R073

Donidalorsen Exposure-Response Analysis: Hereditary Angioedema Attack Rate Versus Plasma Prekallikrein Concentration Relationship

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BACKGROUND

- Donidalorsen, an investigational $GalNAc_3$–conjugated antisense oligonucleotide, specifically targets and degrades prekallikrein mRNA in hepatocytes to reduce plasma prekallikrein (PKK)[1,2]
  - *Reduced plasma PKK concentration stabilizes the dysregulated kallikrein-kinin system in patients with HAE, leading to decreased HAE attacks and improved disease control[3]*
  - *80 mg donidalorsen administered subcutaneously every 4 weeks (Q4W) or every 8 weeks (Q8W) has been evaluated in the double-blind placebo-controlled Phase 2 and Phase 3 studies[3,4]*
  - *In the Phase 2 open label extension study, a switch in dosing regimen from 80 mg Q4W to Q8W was allowed if patients were HAE attack-free for 12 or more weeks after entering the OLE[5]*
- Here we characterize the quantitative relationship between HAE attack rate and plasma PKK concentrations following 80 mg donidalorsen. A quantitative model was used to evaluate Q4W and Q8W regimens tested in the donidalorsen clinical trials

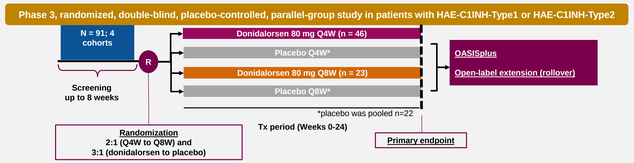
METHODOLOGY

- The exposure-response (E-R) analysis was performed using data from the pivotal Phase 3 OASIS-HAE study (NCT05139810) in patients with HAE, and the data from the Phase 2 Study (NCT04030598) in patients with HAE were used for external validation of the final model
  - *As an independent variable in the model, individual-predicted systemic PKK concentrations expressed as the every 4-weeks average concentration for the per 4 weeks attack rate analysis*
  - *PKK concentration metrics were derived for each donidalorsen treated participant based on the population PK/PKK Model developed using the donidalorsen clinical trials*
  - *As HAE attacks are counted in the datasets, the per 4 weeks attack rate endpoint for individual patients was evaluated using Poisson regression techniques*
  - *The following covariates were assessed in the model: body weight, age, sex, baseline PKK concentration, baseline 4-week HAE attack rate, and anti-drug antibodies (ADA) status as defined by presence of treatment-emergent ADAs*
- Simulations were conducted with the developed HAE attack rate vs. PKK concentration model to support the dosing regimen (Q4W or Q8W) evaluated in the clinical studies, including the option to switch to Q8W regimen for patients who are attack-free for more than 3 months on Q4W regimen

RESULTS

- A total of 84 participants from the Phase 3 OASIS-HAE study (41 participants randomized to 80 mg Q4W, 21 participants to 80 mg Q8W and 22 to placebo) were included in the analysis. For model external validation, 11 participants randomized to Q4W and 6 to placebo in the Phase 2 study were included

Figure 1: Phase 3 OASIS-HAE Study Design

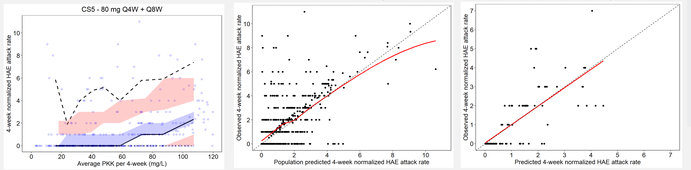


Abbreviations: HAE=hereditary angioedema; Q4W=every 4 weeks; Q8W=every 8 weeks; AECT=Angioedema Control Test; AE-QoL= Angioedema Quality of Life Questionnaire

Table 1: Summary of Select Baseline Covariates of the Patients from Phase 3 OASIS-HAE study Included in the Modeling Analysis

