STATISTICAL ANALYSIS PLAN (SAP)

Study Title: A Double-blind, Randomized-withdrawal, Placebo-controlled Study to Evaluate the Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as Add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection in Adult Renal Transplant Recipients

Investigational Medicinal Product: C1-INH (C1-esterase Inhibitor, Human)

Protocol Number: CSL842_3001

Version: FINAL 1.0

Version Date: 10-Dec-2020

Sponsor:

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1 Modification History

Version	Effective Date	Author of Modification	Reason for Change
0.2 (misleading version numbering, had been version 1.0)	21/Jun/2018	PPD	N/A – First Version
1.0	13/Dec/2018	PPD	Implementation of sponsor comments
2.0	27Nov2020	PPD	Updated document following study termination decision by sponsor
3.0	08Dec2020	PPD	Implementation of sponsor review comments
Final 1.0	10Dec2020	PPD	NA

2 List of Abbreviations

Abbreviation	Term
ABMR	Antibody-Mediated Rejection
AE	Adverse Event
AMR	Antibody-mediated Rejection
ADaM	Analysis Data Model
CDISC	Clinical Data Interchange Standards Consortium
C1-INH	C1-esterase Inhibitor
Cg	Chronic Glomerulopathy
CP	Conditional Power
CSL	CSL Behring LLC
DGF	Delayed Graft Function
DSA	Donor-specific Antibody
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IDMC	Independent Data Monitoring Committee
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
IVIg	Intravenous Immunoglobulin
CCI [redacted]	
CCI [redacted]	
PK	Pharmacokinetic
RIS	Run-in Safety
RWS	Randomized Withdrawal Safety
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
S_{cr}	Serum Creatinine
TEE	Thromboembolic Events

3 Purpose

This is the statistical analysis plan (SAP) for the Clinical Study Report for study CSL842_3001. This SAP provides details of the planned statistical analyses of the primary and relevant secondary endpoints for which data are available. This study was terminated by the sponsor on September 15, 2020 for administrative reasons. At the time of termination, 13 subjects were randomized and 2 subjects were still in treatment (1 subject in TP2 and another subject in re-treatment). The study database will be locked after the completion of the dosing regimens of these 2 subjects. Based n the termination of the study, many analysis discussed in the protocol will not be able to be performed (for example, all 4 year endpoints are unattainable).

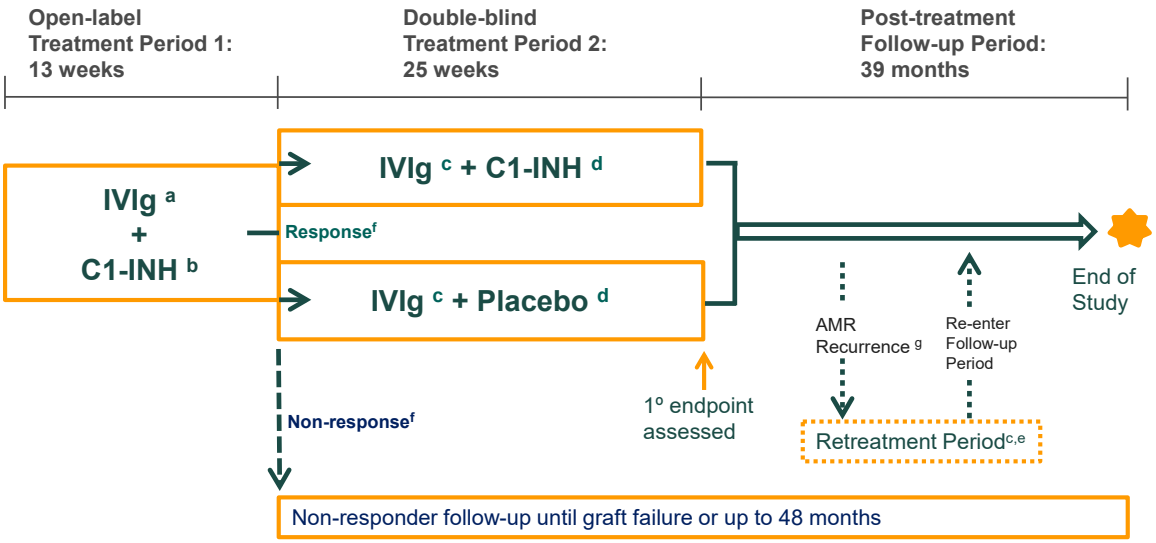
This SAP complies with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. It is based upon the Clinical Study Protocol (dated 01-March-2017) and Study Protocol Amendment Version 1.0 (dated 30-August-2017), Study Protocol Amendment Version 2.0 (dated 23-January 2019), and Study Protocol Amendment Version 3.0 (dated 31-January 2020).

4 Study Design

4.1 Study Design

Study CSL842_3001 is a randomized withdrawal, double-blind, placebo-controlled, multi-center study. A schematic of the design is shown in Figure 1. Full details may be found in Section 3 of the Clinical Study Protocol.

Figure 1 Study Overview



AMR = antibody-mediated rejection; C1-INH = C1-esterase inhibitor; human; IVIg = intravenous immunoglobulin; MFI = mean fluorescence intensity; TP1 = Treatment Period 1; Treatment Period 2

Note: Post-treatment Follow-up Period is for responders.

[a] Intravenous immunoglobulin (IVIg) will be administered every 4 weeks to all subjects at a dose of 2 grams/kg. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days. Plasmapheresis may be administered based on local DSA results and Principal Investigator's judgement.

[b] Intravenous (IV) C1-INH (60 IU/kg) will be administered to each subject over the first 13 days of TP1for a total of 5 doses. Thereafter, subcutaneous (SC) C1-INH (60 IU/kg twice weekly) will be administered to each subject for the remainder of TP1.

[c] If DSA ≥ 2000 MFI in local lab in TP2 or Retreatment Period, IVIg may be administered to subjects at a dose of 2 grams/kg every 4 weeks. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days. Plasmapheresis may be administered based on local DSA results and Principal Investigator's judgement (Section 5.4.2 of the protocol).

[d] During the TP2, eligible subjects will be randomized 1:1 to receive treatment with investigational product (C1-INH [60 IU/kg] or placebo) subcutaneously twice weekly.

[e] Retreatment Period(s) are blinded and subjects will receive the same investigational product treatment assignment as received during Treatment Period 2.

[f] Response is defined as an End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) that is ≥ 20 mL/min/1.73 m^2 and ≥ 90% of the baseline eGFR (mean of Screening and the Day 1 eGFR)).

[g] AMR Recurrence or persistence in Responder Follow-up Period is proven by biopsy, evidenced by infiltrating neutrophils and/or monocytes with or without the presence of C4d (g > 0, v > 0, and/or ptc > 0 (if C4d is negative, g + ptc ≥ 2, (Section 8.1.3.3 of the protocol).

- During open-label TP1, all eligible subjects will receive treatment with C1-INH (60 IU/kg) in combination with standard of care for 13 weeks. At the conclusion of TP1, subjects who demonstrate a treatment response (see Section 8.2.9) will be randomized to continue in the study in TP2. Subjects who are considered non-responders will enter the Non-responder Follow-up Period during which they will be followed for up to 48 months.
- During the blinded TP2, randomized subjects will either continue treatment with C1-INH (60 IU/kg) or begin treatment with placebo (both in combination with IVIg and plasmapheresis) for 25 weeks, according to the randomization schedule.
- At the conclusion of TP2, randomized subjects will enter the Responder Follow-up Period, where they will be observed for approximately 39 months until Study Month 48.

Randomized subjects who experience a biopsy-proven AMR recurrence or who have persistent AMR during the Responder Follow-up will be permitted to undergo blinded retreatment with either C1-INH or placebo (both in combination with standard of care treatment). Subjects who participate in a Retreatment Period will receive blinded investigational product (C1-INH or placebo) according to their TP2 treatment assignment, in combination with standard of care.

4.2 Study Objectives and Endpoints

4.2.1 Primary Objective and Endpoint

4.2.1.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.

4.2.1.2 Primary Endpoint

Table 1 Primary Endpoint

Endpoint	Summary Measure
Loss-of-response during TP2.	Proportion of subjects with loss-of-response at the End-of-TP2. Loss-of-response at the End-of-TP2 is defined as any 1 of the following 3 conditions: • End-of-TP2 eGFR (mean of Week 36 and Week 38 eGFR) that is not stable, defined as: o End-of-TP2 eGFR that is < 90% of the End-of-TP1 eGFR for subjects whose End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) is ≥ 100% of baseline, o End-of-TP2 eGFR that is < 90% of baseline for subjects whose end-of- TP1 eGFR is ≥ 90% of baseline and <100% of baseline, • Allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first), • Subject death by any cause.

eGFR = estimated glomerular filtration rate; TP1= Treatment Period 1; TP2 = Treatment Period 2

4.2.1.3 Intended Primary Study Hypothesis

Corresponding to the primary objective, the superiority of C1-INH relative to placebo are measured by the primary endpoint, proportion of subjects with loss of response at the End-of-TP2, based on the Modified Intent-to-Treat analysis. The null hypothesis was to be tested using the Wald statistic derived from maximum likelihood estimation of the logistic model with a Type I error rate of 0.05 (two-sided test). Symbolically, the null and alternative hypotheses are expressed as follows:

H_0: $\beta_T = 0$ vs H_1:$\beta_T \neq 0$

where β_T is the coefficient of treatment in the logistic regression model.

Since the study terminated early, there will be no formal hypothesis testing for any endpoints.

4.2.2 Secondary Objectives and Endpoints

4.2.2.1 Secondary Objectives

The secondary objectives of the study are:

1. To further evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.
2. To evaluate the safety of C1-INH in the treatment of refractory AMR in renal allograft recipients.
3. To evaluate the pharmacokinetics (PK) of C1-INH during the treatment of refractory AMR in renal allograft recipients.

4.2.2.2 Secondary Endpoints

Table 2 Secondary Endpoints

Secondary Objective	Endpoints	Summary Measure
1	All-cause allograft failure through the Responder Follow-up Period	Proportion of subjects with all-cause allograft failure through the Responder Follow-up Period (ie, within 48 months after enrollment). Allograft failure is defined as 1 of the following: • Allograft nephrectomy, institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first, OR • Subject death by any cause.
1	Change in eGFR from baseline to TP1	The difference between the End-of-TP1 eGFR and baseline eGFR.
1	Change in eGFR from TP1 to the End-of -TP2.	The difference between the End-of-TP2 eGFR and the End-of-TP1 eGFR.
1	The rate of change of eGFR.	The rate of change of eGFR during TP2 as defined by the slope of the mean regression of eGFR over time in TP2.
1	Time (weeks) to all-cause allograft failure through the Responder Follow-up Period	Time (weeks) to all-cause allograft failure through the Responder Follow-up Period (ie, within 48 months after enrollment).

Secondary Objective	Endpoints	Summary Measure
1	Responder status at the End-of-TP1.	Proportion of responders at the End-of-TP1. Response is defined as End-of-TP1 eGFR that is ≥ 20 mL/min/1.73 m^2 and ≥ 90% of the baseline eGFR.
1	Subject death through the Responder Follow-up Period.	Proportion of subjects surviving through the Responder Follow-up Period.
2	Any AE assessed as related to investigational product during TP1 and during TP2.	Proportion of subjects with any AE assessed as related to investigational product.
3	Pre-dose C1-esterase inhibitor functional activity at Day 1, Week 12, and Week 38.	Mean pre-dose C1-esterase inhibitor functional activity at Day 1, Week 12, and Week 38.
3	For the subset of subjects with sequential PK sampling, C1-esterase inhibitor functional activity $C_{max,}$ and AUC_{0-t} after IV and/or SC administration of C1-INH.	C1-esterase inhibitor functional activity C_{max} and AUC_{0-t} for IV and SC administration.

AE = adverse event; AUC_{0-t} = area under the plasma-concentration time curve 0 to a definite time; C_{max} = maximum concentration; eGFR = estimated glomerular filtration rate; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous; TP1 = Treatment Period 1; TP2 = Treatment Period 2

4.2.2.3 CCI [redacted]

CCI [redacted]

4.2.2.4 CCI [redacted]

CCI [redacted]

CCI

[redacted]

4.3 Study Treatments

Dose and Dosing Regimen

A summary of dose and dosing regimen is shown in Table 4.

