Statistical Analysis Plan

NCT Number: NCT05437211

Title: Ability of a Virtual-reality Based Solution Aiming to Reduce Patient Burden Related to Repetitive Intravenous Perfusions. A Proof-of-concept Study in Hemophilia Patients Receiving Prophylactic Factor VIII or Factor IX Infusions

Study Number: TAK-660-4013

Document Version and Date: Version 1.0, 14 May 2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

eXYSTAT Biometric Expertise	**STATISTICAL ANALYSIS PLAN** CONFIDENTIAL

Takeda

STATISTICAL ANALYSIS PLAN

DoL-x Poc STUDY

Protocol Title:

Ability of a virtual reality-based solution aiming to reduce patient burden related to repetitive intravenous perfusions. A proof-of-concept study in haemophilia patients receiving prophylactic Factor VIII or Factor IX infusions

Protocol Number: TAK-660-4013, Version 3.0, 28 February 2023

Compound Number: NA

Short Title: DoL-x Poc

Sponsor Name: Takeda France SAS

Legal Registered Address: 112 avenue Kléber 75116 Paris, France

Regulatory Agency Identifier Number(s):

Registry **ID :** NCT05437211

Signatures

The undersigned have approved this Statistical Analysis Plan for use in this study.

[redacted] 14-mai-2024

[redacted] Date

[redacted] Rare Diseases

Takeda

[redacted] 14-May-2024

[redacted] Date

Biostatistician

eXYSTAT

[redacted] 14-mai-2024

[redacted] Date

Biostatistician [redacted]

eXYSTAT

Table of Contents

Documentation

A. General information

Protocol	TAK-660-4013
Related documents	• Protocol version 3.0 (28FEB2023) • ICHE9 • CRF version 4.0 (24FEB2023) • MDH version 1.0 (13MAY2024) • Minutes of data review committee (30APR2024)
Document Owner	eXYSTAT

B. Version History

This statistical analysis plan (SAP) for Study DoL-x Poc is based on the protocol dated 28FEB2023.

SAP Version	***Date***	***Change***	***Rationale***
1.0	*14MAY2024*	*Not applicable*	*Original version*

List of Abbreviations

3D	Three-dimensional
ANCOVA	Analysis of Covariance
AE	Adverse event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
A-VAS	Visual analogue scale for anxiety
CRF/eCRF	Case report form/electronic case report form
CRO	Clinical research Organization
EDC	Electronic data capture
EQ-5D-3L	European Quality of Life 5 dimensions 3 levels
EQ-5D-Y	European Quality of Life 5 dimensions four youth
HLGT	High-level group term
HLT	High-level term
ICH	International Conference on Harmonisation
IRBs/ECs	Institutional Review Boards/Ethics Committees
IV	Intravenous
LLT	Low-level term
LSMeans	Least-Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MMAS-4	4-item Morisky Medication Adherence Scale
MMRM	Mixed-effects model for repeated measures
MR	Reference method
NSAID	Non-steroidal anti-inflammatory drug
PGIC	Patient's Global Impression of Change
PHQ-9	Patient Health Questionnaire (module 9 for depression)
PRO/ePRO	Patient reported outcome/electronic patient reported outcome
PT	Preferred term
PV	Pharmacovigilance
P-VAS	Visual analogue scale for pain
SAP	Statistical Analysis Plan
SOC	System organ class
STAI-S	State Anxiety Inventory

