Safety, Tolerability and Efficacy of Aleniglipron in Doses Up to 240 mg in People Living with Obesity: The Phase 2 ACCESS II Trial

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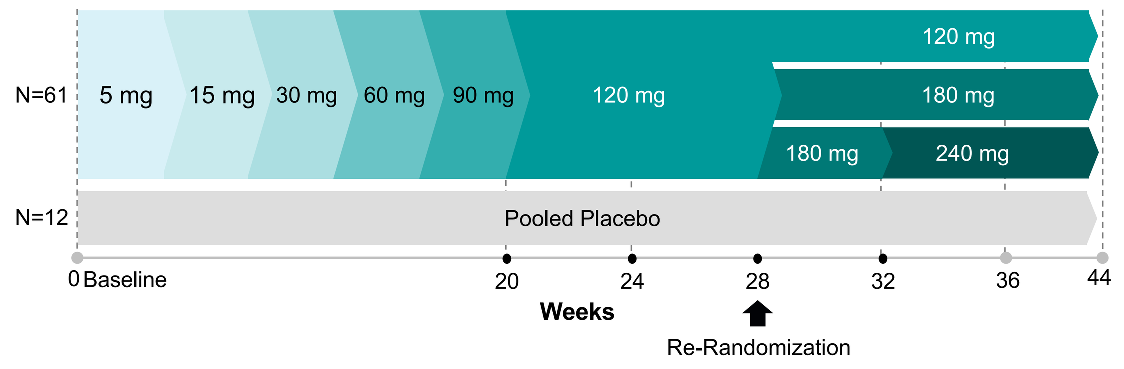
Introduction

- Oral therapies for weight management can overcome challenges with injectable peptide-based medications
  - Peptides are more expensive, difficult to produce, require cold-chain logistics for shipping and storing
  - Administration by injection has associated challenges for many patients
- Aleniglipron is an oral small molecule GLP-1RA in development for the treatment of obesity and T2DM
- The ACCESS trial met its primary endpoint at Week 36 with a placebo-adjusted LS mean (95% CI) body weight change from baseline of −8.2% (−11.1 to −5.3%), −9.8% (−12.5 to −7.2%), and −11.3% (−13.9 to −8.6%) for the aleniglipron 45, 90, and 120 mg arms, respectively (p<0.0001, all doses vs. placebo), with no apparent weight loss plateau at the end of the double-blind period (1032-OR, Rosenstock *et al.*)
- The phase 2 ACCESS II trial evaluated treatment with aleniglipron in participants living with obesity or overweight + ≥1 comorbidity at doses higher than ACCESS

