Population Pharmacokinetics (PK) and Pharmacodynamics (PD) of Pegozafermin, a Novel GlycoPEGylated FGF21, in a Phase 2 Study in Severe Hypertriglyceridemia

Leo Tseng[1], Kemal Balic[1], Teresa Parli[1], Hank Mansbach[1], Rada M. Savic[2]
[1]89bio, Inc., R&D, 655 Montgomery Street, 15th floor, San Francisco, CA, USA; [2]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco

PURPOSE

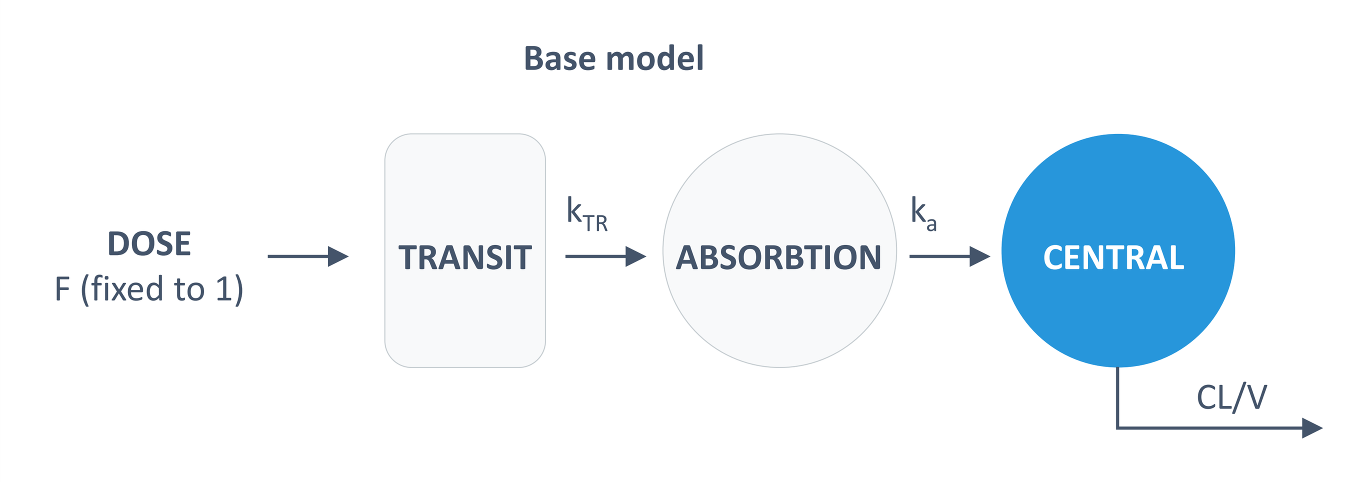
- Pegozafermin (PGZ) is a specifically engineered, long-acting glycoPEGylated analog of fibroblast growth factor 21 (FGF21) under development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and severe hypertriglyceridemia (SHTG).
- In a randomized Phase 2 trial (ENTRIGUE) in SHTG (triglycerides [TG] ≥ 500 mg/dL), PGZ-treated patients showed a significant reduction in median TG levels versus placebo (57.3% for pooled PGZ versus 11.9% for placebo, with placebo-corrected difference of −43.7%, 95% confidence interval (CI): −57.1%, −30.3%; P < 0.001).[1] Pharmacokinetics (PK) and pharmacodynamics (PD) data from this study were analyzed using a population modeling approach to support dose selection for Phase 3 studies. Weekly doses of 20 mg and 30 mg are currently being investigated in the Phase 3 (ENTRUST) SHTG Study (NCT05852431).

METHODS

- Subjects in this analysis included PGZ treatment groups at 9 mg (n=12), 18 mg (n=21), 27 mg (n=18) administered once-weekly (QW) and at 36 mg (n=16) administered once-every-two-weeks (Q2W).
- PK and PD (TG) data were characterized based on a population nonlinear mixed-effects modelling approach using NONMEM 7.4.2. A prior PGZ PK model was used as template and the model was then adjusted with new data.[2]
- POP PK/PD modeling included patients with dosing history/PK data + TG data (n= 67 IDs; 736 DVs). PK profile was first reconstructed for each patient using estimated PK individual parameters. A PKPD model for TG over time as a function of individual predicted plasma concentration *(Cp)* was then built.
- Simulation-based diagnostics, such as visual predictive checks (VPC), were used for model evaluation. Tested covariates included sex, age, weight, ethnicity, race and immunogenicity for PK and additional parameters (ALT, AST, HbA1c) added for PD. The effects of covariates were assessed using a method involving stepwise testing of linear and nonlinear relationships in a forward selection (*P* < 0.01) followed by a backward elimination (*P* < 0.05) procedure.