1. Introduction

The treatment of some medical conditions is based on intensive intravenous therapy that may lead to a real treatment burden for patients (pain, anxiety, decrease in quality of life…) and relatives, and then to treatment avoidance and poor adherence which can contribute to poor medical outcomes. In this context, this proof-of-concept study is designed to assess the ability of a virtual-reality based solution aiming to reduce the treatment burden in patients and relatives. The studied population will be haemophilia patients receiving prophylactic Factor VIII or Factor IX infusions.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To describe the evolution of the treatment burden in haemophilia patients receiving prophylactic Factor VIII or Factor IX infusions, under a virtual reality-based solution, as well as for patient relatives and health care professionals	Before and after each Factor VIII or Factor IX infusion Anxiety (patients and relatives) using an Anxiety Visual Analogue Scale (A-VAS). • Absolute and relative variation • Decrease of 2 points out of 10 in the A-VAS After each Factor VIII or Factor IX infusion Pain (patients) using a Pain Visual Analogue Scale (P-VAS). • Absolute and relative variation • Decrease of 2 points out of 10 in the P-VAS At inclusion and at end of follow-up (week 4) Quality of life measured with the European Quality of Life 5 Dimensions 3- levels (EQ- 5D- 3L questionnaire (patients and relatives) - one scale for adults and one scale for children (EQ-5D-Y) • Absolute and relative variation • Decrease of 2 points out of 10 in the VAS Anxiety using the State-Trait Anxiety Inventory STAI-Y (patients and relatives) including 2 types of anxiety: State and Trait. 20 items for each type of anxiety (score from 20 to 80) • Absolute and relative variation

	• Decrease of at least one level of anxiety state (STAI-S) severity. Severity is defined as a score on STAI-S 20-35 (very low) 36-45 (low) 46-55 (moderate) 56-65 (high) 66-80 (very high) Depression using PHQ-9 Depression Severity (patients and relatives): 9 items (score from 0 to 27). • Absolute and relative variation • Decrease of at least one level of depression severity. Severity is defined as a score on PHQ-9: 0-5 (none) 5-10 (mild) 10-15 (moderate) 15-20 (moderately severe) 20-27 (severe). Adherence to infusions using MMAS-4 • Absolute variation and changes in classes (0-1: low adherence; 2-3: medium adherence; 4: high adherence) • Score at 4 (high adherence) at the end of follow-up. At the end of follow-up (week 4) Adherence to virtual-reality based solution at the end of follow-up using MMAS-4 • Score in classes (0-1: low adherence; 2-3: medium adherence; 4: high adherence). • Global Impression of Change (GIC) Scale at the end of follow-up (patients, relatives, and caregivers) • Value at 3 or more.
• To describe the satisfaction of patients, relatives, and health care professionals with the virtual reality-based solution	At the end of follow-up (week 4) • Satisfaction, Willingness to Continue the virtual-reality based solution: Patient, Caregiver and relatives using a 4-point Likert scale • Score at 3 or 4 (satisfied or very satisfied) Preference for the virtual reality-based solution: Patient Caregiver and relatives using a binary question • Preference for the virtual-reality based solution versus no virtual-reality based solution

• To describe the tolerance of the virtual reality-based solution	Incidents related to the virtual-reality based solution, adverse events related to the infusions of Factor VIII or Factor IX, or VR-based solution, serious adverse events
Exploratory	
• To describe the evolution of drug therapies used by patients for pain and anxiety, under the virtual reality-based solution	Drug therapies used by patients for pain and anxiety at inclusion and end of follow-up

1.2. Study Design

This is an interventional (with minimal risks and constraints), prospective, national, and multicentre proof-of- concept study designed to describe, in France, the evolution of the treatment burden of haemophilia patients receiving prophylactic Factor VIII or Factor IX infusions, using a virtual-reality based solution, as well as for patient relatives and health care professionals.

The duration of the clinical study will be 4 weeks for each patient enrolled.

The virtual-reality based solution to be studied is provided in a medical device CE marked and specifically developed by Deepsen, a French company specialized in e-health solutions to reduce pain.

The studied solution comprises:

infusions in satisfactory conditions, notably as regards safety, as well as VAS for pain and anxiety to be complete between the inclusion and the Week 4 visit

- A 3D mask (to be used during infusions) including

o Simulation of infusions themselves (before infusion)

o A relaxing and distracting content (during and after infusions)

The content of the different parts of the studied solution is adapted to the person who will oversee the infusions when not performed by the healthcare professional (patient or family).

