



Pharmacokinetics and Biochemical Efficacy of an α_1 -Proteinase Inhibitor (Aralast NP) in α_1 -Antitrypsin Deficiency: a Cross-Product Retrospective Comparability Analysis

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ABSTRACT

Introduction: Augmentation therapy with plasma-derived α_1 -proteinase inhibitor (A1PI) products is currently the only approved disease-specific therapy for α_1 -antitrypsin deficiency (AATD), a genetic disorder associated with decreased levels of A1PI. Systemic trough levels of A1PI in plasma or serum are widely accepted as a biochemical efficacy endpoint in clinical trials for A1PI products.

Methods: Retrospective analyses utilizing data from three clinical studies in patients with AATD were conducted to evaluate the pharmacokinetic(s) (PK) and biochemical efficacy comparability of Aralast NP and two other A1PI augmentation therapies, Aralast and Prolastin. All three A1PI products were administered as either single or multiple 60 mg/kg intravenous infusions. PK and biochemical efficacy comparability analyses were conducted by evaluating antigenic and functional A1PI serum or plasma concentration data from each of the three studies.

Results: Comparable PK parameters were demonstrated between the three products for antigenic A1PI levels following a single infusion, with baseline-corrected and uncorrected geometric mean ratios for peak and systemic exposure ranging from 89.0% to 99.6%, with 90% confidence intervals within the 80–125% reference interval for bioequivalence. Biochemical efficacy comparability analyses of Aralast and Prolastin after multiple infusions at steady state showed geometric mean ratios for uncorrected and baseline-corrected antigenic and functional A1PI trough concentrations over weeks 8–11, and for individual weeks, that ranged from 75.8% to 106.6%, with the majority of the 90% confidence intervals falling either within the 80–125% interval or in proximity to it. Nonparametric superpositioning at steady state suggested that predicted trough concentrations for Aralast NP were comparable to the observed concentrations for Aralast and Prolastin.

Conclusion: These retrospective analyses provide robust evidence that Aralast NP has biochemical efficacy and PK comparable to that of Aralast and Prolastin, supporting the use of any of these A1PI products for the treatment of patients with AATD.

Trial Registration Numbers: ClinicalTrials.gov identifiers, NCT00242385 and NCT00396006.

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Keywords: α_1 -proteinase inhibitor; α_1 -antitrypsin deficiency; Biochemical efficacy; Pharmacokinetic comparability

Key Summary Points

Why carry out this study?

Patients with α_1 -antitrypsin deficiency (AATD) have decreased levels of α_1 -proteinase inhibitor (A1PI), which can predispose patients to A1PI-associated lung disease and emphysema

Augmentation therapy with plasma-derived A1PI products is currently the only approved disease-specific therapy for AATD, and there remains an unmet need for alternative plasma-derived therapeutic options

These retrospective analyses aimed to evaluate the pharmacokinetic(s) (PK) and biochemical efficacy comparability of Aralast NP and two other A1PI augmentation therapies, Aralast and Prolastin

What was learned from the study?

These retrospective analyses, utilizing data from three clinical studies, provide robust evidence that Aralast NP has PK and biochemical efficacy comparable to that of Aralast and Prolastin, supporting the use of any of these A1PI products for the treatment of patients with AATD

elastase, a serine protease [2, 3]. In patients with AATD, neutrophil elastase activity is not regulated, resulting in inflammation and tissue damage that can predispose patients to A1PI-associated lung disease and emphysema [2, 3]. Some pathological *SERPINA1* variants can also cause A1PI proteins to be retained in hepatocytes, resulting in cell damage and predisposing patients to liver disease [2].

Augmentation therapy with 60 mg/kg weekly intravenous (IV) infusions of A1PI purified from pooled human plasma has been shown to slow the progression of emphysema in patients with AATD [4, 5]. Aralast [α_1 -proteinase inhibitor (human), Baxalta US Inc., Lexington, MA, USA] was approved as an augmentation therapy by the US Food and Drug Administration in 2002 and is indicated for patients with congenital AATD and clinically evident emphysema [6, 7]. Aralast NP [α_1 -proteinase inhibitor (human), Baxalta US Inc., Lexington, MA, USA] has the same indication as Aralast and replaced this product in 2007 [7, 8]. Both Aralast and Aralast NP contain the same active plasma A1PI components with identical formulations; however, the manufacturing process for Aralast NP has been modified to reduce the likelihood of C-terminal lysine truncation [8–10].

The current retrospective analyses aim to evaluate the pharmacokinetic(s) (PK) and biochemical efficacy comparability of Aralast NP and two other A1PI augmentation therapies, Aralast and Prolastin [α_1 -proteinase inhibitor (human), Grifols Therapeutics LLC, Research Triangle Park, NC, USA]. Data from three clinical studies were utilized in these analyses. These were a phase 3 study (study 1) designed to compare Aralast with Prolastin in patients with congenital AATD (study 1 was not registered on ClinicalTrials.gov as the study was initiated in 1997, the same year the registry was created); a phase 1 study (NCT00242385; study 2) designed to demonstrate the PK comparability of a single IV infusion of Aralast NP and Aralast in patients with severe congenital AATD; and a phase 4 study (NCT00396006; study 3) designed to assess the efficacy and safety of Aralast NP in patients with severe congenital AATD [11–13]. These analyses should help to provide a more comprehensive understanding of the PK and

INTRODUCTION

α_1 -proteinase inhibitor (A1PI) deficiency, also known as α_1 -antitrypsin deficiency (AATD), is a hereditary, co-dominant, autosomal disorder associated with decreased levels of A1PI, a serine protease inhibitor encoded by the highly polymorphic *SERPINA1* gene [1, 2]. A1PI is predominantly synthesized by hepatocytes, and functions in the lungs by inhibiting neutrophil

biochemical efficacy comparability across A1PI augmentation therapies.

METHODS

Study Designs

All three clinical studies were approved by the respective institutional review boards or independent ethics committees at all participating sites, and written informed consent was obtained from each patient prior to enrollment.

Study 1

The methodology for this study has been published previously [13]. Briefly, study 1 was a phase 3, multicenter, randomized, double-blind, controlled study designed to compare Aralast (formerly known as Respitin) with Prolastin in patients 18 years of age or older with congenital AATD (serum A1PI levels < 11 $\mu\text{M/L}$) and emphysema. Patients were excluded if they had received any A1PI augmentation therapy within the preceding 6 months. In the double-blinded period, patients were randomized to receive 60 mg/kg weekly IV infusions of either Aralast or Prolastin for 10 weeks. This was followed by an open-label period from week 11 to week 23 during which all patients received 60 mg/kg weekly IV infusions of Aralast. At the time of the study, both Aralast and Prolastin were available as sterile lyophilized preparations. A study design schematic is shown in Fig. 1a.

