Summary Basis for Regulatory Action

Date: 08 September 2017

From: L. Ross Pierce, M.D., Chair of the Review Committee

***BLA Efficacy Supplement* STN#:** 103174/6160

Applicant Name: Grifols Therapeutics Inc.

Date of Submission: 10 November 2016

Goal Date: 10 September 2017

Proprietary Name/ Established Name: PROLASTIN®-C [LIQUID] / Alpha-1-Proteinase Inhibitor (Human)

Indication: PROLASTIN-C LIQUID is an $Alpha_1$-Proteinase Inhibitor (Human) ($Alpha_1$-PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of $Alpha_1$-PI ($alpha_1$-antitrypsin deficiency).

Recommended Action:
The Review Committee recommends approval of this product efficacy supplement.

Review Office Signatory Authority:
Tejashri Purohit-Sheth, M.D.
Director, Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissue and Advanced Therapies

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA.

Document Title	**Reviewer Name, Document Date**
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Clinical: L. Ross Pierce, M.D., 29 August 2017 OBE/DE: Patricia Rohan, M.D. 8 May 2017 BiMo: Bhanu Kannan 25 July 2017
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Jiang (Jessica) Hu, Ph.D. 25 May 2017
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	CMC: Jennifer Reed, Ph.D. 31 August 2017 Facilities: Sean Byrd 31 July 2017 EIR: N/A (criteria for needing GMP inspection not met per CBER SOPP 8410)
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Pharm-Tox: Evi Struble, Ph.D. 8 July 2017
Clinical Pharmacology Review(s)	Xiaofei Wang, Ph.D. 9 August 2017
Labeling Review(s) • *APLB (OCBQ/APLB)*	Kristine Khuc, Pharm.D. 10 July 2017
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	N/A
Advisory Committee Transcript	N/A

1. Introduction

PROLASTIN-C LIQUID is a liquid, 0.25 M alanine-stabilized formulation of Alpha$_1$-Proteinase Inhibitor (Human) (A_1-PI) intended to carry the existing indication of licensed PROLASTIN-C for the chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of Alpha$_1$-PI (alpha$_1$-antitrypsin deficiency, AATD). PROLASTIN-C LIQUID has not been marketed in any country. PROLASTIN was licensed in the United States in 1987 as the first member of the class of A_1-PI products. Licensure relied on the assessment of biomarkers, serum and lung epithelial lining fluid (ELF) levels of antigenic and functional A_1-PI, to establish substantial evidence of effectiveness because there was uncertainty at the time regarding whether a randomized controlled clinical trial using a clinical endpoint such as forced expiratory volume in one second (FEV_1) was feasible. PROLASTIN was eventually replaced with PROLASTIN-C (approved 16 October 2009 under STN 103174/5520), also a lyophilized product for reconstitution, which represented a major manufacturing change. The proposed trade name, PROLASTIN-C

LIQUID, is referred to by the applicant in the supplement as Liquid Alpha$_1$-Proteinase Inhibitor or Liquid Alpha$_1$-PI.

2. Background

Individuals with Alpha$_1$-Antitrypsin Deficiency (AATD, also known as Alpha$_1$-Proteinase Inhibitor Deficiency) have low serum Alpha$_1$-Antitrypsin (AAT) levels and increased risks of chronic obstructive lung disease (COPD), emphysema, and, less frequently, liver disease. Many AAT-deficient patients with emphysema have symptoms of asthma with a reversible component to their airway obstruction. Approximately 150 genetic forms of the disease have been discovered, but the vast majority of subjects with severe deficiency, i.e., those who have levels of serum A_1-PI below 11 mM, have the Pi*ZZ genotype/phenotype. This genotype is due to a point mutation in the gene coding for A_1-PI, resulting in misfolding of the protein, impaired secretion from hepatocytes (the primary source of A_1-PI synthesis) and accumulation of the misfolded protein in hepatocytes. Patients with AATD who have developed symptomatic lung disease experience airways obstruction and dyspnea, and are subject to periodic exacerbations of COPD characterized by increases in dyspnea, increase in sputum volume, and/or increase in sputum purulence. Even among people with the same genetic form and similar levels of A_1-PI in their blood, there is tremendous diversity in clinical severity. A substantial percentage of individuals with severe AATD never appear to develop symptomatic lung disease during their lifetimes. Others, depending on their smoking history and other factors poorly understood, develop emphysema starting anywhere from in their 30s to their 60s. Progression of emphysema in AATD may lead to respiratory failure and death or a need for lung transplantation.

