Abstract #307-OR

Efficacy and Safety of Oral Small Molecule GLP-1 Receptor Agonist TERN-601 in Healthy Participants with Obesity or Overweight — A First-In-Human Study

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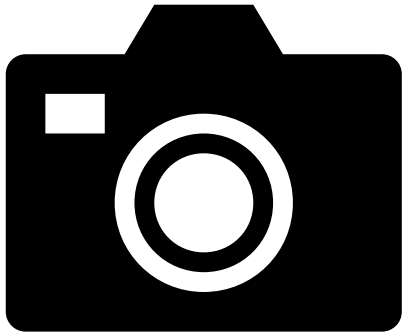
Presenter Disclosure

- Employee of Terns Pharmaceuticals
- Stock/Shareholder of Terns Pharmaceuticals



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TERN-601: An Oral GLP-1RA with Unique Pharmaceutical Properties

	TERN-601 Property	Advantage
Drug Product	Immediate Release Tablet	Convenient once-daily oral dosing without regard to food[2]
In vitro EC_{50}	2.9 nM[1]	Potent EC_{50} allows for sustained target coverage at clinically relevant exposures
Solubility	Low	Prolonged absorption leading to sustained target coverage
Gut Permeability	High	
Gut wall: Plasma Concentration Ratio	5:1[1]	High levels of GLP-1R activation in gut
Plasma Protein Binding	>99%[1]	Improved tolerability

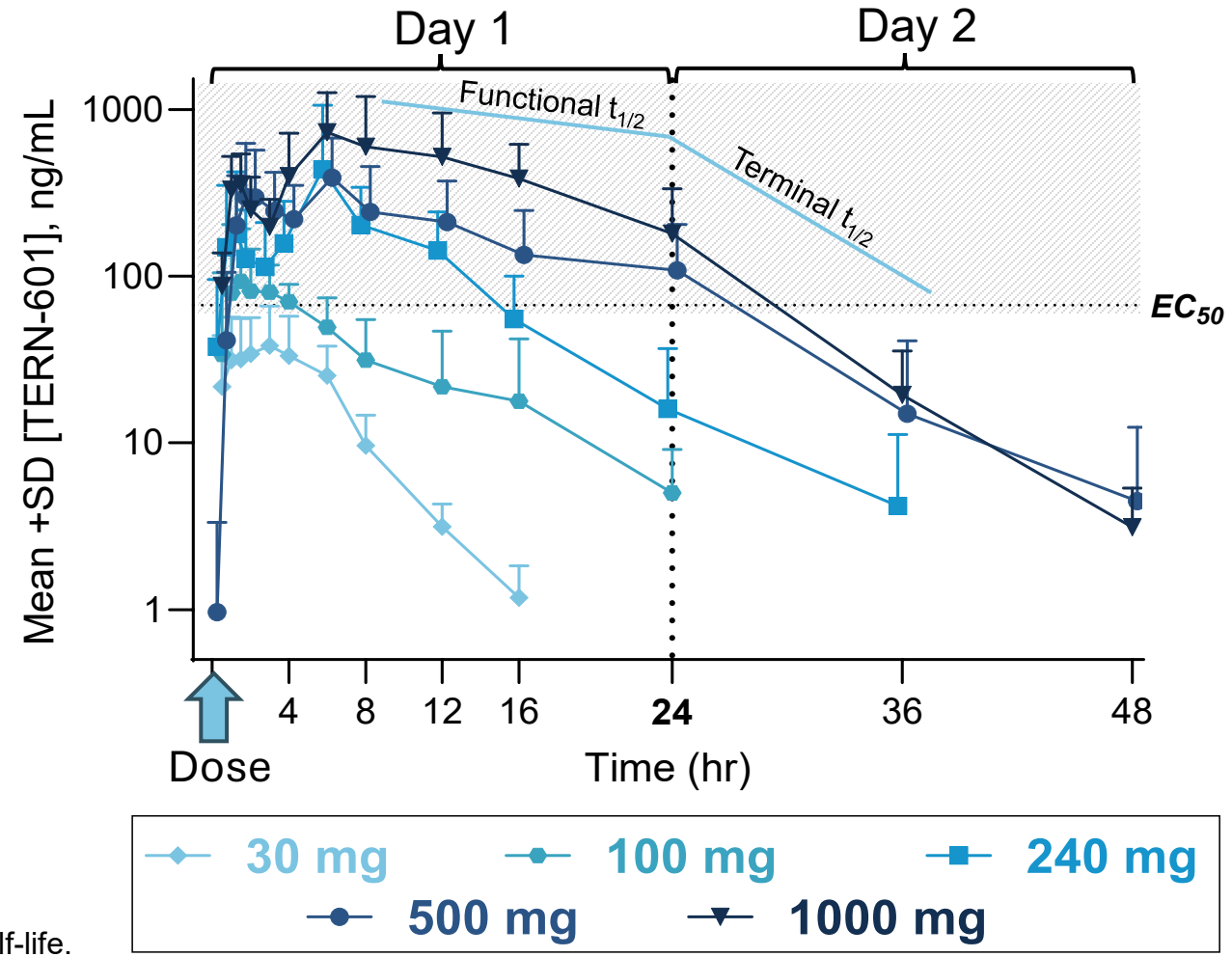
- Robust on-target activity in preclinical models of food intake, gastric emptying, glycemic control, and weight loss at clinically relevant exposures[1]