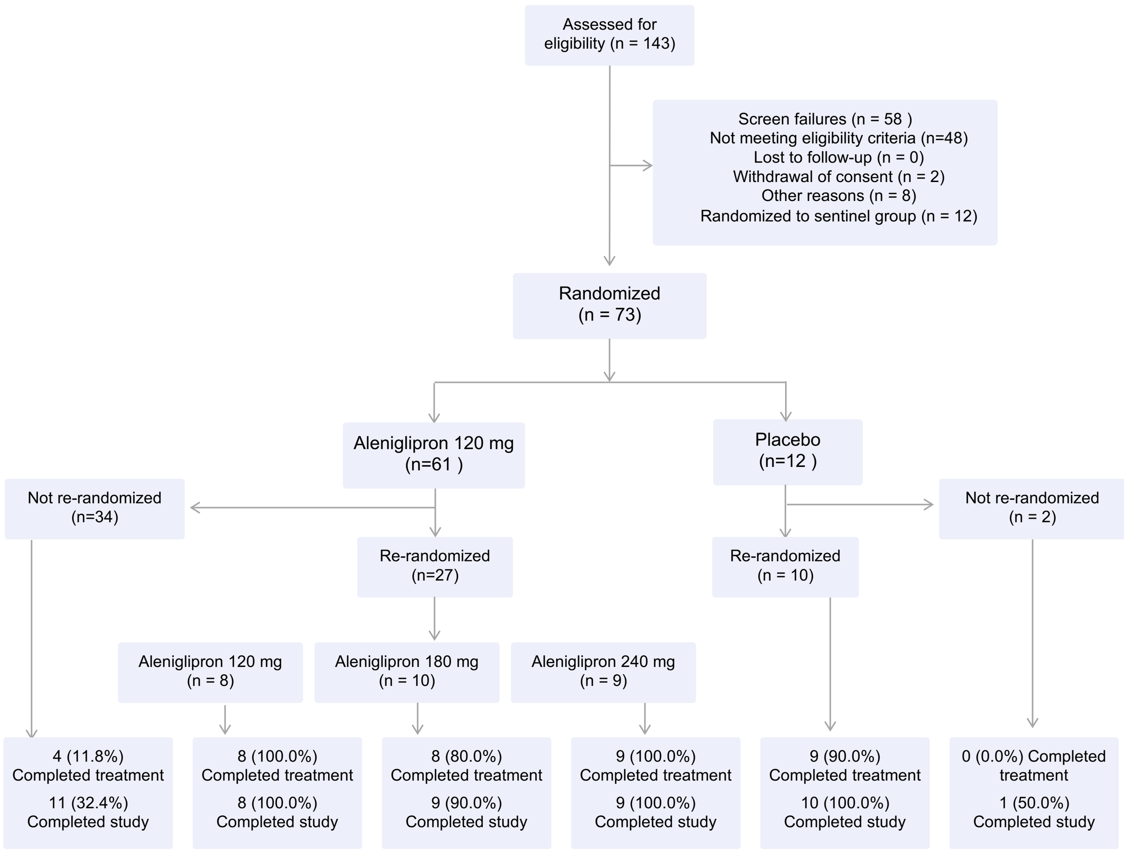
Methods

- The ACCESS II trial enrolled participants living with obesity or overweight + ≥1 weight-related comorbidity
  - Key inclusion criteria: age ≥18 years and <80 years, screening HbA1C <6.5%, weight-related comorbidities included previous/current diagnosis of: hypertension, dyslipidemia, documented obstructive sleep apnea, cardiovascular disease, or metabolic dysfunction-associated steatohepatitis (MASH)
  - 73 participants were randomized 5:1 aleniglipron to placebo. Following IDMC participants were re-randomized to either 120 mg, 180 mg, or 240 mg aleniglipron
  - Randomization was stratified by baseline BMI (≤ or > 35 kg/m²) and sex
- Study endpoints
  - Primary: Safety and tolerability of doses up to 240 mg aleniglipron compared with placebo
  - Exploratory: Body weight changes in re-randomized participants at week 44 compared with placebo
- Statistical methods
  - The efficacy endpoints were analyzed by the efficacy estimand: only data collected before the occurrence of any intercurrent events (ICEs) (+2 days) will be used in the MMRM analysis; ICE is handled by the hypothetical strategy
    - Missing data after ICE were implicitly imputed through MMRM

Trial schema



CONSORT flow diagram



CONSORT diagram illustrating screening, randomization to aleniglipron treatment arms, and re-randomization to higher doses of aleniglipron following IDMC approval

Baseline demographics and clinical characteristics

Characteristics Mean (SD) or N (%)	Aleniglipron Overall N=61	Placebo N=12
Age, years	49.8 (14.5)	51.8 (12.9)
Sex, female	38 (62.3)	8 (66.7)
Weight, kg	116.2 (31.9)	104.3 (12.8)
Body mass index, kg/m²	39.9 (8.4)	36.8 (5.1)
HbA1c, %	5.6 (0.35)	5.4 (0.36)
HbA1c ≥5.7%, n (%)	27 (44.3)	3 (25.0)
Systolic Blood Pressure, mmHg	122.2 (12.2)	122.6 (11.4)
Diastolic Blood Pressure, mmHg	78.7 (7.0)	82.3 (9.2)
Ethnicity (Hispanic or Latino)	15 (24.6)	3 (25.0)
QTcF Interval, Aggregate (ms)	403.6 (24.0)	403.0 (19.3)
ECG Heart Rate (beats/min)	66.8 (10.4)	68.5 (11.6)
Cholesterol, mg/dL	180.6 (34.6)	157.5 (29.3)
HDL Cholesterol	49.1 (10.4)	44.7 (9.1)
Triglycerides	115.6 (49.9)	113.0 (49.0)
LDL Cholesterol	108.4 (30.9)	90.3 (22.7)
Fasting Glucose, mg/dL	95.8 (10.0)	96.8 (11.8)