PK POP MODEL

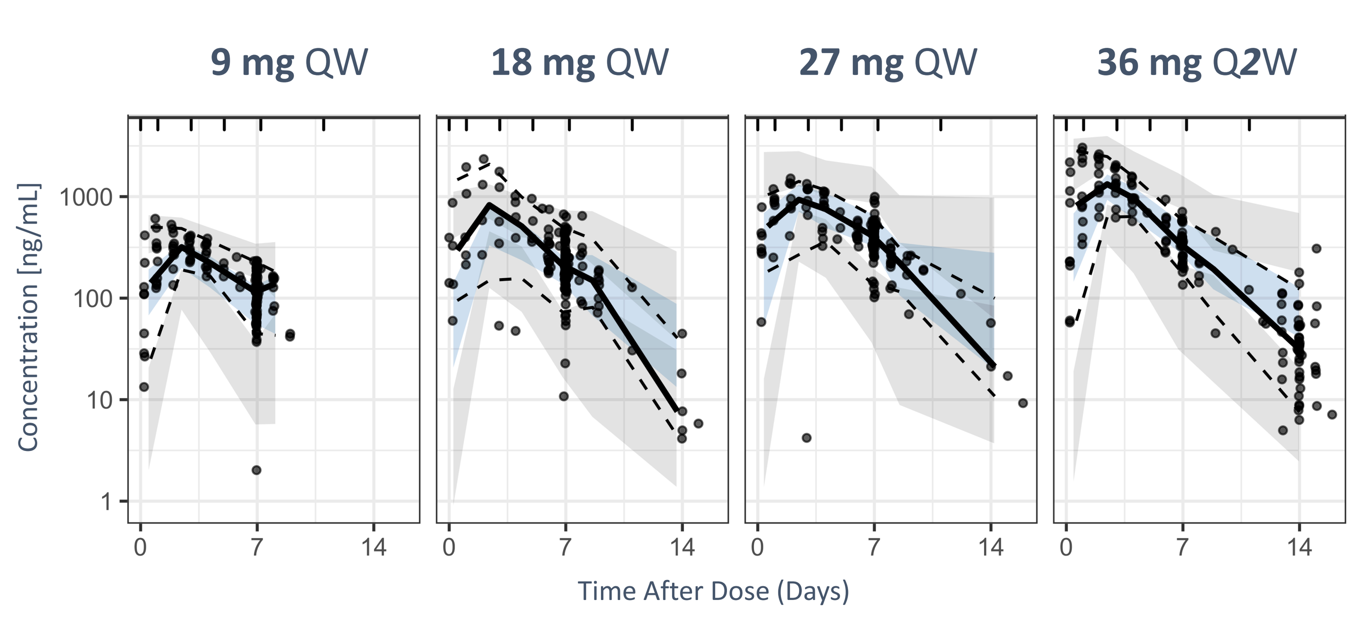
Pop PK Model Structure



Pop PK Model Parameters

Parameter (units)	Estimate (RSE%)	BSV (RSE%)
k_a (h^{-1})	0.0381 (16)	87% (19)
MTT [$1/k_{TR}$] (h)	5.68 (57)	169% (42)
F	1 *(fixed)*	-
V (L)	18.5 (23)	29% (25)
CL (L/h)	0.24 (11)	25% (16)
CL-WT	0.0062 (37)	-
Residual variability		
Additive error (ng/mL)	21.3 (40)	-
Proportional error (CV%)	0.294 (9)	-

Pop PK Profiles



Upper and lower gray areas represent 2.5th and 97.5th prediction interval with uncertainty, respectively. Symbols are observed data. Dashed lines are 2.5th and 97.5th observed percentiles of the data. Blue area represents predicted median with uncertainty.