This prior approval efficacy supplement is the third prior approval supplement (PAS) that has been submitted for this particular liquid A_1-PI product. The first was submitted in September 2012 and was based on in vitro comparability data, between PROLASTIN-C and PROLASTIN-C LIQUID. FDA indicated to the applicant a need for preclinical toxicology evaluation and could not exclude a possible need for a clinical trial, and the PAS was withdrawn in November 2012. A second PAS was submitted in November 2013 with the requested preclinical data, resulting in a Refuse to File letter issued on 06 January 2014. A Type A meeting to discuss the clinical trial requested by FDA was held in February 2014 (CRMTS 9306).

3. Clinical/Statistical/Pharmacovigilance

a) Clinical Program

The applicant submitted a final study report for the single clinical study conducted to support regular approval of PROLASTIN-C LIQUID: Protocol GI11402. This was a multi-center, randomized treatment sequence, double-blind crossover study conducted at six sites in the United States to assess the safety, immunogenicity, and pharmacokinetics (PK) of weekly infusions of 60 mg/kg of PROLASTIN-C LIQUID (Liquid Alpha$_1$-PI) compared to 60 mg/kg weekly infusions of licensed PROLASTIN-C (currently approved lyophilized product) in 32 subjects with emphysema and severe

alpha$_1$-anti-trypsin deficiency (AATD). The trial consisted of a Screening Period (seven to 21 days), Treatment Period 1 (eight weeks; Weeks 1 [Baseline] to 8), Treatment Period 2 (eight weeks; Weeks 9 to 16), and an off-treatment Follow-Up Period (four weeks; Weeks 17 to 20). Subjects were permitted to continue prior A_1-PI augmentation therapy during the screening period.

Key study inclusion criteria included male and female subjects age 18 to 70 years of age, inclusive, who had a diagnosis of congenital AATD with an allelic combination of ZZ, SZ, Z(null), (null)(null), S(null), or listed/approved "at-risk" alleles who had a documented total serum alpha$_1$-PI level < 11 µM and who had a post-bronchodilator Forced Expiratory Volume in one second (FEV_1) ≥ 30% and < 80% of predicted and FEV_1/forced vital capacity (FVC) < 70% (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage II or III).

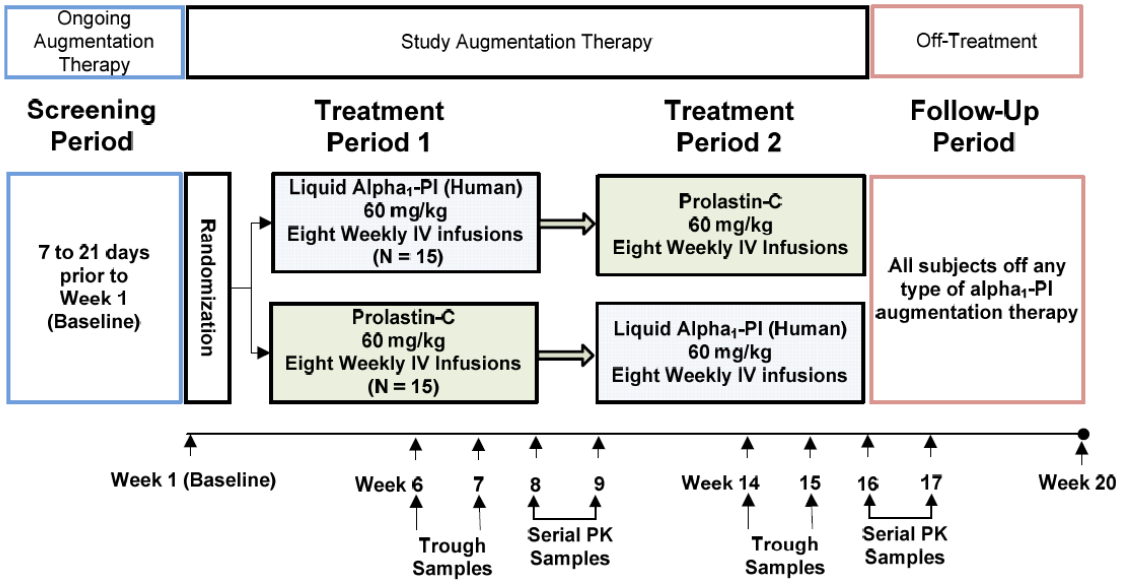
Subjects were randomized 1:1 based on a computer-generated randomization schedule to one of the following treatment sequences for study Treatment Periods 1 and 2:

#1 – PROLASTIN-C LIQUID (Liquid A_1-PI) followed by PROLASTIN-C

#2 – PROLASTIN-C followed by PROLASTIN-C LIQUID (Liquid A_1-PI)

The study schema is shown below.