Table 4 Summary of dose and dosing regime

Timeframe	Intravenous Administration	Subcutaneous Administration
Treatment Period 1: The Day 1 Visit to the Day 13 Visit[a]	60 IU/kg C1-INH	Not applicable
Treatment Period 1: The Day 14 Visit to the Week 12 2nd Visit[a]	Not Applicable	60 IU/kg C1-INH
Treatment Period 2: Week 13 to the Week 38 Visit[b]	Not Applicable	60 IU/kg C1-INH OR 0.12 mL/kg Placebo
Re-treatment Period: The Retreatment Day 1 Visit to the Retreatment Week 26 Visit.[c]	Not Applicable	60 IU/kg C1-INH OR 0.12 mL/kg Placebo

IV = intravenous; SC = subcutaneous

[a] Treatment Period 1 is open-label and each subject will receive C1-INH. C1-INH (60 IU/kg) will be administered IV to each subject over the first 13 days of Treatment Period 1 for a total of 5 doses. Thereafter, C1-INH (60 IU/kg twice weekly) will be administered SC to each subjects for the remainder of Treatment Period 1. The first dose of randomized investigational product will be administered to responders at the Week 13 Visit.

[b] Treatment Period 2 is blinded and subjects will be randomized 1:1 to treatment with investigational product (C1-INH [60 IU/kg] or placebo) subcutaneously twice weekly.

[c] Retreatment Period(s) are blinded and subjects will receive the same investigational product treatment assignment as received during Treatment Period 2.

Note: Week 13 is the final visit of Treatment Period 1 for non-responders and the first visit of Treatment Period 2 for responders.

Treatment Period 1

C1-INH will be administered to all subjects during Treatment Period 1 in an open-label manner. Five doses of C1-INH will be administered intravenously to subjects at the Day 1, 4, 7, 10, and 13 Visits. Intravenous C1-INH will be administered at the study site during site visits. Subcutaneous C1-INH will be administered every 3 to 4 days (ie, twice weekly) beginning at the Day 14 Visit and for the remainder of Treatment Period 1. Subcutaneous C1-INH is required to be administered at the study site during site visits, but at other times may instead be administered at home by a medical professional ((eg, a home visit nurse) or by the subject under the supervision of a medical professional.

Treatment Period 2

Investigational product (ie, C1-INH or placebo) will be administered to all subjects during Treatment Period 2 in a double-blind manner. Subcutaneous investigational product will be administered every 3 to 4 days (ie, twice weekly) during Treatment Period 2. Subcutaneous C1-INH is required to be administered at the study site during site visits, but at other times may instead be administered at home by a medical professional (eg, a home visit nurse) or by the subject under the supervision of a medical professional.

Retreatment Period

Subjects may undergo retreatment during the Responder Follow-up Period with the blinded investigational product to which they were randomized in TP2. Retreatment may occur following a diagnosis of recurrent or persistent AMR by biopsy, evidenced by infiltrating neutrophils and/or monocytes with or without the presence of C4d (glomerulitis [g] > 0, intimal arteritis [v] > 0, and/or peritubular capillaritis [ptc] > 0; if C4d is negative, g+ptc ≥ 2). Retreatment may start at any time during the Responder Follow-up Period, and will last for 26 weeks or until the Month 48 Visit, whichever occurs first. The Retreatment Period may also be shorter than 26 weeks at the investigator's discretion.

During the Retreatment Period, SC investigational product will be administered twice weekly (approximately every 3 to 4 days). During the Retreatment Period (if needed), SC C1-INH will be administered either at the site or may be dispensed to the subject and administered SC at home either by a medical professional or by the subject under the supervision of a medical professional.

Subcutaneous Administration of the Investigational Product

Subcutaneous administration of the investigational product should be via a single SC injection in the abdomen, thigh, upper arm, or other appropriate location. The twice weekly administration of investigational product beginning at the Day 14 Visit and during any Retreatment Period (if applicable). The suggested interval between each administration of investigational product is 3 or 4 days (ie, twice weekly). In addition, the investigational product should ideally be administered at approximately the same time on each day. A missed injection should be administered as soon as possible, unless within 24 hours of the next scheduled injection; in this situation, the missed injection should be omitted, and the administration of investigational product should occur at the next scheduled day and time. The volume of investigational product to be administered will be based on each subject's body weight (from the Screening physical examination) and will not be adjusted during the study.

Description of Investigational Products

The investigational products for this study are C1-INH and placebo. A description of C1-INH and Placebo and given in Table 5 and Table 6 respectively.

Table 5 Description of C1-INH

Substance name	C1-esterase Inhibitor, Human (500 IU/mL)
Active substance	C1-esterase inhibitor (human)
Trade name	Not applicable
Dosage form	Lyophilized powder for reconstitution; 1500 IU C1-INH per single-use vial.
Dose	60 IU/kg
Mode of administration	Intravenous / subcutaneous injection

Before use, each vial of C1-INH is reconstituted with 3 mL water for injection. 60 IU/kg C1-INH is equivalent to a volume of 0.12 mL/kg.

Table 6 Description of Placebo

Substance number	Not applicable
Substance	Excipients of C1-INH plus albumin
Trade name	Not applicable
Dosage form	Lyophilized powder for reconstitution
Dose	0.12 mL/kg
Mode of administration	Subcutaneous injection

Before use, each vial of placebo is reconstituted with 3 mL water for injection.

The volume of placebo will be based on the body weight obtained with vital signs assessment at the Screening Visit, and will not be changed through the study. The actual dose of placebo will be rounded to the lowest 1 mL as if the subject receiving C1-INH.

4.4 Randomization Procedures and Blinding

Randomization Procedures

All subjects will receive open-label C1-INH during Treatment Period 1. Subjects who are eligible for Treatment Period 2 will be assigned to either continued C1-INH or matched placebo in accordance with a computer-generated randomization list. Investigational product assigned in Treatment Period 2 will be allocated on a 1:1 ratio. The randomization will be stratified on the following 2 factors:

- Donor Specific Antibodies (DSA): sensitized prior to transplantation versus de novo. De novo is defined as the development of DSA after transplantation. In the case of both sensitized and de novo, the subject will be considered sensitized for stratification purposes.
- AMR severity: severe versus non-severe (ie all other severities). Severe AMR is defined as new onset oliguria (< 400 cc / 24 hours) or anuria with the current episode of AMR.

Therefore, there will be a total of 4 strata (2 factors, 2 levels per factor). The randomization will be permuted block within each stratum. Treatment assignment will be determined centrally. The randomization list will be generated and managed by the study's interactive response technology (IRT) external service provider.

The study database will be locked once all the randomized subjects currently in the study complete week 38 visit and re-treatment period as described in Section 3. The study will be unblinded for final analysis of the primary efficacy endpoint.

Maintaining the Blind

Treatment Period 1 is open-label. Treatment Period 2 is double-blind. During Treatment Period 2, the blind will be maintained for investigational site staff, including investigators, subjects, and CSL.

Emergency Unblinding

In emergency situations involving the safety of the subject, the investigator may break the blind using the IRT system. The reason for unblinding the randomization code must be fully documented. Emergency unblinding will be performed using the IRT. Steps for navigating the IRT for emergency unblinding are defined in the IRT manual.

4.5 Determination of the Sample Size

Sample Size Based on the Primary Efficacy Endpoint

The sample size is based on the primary efficacy endpoint of loss-of-response status (binary endpoint of loss-of-response or not), at the End-of-TP2 (ie, within 25 weeks after randomization). The null hypothesis is that there is no difference between C1-INH and placebo with respect to the proportion of subjects with loss-of-response at the End-of-TP2. Let p_0 and p_1 be the expected proportion of subjects with loss-of-response in TP2 in the placebo and C1-INH treatment groups, respectively. The alternative is that there is a difference between the treatment groups. That is, H_0: $p_0 = p_1$ versus H_1: $p_0 \neq p_1$.

The power procedure in SAS STAT software (Cary, NC SAS Institute Inc.) was used to estimate the sample size, based on the likelihood ratio chi-square test. Determination of the sample size was based on the following assumptions:

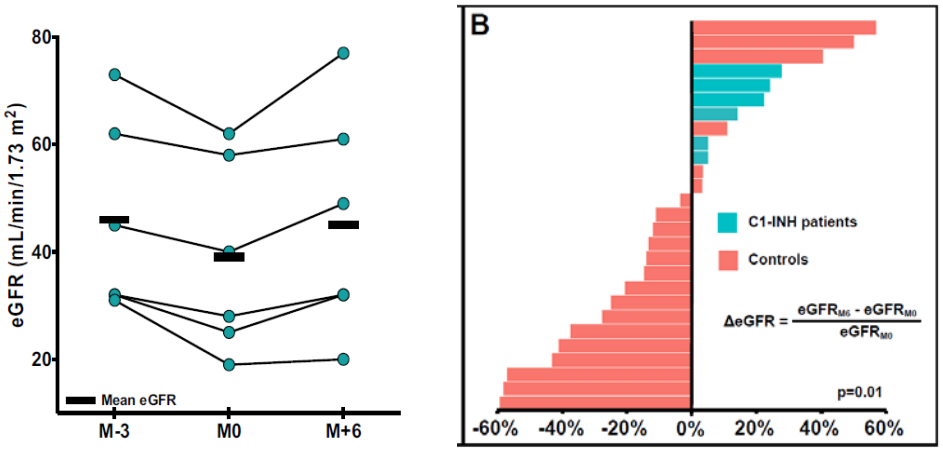
- The proportions of subjects experiencing loss-of-response at the End-of-TP2 will be 0.75 with placebo and 0.30 with C1-INH.
- There will be at least 90% power to detect a statistically significant effect with two-sided test with alpha = 0.05.
- Logistic regression model with treatment effect will be used for the primary efficacy analysis. Wald test statistic for treatment effect from Logistic regression has approximately same distribution as chi-square [Fleiss et al, 2003]. Therefore, the sample size calculation based on chi-square test is used to ensure similar power for hypothesis testing.
- Treatment allocation will be 1:1.

- The planned interim analysis for futility will not impact the type 1 error for the final analysis.

Under these assumptions, a total of 60 subjects (30 randomized to C1-INH and 30 randomized to placebo) will provide approximately 95% power. The study was planned to enroll a sufficient number of subjects (up to 175) to ensure that 60 subjects are randomized.

The assumptions above are based on a prospective single-arm pilot study to investigate the C1- INH added to high-dose IVIG for the treatment of acute AMR non-responsive to conventional therapy [Viglietti et al, 2016a]. A total of 6 subjects received C1-INH and IVIg for 6 months. The primary endpoint was change in eGFR. These were compared to a historical control of 21 subjects who received IVIg. In the prospectively treated C1-INH group, 0/6 subjects experienced decline in eGFR at 6 months (0; 95% confidence interval [CI], 0 to 46%); and 4/6 subjects had a greater than 20% increase in eGFR (67%; 95% CI, 22% to 96%). In the historical control group, 15/21 subjects (71%; 95% CI, 48% to 89%) experienced decline in eGFR during a comparable 6-month period. The results are presented in Figure 2.

Figure 2 Individual variations of eGFR in C1-INH patients



Left: Distributions of eGFR at time of initial diagnosis (M-3), at the end of first line treatment (SOC; M0) and at the end of C1-INH treatment (M+6) in 6 patients. Right: Individual variations in eGFR between M0 and M+6 in C1-INH patients (green) and historical controls (red). From Viglietti et al. (Viglietti et al, 2016b)

Power for the analysis of all-cause allograft failure

Allograft survival status (or all-cause allograft failure) at the end of 48 months after enrollment represents clinical confirmation of the effect on the allograft of improving eGFR.

The primary comparison of the proportion of subjects with allograft survival will be between the subjects randomized to placebo or C1-INH. It is anticipated that very few subjects will be lost to follow-up as standard of care mandates close follow up by the transplanting center. This endpoint will be analyzed after all subjects have been followed for 4 years after enrollment.

