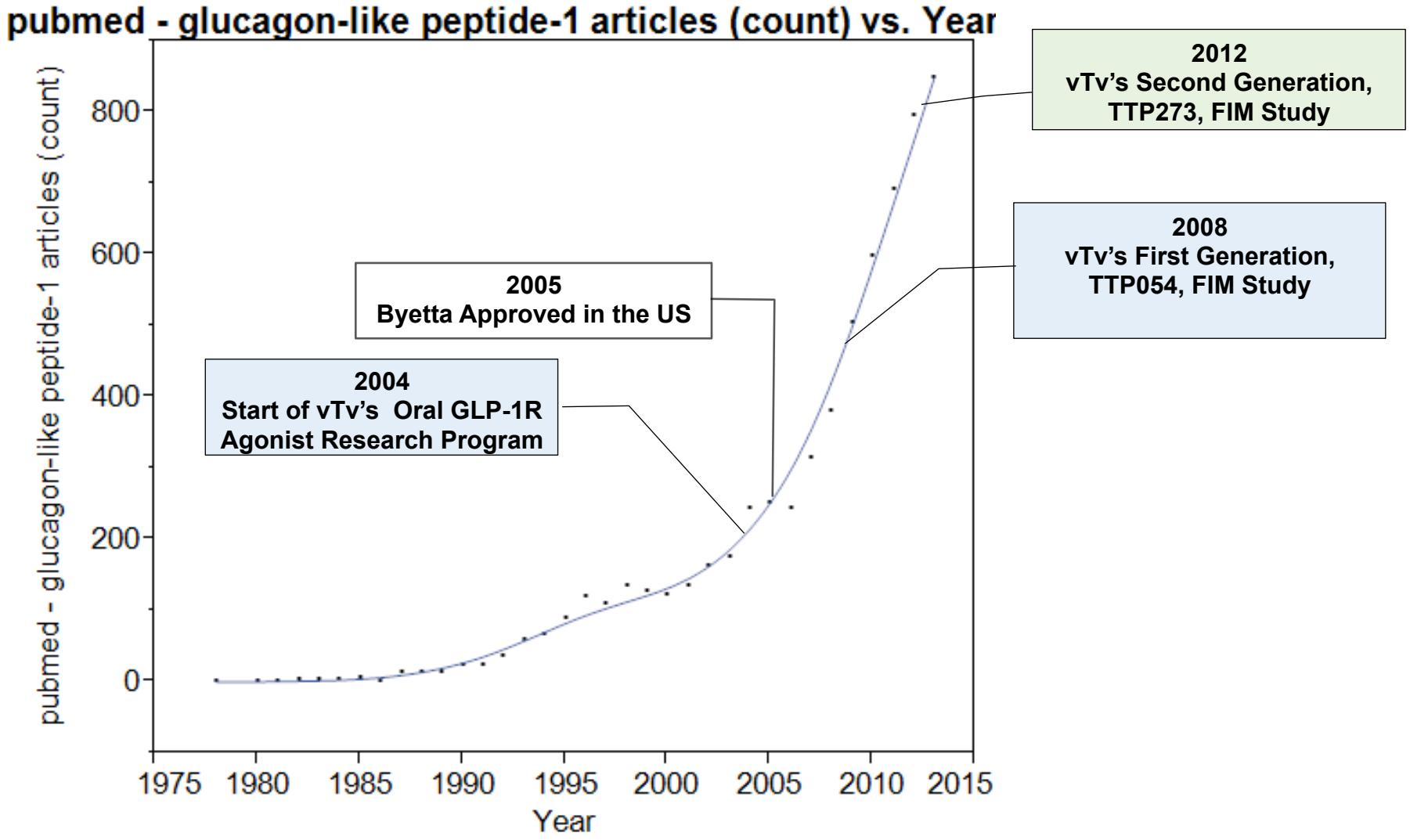
Therapeutics

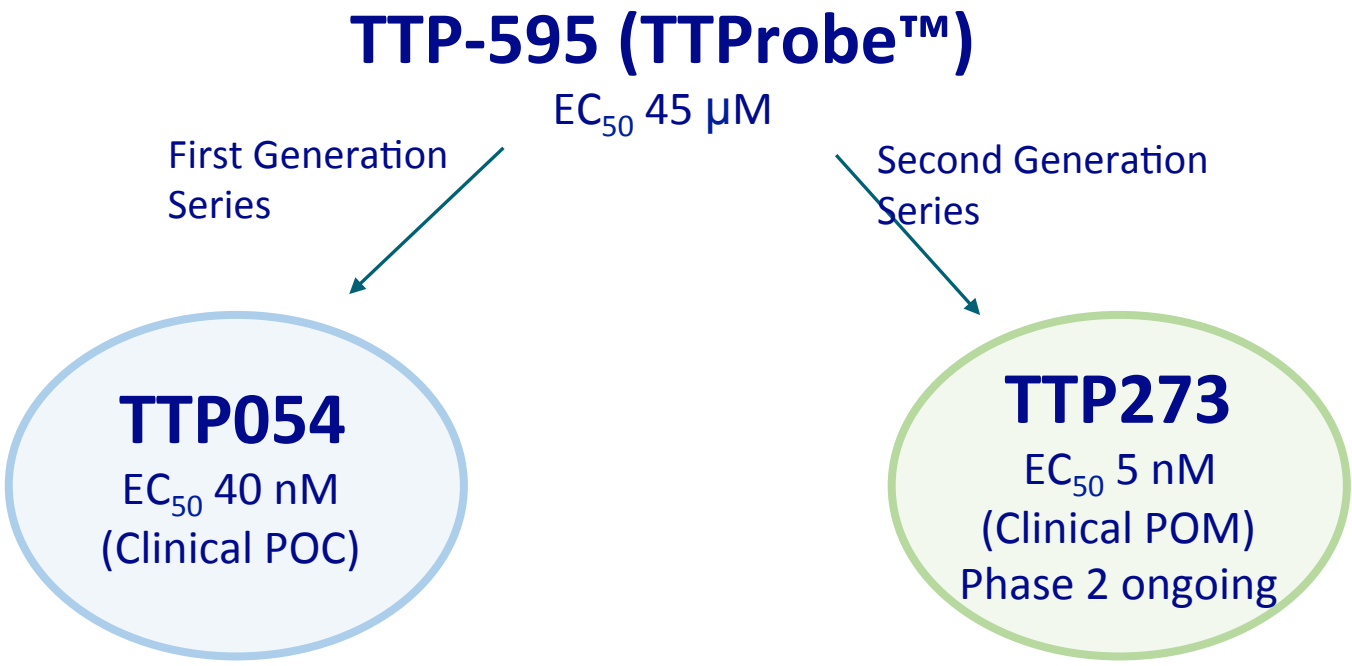
Oral Small Molecule GLP-1 Receptor (GLP-1R) Agonists for Type 2 Diabetes (T2DM) with Negligible Nausea and Vomiting

vTv Identified the First Oral Small Molecule (allosteric) Agonists of the GLP-1 Receptor in 2004



