PRS record reference: **NCT03369444**

Trial Title**: A Phase I/II, Open label, Multicentre, Ascending Single Dose, Safety Study of a Novel Adenoassociated Viral Vector (FLT180a) in Patients With Haemophilia B**

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Final Version 1.2, 29Jan2021

Revision History

Version #	Date (dd-mmm-yyyy)	[redacted]	Revision Summary
Draft v0.1	05Oct2017		Initial Release Version
Draft v0.2	04Oct2019		Revision after protocol amendment
Draft v0.3	20Nov2019		Revision after protocol amendment
Final v1.0	27Mar2020		Final Release Version
Final v1.1	22May2020		Final Release Version after protocol amendment and request of treatment related AEs updates
Final v1.2	29Jan2021		Final Release Version including COVID-19 related TLFs and updates after dry-run in TLFs

I confirm that I have reviewed this document and agree with the content.

Syneos Health
[redacted] **Date** (dd-Mmm-yyyy)
[redacted] **Date** (dd-Mmm-yyyy)
University College London
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TABLE OF CONTENTS

Contents

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AAV	Adeno-Associated Virus
ABR	Annualised Bleeding Rate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CI	Confidence Interval
CRF	Case Report Form
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
FAS	Full Analysis Set
FIX	Factor IX
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GPP	Good Pharmacoepidemiology Practice
HAL	Haemophilia Activities List
HB	Haemophilia B
hFIX	Human Factor IX
HJHS	Haemophilia Joint Health Score

Abbreviation	Description
ICH	International Conference on Harmonization
IV	Intravenous
kg	kilogram
LFT	Liver Function Test
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
OR	Observational Research
PASS	Post Authorisation Safety Study
PAES	Post Authorisation Efficacy Study
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
QoL	Quality of Life
QTc	Corrected QT Interval
QTcF	Fridericia's Corrected QTc
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TAT	Thrombin-antithrombin complex
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
TMG	Trial Management Group
TSC	Trial Steering Committee

Abbreviation	Description
vg	Vector Genome
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule

2. PURPOSE

The purpose of this Statistical Analysis Plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures (TLFs).

2.2. TIMINGS OF ANALYSES

The final study analysis of safety and efficacy is planned after all patients complete the Week 26 visit or terminate early from the study.

Additional data cut-off and descriptive summaries may be performed for specific purposes including: to support regulatory submissions, to conduct new post-hoc data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

3. STUDY OBJECTIVES

3.1. PRIMARY

Safety

To assess the safety of systemic administration of FLT180a in adults with HB at up to 3 different dose cohorts.

Efficacy

To assess FIX levels following systemic administration of FLT180a, at the terminal dose level.

3.2. SECONDARY

- To investigate the endogenous production of FIX following systemic administration of FLT180a at up to 3 different dose cohorts.
- To investigate the effectiveness of a single administration of FLT180a on annualised bleeding rate and exogenous FIX consumption.
- To assess the immune response to the FIX transgene product following systemic administration of FLT180a.
- To assess viral shedding in various body fluids after systemic administration of FLT180a.

3.3. EXPLORATORY

- To assess the immune response to the AAV-S3 capsid proteins following systemic administration of FLT180a.
- Following a single administration of FLT180a:
- To investigate the impact of endogenous production of FIX on functional status and disability in HB.
- To investigate the impact of endogenous production of FIX on quality of life (QoL) in HB.
- To investigate the impact of endogenous production of FIX on physical activity in HB.

- To investigate the impact of endogenous production of FIX on haemophilia health status in HB.
- To investigate the impact of endogenous production of FIX on joint health in HB.
- To investigate the impact of endogenous production of FIX on health resource utilisation in HB.

3.4. BRIEF DESCRIPTION

This is a phase I/II, open label, multicentre, ascending single dose, safety study of FLT180a in up to 24 patients with severe (FIX activity <1%) or moderately severe (FIX activity 1-2% with severe bleeding phenotype) HB. Patients who provide consent to participate in this study will be screened for eligibility and will have historical data on bleeding and FIX consumption documented from the previous 3 years' medical notes. During the screening period patients will complete a diary to prospectively record on-going bleeding events and FIX consumption. Patients will be monitored through a comprehensive battery of safety assessments at outpatient visits for a period of 26 weeks, following which the patient will enter a period of long-term follow-up conducted under a separate extension protocol.

3.4.1. Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will meet to provide independent advice on data and safety aspects of the trial. Meetings of the committee will be held to review patient data prior to a dose escalation decision, in the case a DLT occurs, selection of the terminal dose or any other issue or safety concern the Trial Management Group (TMG) feel they need advice on from the DMC (i.e. dose reduction). A positive recommendation from the DMC will be mandatory prior to dose escalation and selection of the terminal dose level.

A Trial Steering Committee (TSC) will review the recommendations of the independent DMC and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary.

Dose escalation may occur provided there is no more than 1 DLT at any dose level and if the resulting FIX activity fails to reach the target level.

Syneos Health Biostatistics is not responsible for producing the outputs for the above dose escalation meetings.

3.4.2. Dose Escalation

This is a first-time-in-human trial and as such an ascending-dose design has been implemented to enable dose evaluation in a step-wise manner. Three (3) dose cohorts of vector (low, middle and high) will be tested in the dose escalation. Two patients will be tested at each dose cohort with an additional patient added in the event of a DLT (2+1 design). Dose escalation may occur provided there is no more than 1 DLT at a dose cohort and if the resulting FIX activity fails to reach the target level. The goal for FIX response is to maximize the number of patients who achieve a FIX activity in the range 70-150% whilst minimizing the risk of overshooting the normal physiological range. A FIX activity in the range 70-150% represents normalisation to a level at which patients may undergo surgical procedures without the requirement for additional exogenous factor concentrates. The dose will be escalated in increments to a maximum dose of 4×10^{12} vg/kg (high dose). In order to reduce the risk of overshooting the normal physiological range, reduction of the dose level within a dose cohort may occur if FIX activity exceeds pre-defined levels in the initial patients. Where a dose reduction occurs the 2+1 design will apply at that new dose level within the cohort. Additional patients may be added to a dose cohort to ensure adequate characterisation of any DLT, safety issues not meeting DLT criteria, or the FIX response, at the request of the trial management group and data monitoring committee and at the discretion of the Sponsor.

The Sponsor, trial management group and data monitoring committee will select the terminal dose level based on the patient FIX activity levels. The aim will be to ensure the majority of patients will reach a FIX activity within normal limits and in the absence of dose-limiting AEs, the terminal dose level will be expanded to 14 patients. This design minimises the number of patients that would need to be dosed at suboptimal levels whilst allowing evaluation of safety with the option to expand a group on observation of dose-limiting AEs. An extended 6-week interval will be observed between the first and second patient on study to monitor for any unanticipated delayed AEs. Subsequently, whilst dose escalation is ongoing, the study mandates a minimum 4-week interval between patients during which time efficacy and safety will be reviewed prior to a decision to dose the next patient. Once the terminal dose level is agreed and cohort expansion initiated, the dosing interval between patients will be reduced to 48 hours.

On completion of the study, patients will be followed for up to 15 years under a separate extension protocol.

3.5. PATIENT SELECTION

Patient enrolment at a site will only commence once the trial has:

- documented Ethics Committee, Competent Authority and Local Institution approval.
- been initiated on behalf of the sponsor.
- been issued with a site activation letter on behalf of the sponsor.

Patients may only be enrolled at approved trial sites.

3.5.1. Inclusion Criteria

The inclusion criteria are defined in the protocol Section 8.1.

3.5.2. Exclusion Criteria

The exclusion criteria are defined in the protocol Section 8.2.

3.6. DETERMINATION OF SAMPLE SIZE

The number of patients enrolled in the dose escalation Phase I/II study will depend on the number of DLTs observed in each cohort and the number of dose levels evaluated. The study will include a minimum of 14 and a maximum of 24 patients. A total of 14 patients will be enrolled at the selected terminal dose level. Because of the limited number of patients in the HB population (an estimated incidence of 1 in 30,000 male births), the sample size of this study is based on pragmatic rather than statistical considerations.

The 2+1 dose escalation aims to minimise the number of patients that would need to be dosed at suboptimal levels whilst allowing evaluation of safety, with the option to expand a group on observation of dose-limiting adverse events.

3.7. TREATMENT ASSIGNMENT & BLINDING

Blinding will not be used in this study. An open-label design is appropriate to study the effects of FLT180a at various doses in this Phase I/II study, and allow unblinded review of study data to make informed decisions regarding dose escalation.

3.8. ADMINISTRATION OF STUDY MEDICATION

FLT180a will be administered as a single dose, slow intravenous infusion (IV). The planned dose escalation scheme is as follows:

- Cohort 1 (low dose): 6 x 10^{11} vector genomes (vg)/kilogram (kg) of body weight);
- Cohort 2 (intermediate dose): 2 x 10^{12} vg/kg;
- Cohort 3 (high dose): 4 x 10^{12} vg/kg.

The dose level within a cohort may be reduced based on observed FIX activity levels, (see Section 12.3.3 of the protocol):

- Cohort 2 (intermediate dose): 2 x 10^{12} vg/kg can be reduced to:
  - 1.5 x 10^{12} vg/kg
  - 1.3 x 10^{12} vg/kg
  - 1 x 10^{12} vg/kg
  - 8 x 10^{11} vg/kg
- Cohort 3 (high dose): 4 x 1012 vg/kg can be reduced to:
  - 3 x 10^{12} vg/kg

As this is a first-in-human study, an extended 6-week interval will be observed between the first and second patient to monitor for any unanticipated delayed AEs.

During the dose escalation phase of the trial, review of FIX data at a dose of 1.3 x10^{12} vg/kg, is suggestive of the impact of body weight on expression levels. A dose capping at 90 kg is being introduced at this dose (1.3 x10^{12} vg/kg) to ensure that patients FIX activity levels, at steady state are ideally in the target range.

3.9. STUDY PROCEDURES AND FLOWCHART

Patients will undergo the screening assessments described in Section 11.1.1 of the protocol and the Schedule of Assessments (Table 1: Schedule of Assessments) up to 52 weeks prior to Study Day 0 (gene therapy infusion). Due to the risk of bleeding in this patient group, a washout from the patients' FIX concentrate regimen is not mandated as part of this protocol. The investigator must however be able to demonstrate, from the patients' medical records, a documented FIX activity level of <1% for severe patients or <2% for moderately severe patients. If (at the investigators discretion) a FIX concentrate washout is undertaken during the screening period, a minimum of 5 days washout is required.

