TRANSTECH PHARMA

155-OR

TTP273, an Orally-Available Glucagon-Like Peptide-1 (GLP-1) Agonist, Notably Reduces Glycemia in Subjects with Type 2 Diabetes Mellitus (T2DM)

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Presenter Disclosure Information

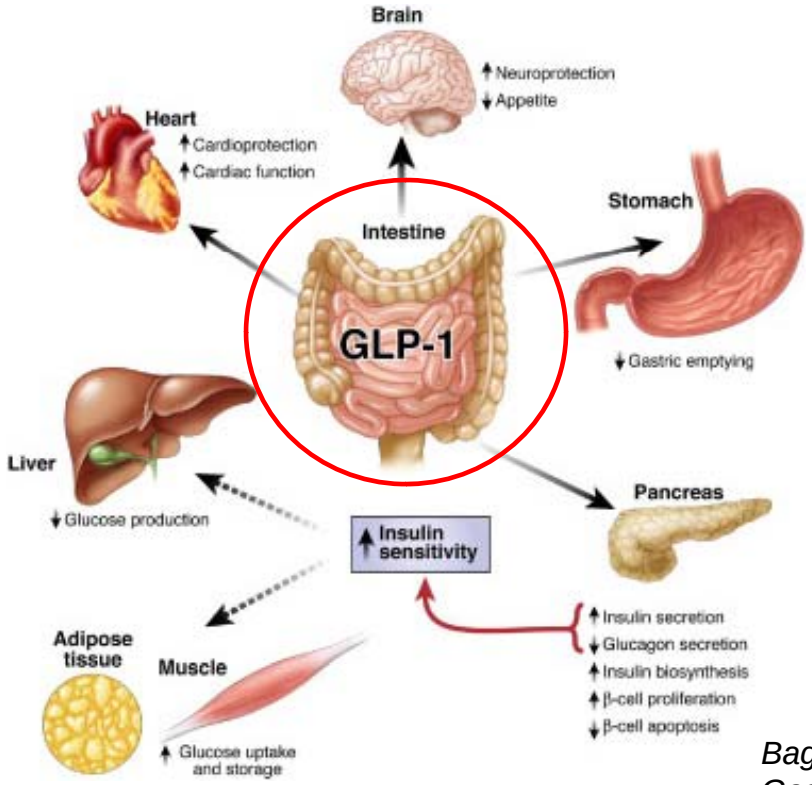
The American Diabetes Association requires the following disclosure to the participants:

Stephanie Gustavson, PhD, MSCI

Employee of TransTech Pharma, LLC

Background

- GLP-1 Receptor Agonism: a validated target



Baggio LL and Drucker DJ. 2007. Gastroenterology 132: 2131-57

- Currently marketed GLP-1 mimetics:
  - Injectable agents
  - Robust efficacy; notable gastrointestinal (GI) side effects

Expected Benefits of an Oral, Small Molecule, Non-Peptide GLP-1 Receptor Agonist

- More physiological than peptides: delivered at the site of secretion of native GLP-1 (intestine)
  - Efficacy contributions from gut (direct & indirect via neural signaling) & systemic
- Superior tolerability vs. peptide GLP-1 analogues
  - Low incidence of GI AEs
- No antibody formation
- Trend towards lowering of body weight, triglycerides, cholesterol and blood pressure
  - May reduce cardiovascular risk
- Ideal for combination with existing oral agents (including fixed-dose combinations)
- Convenience/Compliance

1st in Class: Oral, Small Molecule, Non-Peptide GLP-1R Agonists

	TTP054 (First Generation)	TTP273 (Second Generation)
Overview	***Achieved POC for Program*** ❖ *HbA_{1c} reduction with no GI side effect signal*	***Achieved POM*** ❖ *Glucose reduction with no GI side effect signal* ❖ *More potent than TTP054* ❖ *Appears more efficacious (based on short-term glucose lowering) than TTP054*
Clinical Status	Phase 2: 3 months in patients with T2DM ❖ **TTP054-201 (#156 Oral)**	Phase 1: 14 days in patients with T2DM ❖ **TTP273-102 (#155 Oral)**