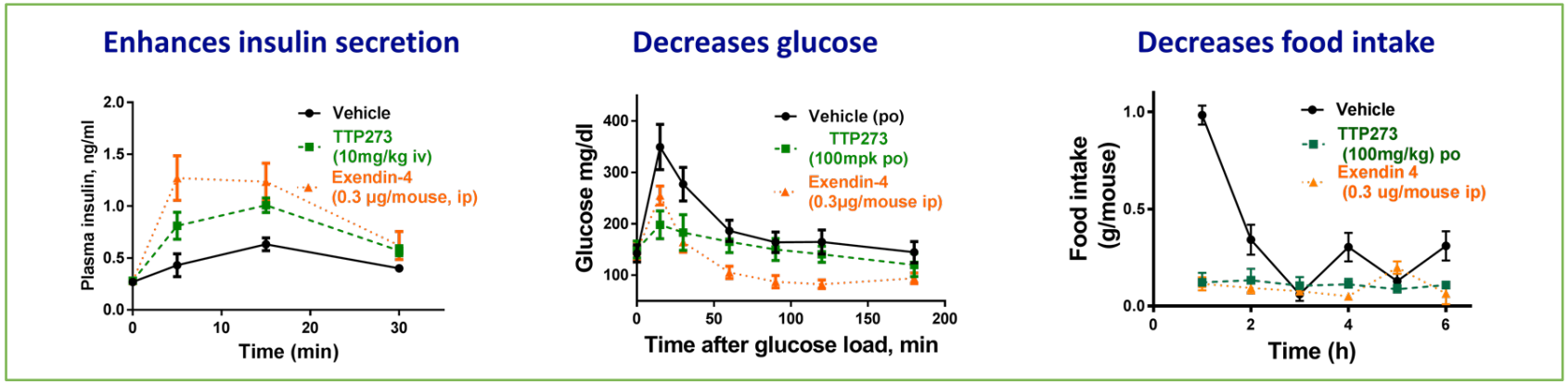
vTv's GLP-1R Agonists Program Genesis

- Coordinated utilization of data from cell EC50 assays, liver microsome stability, and pharmacokinetics led to potent lead series which resulted in 2 clinical candidates



vTv's Oral GLP-1R Agonists

- Novel, small, orally bioavailable molecules that activate the human GLP-1R
- Stand-alone allosteric GLP-1 receptor agonists
- Specific for the GLP-1 receptor
  - Functional bias for G-protein signaling
- Typical GLP1 Pharmacology in animals and humans
  - Enhances insulin secretion in response to glucose
  - Decreases glucose
  - Decreases food intake and body weight



(Rodent: EC_{50}34nM; 34% activation)

Oral Small Molecule GLP-1 Receptor (GLP-1R) Agonists with Negligible Nausea and Vomiting

TTP054-108 Phase 1b T2D on Metformin 4w

	Nausea	Vomiting
Placebo (n=21)	0	1
200QD (n=11)	1	1
400QD (n=9)	1	1
200BID (n=10)	0	0
400BID (n=4)	0	0

TTP054-201 Phase 2 T2D on Metformin 12w

	Nausea	Vomiting
Placebo (n=50)	3	2
200QD (n=27)	1	0
400QD (n=51)	0	0
800QD (n=56)	4	3