Before the clinical study itself, a test phase was conducted in a limited number of patients (n=8) to validate the proper functioning of the hardware and software solution, and its appropriation by patients and caregivers (learning agility, understanding of modules and objectives, and actions to be taken if technical problems). This phase was conducted at the Lyon centre (National Reference Centre for Haemophilia and other rare bleeding disorders) that will be also involved in the study itself. This test phase will consist of a single visit for patients. These patients will be allowed to participate in the clinical study itself, after a period of 4 months minimum with no use of the virtual reality-based solution. These patients will be selected to present different characteristics in terms of age and autonomy with Factor VIII infusions (2 patients for each of the 4 following subgroups: autonomous children, autonomous adults, non-autonomous children, and non-autonomous adults). This test phase is not included in this SAP.

During the clinical study itself, included patients will be followed up for 4 weeks, with the following steps:

1. Inclusion visit:

a. Firstly, Factor VIII or Factor IX infusion performed at hospital as usual, with no use of the virtual reality-based solution, and baseline evaluation

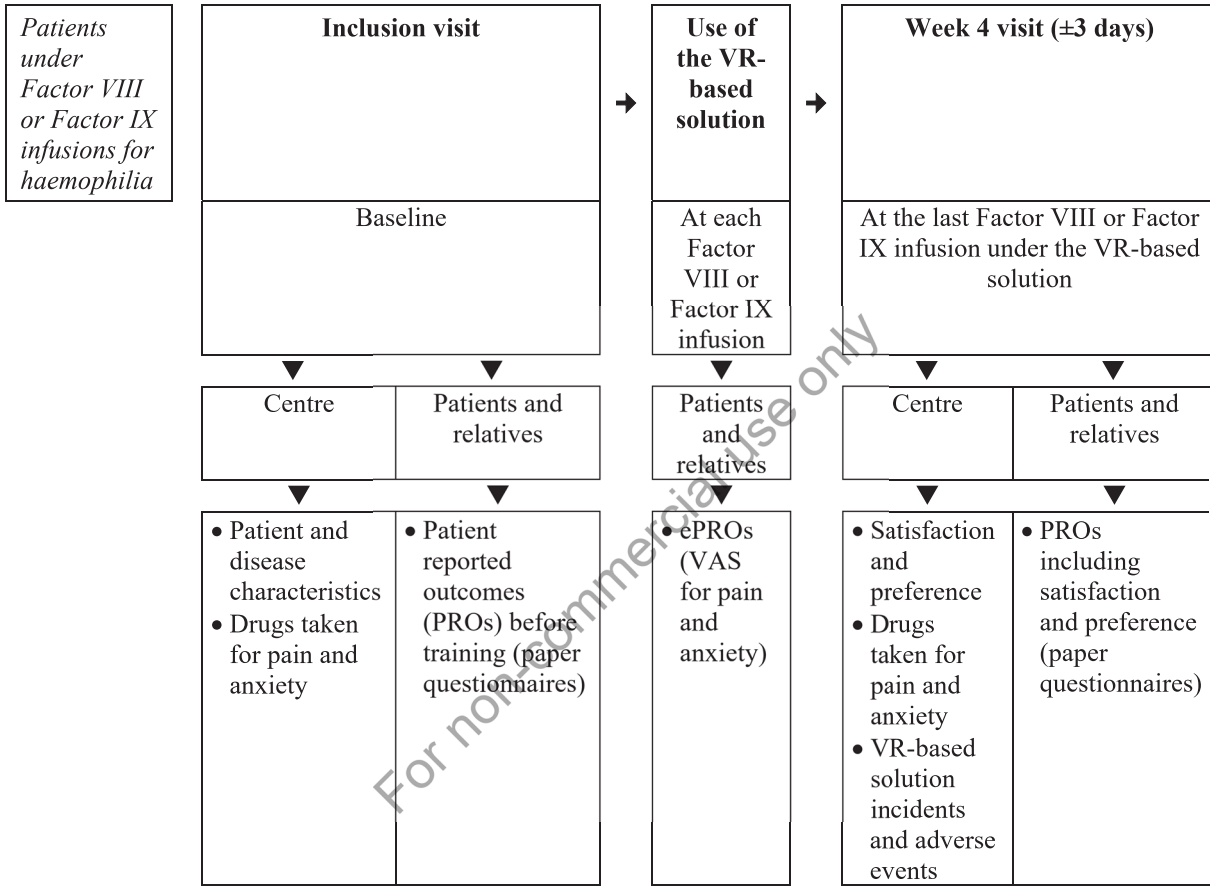
b. Secondly, training with the virtual reality-based solution

