EASL CONGRESS
7-10 May 2025
Amsterdam, the Netherlands
Publication Number: SAT-430

Population Pharmacokinetic/Pharmacodynamic Modelling of Novel Thyroid Hormone Receptor beta Agonist ALG-055009 Reveals Statistically Significant Correlation between Exposure and Key Efficacy Endpoints

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BACKGROUND AND AIMS

- ALG-055009 is a novel next generation thyroid hormone receptor (THR)-beta agonist with beta selectivity and in vitro potency exceeding that of first-generation drugs. In the randomized, double-blind, placebo-controlled Phase 2a HERALD study, 12 weeks of once daily ALG-055009 treatment in subjects with presumed metabolic dysfunction-associated steatohepatitis (MASH) and F1-F3 fibrosis was well-tolerated and met the primary endpoint, demonstrating significant reductions in liver fat (Loomba et al. AASLD 2024).
- This analysis aimed to provide a robust characterization of the dose–exposure–response relationships and a better understanding of ALG-055009's efficacy—drawing on the totality of pharmacokinetic (PK) and efficacy data—to inform Phase 2b dose selection and justification.

METHODS

- ALG-055009 PK data were collected from two healthy volunteer studies (n= 91 subjects and 2233 samples) and one MASH patient study (n = 78 subjects and 726 samples), after single or multiple once-daily dosing of 0.1-4.0 mg ALG-055009.
- Nonlinear mixed effects modeling was used to characterize the population PK. Covariates tested on plasma ALG-055009 PK included weight, sex, ethnicity, food status, drug formulation.
- Individual exposure parameters were used to investigate the relationship with key efficacy parameters.
- Exposure-safety analysis was not conducted as there was no significant adverse events on the HERALD Study.
- The exposure-efficacy dataset consisted of 97 subjects receiving daily oral administration of ALG-055009 at 0.3 (n = 18), 0.5 (n = 21), 0.7 (n = 20) or 0.9 mg (n = 17) or placebo (n = 21).
- Non-linear regression and logistic regression were used to model the exposure-response relationships of percent liver fat change from baseline as measured by MRI-PDFF and proportion of responders of ≥30% relative liver fat reduction, respectively.
- Covariates tested on the exposure-response relationship included weight, sex, ethnicity (Hispanic/Latino vs others), PNPLA3 genotype (CC vs non-CC), baseline liver fat, concomitant medications (stable use of statin, GLP-1 receptor agonists)

Table 1: Baseline Characteristics Generally Balanced Across Dose Groups

Characteristic	0	0.3	0.5	0.7	0.9
N	21	18	21	20	17
Age (yr)	52 [25, 69]	54 [25, 72]	52 [22, 74]	51 [26, 69]	52 [24, 72]
Weight (kg)	114 [61, 146]	103 [72, 153]	116 [63, 174]	100 [69, 171]	112 [88, 150]
BMI (kg/m2)	40.9 [28.3, 57.9]	38.6 [26.3, 51.6]	37.5 [29.3, 57.9]	35.0 [26.1, 53.7]	41.0 [30.6, 54.2]
Male	1/21 (4.8%)	7/18 (38.9%)	14/21 (66.7%)	6/20 (30.0%)	9/17 (52.9%)
Statin	4/21 (19.0%)	10/18 (55.6%)	6/21 (28.6%)	8/20 (40.0%)	6/17 (35.3%)
GLP-1 RA	4/21 (19.0%)	3/18 (16.7%)	5/21 (23.8%)	5/20 (25.0%)	1/17 (5.9%)
Baseline Fat Fraction (%)	17.7 [10.2, 27.7]	16.4 [10.1, 32.4]	17.8 [10.3, 28.0]	19.0 [11.7, 31.0]	15.7 [10.6, 41.7]
Week 12 Fat Fraction Change (%)	7.2 [-32.4, 36.4]	-12.5 [-75.4, 40.1]	-16.9 [-48.9, 33.7]	-38.9 [-64.7, 34.4]	-36.4 [-62.1, 3.6]
Cavg (ng/mL)	0.0 [0.0, 0.0]	6.8 [4.4, 22.2]	11.9 [5.6, 39.2]	18.6 [7.2, 35.9]	22.5 [13.3, 60.7]
Daily AUC (ng/mL*hr)	0 [0, 0]	163 [107, 532]	286 [134, 941]	446 [172, 861]	539 [319, 1456]

Continuous variables shown as median [min, max]; Binary variables shown as count/total (%)

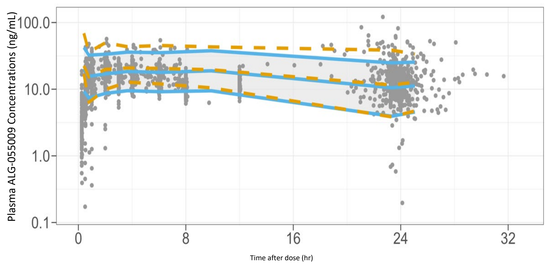
RESULTS

- Baseline characteristics of subjects in the exposure-response analysis dataset were generally balanced across treatment groups (**Table 1**).
- ALG-055009 population PK was best described by a one compartment model with first order absorption rate and absorption lag time; all parameters estimated with good precision (**Table 2, Figure 1**). Final covariate popPK model included weight on clearance and volume, formulation on bioavailability and absorption rate, and food status on absorption rate and lag time (**Table 2**).
- Greater change from baseline in liver fat at Week 12 ($p<0.001$, **Figure 2**) and proportion of subjects achieving more than 30% relative liver fat reduction ($p<0.001$, **Figure 3**) showed statistically significant association with increased ALG-055009 exposure. The significant exposure-response relationship in both efficacy endpoints supports a causal treatment effect of ALG-055009. ALG-055009 steady-state area under the plasma concentration-time curve (AUC) between 500-1500 ng.h/mL appeared to have optimal efficacy profile (**Figures 2 and 3**).
- All covariates tested, including demographics, weight, baseline liver fat, PNPLA3 genotype and relevant concomitant medication use (statins or GLP-1 receptor agonists), did not have statistically significant effects on the exposure-efficacy relationship (**Table 3**).
- A simulation study of PK and key efficacy endpoints in a virtual population of 1000 subjects with covariate distributions from the HERALD study provided rank order of efficacy for dosing regimens with and without dose cut-offs at selected body weights (**Table 4**).