Tolerability profile in re-randomized group

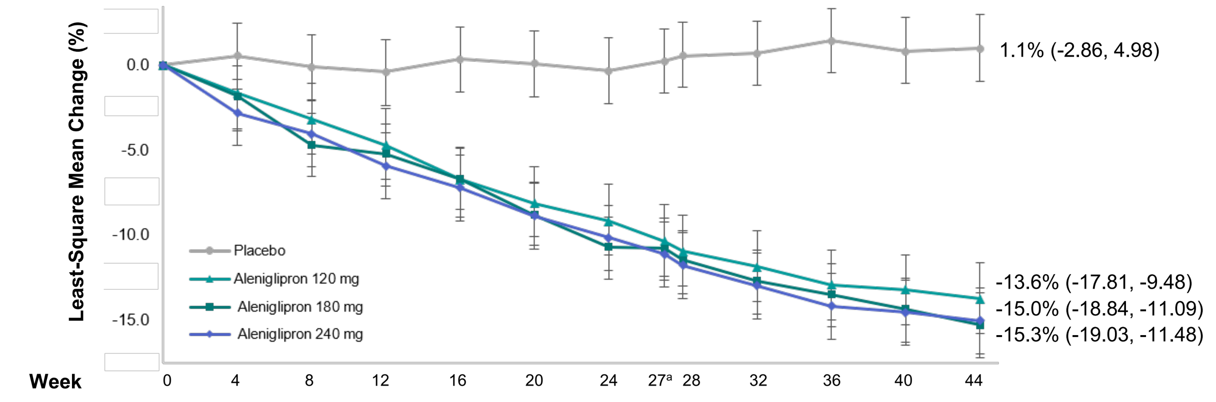
N (%)	Aleniglipron 120 mg N=8	Aleniglipron 180 mg N=10	Aleniglipron 240 mg N=9	Placebo N=10
Pre re-randomization (Weeks 0-28, maximum dose aleniglipron 120 mg)				
Any TEAE	7 (87.5)	9 (90.0)	9 (100.0)	6 (60.0)
Any SAE	0	0	0	0
Any TEAE leading to Treatment Discontinuation	0	0	0	0
Nausea	3 (37.5)	7 (70.0)	6 (66.7)	0
Vomiting (Overall)	1 (12.5)	2 (20.0)	1 (11.1)	1 (10.0)
Diarrhea	1 (12.5)	4 (40.0)	5 (55.6)	1 (10.0)
Constipation	0	4 (40.0)	2 (22.2)	1 (10.0)
Post re-randomization (Weeks 28-44, maximum dose as indicated in dose arm)				
Any TEAE	2 (25.0)	5 (50.0)	5 (55.6)	3 (30.0)
Any SAE	0	0	0	0
Any TEAE leading to Treatment Discontinuation	0	1 (10.0)	0	0
Nausea	0	2 (20.0)	3 (33.0)	0
Vomiting (Overall)	1 (12.5)	1 (10.0)	4 (44.4)	0
Diarrhea	0	0	0	0
Constipation	0	0	0	0