TTP273-102 Study Design

- Randomized, placebo-controlled, investigator- and patient- blind, sponsor-open, multiple dose study (14 days)
  - TTP273 effects on safety, tolerability, PK, and PD
- Patients with T2DM on stable doses of metformin
- 3 week inpatient design
  - Inpatient Days -5 to 16; 23-point mean daily glucose and MMTT on Days -1 & 14
  - Isocaloric diets provided/encouraged
  - Subjects required to consume full menu Days -1 &14
- 10 cohorts; n=12 (9 active; 3 placebo) per cohort
- QD PO Dosing (6 Cohorts)
  - 25 mg QD
  - 50 mg QD
  - 75 mg QD
  - 100 mg QD
  - 150 mg QD
  - 450 mg QD

Alternative PO Dosing Regimens (4 Cohorts)

- 75 mg QPM
- 25 mg BID
- 75 mg BID
- 150 mg BID

Disposition, Demography, & Pharmacokinetics

- 112 subjects randomized/dosed at a single site
  - N=108 completed; 4 withdrew
    - Two PBO (one AE [LFTs increased], one "other" [hyperglycemia])
    - Two actives (one AE [nausea; 75 mg QD], one "other" [death in family; 450 mg QD])
- Mean (±SD) baseline characteristics were relatively balanced amongst groups

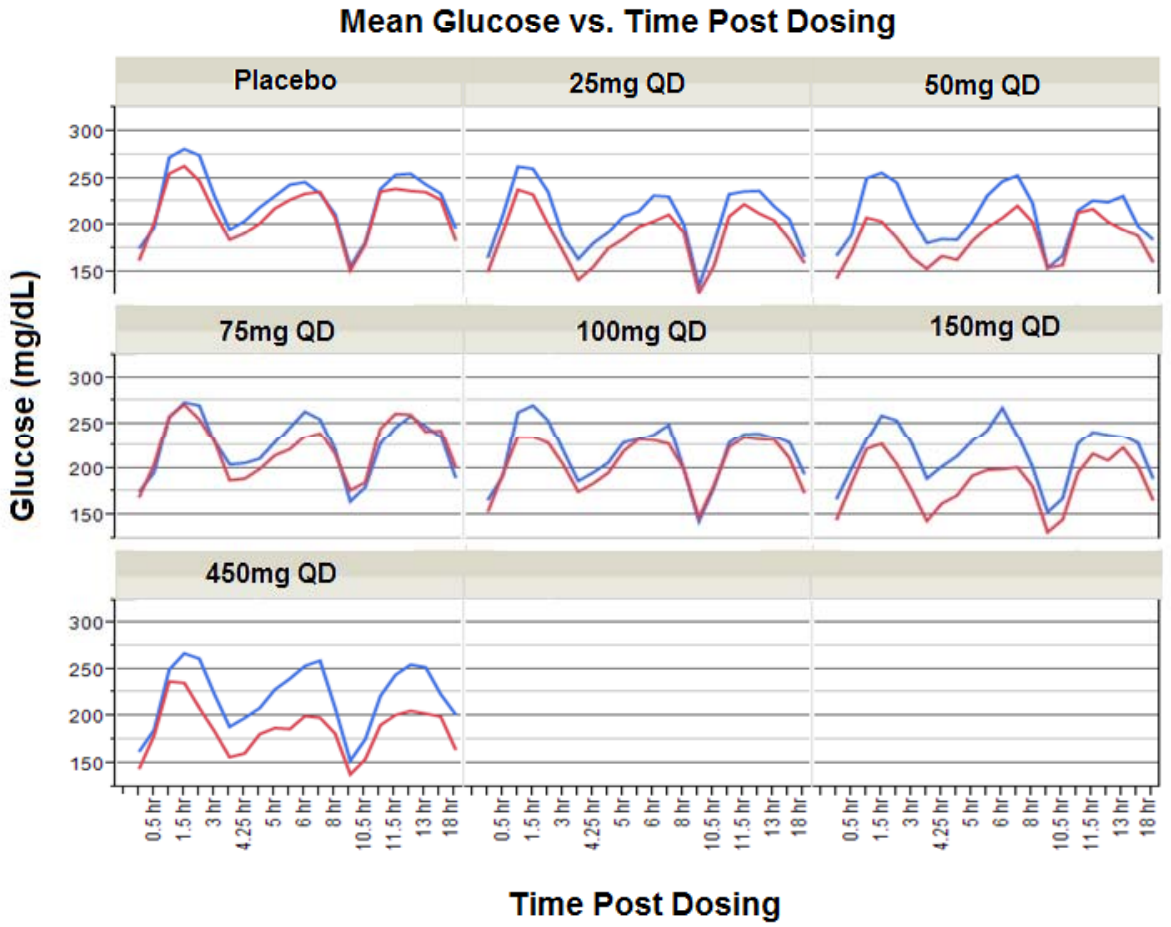
	All Subjects	All Placebo	All Active
Sample size	112	29	83
Gender; Male (%)	59 (53%)	16 (55%)	43 (52%)
Age in yrs; Mean ± SD (Min,Max)	58 ± 6 (43,70)	57 ± 6 (44,68)	58 ± 6 (43,70)
HbA_{1c} (%); Mean ± SD (Min,Max)	8.1 ± 0.7 (6.7,9.8)	8.4 ± 0.8 (7.3,9.8)	8.0 ± 0.7 (6.7,9.7)
BMI in kg/m^2; Mean ± SD (Min,Max)	32 ± 4 (23,43)	31 ± 4 (23,39)	32 ± 4 (23,43)