Treatment-eligible patients will report to the study site on the day prior to receiving the gene therapy infusion (Day -1, NB. Day -1 assessments maybe conducted as early as Day -3 for logistical reasons). On Day 0, FLT180a will be administered as a single dose by slow IV infusion into a peripheral vein, and the patient will remain in the study centre for at least 12 hours and until the investigator has deemed the patient as fit to be discharged. The first 2 patients treated at each dose level will remain at the study centre for 24 hours following infusion prior to discharge.

Patients who are on prophylactic therapy with FIX concentrates will remain on their usual dosing schedule and will be closely monitored for the FIX activity levels after

screening and administration of FLT180a. If FIX activity levels ≥3% are reached then prophylaxis will be held pending a repeat analysis within a period of 72 hours. If the FIX activity levels are ≥3% at that time then prophylaxis will be stopped with continued/regular assessment of FIX activity levels and occurrence of spontaneous bleeding.

Patients will be required to undergo study evaluations at intervals over the 26-week post treatment period. These will take place either at the study infusion site or at their normal haemophilia treatment centre.

On completion of the study, patients will enter a period of long-term follow-up for up to 15 years conducted under a separate extension protocol.

The timing of study assessments is provided in Table 1.

Table 1: Schedule of Assessments

Procedure	**Week**	**Day**					**Week***									
	-52 to -1[A]	**-1[B]**	**0**	**+1**	**+2**	**+4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Window						**+ / - 1 day**										
Informed Consent	X	For Days -1 to +4 please see Table 2: Detailed Schedule of Assessments for Infusion Week														
Demographics and Medical History	X															
Bleeding History (incl. Target Joint Assessment)	X															
Prior and Concomitant Medications	X						X	X	X	X	X	X	X	X	X	X
Physical Examination[C]	X						X	X	X	X	X	X	X	X	X	X
Vital Signs[D]	X						X	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X		X				X		
Adverse Event Assessment	X						X	X	X	X	X	X	X	X	X	X
Joint Evaluation (HJHS)	X															
Liver Ultrasound[E]	X															
AAV Antibody Screen[F]	X[G]															
FIX Antigen	X															
FIX Genotype[H]	X															
HBV, HCV, HIV CMV Screen[I]	X															
Baseline FIX Activity[J]	X															
FIX Activity Trough	X															
Diary Completion for Bleeding Events and FIX Consumption		→														→
QoL (EQ-5D-5L and Haem-A-QoL), Disability (WHODAS 2.0), Physical Activity (HAL 2005), Haemophila Health Status (PROBE) and Health Resource Utilisation[K]	X															
Liver Function Test (Local)[L, M]							X[N]	X[N]	X[N]	X[N]	X[N]	X[O]	X[O]	X[O]	X[O]	X[O]
FIX Activity Level (Local)[M]							X[N]	X[N]	X[N]	X[N]	X[N]	X[O]	X[O]	X[O]	X[O]	X[O]

Procedure	**Week**	**Day**					**Week***									
	-52 to -1[A]	**-1[B]**	**0**	**+1**	**+2**	**+4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Window						**+ / - 1 day**										
Haematology, Chemistry incl. CRP, Coagulation Screen (Local)[P]		For Days -1 to +4 please see Table 2: Detailed Schedule of Assessments for Infusion Week					X	X	X	X	X	X	X	X	X	X
Haematology, Chemistry incl. CRP, Coagulation Screen (Central)	X						X	X	X	X	X	X	X	X	X	X
Liver Function Test (Central)	X						X	X	X	X	X	X	X	X	X	X
FIX Activity Level (Central)[F]							X	X	X	X	X	X	X	X	X	X
FIX Inhibitor Level	X						X	X	X			X			X	
AAV-S3 Antibody Titre[F]							X	X				X				
Mononuclear Cells (Elispot)							X	X	X	X	X	X	X	X	X	X
Mononuclear Cells (Research) - Optional																
Research Plasma Samples - Optional							X	X	X	X	X	X	X	X	X	X
FIX Activity Research Plasma Samples							X			X						
Immune Response Research Plasma Samples							X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]
Prophylactic Immunosuppressants[R]									- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - →
Test for Reactivation of Hepatitis[S]										X		X		X		X
Test for CMV[T]									X	X	X	X	X	X	X	X
Test for Tacrolimus Level[U]									X	X	X	X	X	X	X	X
PCR of Vector Genomes in Plasma, Saliva, Urine, Stool and Semen							X[V]	X[V]	X[V]	X[V]	X[V]	X[V]	X[V]	X[V]	X[V]	X[V]

Procedure	Week*															
	11	12	13[W]	14	15[W]	16	17[W]	18[W]	19[W]	20	21[W]	22[W]	23[W]	24[W]	25[W]	26/EOS[X]
Visit Window	+ / - 1 day		+ / - 3 days													
Informed Consent																
Demographics and Medical History																
Bleeding History (incl. Target Joint Assessment)																
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[C]	X	X		X		X				X						X
Vital Signs[D]	X	X		X		X				X						X
12-lead ECG																X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Joint Evaluation (HJHS)																X
Liver Ultrasound[E]																X
AAV Antibody Screen[F]																
FIX Antigen		X														X
FIX Genotype[H]																
HBV, HCV, HIV CMV Screen[I]																
Baseline FIX Activity[J]																
FIX Activity Trough																
Diary Completion for Bleeding Events and FIX Consumption	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
QoL (EQ-5D-5L and Haem-A-QoL), Disability (WHODAS 2.0), Physical Activity (HAL 2005), Haemophila Health Status (PROBE) and Health Resource Utilisation[K]																X
Liver Function Test (Local)[L, M]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X

Procedure	Week*															
	11	12	13[W]	14	15[W]	16	17[W]	18[W]	19[W]	20	21[W]	22[W]	23[W]	24[W]	25[W]	26/EOS[X]
Visit Window	+ / - 1 day		+ / - 3 days													
FIX Activity Level (Local)[M]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X
Haematology, Chemistry incl. CRP, Coagulation Screen (Local)[P]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology, Chemistry incl. CRP, Coagulation Screen (Central)	X	X		X		X				X						X
Liver Function Test (Central)	X	X		X		X				X						X
FIX Activity Level (Central)[F]	X	X		X		X				X						X
FIX Inhibitor Level		X				X				X						X
AAV-S3 Antibody Titre[F]		X														X
Mononuclear Cells (Elispot)	X	X		X		X				X						X
Mononuclear Cells (Research) - Optional																X
Research Plasma Samples - Optional	X	X		X		X				X						X
FIX Activity Research Plasma Samples																X
Immune Response Research Plasma Samples	X[Q]	X[Q]		X[Q]		X[Q]				X[Q]						X
Prophylactic Immunosuppressants[R]	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ▶						
Test for Reactivation of Hepatitis[S]		X		X		X		X		X						
Test for CMV[T]	X	X	X	X	X	X	X	X	X	X						
Test for Tacrolimus Level[U]	X	X	X	X	X	X	X	X	X	X						
PCR of Vector Genomes in Plasma, Saliva, Urine, Stool and Semen	X[V]	X[V]		X[V]		X[V]				X[V]						X[V]

Abbreviations: AAV = adeno-associated virus; CMV = cytomegalovirus; CRP = C-reactive protein; ECG = electrocardiogram; EOS = end of study; FIX = Factor IX; HAL = haemophilia activity list; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HJHS = Haemophilia Joint Health Score; PCR = polymerase chain reaction; QoL = quality of life; WHODAS = World Health Organisation Disability Assessment Schedule.

* Week 1 visit is Day +7, Week 2 visit is Day +14, Week 3 visit is Day +21, Week 4 visit is Day +28 etc.