Protocol ID GT11402 study schema



Note: Liquid Alpha$_1$-PI (Human) and PROLASTIN-C LIQUID are synonymous.

Trough samples for period 1 were drawn prior to infusions at weeks 6, 7, 8 and 9; and for period 2 prior to infusion at weeks 14, 15, 16, and 7 days after the last dose (at week 17). "Baseline" corrected area under the curve (AUC) was obtained by using the week 20 blood sample to subtract the contribution from endogenous A_1-PI, representing a 4-week wash-out of exogenous A_1-PI (test product).

The primary pharmacokinetic (PK) endpoint was a formal bioequivalence test performed for serum antigenic A_1-PI $AUC_{0\text{-}7days}$ without baseline correction. Note that the serum antigenic A_1-PI level is a mass-based measurement. The applicant also measured serum functional A_1-PI levels using the anti-neutrophil elastase capacity assay (ANEC) and calculated serum functional A_1-PI $AUC_{0\text{-}7\ days}$ from these measurements.

Thirty-two subjects were randomized and dosed in either of the 2 randomization treatment sequences (16 subjects in each sequence). All 32 subjects received at least one dose of study medication and are included in the safety population. One subject in the PROLASTIN-C LIQUID /PROLASTIN-C treatment sequence was discontinued prematurely after week 1 during period 1 for lack of home health care service, did not have sufficient/valid A_1-PI concentration data to facilitate calculation of PK parameters, and was excluded from the PK population. One subject in the PROLASTIN-C / PROLASTIN-C LIQUID treatment sequence was lost to follow-up after receiving both treatments and was included in the PK population.

Demographic variables were reasonably balanced between randomized treatment sequences.

The applicant and FDA concluded that the primary PK objective was achieved, in that PK bioequivalence of the 2 treatments was demonstrated based on the statistical analysis of serum A_1-PI $AUC_{0\text{-}7days}$ (antigenic content). The 90% confidence interval for the geometric least-squares mean ratio of PROLASTIN-C LIQUID / PROLASTIN-C for serum antigenic A_1-PI $AUC_{0\text{-}7days}$ fell within the pre-specified 80 to 125% PK equivalence limits. "Baseline"-corrected serum A_1-PI $AUC_{0\text{-}7days}$ also fell within PK equivalence limits.

PK parameters for steady-state serum antigenic A_1-PI as calculated by the applicant are shown below.

Applicant's Table 11-2: Summary of Steady-State PK Parameters (Antigenic Content) (PK Population, 4-week post-treatment "baseline"-corrected)

Treatment	$AUC_{0\text{-}7days}$ (mg*h/mL) n Mean (%CV)	Corrected $AUC_{0\text{-}7\ days}$ [a] (mg*h/mL) n Mean (%CV)	C_{max} (mg/mL) n Mean (%CV)	t_{max} (hours) n Median (range)	$t_{1/2}$ (hours) n Mean (%CV)	CL (mL/kg/h) n Mean (%CV)
Liquid Alpha$_1$-PI N=31	30 203.20 (11.3)	29 153.49 (14.2)	30 2.54 (15.3)	30 0.64 (0.28–2.25)	30 156.39 (18.0)	29 0.40 (14.0)
Prolastin-C N=31	28 198.38 (12.7)	27 147.67 (17.9)	28 2.49 (20.0)	28 0.69 (0.28–4.33)	28 164.10 (21.1)	27 0.42 (22.1)

[a] Corrected $AUC_{0\text{-}7\ days}$ is calculated using the concentrations corrected for endogenous concentration measured at Week 20.

Note: Liquid Alpha$_1$-PI and PROLASTIN-C LIQUID are synonymous.

The applicant's statistical analysis results for the primary endpoint are presented below.