- Pharmacokinetics increased in linear, dose-responsive manner
  - Tmax ~2 hours
  - Half-life ~6 hours

Safety Summary

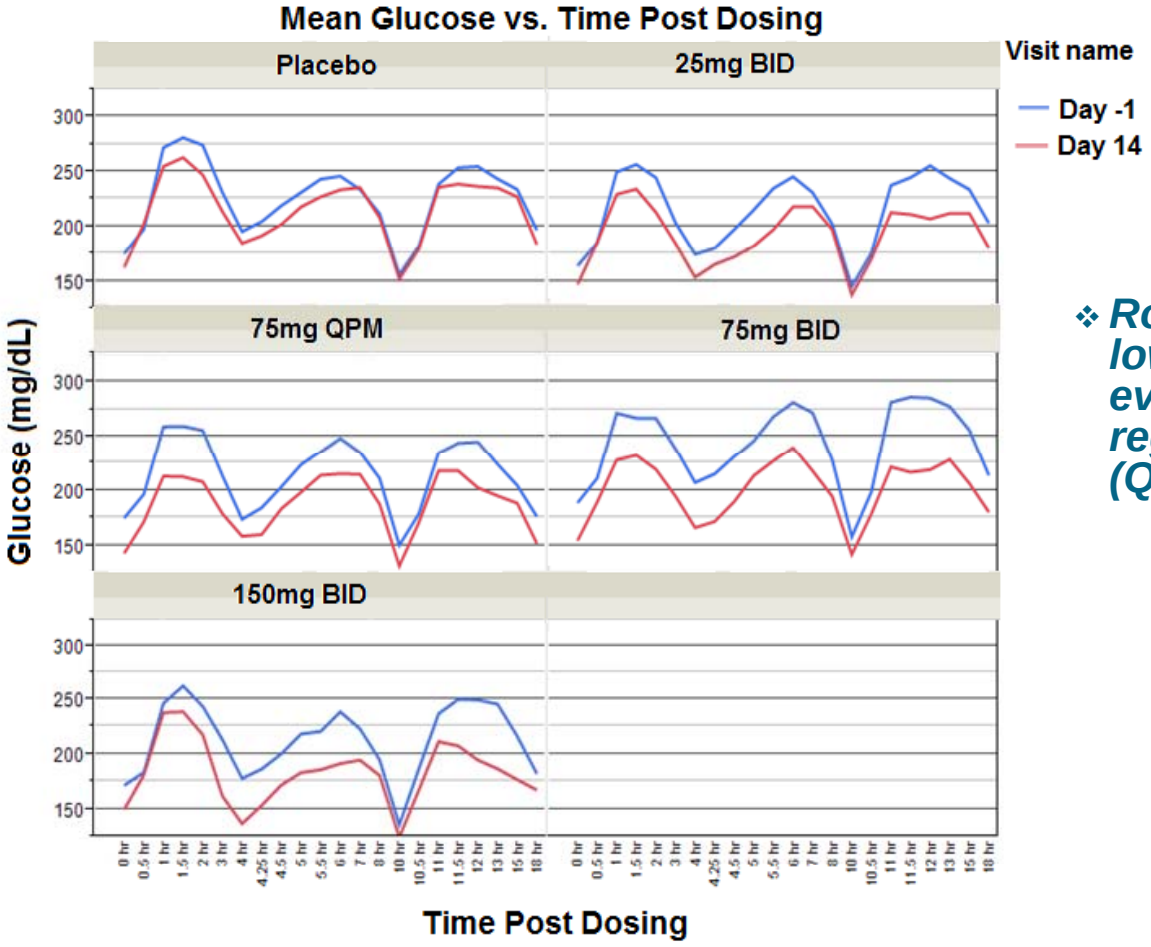
- All doses were safe and well tolerated
  - No SAEs
  - No hypoglycemia in any patient
  - Two discontinuations due to an AE
    - 1 placebo: elevated LFTs
    - 1 active (75 mg QD): nausea
- AEs were generally mild and similar in incidence between placebo and active dose groups
- Small number of GI AEs: mostly mild, resolved spontaneously with continued study drug administration, no dose response relationship
  - Minimal incidence of nausea (n=4 total of 112 randomized) and vomiting (n=1), with no dose response
  - Most common GI AE was diarrhea
    - No clear dose response
    - Often occurred on meal-challenge days when the timed consumption of meals was required