2. Evaluations at the time of the following infusions, using the virtual reality-based solution (at home with or without the help of a nurse, or at hospital according to usual practices)

3. Final visit to hospital 4 weeks after inclusion, for evaluations at the time of the last infusion during follow-up.

The virtual reality-based solution to be studied could lead clinicians to changes in the current management of haemophilia patients (e.g.: potential decrease in analgesics or anxiolytics). This study is therefore through (and in accordance with) the reference MR-001 method defined in France for interventional studies with minimal risks and constraints (This category of studies id defined in the decree of April 12th, 2018; NOR: SSAP1810239A; JORF No 0089, dated on 2018, April 17).

Figure 1: Study Design Flow Chart



2. General Considerations

The Statistical Analysis Plan (SAP) is finalized and approved by the Scientific Committee before the database lock.

Statistical analysis will be performed by eXYSTAT under the supervision of the sponsor and the Scientific Committee. All statistical analyses will be performed in accordance with this SAP using SAS® release 9.4. All computer programs and macros will be developed and validated according to eXYSTAT standard operating procedures. An internal review by the lead statistician in charge of the project will be performed, including SAS® codes and programming, SAS® logs and outputs and edition of the TFL. Then, an external review of the TFL will be performed by another statistician and the medical writer.

Quantitative data will be summarized by the following descriptive statistics: number of data available, number of missing data, mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum and maximum. When relevant, the associated 95%confidence interval will also be presented.

Qualitative data will be summarized by the following descriptive statistics: number of data available, number of missing data, frequency, and percentage for each modality. The percentages will be based on the number of data available. When relevant, the associated 95% confidence interval will also be presented.

When specified, the following derived variables will be used:

- Absolute change from baseline B at visit V (unit) = Value at V (unit) – Value at B (unit)
- Relative change from B at V (%) = 100 * Absolute change from B at V (unit) / Value at B (unit)

In case of null value at B, the relative change will be considered as missing.

All the analyses will be presented in 3 columns according to subgroups: autonomy, without autonomy, and total. The risk 1 error (α) will be set to 5% (two-sided).

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision):

- Raw data: same number of decimals as collected,
- Derived data: The appropriate number of decimal places will be determined by general practice, mathematical rationale, or scientific rationale (e.g. age should be presented in whole numbers),
- Mean, standard deviation, median, first and third quartiles: reported to one decimal place greater than the raw/derived data that they summarize,
- Minimum and maximum: same precision as the raw data,
- Percentage: one decimal place,
- P-values: three decimal places (e.g.: p=0.037), after rounding. P-values which are less than 0.001 will be presented as ‘<0.001’.

Conventions for time calculations:

- Time between 2 dates in days = (Date 2 – Date 1 + 1)

- Time between 2 dates in weeks = (Date 2 – Date 1 + 1)/7
- Time between 2 dates in months = (Date 2 – Date 1 + 1)/30.4375
- Time between 2 dates in years = (Date 2 – Date 1 + 1)/365.25

Descriptive analysis is performed overall and by group.

2.1. Decision Criteria

If the p value is significant for at least one endpoint among pain, anxiety, depression or quality of life, this proof-of-concept study will be considered as positive.

2.2. Multiplicity Adjustment

No handling for multiplicity is considered for the analysis of the different endpoints.