Tolerability profile Week 0 to Week 44

	Not re-randomized		Re-randomized			
N, %	Aleniglipron N = 34	Placebo N = 2	Aleniglipron 120 mg N = 8	Aleniglipron 180 mg N = 10	Aleniglipron 240 mg N = 9	Placebo N = 10
Any TEAE	32 (94.1)	2 (100.0)	7 (87.5)	10 (100.0)	9 (100.0)	6 (60.0)
Nausea	26 (76.5)	0	3 (37.5)	7 (70.0)	7 (77.8)	0
Vomiting	20 (58.8)	0	2 (25.0)	3 (30.0)	4 (44.4)	1 (10.0)
Diarrhea	12 (35.3)	0	1 (12.5)	4 (40.0)	5 (55.6)	1 (10.0)
Constipation	8 (23.5)	1 (50.0)	0	4 (40.0)	2 (22.2)	1 (10.0)
Abdominal distension	6 (17.6)	0	1 (12.5)	2 (20.0)	1 (11.1)	0
Dyspepsia	1 (2.9)	0	0	4 (40.0)	1 (11.1)	0
Gastro-oesophageal reflux disease	3 (8.8)	0	1 (12.5)	0	2 (22.2)	0
Eructation	3 (8.8)	0	0	2 (20.0)	0	0
Abdominal pain upper	4 (11.8)	0	0	0	0	0
Headache	10 (29.4)	0	1 (12.5)	2 (20.0)	3 (33.3)	0

AEs occurring in >5% of main study group, all aleniglipron

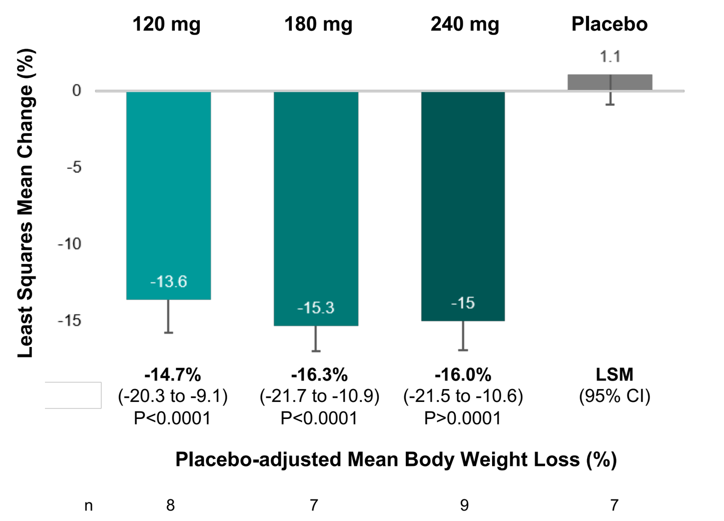
Body weight loss over time in re-randomized group



Week	0	4	8	12	16	20	24	27[a]	28	32	36	40	44
Aleniglipron 120 mg	8	8	8	8	8	8	8	8	8	8	8	8	8
Aleniglipron 180 mg	10	10	10	10	10	9	10	10	10	9	9	9	7
Aleniglipron 240 mg	9	9	9	9	9	9	8	9	7	9	9	9	9
Placebo	10	10	10	10	10	10	7	10	9	10	10	7	7

