.7 (3.0) (n=45) p=0.0003
<5 yrs OIC duration	1.0 (1.6) (n=25)	2.1 (2.9) (n=18)	2.6 (2.4) (n=22)	1.8 (2.4) (n=27)	1.6 (1.7) (n=25)	2.8 (2.6) (n=18)	3.0 (2.7) (n=22)	2.9 (2.4) (n=27)
≥5 yrs OIC duration	0.7 (1.3) (n=25)	1.2 (1.4) (n=28)	2.6 (2.4) (n=25)	3.6 (4.2) (n=18)	2.3 (1.8) (n=25)	2.7 (2.0) (n=28)	3.8 (2.7) (n=25)	4.9 (3.5) (n=18)

EA population; no imputation. P-values were based on a mixed-effect model repeated measures with baseline as covariate.

Table 3: GI-Related Adverse Events Occurring in at Least 2 Patients in Any Group

Safety Population	Placebo (N=54)	Axelopran 5 mg (N=56)	10 mg (N=53)	15 mg (N=52)	All Axelopran (N=161)
No. of Patients and Percentage with GI AEs	11 (20.4%)	13 (23.2%)	15 (28.3%)	14 (26.9%)	42 (26.1%)
Abdominal Pain	6 (11.1%)	7 (12.5%)	6 (11.3%)	8 (15.4%)	21 (13.0%)
Abdominal Pain Upper	1 (1.9%)	2 (3.6%)	3 (5.7%)	2 (3.8%)	7 (4.3%)
Diarrhea	0	4 (7.1%)	6 (11.3%)	4 (7.7%)	14 (8.7%)
Flatulence	3 (5.6%)	1 (1.8%)	2 (3.8%)	1 (1.9%)	4 (2.5%)
Nausea	2 (3.7%)	4 (7.1%)	8 (15.1%)	3 (5.8%)	15 (9.3%)
Vomiting	1 (1.9%)	4 (7.1%)	1 (1.9%)	0	5 (3.1%)

Efficacy Endpoints by Baseline Opioid Dose (con't)

- Using a pre-specified responder definition, there was a dose-response relationship between responder rate and axelopran dose for the overall population and both OIC duration groups (Fig. 3).

Tolerability and Safety

- Axelopran was generally well tolerated, with overall treatment emergent adverse events (TEAEs) similar between axelopran and placebo and gastrointestinal (GI) TEAEs predominant (Table 3).
- The majority of GI-related AEs were associated with treatment initiation, mild-to-moderate, and resolving within a few days.
- No treatment-related serious adverse events (SAEs) were reported.
- No clinically significant laboratory, ECG, or vital sign abnormalities were observed.

Axelopran Conclusions

- 10mg and 15mg demonstrated a clinically meaningful, sustained response in CSBM and SBM frequency over the 5-week treatment period in patients irrespective of their duration of OIC.
- Generally well-tolerated with no treatment-related SAEs.
- Majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate.

References

1. Walsh, T.D. (2000). Seminars in Oncology, 27, 45-63.
2. Walsh, T.D. (1990). J. Pain Symptom Manage., 5, 362-367.
3. Holzer, P. (2012). Current Pharmaceutical Design, 18, 6010-6020.
4. Vickery, R., et al. PainWeek 2012, Las Vegas, NV, September 5-8. Poster #121.