Study 2

Study 2 was a phase 1, randomized, multicenter, single-dose, double-blind, crossover study (NCT00242385) designed to characterize the PK profile of Aralast NP and demonstrate the PK comparability of Aralast NP and Aralast in patients 18 years of age or older with severe congenital AATD (endogenous serum A1PI levels < 8 μM). Patients were excluded if they had received any A1PI augmentation therapy within 42 days prior to the first study infusion. The study consisted of two successive treatment periods. In the first treatment period, patients

were randomized to receive a single 60 mg/kg IV infusion of either Aralast or Aralast NP on day 1. This was followed by a washout period approximately ten times the half-life of the study products. In the second treatment period, patients crossed over and received a single 60 mg/kg IV infusion of the alternate treatment on day 43. At the time of the study, both Aralast NP and Aralast were available as sterile lyophilized preparations. A study design schematic is shown in Fig. 1b.

Study 3

Study 3 was a phase 4, multicenter, open-label, non-randomized study (NCT00396006) designed to assess the efficacy and safety of Aralast NP in patients 18 years of age or older with severe congenital AATD (endogenous serum A1PI levels < 40 mg/dL, i.e., 7.69 μM). Patients were excluded if they had received any A1PI augmentation therapy within 28 days prior to screening. Patients received at least eight consecutive 60 mg/kg weekly IV infusions of Aralast NP. At the time of the study, Aralast NP was available as a sterile lyophilized preparation. A study design schematic is shown in Fig. 1c.

PK Sample Collection and Measurements

In study 1, serum samples were taken at enrollment and prior to each weekly infusion to measure antigenic and functional serum A1PI levels. Antigenic serum A1PI levels following the first study infusion were also measured pre-infusion, post-infusion (1 \pm 0.25 h, 2 \pm 0.25 h, 6 \pm 0.5 h, and 12 \pm 0.5 h), and every subsequent 24 h (\pm 6 h) through to study day 7. Antigenic serum A1PI levels were measured by nephelometry, and functional serum A1PI levels were measured by an anti-neutrophil elastase capacity assay. Antigenic and functional A1PI serum levels measured during the initial 10-week infusion period were utilized in the PK and biochemical efficacy comparability analyses, along with the antigenic serum A1PI levels measured following the first single infusion of either Aralast or Prolastin.

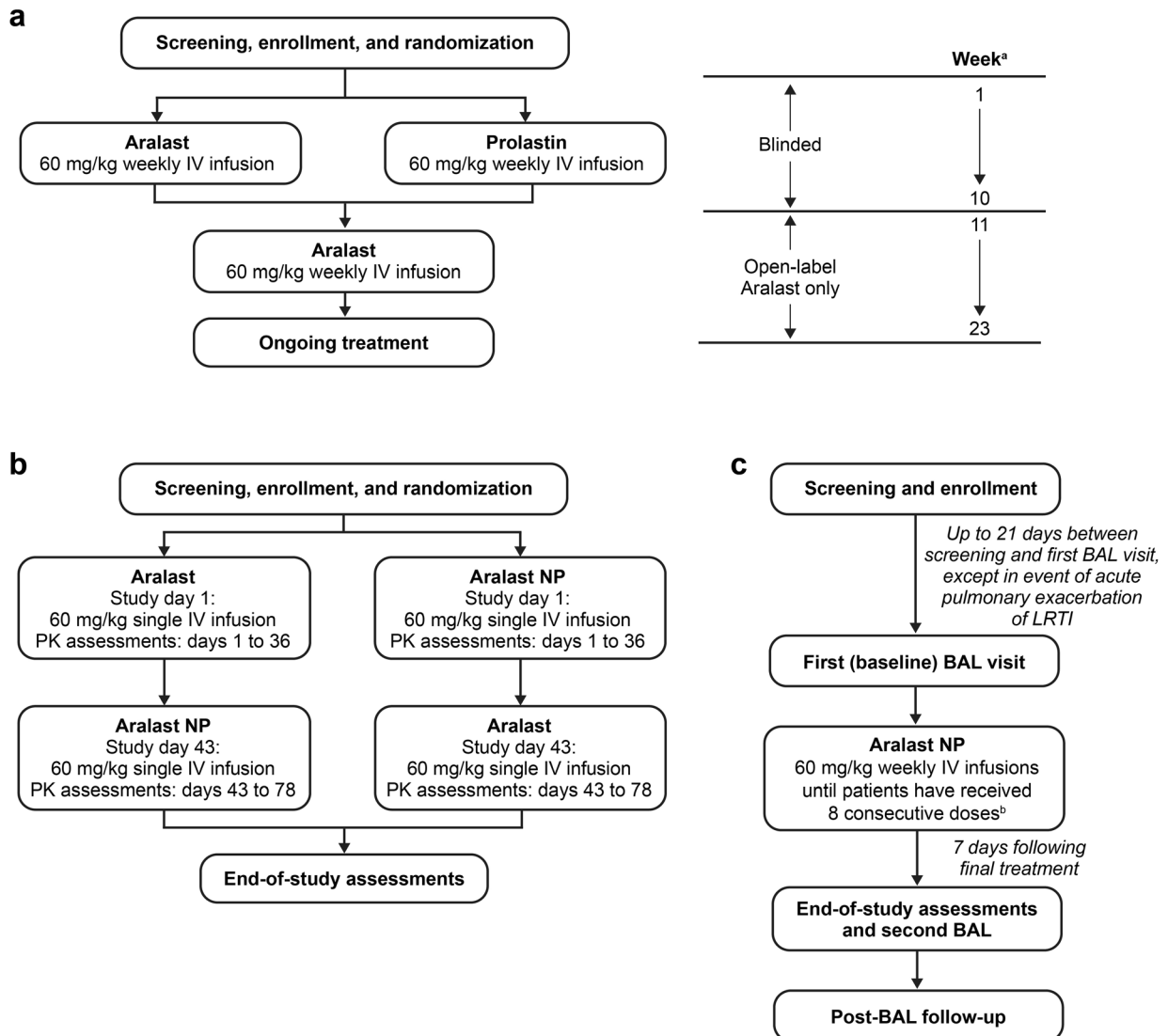


Fig. 1 Study design schematics for **a** study 1, **b** study 2, and **c** study 3. ^aAll samples were taken immediately prior to infusion and represented the trough level of the previous week's infusion. ^bThe eight consecutive weekly doses of Aralast NP were to be administered without interruption and without chronic obstructive pulmonary disease exacerbation or LRTI. If treatments were missed, the count

restarted. If a moderate or severe acute pulmonary exacerbation or LRTI occurred, the count restarted 2 weeks after either the pulmonary exacerbation or LRTI was no longer evident. *BAL* bronchoalveolar lavage, *IV* intravenous, *LRTI* lower respiratory tract infection, *PK* pharmacokinetic

In study 2, antigenic plasma A1PI levels were measured pre- and post-infusion on day 1 and subsequently on days 2, 3, 4, 5, 8, 10, 12, 15, 19, 22, 26, 29, 33, and 36. Following the washout period, antigenic plasma A1PI levels were also measured pre- and post-infusion on day 43 and subsequently on days 44, 45, 46, 47, 50, 52, 54,

57, 61, 64, 68, 71, 75, and 78. Antigenic plasma A1PI levels were measured using a validated enzyme-linked immunosorbent assay. The antigenic plasma A1PI levels measured in study 2 were used in the PK comparability analyses.