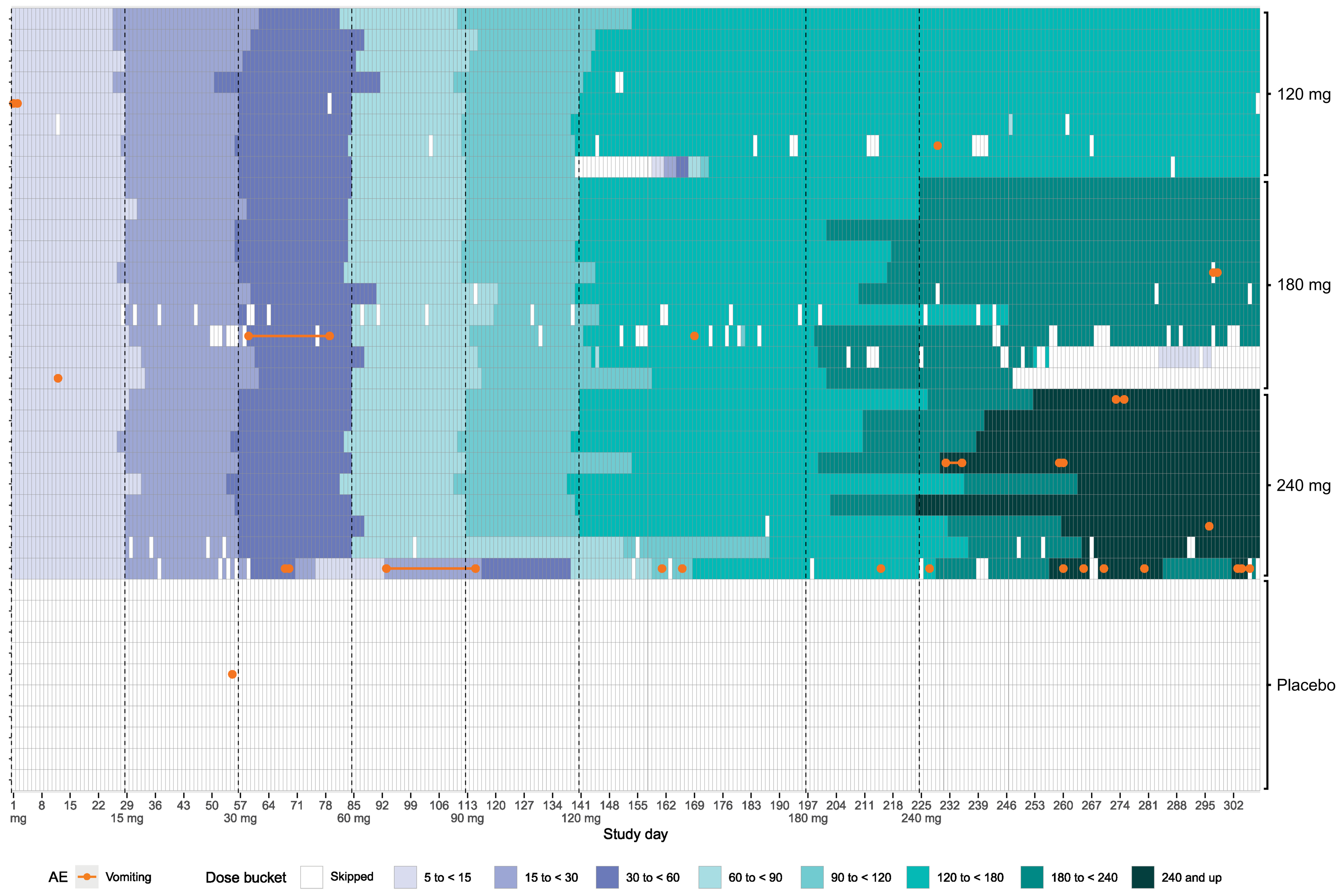
[a]Week 27 visit was the re-randomization assignment visit. Week 28 visit was the first dose increase for re-randomized participants increasing above 120 mg aleniglipron

Change in body weight from baseline (Week 0) to Week 44



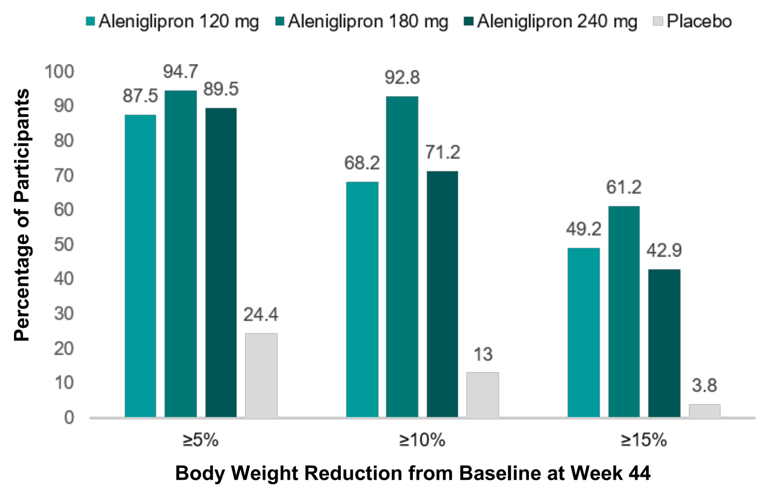
*LS Mean Difference based on Primary Efficacy Estimand and MMRM model