Pop PK Summary Results

- Pharmacokinetic data were characterized based on a population nonlinear mixed-effects modelling approach using the software NONMEM 7.4.2.
- 1 compartment PK model with one additional transit absorption compartment adequately describes the data. The model was adjusted for flip-flop kinetics.
- IIV was estimated on ka, CL, V and MTT parameter.
- Covariate identification was done using the stepwise covariate modelling (SCM) through the PsN software. Significant covariate included in the final model was WT on CL.
  - 6% change in CL for each 10 kg change in body weight

POP PD

Longitudinal TG Model

$$E = \frac{Emax \times Cp(t)}{Cp(t) + EC50}$$

$$\frac{dTG}{dt} = Kin - Kout \times (1 + E) \times TG$$

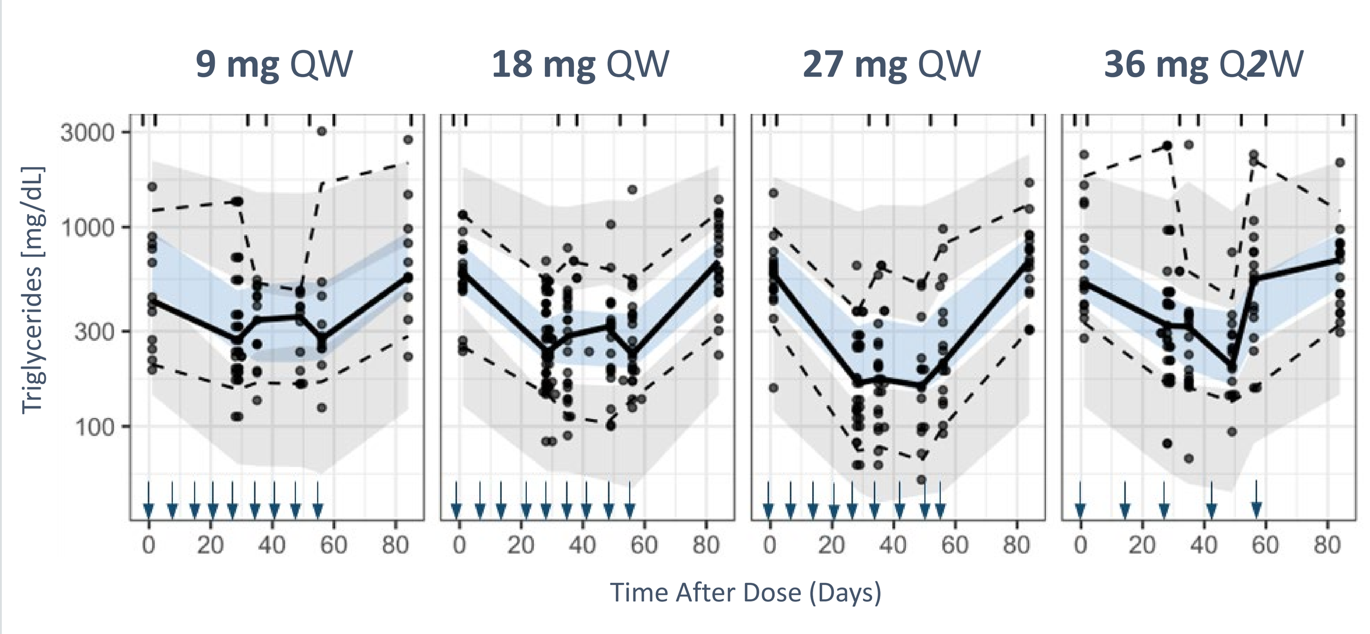
Longitudinal TG Model Parameters

Parameters	Estimates	IIV %
Baseline	727	42%
Kout (h^{-1})	0.004	-
Emax (%)	7.4	86%
EC50 (ng/mL)	1180	226%
w (%)	35%	-

*Kin=Base*Kout*
w: Proportional residual error

POP PD

Pop TG Profiles



Upper and lower gray areas represent 2.5th and 97.5th prediction interval with uncertainty, respectively. Symbols are observed data. Dashed lines are 2.5th and 97.5th observed percentiles of the data. Blue area represents predicted median with uncertainty. Pre-dose samples for the first dose were taken on Day 0. Arrows indicate dosing day.

Pop PD Summary

- An indirect response model was used to describe the longitudinal effect on TG. No significant covariates were identified.
- Pop PK/PD modeling data showed that 27 mg QW dose was the most efficacious as demonstrated by more pronounced reductions in TG as compared to the other doses.

CONCLUSIONS

- Population PK/PD modeling provides rationale to support dose selection for the recently initiated Phase 3 ENTRUST study in SHTG. PGZ 30 mg QW was selected to maximize efficacy and 20 mg QW was selected not only for its efficacious effect, but also to allow the sponsor to further explore the efficacy and tolerability profiles between two doses.
- Among covariates examined, only body weight can affect PGZ pharmacokinetics.

REFERENCES

[1]*Nat Med.* 2023; 29(7): 1782–1792.
[2]*Clin Pharmacol Ther* 2023 Dec;114(6):1323-1331.