Poster # I-36

Population Pharmacokinetics of Vadadustat, a Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor for Treatment of Anemia Associated With Chronic Kidney Disease

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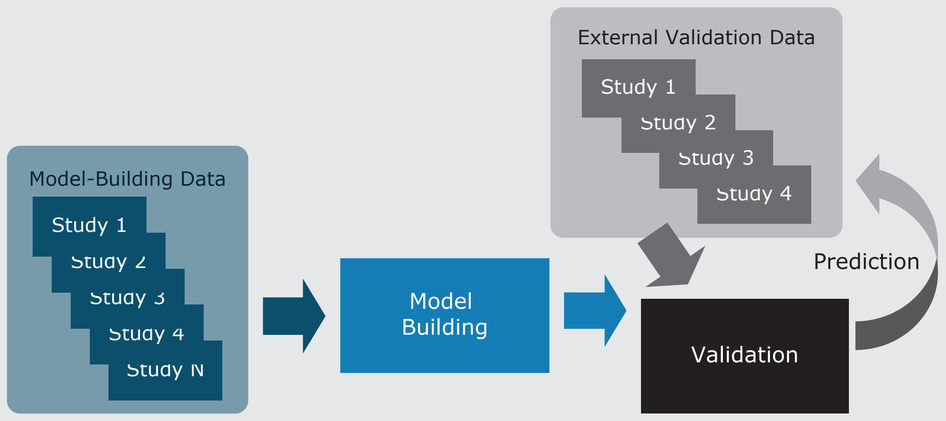
POPULATION PK IN THE OVERALL MODELING FRAMEWORK

Vadadustat

Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, a class of drugs that stabilize HIF and stimulates endogenous erythropoietin and red blood cell production. It is indicated for treatment of anemia associated with CKD and is an alternative to ESAs.

- Approved in EU and Japan; under review in US and other countries
- Vadadustat is given once daily to patients with CKD anemia
- Starting daily dose is 300 mg
  - Dose adjusted up or down as needed depending on Hb response (target Hb range: 10–11 g/dL in US; 10–12 g/dL in EU and RoW)
  - Minimum dose of 150 mg; maximum is 600 mg, with dose adjustments every 4 weeks in 150-mg increments

Figure 1. PK Modeling Took an External Validation Approach



- Model construction was based on a data subset comprised of selected phase 1, 2, and 3 studies
- Validation dataset included pivotal global phase 3 trials
- Covariate selection informed by prior knowledge and stepwise covariate selection
- Model construction and validation were carried out in NONMEM, 7.3 (Icon, Ellicot City, MD, US) with KIWI (Simulations Plus, Buffalo, NY, US) for post-processing

Project Objectives

- Support for subsequent exposure-response modeling
- Guidance for switching from ESAs to VADA
- Dose selection for potential modified dosing regimens (TIW and/or QD)
- Pediatric dosing recommendations
- Support for expanded labeling