Applicant's Table 11-4: Results of Statistical Analysis of Key PK Parameters (Alpha$_1$-PI Antigenic Content) at Steady-State (PK Population)

		$AUC_{0\text{-}7days}$ (mg*h/mL)			
Treatment	**N**	**Geometric Mean**	**Geometric LSM**	**Geometric LSM Ratio**	**90% CI of Geometric LSM Ratio**
Liquid Alpha$_1$-PI	30	201.96	203.57	1.05	1.03, 1.08
Prolastin-C	28	196.85	193.71		
		Corrected $AUC_{0\text{-}7days}$ (mg*h/mL)[a]			
Treatment	**N**	**Geometric Mean**	**Geometric LSM**	**Geometric LSM Ratio**	**90% CI of Geometric LSM Ratio**
Liquid Alpha$_1$-PI	29	152.05	153.38	1.07	1.03, 1.11
Prolastin-C	27	145.16	143.33		

[a] Corrected $AUC_{0\text{-}7\ days}$ is calculated using the concentrations corrected for endogenous concentration measured at Week 20.

Note: Liquid Alpha1-PI and PROLASTIN-C LIQUID are synonymous.

The applicant's conclusions regarding bioequivalence of PROLASTIN-C and PROLASTIN-C LIQUID, based on both antigenic and functional (anti-neutrophil elastase capacity, ANEC) A_1-PI AUCs, were confirmed by the FDA Clinical Pharmacologist.

Averaging the steady-state trough serum antigenic A_1-PI levels of weeks 6 through 9 of period 1 and of weeks 14 through 17 of period 2, the mean results for PROLASTIN-C LIQUID and PROLASTIN-C were 17.7 μM (n = 31) and 16.9 μM (n = 29), respectively. Note that normal (PI*MM genotype) levels of serum antigenic A_1-PI range from 20 to 53 μM. Thus, at the currently recommended dosage of 60 mg/kg weekly IV, normal serum A_1-PI levels are not maintained at trough for either product.

Mean steady-state trough functional serum A_1-PI activity, averaged over the above four-week intervals, for PROLASTIN-C LIQUID was 13.6 $\pm$ 3.0 μM and for PROLASTIN-C was 13.2 $\pm$ 2.8 μM.

The review team confirmed that PK equivalence has been demonstrated between PROLASTIN-C LIQUID and PROLASTIN-C.

It should be noted that, in a prior PK crossover study in 24 AATD subjects described in the approved PROLASTIN-C package insert, PROLASTIN-C was determined to be bioequivalent to PROLASTIN. Results from this earlier study and from study GI11402 are shown in the composite table below.

Steady-State Mean Serum A_1-PI Trough Levels in 2 Studies

	PROLASTIN-C Liquid	**PROLASTIN-C**	**PROLASTIN**
A_1-PI Antigenic[1] μM	17.7 ± 2.7	16.7 ± 2.7	
A_1-PI Antigenic[2] μM		16.9 ± 2.3	16.7 ± 2.7
A_1-PI Functional[1] μM	13.6 + 3.0	13.2 + 2.8	
A_1-PI Functional[2] μM		11.8 + 2.2	11.0 + 2.2

[1] PROLASTIN-C Liquid versus PROLASTIN-C PK Crossover Trial (n = 31)
[2] PROLASTIN-C versus PROLASTIN PK Crossover Trial (n = 24)
Table entries adapted from PROLASTIN-C PI and calculated from Applicant's Table 11-6.

Results of CBER Bioresearch Monitoring (BIMO) inspections:

CBER's Bioresearch Monitoring (BIMO) inspection assignments were issued for two clinical sites that participated in the conduct of Study GTI1402, and one central laboratory that performed testing of the pharmacokinetic samples collected from the participating study sites. The inspections did not reveal any substantive problems impacting the submitted data in this supplemental BLA.

b) Pediatrics

The requirements under the Pediatric Research Equity Act (PREA) do not apply to this product because it has orphan product designation for the requested indication. Emphysema has not been known to develop in pediatric individuals with severe AATD.

c) Other Special Populations

Clinical studies of PROLASTIN-C LIQUID did not include sufficient numbers of subjects aged 65 and over to definitively determine whether they respond differently from younger subjects.

4. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The firm's Alpha-1 Proteinase Inhibitor (A_1-PI, PROLASTIN) was initially developed as a lyophilized formulation. In 2009, a modified manufacturing process (PROLASTIN-C)

was approved, in which solvent-detergent treatment and nanofiltration steps were incorporated for pathogen inactivation / removal, replacing heat treatment. The current efficacy supplement supports PROLASTIN-C LIQUID, which is a new, liquid formulation of PROLASTIN-C. Upstream manufacturing for PROLASTIN-C LIQUID is identical to that of PROLASTIN-C. At final formulation of PROLASTIN-C LIQUID, 0.25 M alanine is added as an excipient, and the final lyophilization step is removed, obviating the need for reconstitution.