2.3. Impact of Intercurrent Events Strategies

Not applicable. Estimand approach is not used for this analysis.

2.4. Handling of Missing Data

Missing data will not be replaced and only observed data will be analyzed.

For incomplete dates, following conventions will be used:

- For baseline data: missing dates will not be replaced
- For safety dates, survival dates and concomitant treatment dates:
  - For missing start day: ‘01’ is used. Except if the calculated date is anterior to first intake date (in this case, missing start date will be first intake date).
  - For missing start month or year: missing data will not be replaced
  - For missing end day: last day of the month’ is used
  - For missing end month or year: missing data will not be replaced
- For all other criteria, missing dates will remain missing.

3. Analysis Sets

Included set (IS)

The included set will include all included patients with or without assessment at the end of the week 4 visit.

Full Analysis set (FAS) – Primary population

The full analysis set will include all included patients for whom at least one assessment at the week 4 visit is available. The number and percentage of patients included in the FAS will be described with the reason for non-inclusion in the FAS. The number and percentage of patients prematurely discontinued with the reason for premature discontinuation will also be provided.

To describe the population, the following analysis will be provided:

- Number of selected patients, included patients, selected and not included patients with reason for non-inclusion.
- Number of patients in IS and FAS populations in each subgroup
- Listing of protocol deviations
- Number and percentages of prematurely discontinued patients
- Number and percentages of patients present at each visit
- Study duration (time from screening visit) will be described.

4. Analyses Supporting Primary Objective(s)

4.1. Primary endpoints

4.1.1. Definition of Endpoint(s)

4.1.2. Main Analytical Approach

All analyses will be performed in the FAS population. Quantitative paired variables will be compared to assess the change from baseline significance using the MMRM model or/and Wilcoxon signed rank test. Changes will be associated with their exact 95% two sided Clopper-Person confidence interval.

4.1.2.1. Anxiety (patients and relatives) using an Anxiety Visual Analogue Scale (A-VAS)

The A-VAS scale will be available before and after each injection for a theoretical total number of twelve injections at a maximum (up to 3 injections per week during the 4 weeks). The effect on anxiety will be analysed using three different approaches: all the values before injection, then all the values after injection and finally the absolute changes after injection minus before injection.

If autonomous patient: VAS completed in the eCRF at each visit and at each injection by the patient

If non autonomous patient: VAS completed in the eCRF at each visit by the relative and at each injection by the patient

The selection of VAS values will be done by prioritizing the tablet values to the mask values. All values reported outside the perfusion's windows will be not considered.

The disposition of the VAS will be described as the number of VAS per patient and the number of VAS at each visit and each injection. The completion rate corresponding to the number of VAS done divided by the number that should have been done according to the number of weekly perfusions entered at inclusion will be calculated for each patient.

1- Absolute and relative variation from baseline value before injection will be described using a mixed-effects model for repeated measures (MMRM) analysis with patient, group (acquired autonomy or without autonomy), and injection number as explanatory variables and baseline score as covariate. Patient will be fitted as a random effect, and compound score covariance structure will be used for all models. The Least Squares Mean differences will be reported and plotted with corresponding 95% CIs at each injection. Overall effect will be estimated using this model with corresponding 95% Cis and associated p-value.

   The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS will be described at each injection with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS at least once during study will be described with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS between baseline and week4 will be described with the associated 95% two-sided exact confidence interval.

2- Absolute and relative variation from baseline value after injection will be described using a mixed-effects model for repeated measures (MMRM) analysis with patient, group (acquired autonomy or without autonomy), and injection number as explanatory variables and baseline score as covariate. Patient will be fitted as a random effect, and compound score covariance structure will be used for all models. The Least Squares Mean differences will be reported and plotted with corresponding 95% CIs at each injection. Overall effect will be estimated using this model with corresponding 95% CIs and associated p-value.