	80 mg Q4W (N=41)	80 mg Q8W (N=21)	Placebo (N=22)	Overall (N=84)
Baseline per 4-week normalized HAE attack rate				
Mean (SD)	3.62 (2.18)	3.17 (2.14)	2.90 (1.66)	3.32 (2.04)
Median (CV%)	3.29 (60.1)	2.71 (67.4)	2.50 (57.2)	2.85 (61.6)
[Min, max]	[0.509, 10.0]	[0.683, 8.40]	[1.02, 8.09]	[0.509, 10.0]
Predicted PKK (mg/L) at baseline				
Mean (SD)	126 (31.8)	144 (41.1)	118 (27.0)	128 (34.2)
Median (CV%)	116 (25.3)	134 (28.6)	111 (22.9)	122 (26.7)
[Min, max]	[90.6, 276]	[86.2, 248]	[76.5, 162]	[76.5, 276]

Figure 2: Model Goodness-of-fit for Phase 3 Study OASIS-HAE and Phase 2 Study

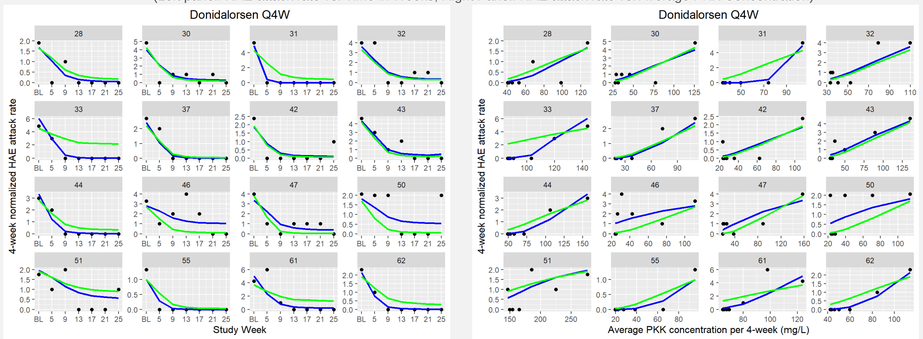


Left panel: Model predictions were rounded to the nearest integer to mimic the nature of the observed data before calculating summary statistics presented in the Visual Predicted Checks. Open blue circles represent the individual data points. The solid black line is the median observed every 4-weeks normalized HAE attack rate. The dotted and dashed black lines are the observed 5th and 95th percentiles, respectively. The blue area represents the 95% CI of the simulated median, and the red areas are the 95% CI of the simulated 5th and 95th percentiles, respectively, based on 1000 replicates. scatterplot smoothing; **Middle and Right panels**: Black dots are individual data points. The black dashed line is the identity line. The red line is the LOESS regression line

RESULTS: HAE ATTACK RATE VS. PLASMA PKK CONCENTRATION RELATIONSHIP

- The final model well described the time course of HAE attack rate as a function of average PKK concentrations modeled as a sigmoidal relationship and baseline attack rate as a covariate
- Age, body weight, sex or treatment-emergent anti-drug antibody status were not identified as significant covariates for the HAE attack rate model parameters
- The baseline-normalized HAE attack rate over time (every 4-weeks) following donidalorsen was assessed to be independent of baseline attack rate or baseline PKK concentrations suggesting a generally comparable and clinically meaningful response across the patient population
- The average PKK concentration that leads to 90% reduction from the maximum attack rate was estimated to be 47.1 mg/L, corresponding to approximately a 62% reduction in per 4-weeks average PKK concentrations from baseline in PKK

Figure 3: Representative Individual Plots of per 4-week Normalized HAE Attack Rate Versus Study Week in Phase 3 OASIS-HAE. (Left panel: HAE attack rate vs. Time in Weeks; Right Panel: HAE attack rate vs. Average PKK Concentration)



Observed per 4-week normalized HAE attack rates are represented by the black dots. The green and blue solid lines represent the population-predicted (PRED) and individual-predicted (IPRED) per 4-week Normalized HAE attack rate.
Abbreviations: BL=baseline; HAE=hereditary angioedema; Q4W=every 4 weeks;

Table 2: Parameter Estimates of the Final per 4-week normalized HAE attack rate Model

Parameter	Estimate (RSE%)	Bootstrap Statistics*		Shrinkage
		Median	95% CI	
E_{max}	4.50 (9.6%)	4.54	[3.31, 5.78]	-
EC_{50} (mg/L)	110 (0.8%)	111	[85.7, 124]	-
Hill	2.60 (16%)	2.61	[1.84, 4.20]	-
b_{HAE}	1.03 (7.9%)	1.03	[0.85, 1.19]	-
b_{PKK}	0.13 (14.3%)	0.13	[0.04, 0.18]	-
Interindividual Variability				
IIV on E_{max} (CV%)	27.9 (28.8%)	26.5	[7.0, 42.2]	42.7
IIV on Hill (CV%)	131 (14.6%)	129	[82.2, 255]	27.1
Secondary Parameters				
EC_{10}	47.1	-	-	-
EC_1	18.7	-	-	-