PROLASTIN-C LIQUID, like its predecessor product PROLASTIN-C, is manufactured from pooled human plasma using the cold ethanol fractionation method and a multi-step purification process. The plasma is collected from healthy donors in plasmapheresis centers located in the United States only. Donor screening and testing of plasma for viral markers and viral nucleic acids are carried out to ensure absence of clinically significant viruses. Plasma manufacturing pools are tested for markers of viral infection by serology (HCV, HIV, HBsAg) and NAT (HCV, HIV, HBV, B19) technology before entering the manufacturing process. Starting plasma is fractionated using a modified (b) (4) to yield Fraction IV-1 paste. After PEG precipitation and filtration to remove impurities and lipids, solvent / detergent treatment is performed to inactivate enveloped viruses. Further purification of A_1-PI is achieved by sequential anion exchange chromatography and cation exchange chromatography. The cation exchange (b) (4) containing purified A_1-PI is nanofiltered to remove pathogens, then (b) (4) . Concentrated nanofiltrate is formulated in sodium phosphate buffer containing (b) (4) sterile filtered to produce the final Sterile Bulk. Robust pathogen removal is achieved across the manufacturing process, as illustrated in the following chart.

Pathogen Removal in the PROLASTIN-C / PROLASTIN-C LIQUID Manufacturing Process

Process Step	Enveloped Viruses				Non-enveloped		
	HIV-1	BVDV	PRV	VSV	Reo3	HAV	PPV
Cold Ethanol Fractionation	(b) (4)	(b) (4)	(b) (4)	ND†	≥ 2.1	1.4	1.0
PEG Precipitation	4.3	2.8	3.3	ND	3.3	3.0	3.2
Depth Filtration	≥ 4.7	4.0	≥ 4.8	ND	≥ 4.0	≥ 2.8	≥ 4.4
Solvent/Detergent Treatment	≥ 6.2	≥ 4.6	≥ 4.3	5.1	NA††	NA	NA
15 nm Virus Removal	≥ 6.9	≥ 4.7	≥ 5.2	≥ 5.1	≥ 4.3	≥ 5.5	4.2
Accumulated Virus Reduction	(b) (4)	(b) (4)	(b) (4)	≥ 10.2	≥ 13.7	≥ 12.7	≥ 12.8

HIV: Human immunodeficiency virus
BVDV: Bovine viral diarrhea virus, model for hepatitis C virus
PRV: Pseudo-rabies virus, model for large enveloped DNA viruses e.g. herpes virus
VSV: Vesicular stomatitis virus, model for enveloped viruses
Reo3: Reovirus type 3, model for non-enveloped viruses

HAV: Hepatitis A virus
PPV: Porcine parvivirus, model for human parvovirus B19

Drug Product Specifications

Review personnel evaluated the specifications and validation of analytical methods for PROLASTIN-C LIQUID. Final specifications and acceptance limits for PROLASTIN-C LIQUID were within ranges established by PROLASTIN-C and other $Alpha_1$ Proteinase Inhibitor products, and were found acceptable. PROLASTIN-C LIQUID is appropriately tested for quality attributes and validated methods are used in control and release testing of starting materials, process intermediates, drug product, and stability samples. Specifications for PROLASTIN-C LIQUID were derived from conformance batches and product data from PROLASTIN-C manufacture, and the outcome of clinical studies.

Product Specifications

Test Items	Release Criteria	Shelf-Life Criteria
Alanine		0.20 to 0.30 M
Appearance (Visual)		Clear, Colorless or pale yellow or pale green
pH (b) (4)		6.6 to 7.4
Sodium		NMT 100 mEq/L
Phosphate		0.013 to 0.025 M
(b) (4)		(b) (4)
IgA		(b) (4)
Protein		Report mg/mL
(b) (4)		(b) (4)
(b) (4)		(b) (4)
$Alpha_1$-PI Potency: Concentration	(b) (4)	(b) (4)
$Alpha_1$-PI Potency: Vial Content	(b) (4)	(b) (4)

Specific Activity	(b) (4)	NLT 0.7 mg/mg
Sterility, (b) (4)		No growth
Pyrogen, (b) (4)		Complies
Safety, (b) (4)		Complies
Fill Volume Check		NLT Labeled Volume (20 mL)
Identity Testing for Packaged Final Container	Verification of presence of $Alpha_1$-PI	
(b) (4)	(b) (4)	(b) (4)

Stability of Final Drug Product

The stability study data provided in the PROLASTIN-C LIQUID supplement were judged by the review team to be sufficiently supportive of the proposed storage conditions of 24 months at 2 to 8°C, with up to one month under controlled room temperature conditions not more than 25°C.