The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS will be described at each injection with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS at least once during study will be described with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS between baseline and week4 will be described with the associated 95% two-sided exact confidence interval.

3- Absolute and relative variation between after and before injection will be described using a mixed-effects model for repeated measures (MMRM) analysis with patient, group (acquired autonomy or without autonomy), and injection number as explanatory variables. Patient will be fitted as a random effect, and compound score covariance structure will be used for all models. The Least Squares Mean differences will be reported and plotted with corresponding 95% CIs at each injection. Overall effect will be estimated using this model with corresponding 95% Cis and associated p-value.

The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS will be described at each injection with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS at least once during study will be described with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the A-VAS between baseline and week4 will be described with the associated 95% two-sided exact confidence interval.

For each patient, a spaghetti plot with A-VAS value will be presented.

4.1.2.2. Pain (patients) using a Pain Visual Analogue Scale (P-VAS)

If autonomous patient: VAS completed in the eCRF at each visit and at each injection by the patient

If non autonomous patient: VAS completed in the eCRF at each visit by the relative and at each injection by the patient

The disposition of the VAS will be described as the number of VAS per patient and the number of VAS at each visit and each injection.

The P-VAS scale will be available after each injection for a theoretical total number of approximately twelve injections (3 injection per week during the 4 weeks). Absolute and relative variation from baseline value after injection will be described using a mixed-effects model for repeated measures (MMRM) analysis with patient, group (acquired autonomy or without

autonomy), and injection number as explanatory variables and baseline score as covariate. Patient will be fitted as a random effect, and compound score covariance structure will be used for all models. The Least Squares Mean differences will be reported and plotted with corresponding 95% CIs at each injection. Overall effect will be estimated using this model with corresponding 95% Cis and associated p-value. The number of patients with a decrease from baseline of 2 points out of 10 in the P-VAS will be described at each injection with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the P-VAS at least once during study will be described with the associated 95% two-sided exact confidence interval. The number of patients with a decrease from baseline of 2 points out of 10 in the P-VAS between baseline and week4 will be described with the associated 95% two-sided exact confidence interval.

For each patient, a spaghetti plot with P-VAS value will be presented.

The correlation between the variation (absolute and relative) of A-VAS before and after each injection and the P-VAS after each injection will be evaluated using linear regression model. Patient will be fitted as a random effect. The Pearson linear determination coefficient R^2 with the associated 95% confidence interval will be calculated.

4.1.2.3. Quality of life measured with the EQ- 5D- 3L questionnaire

The EQ-5D family of instruments has been developed to describe and value health across a wide range of disease areas. They are also frequently used in research into health in the general population. There are three versions of the instrument: EQ-5D-5L, EQ-5D-3L and EQ-5D-Y. For over 30 years, they have been widely used in clinical trials, population studies and in real-world clinical settings. The EQ-5D is used worldwide and has been translated into numerous languages through a closely monitored translation process.

Each EQ-5D instrument comprises a short descriptive system questionnaire and a visual analogue scale (EQ VAS) that are cognitively undemanding, taking only a few minutes to complete. The questionnaire provides a simple descriptive profile of a respondent's health state.

The EQ-5D-3L descriptive system comprises the following five dimensions, each describing a different aspect of health: MOBILITY, SELF-CARE, USUAL ACTIVITIES, PAIN/ DISCOMFORT and ANXIETY/DEPRESSION. Each dimension has three response levels of severity: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by checking the box next to the most appropriate response level of each of the five dimensions. The EQ VAS records the respondent's self-rated health on a vertical VAS that ranges from 'The best health you can imagine' to 'The worst health you can imagine'. This information can be used as a quantitative measure of health outcome as judged by individual respondents.

The EQ-5D-3L has a descriptive system that comprises five health dimensions and has three severity levels: no problems, some problems, extreme problems. Implicitly designed to be used by adults, the wording used in the descriptive system questionnaire and EQ VAS is slightly different from the EQ-5D-Y. EQ-5D-Y health states can be described using the 5-digit code or represented by a single summary number (index value), which reflects how good or bad a health state is according to the preferences of the general population of a country.