[A] The screening period can be up to 52 weeks to allow for controlled prospective collection of bleeding event and FIX consumption data via the patient diary. A patient can move forward to Day -1 assessments and dosing as dosing slots are available. There is no minimum time frame for the data collection. ALL screening assessments should be completed in a timely manner (~2 weeks) following consent to confirm patient eligibility. The patient should be contacted ~every 4 weeks through the screening period to check on diary completion and collect details on any AEs. A repeat AAV Antibody screen is mandated within 4 weeks of dosing. If the screening period for a patient is longer than 16 weeks then a repeat of the central laboratory screening bloods (FIX Antigen/ HBV, HCV, HIV, CMV Screen/ Haematology, Chemistry incl. CRP, Coagulation Screen/ Liver Function Test/ FIX Activity Level/ FIX Inhibitor Level) will be required within 4 weeks of dosing and the patient reported outcomes should also be repeated at Day -1.
[B] The Day -1 assessments can be conducted as early as Day -3 for logistical reasons, if required.
[C] Height (screening only) and weight (screening) will also be measured. Waist circumference (cm), hip circumference (cm), neck circumference (cm) and bioimpedance will be measured at screening.
[D] Vital signs include pulse, blood pressure.
[E] Dependent on results of liver ultrasound further investigations including fibroscan/MRI/elastography may be carried out.
[F] Two aliquots will be taken at each timepoint.
[G] A negative assay (transduction inhibition assay) outcome must be documented within 4 weeks of dosing. Repeat testing may be indicated due to the long screening window.
[H] Blood sample to be taken and sent to the central laboratory for testing if not already documented in the medical records.
[I] HCV antibody testing followed by HCV RNA load. HCV RNA viral load only indicated for patients with history of HCV and positive HCV antibody test. CMV IgG testing followed by CMV PCR. CMV PCR only indicated for a positive CMV IgG.
[J] Established following 5 days washout or from documented medical records.
[K] For Health Resource Utilisation at screening a 6-month history will be collected and at EOS all Health Resource Utilisation since Screening (or Day -1) will be collected.
[L] Albumin, alkaline phosphatase, direct bilirubin, indirect bilirubin, total bilirubin, alanine aminotransferase, aspartate aminotransferase.
[M] Frequency to be increased in response to an upward trend in LFTs and in line with guidance in section 9.4.
[N] Three times per week. The tests should be as evenly spaced through the week as possible, for example: Monday, Wednesday and Friday. On days where other clinic assessments are not required these samples may be taken at study site or at an alternative location (e.g. patient's home).
[O] Twice weekly. The tests should be as evenly spaced through the week as possible, for example: Monday and Thursday or Tuesday and Friday. On days when other clinic assessments are not required these samples may be taken at study site or at an alternative location (e.g. patient's home).
[P] Complete blood count with differentials and platelets. Chemistry incl. CRP to include sodium, potassium, phosphate, blood urea nitrogen or urea, serum creatinine (and estimated GFR), CRP. Coagulation screen to include prothrombin time and activated partial thromboplastin time.
[R] A weight based immunosuppressant regimen will be initiated at the Week 3 visit. For details see section 9.4. Local LFT and FIX activity level monitoring should occur at least weekly while patient is on immunosuppression (prophylaxis or treatment of breakthrough) and for two weeks following cessation.
[S] Local testing. Only required for patients with history of Hepatitis B or C, commencing at Week 4 and continuing every 2 weeks until prophylactic immunosuppressant regimen completed. Tests should be undertaken to coincide with use of immunosuppression if outside of the prophylactic regimen. On days where other clinic assessments are not required these samples may be taken at study site or at an alternative location (e.g. patient's home).
[T] Local testing. For patients positive for CMV (IgG) at screening weekly CMV PCR testing for the duration of the immunosuppressant regimen. Tests should be undertaken to coincide with use of immunosuppression if outside of the prophylactic regimen. On days where other clinic assessments are not required these samples may be taken at study site or at alternative location (e.g. patient's home). Management guidelines in the case of CMV reactivation can be found in Appendix 2.
[U] Local testing. Tacrolimus levels should be tested at each blood draw until levels are in the therapeutic range and weekly thereafter for the duration the patient is taking tacrolimus in the immunosuppressant regimen. Tests should be undertaken to coincide with use of tacrolimus if outside of the prophylactic regimen. On days where other clinic assessments are not required these samples may be taken at study site or at an alternative location (e.g. patient's home). Management guidelines for tacrolimus dosing can be found in Appendix 3.
[V] Three times within 7-10 days following vector infusion then weekly until 3 consecutive samples are negative.
[W] Blood draws may be taken either at study site or at alternative location (e.g. patient's home). The intention should be for at least one of the two blood draws per week to be conducted at study site.
[X] In the event of patient discontinuation / withdrawal every effort should be made to complete week 26/end of study procedures.

Table 2: Detailed Schedule of Assessments for Infusion Week

Procedure	Day -1[a]	Day 0 (Infusion Day)																Day		
		Pre-dose[b]	Timepoint (minutes) during Infusion					Timepoint (hours) from End of Infusion												
			0	+15	+30	+45	+60	+1	+2	+3	+4	+5	+6	+8	+10	+12	+16	+20	+1	+2	+4
Window	**- 2 days**			**+/- 5 mins**				**+/- 10 mins**						**+/- 15 mins**							**+/- 1 day**
Informed Consent[c]	X																				
Physical Examination[d]	X																	X	X	X
Vital Signs[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]	X	X	X
12-lead ECG	X																	X		
QoL (EQ-5D-5L and Haem-A-QoL), Disability (WHODAS 2.0), Physical Activity (HAL 2005), Haemophila Health Status (PROBE) and Health Resource Utilisation[g]	X[h]																			
FLT180a Administration			X	→	→	→	→														
Diary Completion for Bleeding Events and FIX Consumption	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Day -1[a]	Day 0 (Infusion Day)																Day		
		Pre-dose[b]	Timepoint (minutes) during Infusion					Timepoint (hours) from End of Infusion												
			0	+15	+30	+45	+60	+1	+2	+3	+4	+5	+6	+8	+10	+12	+16	+20	+1	+2	+4
Window	**- 2 days**			**+/- 5 mins**				**+/- 10 mins**						**+/- 15 mins**							**+/- 1 day**
Local Lab Tests																					
Haematology, Chemistry incl. CRP, Coagulation Screen[i]	X	X												X					X	X	X
Liver Function Test[j]	X	X												X					X	X	X
FIX Activity Level	X	X																		X	X
Central Lab Tests																					
Haematology, Chemistry incl. CRP, Coagulation Screen	X																			X	X
Liver Function Test	X																				
FIX Activity Level[k]	X	X																			
AAV Antibody Screen[k]	X																				
Mononuclear Cells (Elispot)	X																				
Mononuclear Cells (Research) - Optional	X																				
Research Plasma Sample - Optional	X																				
Immune Response Research Plasma Sample	X																				

Procedure	Day -1[a]	Day 0 (Infusion Day)																Day		
		Pre-dose[b]	Timepoint (minutes) during Infusion					Timepoint (hours) from End of Infusion												
			0	+15	+30	+45	+60	+1	+2	+3	+4	+5	+6	+8	+10	+12	+16	+20	+1	+2	+4
Window	**- 2 days**			**+/- 5 mins**				**+/- 10 mins**						**+/- 15 mins**							**+/- 1 day**
PCR of Vector Genomes in Plasma, Saliva, Urine, Stool and Semen	X																			X[l]	X[l]

Abbreviations: AAV = adeno-associated virus; CRP = C-reactive protein; ECG = electrocardiogram; PCR = polymerase chain reaction.

[a] The Day -1 assessments can be conducted as early as Day -3 for logistical reasons, if required.
[b] Approximately 1 hour before infusion.
[c] The 'pre-infusion' dosing stage informed consent may occur prior to day -1.
[d] Weight (Day -1) will also be measured. Waist circumference (cm), hip circumference (cm), neck circumference (cm) and bioimpedance will be measured at Day -1.
[e] Vital signs from day -1 to day +4 include pulse, blood pressure, respiration rate and temperature.
[f] 16 and 20 hour timepoints are only required for the first two patients in each cohort.
[g] For Health Resource Utilisation at Day -1 all Health Resource Utilisation since Screening will be collected.
[h] Only to be completed if patients had been in the screening period for more than 16 weeks.
[i] Complete blood count with differentials and platelets. Chemistry incl. CRP to include sodium, potassium, phosphate, blood urea nitrogen or urea, serum creatinine (and estimated GFR), CRP. Coagulation screen to include prothrombin time, activated partial thromboplastin time.
[j] Albumin, alkaline phosphatase, direct bilirubin, indirect bilirubin, total bilirubin, alanine aminotransferase, aspartate aminotransferase.
[k] Two aliquots will be taken at each timepoint.
[l] Three times within 7-10 days following vector infusion then weekly until 3 consecutive samples are negative.

4. ENDPOINTS

4.1. PRIMARY ENDPOINTS

Safety

Safety as assessed by the reporting of AEs according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Efficacy

The following primary endpoints will be analysed:

1. The proportion of patients achieving clinical FIX response at Week 26, at the terminal dose level. A clinical FIX response is defined as achieving a FIX activity of 5% to 150%.

2. The proportion of patients also achieving normalised FIX response at Week 26, at the terminal dose level. A normalised FIX response is defined as achieving FIX activity in the normal range (50-150%).38

4.2. SECONDARY ENDPOINTS

Safety

Safety as assessed by reporting of abnormal or change from baseline findings from routine safety assessments including, laboratory assessments, vital signs, ECG, physical exam and liver ultrasound.

Endogenous FIX Production

- The proportion of patients achieving FIX activity at or above 5%, 15%, 30%, 40%, 50% and 70% but no more than 150% of normal, at each scheduled visit.
- The proportion of patients achieving FIX activity at or above 5%, 15%, 30%, 40%, 50%, 70% and 150% of normal, at each scheduled visit.
- Absolute change from baseline in FIX activity.

Haemostatic Effectiveness

- Change from baseline in annualised bleeding rate.
- Change from baseline in FIX concentrate consumption.

In order to ensure enough time has elapsed for the patient to have endogenous FIX activity to protect the patient from spontaneous bleeding episodes, the calculation period for haemostatic effectiveness will be from day 15 inclusive.

Immune Response

Immune response to the FIX transgene product (i.e., development of inhibitors) will be assessed by measurement of the level of inhibitors.

Shedding

Clearance of vg in plasma, saliva, urine, stool, and semen.

4.3. EXPLORATORY ENDPOINTS

Haemostatic effectiveness

Exploration of the correlation between FIX levels and bleeding events over time.

Immune Response

- Immune response to the AAV-S3 capsid will be assessed by measurement of the S3 neutralising antibody titre.
- T-cell responses to AAV-S3 capsid in peripheral blood mononuclear cells.

Disability Status

Change from baseline in World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) score.

Physical Activity

Change from baseline in Haemophilia Activities List (HAL) 2005.

Health Related Quality of Life

Change from baseline in the EQ-5D-5L and the Haem-A-QoL score.

Haemophilia Health Status

Change from baseline in the PROBE score.

Assessment of Joint Health/Function

Change from baseline in the Haemophilia Joint Health Score (HJHS).

Health Resource Utilisation

- Number of haemophilia related medical appointments and medical activities.
- Number of visits at site.
- Number of emergency room visits.
- Number of hospitalisations related to haemophilia.
- Length of hospital stay.
- Number of days lost from education or work by patients and caregivers due to bleeding episodes.
- Number of physiotherapy sessions, specialist consultations and appointments with professional caregivers.

5. ANALYSIS SETS

5.1. SCREENED SET

The Screened Set will include all patients screened. This set will be used for the listing and summarisation of patient disposition and protocol deviations.

5.2. FULL ANALYSIS SET

The Full Analysis Set (FAS) will include all patients who received FLT180a. This will be the primary population for all analyses of safety, efficacy and baseline characteristics and for the presentation of patient data in all data listings, with the exception of patient disposition and protocol deviations summarized in the Screened Set.

5.3. PER PROTOCOL SET

The per-protocol (PP) set will include all patients from the full analysis set, excluding those patients with major protocol deviations, which on review are determined to result in exclusion of the patients data from the PP set (following the process described in section 14.11 of the protocol). This review will be done during the final PD review meeting before database lock. The PP set will be used for sensitivity analyses of the primary efficacy endpoint as described in section 8.