[1]Jones C, et al. *Diabetes*. 2023;72(Suppl 1):767-P and unpublished data; [2]Nelson C, et al. *Diabetes*. 2025;74(Suppl 1):767-P.
GLP-1RA, glucagon-like peptide-1 receptor agonist; EC_{50}, concentration at which 50% of maximal activity is observed.

Pharmaceutical Properties Result in a PK Profile that Provides Effective and Continuous Target Coverage with Once-Daily Dosing

- Up to 24-hr plasma coverage over EC_{50} at doses of ≥240 mg supports once-daily dosing
- Low solubility leads to prolonged absorption with increasing dose resulting in a functional $t_{1/2}$ of ~9–10 hours
  - No accumulation with multiple dosing due to rapid elimination phase

Prolonged Plasma Coverage Over EC_{50}



EC_{50}, concentration at which 50% of maximal activity is observed; $t_{1/2}$, half-life.

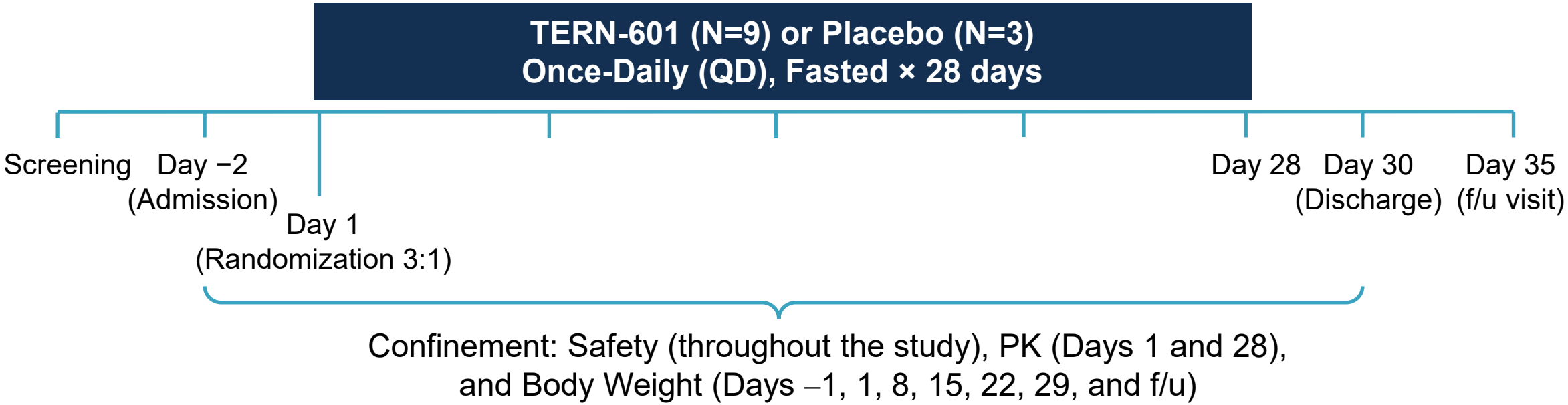
Phase 1 28-Day Study: Randomized, Double-Blind Placebo-Controlled Trial Evaluated Multiple Dose Levels of TERN-601

Study Population:

- Adults (18–65 years of age)
- BMI of 27 to <40 kg/m^2
- HbA1c <6.5%

Study Objectives:

- Primary: Safety and tolerability
- Secondary: TERN-601 PK
- Exploratory: Change in body weight

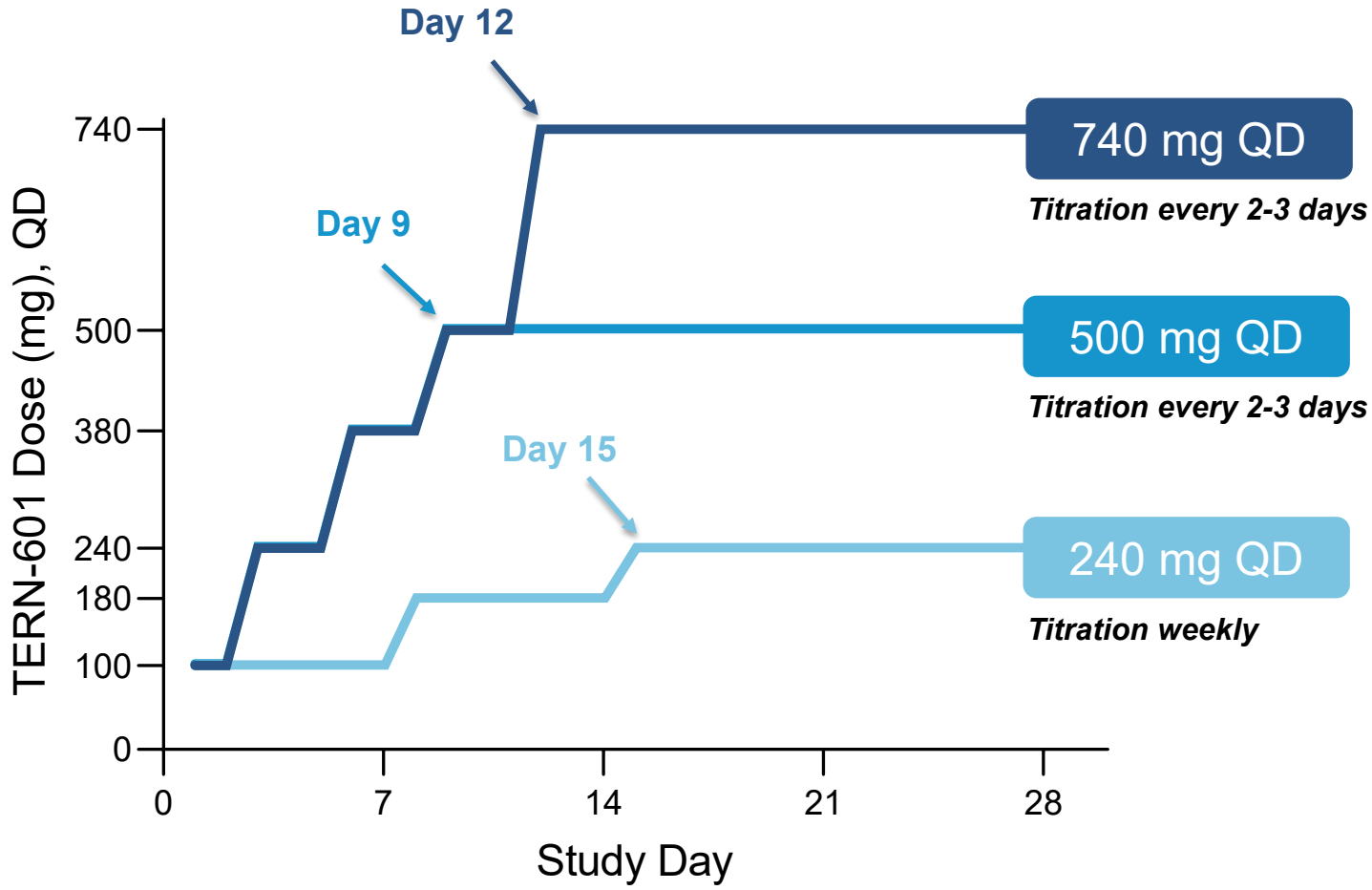


BMI, body mass index; f/u, follow-up; PK, pharmacokinetics,

28-Day Study Design Assessed Tolerability of Rapid Titration

Safety/tolerability data guided titration schedule for subsequent cohorts

Titration Schedule for 28-Day Cohorts



Baseline Characteristics Well-Balanced Across 28-Day Cohorts

BMI consistent across groups (~30 kg/m^2); predominantly White, male participants (≥70%)