In study 3, antigenic plasma A1PI levels were measured prior to bronchoalveolar lavage at

baseline (prior to infusion) and prior to bronchoalveolar lavage after at least 8 weeks of treatment. Antigenic plasma A1PI levels were measured by nephelometry. The antigenic plasma A1PI levels measured in study 3 were used in the biochemical efficacy comparability analyses.

Assays to determine circulating A1PI levels previously used serum, as in study 1, but subsequently changed to plasma in studies 2 and 3. Plasma and serum matrices are comparable for the assays in the determination of circulating A1PI levels.

PK and Biochemical Efficacy Comparability Analyses

All PK and biochemical efficacy comparability analyses were performed using standard techniques as implemented in Phoenix WinNonlin, version 8.1 (Certara LP 2018; Princeton, NJ, USA). Statistical analyses consisted of summary descriptive statistics, Helmert transformation to assess steady state, and linear mixed-effects modeling to evaluate differences among treatment groups, study centers, and time. PK and biochemical efficacy comparability were assessed using standard statistical approaches for evaluating bioequivalence. No interpolation was performed for any missing data. When available, both baseline-corrected and uncorrected antigenic and functional A1PI levels were used for data analyses. Any baseline-corrected data that were negative were flagged and treated as missing.

Antigenic A1PI PK parameter estimates in serum (study 1) or plasma (study 2) following a single infusion were calculated using noncompartmental PK methods and included the maximum observed drug concentration (C_{max}), the area under the concentration–time curve (AUC) from time 0 to the last measurable concentration (AUC_{0-t}), the AUC from time 0 to infinity (AUC_{0-inf}), and the terminal elimination phase half-life ($t_{1/2}$). AUC_{0-inf} was not calculated for study 1 because truncated sampling times at approximately 7 days post-infusion resulted in the extrapolated portion of the AUC_{0-inf} being greater than 20% for nearly all patients.

The achievement of a steady-state serum A1PI trough concentration following multiple infusions was assessed using Helmert transformation [14]. The first contrast test compared the geometric mean concentration at the first post-dose trough sample (week 2) with the pooled geometric mean over all remaining timepoints (weeks 3–11). Testing continued to the next post-dose trough sample (e.g., week 3) compared with the remaining timepoints (e.g., weeks 4–11) until the contrast was not statistically significant ($p > 0.05$). The dosing interval at which this occurred was considered the point at which steady state was attained.

Linear mixed-effects modeling was performed for studies 1 and 2 to assess the significance of treatment, study center, and time on the PK parameter estimates. $p < 0.05$ was considered significant.

For single infusions, PK comparability was assessed on the basis of the 90% confidence intervals (CI) for the ratio of the population geometric means of antigenic A1PI C_{max} , AUC_{0-t} , and AUC_{0-inf} (study 2 only). For multiple infusions, time was specified as a repeated measurement on patients, and PK and biochemical efficacy comparability was assessed on the basis of the 90% CI for the ratio of the population geometric means of antigenic and functional A1PI steady-state trough levels. The interval of 80–125%, as defined in guidance on bioequivalence by the US Food and Drug Administration [15], was used as a reference for PK and biochemical efficacy comparability assessments.

Mean single-dose plasma concentrations and 90% CI of the means from study 2 were calculated and used for nonparametric superpositioning. Steady-state plasma concentration–time profiles were predicted for Aralast NP at 60 mg/kg weekly IV infusions for 10 consecutive weeks. Observed A1PI concentrations from studies 1 and 3 were plotted alongside the nonparametric-superpositioning-derived steady-state A1PI concentration predictions.

RESULTS

Single-Dose PK Comparability

In study 1, antigenic serum A1PI concentrations were available for 14 patients who received Aralast and for 13 patients who received Prolastin. Figure 2 shows mean \pm standard deviation (SD) baseline-corrected and uncorrected antigenic A1PI serum concentration–time profiles following a single IV infusion of either Aralast or Prolastin. Baseline-corrected and uncorrected antigenic A1PI PK parameters are presented in Table 1. Mean C_{\max} and AUC_{0-t} PK parameters were comparable between Aralast and Prolastin. The calculated mean \pm SD $t_{1/2}$ values for baseline-corrected antigenic A1PI were consistent between Aralast and Prolastin: 3.6 ± 1.4 days and 3.4 ± 0.5 days, respectively. The geometric mean ratios (GMRs) (Aralast/Prolastin) for C_{\max} and AUC_{0-t} were in the range of 89.0% to 94.9%, with the 90% CI within the 80–125% interval for both baseline-corrected and uncorrected PK parameters (Table 1). The linear mixed-effects model showed that neither treatment nor study center had a significant effect on baseline-corrected or uncorrected antigenic serum A1PI C_{\max} or AUC_{0-t} .

In study 2, antigenic plasma A1PI concentrations were available for 25 patients who completed the crossover study. Figure 3 shows mean \pm SD baseline-corrected and uncorrected antigenic A1PI plasma concentration–time profiles following a single IV infusion of either Aralast NP or Aralast. Baseline-corrected and uncorrected antigenic A1PI PK parameters are presented in Table 1. Mean C_{\max} , AUC_{0-t} , and AUC_{0-inf} PK parameters were comparable between Aralast NP and Aralast. The calculated mean \pm SD $t_{1/2}$ values for baseline-corrected antigenic A1PI were consistent between Aralast NP and Aralast: 6.0 ± 2.3 days and 6.3 ± 2.2 days, respectively. The GMRs (Aralast NP/Aralast) for C_{\max} , AUC_{0-t} , and AUC_{0-inf} ranged from 91.2% to 99.6%, with the 90% CI within the 80–125% interval for both baseline-corrected and uncorrected PK parameters (Table 1). The linear mixed-effects model showed that treatment, sequence, and period

