STATISTICAL ANALYSIS PLAN

Protocol title:	**A Non-Controlled, Open-Label, Multicenter, Study of Efficacy of rFVIIIFc for Immune Tolerance Induction (ITI) in Severe Hemophilia A Subjects With Inhibitors Undergoing the First ITI Treatment**
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VERSION HISTORY

This statistical analysis plan (SAP) for study 997HA402/LPS16473 is based on the protocol dated 11-jul-2019.

The first patient was enrolled on 08-dec-2017. An interim SAP was approved on 19-mar-2019. The first interim analysis was performed on 12-apr-2019.

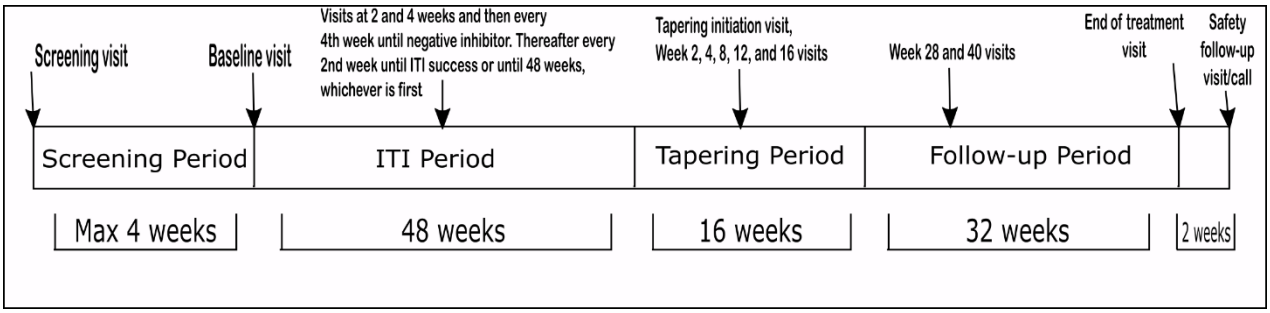
1 INTRODUCTION

Abbreviations used in this document are provided in Section 5.1.

1.1 STUDY DESIGN

This is an open-label, single-arm, interventional, multicenter study designed to explore the use of rFVIIIFc (recombinant coagulation factor VIII Fc fusion protein)(1)(2) for ITI (Immune Tolerance Induction). The study will be conducted in male patients of any age with severe hemophilia A and high-titer inhibitors (historical peak ≥5 BU/mL), who have been previously treated with any plasma-derived FVIII or recombinant conventional or EHL (extended half-life) FVIII and are undergoing ITI treatment for the first time.

The study period consists of 1) a 4-week (1-month) Screening Period; 2) a maximum of a 48-week (12-month) ITI Period; 3) a minimum of a 16-week (4-month) Tapering Period after all criteria for tolerization have been met; and 4) a 32-week (8-month) Follow-Up Period. Only patients who achieve ITI success will enter the Tapering and Follow-Up Periods. During the Tapering and Follow-Up Periods, the patient's dose will be adjusted to achieve the prophylactic dose. However, if FVIII peak activity levels rise above 200 IU/dL after the inhibitors are negative but before all the ITI success criteria are met, the dose may be adjusted according to Investigator judgment to maintain the FVIII peak activity levels between 100 and 200 IU/dL. This dose reduction will not be considered part of the Tapering Period, and the patient will maintain the schedule of assessments per the ITI Period.



1.2 OBJECTIVE AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To describe the time to tolerization (ITI success, i.e., inhibitor titer <0.6 BU/mL, rFVIIIFc incremental recovery [IR] ≥66% of the expected IR, and t½ ≥7 hours) with rFVIIIFc in patients within a maximum of 12 months (48 weeks) of ITI treatment.	• Time to tolerization with a maximum of 12 months (48 weeks) of ITI treatment offered in the study (tolerization defined as inhibitor titer <0.6 BU/mL, rFVIIIFc incremental recovery [IR] of ≥66% of expected, and half-life [t½] of ≥7 hours).

Objectives	Endpoints
Secondary	
• To describe the outcome of ITI treatment • To describe the relapse rate over the 48-week (12-month) period following successful ITI performed with rFVIIIFc • To describe the intercurrent bleeding during the ITI Period and during the 48-week (12-month) period after successful ITI performed with rFVIIIFc • To describe the safety and tolerability of rFVIIIFc when used for ITI • To evaluate the impact of ITI treatment with rFVIIIFc on health economics and adherence	• ITI success: - Confirmed negative titers consisting of 2 consecutive negative inhibitor assessments within 2 weeks (±3 days) based on local laboratory results <0.6 BU/mL by the Nijmegen-modified Bethesda assay; determination of negative titer based on the Bethesda assay is acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay. - IR ≥1.32 IU/dL per IU/kg in 2 consecutive assessments representing ≥66% of the expected IR 2 IU/dL per IU/kg. - $t_{½}$ ≥7 hours. • Occurrence of relapse (defined as confirmed positive inhibitor titer ≥0.6 BU/mL, abnormal recovery after tolerance is achieved, and $t_{½}$ <7 hours) during the Tapering or Follow-Up Periods • Number of bleeding episodes during the ITI Period and during the 48-week (12-month) period after successful ITI performed with rFVIIIFc • Adverse events and serious adverse events • Number of days away from work or school • Number of hospitalization days • Adherence (defined as percentage of administered doses versus planned doses) • Consumption of rFVIIIFc (measured in total rFVIIIFc use)
Tertiary/exploratory	
[redacted]	