Mean (SD)	Placebo (N=9)	240 mg QD (N=10)	500 mg QD (N=9)	740 mg QD (N=9)
Age, year	41.4 (9.2)	44.7 (10.7)	46.7 (12.7)	46.7 (12.1)
Male, N (%)	7 (78%)	7 (70%)	8 (89%)	7 (78%)
White, N (%)	7 (78%)	10 (100%)	7 (78%)	8 (89%)
Weight, kg	90.9 (7.8)	93.4 (14.2)	95.0 (10.6)	93.3 (13.7)
BMI, kg/m^2	29.7 (1.6)	30.6 (2.8)	31.2 (2.1)	30.1 (2.2)
HbA1c, %	5.6 (0.2)	5.5 (0.3)	5.6 (0.3)	5.5 (0.2)

BMI, body mass index; HbA1c, hemoglobin A1c; N, number of participants in analysis set; SD, standard deviation.

Treatment-Emergent Adverse Events were Generally Mild

Majority (>95%) of Adverse Events were Mild (Grade 1)

Treatment Emergent AEs by Maximum Severity

Event, N (%)	Placebo (N=9)	240 mg QD (N=10)	500 mg QD (N=9)	740 mg QD (N=9)
Grade 1 (Mild)	5 (55.6%)	5 (50%)	9 (100%)	3 (33.3%)
Grade 2 (Moderate)	0	1 (10%)	0	6 (66.7%)
Grade ≥3 (Severe)	0	0	0	0
Serious Adverse Events	0	0	0	0

- No severe (Grade 3+) or serious adverse events
- Majority of AEs consistent with GLP-1RA class (e.g., gastrointestinal)
- No dose interruptions, reductions or discontinuations due to treatment-related TEAEs
- No clinically meaningful changes in ECGs, heart rate or blood pressure

TEAE, treatment emergent adverse event; ECG, electrocardiogram; N, number of participants in analysis set; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Majority of GI AEs were Mild Despite Rapid Titration

Frequency and severity of GI AEs increased with dose; not dose-limiting

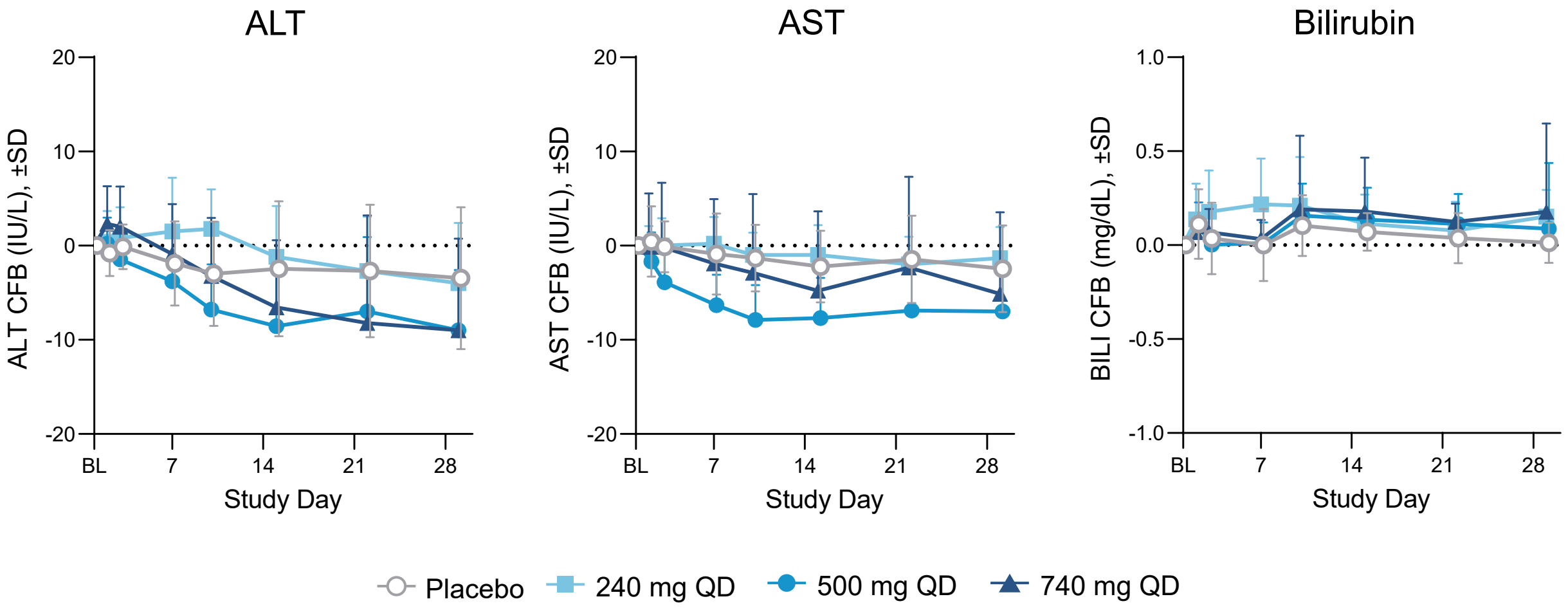
Treatment Emergent GI AEs by Maximum Severity