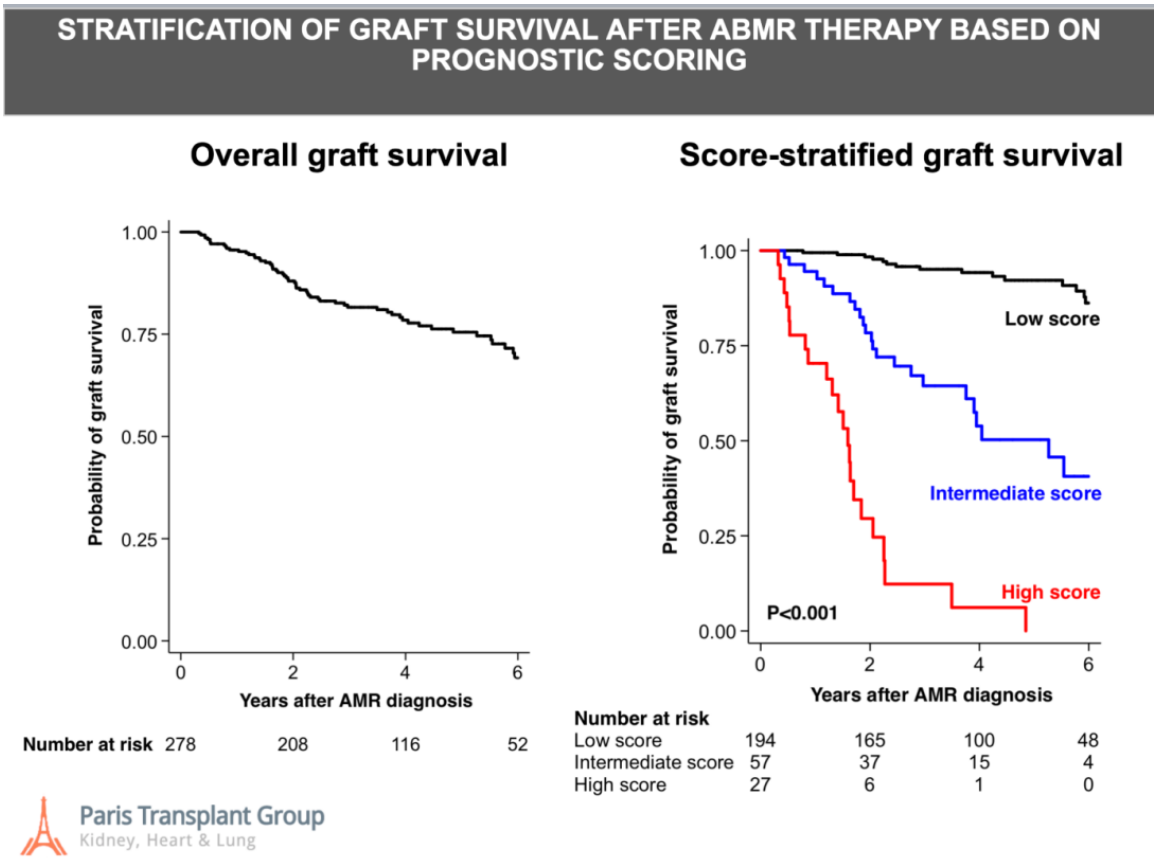
The power for hypothesis testing of this endpoint was estimated using the power procedure in SAS STAT under the following assumptions:

- The proportions of subjects with allografts surviving at 4 years after enrollment will be 0.25 with the placebo cohort and 0.75 in the C1-INH cohort.
- Alpha = 0.05 (two-sided test).
- Logistic regression model with treatment effect will be used for the primary efficacy analysis. Wald test statistic for treatment effect from Logistic regression has approximately same distribution as chi-square [Fleiss et al, 2003]. Therefore, the sample size calculation based on chi-square test is used to ensure similar power for hypothesis testing.
- Approximately 30 subjects in each randomized treatment groups.

There is greater than 90% power to detect the specified target difference between C1-INH and placebo groups based on sample size of 60 (approximately 30 in the C1-INH cohort and approximately 30 in the placebo cohort).

The 4-year graft survival for placebo of 25% is based on data presented at the American Transplant Congress in Boston [Viglietti et al, 2016b], as shown in Figure 3. This study involved follow-up of kidney transplant recipients with biopsy-proven active AMR diagnosed between 2007 and 2013. Among the subjects who have not responded to standard of care, the 4-year graft survival ranged from approximately 10% to 40% for subjects with high and intermediate risk scores, respectively. The 4-year graft survival for C1-INH of 75% represents what would be expected for subjects who are successfully treated.

Figure 3 Stratification of Graft Survival After ABMR Therapy Based on Prognostic Scoring



Source: Viglietti et al, 2016b American Transplant Congress Abstract #198

4.6 Planned Interim Analyses and Reviews

The study will be monitored by an Independent Data Monitoring Committee (IDMC). The meeting frequency, specific responsibilities, and composition of the IDMC will be outlined in a separate document, the IDMC charter.

The study was terminated by the sponsor on 15 September 2020, therefore, no interim analysis will be conducted.

5 Changes in the Conduct of Planned Analyses

There are changes in the planned analyses (from those specified in the protocol) following the sponsor's decision to terminate the study. There will be no analysis of the endpoints below Data from these endpoints will be presented only in subject listings.:

- Secondary endpoint of proportion of subjects with all-cause allograft failure through the Responder Follow-up Period,
- Time to all-cause allograft failure through 48 months after enrollment,
- Change in eGFR from End-of-TP1 to the End-of-TP2,
- Rate of change of eGFR in Treatment Period 2,
- CCI [redacted],
- Plasmapheresis sessions,
- CCI [redacted],
- CCI [redacted],
- CCI [redacted],
- Trough IVIg concentrations at designated time points,
- CCI [redacted],

For other endpoints the statistical analysis was reduced as described in the sections of this SAP.

6 Study Analysis Sets

6.1 Screened Analysis Set

The Screened analysis will comprise all subjects who provided written informed consent and who underwent study screening procedures.

6.2 Enrolled Analysis Set

The Enrolled Analysis Set will comprise all subjects in the Screened Analysis Set who did not fail screening.

6.3 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis will comprise all subjects who were randomized. Subjects will be classified according to the investigational product to which they were assigned (ie, continued C1-INH or placebo) regardless of what was actually received. This will be the primary analysis

set for the analysis of efficacy data. Any subject who received a randomization identification number will be considered to have been randomized.

6.4 Modified Intent-to-Treat Analysis Set

All subjects randomized under the original protocol and under all protocol amendments will be included in the Modified ITT (mITT) population except the subjects randomized prior to Amendment 3 who did not satisfy the eligibility criteria updated in Amendment 3. The mITT Analysis Set will be the primary analysis set for the analysis of efficacy data.

6.5 Safety Analysis Sets

Run-in Safety Analysis Set

The Run-in Safety (RiS) Analysis Set will comprise all subjects who received at least one dose of C1-INH during Treatment Period 1.

Randomized Withdrawal Safety Analysis Set

The Randomized Withdrawal Safety (RWS) Analysis Set will include all subjects in the ITT Analysis Set who received at least one dose of the investigational product after randomization during Treatment Period 2. The RWS Analysis Set will be based on the investigational product actually received (ie, continued C1-INH or placebo) during Treatment Period 2. If a C1-INH treatment subject receives one or two doses of placebo and then this is corrected for all subsequent doses they will be classified in the C1-INH treatment group.

6.6 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will comprise all subjects who received ≥ 1 dose of C1- INH and who have ≥ 1 measurable level of C1-INH functional activity or C1-INH antigen concentration.

6.7 CCI

CCI

7 General Considerations

Analysis datasets will be created according to CDISC standards, and data will be displayed according to reporting standards in this SAP and tables, figures and listings (TFL) formats.

SAS version 9.3 or higher will be used to perform all data analyses and to generate TFLs.

All ICH required data in the database will be presented in data listings.

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, Q1, Q3, minimum and maximum. Other descriptive statistics (eg, quartiles, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics required identified with the analysis in the applicable SAP section.

All listings will include subject number, treatment group. The laboratory normal reference ranges will be provided and clinical laboratory test results outside the normal reference range will be flagged in the laboratory data listings.

Summary statistics of central tendency will be reported to one more decimal place than the collected data. Summary statistics of variability will be reported to one more decimal place than the commensurate measure of central tendency. For example, the mean and median for age will be reported to one decimal place because it is collected in full years. The standard deviation of age will then be reported to 2 decimal places.

Formatting for dates and times will be: descriptive percentages and proportions will be displayed to one decimal place. Percentages and proportions to be tested will be calculated to 4 decimal places. Durations for events will be display to 1 decimal place.

- Dates only – ddmmmyyyy
- Times only – hh:mm or hh:mm.ss
- Dates and times – ddmmmyyyy hh:mm or ddmmmyyyy hh:mm:ss

In general, only scheduled visits will be included in by-visit summaries. However, worst-case or best-case values (as appropriate) will be derived using both scheduled and unscheduled visits. In general, assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times, other than those indicated in the Schedule of Assessments. However, exceptions may apply for creatinine / eGFR.

Actual rather than planned sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots and listing of PK concentration data. Planned times will be used in the descriptive summaries and in mean and median plots. Concentration-time data will be listed according to actual sampling times relative to dosing time.

Deviations from the analyses in this SAP will be identified in the CSR.

7.1 Multicenter Studies

Data from all participating sites will be pooled prior to analysis.

7.2 Treatment Descriptors

The following treatment group descriptor will be used on all applicable displays:

Treatment Group		**Order of Treatment Groups**
Code	**Description**	
A	Placebo	1
B	C1-INH	2

7.3 Multiple Comparisons and Multiplicity

No formal hypothesis testing is planned due to small number of subjects randomized in this study when the study was terminated by the sponsor. Hence multiplicity is not applicable.

8 Data Handling Conventions

8.1 Missing Data

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such provided in the collection instrument.

8.1.1 Imputation of Non-Date Missing Data

Non-date Clinical Data

All available data will be analyzed using suitable statistical methods. For analysis of percent responders, all subjects in the appropriate analysis set (ITT Analysis Set or mITT Analysis Set) will be included in the denominator when calculating the percentages; any subject who drops out of the study at any time after randomization will be defined for the purpose of analysis as a non-responder.

Subjects with the designation of treatment relationship for adverse events (AEs) and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”.

In summaries of absolute values and change from baseline, subjects with missing baseline values will not be included in baseline rows or in the change from baseline summary statistics.

8.1.2 Imputation of Partial Dates

Imputed dates will not be used to derive study day, duration (eg, duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date for overall survival. Imputed dates will be displayed in listings and identified as imputed.

Partial date imputation will follow Analysis Data Model (ADaM) conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D = 'Day': indicates that the day portion of the date is imputed

M = 'Month': indicates that the month and day portions of the date are imputed

Y = 'Year': indicates that the entire date (year, month, and day) is imputed

Algorithms for imputing partial dates for AE and concomitant medications are below.

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. They will not be used to calculate duration of AEs. If an AE start or end date is missing, then the duration of the AE will be set to missing.

Adverse Events

Impute start and end dates for use to derive the reference variables for adverse event start relative to treatment; include any imputed dates in analysis datasets with an identifier as imputed. The reference variables will be used to differentiate as Before-therapy, On-Therapy and Follow-up for AEs (see Section 8.3.2).

Date	Missing Element	Rule
Start Date	day, month, and year	Do not impute completely missing AE start dates, AE will be assumed as treatment emergent
	day and month	• If the onset year is after the year of the first dose of study drug, then the AE is treatment-emergent. • If the onset year is the same as the year of the first dose of study drug and the end date is not before the first dose of study drug, then the AE is treatment-emergent. • If the onset year is the same as the year of the first dose of study drug and the end date is before the first dose of study drug, then the AE is not treatment-emergent. • If the onset year is before the year of the first dose of study drug, then the AE is not treatment-emergent.

Date	Missing Element	Rule
	day only	• If the start yyyy-mm is after the yyyy-mm of first dose of study drug, then the AE is treatment-emergent. • If the start yyyy-mm is the same as the yyyy-mm of the first dose of study drug and the end date is not before the first dose of study drug, then the AE is treatment-emergent. • If the start yyyy-mm is the same as the yyyy-mm of the first dose of study drug and the end date is before the first dose of study drug, then the AE is not treatment-emergent. • If the onset yyyy-mm is before the yyyy-mm of the first dose of study drug, then the AE is not treatment-emergent.
End Date	any date element	No imputation for completely or partially missing AE end dates; as applicable, report the AE as ongoing and the AE duration as missing.

Concomitant Medication

Impute start and end dates for use to derive the reference variables for concomitant medication start and end relative to treatment; include any imputed dates in analysis datasets with an identifier as imputed. The reference variables will be used to differentiate before, during and after treatment for the concomitant medication.

Date	Missing Element	Rule
Start Date	day, month, and year	Do not impute completely missing concomitant medication start dates.
	day and month	• If the onset year is after the year of the first dose of study drug, then the CM is concomitant. • If the onset year is the same as the year of the first dose of study drug and the end date is not before the first dose of study drug, then the CM is concomitant. • If the onset year is the same as the year of the first dose of study drug and the end date is before the first dose of study drug, then the CM is prior. • If the onset year is before the year of the first dose of study drug, then the CM is prior.