Participant experience for re-randomized group, Week 0 to Week 44



Each row indicates an individual participant. Vertical black line indicates post-re-randomization visit and doses increasing above 120 mg aleniglipron. Orange lines indicate intermittent events of vomiting. Orange dots represent events of vomiting of 1 day duration. Vertical dashed lines indicate time of titration to next dose, every 4 weeks

Categorical achievement of 5, 10, 15% body weight reduction at Week 44



Categorical body weight reduction from baseline to Week 44 in participants who were re-randomized: 120 mg arm: n = 8; 180 mg arm: n = 7; 240 mg arm: n = 9; Placebo : n = 7

Change from baseline in clinical parameters

Change from baseline at Week 44, mean (SD)	Aleniglipron 120 mg (N=8)	Aleniglipron 180 mg (N=10)	Aleniglipron 240 mg (N=9)	Placebo (N=10)
Systolic blood pressure (mmHg)	1.1 (4.38)	-1.9 (4.51)	-8.8 (4.11)	2.5 (4.52)
Diastolic blood pressure (mmHg)	-0.3 (3.08)	-0.4 (3.03)	-5.2 (2.89)	-3.7 (3.10)
QTcF Interval, Aggregate (ms)				
Pre-dose[a]	-0.9 (5.05)	-4.6 (5.25)	-1.4 (4.57)	6.2 (5.31)
3 h Post-dose[b]	-4.0 (4.19)	-8.6 (4.33)	-1.5 (3.75)	-4.8 (4.10)
ECG Heart Rate (beats/min)[c]	5.9 (3.04)	5.0 (2.97)	4.3 (2.86)	1.5 (3.01)
Hemoglobin A1C (%)	-0.35 (0.160)	-0.46 (0.199)	-0.41 (0.252)	0.01 (0.186)
Fold Change from baseline, LS mean (SE)				
Cholesterol	0.95 (0.06)	1.04 (0.06)	0.90 (0.05)	1.04 (0.06)
HDL Cholesterol	0.94 (0.05)	1.14 (0.06)	0.98 (0.05)	1.08 (0.06)
Triglycerides	0.84 (0.08)	0.76 (0.08)	0.77 (0.07)	1.18 (0.12)
LDL Cholesterol	0.96 (0.09)	1.04 (0.09)	0.89 (0.08)	1.03 (0.09)
Fasting Glucose	1.03 (0.05)	0.93 (0.04)	0.97 (0.04)	1.02 (0.04)
hsCRP	0.77 (0.29)	0.70 (0.26)	0.59 (0.21)	1.00 (0.37)

[a]All comparisons are made to baseline prior to any dose of study drug measurement prior to Week 44 dose
[b]Measurement 3 hours after Week 44 dose [c]Measurements are pre-dose. Estimate based on MMRM

Conclusions

- Following 4-week titrations up to 180 and 240 mg of once daily oral small molecule aleniglipron:
  - GI AEs were comparable at the 180 mg dose compared with 120 mg dose, supporting using higher dosing of aleniglipron in future studies
  - Low AE-related discontinuations post-rerandomization suggest safety and tolerability of higher doses
  - Aleniglipron efficacy results with doses from 120 to 240 mg in ACCESS II show body weight loss ranging from 14.7% to 16.3% (placebo-adjusted)
  - No events of drug-induced liver injury were identified even at higher doses of aleniglipron (data not shown), indicating a lack of off-target effects
- Further improvements in tolerability have been observed with a 2.5 mg starting dose of aleniglipron compared with the 5 mg starting dose used in this study (Poster 3101-LB, Smith *et al.)*
- These results further support the development of aleniglipron into Phase 3 studies for the treatment of obesity