24-Hour Glucose Profile:
QD Dosing Regimens



- ***Robust, dose responsive glucose lowering***
- ***PD maximized at 150 QD***

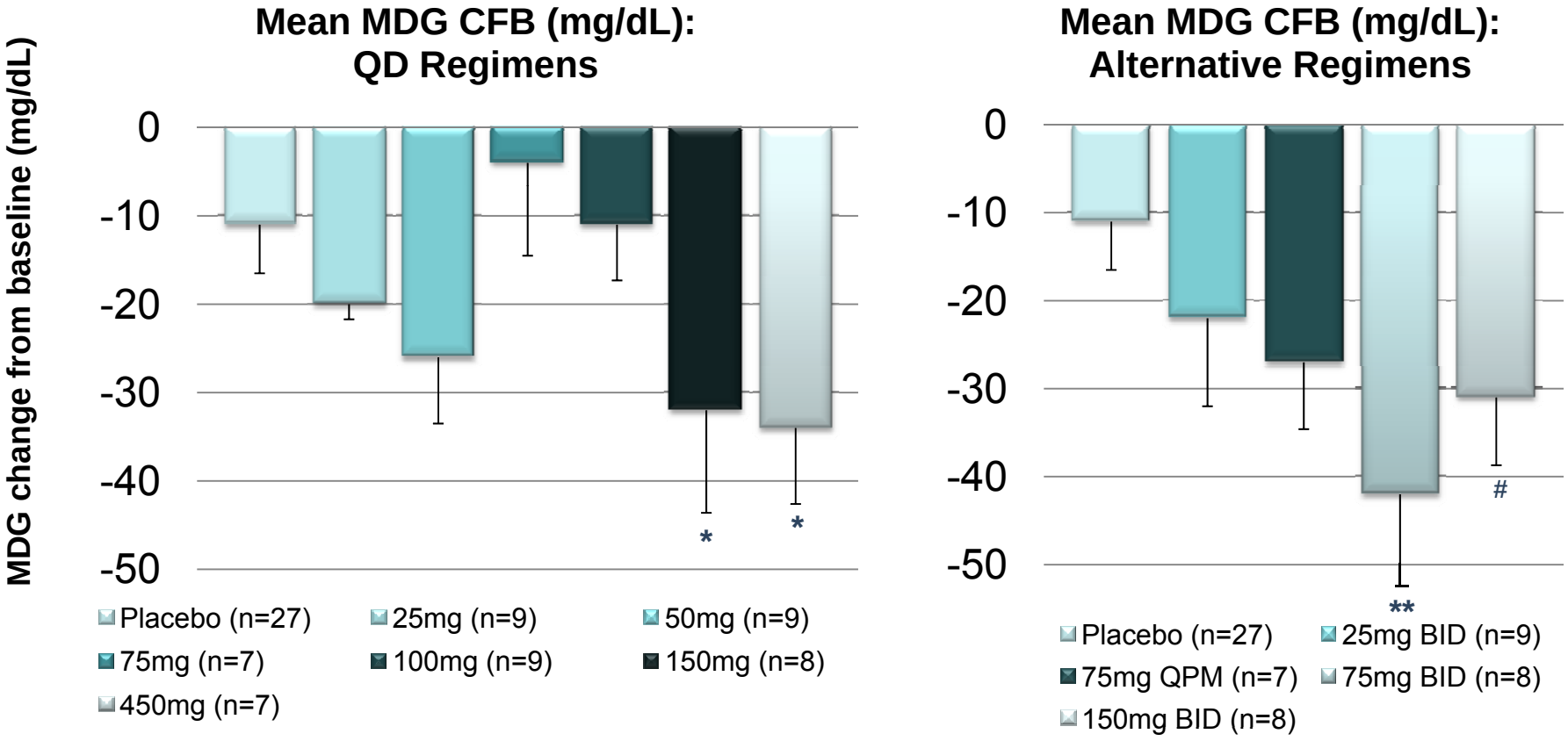
24-Hour Glucose Profile:
Alternative Dosing Regimens



