PI-132

Dose-Response and Exposure-Response Modeling of Alpha-1 Proteinase Inhibitor (A_1-PI) in Patients with A_1-PI Deficiency Based on RAPID and RAPID Extension Trials

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Background/Aim:

- Alpha-1 antitrypsin deficiency (AATD) is a rarely diagnosed genetic disorder estimated to affect 1–4% of COPD patients[1]
- AATD is characterized by decreased circulating levels of alpha-1 proteinase inhibitor (A_1-PI), which regulates the activity of neutrophil elastase (NE)
- In A_1-PI deficient patients, NE degrades lung tissue and this can lead to clinical emphysema
- The **R**andomized, placebo-controlled trial of augmentation therapy in **A**lpha-1 **P**roteinase **I**nhibitor **D**eficiency (RAPID; NCT00261833) compared the safety and efficacy of weekly administration of 60 mg/kg IV doses of purified human A_1-PI with placebo[2]
- The RAPID Extension trial (NCT00670007) was a two-year open-label extension of the RAPID trial[2]
- Using data from the RAPID and RAPID Extension trials, this analysis aimed to characterize the relationships between dose and A_1-PI concentration (dose-exposure), and between A_1-PI concentration and lung density decline (exposure-response)
- The impact of covariates on dose-exposure and on exposure-response, were also evaluated

Methods:

- Median (post-baseline) trough A_1-PI concentrations were obtained from patients enrolled in RAPID and RAPID Extension
- The dose-exposure analysis included all randomized patients with at least one post-baseline recorded A_1-PI concentration (Table 1)

Table 1: Sample sizes for analysis data sets

Analysis Set	Enrolled in RAPID		Enrolled in RAPID & RAPID Extension	
	Placebo	Active	Placebo	Active
All available data	87	93	64	76
Dose-exposure analysis data set	81	89	64	74
Exposure-response data set	78	86	61	73

- Dose-exposure was assessed using time-aggregated A_1-PI concentration modeled as a function of average dose
  - Two distinct aggregate dose measures were computed for each subject, corresponding to the two phases of the study
- Exposure-response analysis included all subjects in the dose-exposure model who had at least one CT-lung density measurement (Table 1)
  - Exposure-response was assessed using a disease progression model with the ability to accommodate the two-phase structure of combined RAPID/RAPID Extension trials and utilized CT lung density measurements (TLC) as the clinical endpoint
- The effects of the following baseline covariates were assessed in each model
  - Dose-exposure: weight (kg), A_1-PI. Final model:

$$C_{ij} = (\theta_1 \exp(\eta_{1,i})(C_i^{base}/5.5)^{\theta_7} + \theta_2(WT_i/77)^{\theta_3}(C_i^{\text{base}}/5.5)^{\theta_4} D_{ij})\exp(\epsilon_{ij})$$

  - Exposure-response: lung density (TLC), A_1-PI, FEV1. Final model:

$$DP_{i1} = (\theta_2 + \eta_{2,i}) + (\theta_3 + \eta_{3,i})C_{i1}^* + \theta_4 (FEV1_i - FEV1_{median})$$

$$DP_{i2} = (\theta_2 + \eta_{2,i}) + (\theta_3 + \eta_{3,i})C_{i2}^* + \theta_4 (FEV1_i - FEV1_{median}) + (\theta_5 + \eta_{5,i})$$

Results:

Dose-exposure analysis

- Final parameters for the dose-exposure model are shown in Table 2, including the effect of covariates - baseline weight and baseline A_1-PI
  - Of particular interest is the baseline weight effect on slope ($\theta_3 = 0.8507$), which is consistent with allometric scaling of clearance according to Kleiber's Law

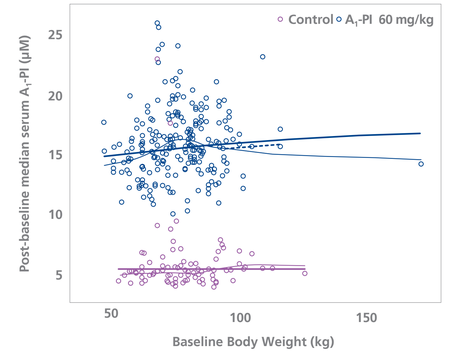
Table 2: Parameters for final dose-exposure model