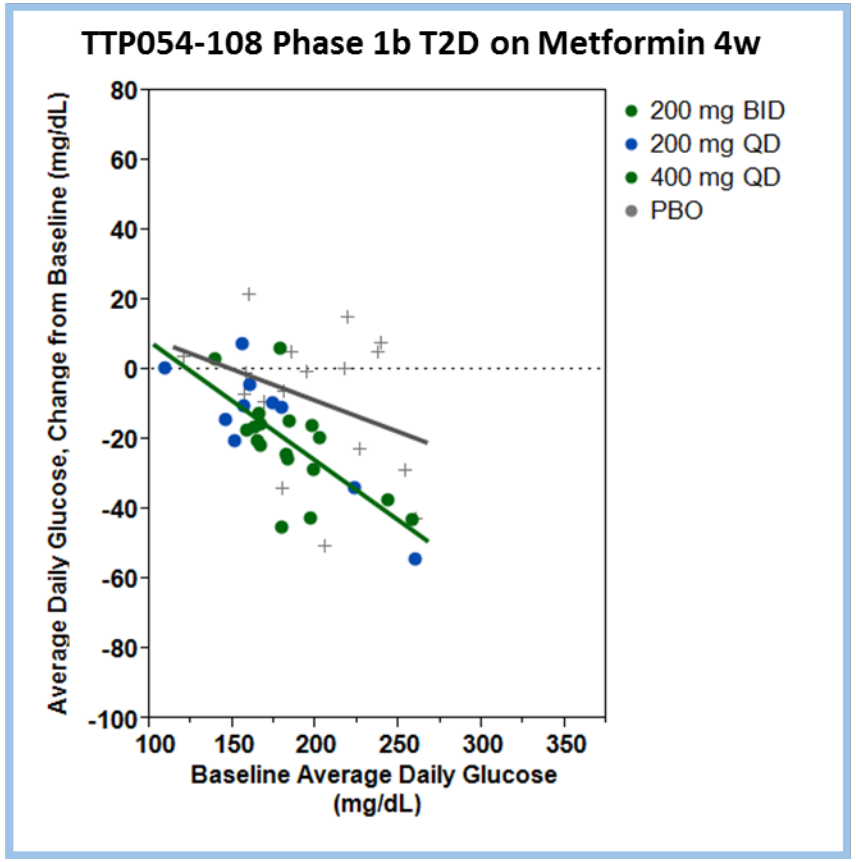
TTP273-102 Phase 1b T2D on Metformin 2w

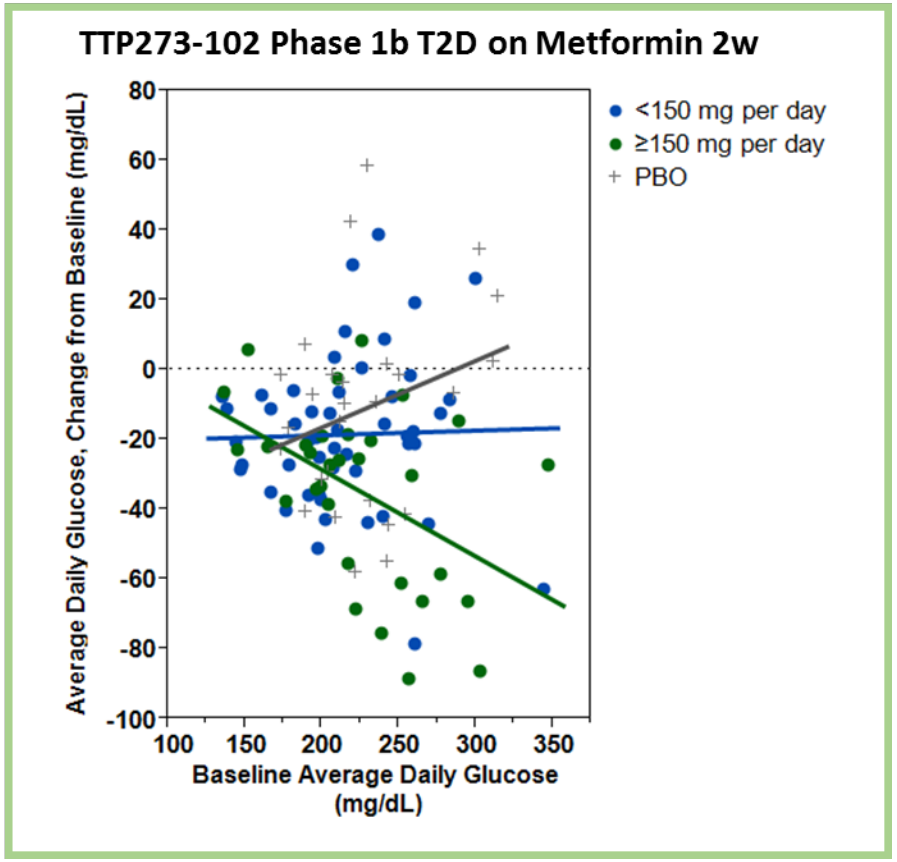
	Nausea	Vomiting
Placebo (n=29)	0	0
25QD (n=9)	1	0
50QD (n=9)	0	0
25BID (n=9)	0	0
75QD (n=8)	1	0
75QPM (n=7)	0	0
100QD (n=9)	0	1*
150QD (n=9)	0	0
75BID (n=8)	1	0
150BID (n=8)	1	0
450QD (n=7)	0	0

*unrelated to study drug

- TTP054 and TTP273 are safe and well tolerated at all doses tested
  - Negligible Nausea and Vomiting
  - No evidence of Hypoglycemia

