

Oral Small Molecule GLP-1 Receptor (GLP-1R) Agonists for Type 2 Diabetes (T2DM) with Negligible Nausea and Vomiting

Introduction

GLP-1R is a well validated target for the treatment of T2DM, with multiple marketed injectable GLP-1 analogues/mimetics that provide glycemic control and weight loss in T2DM patients. Although the peptides targeting GLP-1 receptor are generally safe, the use of these agents are limited by two major factors: 1) all are injectable and 2) the primary side effects of nausea and vomiting make this treatment approach intolerable for some patients.

TTP054 and TTP273 are oral small molecule (non-peptide) GLP-1R agonists that are delivered near the site of secretion of GLP-1 (the gut) and have clinically demonstrated efficacy by improving glycemic control and reducing body weight with superior tolerability than the peptide GLP1 analogues/mimetics.

Phase 1b (TTP273 and TTP054) and Phase 2 (TTP054) Studies

Study Design:

Type 2 Diabetic Subjects on Stable Doses of Metformin

- TTP054-108: 4 cohorts evaluated QD or BID dosing (200-400mg) with TTP054 for 4 weeks
- TTP273-102: 10 cohorts evaluated QD, QPM or BID dosing (25-450mg) with TTP273 for 2 weeks
- TTP054-201: 4 arms evaluated 200-800 mg QD dosing for 3 months
- Subjects on oral anti-diabetic medications other than metformin were required to washout (4 weeks) prior to start
- In Phase 1b studies, a meal tolerance test was administered on Day -1 and last day of study (Day 28, TTP054-108 and Day 14, TTP273-102)
- Subjects in the TTP273 phase 1b study were required to consume an isocaloric diet for the entire study

Baseline Characteristics:

Baseline characteristics were relatively balanced amongst groups in each study

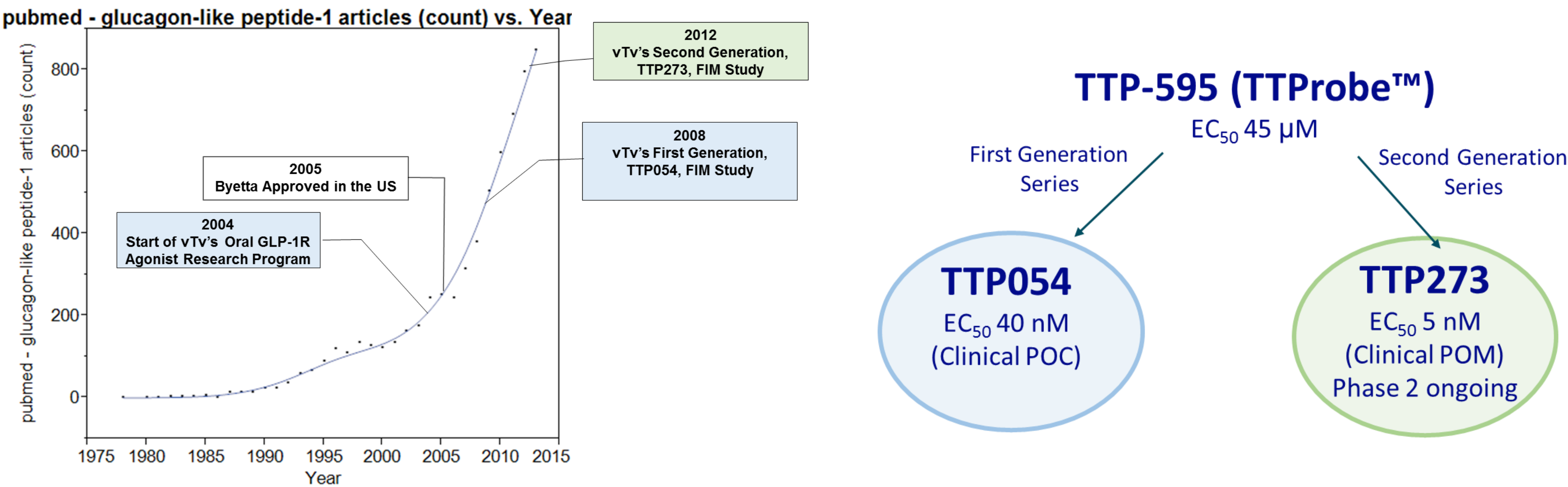
TTP273-102 Baseline Parameter	Pooled Placebo	25 mg QD	50 mg QD	75 mg QD	100 mg QD	150 mg QD	450 mg QD	25 mg BID	75 mg BID	150 mg BID	75 mg QPM
Sex (M/F)	N=29 13/16	N=9 5/4	N=9 3/6	N=8 5/3	N=9 7/2	N=9 4/3	N=7 4/5	N=9 3/5	N=8 5/3	N=8 2/5	N=7 2/5
Ethnicity (% Hispanic)	21	11	67	38	11	78	43	11	13	25	14
Race*	0/1/3/25	0/0/2/7	0/1/5/3	0/0/3/5	0/0/1/8	0/0/5/4	0/0/2/5	0/0/1/8	0/0/1/7	0/0/0/8	0/0/1/6
Age (years) Mean	56	55	56	54	58	51	61	58	58	62	57
BMI (kg/m ²) Mean	31	31	32	34	32	29	31	30	31	33	33
HbA1c (%) Mean	8.4	7.9	7.9	8.4	7.6	8.0	8.0	8.4	7.9	8.1	8.4