Par.	Description	Estimate	95% LB	95% UB
θ_1	Log A_1-PI exposure for placebo (μM)	5.4180	5.2273	5.6153
θ_2	A_1-PI slope w.r.t. dose rate (μM/(mg/Day))	0.0152	0.0146	0.0158
θ_3	Baseline weight effect on slope	-0.8507	-1.0198	-0.6817
θ_4	Endogenous A_1-PI effect on slope	-0.1186	-0.2745	-0.0372
θ_7	Endogenous A_1-PI effect (independent of dose)	0.7293	0.6195	0.8391
ω_1	Inter-individual SD for log A_1-PI exposure for placebo	0.0662	0.0155	0.2831
σ	Residual SD	0.1480	0.1308	0.1675

LB = lower bounds; UB = upper bounds; w.r.t = with regard to

- The dose-exposure model was used to predict A_1-PI concentrations as a function of covariate settings
  - Baseline weight and A_1-PI had a small effect on post-baseline A_1-PI levels
- Weight-based dosing at 60 mg/kg/week maintained steady-state concentrations above the theoretical protective threshold of 11 μM for ≥98% of treated patients (Figure 1)
  - Two control patients with post-baseline steady-state A_1-PI levels above the protective threshold (11 μM) were of the PI*MZ genotype

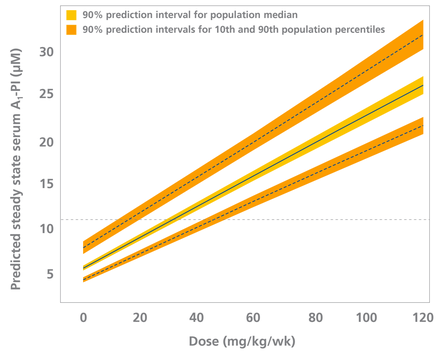
Figure 1: Predicted A_1-PI exposure levels as a function of body weight



Thick solid lines = model predictions; thin solid lines = a LOESS smooth; Dashed line = a LOESS smooth with outlying (kg > 150) individual removed

- The dose-exposure model predicted a linear relationship between dose and steady-state serum A_1-PI (Figure 2)
  - The model predicted continuously increasing exposure with increasing dose, with no evidence of a plateau

Figure 2: Predicted distribution of exposure levels as a function of dose, based on bootstrap population simulations



Exposure-response analysis

- Final parameters for the exposure-response model are shown in Table 3
  - The model includes the covariates weight and baseline A_1-PI, and was expanded to incorporate the effect of baseline FEV1 on 'natural' decline

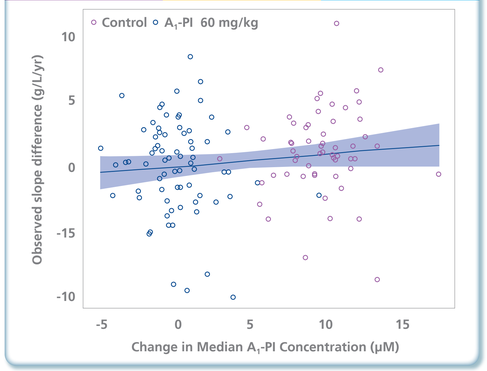
Table 3: Parameters for final exposure-response model

Par.	Description	Estimate	95% LB	95% UB
θ_1	Pre-treatment lung density (g/L)	46.8898	44.5295	49.2501
θ_2	Lung density decline rate for Placebo (g/L/yr)	-2.1789	-2.6142	-1.7436
θ_3	A_1-PI exposure effect on lung density decline rate ((g/L/yr)/(μM))	0.0625	0.0147	0.1103
θ_4	Baseline FEV1 effect on decline rate ((g/L/yr)/L)	0.5600	0.1249	0.9952
θ_5	Change in decline rate in RAPID Extension phase (g/L/yr)	0.2025	-0.970	0.7020
ω_1	IIV SD for pre-treatment lung density	15.2815	13.6944	17.0525
ω_2	IIV SD for lung density decline rate	1.3176	0.9019	1.9250
ω_3	IIV SD for concentration effect on decline rate	0.0903	0.0276	0.2956
ω_{12}	IIV correlation: pre-treatment vs. decline	-0.2695	-0.5587	0.0782
ω_{13}	IIV correlation: pre-treatment vs. conc. effect on slope	0.2629	-0.3331	0.7087
ω_{23}	IIV correlation: decline vs. conc. effect	-0.7546	-0.9267	-0.3213
ω_5	IIV SD for study phase effect on decline rate	0.2322	0.0000	6644.5198
σ	Residual SD	2.5985	2.4519	2.7539