Objectives	Endpoints
	[redacted]

1.2.1 Estimands

Not applicable.

2 SAMPLE SIZE DETERMINATION

Because the number of patients who have severe hemophilia A and have developed inhibitors is small, the determination of sample size for this study is constrained by the availability of patients. To describe the duration of time needed to develop tolerization from the onset of ITI, the study plans to prospectively enroll up to 30 patients who are to receive ITI for the first time.

3 ANALYSIS POPULATIONS

For the purpose of statistical analyses, 3 analysis sets are defined based on the following criteria:

Table 2 - Populations for analyses

Population	Description
ITI full analysis set (ITIFAS)	This set will include all patients who received at least 1 infusion of rFVIIIFc. All analyses describing efficacy and safety during the ITI treatment period will be based on this analysis set. This analysis set will also be used for analysis of endpoints which summarize cumulative results from ITI, tapering, and follow-up periods.
Tapering period full analysis set (TPFAS)	This set will include all patients who entered the tapering period of the study. All analyses describing efficacy and safety during this study phase will be based on this analysis set. This analysis set will also be used for analysis of endpoints which summarize cumulative results from tapering and follow-up periods.
Follow-up period full analysis set (FUPFAS)	This set will include all patients who entered the follow-up period of the study. All analyses describing efficacy and safety during this study phase will be based on this analysis set.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

Continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, minimum, and maximum. The 25th (Q1) and 75th (Q3) percentiles and 95% confidence intervals may be presented where appropriate. Categorical and ordinal data will be summarized using the count and percentage of patients.

In general, event time variables will be summarized in two ways. For the subset of patients who experience the event of interest, the data will be summarized using standard descriptive statistics for continuous variables as described above. In addition, Kaplan-Meier estimates will be provided for ITI full analysis set regardless whether a patient experiences the event of interest. Patients who do not reach an event will be censored on the date of the last on-study follow-up visit unless otherwise specified in the SAP.

The baseline value is defined as the last available value before the first dose of ITI with rFVIIIFc.

Unless otherwise specified, analyses will be performed for all treated patients.

Observation period

The observation period will be divided into 3 segments:

- **ITI period** starts on the day of the first dose of ITI with rFVIIIFc. For those who successfully tolerized and entered the tapering period, the end of the ITI period is the day before the first visit of the tapering period. For those who did not successfully tolerize per protocol, the end of the ITI period is the day of the last study visit.
- **Tapering period** starts on the day of first visit of the tapering period and ends on the day of the last visit of the tapering period. For those who did not enter the follow-up period, the tapering period ends on the day of the last study visit.
- **Follow-up period** starts on the day after the last visit of the tapering period and ends on the day of the last study visit.

4.2 PARTICIPANT DISPOSITIONS

Patient disposition will be summarized for all enrolled in the study. The number (%) of patients included in each of the analysis populations (ITIFAS, TPFAS, and FUPFAS) listed in Table 2 will be summarized.

The number (%) of patients in the following categories will be provided (overall and by study period):

- Enrolled patients
- Participants who completed the study period as per protocol

- Participants who did not complete the study period as per protocol and main reason for study discontinuation

In addition, the number (%) of patients enrolled will be summarized by geographical region, country and site. The number (%) of patients attending key study visits will be summarized by visit for ITIFAS.

A listing including the duration in the study, date of the last visit/period, and the reason for early termination/withdrawal for patients who did not complete the study will be provided.

Protocol deviations

Protocol deviations will be recorded, monitored throughout the study and finalized at the end. Major and minor protocol deviations/violations are to be pre-specified prior to database lock. There is no plan of excluding patients from statistical analyses as the result of protocol deviation. Critical and major protocol deviations (programmatic or manual) will be summarized in the enrolled population.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

The primary endpoint of this study is time to tolerization with a maximum of 48 weeks (12 months) of ITI treatment offered in the study (tolerization defined as inhibitor titer <0.6 BU/mL, rFVIIIFc incremental recovery [IR] ≥66% of the expected IR, and t½ ≥7 hours).