MODEL BUILDING AND QUALIFICATION

Table 1. Data for Vadadustat Population PK Model

Study	N	Description	PK	PD
Model Building				
CI-0001	36	SAD in healthy volunteers (80–1200 mg)	Dense	–
CI-0002	24	MAD in healthy volunteers (500, 700, 900 mg) for 10 days	Dense	+
CI-0003	22	SAD in patients with Stage 3 and 4 NDD-CKD (500 mg)	Dense	–
CI-0005	68	42-day treatment, stage 3 and 4 NDD-CKD (240–630 mg)	Sparse	+
CI-0007	124	20-week study in patients with NDD-CKD (150, 300, 450 mg/d)	Sparse	+
CI-0009	12	Single-dose before and after hemodialysis in patients with DD-CKD	Dense	–
CI-0011	91	16-week study in patients with DD-CKD (300, 450 mg QD, and 450 mg TIW)	Sparse	+
CI-0020	36	10-day bridging study in healthy Japanese volunteers (150, 300, 600 mg)	Dense	–
CI-0021	37	Efficacy and safety in Japanese patients with NDD-CKD not treated with ESAs (150, 300, 600 mg)	Sparse	–
CI-0022	38	Efficacy and safety in Japanese patients with DD-CKD not treated with ESAs (150, 300, 600 mg)	Sparse	–
CI-0025	123	20-week optimized dosing with tiered ESA (higher QD and TIW) (300–600 mg initial dose)	Dense	+
CI-0034	37	10-day PK/PD study with higher doses (600–900 mg) in patients with DD-CKD	Dense	+
J-01	148	Phase 3 efficacy and safety in Japanese patients with NDD-CKD	Sparse	+
J-03	155	Phase 3 efficacy and safety in Japanese patients with DD-CKD	Sparse	+
Total	**951**			
		Model Verification		
CI-0014	874	Safety and efficacy study in patients with NDD-CKD not treated with ESAs	Sparse	+
CI-0015	869	Safety and efficacy study in patients with NDD-CKD treated with ESAs	Sparse	+
CI-0016	179	Safety and efficacy study in patients with DD-CKD not treated with ESAs	Sparse	+
CI-0017	1756	Safety and efficacy study in patients with DD-CKD treated with ESAs	Sparse	+
Total	**3678**			

N reflects patients with PK samples, not overall study enrollment.

Two-Compartment Model Fit Well

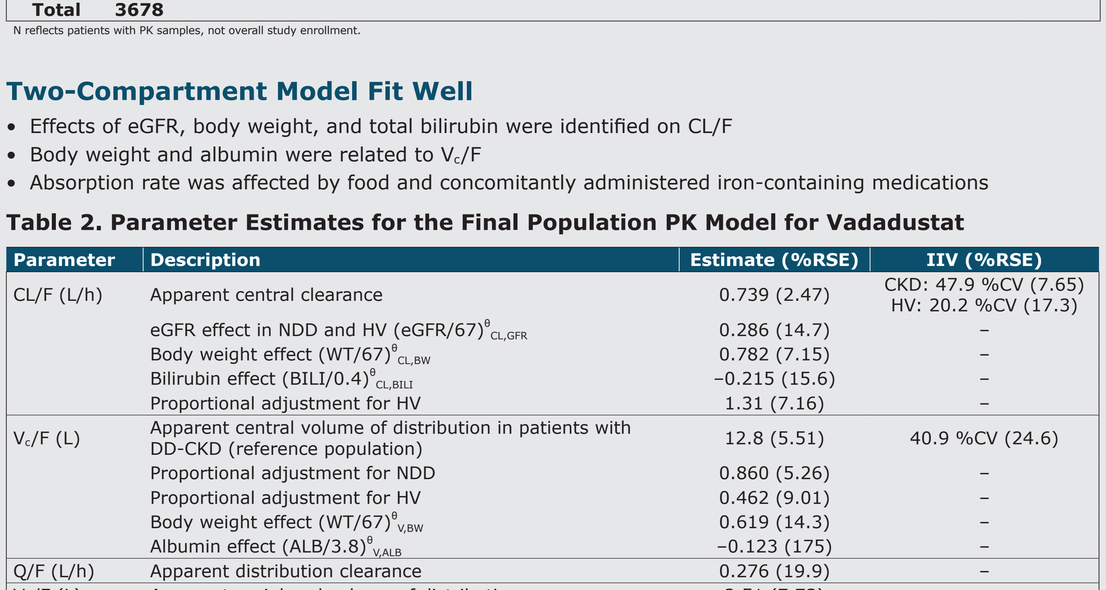
- Effects of eGFR, body weight, and total bilirubin were identified on CL/F
- Body weight and albumin were related to V_c/F
- Absorption rate was affected by food and concomitantly administered iron-containing medications