Event, N (%)	Placebo (N=9)	240 mg QD (N=10)	500 mg QD (N=9)	740 mg QD (N=9)
Titration Schedule	N/A	Every week	Every 2-3 days	Every 2-3 days
Nausea				
Grade 1 (Mild)	2 (22.2%)	0	7 (77.8%)	2 (22.2%)
Grade 2 (Moderate)	0	0	0	6 (66.7%)
Vomiting				
Grade 1 (Mild)	0	0	4 (44.4%)	6 (66.7%)
Grade 2 (Moderate)	0	0	0	1 (11.1%)
Diarrhea				
Grade 1 (Mild)	0	0	2 (22.2%)	2 (22.2%)
Grade 2 (Moderate)	0	0	0	0
Constipation				
Grade 1 (Mild)	0	1 (10.0%)	0	5 (55.6%)
Grade 2 (Moderate)	0	1 (10.0%)	0	0

AE, adverse event; GI, gastrointestinal; N, number of participants in analysis set.

No Clinically Meaningful Changes in Liver Enzymes

Liver enzymes remained ≤1.5 × ULN throughout treatment

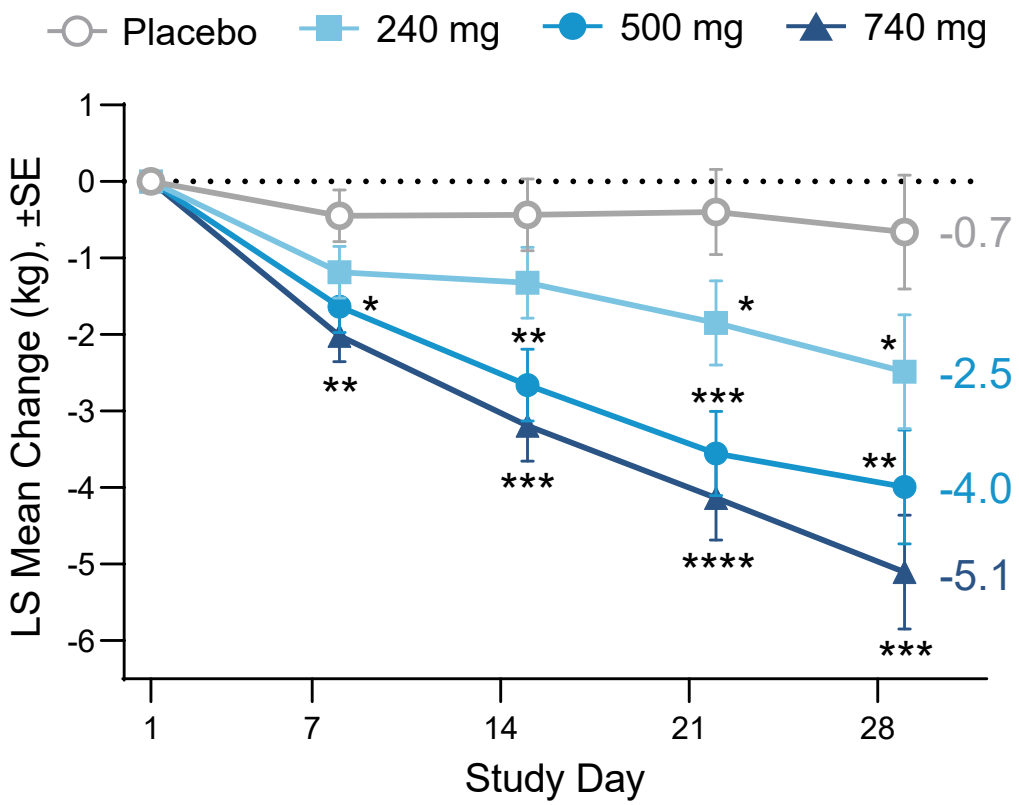


ULN, upper limit of normal; ALT, alanine transaminase; AST, aspartate transaminase; BILI, Bilirubin; CFB, change from baseline; SD, standard deviation.