Negative inhibitor

Inhibitor titer value <0.6 BU are considered negative. To confirm that a patient's inhibitor titer has reached negativity, a consecutive second sample with a titer value <0.6 BU at the next visit is required.

Results from local lab will be used for this determination. If the local lab results are not available, the results from the central lab will be used. Occurrence and date of negative titer associated with ITI success will be recorded in the eCRFs by the investigator.

Normal incremental recovery (IR)

IR ≥1.32 IU/dL per IU/kg (≥66% of the expected IR 2 IU/dL per IU/kg) is considered normal IR. To confirm the occurrence of normal IR, a consecutive visit with a normal IR is required.

Results from local lab will be used for this determination. If the local lab results are not available, the results from the central lab will be used. Occurrence and date of normal IR will be recorded in the eCRFs by the investigator.

Half life ≥7 Hours

Achieving $t_{½}$ ≥7 hours is the final PK goal of the ITI treatment. Results from local lab will be used for this determination. If the local lab results are not available, the results from the central lab will be used.

Occurrence and date of $t_{½}$ ≥7 hours will be recorded in the eCRFs by the investigator.

4.3.2 Main analytical approach

Time to tolerization will be summarized using descriptive statistics of number of observations, mean, standard deviation, median, 25th and 75th quartiles, minimum, and maximum. Kaplan-Meier estimates for median, 25th and 75th quartiles will also be provided. A Kaplan-Meier plot showing percentage of patients who tolerized against time from the first ITI infusion will be generated. Patients not achieving ITI success during the ITI Period (48 weeks) will be censored at the latest time with positive inhibitor titer data for this analysis. The ITIFAS will be used.

4.3.3 Sensitivity analysis

Not applicable.

4.3.4 Supplementary analyses

Additional analyses associated with primary endpoint

Time to negative titer, time to normal incremental recovery, and time to $t_{1/2}$ ≥7 hrs will be summarized using descriptive statistics for patients who meet the criteria for negative inhibitor, normal recovery, and $t_{1/2}$ ≥7 hrs, respectively. Individual patient listing tabulating outcome of ITI treatment, duration on ITI, times to negative inhibitor titer, normal recovery, and tolerization, duration in Tapering Period, duration in Follow-up Period, status of relapse, and duration from ITI success to relapse will be provided.

Factor activity levels from local and central laboratories will be tabulated in individual patient listing by study visit and time points of blood sample. The associated IR in IU/dL per IU/kg, t1/2, and the investigator's assessment on whether a patient has met the criteria of IR and t1/2 for ITI success will also be tabulated.

Exploratory analysis for the final data

Agreement between local and central laboratory results on the determination on negative titer, normal IR and $t_{1/2}$ >=7 hrs for ITI success will be summarized. Scatter plots for inhibitor titer will be presented for the ITI period, showing the local laboratory results on the x-axis and the central laboratory results on the y-axis. A line crosses diagonal will be plotted to indicate perfect correlation. Scatter plots for IR in IU/dL per IU/kg and t1/2 will be provided by study period.

Time to negative inhibitor

This is defined as the number of days from the first infusion of ITI with rFVIIIFc to the date of first negative titer with a subsequent confirmatory negative titer associated with ITI success.

Time to normal IR

This is defined as the number of days from the first infusion of ITI with rFVIIIFc to the date of first normal IR with a subsequent confirmatory normal IR associated with ITI success.

Time to half life ≥7 Hours

This is defined as the number of days from the first infusion of ITI with rFVIIIFc to the date of t½ ≥7 hours.

Time from negative inhibitor titer to t½ ≥7 hours

This is defined as the number of days from the date of confirmed negative inhibitor titer to the first date of t½ ≥7 hours.

4.3.5 Subgroup analyses

No specific subgroup analysis has been planned as the result of the small number of patients for the study. If sample size permits, subgroup analysis may be conducted by age, race, and patient status on ITI success and relapse after ITI success.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Key/Confirmatory secondary endpoint(s)

4.4.1.1 Definition of endpoint(s)

ITI Outcome

Each patient will be assigned to one of the following 5 categories of outcomes of ITI treatment.

<u>ITI success</u>

A patient is categorized as an ITI success if the following 3 criteria are all met:

- Confirmed negative titers consisting of 2 consecutive negative inhibitor assessments within 2 weeks (±3 days) based on local laboratory results <0.6 BU/mL by the Nijmegen-modified Bethesda assay; determination of negative titer based on the Bethesda assay is acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay.
- IR ≥1.32 IU/dL per IU/kg in 2 consecutive assessments representing ≥66% of the expected IR 2 IU/dL per IU/kg.
- t½ ≥7 hours.