5.4. PROTOCOL DEVIATIONS

Protocol deviations will be addressed during monitoring on an ongoing basis. All protocol deviations are to be recorded with the indication of whether they are major as determined by the study management team, in cooperation with data management, medical monitoring, and the sponsor. These data will be imported into SAS and listed only, including the assignment of minor or major, and whether the deviation led to exclusion for the PP set.

All protocol deviations will only be listed for all patients in the Screened Set, including the date the deviation occurred, the visit name and their assignment of minor or major. Major protocol deviations related to COVID-19 will also be tabulated in the Screened Set, while all protocol deviations related to COVID-19 will be listed in the Screened Set.

A review of the protocol deviations will be performed before database lock to identify the patients that should be excluded from the per-protocol analysis set due to major protocol deviations.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

This section describes the analysis methods that relate to all or some of the analysis sections that follow. It describes the general guidelines for analysis as well as the following items:

- SAS version 9.4 or higher will be used.
- Syneos Health will be responsible for reporting the demographic, safety and efficacy data.
- Disposition will be presented for all patients in the Screened Set by dose level and overall
- Demography/baseline characteristics and safety endpoint summaries will be presented for all patients in the FAS, by dose level and overall.
- Efficacy summaries will be presented for all patients in the FAS, by dose level and overall.
- The total number of patients in the dose level will be used as the denominator for percentage calculations, unless stated otherwise in the table shell.
- Continuous variables will be summarised using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarised using number of observations (n), frequency and percentages of patients.
- All patients entered into the database, including screen failures, will be included in the disposition listings. Screen failure data will be included at the end of the appropriate listings and labelled ‘Screen Failures’.
- All safety data will be entered in to the patient listings.
- In general, the listings will be presented by dose level and sorted by patient number and assessment date (and time) if applicable.
- Multiple assessments at a given time point (planned, repeat) will not be included in summary tables unless specified otherwise, but will be included in the listings. If there are multiple results at a given visit, e.g. a repeated lab test within a visit, the earliest value will be used.

- In general unscheduled visit data will be listed but not included in the summary tables by time point. However unscheduled visit data will be used for the LOCF methodology for the primary efficacy analysis. Also, for shift tables, unscheduled data will be included to identify the worst case post FLT180a dose.

6.2. KEY DEFINITIONS

The Study Day is the day relative to the date of dose of study product (FLT180a), where Day -1 is the day before the first dose of study product and Day 0 is the day of study product administration.

As this is a single dose study, the first and last dose date is defined as the first non-missing date where a non-zero dose of study product was recorded.

The end of the study will be defined as the point when the last patient has completed the last study visit at Week 26, or sooner in the case of premature discontinuation.

Unless otherwise specified, baseline is the last non-missing observation before the start of study product, which is expected to be at Study Day -1 or Screening if the Day -1 data are not available.

6.3. MISSING DATA

Missing data is expected due to the patient population, and general features of clinical studies. Reasons for missing data will be categorised as

- (D) patient died
- (W) patient withdrew informed consent or became lost to follow-up
- (M) missing assessment (may be a complete visit) could not be performed for a reason not covered by one of the reasons above.

Number and percentage (based on the number of treated patients) of missing values and reasons (categories as defined above) will be summarised by visit for FIX levels.

LOCF methodology will be used for the primary efficacy analysis, irrespective of the reason why the data is missing, if known. Sensitivity analysis will be performed as described in section 14.6.2 of the protocol and section 8 of this SAP. Analyses will be performed considering all data observed for the respective analysis sets. All other missing data will not be replaced.

For the purpose of assigning adverse events (AEs) and concomitant medications, the following rules will be applied for partial/missing start and end dates:

Partial/missing start date:

- Missing day: impute the first day of the given month unless the month and year are the same as the month and year of the first dose of study drug, then impute first dose date.
- Missing day and month: impute the date as 1st January unless the year is the same as the year of first dose date, then impute first dose date.
- Completely missing: impute first dose date unless the end date suggests the event/medication could have started before this, in which case impute the 1st January of the same year as the end date.

Partial/missing end date:

- Missing day: impute the last day of the month unless month is same as month of end of study visit, then impute day prior to end of study visit.
- Missing day and month: impute 31st December unless year is the same as end of study visit, then impute day prior to end of study visit.

Completely missing end dates will not be imputed.

Regarding the laboratory data with values <BQL/<LLOQ, imputation will be done only for the summarization in tables. The values will be replaced with the respective BQL/LLOQ value.

6.4. VISIT WINDOWS

Week 26/end of study (EOS) will be defined as the last available study visit for those patients who dropped out of the study early. The EOS visits for patients who withdraw early can either be slotted into the next scheduled time point after withdrawal, or reported as an “Week 26/EOS” visit in situations where there is no suitable time point to slot them to, like in the case of variables that are only collected at Week 26. The slotting of patients into the next scheduled time point after withdrawal will be handled during the analysis datasets creation (ADaM) by the programming team. New variables for time point will be created as the original, but with the slotting being performed only for patients who withdraw early.

6.5. POOLING OF CENTRES

No pooling of centres is planned.

6.6. SUBGROUPS

Subgroup analysis will be performed where appropriate including:

- Patients receiving on-demand therapy
- Patients on conventional prophylaxis therapy
- Patients on extended half-life prophylaxis therapy
- Baseline FIX level
- Baseline HJHS score.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. PATIENT DISPOSITION AND WITHDRAWALS

Patient disposition will be summarised for all patients in the Screened Set by dose level. The summary table will show the frequency and percentage of patients in each of the analysis sets, the frequency and percentage of patients who discontinued the study prematurely along with the primary reasons for early withdrawal and the frequency and percentage of patients who will participate in the 15-year long-term follow-up.

Reasons for early withdrawal from the study will also be listed, including the date of withdrawal.

Eligibility criteria, screening failures (including date and primary reason for failure), and informed consent will be listed only for all patients in the Screened Set.

Missing assessments, as well as, missing visits due to COVID-19 will also be listed only in the Screened Set.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All demographic and baseline characteristic data will be summarised by dose level and overall, using descriptive statistics for all patients in the FAS.

Race and ethnicity will be summarised by the number and percentage of patients in each category.

Age (years), age at infusion (years), height (cm) and weight (kg) captured at Screening, body mass index (BMI; kg/m^2), Body Surface Area (BSA; m^2), Ideal Body Weight (IBW;kg) and Lean Body Weight (LBW; kg) will be summarised as continuous variables, where:

- Age at infusion (years) = (Date of infusion - date of birth + 1) / 365.25, truncated to complete years.
- BMI (kg/m^2) = Weight at Screening (kg) / [Height at Screening (m)]^2.
- BSA (m^2) ={ [Height at Screening (cm) x Weight at Screening (kg)]/3600}^0.5.
- IBW (kg) is computed in men as 50 + 2.3 kg per inch over 5 feet and women as 45.5 + 2.3 kg per inch over 5 feet .
- LBW (kg) is computed in men as (0.407 x weight(kg)) +(0.267 x height in centimetres) -19.2 and in women as (0.252 x weight(kg)) +(0.473 x height in

centimetres) -48.3

Unless otherwise stated, percentages will be calculated out of the number of patients in the FAS.

All demography data will be listed.

7.3. MEDICAL HISTORY

Descriptions of medical history findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later. Medical history, as recorded at Screening, will be summarised for the FAS by the number and percentages of patients within each system organ class (SOC) and preferred term (PT), by dose level and overall.

Medical history will also be listed for all patients in the FAS.

Medical history will be sorted by dose level and descending overall frequency, by SOC and PT in the summary table. Medical history data listings will be sorted by dose level, patient number, start date, SOC and PT.

7.4. OTHER BASELINE CHARACTERISTICS

7.4.1. Haemophilia B Medical History

Haemophilia B specific medical history, as recorded at Screening, will be summarised for the FAS by dose level and overall.

Haemophilia B severity and Factor IX Mutation Genotype will be summarised by the frequency and percentage of patients in each category.

Information on the patient's CRM+ status, HLA typing and PK analysis of how they clear FIX concentrate will be collected and summarized.

HB medical history will also be listed for all patients in the FAS.

Target joint Assessment data will be collected at screening and listed only for all patients in the FAS.

7.4.2. Bleeding events history

The number of bleeding episodes over the last 3 years will be summarised as continuous variables using descriptive summary statistics.

For patients with detailed historic bleeding events records, the number of bleeding episodes over the last 3 years will also be summarized by location, severity, type of bleed, and by whether the bleed was treated with Factor IX, and/or transfusion.

The number of bleeding episodes will also be annualized.

7.4.3. FIX Concentrate Consumption history

The total FIX Concentrate Consumption over the last 3 years (IU) will be summarised as continuous variables using descriptive summary statistics.

For patients with detailed historic FIX Concentrate Consumption records, the total FIX Concentrate Consumption over the last 3 years will also be summarized by type of bleeding episode (i.e., spontaneous or traumatic), location of bleeding episode (i.e., joint, soft tissue or muscle), and by whether the FIX concentrate was given for prevention.

The annualised total units of factor IX consumption will be summarised.

7.4.4. AAV Antibody Screen

During the screening period, a blood sample will be taken from the patient to determine the presence or absence of neutralising antibodies to the AAV-S3 serotype.

A negative result from a transduction inhibition assay within 4 weeks of dosing is required to confirm eligibility. Two samples may be tested within the screening period.

Procedures for collection, processing, storing, and transporting of samples to the laboratory are fully described in the study Laboratory Manual.

All AAV-S3 antibody screen data (result from screening that is part of the Eurofins lab data provided to Syneos Health) will be listed only for all patients in the FAS.

7.4.5. HBV, HCV, HIV, CMV Screen

A blood sample will be taken at screening to assess the following:

- Hepatitis B virus (HBV) surface antigen (HBsAg);
- Anti-hepatitis C virus (anti-HCV) antibodies;
- Human immunodeficiency virus 1 and 2 (anti-HIV1/2) antibodies.

- Cytomegalovirus IgG antibodies and Cytomegalovirus PCR. CMV PCR only indicated if patients are positive on CMV IgG.

Procedures for collection, processing, storing, and transporting samples to the laboratory are fully described in the study Laboratory Manual. All HBV, HCV (followed by HCV RNA load in case of positive HCV antibody test) CMV and HIV screen data will be listed only for all patients in the FAS.