TTP054-108 Baseline Parameter	Pooled Placebo	400 mg BID	400 mg QD	200 mg BID	200 mg QD
Sex (M/F)	N=21 13 / 8	N=4 1/3	N=9 5/4	N=10 6/4	N=11 8 / 3
Ethnicity (% Hispanic)	14	0	22	10	46
Race*	1/1/7/12	0/0/3/1	1/1/3/4	1/0/2/7	4/0/2/5
Age (years) Mean	51	55	46	50	50
BMI (kg/m ²) Mean	32	30	31	33	33
HbA1c (%) Mean	8.2	7.7	8.1	8.3	7.7

TTP054-201 Baseline Parameter	Pooled Placebo	200 mg QD	400 mg QD	800 mg QD
Sex (M/F)	N=50 27/23	N=27 22/5	N=51 33/18	N=56 31/25
Ethnicity (% Hispanic)	74	59	82	41
Race*	1/1/3/45	1/0/3/23	1/1/3/46	2/2/15/37
Age (years) Mean	53	56	55	58
BMI (kg/m ²) Mean	31	31	31	32
HbA1c (%) Mean	8.7	8.8	8.6	8.1

*Race (Other/Asian/Black/White)

vTv's GLP-1R Agonists Program Genesis



Safety Results:

TTP054 and TTP273 have Comparable Safety Profiles: Negligible Nausea and Vomiting and No Evidence of Hypoglycemia

TTP054-108 Phase 1b T2D on Metformin 4w	Diarrhea	Nausea	Vomiting
Placebo (n=21)	0	0	1
200QD (n=11)	0	1	1
400QD (n=9)	0	1	1
200BID (n=10)	0	0	0
400BID (n=4)	0	0	0