Early withdrawal (outcome not determinable) during ITI period

Unable to determine ITI outcome due to withdrawal prior to completing ITI Period (48 weeks of ITI treatment). For these patients, their status will be further categorized into:

- Positive inhibitor titer
  - Inhibitor titer reduced (≥20%) from baseline but not yet negative
  - Inhibitor titer remains the same (±20%) as baseline
  - Inhibitor increased (≥20%) from baseline
- Negative inhibitory titer
- Negative inhibitory titer and normal IR

ITI treatment failure (those with at least 36 weeks or 48 weeks of ITI treatment)

Treatment failure is defined for the following two scenarios:

- Patients complete at least 9 months of ITI treatments (Week 36 [Month 9] visit) and experience no downward trend of ≥20% in the inhibitor titer comparing to titer at the end of the initial 3 months of treatment (Week 12 [Month 3] visit).
- Patients competed 48 weeks of ITI treatment and inhibitor titer remains positive (≥0.6 BU/mL) at Week 48 (Month 12) visit including those who achieve the first negative titer at Week 48 (Month 12) but are not confirmed with a consecutive second negative tier and subsequently with IR ≥1.32 IU/dL per IU/kg or $t_{½}$ ≥7 hours after 48 weeks of ITI treatment

Patients who have been determined to have failed ITI will then proceed to the End of Treatment (EOT) Visit.

Partial success

The determination of partial success will be made only among patients who have completed the ITI period (Week 48 [12 months] visit) but do not fulfill the criteria for ITI success or treatment failure.

Partial success is defined as achieving negative inhibitor titer and one of the PK parameters of ITI success: IR ≥1.32 IU/dL per IU/kg OR $t_{½}$ ≥7 hours.

Patients who have been determined to have achieved only partial success will then proceed to EOT Visit.

Ongoing

This category is only applicable for the interim analysis for the patients who do not meet the definitions for the 4 categories of ITI outcomes as described above. For patients who are ongoing, their status will be further categorized into:

- Positive inhibitor titer
  - Inhibitor titer reduced (≥20%) from baseline but not yet negative
  - Inhibitor titer remains the same (+/- 20%) as baseline
  - Inhibitor increased (≥20%) from baseline
- Negative inhibitory titer
- Negative inhibitory titer and normal IR

The ITIFAS will be used for this analysis.

Occurrence of relapse after successful ITI

Occurrence of relapse is defined as the proportions of patients who reach ITI success and later meet criteria of relapse during the Tapering Period, Follow-up Period, and the two Periods combined.

Relapse

Relapse is defined as confirmed positive inhibitor titer ≥0.6 BU/mL and IR < 1.32 IU/dL after tolerance is achieved, during the Tapering or Follow-Up Periods. The samples for IR derivation need to meet the criteria of 24-hour wash-out period.

Results from local lab will be used for this determination. In the event that the local lab results are not available, the results from the central lab will be used. Occurrence and dates of positive inhibitor titer and lose of normal IR will be recorded in the eCRFs by the investigator.

Time to Relapse

This is defined as the number of days from the date of ITI success to the date of the first confirmed case of relapse.

Number of bleeding episodes

Annualized rate of the number of bleeding episodes during ITI Period will be calculated for each patient in the ITIFAS who had been observed for at least 90 days:

$$\text{annualized bleeding rate} = \frac{\text{number of bleeding episodes}}{(\text{length of study period in days}/365.25)}$$

Bleeding Episode

If a break-through bleed is not resolved right away, a patient may make multiple reports of the same bleed. To determine if multiple reports of bleeds belong to the same bleeding episode, the following definition is to be used.

Bleeds which receive treatment(s)

A bleeding episode is considered to start from the first report of bleeding. Additional reports of bleeds at the same location will be considered as the same bleeding episode if the injection to treat the bleed occur ≤72 hours of the previous infusion. A reported bleed will be considered a new bleeding episode if the infusion to treat the bleed occurs > 72 hours after the previous infusion to treat a bleed in the same location.

Any bleeding at a different location is considered a separate bleeding episode, regardless of the time from the last injection.

Bleeds which were un-treated

After the first report of bleeding, subsequent reports from the same location will be considered as the same bleeding episode if they occur ≤72 hours from the previous report of bleed. Reports of bleeding events 72 hours after the previous report of a bleed at the same location will be considered a new bleeding episode.

Spontaneous Bleeding Episode

Bleeding episodes are classified as spontaneous if a parent/caregiver records a bleeding event when there is no known contributing factor such as a definite trauma or antecedent "strenuous" activity. The determination of "strenuous" is at the discretion of the Investigator, and the parent/caregiver/patient will be instructed on this by the Investigator.

Traumatic Bleeding Episode

Bleeding episodes are classified as traumatic if the parent/caregiver records a bleeding episode even when there is a known or believed reason for the bleeding. For example, if a patient exercises strenuously and then has a bleeding episode in the absence of any obvious injury, the bleeding episode will still be recorded as traumatic. Target joint bleeding episodes can be traumatic if a known action leads to bleeding into the joint. The Investigator considers whether events resulting in a traumatic bleeding episode qualify as AEs and reports as such.