Stability Parameters

Test	Acceptance Criteria
Visual Inspection/Appearance	Clear, Colorless or pale yellow or pale green
pH, (b) (4)	6.6 to 7.4
(b) (4)	(b) (4)
$Alpha_1$-Proteinase Inhibitor Potency	(b) (4)
Sterility	No Growth

Conclusion: The CMC reviewers find that sufficient data and information have been provided on the chemistry, manufacturing, and controls to support licensure of PROLASTIN-C LIQUID.

b) CBER Lot Release (only applicable for BLAs)

Due to extensive manufacturing experience and a sufficient history of satisfactory release testing results, PROLASTIN was exempted from Lot Release in 2001. Currently, at the beginning of each quarter every year, the firm submits two final container samples of PROLASTIN-C and a release protocol for the first lot manufactured bearing the U.S. license number. Detailed information about lots manufactured, released, reworked/reprocessed, and rejected is submitted twice yearly. No changes to product surveillance or lot release procedures are recommended related to the current efficacy supplement supporting PROLASTIN-C LIQUID.

c) Facilities review/inspection

The facilities review memo is consistent with a recommendation for approval. Responses to information requests were deemed acceptable. No GMP facilities inspection was required, as criteria requiring an inspection per CBER SOPP 8410 were not met.

d) Environmental Assessment

Because the applicant confirmed that there would be no increase in total distribution of PROLASTIN-C plus PROLASTIN-C LIQUID over the current distribution of PROLASTIN-C with the approval and marketing of PROLASTIN-C LIQUID, a categorical exclusion of environmental assessment was not required.

e) Product Comparability

The manufacturing of PROLASTIN-C LIQUID is identical to the currently licensed process for PROLASTIN-C from plasma pooling through fractionation and purification, up to and including the (b) (4) of nanofiltrate. At final formulation of the liquid product, sodium phosphate and alanine excipient to enhance stability are added to the final bulk. Release characteristics of PROLASTIN-C LIQUID are comparable to PROLASTIN-C. As expected for a liquid formulation, PROLASTIN-C LIQUID shelf life is shorter than that of the lyophilized product.

5. Nonclinical Pharmacology/Toxicology

In this PAS, Grifols Therapeutics Inc. submitted two repeated dose toxicology studies, one pharmacokinetic (PK) study, and one neoantigenicity study performed in rabbits using PROLASTIN-C LIQUID administered intravenously. Other studies submitted in support of the application were performed with older formulations of the product, PROLASTIN-C and PROLASTIN-C MP.

The repeated dose study indicated that administration of A_1PI products for 5 days in rabbits resulted in the development of IgM and IgG antibodies. This is an expected response to administration of a human protein to animals. The neoantigenicity study demonstrated there were no new epitopes or increased immunogenicity of PROLASTIN-

C LIQUID compared to the approved product, PROLASTIN-C. Thus, the animal studies demonstrated that 600 mg/kg PROLASTIN-C LIQUID administered intravenously in rabbits, a dose 10 times higher than the human dose, can be considered the NOAEL.

A safety assessment of alanine as an excipient was also submitted showing that the safety margins are sufficient to conclude that administration of 60 mg/kg PROLASTIN-C LIQUID is not likely to pose a toxicity risk for humans.

6. Clinical Pharmacology

Grifols' PROLASTIN-C is a lyophilized preparation of purified human $Alpha_1$-PI that is reconstituted with sterile water. PROLASTIN-C is approved for the chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of $Alpha_1$-PI ($alpha_1$-antitrypsin deficiency). In the current PAS, Grifols developed a new alanine-stabilized liquid formulation of human plasma-derived $alpha_1$-PI. The manufacturing process for PROLASTIN-C LIQUID is the same as that for PROLASTIN-C until the final formulation step where alanine is added as a stabilizer versus sodium chloride and the product is provided in the final container as a liquid instead of a lyophilized powder. Compared to lyophilized $Alpha_1$-PI, use of Liquid $Alpha_1$-PI may shorten the preparation time and eliminate the potential for reconstitution errors.