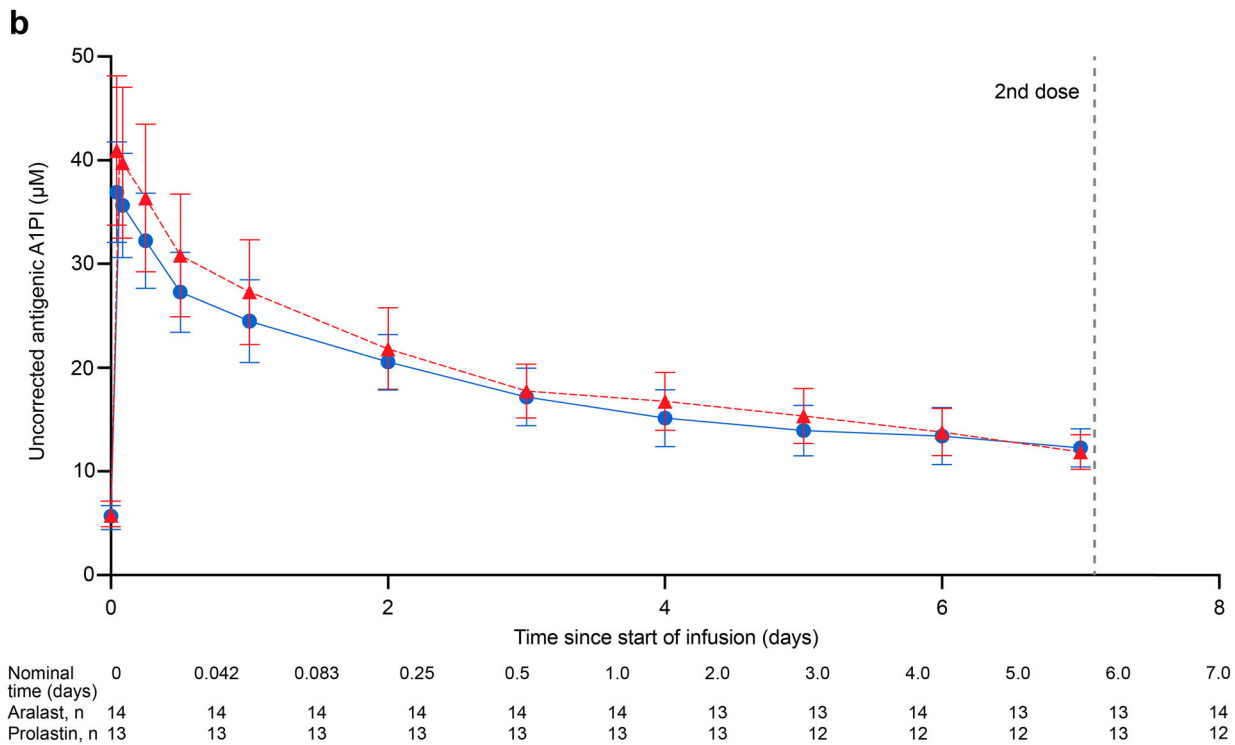
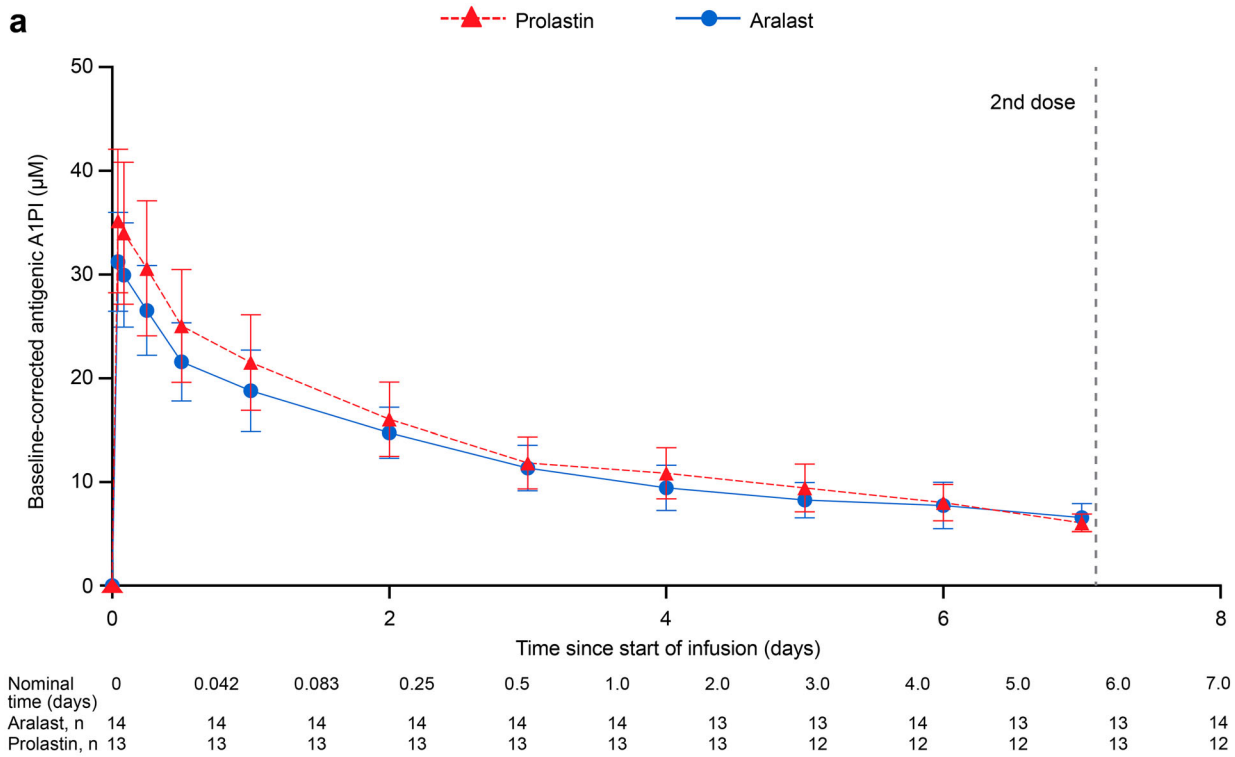
did not have a significant effect on baseline-corrected or uncorrected antigenic plasma A1PI C_{\max} , AUC_{0-t} , or AUC_{0-inf} .