7.4.6. Baseline FIX activity; FIX Activity Trough; FIX Antigen Level

Blood samples will be taken for central evaluation of FIX activity, FIX activity trough (during screening period) and FIX antigen level (during screening period, week 12 and week26/EOS). All collected data (including date and time of collection of samples or reason for not collected) will be listed only for all patients in the FAS. Baseline FIX activity will be established for all patients by the investigator, who must be able to demonstrate a documented FIX activity level of <1% for severe patients or <2% for moderately severe patients from the patients' historical medical records. For patients where a washout is undertaken as part of this protocol, and a minimum of 5 days off therapy is required, the FIX activity trough sample will also be used as the baseline value (defined as the last non-missing observation before the start of study product, which is expected to be at Study Day -1 or prior: Screening).

7.4.7. Corticosteroids and Immunosuppressants Distribution

All patients will be provided with a take-home pack of immunosuppressants (prednisolone, azathioprine, mycophenolate mofetil, prednisone methylprednisolone, tacrolimus) at Screening, under the direction of the investigator.

Immunosuppressants distribution, as recorded at Screening, will be listed only for all patients in the FAS, by dose level and overall, including whether immunosuppressants were distributed, the reason if not distributed and the date of distribution. Tacrolimus levels testing data will also be listed for all patients in the FAS by dose level including "Age at specimen collection" as derived in the eCRF.

7.5. MEDICATION

Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organisation Drug Dictionary (WHO-DD). Medications will be classified as concomitant or prior, as defined in the sections 7.5.1 and 7.5.2 respectively, and summarised by ATC class (level 2), sub-class (PT) and classification (prior or concomitant) for all patients in the FAS. Any concomitant medication will be recorded at each visit, including the

medication/therapy name, indication, dose, unit, frequency, route, and start and end dates.

Prior and concomitant medications will be summarized. All prior and concomitant medications will be listed, with a flag identifying prior medications.

The summary tables will show the frequency and percentage of patients, in each group with at least one usage of medication for the given classification on the sub-class level within each ATC class, dose level and overall, sorted by descending overall frequency of ATC class and PT.

Percentages will be calculated out of the number of patients in the FAS.

7.5.1. Prior Medication

Prior medications includes all medications received from 30 days prior to the initial informed consent up until the time of FLT180a infusion.

7.5.2. Concomitant Medication

Concomitant medications (CMs) refer to all medications taken between the date of investigational product infusion and the week 26/end of study visit, inclusive. Medications without a start and end date will be defined as concomitant. Medications where start date is missing but end date clearly indicates that the medication was ended prior to the start of study drug will be defined as prior. Partial medication dates will be imputed as detailed in Section 6.3.

8. EFFICACY

All efficacy analyses will be performed for all patients in the FAS, by dose level and overall, however analyses of primary endpoint are for the patients who received the terminal dose level. The principal/main time point for the evaluation of efficacy is Week 26, but efficacy at other time points will be assessed.

The choice of a 26-week endpoint is based on previous experience with AAV gene therapy for HB (Nathwani et al) in which patients achieved steady-state FIX levels by 16 weeks post gene therapy. Based on this, it is anticipated that the patients FIX activity will have reached a stable level by 26 weeks, thus this is an appropriate point at which to measure activity.

The FIX response will be derived for each patient based on the FIX activity level measured at the central laboratory. Clinical FIX response is defined as achieving FIX activity of 5-150% and normalised FIX response is defined as achieving FIX activity in the normal range (50-150%).

The two primary endpoints will be analysed on the full analysis set, for the patients who received the terminal dose level. The proportion of patients achieving clinical FIX response at Week 26 along with their 95% Cis (exact confidence intervals for binomial proportions), will be summarised for the patients who received the terminal dose level.

For the primary analysis, last-observation-carried forward (LOCF) methodology will be used to impute any missing FIX value at Week 26, by the last non-missing FIX value (including both scheduled and unscheduled visits).
For the primary analysis, FIX response will be assessed whether or not the patient is receiving or has been receiving immunosuppressants due to transaminitis outside the period of prophylactic corticosteroid treatment.

The proportion of patients also achieving normalization will be summarised in a similar manner.

8.1. SENSITIVITY ANALYSIS

Sensitivity analyses of the primary endpoint will be performed:

- The proportion of patients achieving clinical or normalised FIX response at Week 26 with patients with a missing FIX response at Week 26 being considered as a non-responder will be summarised.
- The proportion of patients achieving clinical or normalised FIX response at Week 26 excluding those patients who have received immunosuppressants in the previous 42 days (6 weeks) before the Week 26 assessment, will also be summarised.

- The proportion of patients achieving clinical or normalised FIX response at Week 26 excluding those patients with major protocol deviations (per-protocol set) will also be summarised.

8.2. ENDOGENOUS FIX PRODUCTION

The FIX response will be derived for each patient based on FIX activity level measured at the central laboratory. Baseline FIX activity level will be defined as described in section 11.4.2.1 of the protocol. The proportion of patients achieving FIX activity at or above 5%, 15%, 30%, 40%, 50% and 70% but no more than 150% of normal at week 26, at each scheduled visit, will be summarised by dose and overall.

The proportion of patients achieving FIX activity at or above 5%, 15%, 30%, 40%, 50%, 70% and 150% of normal, at each scheduled visit, will be summarised by dose and overall.

Change from baseline in FIX activity as a percentage of normal values will be summarised in tabular and graphical format for each patient, by dose and overall.

Patients achieving FIX activity above 150% of normal will be summarised by dose and overall.

8.3. HAEMOSTATIC EFFECTIVENESS

8.3.1. Annualised Bleeding Rate (ABR)

Bleeding episodes will be entered in to the patient's diary and will include:

- Bleeding episode number;
- Location;
- Severity and type of bleed (spontaneous, traumatic etc.);
- Date and time of onset and resolution of bleed.
- whether the bleed was treated with Factor IX, and/or transfusion given (with additional details)

The number of breakthrough bleeding episodes (spontaneous and traumatic) following FLT180a infusion will be summarised using descriptive statistics by dose level and overall.

The number of breakthrough bleeding episodes will also be annualised, and compared with the patient's own baseline bleeding history as described in section 7.4.2.

The ABR at post-dose (Day 15 to Week 26/EOS) will be calculated for each patient as:

ABR at post-dose = (Total Number of Post-Dose Bleeding Events/ Number of days during calculation period)*365.25;

where:

Number of days during calculation period = (last date of diary completion – date of Day 15) + 1

These values and changes from baseline will be summarised using descriptive statistics (n, mean, standard deviation, median, range and inter-quartile range) by dose level and overall. Additionally, the 95% confidence interval for the median change from baseline will be included in the table, using the distribution free percentile confidence limits[44)]. The comparison of post-dose values with baseline values will be conducted using the Wilcoxon signed-rank test for paired samples.

All bleeding events data will also be listed for all patients in the FAS.

8.3.2. Factor IX Concentration Consumption

For each dose of FIX concentrate administered, the patient will record the following information in to the patient's diary:

- FIX concentrate name (coded)
- Total dose given in total international unit (IU);
- Reason for administration (i.e., prevention or bleeding episode);
- Bleeding episode number;
- Date and time of administration;
- End date;
- Frequency of administration;
- Total doses given.

The dose (IU/kg) of factor IX concentrate used overall and by type of bleeding episode (i.e., spontaneous or traumatic) and location of bleeding episode (i.e., joint, soft tissue or muscle) will be summarised with descriptive statistics. The annualised total units of factor IX consumption will be calculated and compared with the patient's own baseline factor concentrate history as described in section 7.4.3.

The total Units (IU) of FIX concentrate at post-dose (Day 15 to Week 26/EOS) will be calculated for each patient as:

Annualised Total Units (IU) of FIX concentrate at post-dose = (Total Post-Dose FIX Concentrate Consumption [IU] / Number of days during calculation period)*365.25;

where:

Number of days during calculation period =

(last date of diary completion – date of Day 15) + 1

These values and changes from baseline will be summarised using descriptive statistics (n, mean, standard deviation, median, range and inter-quartile range) by dose level and overall. Additionally, the 95% confidence interval for the median change from baseline will be included in the table, using the distribution free percentile confidence limits[44)]. The comparison of post-dose values with baseline values will be conducted using the Wilcoxon signed-rank test for paired samples.

All FIX concentration consumption data will also be listed for all patients in the FAS.

8.4. IMMUNE RESPONSE

8.4.1. FIX Inhibitor

Blood samples for assessment of FIX neutralising antibody development (inhibitor) will be drawn in accordance with Table 1: Schedule of Assessments. Procedures for collection, processing, storing, and transporting to the central laboratory are fully described in the study Laboratory Manual.

Immune response to the FIX transgene product (i.e., development of inhibitors) will be assessed by measurement of the level of inhibitors. Descriptive statistics (number of observations, mean, standard deviation, minimum, median, and maximum values) will be calculated for immune response laboratory tests at applicable visits.

8.4.2. Vector Shedding

Plasma, saliva, urine, stool and semen samples for PCR of vector genome will be taken in accordance with Table 1: Schedule of Assessments. Clearance of vector genomes in plasma, saliva, urine, stool, and semen will be summarized for all patients in the FAS by dose level and overall. The time to unquantifiable result by body fluid will be summarized and listed.

All shedding data will also be listed for all patients in the FAS.

8.4.3. Liver Ultrasound

A liver ultrasound will be conducted in accordance with the study schedule (Table 1: Schedule of Assessments). Any clinically significant deviations from Screening should be reported as an adverse event.

Liver ultrasound data will be listed only for all patients in the FAS by dose level and overall.

9. SAFETY

The FAS will be used for all safety analyses. Safety will be assessed on the basis of AE reports, laboratory parameters, vital signs, 12-lead ECG and physical examination data.

All safety summaries will be presented, by dose level and overall.

9.1. EXTENT OF EXPOSURE

Study product (FLT180a) is to be administered to patients as a single dose by slow IV infusion route at Day 0.

All exposure to investigational product will be listed only for all patients in the FAS by dose level and overall. The following information on the investigational product will be collected:

- Was vector infusion administered;
- Reason not administered;
- Date of vector infusion;
- Dose;
- Start and stop times of vector infusion;
- If the fusion was interrupted;
- Volume administered (mL).