Date	Missing Element	Rule
	day only	• If the start yyyy-mm is after the yyyy-mm of first dose of study drug, then the CM is concomitant. • If the start yyyy-mm is the same as the yyyy-mm of the first dose of study drug and the end date is not before the first dose of study drug, then the CM is concomitant. • If the start yyyy-mm is the same as the yyyy-mm of the first dose of study drug and the end date is before the first dose of study drug, then the CM is prior. • If the onset yyyy-mm is before the yyyy-mm of the first dose of study drug, then the CM is prior.

Date of Birth

Imputation for birth date is only needed if age is missing on eCRF and needs to be recalculated. An incomplete birth date will be imputed as follows:

If only the day is missing – the missing day will be imputed as 15th of the month.

If day and month is missing – missing day and month will be imputed by 1st of July.

A completely missing birth date will not be imputed.

8.2 Derived Variables

The following sections provide a general description of the derived variables for data analyses.

8.2.1 Reference Dates

Reference dates are used to assign study periods relative to treatment.

There are three reference dates:

- Because age is an eligibility requirement, the reference date for age is the date of screening.
- The safety reference date is the date of first C1-INH dosing in Treatment Period 1 and will be used to calculate study day for safety measures.
- The reference date for efficacy endpoints is the date of first intake of randomized study treatment in Treatment Period 2 and will be used to calculate study day for efficacy measures.

8.2.2 Study Day for Safety Measures

If the date of interest occurs on or after the safety reference date, then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date, then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

8.2.3 Study Day for Efficacy

The study day for efficacy will be calculated in the same manner as the study day for safety measures but will consider the reference date for efficacy. There is no efficacy Study Day 0.

Timings for safety events and interventions

Safety events and interventions will be classified as follows:

Before-treatment: Date is strictly prior to the first administration of open-label C1-INH.

Treatment-emergent or On-Treatment: Date is between the first administration of open-label C1-INH and 30 days after the investigational product stop date.

Post-treatment: Date is strictly more than 30 days after the investigational product stop date.

8.2.4 Durations

Durations (eg, the duration of an adverse event) and elapsed time will be calculated in days using the SAS DATDIF function.

When reporting durations which are calculated in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms for time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

8.2.5 Baseline Definition

Baseline for non-laboratory and laboratory data (except creatinine for eGFR) is defined as the most recent, non-missing value prior to or on the first study treatment dose date/time in Treatment Period 1 (for non-laboratory it is referred to eCRF data and for laboratory data it is referred to local laboratory data).

For subjects who did not receive study treatment during the study, a baseline value will not be calculated. The most recent, non-missing value prior to or on the study treatment dose date / time is based on scheduled assessments only.

Baseline eGFR has been defined as follows in original protocol and amendments:

- For subjects randomized prior to Protocol Amendment 1, dated November 28, 2017, the nadir (minimum) of the eGFR values from screening and Day 1 will be used as the baseline.
- For subjects randomized after Protocol Amendment 1 the mean of the screening and Day 1 values will be used as the baseline.

For the purpose of analysis, baseline eGFR is defined as the mean of the screening and Day 1 values.

Note that a set of vital signs or laboratory values may have different dates for baseline values.

8.2.6 Change From Baseline

Change from baseline will only be calculated for measures that have post-baseline records. Change from baseline will be calculated as:

- visit value – baseline value.

Percentage change from baseline will be calculated as:

- (change from baseline / baseline value) * 100

8.2.7 Multiple Assessments

All data will be reported according to the nominal visit date/time for which it was assessed (that is, no visit windows will be applied during dataset creation).

If multiple assessments for the same visit occur, it will be distinguished why this is the case. If a laboratory sample was repeated due to technical problems the results from the valid sample(s) for this visit – the non-missing results – will be used in the analysis. If a laboratory sample was repeated as safety follow-up to monitor abnormal values of the initial sample, the initial sample (revealing the abnormal values) of this visit will be used in the analysis.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

8.2.8 Actual Treatment

The subjects' actual treatment will be derived from exposure data. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment for the entire time of treatment, then actual treatment is the different treatment (the treatment actually received).

8.2.9 Derived Variables

Start and End of Retreatment Periods

Neither the start and end date of optional Retreatment Period(s) nor the number of individual Retreatment Period(s) will be explicitly recorded in the eCRF. So, the start date of a Retreatment Period will be derived by using the visit date associated with the label of first visit in a Retreatment Period, ie using a visit label of "RT – Day 1 (x)", x – counter of individual Retreatment Period. The end date of a Retreatment Period will be derived in the same way by using the last available date in a chronological order of visit labels in a Retreatment Period, ie using a visit label of "RT – Day 182 (x)", x – counter of individual Retreatment Period. The individual number of Retreatment Period will be derived from the counter (in brackets) given in the visit label of Retreatment Periods.

For analysis purpose, a Retreatment Period will start with the first documented study drug intake on or after first retreatment visit which was identified via the visit label. The end of the Retreatment Period will be identified in a similar way. It will be the last intake of study drug before or on the last retreatment visit which was identified via the visit label.

Demographics

Years of Age

Years of age will be derived as the number of complete years between a subject's birth date and the date of informed consent.

Body mass index

Body mass index (BMI) will be derived using the following formula:

BMI (kg/m^2) = Weight (kg) / [Height (m)]^2

The height at Screening and the dry weight obtained from the medical history will be used. If the dry weight is missing, the weight at Screening will be used. If the weight at Screening is missing, the Day 1 weight will be used.

Efficacy

Estimated glomerular filtration rate (eGFR)

eGFR will be derived using the following MDRD formula [Levey et al, 2008]:

$$eGFR\ (mL/min/1.73m^2) = [(175)\ x\ (standardized\ S_{cr}^{-1.154})\ x\ (age^{-0.203})\ x\ (1.212, if\ black)\ x\ (0.742, if\ female)]$$

The serum creatinine (S_{cr}) is expressed as mg/dL. The years of age will be derived based on the subject birth date and the date that the S_{cr} sample was taken.

eGFR at the End of Treatment Period 1 (End-of-TP1)

The mean of Week 11 and Week 12 eGFR measurements. If one of the measurements is missing it is then the non-missing value.

eGFR at the End of Treatment Period 2 (End-of-TP2)

The mean of Week 36 and Week 38 eGFR measurements. If one of the measurements is missing it is then the non-missing value.

Response to Open-Label C1-INH at End of Treatment Period 1 (End-of-TP1)

Responders are defined as subjects whose End-of-TP1 (the mean of Week 11 and Week 12) eGFR ≥ 90% of baseline and ≥ 20 mL/min/1.73 m^2. The baseline eGFR is defined as the mean of the screening and Day 1 values in Section 8.2.5.

Loss of Response During Treatment Period 2

Loss-of-response at the End-of-TP2 is defined as any 1 of the following 3 conditions:

- End-of-TP2 eGFR (mean of Week 36 and Week 38 eGFR) that is not stable, defined as:
  - End-of-TP2 eGFR that is < 90% of the End-of-TP1 eGFR for subjects whose End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) is ≥ 100% of baseline;

- End-of-TP2 eGFR that is < 90% of baseline for subjects whose End-of-TP1 eGFR is ≥ 90% of baseline and < 100% of baseline.

- Allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first)
- Subject death by any cause.

All-Cause Allograft Failure

All-cause allograft failure within 48 months after enrollment is defined as 1 of the following, whichever occurs first:

- Allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first), OR
- Subject death by any cause.

No subject has reached 48 months after enrollment due to study termination.

8.3 Study Periods Relative to Treatment

8.3.1 Time in Relation to Treatment

Safety data (AEs and concomitant medications) will be assigned to the study time periods defined below (refer to Section 8.1.2 for imputation of incomplete or missing dates).

Before-therapy is defined as the date/time prior to the first start of subject's infusion with study treatment.

On-therapy is defined as the time from the first start of an infusion of study treatment in Treatment Period 1 up to 30 days after last study drug administration in Treatment Period 2. If a subject had a Retreatment Period, the time still on drug in Retreatment Period (extended to +30 days after last drug in Retreatment Period) will be accounted as On-therapy. In case a subject has more than one Retreatment Periods, the time between Retreatment Periods will be accounted for Follow-up.

Follow-up is defined as any time after last study drug administration in Treatment Period 2 plus 30 days. Time of Retreatment Periods are to be excluded from Follow-up, please refer to On-therapy.

8.3.2 Study Time Periods for AEs

AEs occurring On-Therapy or during Follow-up will be handled as treatment-emergent AEs.

8.3.3 Study Time Periods for Prior and Concomitant Medications

Prior medications are those ending in the before-therapy period.

Concomitant medications include those that start during the before-therapy period and continue into the on-therapy and Follow-up periods as well as those that start during the on-therapy and Follow-up time periods. Therapies that start during the before-therapy period and have a missing end date will be assumed to continue into the on-therapy period and, therefore, will also be considered concomitant medications.

9 Study Population

Only data of subjects who provided informed consent (informed consent date available in the database) will be included in the statistical analysis.

Unless otherwise stated, all tables and listings in this section will be based on the mITT and / or Safety Analysis Set, and all summaries and data listings will use treatment descriptors as specified in Section 7.2.

9.1 Disposition of Subjects

The following summaries will be provided by treatment group and for the Screened Analysis Set, as appropriate:

Subject disposition presenting the number and percentages of:

- subjects screened,
- subjects ineligible/failed screening,
- reason for screening failure,
- subjects eligible for Treatment Period 1,
- subjects treated with open-label study medication in Treatment Period 1,
- subjects completed Treatment Period 1,
- subjects discontinued during Treatment Period 1 (before Week 13) and reasons for discontinuation,
- subjects eligible for randomization in Treatment Period 2 (subjects reached week 13 and responded to treatment in Treatment Period 1),
- subjects randomized,
- subjects treated with blinded study medication during Treatment Period 2,
- subjects completed Treatment Period 2,

- subjects discontinued during Treatment Period 2 (before Week 38) and reasons for discontinuation,
- Subjects discontinued from study before week 208,
- subjects available by visit (Treatment Period 1, Treatment Period 2), a subject will be considered to have attended a visit if a visit date is recorded (provided for RiS Analysis Set and RWS Analysis Set).

Number and percentage of subjects in the following analysis sets will be presented:

- Screened Analysis Set,
- Enrolled Analysis Set,
- RiS Analysis Set,
- RWS Analysis Set,
- mITT Analysis Set,
- PK Analysis Set,
- CCI .

Number and percentage of subjects in the following categories will be presented:

- Subjects applicable to original protocol,
- Subjects applicable to amendment 1,
- Subjects applicable to amendment 2,
- Subjects applicable to amendment 3.

Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A listing will be provided including date of informed consent, date of randomization, date of first treatment (Treatment Period 1, Treatment Period 2, Retreatment Period[s]), study completion, reason if not completed, and assignment to analysis sets.

9.2 Protocol Deviations

The following listings will be provided for the Enrolled Analysis Set:

- All inclusion / exclusion and major protocol deviations.
- All other protocol deviations.

9.3 Demographic and Baseline Characteristics

9.3.1 Demographics

The following demographic characteristics will be summarized using descriptive statistics or frequency counts, as appropriate:

- Age,
- Age group (< 65 years and ≥65 years),
- Sex,
- Ethnicity,
- Race and racial combinations,
- Height,
- Weight,
- BMI,
- Diagnosis of HIV,
- Diagnosis of HBV,
- Diagnosis of HCV.

The weight to be summarized as part of demographics will be the dry weight based on medical history. If the dry weight is missing, the weight at Screening will be used. If the weight at Screening is missing, the Day 1 weight will be used. Demographics will be summarized for the RWS Analysis Set and overall and for RiS Analysis Set.

9.3.2 Baseline Characteristics

The following will be summarized using descriptive statistics or frequency counts, as appropriate:

- Allograft / allograft donor characteristics,
- Diagnosis and disease characteristics.

Baseline characteristics will be summarized for the RWS Analysis Set and overall and for RiS Analysis Set.