Steady-State Biochemical Efficacy Comparability

Trough serum concentrations were available for 13 patients who received Aralast and for 13 patients who received Prolastin in study 1. Figure 4 shows mean \pm SD baseline-corrected and uncorrected antigenic and functional A1PI serum concentration–time profiles following multiple IV infusions of either Aralast or Prolastin. All patients demonstrated an increase in trough concentrations with repeat A1PI infusions prior to reaching steady state. The Helmer transformation method confirmed that steady state was attained for antigenic and functional A1PI serum concentrations prior to week 8, specifically after the second administration of Aralast and the third administration of Prolastin. The linear mixed-effects model of antigenic serum A1PI trough concentrations (baseline corrected and uncorrected) showed that treatment and study center had a significant effect, but there was no significant interaction for time \times treatment or time \times study center. The linear mixed-effects model of functional A1PI trough concentrations (baseline corrected and uncorrected) showed a significant effect of study center. No other significant interactions were observed for functional A1PI trough concentrations. The GMRs for uncorrected and baseline-corrected antigenic and functional A1PI trough concentrations over weeks 8–11, and for individual weeks, ranged from 75.8% to 106.6%, with the majority of the 90% CI falling either within the 80–125% interval or in proximity to it (Table 2).

Nonparametric Superpositioning

Figure 5 shows the mean (90% CI) predicted profile for 60 mg/kg weekly IV infusions of Aralast NP plotted alongside observed baseline-corrected antigenic A1PI trough concentrations for Aralast and Prolastin from study 1 and Aralast NP from study 3. The predicted



◀ **Fig. 2** Study 1 mean \pm SD **a** baseline-corrected and **b** uncorrected antigenic A1PI serum concentration–time profiles after a single IV infusion. Baseline-corrected values were calculated by subtracting baseline (pre-infusion) concentrations from subsequent concentration–time values. *A1PI* α_1 -proteinase inhibitor, *IV* intravenous, *SD* standard deviation

concentrations for Aralast NP are comparable to the observed concentrations from studies 1 and 3.

DISCUSSION

Circulating A1PI trough level is a clinical biochemical efficacy endpoint for A1PI products, and the comparability in biochemical efficacy between A1PI products is an essential component in the clinical development of augmentation therapies. Data from three clinical studies served as the basis for retrospective analyses to evaluate the PK and biochemical efficacy comparability of Aralast NP and two other A1PI augmentation therapies, Aralast and Prolastin,

Table 1 PK comparability of baseline-corrected and uncorrected antigenic A1PI PK parameters after a single IV infusion

Baseline correction	Dependent	Study 1 Aralast versus Prolastin			Study 2 Aralast NP versus Aralast		
		Aralast mean \pm SD	Prolastin mean \pm SD	GMR Aralast/ Prolastin, % (90% CI)	Aralast NP mean \pm SD	Aralast mean \pm SD	GMR Aralast NP/ Aralast, % (90% CI)
Corrected ^a	C_{max} (μ M)	31.4 \pm 4.8	35.6 \pm 7.0	89.0 (80.2, 98.7)	31.4 \pm 6.2	31.8 \pm 5.5	98.6 (93.5, 104.1)
	AUC_{0-t} (day \times μ M)	88.0 \pm 14.8	95.5 \pm 16.8	92.4 (82.3, 103.7)	99.2 \pm 26.0	107.7 \pm 23.4	91.2 (83.4, 99.7)
	AUC_{0-inf} (day \times μ M)	–	–	–	106.4 \pm 30.3	114.3 \pm 27.4	92.5 (84.2, 101.6)
	$t_{1/2}$ (day)	3.6 \pm 1.4	3.4 \pm 0.5	–	6.0 \pm 2.3	6.3 \pm 2.2	–
Uncorrected	C_{max} (μ M)	37.1 \pm 4.8	41.3 \pm 7.3	90.6 (82.7, 99.4)	36.4 \pm 6.8	36.5 \pm 6.2	99.6 (94.7, 104.6)
	AUC_{0-t} (day \times μ M)	128 \pm 17.9	136 \pm 19.7	94.9 (86.5, 104.2)	267 \pm 56.7	271.2 \pm 56.5	98.6 (96.3, 100.9)
	AUC_{0-inf} (day \times μ M)	–	–	–	453.8 \pm 161.5	492.7 \pm 225.3	95.4 (86.2, 105.7)
	$t_{1/2}$ (day)	7.4 \pm 6.9	5.7 \pm 0.9	–	25.4 \pm 13.3	30.7 \pm 22.1	–

^aBaseline-corrected values were calculated by subtracting baseline (pre-infusion) concentrations from subsequent concentration–time values

A1PI α_1 -proteinase inhibitor, AUC_{0-inf} area under the concentration–time curve from time zero to infinity, AUC_{0-t} area under the concentration–time curve from time zero to the last measurable concentration, *CI* confidence interval, C_{max} maximum observed drug concentration, *GMR* geometric mean ratio, *IV* intravenous, *PK* pharmacokinetic, *SD* standard deviation, $t_{1/2}$ terminal elimination phase half-life