The Length of Exposure, defined from start of infusion to last point of follow up in the study, and not just the duration of the infusion itself, will be summarized in a table using descriptive statistics, by dose level and overall.

9.2. TREATMENT COMPLIANCE

Not applicable (N/A).

9.3. ADVERSE EVENTS

All patients in the FAS will be included in the adverse event (AE) summaries.

AEs will be summarised by the system organ class (SOC) and preferred term (PT) based on the MedDRA dictionary version 20.0 or later. The Common Terminology Criteria for

Adverse Events (CTCAE) grades will be summarised by SOC and PT, using the National Cancer Institute (NCI) CTCAE version 5.0.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that commence on or after the first dose of FLT180a or, if present prior to first dose, then increased in severity. Partial AE start and end dates will be imputed (Section 6.3).

The relationship of FLT180a as well as of 3 other immunosuppressant drugs (prednisolone or prednisone, methylprednisolone, tacrolimus) to AEs will be recorded in the eCRF. If the relationship to study drug (FLT180a) is missing for TEAEs then the relationship will be counted as related for the summary tables. Similarly, missing intensity/severity for TEAEs will be counted as Grade 3 i.e. severe for the summary tables.

The summary tables will include the frequency and percentage of patients, as well as the number of events. Percentages will be based on the number of patients. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum intensity, a patient will be counted once at the highest intensity level for which the event occurred at the SOC level and the highest intensity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

All AE tables will be ordered by descending frequency for each dose level and overall.

The following AE tables will be provided:

- An overall summary of the number and percentage of patients reporting TEAEs, serious TEAEs, FLT180a-related TEAEs, serious FLT180a-related TEAEs, TEAEs leading to death and DLTs in each dose level;
- TEAEs overall and by system organ class and preferred term;
- TEAEs by maximum severity, overall and by system organ class and preferred term, by system organ class and preferred term;
- TEAEs by maximum relationship to FLT180a, overall and by system organ class and preferred term;
- Serious TEAEs, overall and by system organ class and preferred term;

- Serious FLT180a-related TEAEs, overall and by system organ class and preferred term;
- TEAEs with an outcome of death, overall and by system organ class and preferred term.

Only the TEAEs will be included in the summary tables, however all AEs will be included in the listings. TEAEs will be flagged in the listings. Additional listings will be provided for serious adverse events, important medical events, deaths and DLTs. Relationship to immunosuppressants will only be reported in listings.

For the purpose of this study, important medical events defined in the protocol section 13.2.9 will be reported in line with SAE reporting procedures. AEs considered as meeting the definition will be flagged by the investigator in the eCRF and identified as such in listings.

9.4. LABORATORY EVALUATIONS

All patients in the FAS will be included in the safety laboratory analysis.

The following laboratory tests will be performed at a central laboratory to assess safety.

- Haematology: complete blood count with differential, platelet count
- Chemistry incl. CRP: sodium, potassium, chloride, phosphate, CO2, glucose, blood urea nitrogen, serum creatinine, C-reactive protein.
- Coagulation screen: prothrombin time, prothrombin split fragments 1+2 (F1+2), D-dimer, TAT.
- Liver Function Tests: albumin, alkaline phosphatase, direct bilirubin, indirect bilirubin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, total protein.

The following laboratory tests will be performed at a local laboratory to assess safety.

- Haematology: complete blood count with differential, platelet count.
- Chemistry incl. CRP: sodium, potassium, phosphate, blood urea nitrogen or urea, serum creatinine, C-reactive protein.
- Coagulation screen: prothrombin time, activated partial thromboplastin time.
- Liver Function Tests: albumin, alkaline phosphatase, direct bilirubin, indirect bilirubin, total bilirubin, alanine aminotransferase, aspartate aminotransferase.
- hFIX activity level.

Full local laboratory safety blood samples will be taken in accordance with Table 1: Schedule of Assessments.

Blood samples for reactivation of hepatitis, tacrolimus levels and CMV PCR testing will be drawn in accordance with Table 1: Schedule of Assessments and Section 9.4 of the protocol and analysed locally.

For the analyses, results from the central laboratory will be used; but all local and central labs results will be listed.

Laboratory data (absolute values and absolute change from baseline [Day -1]) will be summarised by visit, dose level and overall. All summaries will be based on results in

International System of Units (SI units); conversion will be performed at SDTM level prior to the transfer to Syneos Health Biostatistics. All laboratory values will be categorised according to their normal ranges, where normal ranges exist.

Toxicity grading following the NCI CTCAE grades version 5.0 will also be derived for laboratory variables where applicable. If this results in the criteria for more than one grade being met, the highest (worst) CTCAE grade will be assigned.

Summary statistics (mean, median, standard deviation, minimum, maximum and number of observations) will be presented for all continuous assessments. In general, any quantitative assessments will be summarised for all patients using the number and percentage of patients with the given result. Percentages will be calculated out of the number of patients with non-missing data.

Shift tables for haematology and biochemistry from baseline CTCAE toxicity to the maximum grade on treatment for each parameter will be provided. Patients with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. Unscheduled data will be included in "worst post-baseline" summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0," which is defined as normal.

For non-CTCAE gradable haematology and biochemistry tests, a shift table will be provided showing shifts relative to the normal ranges. This summary of normal range category changes illustrates the number and percentage of patients who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the planned time normal range category and the worst-case on-therapy normal range category. Only laboratory tests which cannot be graded per CTCAE v5.0 specified criteria will be included.

Patients with missing baseline value are to be assumed to have normal baseline value since worst-case can be either 'High' or 'Low'. If a patient has a 'Decrease to Low' and an 'Increase to High' during the same time interval, then the patient is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a patient was 'High' at baseline and decreases to 'Low' during the time interval, the patient is counted in the 'Decrease to Low' category. Likewise, if a patient was 'Low' at baseline and increases to 'High' during the time interval, the patient is counted in the 'Increase to High' category. Patients are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range 'High' and no normal range 'Low' values during the time interval;

- 'High' at baseline and do not change to 'Low' during the time interval;
- 'Low' at baseline and do not change to 'High' during the time interval.

All laboratory results in original and SI units will be included in data listings. Tests will be summarised and listed in the order given in the eCRF. Values outside of their normal ranges will be flagged in the data listings. Clinically significant haematology and biochemistry results will also be presented in a separate listing. C-Reactive Protein (CRP) data will be listed only for all patients in the FAS.

9.5. VITAL SIGNS

All patients in the FAS will be included in the vital signs analysis.

Measurements of vital signs (blood pressure, pulse, temperature, and respiratory rate) will be performed according to the study schedule. Height and weight (will be recorded at Screening and Dosing Day -1 visits respectively, so will be summarised with the patient demographics. Respiration rate and temperature will be recorded at Day -1 and Day +1, +2 and +4 visit only.
Any clinically significant deviations from vital signs at Day -1 should be reported as an adverse event.

Baseline for vital signs will be the result prior to the first dose of study treatment. Absolute change from baseline will be calculated for the post dose time points. Absolute change from baseline is calculated as the result at visit minus the baseline result.

Vital signs data will be fully described using descriptive statistics. Continuous variables will be summarised using summary statistics, whilst categorical values will be summarised using the frequency and percentage of patients within each category.

All vital signs data will be listed chronologically and summarised by parameter, visit and time point, dose level and overall.

9.6. 12-LEAD ELECTROCARDIOGRAM

A 12-lead ECG will be conducted in accordance with the study schedule. ECG data will be classified as "Normal", "Abnormal, Not Clinically Significant" or "Abnormal, Clinically Significant".

Any clinically significant deviations from Day -1 should be reported as an adverse event.

ECG data will be summarised by parameter, visit, dose level and overall for all patients in the FAS. Summary tables will show the number and percentage of patients with normal, abnormal non-clinically significant (NCS) or abnormal clinically significant (CS) findings at each visit.

Shift tables for ECG findings from baseline to the worst case result on treatment will be provided. Patients with both a non-missing baseline and at least one non-missing post-baseline finding will be included in the shift table. Unscheduled data will be included in the "worst post-baseline" summary, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. A categorical summary of QTcF Interval by Visit will also be provided.

Summary tables by visit and time point and change from baseline to visit and time point for each ECG parameter (heart rate (bpm), PR interval (msec)), QRS interval (msec), QT interval (msec), QTcB interval (msec) and QTcF interval (msec) will be provided.

All ECG data, including individual parameter results, will also be listed chronologically for all patients in the FAS by dose level and overall.

9.7. PHYSICAL EXAMINATION

A full physical examination will be performed at every study visit and will comprise of measurements of the routine medical examination of the following body systems: head, neck, ears, nose, throat (ENT), eyes, chest, pulmonary system, cardiovascular system, abdomen, skin and lymph nodes. The musculoskeletal and neurological systems will be assessed. All patients in the FAS will be included in the physical examination analysis.

Body systems will be classified as "Normal", "Abnormal NCS" or "Abnormal CS" and abnormalities are described.

Physical examination findings will be fully summarised using the frequency and percentage of patients under each classification for each body system. Summary tables will be sorted by parameter, visit/time point and by dose level and overall.

Results from physical examinations will also be listed chronologically.

10. EXPLORATORY

10.1. FIX LEVELS AND BLEEDING EVENTS

In terms of an exploratory analysis, FIX concentration levels and bleeding events will be tested for possible associations. FIX levels will be categorized based on activity range of interest : <5%, 5-30%, 30-50% and >50%, while bleeding events will be categorized based on severity and type of bleed (spontaneous, traumatic etc.) and whether the bleed was treated and/or transfusion given. A table will summarize the proportion of bleeding events by FIX by visit and dose level and total. Additionally, a spaghetti plot will be created, in which the y-axis will be the FIX activity and x-axis the Weeks, while the presence of bleeding event will be determined by a cross in the line. This plot can be created by dose level and total.

10.2. AAV-S3 CAPSID

Immune response to the AAV-S3 capsid will be assessed by measurement of the S3 neutralising antibody titre. Procedures for collection, processing, storing, and transporting to the central laboratory are fully described in the study Laboratory Manual.

T-cell responses to AAV-S3 capsid in peripheral blood mononuclear cells will also be assessed.