- Allograft / allograft donor characteristics: age, sex, ethnicity, race, biological relative, blood group, status at time of donation (alive, dead), deceased donor donation type (donation after brain death, donation after circulatory death), deceased donor criteria (kidney standard criteria donor, kidney expanded criteria donor), Kidney Donor Profile

Index (KDPI score), Human Immunodeficiency Virus (HIV) (yes, no), Hepatitis B Virus (HBV) (yes, no), Hepatitis C Virus (HCV) (yes, no),

- Diagnosis and disease characteristics: time since most recent renal transplant, time since AMR diagnosis, time since most recent rejection episode, severity of current AMR episode, total number of renal transplants, primary reason for kidney transplant (diabetes [type 1 and 2], hypertension, polycystic kidney disease, drug toxicity [non-steroidal anti-inflammatory drugs or others], IgA nephropathy, rapidly progressive neuropathy, membranous glomerulopathy, other nephritides, renal artery stenosis, other infectious diseases [HIV; hepatitis; endotoxin], congenital nephropathy [primary NOS], stone disease, renal cancer, other), delayed graft function (yes, no), dialysis within 14 days after most recent transplant (yes, no), presence of DSA prior to kidney transplant (yes, no), de novo DSA post-transplant (yes, no).

The following listings will be provided for RWS Analysis Set and overall and for RiS Analysis Set:

- Demographic characteristics,
- Allograft / allograft donor characteristics,
- Diagnosis and disease characteristics.

9.4 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using CSL Behring Drug coding dictionary (WHO-DDE Enhanced 2016MAR, B2 Format), summarized, and listed. The summary of prior and concomitant medications will show the number and percentage of subjects taking prior/concomitant medications. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary. ATC Level 4 and preferred term of prior/concomitant medications will be used for summaries and listings. If the ATC Level 4 coding is not available for a preferred term, the next available lower level ATC code will be used. The summary will be provided by treatment group for RWS Analysis Set and overall for the RiS Analysis Set.

Concomitant medication start and end dates relative to treatment start and end dates are used to select data to include in summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications with start dates relative to treatment assigned to ('BEFORE', 'DURING') and end dates relative to treatment assigned to ('DURING', 'AFTER').

- Summary of Concomitant Medications with On-Therapy Onset: This summary will contain medications with start dates relative to treatment assigned ('DURING') and end dates relative to treatment assigned to ('DURING', 'AFTER').

In the summary of concomitant medications, each subject is counted once within each unique term. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient “Amoxycillin”.

Concomitant medications will be summarized separately for medications with onset date within the on-therapy period and for medications with onset date within the before-therapy period. Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

Concomitant medications will be summarized for the RWS Analysis Set and overall and for RiS Analysis Set.

9.5 Medical History

Medical history by body system will be summarized in a frequency table by treatment group for RWS Analysis Set and overall and for RiS Analysis Set.

Medical history will also be presented in a by-subject listing for RiS Analysis Set.

10 Efficacy

All efficacy summary will be based on mITT Analysis Set of subjects for Period 2 unless otherwise specified. All efficacy summary will be based on RiS Analysis Set for Period 1 unless otherwise specified.

Subject listings will be provided for the efficacy information based on the mITT Analysis Set.

10.1 Analysis of Proportion of Subjects With Loss of Response at the End-of-TP2

The number and proportion of subjects with loss of response at the End-of-TP2 will be presented by treatment group along with the confidence interval for the difference between the two groups.

Subjects will be considered to have lost response if they drop-out or are lost to follow-up before the response status at the End-of-TP2 could be determined.

Components of loss-of-response at the End-of-TP2 will be summarized by treatment groups in terms of the proportion of subjects with:

- End-of-TP2 eGFR (mean of Week 36 and Week 38 eGFR values) that is not stable, defined as:
  - End-of-TP2 eGFR that is < 90% of the End-of-TP1 eGFR for subjects whose End-of-TP1 eGFR is ≥ 100% of baseline,
  - End-of-TP2 eGFR that is < 90% of baseline for subjects whose End-of-TP1 eGFR is ≥90% of baseline and < 100% of baseline,
- All-cause allograft failure (ie, allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant),
- Death by any cause.

The primary efficacy analysis will be conducted for the mITT Analysis Set.

10.1.1 Subgroup Analyses of Proportion of Subjects With Loss of Response at the End-of-TP2

The proportion of subjects with loss of response at the End-of-TP2 will be summarized by the treatment group for the following subgroups based on the following subgroup analyses outlined below will be conducted for the mITT Analysis Set.

The following subgroups, and possibly others to be described in the SAP, will be summarized by treatment group with respect to the proportion of loss-of-response:

- Geographic region: USA, non-USA,
- DSA by randomization strata: sensitized, de novo,
- DSA by classification: HLA class I, HLA class II, both HLA class I and II,
- AMR severity: severe, non-severe (all other severities),
- Type of donor: deceased, living,
- Recipient race: Black, non-Black,
- Recipient sex: Male, Female,
- Recipient age: < 65 years, ≥ 65 years.

The difference in the proportion of response along with the 95% confidence interval will be also presented for each subgroup.

10.2 Analysis of key Secondary Endpoint Proportion of Subjects With All-Cause Allograft Failure Through the Responder Follow-up Period (ie, Within 48 Months After Enrollment)

No subject will complete the follow-up period of 48 months after enrollment. Therefore, this key secondary analyses cannot be conducted.

10.3 Analysis of Time to All-Cause Allograft Failure Through 48 Months After Enrollment

No formal analysis will be conducted for time to all-cause allograft failure since no subject will complete 48 months after enrollment.

A by-listing of all-cause allograft failure information will be provided for the mITT Analysis Set.

10.4 Analysis of the Change in eGFR From Baseline to End-of-TP1

This analysis will be based on the RiS Analysis Set.

The eGFRs during Treatment Period 1 (ie with open-label C1-INH) will be summarized by scheduled visit using descriptive statistics for the observed values, and changes from baseline (ie missing data will be not imputed).

10.5 Analysis of Responders at the End-of-TP1

This analysis will be based on the RiS Analysis Set.

The proportion of responders at the End-of-TP1 will be presented together with an exact 95% confidence interval. Definition of response at End-of-TP1 is given in Section 8.2.9.

10.6 Analysis of the Change in eGFR From End-of-TP1 to the End-of-TP2

No formal analysis for the change in eGFR from End-of-TP1 to the End-of-TP2 will be conducted.

A by-listing for eGFR of all individual values will be provided. for the mITT Analysis Set.

10.7 Analysis of the Rate of Change of eGFR in Treatment Period 2

No formal analysis of the rate of change of eGFR in Treatment Period 2 will be conducted due to the small number of subjects completing TP2. Mean plot for the change in eGFR from baseline in Treatment Period 2 will be provided for the subjects in the mITT Analysis Set.

10.8 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

10.9 CCI [redacted]

CCI [redacted]

10.10 Analysis of C1-INH Functional Activity

PK parameter of C_{max} and AUC_{0-t} for C1-INH functional activity will be presented in a by-subject listing for the PK Analysis Set (see Section 12).

10.11 CCI [redacted]

CCI [redacted]

10.12 Analysis of Plasmapheresis Sessions

The total number plasmapheresis sessions will be derived for each subject and provided in a by-listing for the mITT Analysis Set.

10.13 CCI [redacted]

CCI [redacted]

10.14 CCI [redacted]

CCI [redacted]

10.15 CCI [redacted]

CCI [redacted]

CCI [redacted]

10.16 CCI [redacted]

CCI [redacted]

10.17 CCI [redacted]

CCI [redacted]

10.18 Trough IVIg Concentrations at Designated Time Points

A by-listing of trough IVIg concentrations at will be presented for the RiS Analysis Set at Week 12 and for the mITT Analysis Set at Week 32.

10.19 CCI

CCI

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10.20 Treatment Compliance

Percentage compliance will be a function of the amount of IMP taken, ie, the actual cumulative administered volume (mL), and the amount of IMP prescribed, ie, the cumulative planned volume (mL).

Percentage compliance to IMP will be calculated as:

compliance (%) = (cumulative administered volume / cumulative planned volume)*100.

Percentage compliance will be summarized by frequencies of < 80%, 80% – 120%, > 120%.

Percentage compliance will be summarized for the RiS Analysis Set for Treatment Period 1 and by treatment group for the mITT Analysis Set for Treatment Period 2. Percentage compliance will be also summarized for the entire study for the mITT subjects randomized to C1-INH in period 2. Also, compliance will be summarized based on intravenous delivery and subcutaneous delivery of C1-INH during Treatment Period 1.

Subjects may undergo retreatment during the post-treatment Follow-up Period with the blinded investigational product to which they were randomized in Treatment Period 2.

The following listings will be provided:

- Randomized and actual treatments,
- Drug accountability data (dispensed and returned),
- Overall compliance.

A by-subject listing will be provided including compliance by treatment period, by delivery system (intravenous and subcutaneous), randomized and actual treatments.

Calculation of compliance and extend of exposure (see Section 11.1) will be based on drug accountability data collected by IRT system (or RAVE) as the eCRF does not contain any such related data fields. Drug accountability data will be part of final study data base.

11 Safety Analyses

Open-label safety events and findings will be defined as those with an onset date prior to the randomization date. Double-blind safety events and findings will be defined as those with an onset date on or after the randomization date.

The RiS Analysis Set will be used for analysis of safety for open label TP1. The RWS Analysis Set will be used for analysis of safety during the double-blind period; summaries will be presented by treatment group and total number of subjects in RWS Analysis Set. Also, safety of RWS subjects randomized to C1-INH will be summarized over the study including periods 1 and 2 and follow-up.

11.1 Extent of Exposure

The extent of exposure to C1-INH in open-label and in double-blind period and to placebo in double-blind period will be summarized using descriptive statistics. Extent of exposure will be described in terms of the following (including intravenous administration and subcutaneous administrations):

- Cumulative administered volume (mL), calculated as sum of single administered volumes in treatment periods,
- Cumulative planned volume (mL), calculated as sum of single planned volumes in treatment periods (planned administration at days 1, 4, 7, 10, and 13 and twice weekly dosing beginning at the day 14 visit in Treatment Period 1 and twice weekly dosing in Treatment Period 2; dosing scheme must be taken into account for cumulative planned dose depending on subjects time in study; the number of administrations in period of twice weekly dosing will be calculated as: ((date of end of twice weekly dosing - date of start of twice weekly dosing +1) / 7) *2,
- Days on treatment, calculated as days between first and last dose in treatment periods;
- Average daily dose, calculated as cumulative administered dose divided by days on treatment for each treatment period,
- For subjects continuing C1-INH in Treatment Period 2 cumulative administered dose, cumulative planned dose, days on treatment and average daily dose will be summarized for the whole C1-INH treatment period.

Extent of exposure for Retreatment Periods will be summarized separately.

For summaries of Treatment Period 1 the RiS Analysis Set will be used. Summaries for Treatment Period 2 will be based on the RWS Analysis Set. Also, exposure summary will be presented for the RWS subjects receiving C1-INH during the entire study (Treatment Period 1 and Treatment Period 2 combined).

A by-subject listing will be provided including treatment period (including re-treatment), cumulative administered volume, cumulative planned volume, days on treatment and average daily dose.

11.2 Adverse Events

Adverse events will be coded to the Preferred Term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary), version 23.0 or higher. Treatment-emergent AEs (TEAEs) are defined as AEs reported at or after the start of the first infusion. All AEs regardless of when they were reported will be listed.

Summaries of TEAEs will count the number of subjects, not the number of events, that is, subjects with multiple occurrences of the same TEAE will be counted once.

The number and percentage of subjects with TEAEs will be reported. Also, the number and percentage of subjects with serious TEAEs, TEAEs by severity, and serious TEAEs related to investigational product will be presented. Adverse events will be presented for Treatment Period 1 and RiS Analysis Set. For Treatment Period 2 summaries will be presented for the RWS Analysis Set. In addition, the summaries will be given for C1-INH over the whole study for RWS Analysis Set and a summary across the whole study will be given for the RiS Analysis Set.

A summary of number and percentage of subjects with any TEAE by maximum severity or grade will be produced. TEAEs will be sorted by System Organ Class (SOC) and PT in descending order of incidence overall treatment arms. The summary will report the number of subjects with at least one TEAE, counted for the maximum severity and, for each PT reported, the number of subjects for each, counted for the maximum severity.

In addition, the frequency and percentage of TEAEs will be summarized and displayed in two ways: 1) in descending order of incidence in whole study for RiS Analysis Set by PT only and 2) in descending order of incidence whole study for RiS Analysis Set by SOC and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

A separate summary will be provided for study treatment-related serious TEAEs. Missing relationship to study treatment will be imputed as described in Section 8.1.2; this summary will also include the number and percentage of TEAEs with a missing relationship to aid in interpretation of the results.

By-subject listings will also be provided with detailed information to support the different AE summaries.

11.3 Adverse Events of Special Interest (AESI)

Adverse events of special interest of Treatment Period 2 will be presented for the RWS Analysis Set. In addition, adverse events of special interest will be summarized for C1-INH over the whole study for RWS Analysis Set and a summary across the whole study will be given for the RiS Analysis Set.