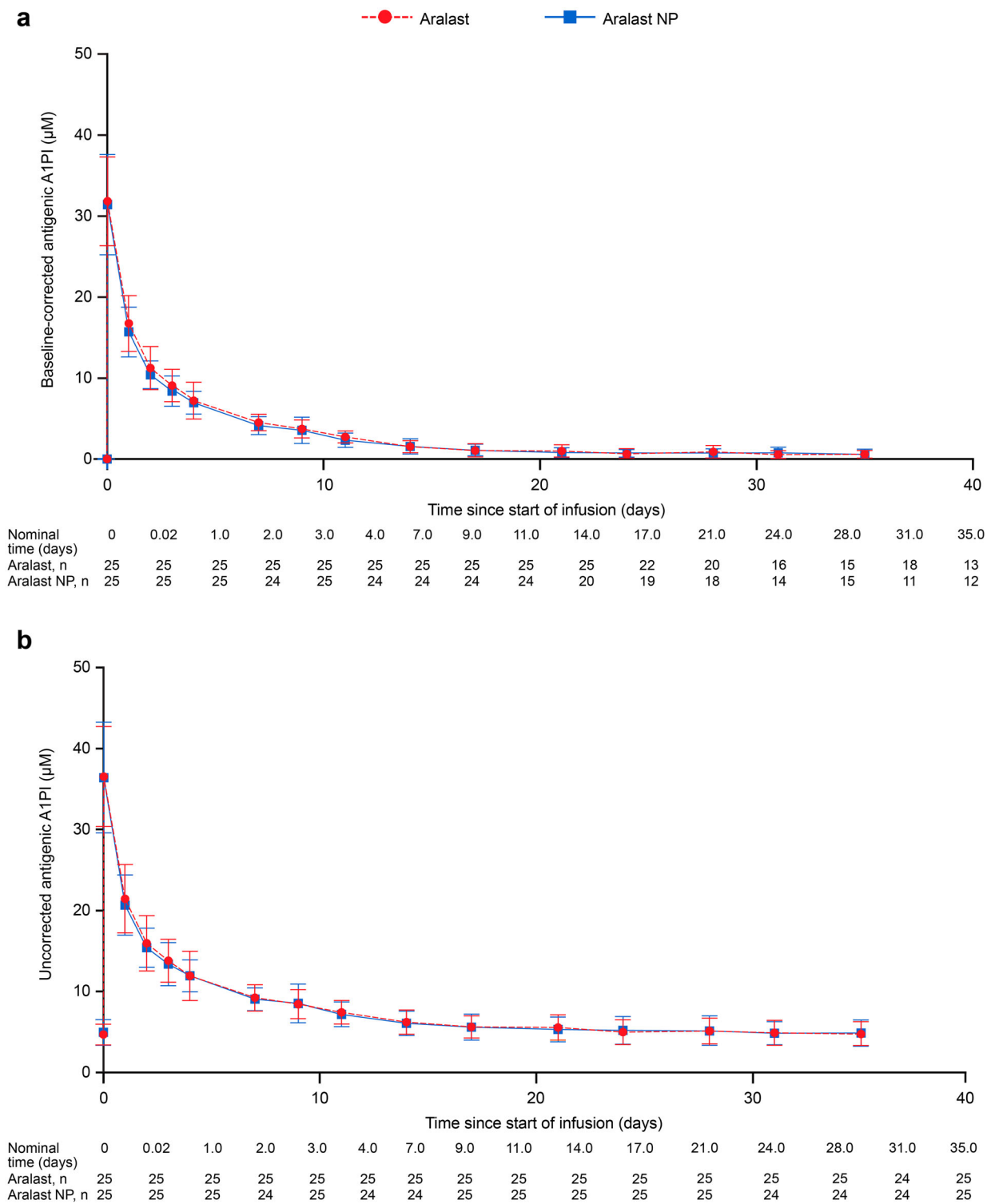
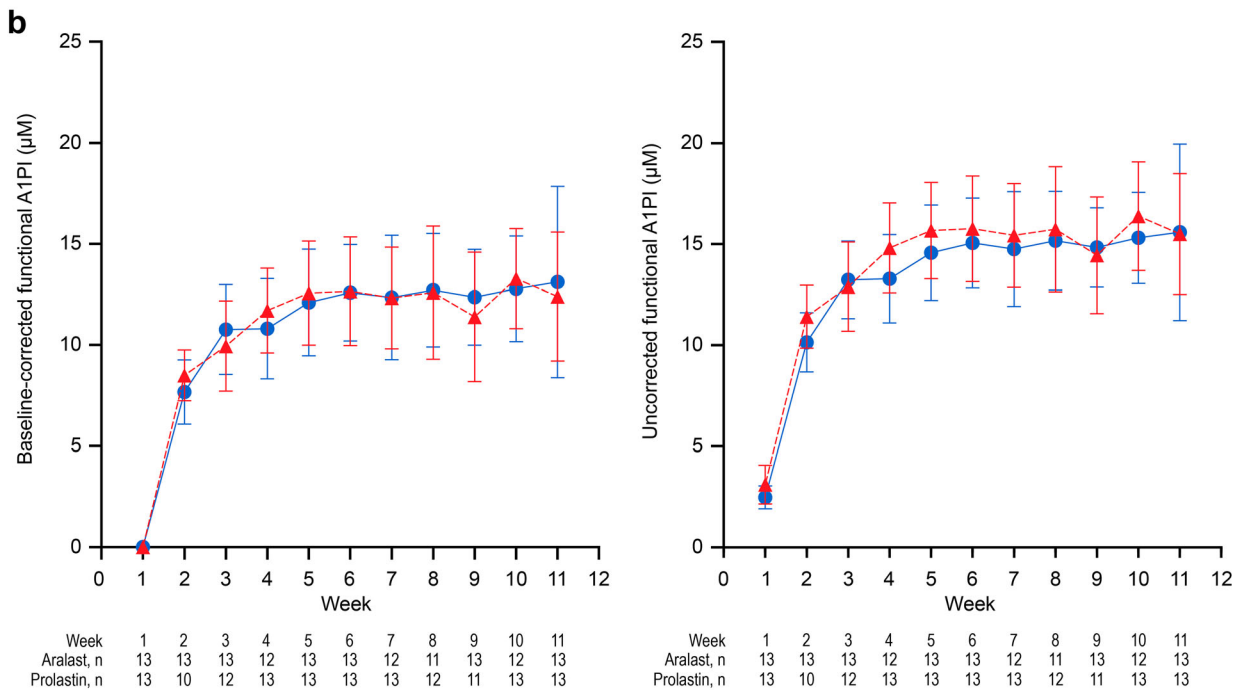
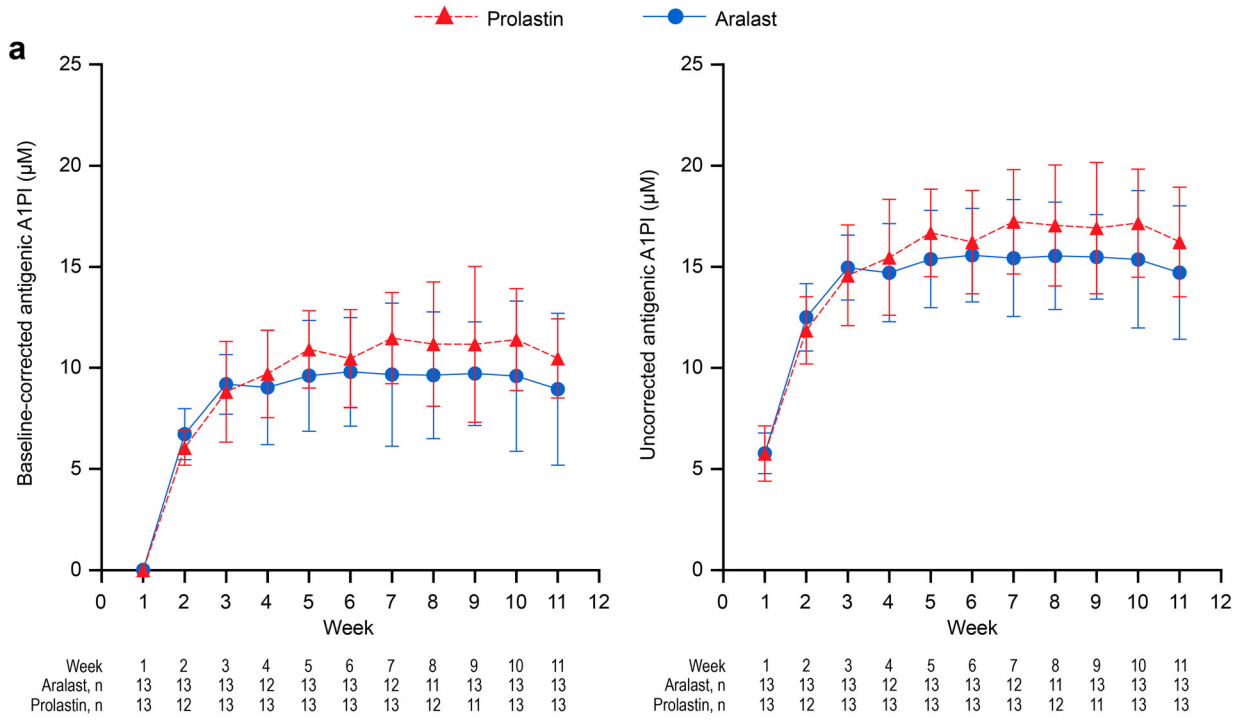