- ***Robust glucose lowering with evening regimens (QPM and BID)***

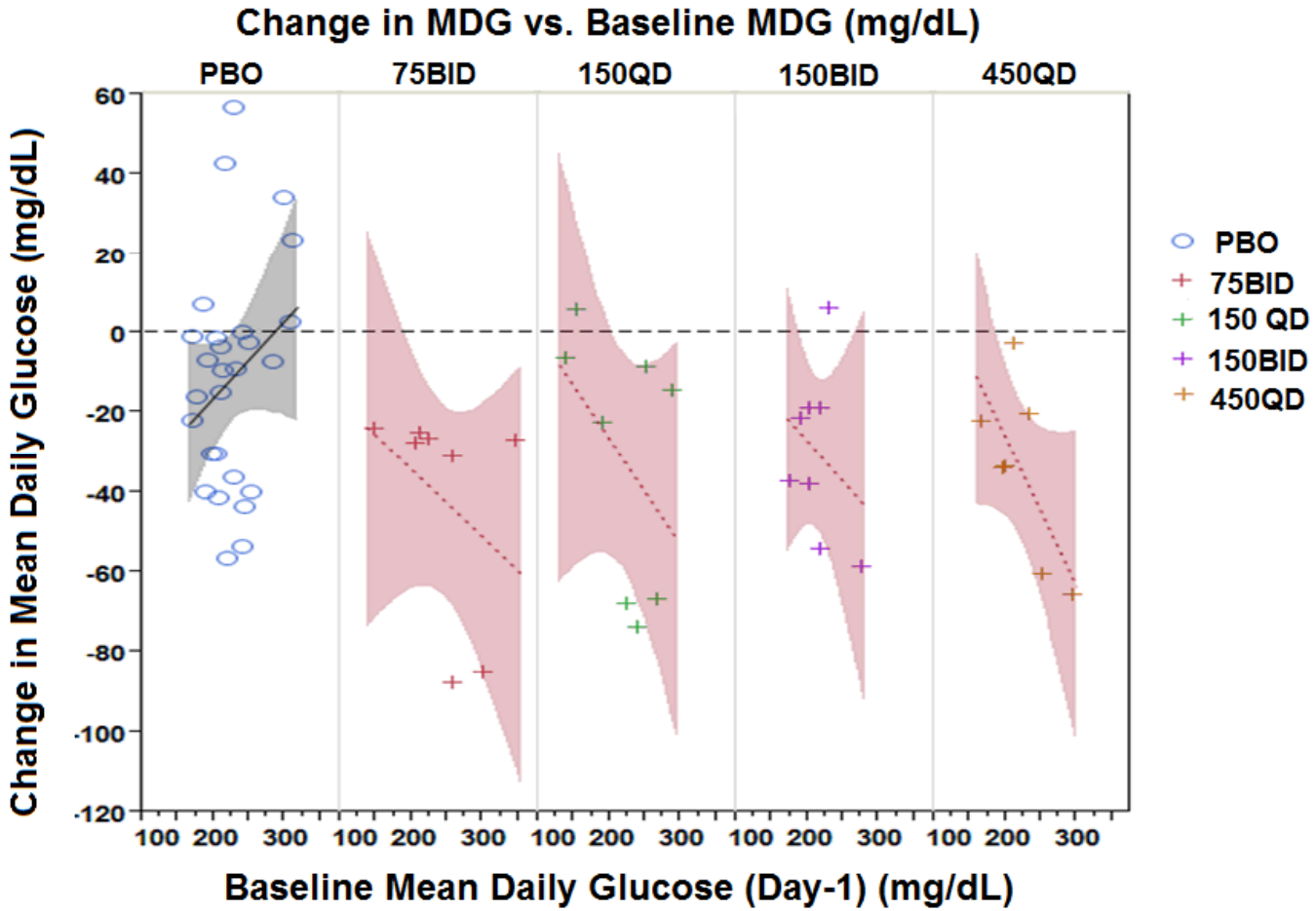
TTP273-102 Mean Daily Glucose (MDG):