Table 2. Parameter Estimates for the Final Population PK Model for Vadadustat

Parameter	Description	Estimate (%RSE)	IIV (%RSE)
CL/F (L/h)	Apparent central clearance	0.739 (2.47)	CKD: 47.9 %CV (7.65) HV: 20.2 %CV (17.3)
	eGFR effect in NDD and HV $(eGFR/67)^{\theta_{CL,GFR}}$	0.286 (14.7)	–
	Body weight effect $(WT/67)^{\theta_{CL,BW}}$	0.782 (7.15)	–
	Bilirubin effect $(BILI/0.4)^{\theta_{CL,BILI}}$	–0.215 (15.6)	–
	Proportional adjustment for HV	1.31 (7.16)	–
V_c/F (L)	Apparent central volume of distribution in patients with DD-CKD (reference population)	12.8 (5.51)	40.9 %CV (24.6)
	Proportional adjustment for NDD	0.860 (5.26)	–
	Proportional adjustment for HV	0.462 (9.01)	–
	Body weight effect $(WT/67)^{\theta_{V,BW}}$	0.619 (14.3)	–
	Albumin effect $(ALB/3.8)^{\theta_{V,ALB}}$	–0.123 (175)	–
Q/F (L/h)	Apparent distribution clearance	0.276 (19.9)	–
V_p/F (L)	Apparent peripheral volume of distribution	2.51 (7.73)	–
Ka (1/h)	First-order absorption rate constant	0.678 (13.6)	–
	Fold-change due to tablet formulation	1.75 (11.2)	–
D1 (h)	Zero-order absorption duration	0.406 (15.1)	–
	Fold-change for effect of food on D1	6.23 (24.7)	–
F1	Fold-change for effect of iron-containing comedications	0.925 (3.19)	–

Model Described the Data Adequately

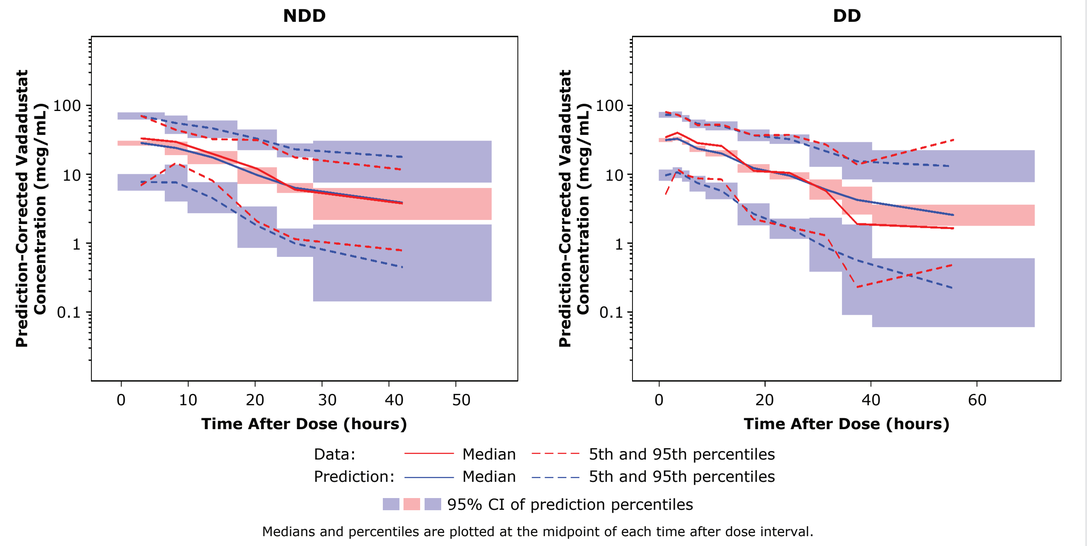
Figure 2. Goodness of Fit Plots for the Final Vadadustat Population PK Model