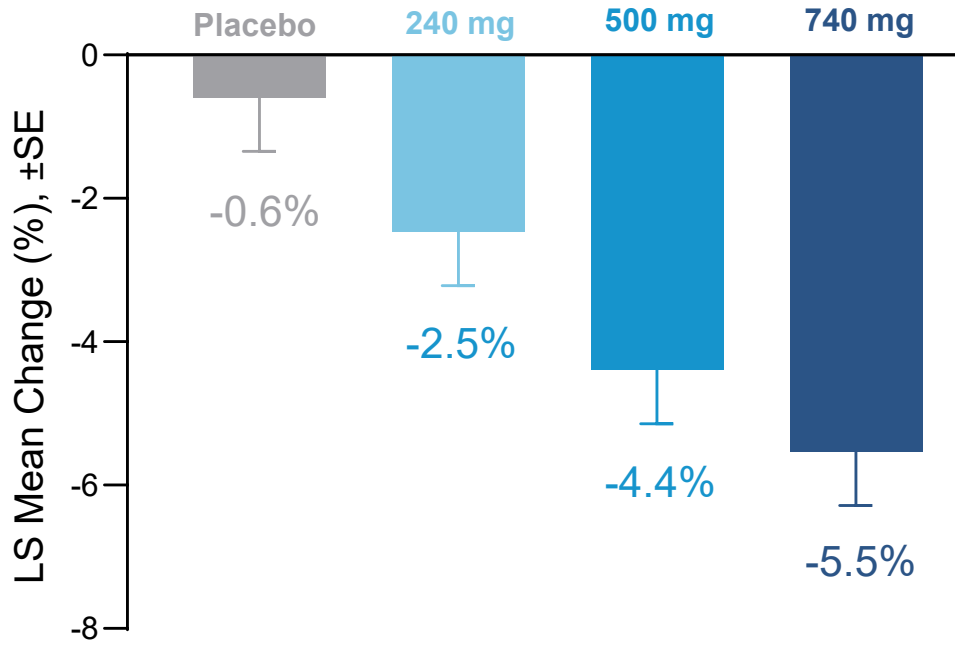
TERN-601 Showed Dose-Dependent Weight Loss Up to 5.5%

Continuous weight loss over treatment period without evidence of plateau

Mean Body Weight Change from Baseline (kg)



Mean Body Weight Change from Baseline (%)