Fig. 3 Study 2 mean ± SD **a** baseline-corrected and **b** uncorrected antigenic A1PI plasma concentration–time profiles after a single IV infusion. Baseline-corrected values were calculated by subtracting baseline (pre-infusion)

concentrations from subsequent concentration–time values. A1PI α₁-proteinase inhibitor, IV intravenous, SD standard deviation



◀**Fig. 4** Study 1 mean \pm SD baseline-corrected and uncorrected **a** antigenic and **b** functional A1PI serum concentration–time profiles after multiple IV infusions. Baseline-corrected values were calculated by subtracting baseline (week 1 pre-dose trough level) concentrations of antigenic or functional A1PI from subsequent trough concentrations. A1PI α_1 -proteinase inhibitor, IV intravenous, SD standard deviation. The uncorrected antigenic A1PI serum concentration–time profile presented in **a** has been adapted from Chest, Vol 122, Issue 1. Stoller JK et al. Biochemical efficacy and safety of a new pooled human plasma α_1 -antitrypsin, Respitin, pages 66–74, Copyright © 2002 with permission from Elsevier on behalf of The American College of Chest Physicians

which were marketed prior to the approval of Aralast NP. These combined analyses demonstrated that Aralast NP has PK and biochemical efficacy comparable to that of Aralast and Prolastin following both single and multiple 60 mg/kg IV infusions. The PK and biochemical efficacy comparability between these A1PI products should assure clinicians that Aralast NP should have the same therapeutic effects as Aralast and Prolastin. Beyond the comparability in biochemical efficacy, i.e., A1PI trough level, these analyses support the conclusion that there is an absence of a significant difference in the rate (C_{max}) and extent (AUC) of exposure with these A1PI products systematically, when administered at the same molar dose.

The biochemical efficacy comparability after multiple doses demonstrated for study 1 is consistent with the primary outcome from the original study, which concluded that Aralast was non-inferior to Prolastin [13]. The 90% CI for the GMRs for some individual weeks was outside of the 80–125% interval. This is likely because study 1 was not prospectively powered to determine bioequivalence but was a non-inferiority comparison of Aralast and Prolastin [13]. Therefore, study 1 was likely to be underpowered for the detection of bioequivalence. Given these limitations, it is important to acknowledge that the bioequivalence criteria have been used in these analyses only as a reference for the PK comparability assessment, and the observed deviations from the

bioequivalence interval are unlikely to be clinically relevant.

Owing to differences in study design, the calculated $t_{1/2}$ values were different between studies 1 and 2. Sampling time was truncated at 7 days post-infusion after the initial dose in study 1; therefore, the calculated $t_{1/2}$ values are not an accurate reflection of the elimination half-life. In study 2, samples were taken up to 35 days post-infusion, enabling a more accurate estimation of $t_{1/2}$ for antigenic A1PI. In each of the respective studies, the calculated $t_{1/2}$ values were comparable between treatments. It is important to note that the estimation of $t_{1/2}$ utilized multiple points on the terminal slope, on the basis of a standard algorithm. In instances where baseline-uncorrected A1PI concentrations did not return to baseline values, the calculated $t_{1/2}$ could be artificially inflated. The $t_{1/2}$ values estimated on the basis of baseline-corrected antigenic A1PI concentration–time profiles are, therefore, more representative of the exogenous A1PI $t_{1/2}$ and were approximately 6 days.

The analyses have shown that steady-state A1PI concentrations were achieved after the second or third infusions. Conventionally, a treatment duration of at least 8 weeks to achieve steady state has been implemented for A1PI studies [7, 16, 17]. The findings from these analyses would, however, support shorter study durations for clinical assessments at steady state.

Plasma-derived A1PI products are currently the only approved disease-specific therapies for AATD [3], and A1PI trough concentration is widely used as a biochemical efficacy endpoint in clinical trials for these products. PK and biochemical efficacy comparability studies are typically conducted using an approved A1PI product as a reference, with the primary endpoint being either circulating trough A1PI levels or systemic exposure (i.e., AUC, after repeat dosing) using either a non-inferiority or a bioequivalence approach [7, 16, 17]. The aim of these retrospective analyses was to evaluate the PK and biochemical efficacy comparability of Aralast NP and two other A1PI augmentation therapies, Aralast and Prolastin. Both Aralast and Prolastin were approved before Aralast NP,

Table 2 Study 1 biochemical efficacy analysis of baseline-corrected and uncorrected antigenic and functional A1PI trough concentrations following multiple IV infusions

Baseline correction	Dependent	Aralast GLSM, μM	Prolastin GLSM, μM	GMR Aralast/Prolastin, %	Lower 90% CI	Upper 90% CI
Corrected antigenic ^a	Weeks 8–11	8.2	10.4	79.5	71.2	88.8
	Week 8	8.6	10.6	81.5	62.1	107.0
	Week 9	8.7	10.2	85.3	66.5	109.2
	Week 10	8.1	10.6	76.4	60.9	95.7
	Week 11	7.5	9.8	75.8	59.6	96.4
Uncorrected antigenic	Weeks 8–11	14.6	16.4	89.2	84.0	94.6
	Week 8	15.0	16.6	90.2	78.6	103.5
	Week 9	15.0	16.5	90.9	80.3	103.0
	Week 10	14.5	16.6	87.1	76.8	98.8
	Week 11	14.0	15.7	88.9	77.5	101.9
Corrected functional ^a	Weeks 8–11	11.8	11.8	99.7	92.1	107.9
	Week 8	12.0	12.0	100.0	83.3	120.1
	Week 9	11.5	10.8	106.6	90.2	125.9
	Week 10	12.2	12.8	94.8	82.3	109.2
	Week 11	11.6	11.5	100.2	82.6	121.4
Uncorrected functional	Weeks 8–11	14.6	15.1	96.6	91.0	102.6
	Week 8	14.7	15.3	95.9	84.0	109.4
	Week 9	14.2	14.0	101.6	90.2	114.4
	Week 10	15.0	16.0	93.4	83.5	104.6
	Week 11	14.4	14.8	97.2	83.9	112.6