- Thromboembolic events
    - Systemic thrombotic or thromboembolic events not including catheter or dialysis related clots are of interest. Identification will be based on the Standardized MedDRA Query (SMQ) Embolic and thrombotic events (narrow),
- Anaphylaxis
    - Anaphylaxis will be identified using the SMQ - Anaphylactic reaction (broad).

Treatment-emergent adverse events of special interest will be summarized by SOC and PT.

A separate by-subject listing will be produced for all treatment-emergent adverse events of special interest based on RiS Analysis Set. A listing of terms included in each SMQ can be found in Section 16.1 and 16.2.

11.4 Deaths and Serious Adverse Events

A by- listing will be generated to provide subject-specific details on subjects who died.

The following summaries will be provided for Treatment Period 2 and the RWS Analysis Set. In addition, a summary for C1-INH over the whole study for RWS Analysis Set and a summary across the whole study will be given for the RiS Analysis Set:

- Serious TEAEs,

- Serious TEAEs related to Study Treatment.

The following listings will be provided for RiS Analysis Set:

- Serious Non-TEAEs,
- Serious TEAEs,
- TEAEs resulting in death.

11.5 Adverse Events Leading to Discontinuation of Study Treatment, Withdrawal from the Study, and Other Significant Adverse Events

The following listings will be provided based on RiS Analysis Set:

- TEAEs Leading to Discontinuation of Study Treatment,
- Non-TEAEs leading to Withdrawal from the Study,
- TEAEs leading to Withdrawal from the Study.

11.6 Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If any subject OR any subject or subject's partner becomes pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

11.7 Clinical Laboratory Evaluations

11.7.1 Clinical chemistry

All clinical chemistry parameters for this study will be summarized by scheduled visit using descriptive statistics. All unscheduled visits will be excluded from these by-visit summaries.

Open-label clinical chemistry data for Period 1 and that for the entire study will be summarized for the RiS Analysis Set. Double-blind clinical chemistry data for Period 2 will be summarized for the RWS Analysis Set by treatment.

The estimated and CCI eGFR will be summarized as part of efficacy, and not part of safety.

Clinical Chemistry parameter to be summarized: Albumin, alkaline phosphatase, ALT, AST, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, sodium, and protein (total).

11.7.2 Hematology

All hematology parameters for this study will be summarized by scheduled visit using descriptive statistics. All unscheduled visits will be excluded from these by-visit summaries.

Open-label hematology data and that for the entire study will be summarized for the RiS Analysis Set.

Double-blind hematology data will be summarized for the RWS Analysis Set by treatment.

Hematology parameter to be summarized: Hemoglobin, hematocrit, red blood cell indices: mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, blood cell counts: basophils, eosinophils, erythrocytes, leukocytes, lymphocytes, monocytes, neutrophils, neutrophil band forms, platelets, and reticulocytes.

DSA: will be included as efficacy endpoint and will therefore be summarized for efficacy.

11.8 Other Safety Measures

11.8.1 Vital Signs

Systolic blood pressure, diastolic blood pressure, heart rate, and weight will be summarized for each scheduled visit using descriptive statistics or frequency counts as appropriate.

Vital signs during Treatment Period 1 will be summarized for the RiS Analysis Set. Vital signs for the entire study will be summarized for the RWS Analysis Set by treatment.

12 Pharmacokinetics

All non-compartmental analyses for the derivation of PK parameters will be performed according to CSL SOP PK-GDL-01 and will be performed by CSL Behring Clinical Pharmacology & Pharmacometrics or their designate by using WinNonlin® version 8.1 or later.

All analyses in this section will be based on the PK population, unless otherwise stated.

The merge of PK concentration data and CRF data to generate a dataset with actual blood sampling times, nominal sampling times, actual time relative to dosing, and PK concentrations of

C1-INH antigen concentrations and C1-INH functional activity will be performed after data base lock by PPD and is specified in Section 12.5.

12.1 PK Sampling Schedule

Blood samples will be taken for measurement of C1-INH antigen concentrations and C1-INH functional activity at the following time points of Day 10 of Treatment Period 1: pre-dose, 0 minutes (start of C1-INH infusion), 15 minutes, 3, 8, 24, and 72 hours after start of infusion and at Week 11 visit (Treatment Period 1) at time points of: pre-dose, 0 minutes (time of C1-INH injection), 24, 48, and 72 hours after injection. PK samples will be drawn in a subset of subjects.

Summary statistics will be provided by nominal (planned) time points.

Concentration data excluded from the derivation of PK parameters will be omitted from summaries and will be flagged with an asterisk in the relevant data listings, with a footnote to indicate that these values have been omitted from subsequent analyses.

12.2 Plasma PK Endpoints

The PK parameters based on data collected on Day 10 following IV administration and Week 10 following SC administration will be derived, using Phoenix WinNonlin, Version 8.1 or higher. The PK parameter derivation is based on actual sampling times and includes imputation of the values below the lower limit of quantification (BLQ) and missing data will be conducted in accordance to CSL SOP PK-GDL-01, Guideline on the Conduct of Non-compartmental Pharmacokinetic Analyses, CSL Behring which gives guidance on how to derive PK parameters in the presence of missing data.

Definition of derived PK Parameter:

Term	Definition
AUC_{0-t}	Area under the concentration time curve from time point zero to the last quantifiable time point.
C_{max}	The maximum (peak) observed C1-INH level.
T_{max}	The time to reach C_{max}.

Term	Definition
C_{trough}	Trough C1-INH, collected prior to the next infusion.

12.3 Summary of C1-INH Antigen and Functional Activity Plasma Concentrations

The handling and imputation of BLQ values for PK parameters derivation is described in PK-GDL-01, Guideline on the Conduct of Non-compartmental Pharmacokinetic Analyses, CSL Behring. The imputation rules below will be used for summary statistics of C1-INH antigen and functional activity plasma concentrations. The summaries will be given by sampling time point (planned time points) and treatment group for the PK Analysis Set.

- The sampling time of pre-dose samples relative to dosing will be set to zero.
- Any BLQ in the listing of individual concentrations will be set to missing.
- Set any pre-dose BLQ to zero for summaries.
- Set any BLQ occurring in the profile or at the end of the profile to missing and exclude missing values from the calculation of the means.
- Calculate mean concentrations at any individual time point if at least 50% of the individual values are available (ie are quantifiable and not missing) at this time point otherwise report as “not calculated (NC)”.

Summary statistics for concentration-time data will include number of observations, mean, standard deviation, coefficient of variation (CV)%, minimum, median and maximum.

A by-subject listing of C1-INH antigen and functional activity plasma concentration data will support the summaries.

12.4 Summary of C1-INH PK Parameters

PK parameters of $C_{max,}$ AUC_{0-t}, C_{trough} and for C1-INH antigen and functional activity will be summarized by treatment group for the PK Analysis Set by descriptive statistics with parameter of n, arithmetic mean, SD, CV% (CV% = 100* standard deviation / mean), minimum, Q25, median, Q75, and maximum.

T_{max} will be summarized by descriptive statistics with parameter of n, minimum, Q25, median, Q75, and maximum.

A by-subject listing of C1-INH PK parameters will be provided.

12.5 Pharmacokinetic Analysis Data Flow

After database lock, PPD will produce the SDTM domains. Domain PC will contain the C1-INH antigen concentrations and C1-INH functional activity concentrations. The PC domain along with domains VS, DM and EX will be provided by PPD. PPD Early Phase Services will derive the PK parameters and produce the PK parameter dataset in Excel format. From this, PPD will produce the SDTM domain PP and eventually the analysis dataset.

Before database lock, PPD will use dummy data for the PK parameters in domain PP to be able to pre-program the planned output.

13 CCI

CCI

14 CCI

CCI

15 References

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16 Appendices

16.1 Standardized MedDRA Query for Embolic and Thrombotic Events (Narrow) (SMQ Code: 20000081)

SMQ Name: Embolic and thrombotic events, arterial (SMQ)			SMQ Code:20000082	
Preferred Term	**Code**	**Level**	**Scope**	**Category**
Acute aortic syndrome	10074337	PT	Narrow	A
Acute myocardial infarction	10000891	PT	Narrow	A
Amaurosis	10001902	PT	Narrow	A
Amaurosis fugax	10001903	PT	Narrow	A
Angioplasty	10002475	PT	Narrow	A
Aortic bypass	10057617	PT	Narrow	A
Aortic embolus	10002897	PT	Narrow	A
Aortic surgery	10061651	PT	Narrow	A
Aortic thrombosis	10002910	PT	Narrow	A
Aortogram abnormal	10057794	PT	Narrow	A
Arterectomy	10071026	PT	Narrow	A
Arterectomy with graft replacement	10003140	PT	Narrow	A
Arterial angioplasty	10081731	PT	Narrow	A
Arterial bypass occlusion	10077766	PT	Narrow	A
Arterial bypass operation	10056418	PT	Narrow	A
Arterial bypass thrombosis	10077765	PT	Narrow	A
Arterial graft	10061655	PT	Narrow	A
Arterial occlusive disease	10062599	PT	Narrow	A
Arterial revascularisation	10084482	PT	Narrow	A
Arterial stent insertion	10061657	PT	Narrow	A
Arterial therapeutic procedure	10052949	PT	Narrow	A
Arterial thrombosis	10003178	PT	Narrow	A
Arteriogram abnormal	10061659	PT	Narrow	A
Arteriogram carotid abnormal	10003195	PT	Narrow	A
Arteriotomy	10078636	PT	Narrow	A
Atherectomy	10063025	PT	Narrow	A
Atherosclerotic plaque rupture	10076604	PT	Narrow	A
Atrial appendage closure	10079735	PT	Narrow	A
Atrial appendage resection	10080843	PT	Narrow	A
Basal ganglia infarction	10069020	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Basilar artery occlusion	10048963	PT	Narrow	A
Basilar artery thrombosis	10063093	PT	Narrow	A
Blindness transient	10005184	PT	Narrow	A
Brachiocephalic artery occlusion	10069694	PT	Narrow	A
Capsular warning syndrome	10067744	PT	Narrow	A
Carotid angioplasty	10071260	PT	Narrow	A
Carotid arterial embolus	10007684	PT	Narrow	A
Carotid artery bypass	10053003	PT	Narrow	A
Carotid artery occlusion	10048964	PT	Narrow	A
Carotid artery stent insertion	10066102	PT	Narrow	A
Carotid artery thrombosis	10007688	PT	Narrow	A
Carotid endarterectomy	10007692	PT	Narrow	A
Cerebellar artery occlusion	10053633	PT	Narrow	A
Cerebellar artery thrombosis	10008023	PT	Narrow	A
Cerebral artery embolism	10008088	PT	Narrow	A
Cerebral artery occlusion	10008089	PT	Narrow	A
Cerebral artery stent insertion	10081893	PT	Narrow	A
Cerebral artery thrombosis	10008092	PT	Narrow	A
Cerebral hypoperfusion	10065384	PT	Narrow	A
Cerebrovascular insufficiency	10058842	PT	Narrow	A
Cerebrovascular stenosis	10061751	PT	Narrow	A
Coeliac artery occlusion	10069696	PT	Narrow	A
Coronary angioplasty	10050329	PT	Narrow	A
Coronary arterial stent insertion	10052086	PT	Narrow	A
Coronary artery bypass	10011077	PT	Narrow	A
Coronary artery embolism	10011084	PT	Narrow	A
Coronary artery occlusion	10011086	PT	Narrow	A
Coronary artery reocclusion	10053261	PT	Narrow	A
Coronary artery surgery	10011090	PT	Narrow	A
Coronary artery thrombosis	10011091	PT	Narrow	A
Coronary endarterectomy	10011101	PT	Narrow	A
Coronary revascularisation	10049887	PT	Narrow	A
Coronary vascular graft occlusion	10075162	PT	Narrow	A
Embolia cutis medicamentosa	10058729	PT	Narrow	A
Embolism arterial	10014513	PT	Narrow	A
Endarterectomy	10014648	PT	Narrow	A
Femoral artery embolism	10068365	PT	Narrow	A
Hepatic artery embolism	10019635	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Hepatic artery occlusion	10051991	PT	Narrow	A
Hepatic artery thrombosis	10019636	PT	Narrow	A
Hypothenar hammer syndrome	10063518	PT	Narrow	A
Iliac artery embolism	10021338	PT	Narrow	A
Iliac artery occlusion	10064601	PT	Narrow	A
Internal capsule infarction	10083408	PT	Narrow	A
Intra-aortic balloon placement	10052989	PT	Narrow	A
Intraoperative cerebral artery occlusion	10056382	PT	Narrow	A
Ischaemic cerebral infarction	10060840	PT	Narrow	A
Ischaemic stroke	10061256	PT	Narrow	A
Lacunar infarction	10051078	PT	Narrow	A
Leriche syndrome	10024242	PT	Narrow	A
Mesenteric arterial occlusion	10027394	PT	Narrow	A
Mesenteric arteriosclerosis	10065560	PT	Narrow	A
Mesenteric artery embolism	10027395	PT	Narrow	A
Mesenteric artery stenosis	10027396	PT	Narrow	A
Mesenteric artery stent insertion	10071261	PT	Narrow	A
Mesenteric artery thrombosis	10027397	PT	Narrow	A
Myocardial infarction	10028596	PT	Narrow	A
Myocardial necrosis	10028602	PT	Narrow	A
Ophthalmic artery thrombosis	10081144	PT	Narrow	A
Papillary muscle infarction	10033697	PT	Narrow	A
Penile artery occlusion	10068035	PT	Narrow	A
Percutaneous coronary intervention	10065608	PT	Narrow	A
Peripheral arterial occlusive disease	10062585	PT	Narrow	A
Peripheral arterial reocclusion	10069379	PT	Narrow	A
Peripheral artery angioplasty	10057518	PT	Narrow	A
Peripheral artery bypass	10072561	PT	Narrow	A
Peripheral artery occlusion	10057525	PT	Narrow	A
Peripheral artery stent insertion	10072562	PT	Narrow	A
Peripheral artery surgery	10082470	PT	Narrow	A
Peripheral artery thrombosis	10072564	PT	Narrow	A
Peripheral embolism	10061340	PT	Narrow	A
Peripheral endarterectomy	10072560	PT	Narrow	A
Popliteal artery entrapment syndrome	10071642	PT	Narrow	A
Post procedural myocardial infarction	10066592	PT	Narrow	A
Postinfarction angina	10058144	PT	Narrow	A
Precerebral artery occlusion	10036511	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Precerebral artery thrombosis	10074717	PT	Narrow	A
Profundaplasty	10078867	PT	Narrow	A
Pulmonary artery occlusion	10078201	PT	Narrow	A
Pulmonary artery therapeutic procedure	10063731	PT	Narrow	A
Pulmonary artery thrombosis	10037340	PT	Narrow	A
Pulmonary endarterectomy	10072893	PT	Narrow	A
Pulmonary tumour thrombotic microangiopathy	10079988	PT	Narrow	A
Renal artery angioplasty	10057493	PT	Narrow	A
Renal artery occlusion	10048988	PT	Narrow	A
Renal artery thrombosis	10038380	PT	Narrow	A
Renal embolism	10063544	PT	Narrow	A
Retinal artery embolism	10038826	PT	Narrow	A
Retinal artery occlusion	10038827	PT	Narrow	A
Retinal artery thrombosis	10038831	PT	Narrow	A
Silent myocardial infarction	10049768	PT	Narrow	A
Spinal artery embolism	10049440	PT	Narrow	A
Spinal artery thrombosis	10071316	PT	Narrow	A
Splenic artery thrombosis	10074600	PT	Narrow	A
Splenic embolism	10068677	PT	Narrow	A
Stress cardiomyopathy	10066286	PT	Narrow	A
Subclavian artery embolism	10042332	PT	Narrow	A
Subclavian artery occlusion	10069695	PT	Narrow	A
Subclavian artery thrombosis	10042334	PT	Narrow	A
Thromboembolectomy	10064958	PT	Narrow	A
Thrombotic microangiopathy	10043645	PT	Narrow	A
Thrombotic thrombocytopenic purpura	10043648	PT	Narrow	A
Transient ischaemic attack	10044390	PT	Narrow	A
Truncus coeliacus thrombosis	10062363	PT	Narrow	A
Vascular pseudoaneurysm thrombosis	10078269	PT	Narrow	A
Vertebral artery occlusion	10048965	PT	Narrow	A
Vertebral artery thrombosis	10057777	PT	Narrow	A
Visual acuity reduced transiently	10047532	PT	Narrow	A