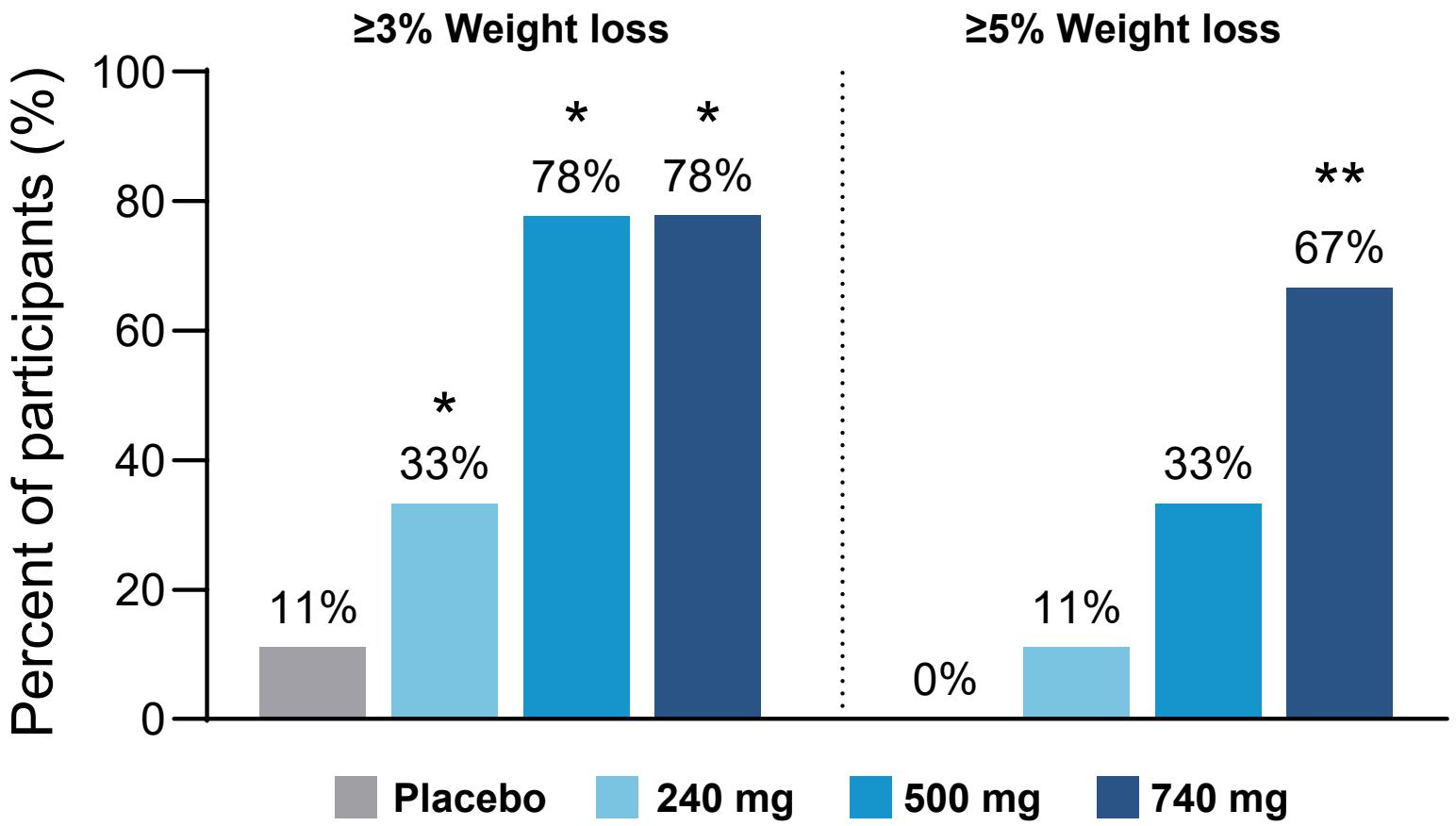


N	9	9	9	9
PBO-adjusted	-	-1.9%	-3.8%	-4.9%
P-value	-	<0.1	<0.01	<0.0001

*p-value <0.1; **p-value <0.01; ***p-value <0.001, ****p-value <0.0001.
LS, Least Squares; N, number of participants in analysis set; PBO, placebo; SE, standard error.