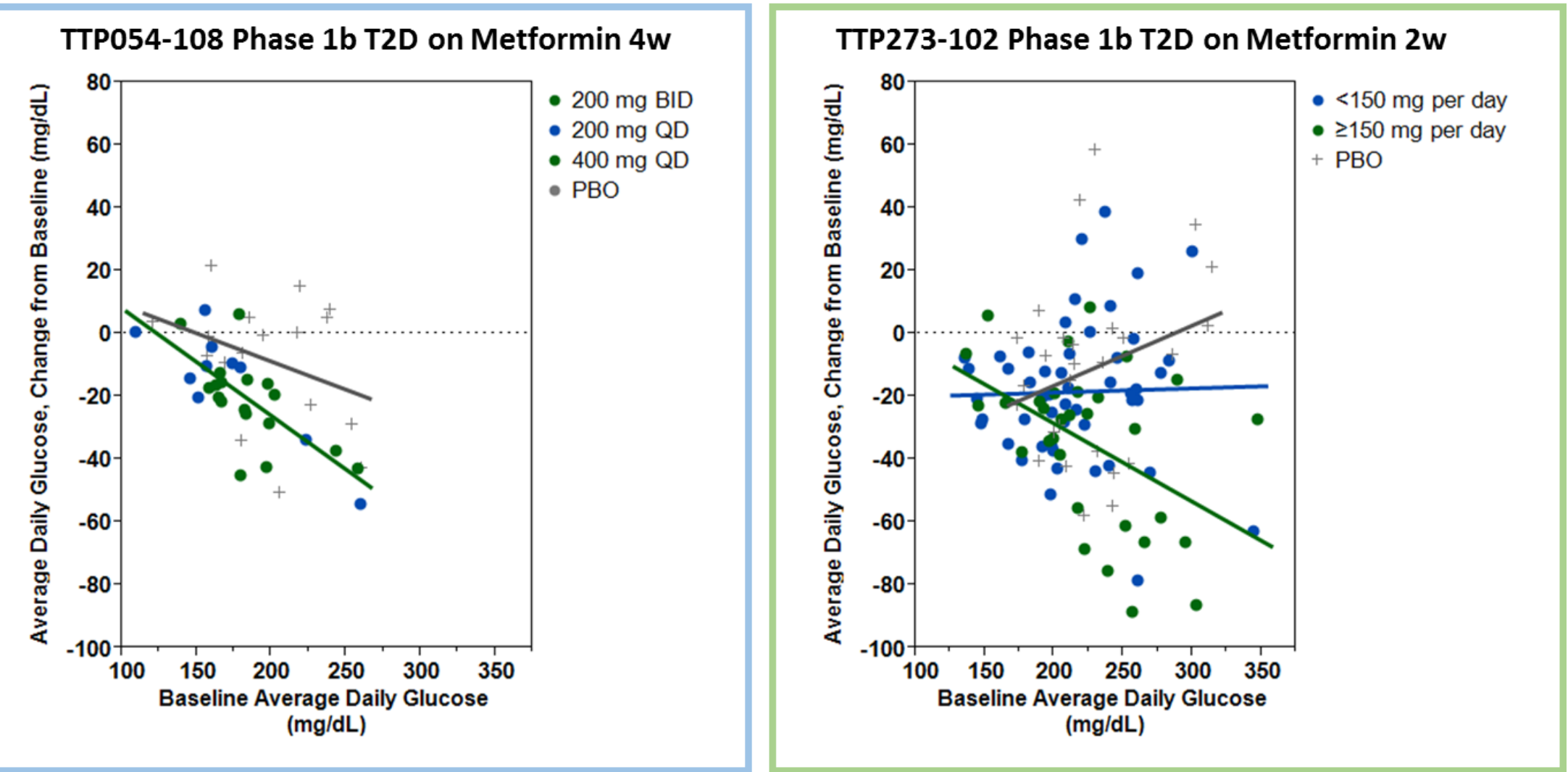
TTP054-201 Phase 2 T2D on Metformin 12w	Diarrhea	Nausea	Vomiting
Placebo (n=50)	0	3	2
200QD (n=27)	0	1	0
400QD (n=51)	1	0	0
800QD (n=56)	3	4	3

TTP273-102 Phase 1b T2D on Metformin 2w	Diarrhea	Nausea	Vomiting
Pooled Placebo (n=29)	3	0	0
25QD (n=9) / PBO (n=3)	0/0	1	0
50QD (n=9) / PBO (n=3)	1/0	0	0
25BID (n=9) / PBO (n=3)	0/0	0	0
75QD (n=8) / PBO (n=3)	2/0	1	0
75QPM (n=7) / PBO (n=3)	0/1	0	0
100QD (n=9) / PBO (n=3)	4/1	0	1*
150QD (n=9) / PBO (n=3)	1/0	0	0
75BID (n=8) / PBO (n=3)	2/0	1	0
150BID (n=8) / PBO (n=3)	1/0	1	0
450QD (n=7) / PBO (n=2)	3/1	0	0