In the current PAS, the applicant submitted results of one multi-center, randomized treatment sequence, double-blind, crossover study to access the safety and pharmacokinetics of PROLASTIN-C LIQUID compared to PROLASTIN-C in subjects with AATD at the dose of 60 mg/kg/week. Pharmacokinetic results indicate that at steady-state, PROLASTIN-C LIQUID is bioequivalent to PROLASTIN-C for $AUC_{0\text{-}7days}$ for both antigenic and functional $Alpha_1$-PI. The Clinical Pharmacology reviewer concluded that, notwithstanding the primary PK endpoint for bioequivalence being based on the antigenic assay, the functional assay results were more important because of their presumed greater biological relevance. On this basis, the applicant was requested to replace the serum antigenic A_1-PI concentration – time curves for PROLASTIN-C LIQUID AND PROLASTIN-C in the Clinical Pharmacology section of draft package insert with corresponding curves using the ANEC functional A_1-PI assay results. The totality of the data, including baseline-adjusted and unadjusted AUCs and mean steady-state trough functional and antigenic A1-PI levels, supported the conclusion of bioequivalence between PROLASTIN-C LIQUID and PROLASTIN-C. The safety profile of PROLASTIN-C LIQUID administered weekly at 60 mg/kg is consistent with that of the approved PROLASTIN-C in lyophilized dosage form.

Overall, the PK study supports a demonstration of the similarity of pharmacokinetic profiles between PROLASTIN-C LIQUID and the approved lyophilized dosage form of PROLASTIN-C at steady-state in subjects with AATD.

7. Safety

Both PROLASTIN-C LIQUID and PROLASTIN-C administration were associated with an acceptable safety profile in this study of limited size and duration. There were no deaths or premature discontinuations due to adverse events (AEs). Only a single SAE was reported, consisting of an infective COPD exacerbation, which occurred during the follow-up period after the PROLASTIN-C dosing period.

The overall incidence of treatment-emergent adverse events (AEs) was 59% (19/32) of subjects during PROLASTIN-C LIQUID treatment and 42% (13/31) during PROLASTIN-C treatment. The most frequent AEs during the PROLASTIN-C LIQUID treatment period were diarrhea, contact dermatitis, and pyrexia which occurred in two subjects each (6%). The most frequent AE during the PROLASTIN-C treatment period was nasopharyngitis, which occurred in two subjects (6%). The only severe-intensity AE was back pain in a subject receiving PROLASTIN-C. Moderate-intensity AEs were more frequent during the PROLASTIN-C LIQUID treatment period (17 AEs in 12 subjects) than during the PROLASTIN-C treatment period (7 AEs in 4 subjects).

AEs that began during or within 72 hours following the end of a test product infusion numbered 16 in 13 subjects for PROLASTIN-C LIQUID and six in five subjects for PROLASTIN-C. The most frequent temporally associated AEs for PROLASTIN-C LIQUID using this definition were fatigue and diarrhea (2 subjects = 6% each). The total number of COPD exacerbations reported during the PROLASTIN-C LIQUID treatment period (13/32, 41%) was somewhat higher than the number reported during the PROLASTIN-C treatment period (10/31, 32%). No COPD exacerbation was reported as an SAE during PROLASTIN-C LIQUID treatment. The sponsor's summary tables of AEs and of COPD exacerbations were verified by the FDA biostatistician.

Suspected adverse reactions plus adverse reactions (ARs) were defined in the protocol to consist of AEs that met either the above criterion for temporal association or were considered at least possibly related to investigational product administration by the investigator or applicant, or which demonstrated at least a 30% excess incidence compared to the other treatment. Such suspected adverse reactions/adverse reactions were somewhat more frequent during the PROLASTIN-C LIQUID treatment period (occurring in 13 subjects, 41%) compared to the PROLASTIN-C treatment period (occurring in 7 subjects, 23%). Among the suspected ARs/ARs meeting these criteria, only diarrhea and fatigue had frequencies during PROLASTIN-C LIQUID treatment that exceeded those during PROLASTIN-C treatment by greater than 5% absolute.

Immunogenicity was assessed by an older assay that was not considered adequate by the Product reviewer, prompting an information request to re-run available stored serum samples using the newer assay that the applicant had developed and validated. It was subsequently agreed to permit the applicant to perform and submit as a PMC a retrospective validation of the immunogenicity assay used in the trial. No subjects had detectable inhibitory assays using the old assay and only one subject had a confirmed positive ELISA anti-A1-PI antibody result. This subject had a positive result at baseline with the titer having fallen at week 9 after exposure to PROLASTIN-C, and it became negative at week 20 four weeks after the PROLASTIN-C LIQUID treatment period.