Abbreviations: b_{HAE}=coefficient for effect of baseline per 4-week normalized HAE attack rate; b_{PKK}=coefficient for the effect of baseline PKK concentration; CI=confidence interval; CV%=percent coefficient of variation; EC_{50}=effective $PKK_{avg,4w}$ associated with 50% reduction from the maximum attack rate; EC_{10}=effective $PKK_{avg,4w}$ associated with 90% reduction from the maximum attack rate; EC_1=effective $PKK_{avg,4w}$ associated with 99% reduction from the maximum attack rate; E_{max}=per-4-week HAE attack rate at infinite PKK concentration; IIV=interindividual variability; PKK=prekallikrein; RSE%=percent relative standard error

Model equation of HAE attack rate vs. PKK concentration relationship:

$$4\ weekly\ HAE\ attack\ rate = \left(\frac{BLRATE}{3}\right)^{b_{HAE}} \cdot E_{max} \cdot \left(\frac{PKK^{Hill}}{\left(\frac{BLPKK}{122}\right)^{b_{PKK}} \cdot EC_{50}^{Hill} + PKK^{Hill}}\right)$$

DOSE-REGIMEN SIMULATIONS

- Model simulated attack rates (per 4 weeks) were nearly identical for 80 mg once monthly vs. every 4-weeks regimen (Fig. 4):
  - *Mean of 0.42 for once monthly versus 0.39 for every 4-weeks, corresponding to mean reduction of 82.9% versus 84.1% and median reduction of 94.6% versus 95.6%, indicating that these 2 regimens were similar with regard to efficacy*
- Predicted response remained robust and comparable when switching patients with no attacks after 3 months of monthly dosing to every 2 months (Fig.5):
  - *If switched at 3 months for patients who remain attack-free, the median attack rate (per 4 weeks) was estimated to be 0.07 (first month of the 2 months dosing interval) and 0.12 (second month of the 2 months dosing interval) at steady-state for every 2 months dosing regimen. These values corresponded to a median reduction of 97.4% and 95.5%, and mean reduction of 94% and 91.3% at steady-state from baseline for the first and second month, respectively*

Figure 4: Simulated Median and 80% PI of per 4-week Normalized HAE Attack Rate Profiles for the 80 mg Q4W and Q1M Dosing Regimens

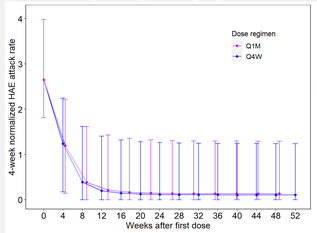
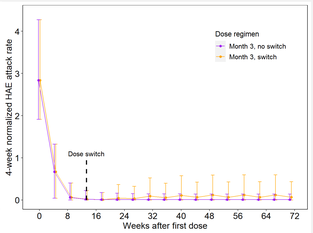


Figure 5: Simulated Median and 80% PI of per 4-week Normalized HAE Attack Rate Profiles for Switching at 3 Months



The dots represent the median, and the error bars represent the 10th and 90th percentiles. A typical patient is defined as having a body weight of 80 kg, a baseline per 4-week normalized HAE attack rate of 3.0, and a baseline PKK concentration of 122 mg/L. Abbreviations: HAE=hereditary angioedema; PI=prediction interval; PKK=prekallikrein; Q1M=every month; Q4W=every 4 weeks

CONCLUSIONS

- A quantitative relationship between HAE attack rate and PKK plasma concentrations was established based on the data from the pivotal Phase 3 Study OASIS-HAE
- Overall, the dosing regimen of donidalorsen tested in the clinical trials is supported by the favorable clinical profiles in patients with HAE (Phase 3 Study OASIS-HAE and Phase 2 study) and the exposure-response analysis presented here

DISCLOSURES

PS, XG, JD, LB, and KBN are employees of Ionis.

HW and HJK are employees of Certara.

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