*unrelated to study drug

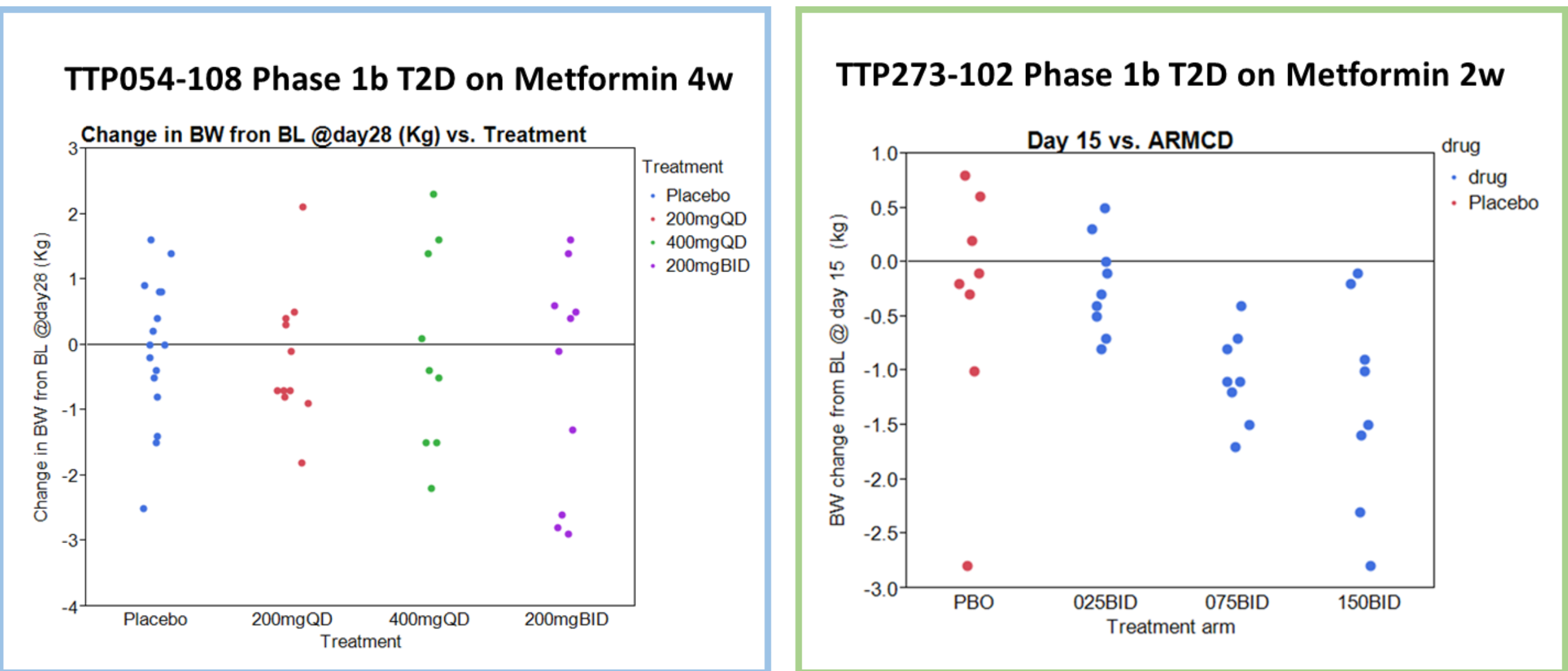
Efficacy Results:

TTP273 Shows Greater Improvement in Glycemic Control than TTP054 in Phase 1b studies