No patterns of clinically meaningful changes in routine safety laboratory tests were observed, but one subject developed moderate thrombocytopenia 29 days after the last PROLASTIN-C LIQUID administration; this was considered unrelated to A_1-PI therapy. One subject experienced a mild elevation in AST to a value $\leq$ 1.5 x the upper limit of normal at weeks 9 and 17 that was considered possibly related. Such changes are relatively common in the placebo arms of randomized clinical trials in a variety of non-hepatic disorders.

No new clear safety signals were evident from the review of safety data, but it appeared that PROLASTIN-C LIQUID could be associated with a somewhat higher incidence of moderate intensity AEs and suspected adverse reactions. None of these were serious.

8. Advisory Committee Meeting

No advisory committee meeting was held in connection with this supplement because (a) this biologic is not the first in its class, (b) the safety profile is similar to that of other drugs approved for this indication, (c) the clinical study design was similar to what had been previously used in support of the approval of PROLASTIN-C, (d) evaluation of the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class, (e) the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease, and (f) outside expertise was not necessary; there were no controversial issues that would have benefited from advisory committee discussion.

9. Other Relevant Regulatory Issues

Out of six clinical investigators for the PK, safety, and immunogenicity study comparing PROLASTIN-C and PROLASTIN-C LIQUID, two had received "significant payments of other sorts." One had received compensation as a member of the Grifols Speakers Bureau, and this was disclosed on the applicant's financial disclosure form. The other had been omitted from the applicant's financial disclosure form; the payment consisted of a grant from the applicant to conduct a rat transplant study involving PROLASTIN. This was discovered in the course of one of the BiMo investigator site inspections. The Clinical Reviewer concluded that, in part due to the objective nature of serum A1-PI level measurements performed at a central laboratory, these potential financial conflicts of interest were unlikely to have resulted in the generation of biased study data from the respective investigator sites.

10. Labeling

The applicant revised the draft package insert based on FDA information requests that reflected input from the Clinical, Pharmacology-Toxicology, and Advertising and Promotional Labeling Branch (APLB) reviewers. The APLB reviewer recommended that consideration be given to shortening the Clinical Pharmacology section of the draft PI, but the Clinical Reviewer elected to retain this previously-negotiated class labeling section of the PI to provide information on AATD and the biomarker, A1-PI levels; this was considered appropriate given FDA's previous reliance on biomarkers to provide evidence of efficacy for this product class. No labeling changes were requested by the

product review team. The revised draft PI submitted September 8, 2017 is considered acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

Approval of this supplement is recommended by the clinical, clinical pharmacology, and product reviewers with no dissentions from other reviewing disciplines.

b) Risk/ Benefit Assessment

Short-term risks of PROLASTIN-C LIQUID as gleaned from the single clinical trial conducted with this agent may include diarrhea and fatigue, and in view of PK equivalence demonstrated between Liquid and licensed PROLASTIN-C, that all potential risks of PROLASTIN-C may pertain to PROLASTIN-C LIQUID as well. These potential risks may include hypersensitivity, upper respiratory tract infection, urinary tract infection, nausea, chest pain, back pain, chills, cough, dizziness, dyspnea, headache, hot flush, oral candidiasis, and, due to its being a plasma-derived product, viral and prion disease transmission.

The beneficial clinical effects of long-term administration of PROLASTIN-C LIQUID, PROLASTIN-C, and PROLASTIN have not been demonstrated. The modestly-sized EXACTLE trial showed no effect of PROLASTIN on COPD exacerbation frequency over 2.5 years compared to placebo, but a possible effect in reducing exacerbation severity. Further insight into possible effects of PROLASTIN-C (and, by extension, PROLASTIN-C LIQUID) on exacerbations, CT lung density, and other efficacy and safety parameters will come from the ongoing SPARTA trial, a three-arm, three-year-treatment duration randomized placebo-controlled clinical study comparing two dose levels of PROLASTIN-C with placebo that is currently being conducted by this applicant.

The clinical reviewer considers that, from a regulatory perspective, it is reasonable to expect that the potential, though unproven, benefits of PROLASTIN-C LIQUID in slowing the progression of emphysema may outweigh the risks of augmentation therapy with this agent, given its relatively benign short-term safety profile.

c) Recommendation for Postmarketing Activities

The applicant's proposed continued routine pharmacovigilance is adequate to monitor postmarket safety.

No clinical reportable postmarketing commitment studies (PMCs) are recommended.