LB = lower bounds; UB = upper bounds; IIV = intra-individual variability

- The exposure-response model was used to predict lung density decline rates as a function of covariate settings
  - Baseline weight and A_1-PI had a small effect on post-baseline A_1-PI levels, with FEV1 showing a greater effect

Figure 3: Changes in rate of 'observed' lung density decline as a function of exposure

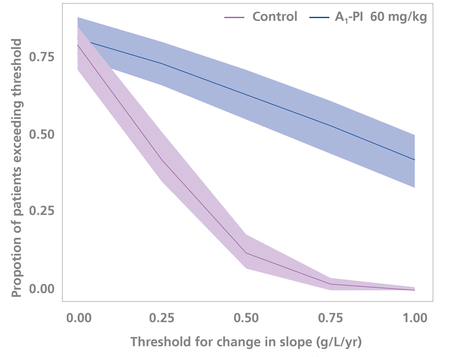


- The exposure-response model showed a trend towards increasing improvement in decline rate with higher A_1-PI exposure (Figure 3)
- Overall, the median decline rate for A_1-PI-treated patients was predicted to be -1.56 g/L/year, compared with -2.17 g/L/yr for placebo-treated patients

Clinical efficacy of A_1-PI therapy

- Point estimates for the 'natural' decline rate were -2.22 g/L/yr from RAPID vs. -2.16 g/L/yr from the 4-year analysis
- Over 4 years an estimated 63% of A_1-PI-treated patients achieved the threshold of ≥0.5 g/L/yr improvement in lung density decline rate, compared with 12% of placebo-treated patients (Figure 4)

Figure 4: Proportion of patients showing improvements in lung density decline rates over a range of thresholds



Estimates are based on baseline covariate settings for reference individual (weight 77 kg; A_1-PI 5.3)

- There is increasing disparity between placebo and A_1-PI therapy with increasing reduction in lung density decline rate (Figure 4)
- A threshold value of 0.5 g/L/yr was used to evaluate the effect of covariates on slope change (Table 4)
  - Weight, baseline A_1-PI and FEV1 had negligible effects on the proportion of patients improving by at least 0.5 g/L/yr compared to a reference individual (weight 77.0 kg; baseline A_1-PI 5.3 μM)

Table 4: Proportion of patients showing a reduction in decline rate of at least 0.5 g/L/yr by covariate settings

Description	FEV1 (L)	Baseline A_1-PI (μM)	Weight (kg)	Dose (mg/kg/wk)	Est.	95% LB	95% UB
- Weight	1.5	5.34	61.45	60	0.63	0.55	0.70
- Baseline A_1-PI	1.5	4.22	76.50	60	0.64	0.56	0.71
- FEV1	1.0	5.34	76.50	60	0.63	0.56	0.71
Ref	1.5	5.34	76.50	60	0.63	0.55	0.71
+ FEV1	2.2	5.34	76.50	60	0.63	0.56	0.71
+ Baseline A_1-PI	1.5	7.68	76.50	60	0.62	0.54	0.69
+ Weight	1.5	5.34	94.46	60	0.63	0.55	0.71
- Dose - FEV1	1.0	5.34	76.50	0	0.13	0.07	0.18
- Dose	1.5	5.34	76.50	0	0.12	0.07	0.18
- Dose + FEV1	2.2	5.34	76.50	0	0.12	0.08	0.18

Ref = reference individual (weight 77.0 kg & baseline A_1-PI 5.3 μM)

Conclusions:

- **A_1-PI exposure was consistent across a range of body weights, supporting weight-based dosing of A_1-PI therapy at 60 mg/kg**
- **≥98% of A_1-PI treated patients attained steady-state plasma levels of ≥11 μM**
- **Reductions in lung density decline rates were maintained over the 4-year combined duration of the trials with weight-based dosing of A_1-PI**
- **Improvements in decline rate of at least 0.5 g/L/yr (approximately a quarter of the estimated 'natural' decline rate) occurred regularly in A_1-PI-treated patients compared to placebo**

References

1. Campos M, Shmuels D, Walsh J. Detection of alpha-1 antitrypsin deficiency in the US. *Am J Med* 2012; 125: 623–624
2. Chapman KR, Burdon JGW, Piitulainen E, *et al.* Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 386: 360–368

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Conflicts of Interest:

MT, OV and JME are employees of CSL Behring. MB was employed by CSL Behring at the time of the study

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