^aBaseline-corrected values were calculated by subtracting baseline (week 1 pre-dose trough level) concentrations of antigenic or functional A1PI from subsequent trough concentrations

A1PI α_1 -proteinase inhibitor, CI confidence interval, GLSM geometric least-squares mean, GMR geometric mean ratio, IV intravenous, PK pharmacokinetic

and these analyses were intended to bridge comparability assessments across studies for these A1PI products. All three A1PI products from the clinical studies used in these analyses were administered as IV infusions and at the

same dose. The three clinical studies were conducted over a period during which two generations of A1PI product were developed (current generation, Aralast NP; earlier generation, Aralast). Consequently, studies 1 and 2 used

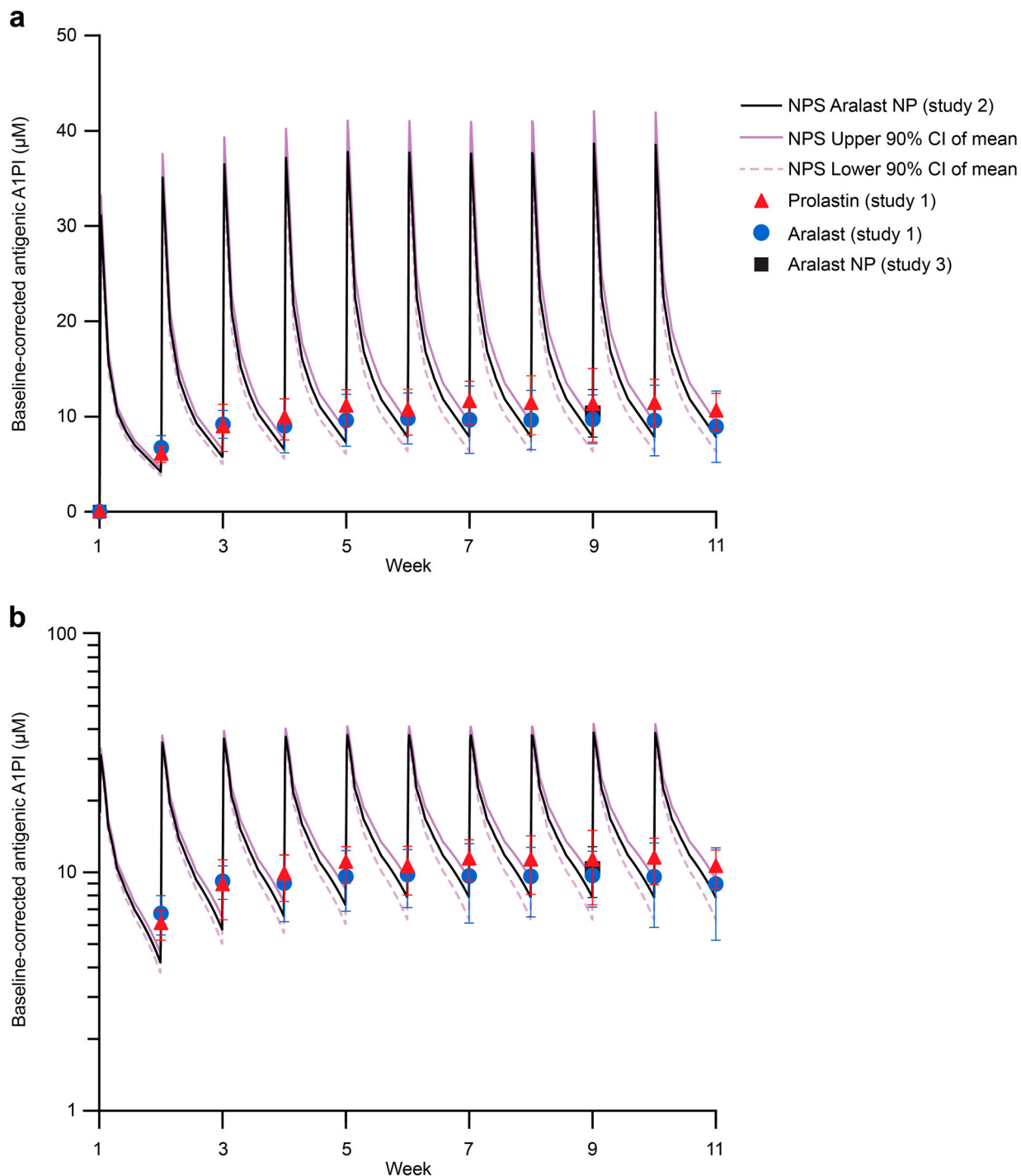


Fig. 5 **a** Linear-scale and **b** log-scale predicted concentration–time profiles for patients receiving Aralast NP compared with observed mean \pm SD baseline-corrected antigenic A1PI trough concentrations after multiple IV infusions. Baseline-corrected values were calculated by

subtracting baseline (week 1 pre-dose trough level) concentrations of antigenic A1PI from subsequent trough concentrations. A1PI α_1 -proteinase inhibitor, CI confidence interval, IV intravenous, NPS nonparametric superpositioning, SD standard deviation

different augmentation therapies as a reference product. However, both Aralast and Aralast NP contain the same active plasma A1PI components with identical formulations [8], and changing the reference product should not have a meaningful impact on the interpretation of PK and biochemical efficacy comparability.

CONCLUSION

These retrospective analyses provide substantial data that Aralast NP, Aralast, and ProLastin have comparable PK and biochemical efficacy, supporting the use of any of these A1PI products for the treatment of patients with AATD. Plasma-derived A1PI products are likely to remain as the predominant treatment approach for patients with AATD for the foreseeable future. The challenges associated with conducting large, randomized trials using clinical outcome measures to evaluate the efficacy of AATD augmentation therapies are well recognized [18], and comparative clinical studies based on PK and biochemical efficacy endpoints continue to be valuable. These PK comparability analyses also provide a more comprehensive and robust basis for designing future clinical trials, in which new products, novel formulations, and dose optimization can be investigated.

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Compliance with Ethics Guidelines All three clinical studies were approved by the respective

institutional review boards or independent ethics committees at all participating sites, and written informed consent was obtained from each patient prior to enrollment.

Data Availability The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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