Number of days away from work or school

If sample size permits (n≥5), number of days missed from school or work per month will be calculated.

Number of hospitalization days

If sample size permits (n≥5), number of hospitalization days per year will be calculated.

Adherence

Percentage of administered doses as registered in the EPD and EDC versus the prescribed doses and percentage of number of days with infusions as registered in the EPD and EDC compared with the prescribed number of days will be calculated.

Adherence to the treatment regimen at each period is defined in 2 ways. Dose adherence is defined as the percentage of administered doses as registered in the EPD and EDC versus the prescribed doses to a patient. Dosing frequency adherence is defined as the percentage of number of days with infusions as registered in the EPD and EDC compared to the prescribed number of days to a patient in that period.

Consumption during ITI

Consumption of rFVIIIFc at each period is defined as the total rFVIIIFc in IU/kg which is received by a patient in that period.

4.4.1.2 Main analytical approach

ITI success

The number and proportion of patients achieving complete ITI success, partial success, treatment failure, undetermined, or ongoing with ITI will be summarized.

The ITIFAS will be used for this analysis.

Occurrence of relapse after successful ITI

Occurrence of relapse will be summarized descriptively by calculating the proportions of patients who reach ITI success and later meet criteria of relapse during the Tapering Period, Follow-up Period, and the two Periods combined. The TPFAS will be used for this analysis.

Time to relapse will be defined as the duration between ITI success and time of relapse. Time to relapse from successful ITI will also be summarized descriptively for patients who relapsed during either the Tapering or Follow-Up Period.

Number of bleeding episodes during ITI, Tapering, and Follow-Up Periods

The number of bleeding episodes during ITI Period will be summarized by month using the ITIFAS. Descriptive statistics for annualized bleeding rate while the patients undergo ITI treatment will also be provided. The same analysis will be conducted by whether the bleeding episode is treated, and by type and location of bleeding episodes.

Patients will only be included in this analysis if they were observed for at least 90 days.

The annualized bleeding episodes will also be summarized for the Tapering and Follow-Up Periods using the TPFAS and by patient status of relapse. Detailed results based on whether a bleeding episode is treated, and type and location of bleeding episodes will also be provided.

Number of days away from work or school

If sample size permits ($n \geq 5$), number of days missed from school or work per month will be summarized descriptively for the ITI Period using the ITIFAS and for the combined Tapering and

Follow-Up Periods using the TPFAS. Otherwise, the data will be tabulated in individual patient listing only.

Number of hospitalization days

If sample size permits (n≥5), number of hospitalization days per year will be summarized descriptively for the ITI Period using the ITIFAS and for the combined Tapering and Follow-Up Periods using the TPFAS. Otherwise, the data will be tabulated in individual patient listing only.

Adherence

Percentage of administered doses as registered in the EPD and EDC versus the prescribed doses and percentage of number of days with infusions as registered in the EPD and EDC compared with the prescribed number of days will be summarized using descriptive statistics for each of the 3 periods separately.

Consumption during ITI

Refer to Section 4.7.1.

4.4.2 Supportive secondary endpoint(s)

Not applicable.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

[redacted]

[redacted]

4.6 MULTIPLICITY ISSUES

Not applicable.

4.7 SAFETY ANALYSES

Safety analyses will either be summarized by study period or listed for all enrolled patients. No statistical testing is planned.

4.7.1 rFVIIIFc exposure

The extent of rFVIIIFc exposure will be assessed by the number of injections, number of days of rFVIIIFc exposure, duration, total amount of consumption, and patient adherence to the regimen, summarized by study period.

Refer to Section 4.4.1.1 for definition of consumption.

Study drug administered

Study drug administered will be listed for all patients. This will include the reason for administration (e.g., regular infusion, IR visit, $t_{1/2}$ visit, other) date and time of administration, dose, and dosing intervals. It will also include lot number and nominal potency of the lots used.

Except for PK doses, the unit body weight dose (IU/kg) for analysis of dosing will be calculated as the total IU (nominal dose) for each injection divided by the patient's most recent weight in kg prior to the dose of study drug.

Dose of 50 IU/kg is to be used for IR and t½ assessments. The actual dose will be calculated based on the actual potency of the vial (between 80 to 125% of nominal strength) and adjusted by actual volume of infusion if partial vials are used.

$$\text{Dose}\left(\text{IU}/\text{Kg}\right) = \frac{\left(\frac{\text{Total volume administerd}}{\text{Volume of vial}}\right)(\text{Actual/Nominal potency of vial})}{\text{Weight(Kg)}}$$

Patients could be infused with the rest of the ITI dose after the 50 IU/kg for IR assessment.

Number of injections and exposure Days

The total number of injections per patient will be summarized descriptively overall and by study period. The number of exposure days is defined as the total number of days in which a patient received infusion during the study and will be summarized descriptively by study period.