Immune response laboratory data will be summarised by visit, dose level and overall. Summary statistics (mean, median, standard deviation, minimum, maximum and number of observations, geometric mean and %CV if appropriate) will be presented for all continuous assessments.

All AAV-S3 capsid data will also be listed for all patients in the FAS.

10.3. HEALTH ECONOMIC ASSESSMENTS

Quality of life will be evaluated using the EQ-5D-5L and Haem-A-QoL. In addition, disability status will be assessed using the WHODAS 2.0 and the physical activity will be assessed using the HAL 2005. Haemophilia health status will be assessed using PROBE. Joint health and function will be evaluated using the HJHS score.

Descriptive statistics will be applied to study the changes in the scores from baseline to end-of treatment in each cohort.

10.3.1. Quality of life

10.3.1.1. Health-Related Quality of Life (QoL)

Health-related quality of life (QoL) will be captured at Screening and Week 26, or Week 26/EOS for patients who dropped out of the study early, and evaluated using Haem-A-QoL.

The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) is a specifically designed measure to capture aspects of QoL for adult patients with haemophilia.

It consists of 46 items (sub-parameters) pertaining to 10 parameters (scales):

- Parameter 1: Physical health;
- Parameter 2: Feelings;
- Parameter 3: View of yourself;
- Parameter 4: Sports and leisure;
- Parameter 5: Work and school;
- Parameter 6: Dealing with haemophilia;
- Parameter 7: Treatment;
- Parameter 8: Future;
- Parameter 9: Family planning;
- Parameter 10: Partnership and sexuality.

For each parameter a summary score will be calculated, as well as an overall total score for the QoL. For computing the summary scores for the Haem-A-QoL, the following steps will be made:

- Assign numbers to the individual response items as:
    - 1 = never, 2 = seldom, 3 = sometimes, 4 = often, 5 = all of the time
- Recode positively worded items (i.e. parameters 1, 2, 3, 6, 7 and 8) so that the numeric values assigned are reversed and high scores reflect not higher but lower quality of life:

- 1 = all of the time, 2 = often, 3 = sometimes, 4 = seldom, 5 = never

- Summing the items belonging to a parameter yields the raw score per parameter. Its range lies between the lowest possible (number of items (n) x 1) and highest possible (number of items (n) x 5); if this raw score is divided by the number of items in the parameter, the resulting standardised parameter score can have any (also decimal) value between 1 and 5. A value of 1 represents the highest possible quality of life rating and a value of 5 represents the lowest possible quality of life rating of the patient.

- Transferring[2] a raw score to a transformed parameter score between 0 and 100 makes it possible to express the parameter score in percent between the lowest (0) and the highest (100) possible value. To obtain the transformed parameter (scale) score (TSS) the following transformation rule has to be applied:

  - $\text{TSS} = 100 \times \frac{\text{Raw score} - \text{Minimal possible raw score (of the parameter/scale)}}{\text{Possible range of raw scores (of the parameter/scale)}}$.

- Producing the total score for Haem-A-QoL involves the addition of the sub-parameter scores (instead of the standardised parameter scores) of a patient using all items of the questionnaire (assorting and recoding as described above). Items may be added to form a total raw score, a total standardised score or a total transformed score, according to the steps details above but using all sub-parameter scores.

The actual values and change from baseline in Haem-A-QoL score will be summarised for the total score and individual parameters using descriptive statistics by dose level and overall for all patients in the FAS.

All QoL data will also be listed by parameter, sub-parameter and overall for all patients in the FAS.

10.3.1.2. EQ-5D-5L QUESTIONNAIRES

The EQ-5D is a standardized Patient Reported Outcome (PRO) for use as a general measure of health outcome. The EQ-5D has 5 questions used to create a descriptive "health state" and a visual analog scale (VAS) to capture a patient's overall health rating. The descriptive system comprises of 5 dimensions mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The 5 questions will be summarized descriptively as categorical variables. The VAS will be summarized as a continuous variable using descriptive statistics for the total scores, change from baseline, and percent change from baseline, where:

% change from baseline = ((Visit Value- Baseline Value)/Baseline Value)*100

10.3.2. Disability Status

Disability status will be captured at Screening and Week 26, or Week 26/EOS for patients who dropped out of the study early, and assessed using the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0).

WHODAS 2.0 is a practical, generic assessment instrument that can measure health and disability at population level or in clinical practice. WHODAS 2.0 captures the level of functioning in six individual parameters of life:

- Parameter 1: Cognition – understanding and communicating;
- Parameter 2: Mobility – moving and getting around;
- Parameter 3: Self-care – attending to one's hygiene, dressing, eating and staying alone;
- Parameter 4: Getting along – interacting with other people;
- Parameter 5: Life activities – domestic responsibilities, leisure, work and school;
    - 5.1: household activities;
    - 5.2: work or school activities.
- Parameter 6: Participation – joining in community activities, participating in society.

For computing the summary scores for the WHODAS 2.0, the scores assigned to each of the items (sub-parameters) – "none" (1), "mild" (2) "moderate" (3), "severe" (4) and "extreme or cannot do" (5) – are summed within each domain for the domain-specific summaries and overall for the total score. Higher WHODAS 2.0 scores demonstrate higher levels of disability.

The scoring of the full version of WHODAS 2.0 takes into account the paid-work status of the respondent, with 32 items being used if the respondent is not in gainful employment. If one item is missing then the score can be used as it is and will be comparable to that of the full 36-item version.

The following approach is used where more than one item is missing:

- If the respondent is not working and has given responses to the 32-item WHODAS 2.0, the score can be used as it is, and will be comparable to that of the full 36-item version.

- In all other situations where one or two items are missing, the mean score across all items within the individual parameter should be assigned to the missing items. This method should not be used if more than two items are missing. In addition, if parameter-wise scores are being computed for domains, the two missing items should not come from the same domain.

If any of the individual responses for domain 5 are rated greater than none (coded as "1") then, in the past 30 days, the number of days the patient demonstrates the respective disability will be recorded and listed only, and will not be used in the derivation of the summary scores. Similarly for domain 6 the below information will be collected and listed only:

- No of Days (in the past 30 days) the difficulty was present;

- No of Days (in the past 30 days) the patient was totally unable to carry out their usual activities or work because of any health condition;

- No of Days (in the past 30 days) the patient had to cut back or reduce their usual activities or work because of any health condition, not counting the days totally unable.

The actual values and change from baseline in the derived WHODAS 2.0 scores will be summarised for the total score and individual parameters (domains) using descriptive statistics by dose level and overall for all patients in the FAS.

All disability data will also be listed by parameter, sub-parameter and overall for all patients in the FAS.

10.3.3. Physical Activity

Physical activity will be captured at Screening and Week 26, or Week 26/EOS for patients who dropped out of the study early, and assessed using the Haemophilia Activities List (HAL) 2005.

The HAL measures the impact of hemophilia on self-perceived functional abilities in adults. It contains 42 multiple choice questions in seven parameters (domains):

- Parameter 1: Lying/sitting/kneeling/standing;

- Parameter 2: Functions of the legs;
- Parameter 3: Functions of the arms;
- Parameter 4: Use of transportation;
- Parameter 5: Self-care;
- Parameter 6: Household tasks;
- Parameter 7: Leisure activities and sports.

For each parameter a composite score will be calculated, as well as an overall summarised score for the HAL. The possible scoring range for the total HAL score is 42.0 - 252.0. For all scores of the HAL, a higher score represents more self-perceived difficulty in performing activities. The scores derived in the CRF will be used.

The actual values and change from baseline in HAL score will be summarised for the total score and individual parameters (domains) using descriptive statistics by dose level and overall for all patients in the FAS.

All physical activity data will also be listed by parameter, sub-parameter and overall for all patients in the FAS.

10.3.4. Health Resource Utilisation

Health resource utilisation will be captured at Screening and Week 26, or Week 26/EOS for patients who dropped out of the study early.

At Screening, a 6-month history will be collected, at Day -1, all Health Resource Utilisation since Screening will be collected and at EOS, all Health Resource Utilisation since Screening (or Day -1) will be collected.

The following items will be recorded in the CRF at each study visit:

- Number of haemophilia related medical appointments;
- Number of emergency room visits;
- Number of hospitalisations related to haemophilia;
- Length of hospital stay;
- Number of physiotherapy sessions; specialist consultations and appointments with professional caregivers;

- Number of days lost from education or work by patients and caregivers due to bleeding episodes.

Health resource utilisation will be summarised for the above parameters using descriptive statistics by visit, dose level and overall for all patients in the FAS.

All health resource utilisation data will also be listed for all patients in the FAS.

10.3.5. Assessment of Joint Health/Function

Joint health/function will be captured at Screening and Week 26, or Week 26/EOS for patients who dropped out of the study early, and assessed using the Haemophilia Joint Health Score (HJHS) score.

The HJHS measures joint health, in the domain of body structure and function (i.e. impairment), of the joints most commonly affected by bleeding in hemophilia: the knees, ankles, and elbows. Each of the six joints are assessed individually and numerically scored in categories of severity, with a total single joint score ranging from 0 to 20. All joints scores, when combined, provides an overall total score range from 0 to 120, where score of 0 corresponds to no identifiable joint impairment. The scores derived in the CRF (Joint Totals as well as HJHS Total Score) will be used.

The actual values and change from baseline in HJHS Total score will be summarised using descriptive statistics by dose level and overall for all patients in the FAS.

All joint health/function data will also be listed for all patients in the FAS.

10.3.6. Haemophilia Health Status

Haemophilia health status will be assessed using PROBE. PROBE stands for Patient Reported Outcomes Burdens and Experiences. The main goal of the PROBE study is to give hemophilia patient organizations patient-reported data on patients' health status and quality of life that they can use to advocate for better care and treatment.

The PROBE questionnaire is comprised of four major sections (demographic data, general health problems, haemophilia-related health problems and health-related quality of life using EQ-5D-5L and EQ-VAS).

All PROBE data will be listed for all patients in the FAS.

Descriptive analyses of the PROBE questionnaire data will be performed separately and are not described in this SAP. Results will be presented separately from the study CSR.

11. INTERIM ANALYSES

There will be no interim analysis in the study.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

In the protocol it is stated that three (3) dose cohort of vector (low, middle and high) will be tested in the dose escalation. However if a dose reduction is deemed necessary, the 2+1 design will apply at that new dose level within the cohort. Dose levels have more interpretation value than cohort, and therefore TLFs would be presented by dose levels (rather than cohorts).