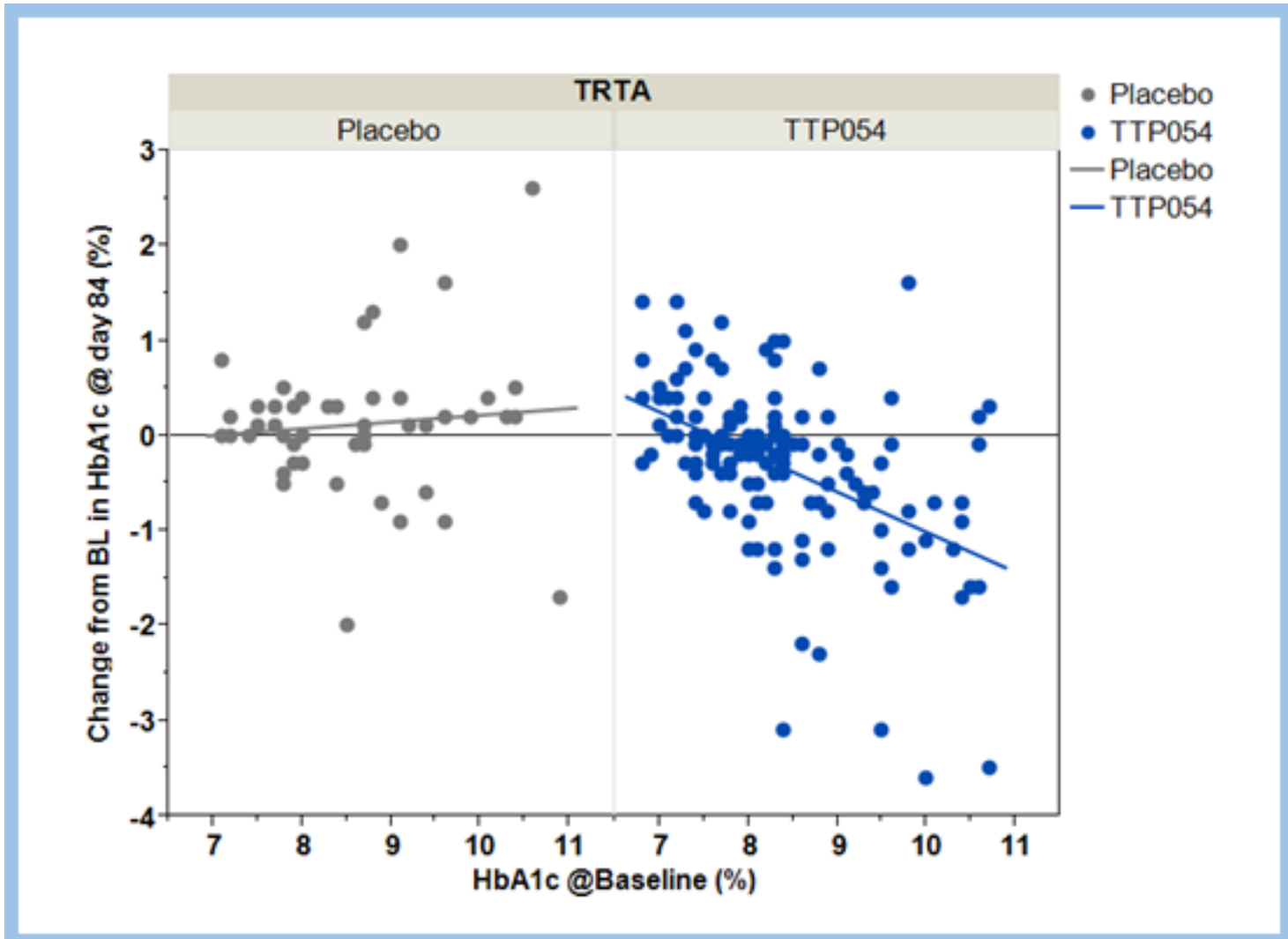
- TTP273 is more efficacious than TTP054 in phase 1b at the same doses despite shorter study duration.
- TTP054 reduces A1c (1%) in the target population (A1c 8-11%) in 3 month Phase 2 study.

TTP273 Seems to Have A Better Effect on Body Weight Loss than with TTP054 in a Phase 1b study



- No weight loss was seen in phase 1b TTP054 trial compared to placebo
- In a 3 month phase 2 study with TTP054, significant body weight loss (1Kg) observed in the target population (A1c 8-11%) at the high dose group (800mg QD)
- TTP273 phase 1b trial showed a trend in weight loss with the BID dose regiments despite shorter study duration and isocaloric diet

TTP054 showed significant reduction in A1c in a 3 month study



- TTP273 is expected to be more efficacious based on better Phase 1 results and *in vitro* potency

	Effects Observed in Patients	vTv GLP1r Agonists	GLP-1 Analogues
Safety	No significant gastrointestinal side effects	✓	✗
Convenience	Oral	✓	✗
	Ideal for co-formulation with existing OADs	✓	✗
	No need for medical device	✓	✗
Efficacy	Lowers blood glucose	✓	✓
	Decreases HbA1c levels	✓	✓
	Weight loss	✓	✓

Conclusion
With a superior safety and convenience profile, TTP273 could provide an alternative to current GLP-1r therapies and expand the use of this therapeutic class