Mean Change from Baseline (CFB) after 14-days of Treatment



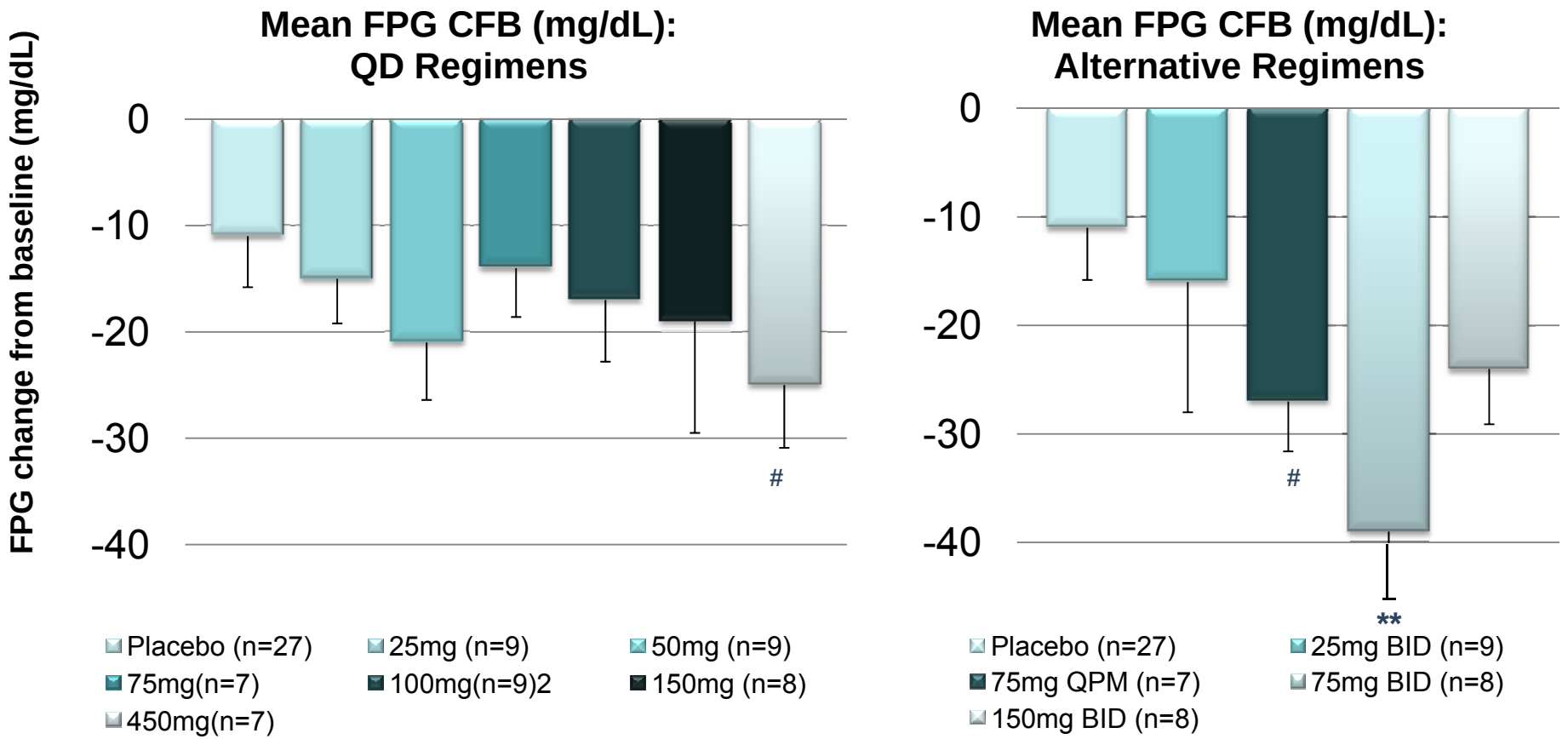
 # P < 0.10 vs. placebo; * P < 0.05 vs. placebo; ** P < 0.01 vs. placebo

MDG at Baseline Influences Response to TTP273



TTP273-102 Fasting Plasma Glucose (FPG):

Mean Change from Baseline (CFB) after 14-days of Treatment



 # P < 0.10 vs. placebo; ** P < 0.01 vs. placebo

Changes in Secondary Parameters

- Study not designed to assess changes in secondary parameters
  - Strict dietary requirements, small sample size, and short duration
  - Yet, numerical, dose-responsive changes occurring in expected direction
- Body weight:
  - Trend for reduction (up to ~2 kg) in several active treatment groups vs. placebo (~0.6 kg)
  - Trend for correlation between mean daily glucose reduction and body weight reduction seen in active treatment groups (but not in placebo group)
- Blood pressure:
  - SBP: trend for reduction (up to ~8 mmHg) in several active treatment groups vs. placebo (~2 mmHg)
  - DBP: trend for reduction (up to ~5 mmHg) in several active treatment groups vs. placebo (~1 mmHg)
- Triglycerides:
  - Trend for reduction (up to ~50 mg/dL) in several active treatment groups vs. placebo (~30 mg/dL)

TTP273-102 Summary

- TTP273 demonstrated robust effects on postprandial & fasting glucose
  - Glucose reduction (40 mg/dL in MDG and FPG) appears more pronounced than TTP054
    - Consistent with the increased *in vitro* potency of TTP273 vs. TTP054
    - Assessments based on TTP054 shorter-term phase 1 studies; no head-to-head comparisons *[Diabetes, 2013 ADA abstract (115-OR)]*
  - Study likely underestimates maximum glycemic reduction
    - Subjects were required to consume isocaloric diets, thus any effect on food intake would not contribute to the PD response in this study
    - Notable placebo effect in the current study, that will likely wane with time (in contrast to active-treatment effects which generally do not wane)
- Secondary endpoints (BW, TG, blood pressure) tended to exhibit numerical, dose-responsive decreases despite the fact the study was <u>not designed</u> to assess such changes
- Negligible nausea/vomiting

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