Duration of rFVIIIFc exposure

Duration of rFVIIIFc exposure is calculated overall and by study period and is defined as last rFVIIIFc administration date – first rFVIIIFc administration date + 1, regardless of the reason for the last dose or any intermittent interruption. If the date of the last dose of rFVIIIFc is missing, the duration of rFVIIIFc will be left as missing.

Duration of rFVIIIFc dosing (weeks) will be summarized using descriptive statistics overall and by study period.

Prophylactic dose (IU/kg) and dosing interval after ITI success

Patients' first and last doses and dosing frequencies during the tapering period, and the last prophylactic doses and dosing frequencies during the follow-up period will be summarized using TPFAS and FUPFAS, respectively.

Consumption

Total consumption of rFVIIIFc during the study (excluding use of study drug for the purpose of surgery, and for the assessment of IR and $t_{1/2}$) will be summarized descriptively using the ITIFAS. Analysis will also be conducted separately for each of the 3 treatment periods using their respective analysis set. Summary statistics of annualized total consumption will also be provided.

The rate for each patient will be annualized in order to account for difference in the duration of ITI treatment based on the equation below:

$$\text{Annualized total consumption} = \text{total consumption} * \frac{365.25}{\text{length in study (days)}}$$

Patients will be included in this analysis only if they were observed for at least 90 days.

Adherence

Overall adherence to dosing regimen of rFVIIIFc (excluding use for the purpose of surgery and for the assessment of IR and $t_{1/2}$) will be calculated in two ways as follows:

$$\text{Dose adherence (\%)} = \frac{\text{total dose administered as registered in diary and EDC}}{\text{total dose prescribed}}$$

$$\text{Frequency adherence (\%)} = \frac{\text{total number of days with infusions as registered in the diary and EDC}}{\text{total number of days on which infusion was prescribed}}$$

This calculation will be done for each study period, and the results will be listed and summarized descriptively using the respective analysis sets.

4.7.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at Sanofi at the time of database lock.

Treatment-emergent adverse events (TEAEs) are AEs that developed, worsened, or became serious on or after the first administration of rFVIIIFc. Note that bleeding episodes in this patient population are not considered as AEs. Bleeding episodes that meet a serious criterion should be reported as serious adverse events (SAE). All bleeding episodes after the Baseline Visit will be captured in the EPD that the patient's parents/caregivers will maintain throughout the study period.

The primary focus of AE reporting will be on TEAEs.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE. (See Section 5.3 for missing data handling.)

AEs and SAEs will be summarized for the following breakdowns:

- Overall (ITI, Tapering, and Follow-up periods combined)
- ITI period
- Post-ITI period (Tapering and Follow-up periods combined)
- Tapering period
- Follow-up period

Multiple occurrences of the same event in the same patient will be counted only once in the tables within a study period. When presented by severity, patients will be counted once for each SOC and preferred term based on the greatest severity within that SOC and preferred term,

respectively. Similarly, when presenting by relationship, patients will be counted once for each SOC and preferred term based on the highest relationship within that SOC and preferred term, respectively.

If the assessment of the relationship to rFVIIIFc is missing for an AE, this AE will be assumed as related to rFVIIIFc. If the severity is missing for the treatment-emergent occurrences of an AE, the severity will be imputed as severe.

The AE tables will be sorted as indicated in Table 3.

Table 3 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	SOCs and preferred terms within each SOC will be sorted alphabetically.[a]

a The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

All adverse event listings will include the onset and resolution study days relative to Study Day 1, which is the date of the first rFVIIIFc treatment as well as the study period during which they occurred.

Analysis of all adverse events

An overview of number (%) of patients with TEAEs in the categories below will be generated (by study period and overall):

- Total TEAEs
- Patient with any TEAE
- Patient with at least one related TEAE
- Patient with any TEAE leading to permanent discontinuation of treatment or study
- Patient with any treatment emergent SAE (TESAE)
- Patient with at least one related TESAE
- Number of deaths

The AE summaries of Table 4 will be generated with number (%) of patients experiencing at least one event.

Table 4 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAEs	Primary SOC and PT
TEAEs by relationship to treatment	Primary SOC and PT
TEAEs by severity	Primary SOC and PT
Severe TEAEs	Primary SOC and PT
Treatment emergent SAEs	Primary SOC and PT

Analysis of deaths

Details on deaths on study will be tabulated in individual patient listing.

Analysis of adverse events of special interest (AESIs)

No adverse events of special interest (AESIs) were defined for this study.