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14. PROGRAMMING CONSIDERATIONS

All tables, listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 or later (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

14.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs or a separate SAS program will be created for each output at the statistical programmer's discretion.
- Each output will be stored in a separate file.
- Output files will be delivered in Word (rtf) format.
- Numbering of TFLs will follow ICH E3 guidance.

14.2. TABLE, LISTING, AND FIGURE FORMAT

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialised text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:
  UCL Protocol 15/0552
  Draft/Final Run <date>
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Analysis Set

14.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified;
- numbers containing fractional portions are decimal aligned.

14.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and

standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the total column in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split

over more than one page, output the subheading followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

14.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Patient specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

15. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010.00 and 03.013.00 provide an overview of the development of such SAS programs.

INC Research SOP 03.009.00 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

16. INDEX OF TABLES

Table 14.2.2.1.1	Endogenous FIX Production by visit
Table 14.2.2.2.1	Endogenous FIX Production: Summary by Visit and Change from Baseline
Table 14.2.2.2.2	Number of Bleeding Episodes and Number of Days during the efficacy period
Table 14.2.2.2.3	Annualised Bleeding Rate (ABR): Summary of Change from Baseline to Post-Dose
Table 14.2.2.2.4	Post Dose Factor IX (FIX) Concentrate Consumption (IU/kg)
Table 14.2.2.2.5	Total Factor IX (FIX) Concentration Consumption: Summary of Change from Baseline to Post-Dose
Table 14.2.2.2.6	Annualised Total Units of Factor IX (FIX) Concentration Consumption: Summary of Change from Baseline to Post-Dose
Table 14.2.2.2.7	Exploratory comparison of bleeding events by FIX activity range
Table 14.2.3.1.1	Health-Related Quality of Life (Haem-A-QoL): Summary by Visit and Change from Baseline
Table 14.2.3.1.2.1	Health Related Quality of Life (EQ-5D-5L): Summary by Visit
Table 14.2.3.1.2.2	Health Related Quality of Life (EQ-5D-5L VAS): Summary by Visit and Change from Baseline
Table 14.2.3.1.3	Health Related Quality of Life (EQ-5D-5L): Shifts in descriptive variables from baseline
Table 14.2.3.2.1	Disability Status (WHODAS 2.0): Summary by Visit and Change from Baseline
Table 14.2.3.3.1	Physical Activity (HAL 2005): Summary by Visit and Change from Baseline
Table 14.2.3.4.1.1	Health Resource Utilisation: Summary at Screening
Table 14.2.3.4.1.2	Health Resource Utilisation: Summary at Day -1 (Baseline)

Table 14.2.3.4.1.3	Health Resource Utilisation: Summary at EOS and Change from Baseline
Table 14.2.3.5.1	Joint Health/Function (HJHS): Summary by Visit and Change from Baseline
Table 14.3.1	Treatment Emergent Adverse Events – Overall Summary
Table 14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.3.1	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity-CTCAE graded
Table 14.3.1.3.2	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity-non CTCAE graded
Table 14.3.1.4	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to FLT180a
Table 14.3.1.5	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.6	Serious FLT180a-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.8	Treatment Emergent Adverse Events with an Outcome of Death by System Organ Class and Preferred Term
Table 14.3.4.1.1.1	Haematology: Summary by Visit and Change from Baseline
Table 14.3.4.1.1.4	Haematology: Shifts in CTCAE Grades
Table 14.3.4.1.1.5	Haematology: Shifts in Baseline for Non-CTCAE Gradable Parameters Relative to the Normal Range
Table 14.3.4.1.2.1	Coagulation: Summary by Visit and Change from Baseline
Table 14.3.4.1.2.4	Coagulation: Shifts in CTCAE Grades
Table 14.3.4.1.2.5	Coagulation: Shifts in Baseline for Non-CTCAE Gradable Parameters Relative to the Normal Range

Table 14.3.4.1.3.1	Clinical Chemistry: Summary by Visit and Change from Baseline
Table 14.3.4.1.3.4	Clinical Chemistry: Shifts in CTCAE Grades
Table 14.3.4.1.3.5	Clinical Chemistry: Shifts in Baseline for Non-CTCAE Gradable Parameters Relative to the Normal Range
Table 14.3.4.2	Vital Signs: Summary by Visit and Change from Baseline
Table 14.3.4.3.1	Summary of Overall ECG Interpretation by Visit
Table 14.3.4.3.2	Summary of ECG Overall Shift from Baseline
Table 14.3.4.3.3	ECG Parameters: Summary by Visit and Change from Baseline
Table 14.3.4.3.4	Categorical Summary of QTcF Interval by Visit
Table 14.3.4.4	Physical Examination Results
Table 14.3.4.5.1	Factor IX (FIX) Inhibitor Level: Summary by Visit
Table 14.3.4.5.2.1	Shedding/PCR of Vector Genomes in Plasma, Saliva, Urine, Stool and Semen: Summary by Visit
Table 14.3.4.5.2.2	Shedding/PCR of Vector Genomes in Plasma, Saliva, Urine, Stool and Semen: Time to unquantifiable result
Table 14.3.4.5.3	AAV-S3 Neutralising Antibody Titre: Summary by Visit
Table 14.3.4.5.4	T-Cell Responses to AAV-S3 Capsid in Peripheral Blood Mononuclear Cells: Summary by Visit

17. INDEX OF FIGURES

18. INDEX OF LISTINGS

Listing Number	Name
Listing 16.2.1.1	Analysis Sets
Listing 16.2.1.2	Dose Levels
Listing 16.2.1.3	Patient Disposition until End of Study
Listing 16.2.1.4	Missing Assessments Due to COVID-19
Listing 16.2.1.5	Missing Visits Due to COVID-19
Listing 16.2.2.1	Protocol Deviations
Listing 16.2.2.2	Protocol Deviations Related to COVID-19 and Related Measures
Listing 16.2.3.1	Inclusion and Exclusion Criteria
Listing 16.2.3.2	Informed Consent and Patient Eligibility
Listing 16.2.4.1	Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3.1.1	Haemophilia B Medical History
Listing 16.2.4.3.1.2.1	Historic Bleeding Events
Listing 16.2.4.3.1.3.1	Historic Factor IX (FIX) Consumption
Listing 16.2.4.3.2	Target Joint Assessment during Screening
Listing 16.2.4.4	Prior and Concomitant Medications
Listing 16.2.4.5	AAV-S3 Antibody Screen
Listing 16.2.4.6	HBV, HCV, CMV, HIV Screen
Listing 16.2.4.7.1	FIX Antigen level (Central Lab)

Listing 16.2.4.7.2	Baseline FIX activity (Local Lab)
Listing 16.2.5.1	Vector Infusion (Administration of FLT180a)
Listing 16.2.5.2	Corticosteroids and Immunosuppressants Distribution
Listing 16.2.5.3	Corticosteroids and Immunosuppressants Administration
Listing 16.2.5.4	Tacrolimus Levels Testing (Local)
Listing 16.2.6.1.1	FIX Activity Level (FIX response – Central Labs)
Listing 16.2.6.1.2	Factor IX (FIX) Antigen
Listing 16.2.6.2.1.1	Diary Completion for Bleeding Events
Listing 16.2.6.2.1.2	Annualised Bleeding Rate (ABR)
Listing 16.2.6.2.2.1	Diary Completion for Factor IX (FIX) Consumption
Listing 16.2.6.2.2	Annualised Total Units of Factor IX (FIX) Concentration Consumption
Listing 16.2.6.3.1	Diary Distribution
Listing 16.2.6.3.2	Disability Status (WHODAS 2.0)
Listing 16.2.6.3.3.1	Physical Activity (HAL 2005)
Listing 16.2.6.3.3.2	Physical Activity (HAL 2005) Adaptations and Using an Aid
Listing 16.2.6.3.4.1	Health Related Quality of Life (EQ-5D-5L)
Listing 16.2.6.3.4.2	Health-Related Quality of Life (Haem-A-QoL)
Listing 16.2.6.4.1	Haemophilia Joint Health Score (HJHS)
Listing 16.2.6.4.2	Health Resource Utilisation
Listing 16.2.6.4.3	Probe Questionnaire
Listing 16.2.6.4.4	Days Lost from Work or Education

Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Serious Adverse Events
Listing 16.2.7.3	Important Medical Events
Listing 16.2.7.4	Adverse Events with an Outcome of Death
Listing 16.2.7.5	Dose Limiting Toxicities (DLTs)
Listing 16.2.8.1.1	Laboratory Reference Ranges
Listing 16.2.8.1.2.1.1	Haematology (Central Labs)
Listing 16.2.8.1.2.1.2	Haematology (Local Labs)
Listing 16.2.8.1.2.2	Haematology: Clinically Significant Laboratory Results
Listing 16.2.8.1.3.1	Coagulation (Central Labs)
Listing 16.2.8.1.3.2	Coagulation (Local Labs)
Listing 16.2.8.1.4.1.1	Clinical Chemistry (Central Labs)
Listing 16.2.8.1.4.1.2	Clinical Chemistry (Local Labs)
Listing 16.2.8.1.4.2	Clinical Chemistry: Clinically Significant Laboratory Results
Listing 16.2.8.1.5	C-Reactive Protein (CRP)
Listing 16.2.8.2.1	Vital Signs
Listing 16.2.8.2.2.1	12-Lead Electrocardiogram (ECG)
Listing 16.2.8.2.2.2	12-Lead Electrocardiogram (ECG) Parameters
Listing 16.2.8.2.3	Physical Examination
Listing 16.2.8.2.4	Liver Ultrasound
Listing 16.2.8.2.5	Reactivation of Hepatitis
Listing 16.2.8.3.1.1	Human Factor IX (hFIX) Inhibitor

Listing 16.2.8.3.1.2	AAV-S3 Antibody Titre
Listing 16.2.8.3.1.3	Mononuclear Cells
Listing 16.2.8.3.2.1	Viral Shedding/PCR of Vector Genomes
Listing 16.2.8.3.2.2	Viral Shedding/PCR of Vector Genomes: Time to unquantifiable result

19. APPENDICES

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