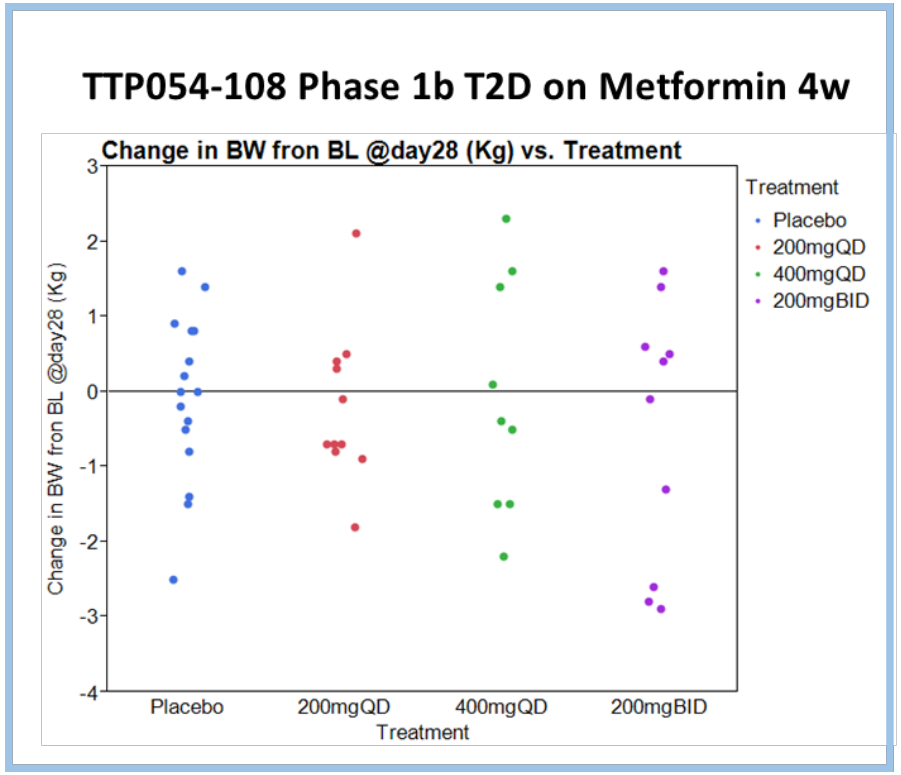
TTP273 Shows Greater Improvement in Glycemic Control than TTP054 in a Phase 1b Trial