MODEL VERIFICATION

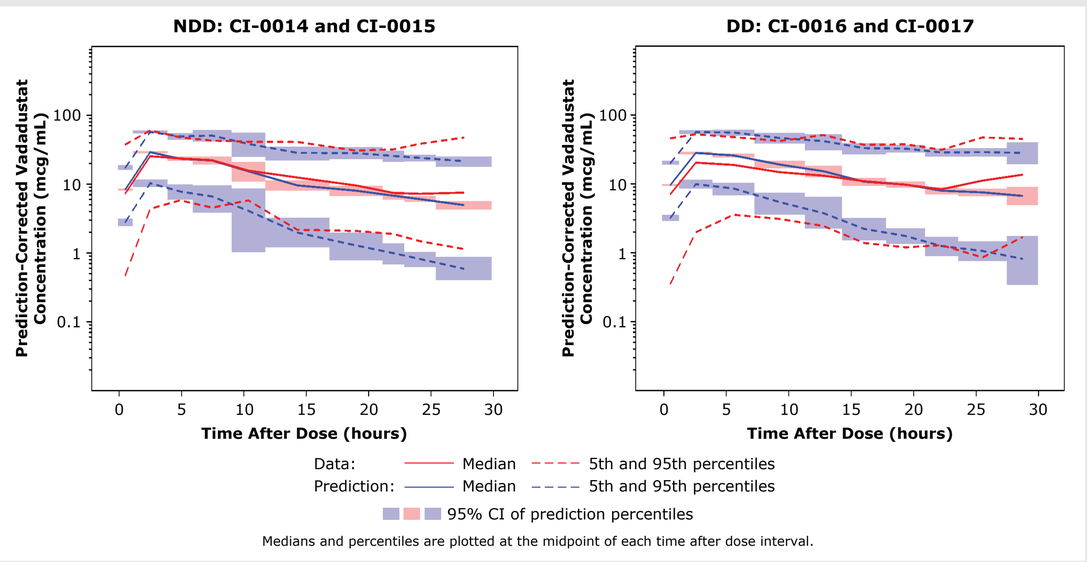
Model Predicted Exposure in the Model-Building Data Subset Well

Figure 3. Visual Predictive Check for the Model-Building Data Subset



Model Used to Predict Phase 3 Results and Generate Exposure Estimates for Each Patient

Figure 4. Visual Predictive Check in Data Subset Used for External Validation



- No additional fitting was done—the phase 1-2 model was used to predict the phase 3 results and to generate individualized exposure metrics (AUC)
- Imprecision around Time = 0 is likely caused by poor characterization of prior dosing time and lack of sampling around C_{max} (less information about absorption)

POPULATION PK MODELING CONCLUSIONS

- The PK model identified covariate effects on the following PK parameters:
  - Absorption rate: prandial state (fed vs fasted)
  - Bioavailability: oral, iron-containing comedications*
  - Clearance: status as patient with CKD, body weight, eGFR (NDD only), bilirubin
  - Central volume: body weight, albumin
- Only the effects of iron-containing comedications were sufficiently important to warrant label changes*
- Aggregated experience from the vadadustat development program showed that other effects on exposure can be overcome by dose adjustment
- Modeling results will be used to predict drug exposure in subsequent PK/PD modeling work

*Note: this work did not evaluate temporal relationship for administration of these medications; label specifies separation of dosing by >2 hours based on additional phase 1 data

Abbreviations: θ, estimated effect parameter; ALB, serum albumin; AUC, area under the curve; BILI, total bilirubin; BW, body weight; CKD, chronic kidney disease; CL/F, apparent central clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; D1, zero-order absorption duration; DD, dialysis-dependent; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; EU, European Union; F1, fold-change; GFR, glomerular filtration rate; h, hour; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor prolyl hydroxylase inhibitor; HV, healthy volunteers; IIV, inter-individual; ka, first-order absorption rate constant; MAD, multiple ascending dose; NDD, non–dialysis-dependent; PD, pharmacodynamic; PK, pharmacokinetic; Q/F, apparent distribution clearance; QD, once daily; RoW, rest of world; RSE, relative standard error; SAD, single ascending dose; TIW, 3 times per week; US, United States; VADA, vadadustat; V_c/F, apparent central volume of distribution; V_p/F, apparent peripheral volume of distribution; WT, body weight.

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Disclosures: JR, RH, and SB are current or former employees and may own stock and/or hold stock options of Simulations Plus, Cognigen Division, which was contracted by Akebia Therapeutics, Inc., to perform the analysis reported here. PG and KD are current employees of Akebia Therapeutics, Inc.

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