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables and vital signs

The following laboratory variables and vital signs variables will be reported.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell count, platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Blood chemistry:
  - Metabolism: glucose, total protein
  - Electrolytes: sodium, potassium, chloride
  - Renal function: serum creatinine, blood urea nitrogen
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin
- Urinalysis:
  - Dipstick urinalysis, including a protein reading; if the protein reading is positive (≥1+), a full laboratory urinalysis will be performed.
- Vital signs: systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature

Quantitative analyses

For all laboratory variables, local laboratory results are reported by the site and captured in the eCRFs. Central laboratory data are not collected for this study. Shifts in normality status of blood chemistry and hematology from baseline to post-baseline and minimum/maximum post-baseline values, respectively, will be provided.

For vital signs, descriptive statistics for results and changes from baseline/pre-injection will be provided by study period and time point (prior or after rFVIIIFc infusion).

4.8 OTHER ANALYSES

4.8.1 PK analyses

Some of the pharmacokinetic parameters are considered exploratory endpoints (Section 4.5.1). Values of all pharmacokinetic parameters will be tabulated in individual patient data listings. No summary statistics will be provided because the pharmacokinetic profiles are anticipated to be idiosyncratically different depending on status of immunotolerance of each patient. Values of pharmacokinetic parameters will be tabulated in individual patient data listings.

4.8.2 Immunogenicity analyses

See Section 4.5.

4.8.3 Physical Examination

A general physical examination will be assessed and recorded as “normal” or “abnormal” at each visit. Abnormalities will be specified. Any persisting abnormalities will be stated each time the examination is performed. Diagnosis of new abnormalities will be recorded as AEs. If any abnormalities are reported at the Screening Visit, they will be recorded as medical history.

The number and percentage of patients with physical examination abnormalities at screening (or baseline if a screening exam is not available) will be presented by body system for ITIFAS. Percentages will be based on the number of patients for whom a screening/baseline physical examination is available. On-treatment physical examination findings will be listed.

4.8.4 Surgery

Patients who plan to have major surgeries are not to be enrolled in the study. Information on minor surgeries collected in the study including the type and reason of surgery, and date/time of surgery will be tabulated in individual patient data listings.

4.9 INTERIM ANALYSES

An interim analysis (IA) is planned for when at least 10 patients have completed at least 24 weeks (6 months) of ITI treatment. Subsequent interim analyses, if conducted, will depend on the number of years required to recruit the targeted number of patients.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	anti-drug antibodies
AE:	adverse event
AESIs:	adverse events of special interest
EDC:	electronic data capture
EHL:	extended half-life
EOS:	end of study
EPD:	electronic patient diary
FUPFAS:	follow-up period full analysis set
HLT:	high level term
IR:	incremental recovery
ITI:	immune tolerance induction
ITIFAS:	ITI full analysis set
LLT:	lower-level term
MedDRA:	medical dictionary for regulatory activities
PT:	preferred term
rFVIIIFc:	recombinant coagulation factor VIII Fc fusion protein
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TESAE:	treatment emergent SAE
TPFAS:	tapering period full analysis set
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history, and disease characteristics at baseline will be summarized using descriptive statistics in the ITIFAS population.

Demographic and baseline characteristics

- age in years as quantitative variable*
- gender (Male, Female)
- race (White, Black or African American, Other)

- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- weight (kg) at Baseline
- height (cm) at Screening

* In the eCRF, age is reported in the unit of week for patients who are ≤2 years of age and in year for those who are >2 years of age. For purpose of the reporting, all ages will be converted to the same unit of year. Data which are reported in week will be divided by 52.

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Number and percentages of patients reporting medical and surgical history will be summarized by body system and preferred term. A patient is counted only once if they report more than one occurrence of medical or surgical history in the same body system. Detailed information on diagnosis and current status associated with a specific history will be provided in a data listing for each patient.

Hemophilia history for time from diagnosis of hemophilia, lowest documented FVIII activity value, presence of family history of inhibitor, blood type, genotype, vaccination within last year will be summarized with descriptive statistics. Bleeding history on the numbers of bleeds per month in the 3 months prior to inhibitor diagnosis and from inhibitor diagnosis to the onset of ITI treatment will be summarized by type as well as overall. Inhibitor history on time from inhibitor detection to the onset of ITI treatment, time from first FVIII treatment to first inhibitor detection, peak historical inhibitor level, number of exposure days at first confirmed inhibitor development, and inhibitor titer prior to ITI initiation will be summarized. The last FVIII treatment and bypassing agent used prior to the study will be summarized by type and regimen.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are all drugs and substances the patient used prior to the first administration of rFVIIIFc. Prior medications can be discontinued before the first administration or still ongoing during the treatment period.
- Concomitant medications are any interventions received by the patient concomitantly to the rFVIIIFc up through the EOS visit. Note that a medication started prior to the first dose of rFVIIIFc and was ongoing during and/or after the first dose of rFVIIIFc will be classified as both prior and concomitant.
- Post-treatment medications are those the patient took in the period running from the end of the concomitant medications period up to the Follow-Up visit/phone call.
- Medications with a start date after the follow-up visit will not be considered concomitant and will not be included in the summary tables.

- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

If a concomitant medication start day is missing or partial, the medication will be assumed to be both a prior and a concomitant medication unless it can be deduced from the partially recorded medication start or stop dates whether a medication is concomitant or prior. See Section 5.3 for handling of missing or partial dates.

The prior and concomitant and post-treatment medications will be summarized for the ITIFAS population. Summaries will be based on the number and percentage of patients taking medications by WHODRUG standardized medication text. Within each WHODRUG standardized medication text a patient will be counted once even if he reported taking the medication more than once. Separate summaries will be provided for prior and concomitant medications. Medications taken after the EOS visit up to the Follow-Up visit/phone call will not be included in the summary table of concomitant medications. Two listings will be provided, one for prior and concomitant medications taken through the EOS visit and the other for the post-treatment medications taken after the EOS visit and prior to the Follow-Up visit/phone call. The summaries will be sorted in alphabetical order.

In this study, for patients who receive breast milk, maternal concomitant medications are also be collected at the same time points as other concomitant therapies, unless the breast milk is derived from a source other than the mother or the mother did not consent. These will be presented in a similar way as other concomitant medications.

Bypassing agents

Number and percentage of patients who used bypassing agents (aPCC [FEIBA] or rFVIIa [NovoSeven]) prior to first dose of ITI with rFVIIIFc and during each of the study periods will be tabulated by type of bypassing agents and regimen (on-demand versus prophylaxis). Total consumption of bypassing agents will be tabulated by type of bypassing agents and by study period as well as combined. Information from different data sources, e.g., concomitant medications, ePD and in-clinic use, will be integrated for this analysis.

Other therapies and procedures

Other therapies administered and concomitant procedures performed within 30 days prior to the first dose of study drug through the end of the study will be listed only, a summary table is not planned.

5.3 APPENDIX 3 DATA HANDLING CONVENTIONS

Description of study days

Study day for an event will be calculated from the first dose of study drug as (date of event – first dose date + 1) if the date of event is on or after the first dose date, or (date of event – first dose

date) if the date of event is before the first dose date. That is, Study Day 1 is the first day of treatment with study drug rFVIIIFc. Study Day -1 is the day immediately preceding Study Day 1. There is no Study Day 0 in this study. Study days will be included in the data listings where indicated on the listing shells. ”NA” for “not applicable” will be used to indicate that a patient did not receive the respective study drug.

Analysis windows for time points

Not applicable

Missing data

Aside from the following, no rFVIIIFcutation of study data will be performed.

For the analysis of AEs and concomitant medications/procedures, if the stop/start date of an AE or a concomitant medication is missing or partial, the corresponding study day will be left blank. However, inferences will be made from the partial and missing dates to classify medications as prior and/or concomitant and AEs as treatment emergent (or not).

For an AE with a partially or completely missing onset date, the following algorithm is used:

- If the onset time of an adverse event (if time is collected) is missing and the date of onset is the date of dosing, the AE is considered a TEAE.
- If the onset day of an adverse event is missing and the month and year of the onset of the AE are either the same or later than the month and year of the first treatment, the AE will be considered a TEAE.
- If the onset day of an adverse event is missing and the month and year of the onset of the AE precede the month and year of the first treatment, the AE will not be considered a TEAE.
- If the onset month of an adverse event is missing and the year of the onset of the AE is either the same as or later than the year of first treatment, then the AE will be considered a TEAE.
- If the onset month of an adverse event is missing and the year of AE onset precedes the year of first treatment, the AE will not be considered a TEAE.
- If the onset day, month, and year of an adverse event are missing, the AE will be considered a TEAE.
- If start date is partial but the stop date can be determined to be before the start of the first dose of study drug, then the AE will not be considered a TEAE.

For concomitant medications with partial dates, if a concomitant medication start day is missing, the medication will be classified as both a prior and a concomitant medication unless the start month and/or year or the medication stop date can be used to determine whether a medication is concomitant or prior using the following algorithm:

- If a concomitant medication has a missing start day, but the month and year are before the start month and year of the first dose of rFVIIIFc and the stop date of the medication is

before the start day of the first dose of rFVIIIFc, the medication will be classified as prior only.

- If the day of the medication start date is missing and the month and year are after the month and year of the first dose of rFVIIIFc, the medication will be classified as concomitant only.
- If the month of the medication start date is missing and the year is before the start year of the first dose of rFVIIIFc and the stop date of the medication is before the start date of the first dose of rFVIIIFc, the medication will be classified as prior only.

6 REFERENCES

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2. Eloctate USPI [Eloctate United States Prescribing Information]. Waltham (MA): Bioverativ; 2017 [revised 2020 Dec]. Available from: https://www.eloctate.com/_assets/pdf/eloctate_pi.pdf. Accessed on March 23, 2021

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