SMQ Name: Embolic and thrombotic events, venous (SMQ)			SMQ Code:20000084	
Preferred Term	**Code**	**Level**	**Scope**	**Category**
Aseptic cavernous sinus thrombosis	10084527	PT	Narrow	A
Axillary vein thrombosis	10003880	PT	Narrow	A
Brachiocephalic vein occlusion	10076837	PT	Narrow	A
Brachiocephalic vein thrombosis	10063363	PT	Narrow	A
Budd-Chiari syndrome	10006537	PT	Narrow	A
Catheterisation venous	10052698	PT	Narrow	A
Cavernous sinus thrombosis	10007830	PT	Narrow	A
Central venous catheterisation	10053377	PT	Narrow	A
Cerebral venous sinus thrombosis	10083037	PT	Narrow	A
Cerebral venous thrombosis	10008138	PT	Narrow	A
Compression garment application	10079209	PT	Narrow	A
Deep vein thrombosis	10051055	PT	Narrow	A
Deep vein thrombosis postoperative	10066881	PT	Narrow	A
Embolism venous	10014522	PT	Narrow	A
Hepatic vein embolism	10078810	PT	Narrow	A
Hepatic vein occlusion	10058991	PT	Narrow	A
Hepatic vein thrombosis	10019713	PT	Narrow	A
Homans' sign positive	10051031	PT	Narrow	A
Iliac vein occlusion	10058992	PT	Narrow	A
Inferior vena cava syndrome	10070911	PT	Narrow	A
Inferior vena caval occlusion	10058987	PT	Narrow	A
Jugular vein embolism	10081850	PT	Narrow	A
Jugular vein occlusion	10076835	PT	Narrow	A
Jugular vein thrombosis	10023237	PT	Narrow	A
Mahler sign	10075428	PT	Narrow	A
May-Thurner syndrome	10069727	PT	Narrow	A
Mesenteric vein thrombosis	10027402	PT	Narrow	A
Mesenteric venous occlusion	10027403	PT	Narrow	A
Obstetrical pulmonary embolism	10029925	PT	Narrow	A
Obstructive shock	10073708	PT	Narrow	A
Ophthalmic vein thrombosis	10074349	PT	Narrow	A
Ovarian vein thrombosis	10072059	PT	Narrow	A
Paget-Schroetter syndrome	10050216	PT	Narrow	A
Pelvic venous thrombosis	10034272	PT	Narrow	A
Penile vein thrombosis	10034324	PT	Narrow	A
Peripheral vein occlusion	10083103	PT	Narrow	A
Peripheral vein thrombus extension	10082853	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Phlebectomy	10048874	PT	Narrow	A
Portal vein cavernous transformation	10073979	PT	Narrow	A
Portal vein embolism	10082030	PT	Narrow	A
Portal vein occlusion	10058989	PT	Narrow	A
Portal vein thrombosis	10036206	PT	Narrow	A
Portosplenomesenteric venous thrombosis	10077623	PT	Narrow	A
Post procedural pulmonary embolism	10063909	PT	Narrow	A
Post thrombotic syndrome	10048591	PT	Narrow	A
Postoperative thrombosis	10050902	PT	Narrow	A
Postpartum venous thrombosis	10036300	PT	Narrow	A
Pulmonary embolism	10037377	PT	Narrow	A
Pulmonary infarction	10037410	PT	Narrow	A
Pulmonary microemboli	10037421	PT	Narrow	A
Pulmonary thrombosis	10037437	PT	Narrow	A
Pulmonary vein occlusion	10068690	PT	Narrow	A
Pulmonary veno-occlusive disease	10037458	PT	Narrow	A
Pulmonary venous thrombosis	10037459	PT	Narrow	A
Renal vein embolism	10038547	PT	Narrow	A
Renal vein occlusion	10056293	PT	Narrow	A
Renal vein thrombosis	10038548	PT	Narrow	A
Retinal vein occlusion	10038907	PT	Narrow	A
Retinal vein thrombosis	10038908	PT	Narrow	A
Septic pulmonary embolism	10083093	PT	Narrow	A
SI QIII TIII pattern	10068479	PT	Narrow	A
Splenic vein occlusion	10068122	PT	Narrow	A
Splenic vein thrombosis	10041659	PT	Narrow	A
Subclavian vein occlusion	10079164	PT	Narrow	A
Subclavian vein thrombosis	10049446	PT	Narrow	A
Superior sagittal sinus thrombosis	10042567	PT	Narrow	A
Superior vena cava occlusion	10058988	PT	Narrow	A
Superior vena cava syndrome	10042569	PT	Narrow	A
Thrombophlebitis	10043570	PT	Narrow	A
Thrombophlebitis migrans	10043581	PT	Narrow	A
Thrombophlebitis neonatal	10043586	PT	Narrow	A
Thrombophlebitis superficial	10043595	PT	Narrow	A
Thrombosed varicose vein	10043605	PT	Narrow	A
Thrombosis corpora cavernosa	10067270	PT	Narrow	A
Transverse sinus thrombosis	10044457	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Vena cava embolism	10047193	PT	Narrow	A
Vena cava filter insertion	10048932	PT	Narrow	A
Vena cava filter removal	10074397	PT	Narrow	A
Vena cava thrombosis	10047195	PT	Narrow	A
Venogram abnormal	10047209	PT	Narrow	A
Venoocclusive disease	10062173	PT	Narrow	A
Venoocclusive liver disease	10047216	PT	Narrow	A
Venous angioplasty	10077826	PT	Narrow	A
Venous occlusion	10058990	PT	Narrow	A
Venous operation	10062175	PT	Narrow	A
Venous recanalisation	10068605	PT	Narrow	A
Venous repair	10052964	PT	Narrow	A
Venous stent insertion	10063389	PT	Narrow	A
Venous thrombosis	10047249	PT	Narrow	A
Venous thrombosis in pregnancy	10067030	PT	Narrow	A
Venous thrombosis limb	10061408	PT	Narrow	A
Venous thrombosis neonatal	10064602	PT	Narrow	A
Visceral venous thrombosis	10077829	PT	Narrow	A