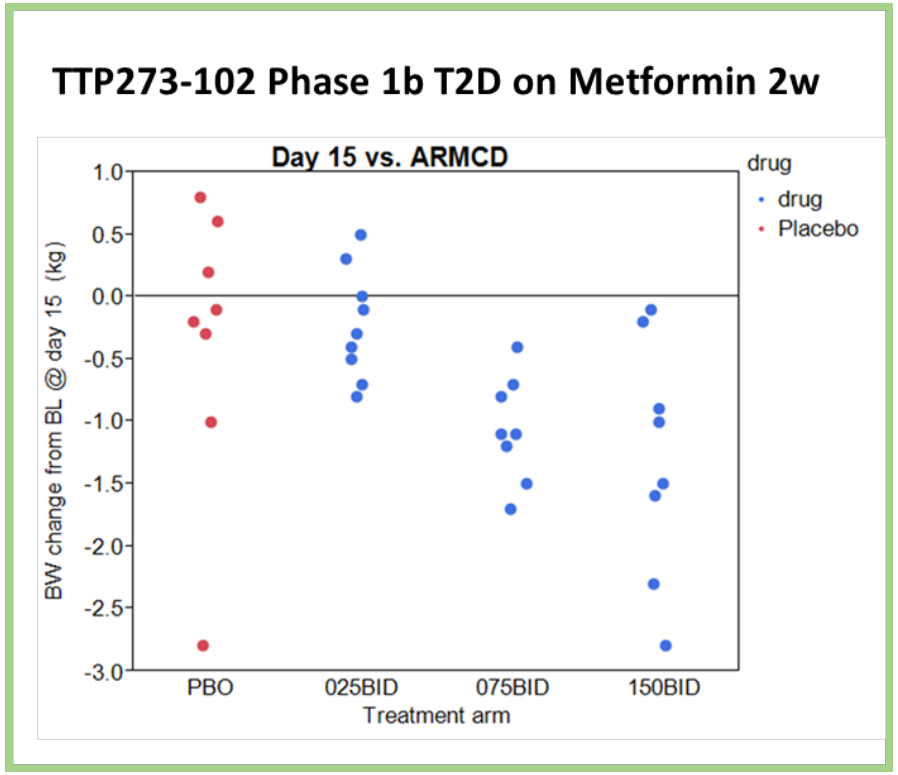




- TTP273 is more efficacious than TTP054 in phase 1b at the same doses despite shorter study duration

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





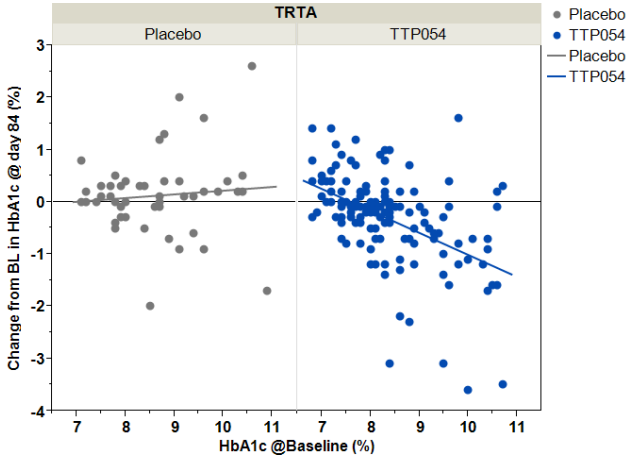
- No weight loss was seen in phase 1b TTP054 trial compared to placebo
- TTP273 phase 1b trial showed a trend in weight loss with the BID dose regiments despite shorter study duration and isocaloric diet
- In a 3 month phase 2 study with TTP054, significant body weight loss (1Kg) observed in the target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

Proof of Concept

Phase 2: TTP054-201

- 3 month, randomized, double-blind, placebo-controlled, parallel group trial in 184 type 2 diabetics on stable doses of metformin
- 7-11.5 % baseline HbA1c
- Arms: Placebo; TTP054 200mg, 400mg and 800mg QD
- Primary endpoint: Change from baseline in HbA1c at 3 months

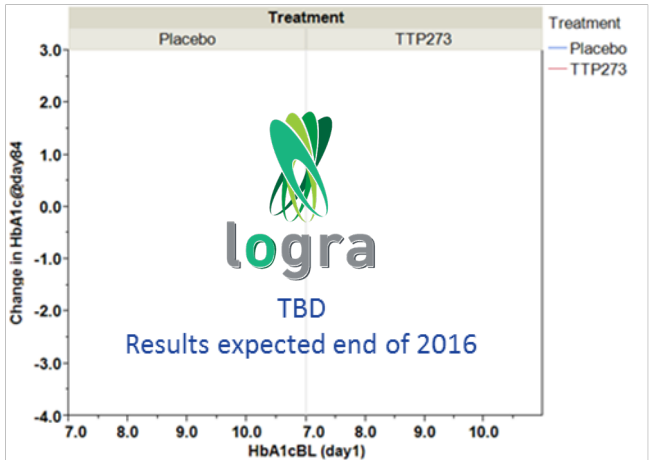
In a 3 month phase 2 study, TTP054 showed significant reduction in A1 c



Phase 2: TTP273-201

- 3 month, randomized, double-blind, placebo-controlled, parallel group trial in 156 type 2 diabetics on stable doses of metformin
- 7.5-10 % baseline HbA1c
- Arms: Placebo; TTP273 150mg once or twice daily
- Primary endpoint: Change from baseline in HbA1c at 3 months

TTP273 expected to be more efficacious based on better Ph1 results and *in vitro* potency



vTv Oral GLP1r Agonists: a Better Alternative to the GLP-1 Analogue therapy

- 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

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

Acknowledgements

- vTv Discovery and development teams
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