Table 2: Population PK Model Structure and Estimated Parameters in Final Model

Model Parameter	Estimate	SE	RSE	CV (%)
Apparent Clearance (CL, L/hr)	1.45	0.1	4.3	--
Apparent Central Volume (V, L)	70.24	3.0	4.3	--
Absorption Rate (KA, /hr)	2.6	0.3	10.0	--
Absorption Lag Time (ALAG, hr)	0.2	0.0	1.4	--
WT on Clearance	0.4	0.1	29.3	--
WT on Volume	1.2	0.1	11.3	--
GELCAP on F	-0.1	0.0	-48.1	--
GELCAP on KA	-1.1	0.1	-4.8	--
FOOD on KA	-0.6	0.0	-7.1	--
FOOD on ALAG	1.4	0.0	1.7	--
Variance CL	0.11	0.01	11	33
Variance V	0.04	0.01	25	20
Variance KA	0.47	0.09	19	69
Residual Variance	0.085	0.001	1	29

Figure 1: Population PK Model Visual Predictive Check



Note: Blue=5th, 50th, 95th percentile predictions of the model. Gold = 5th, 50th, 95th percentiles of data. Shaded region covers 5th to 95th percentile prediction range.

Figure 2: Exposure-Response Relationship for Relative Liver Fat Reduction

Figure 3: Exposure-Response Relationship for Proportion of responders of ≥ 30% relative liver fat reduction

Points (top) indicate whether response occurred for each participant, and the exposure level. Points (middle) are response rates at each exposure group (placebo and 4 quartiles of exposure). Vertical bars are 90% confidence intervals. Blue line is linear logistic regression fit. Shaded region is 90% confidence intervals of the fit. Numbers indicate participants with the response and total N per data point. Bars (bottom) indicate range of exposures per dose group (median, 5th to 95th %ile)

Table 3: Covariate Analysis Results for Exposure-Response Model of Relative Liver Fat Reduction

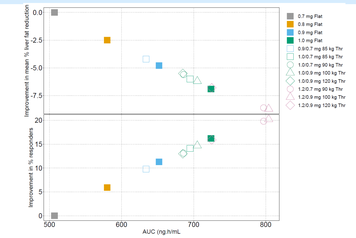
Model	AIC	p-value
Emax model, no covariates	2.16	
Baseline Fat Fraction on E0	3.04	0.302
Baseline Fat Fraction on Emax	1.71	0.126
Baseline Fat Fraction on EC50	3.13	0.322
Weight on E0, Change from Median	2.33	0.186
Weight on Emax, Change from Median	1.82	0.135
Weight on EC50, Change from Median	3.13	0.322
Statin on E0	1.77	0.131
Statin on Emax	4	0.69
Statin on EC50	2.66	0.232
GLP on E0	3.32	0.369
GLP on Emax	3.44	0.407
GLP on EC50	3.5	0.427
Ethnicity on E0, Other vs. Hispanic or Latino	1.23	0.094
Ethnicity on Emax, Other vs. Hispanic or Latino	1.65	0.121
Ethnicity on EC50, Other vs. Hispanic or Latino	1.5	0.111
Genotype on E0, CC vs. non-CC	1.23	0.095
Genotype on Emax, CC vs. non-CC	1.96	0.147
Genotype on EC50, CC vs. non-CC	1.57	0.116

AIC (Akaike Information Criterion)

Table 4: Simulations of efficacy endpoints for different dosing regimens

Description	Mean % liver fat reduction	Proportion of ≥30% Responder (%)
0.7 mg Flat	-26.4	54.3
0.8 mg Flat	-28.9	60.2
0.9/0.7 mg 85 kg Thr	-30.6	64.1
0.9 mg Flat	-31.2	65.6
1.0/0.9 mg 120 kg Thr	-31.9	67.3
1.0/0.7 mg 90 kg Thr	-32	67.4
1.0/0.7 mg 85 kg Thr	-32.4	68.4
1.0/0.9 mg 100 kg Thr	-32.6	69
1.2/0.9 mg 120 kg Thr	-33.2	70.2
1.0 mg Flat	-33.3	70.5
1.2/0.7 mg 90 kg Thr	-35	74.1
1.2/0.9 mg 100 kg Thr	-35.1	74.5

Description note: first number denotes dose level for subjects with body weight ≥ threshold (Thr) and second number denotes dose level for subjects with body weight <85 kg



Note: Improvement in mean % liver fat reduction and % responders (≥30% MRI-PDFF reduction) compared against the base case of 0.7 mg flat dosing

CONCLUSIONS

Population PK and exposure-response models were developed for ALG-055009. There was a statistically significant correlation between exposure and key efficacy endpoints of change from baseline in liver fat and proportion of responders of ≥30% relative liver fat reduction. These models will be used to provide guidance for dose selection for a Phase 2b study in patients with MASH.

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