SMQ Name: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)			SMQ Code:20000083	
Preferred Term	**Code**	**Level**	**Scope**	**Category**
Administration site thrombosis	10075968	PT	Narrow	A
Adrenal thrombosis	10075178	PT	Narrow	A
Angiogram abnormal	10060956	PT	Narrow	A
Angiogram cerebral abnormal	10052906	PT	Narrow	A
Angiogram peripheral abnormal	10057517	PT	Narrow	A
Antiphospholipid syndrome	10002817	PT	Narrow	A
Application site thrombosis	10076026	PT	Narrow	A
Arteriovenous fistula occlusion	10058562	PT	Narrow	A
Arteriovenous fistula thrombosis	10003192	PT	Narrow	A
Arteriovenous graft thrombosis	10053182	PT	Narrow	A
Artificial blood vessel occlusion	10078895	PT	Narrow	A
Atrial thrombosis	10048632	PT	Narrow	A
Basal ganglia stroke	10071043	PT	Narrow	A
Bone infarction	10049824	PT	Narrow	A
Brain stem embolism	10074422	PT	Narrow	A
Brain stem infarction	10006147	PT	Narrow	A
Brain stem stroke	10068644	PT	Narrow	A
Brain stem thrombosis	10062573	PT	Narrow	A
Cardiac ventricular thrombosis	10053994	PT	Narrow	A
Catheter site thrombosis	10079523	PT	Narrow	A
Cerebellar embolism	10067167	PT	Narrow	A
Cerebellar infarction	10008034	PT	Narrow	A
Cerebral congestion	10076929	PT	Narrow	A
Cerebral infarction	10008118	PT	Narrow	A
Cerebral infarction foetal	10008119	PT	Narrow	A
Cerebral ischaemia	10008120	PT	Narrow	A
Cerebral microembolism	10078311	PT	Narrow	A
Cerebral microinfarction	10083668	PT	Narrow	A
Cerebral septic infarct	10070671	PT	Narrow	A
Cerebral thrombosis	10008132	PT	Narrow	A
Cerebral vascular occlusion	10076895	PT	Narrow	A
Cerebrospinal thrombotic tamponade	10052173	PT	Narrow	A
Cerebrovascular accident	10008190	PT	Narrow	A
Cerebrovascular accident prophylaxis	10049165	PT	Narrow	A
Cerebrovascular disorder	10008196	PT	Narrow	A
Cerebrovascular operation	10051902	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Choroidal infarction	10057403	PT	Narrow	A
Collateral circulation	10069729	PT	Narrow	A
Coronary bypass thrombosis	10059025	PT	Narrow	A
Device embolisation	10074896	PT	Narrow	A
Device occlusion	10064685	PT	Narrow	A
Device related thrombosis	10077455	PT	Narrow	A
Diplegia	10013033	PT	Narrow	A
Directional Doppler flow tests abnormal	10013048	PT	Narrow	A
Disseminated intravascular coagulation	10013442	PT	Narrow	A
Disseminated intravascular coagulation in newborn	10013443	PT	Narrow	A
Embolic cerebellar infarction	10084072	PT	Narrow	A
Embolic cerebral infarction	10060839	PT	Narrow	A
Embolic pneumonia	10065680	PT	Narrow	A
Embolic stroke	10014498	PT	Narrow	A
Embolism	10061169	PT	Narrow	A
Eye infarction	10083006	PT	Narrow	A
Fluorescence angiogram abnormal	10083087	PT	Narrow	A
Foetal cerebrovascular disorder	10053601	PT	Narrow	A
Gastric infarction	10084858	PT	Narrow	A
Graft thrombosis	10051269	PT	Narrow	A
Haemorrhagic adrenal infarction	10079902	PT	Narrow	A
Haemorrhagic cerebral infarction	10019005	PT	Narrow	A
Haemorrhagic infarction	10019013	PT	Narrow	A
Haemorrhagic stroke	10019016	PT	Narrow	A
Haemorrhagic transformation stroke	10055677	PT	Narrow	A
Haemorrhoids thrombosed	10019023	PT	Narrow	A
Hemiparesis	10019465	PT	Narrow	A
Hemiplegia	10019468	PT	Narrow	A
Heparin-induced thrombocytopenia	10062506	PT	Narrow	A
Hepatic infarction	10019680	PT	Narrow	A
Hepatic vascular thrombosis	10074494	PT	Narrow	A
Implant site thrombosis	10063868	PT	Narrow	A
Incision site vessel occlusion	10076839	PT	Narrow	A
Infarction	10061216	PT	Narrow	A
Infusion site thrombosis	10065489	PT	Narrow	A
Injection site thrombosis	10022104	PT	Narrow	A
Inner ear infarction	10070754	PT	Narrow	A
Instillation site thrombosis	10073625	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Intestinal infarction	10022657	PT	Narrow	A
Intracardiac mass	10066087	PT	Narrow	A
Intracardiac thrombus	10048620	PT	Narrow	A
Lambl's excrescences	10083691	PT	Narrow	A
Medical device site thrombosis	10076145	PT	Narrow	A
Mesenteric vascular insufficiency	10027401	PT	Narrow	A
Mesenteric vascular occlusion	10074583	PT	Narrow	A
Microembolism	10073734	PT	Narrow	A
Monoparesis	10027925	PT	Narrow	A
Monoplegia	10027926	PT	Narrow	A
Optic nerve infarction	10030936	PT	Narrow	A
Pancreatic infarction	10068239	PT	Narrow	A
Paradoxical embolism	10066059	PT	Narrow	A
Paraneoplastic thrombosis	10079251	PT	Narrow	A
Paraparesis	10033885	PT	Narrow	A
Paraplegia	10033892	PT	Narrow	A
Paresis	10033985	PT	Narrow	A
Peripheral revascularisation	10053351	PT	Narrow	A
Pituitary infarction	10035092	PT	Narrow	A
Placental infarction	10064620	PT	Narrow	A
Pneumatic compression therapy	10059829	PT	Narrow	A
Portal shunt procedure	10077479	PT	Narrow	A
Post procedural stroke	10066591	PT	Narrow	A
Postpartum thrombosis	10077022	PT	Narrow	A
Prosthetic cardiac valve thrombosis	10063176	PT	Narrow	A
Prosthetic vessel implantation	10068628	PT	Narrow	A
Quadriparesis	10049680	PT	Narrow	A
Quadriplegia	10037714	PT	Narrow	A
Renal infarct	10038470	PT	Narrow	A
Renal vascular thrombosis	10072226	PT	Narrow	A
Retinal infarction	10051742	PT	Narrow	A
Retinal vascular thrombosis	10062108	PT	Narrow	A
Revascularisation procedure	10084091	PT	Narrow	A
Shunt occlusion	10040621	PT	Narrow	A
Shunt thrombosis	10059054	PT	Narrow	A
Spinal cord infarction	10058571	PT	Narrow	A
Spinal stroke	10082031	PT	Narrow	A
Splenic infarction	10041648	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Splenic thrombosis	10074601	PT	Narrow	A
Stoma site thrombosis	10074515	PT	Narrow	A
Stroke in evolution	10059613	PT	Narrow	A
Strokectomy	10084735	PT	Narrow	A
Surgical vascular shunt	10058408	PT	Narrow	A
Testicular infarction	10043337	PT	Narrow	A
Thalamic infarction	10064961	PT	Narrow	A
Thrombectomy	10043530	PT	Narrow	A
Thromboangiitis obliterans	10043540	PT	Narrow	A
Thrombolysis	10043568	PT	Narrow	A
Thrombosis	10043607	PT	Narrow	A
Thrombosis in device	10062546	PT	Narrow	A
Thrombosis mesenteric vessel	10043626	PT	Narrow	A
Thrombosis prophylaxis	10043634	PT	Narrow	A
Thrombotic cerebral infarction	10067347	PT	Narrow	A
Thrombotic stroke	10043647	PT	Narrow	A
Thyroid infarction	10043742	PT	Narrow	A
Tumour embolism	10045168	PT	Narrow	A
Tumour thrombectomy	10081994	PT	Narrow	A
Tumour thrombosis	10068067	PT	Narrow	A
Ultrasonic angiogram abnormal	10061604	PT	Narrow	A
Ultrasound Doppler abnormal	10045413	PT	Narrow	A
Umbilical cord occlusion	10076714	PT	Narrow	A
Umbilical cord thrombosis	10071652	PT	Narrow	A
Vaccination site thrombosis	10076190	PT	Narrow	A
Vascular access site thrombosis	10078675	PT	Narrow	A
Vascular device occlusion	10080803	PT	Narrow	A
Vascular graft	10067740	PT	Narrow	A
Vascular graft occlusion	10049060	PT	Narrow	A
Vascular graft thrombosis	10069922	PT	Narrow	A
Vascular operation	10049071	PT	Narrow	A
Vascular stent insertion	10063382	PT	Narrow	A
Vascular stent occlusion	10077143	PT	Narrow	A
Vascular stent thrombosis	10063934	PT	Narrow	A

Preferred Term	Code	Level	Scope	Category
Vasodilation procedure	10058794	PT	Narrow	A
Vessel puncture site occlusion	10076838	PT	Narrow	A
Vessel puncture site thrombosis	10070649	PT	Narrow	A
Visual midline shift syndrome	10066856	PT	Narrow	A
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16.2 Standardized MedDRA Query - Anaphylactic Reaction (Broad) (SMQ Code: 20000021)

SMQ Name: Anaphylactic reaction (SMQ)				SMQ Code: 20000021
Preferred term	**Code**	**Level**	**Scope**	**Category**
Anaphylactic reaction	10002198	PT	Narrow	A
Anaphylactic shock	10002199	PT	Narrow	A
Anaphylactic transfusion reaction	10067113	PT	Narrow	A
Anaphylactoid reaction	10002216	PT	Narrow	A
Anaphylactoid shock	10063119	PT	Narrow	A
Circulatory collapse	10009192	PT	Narrow	A
Dialysis membrane reaction	10076665	PT	Narrow	A
Kounis syndrome	10069167	PT	Narrow	A
Procedural shock	10080894	PT	Narrow	A
Shock	10040560	PT	Narrow	A
Shock symptom	10040581	PT	Narrow	A
Type I hypersensitivity	10045240	PT	Narrow	A
Acute respiratory failure	10001053	PT	Broad	B
Asthma	10003553	PT	Broad	B
Bronchial oedema	10056695	PT	Broad	B
Bronchospasm	10006482	PT	Broad	B
Cardio-respiratory distress	10049874	PT	Broad	B
Chest discomfort	10008469	PT	Broad	B
Choking	10008589	PT	Broad	B
Choking sensation	10008590	PT	Broad	B
Circumoral oedema	10052250	PT	Broad	B
Cough	10011224	PT	Broad	B
Cough variant asthma	10063076	PT	Broad	B

Preferred term	Code	Level	Scope	Category
Cyanosis	10011703	PT	Broad	B
Dyspnoea	10013968	PT	Broad	B
Hyperventilation	10020910	PT	Broad	B
Irregular breathing	10076213	PT	Broad	B
Laryngeal dyspnoea	10052390	PT	Broad	B
Laryngeal oedema	10023845	PT	Broad	B
Laryngospasm	10023891	PT	Broad	B
Laryngotracheal oedema	10023893	PT	Broad	B
Mouth swelling	10075203	PT	Broad	B
Nasal obstruction	10028748	PT	Broad	B
Oedema mouth	10030110	PT	Broad	B
Oropharyngeal oedema	10078783	PT	Broad	B
Oropharyngeal spasm	10031111	PT	Broad	B
Oropharyngeal swelling	10031118	PT	Broad	B
Pharyngeal oedema	10034829	PT	Broad	B
Pharyngeal swelling	10082270	PT	Broad	B
Respiratory arrest	10038669	PT	Broad	B
Respiratory distress	10038687	PT	Broad	B
Respiratory failure	10038695	PT	Broad	B
Reversible airways obstruction	10062109	PT	Broad	B
Sensation of foreign body	10061549	PT	Broad	B
Sneezing	10041232	PT	Broad	B
Stridor	10042241	PT	Broad	B
Swollen tongue	10042727	PT	Broad	B
Tachypnoea	10043089	PT	Broad	B
Throat tightness	10043528	PT	Broad	B
Tongue oedema	10043967	PT	Broad	B
Tracheal obstruction	10044291	PT	Broad	B
Tracheal oedema	10044296	PT	Broad	B
Upper airway obstruction	10067775	PT	Broad	B
Wheezing	10047924	PT	Broad	B
Acquired C1 inhibitor deficiency	10081035	PT	Broad	C
Allergic oedema	10060934	PT	Broad	C
Angioedema	10002424	PT	Broad	C
Circumoral swelling	10081703	PT	Broad	C
Erythema	10015150	PT	Broad	C
Eye oedema	10052139	PT	Broad	C

Preferred term	Code	Level	Scope	Category
Eye pruritus	10052140	PT	Broad	C
Eye swelling	10015967	PT	Broad	C
Eyelid oedema	10015993	PT	Broad	C
Face oedema	10016029	PT	Broad	C
Flushing	10016825	PT	Broad	C
Hereditary angioedema with C1 esterase inhibitor deficiency	10080955	PT	Broad	C
Injection site urticaria	10022107	PT	Broad	C
Lip oedema	10024558	PT	Broad	C
Lip swelling	10024570	PT	Broad	C
Nodular rash	10075807	PT	Broad	C
Ocular hyperaemia	10030041	PT	Broad	C
Oedema	10030095	PT	Broad	C
Oedema blister	10080039	PT	Broad	C
Periorbital oedema	10034545	PT	Broad	C
Periorbital swelling	10056647	PT	Broad	C
Pruritus	10037087	PT	Broad	C
Pruritus allergic	10063438	PT	Broad	C
Rash	10037844	PT	Broad	C
Rash erythematous	10037855	PT	Broad	C
Rash pruritic	10037884	PT	Broad	C
Skin swelling	10053262	PT	Broad	C
Swelling	10042674	PT	Broad	C
Swelling face	10042682	PT	Broad	C
Swelling of eyelid	10042690	PT	Broad	C
Urticaria	10046735	PT	Broad	C
Urticaria papular	10046750	PT	Broad	C
Blood pressure decreased	10005734	PT	Broad	D
Blood pressure diastolic decreased	10005737	PT	Broad	D
Blood pressure systolic decreased	10005758	PT	Broad	D
Cardiac arrest	10007515	PT	Broad	D
Cardio-respiratory arrest	10007617	PT	Broad	D
Cardiovascular insufficiency	10065929	PT	Broad	D
Diastolic hypotension	10066077	PT	Broad	D

Preferred term	Code	Level	Scope	Category
Hypotension	10021097	PT	Broad	D
Hypotensive crisis	10083659	PT	Broad	D
Post procedural hypotension	10084013	PT	Broad	D
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Approved-PPD Approval	
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