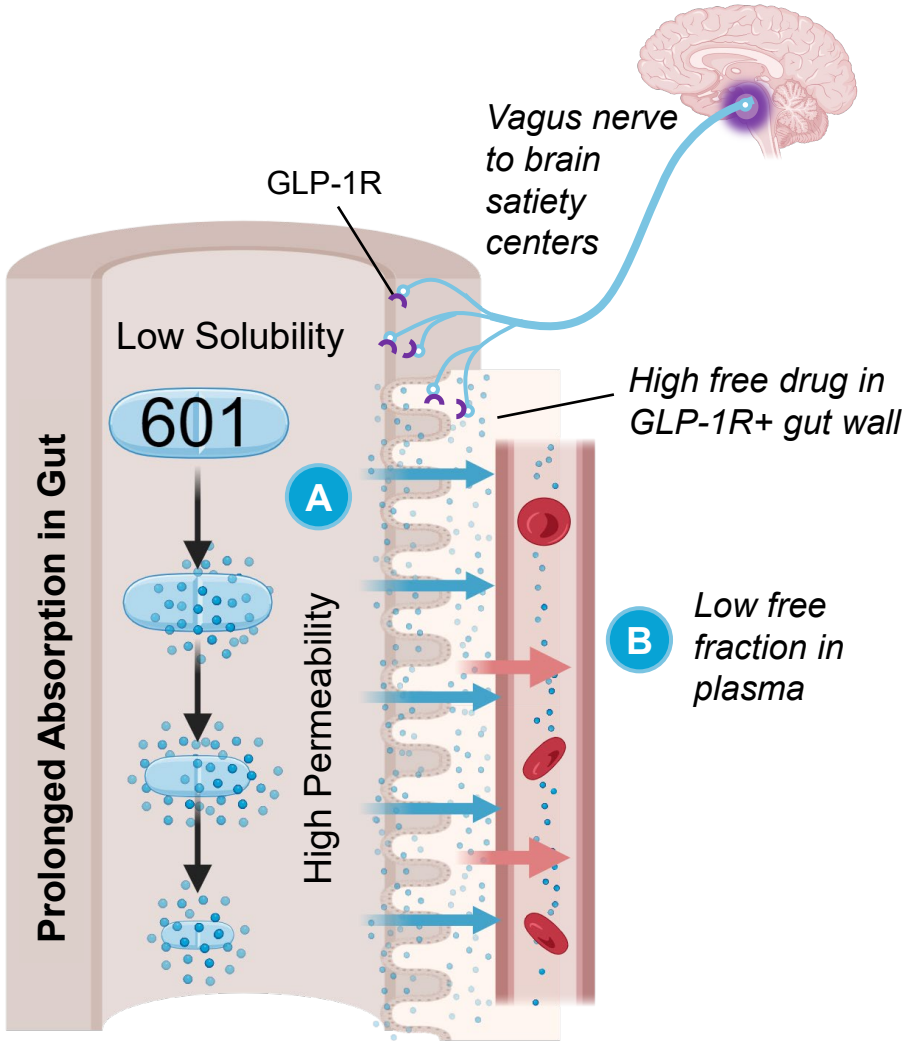
Clinically Meaningful Weight Loss (≥5%) Achieved in 67% of Participants at Top Dose

28-day Body Weight Loss Achieved



*p-value <0.1; **p-value <0.01, relative to placebo.

Distinct Properties Enable Tolerable Higher Doses that Achieve Sustained Target Coverage and Robust GLP-1R Activation



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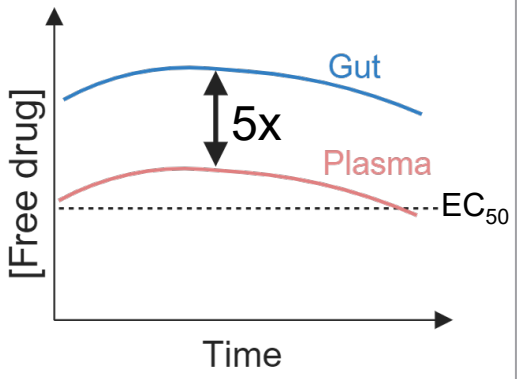
Low solubility & high permeability results in:

- **Prolonged absorption** to achieve **sustained target coverage** allowing **QD dosing**
- **High drug levels in gut wall** that strongly activate GLP-1R in gut triggering satiety centers in brain



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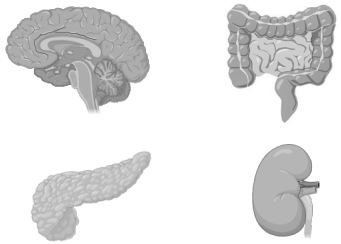
Low free fraction may allow:

- **Tolerable higher doses** that drive both **gut and systemic GLP-1R** activation



GLP-1R, glucagon-like peptide-1 receptor; QD, once-daily.
EC_{50}, concentration at which 50% of maximal activity is observed.

Summary and Conclusions

Over 28 days, TERN-601 dosed once-daily:

- ✓ Was well-tolerated with unremarkable safety findings
  - No treatment-related dose interruptions, reductions, or discontinuations at any dose
  - Treatment emergent adverse events were consistent with the GLP-1RA class
  - All GI adverse events were mild to moderate despite rapid titration schedule
  - No clinically meaningful changes in liver enzymes, vital signs or ECGs
- ✓ Showed significant mean weight loss up to 5.5% (4.9% placebo-adjusted)
  - 67% of participants lost ≥5% baseline body weight at top dose
- ✓ Identified pharmacodynamically and clinically active dose range warranting further evaluation in the ongoing, 12-week, Phase 2 study (NCT06854952) in adults with obesity or overweight

Acknowledgements

- We would like to extend our thanks to the study participants and the clinical research unit staff.

QUESTIONS?

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