Considering scoring following rules will be applied:

- Only ONE response for each dimension.
- Missing values are preferably coded as '9'.
- Ambiguous values (e.g. two boxes ticked for a single dimension) should be treated as missing values.

By selecting for each item of the domains, one of the different levels of severity problem proposed (3 or 5 depending on the questionnaire used). For 3-level questionnaires, the results will be converted to 5 levels with the following rule, to affect an index value:

o 1 will remain 1,

o 2 will be converted to 3,

o 3 will be converted to 5.

For each patient, a unique Health state score will be created by combining the answer given to each dimension. This score will thus be ranging from 11111 (no problems in any domain) to 55555 (severe problems). This score will be after converted into EQ-5D single utility index values anchored at 0 for death and 1 for perfect health, by applying a formula download from the EQ-5D official website, that essentially attaches values (also called weights) to each of the levels in each dimension.

Absolute and relative variation from baseline to week 4 of the health state score value will be described using an ANCOVA model with patient and group (acquired autonomy or without autonomy) as explanatory variables and baseline score as covariate. Patient will be fitted as a random effect, and compound score covariance structure will be used for all models. The Least Squares Mean differences will be reported and plotted with corresponding 95% CIs and associated p-value. The number of patients with a decrease from baseline of 2 points out of 10 in the EQ-5D-3L VAS will be described with the associated 95% two-sided exact confidence interval.

4.1.2.4. Quality of life measured with the EQ- 5D- Y questionnaire

Same analyses described for the EQ-5D-3L scale will be provided.

4.1.2.5. Anxiety using the State-Trait Anxiety Inventory STAI-Y (patients and relatives)

The State-Trait Anxiety Inventory (STAI) is a psychological inventory consisting of 40 self-report items on a 4-point Likert scale. The STAI measures two types of anxiety – state anxiety and trait anxiety. Higher scores are positively correlated with higher levels of anxiety.

Each type of anxiety has its own scale of 20 different questions that are scored. Scores range from 20 to 80, with higher scores correlating with greater anxiety. Each scale asks twenty questions each and are rated on a 4-point scale. Low scores indicate a mild form of anxiety, and high scores indicate a severe form of anxiety.

Absolute and relative variation from week 4 to baseline of the 2 scales of the STAI will be described using an ANCOVA model with patient and group (acquired autonomy or without autonomy) as explanatory variables and baseline score as covariate. Patient will be fitted as a random effect, and compound score covariance structure will be used for all models. The Least Squares Mean differences will be reported and plotted with corresponding 95% CIs and associated p-value. The number of patients with a decrease from baseline of at least one level of anxiety state

(STAI-S) severity will be described with the associated 95% two-sided exact confidence interval. Severity is defined as a score on STAI-S 20-35 (very low) 36-45 (low) 46-55 (moderate) 56-65 (high) 66-80 (very high).

4.1.2.6. Depression using PHQ-9 Depression Severity (patients and relatives)

The Patient Health Questionnaire-9 (PHQ-9) is used to screen for depression and provides an assessment of the severity of depression. The questionnaire is a module of other health questionnaires developed for psychological assessment. The items are based on the diagnostic criteria of the DSM IV («Diagnostic and Statistical Manual of Mental Disorders»).

Scores range from 0 to 27 (nine questions rated on a 4-point scale) with higher scores correlating with greater depression.

Absolute and relative variation from week 4 to baseline of the PHQ-9 will be described using an ANCOVA model with patient and group (acquired autonomy or without autonomy) as explanatory variables and baseline score as covariate. Patient will be fitted as a random effect, and compound score covariance structure will be used for all models. The Least Squares Mean differences will be reported and plotted with corresponding 95% CIs and associated p-value. The number of patients with a decrease from baseline of at least one level of depression severity (PHQ-9) will be described with the associated 95% two-sided exact confidence interval. Severity is defined as a score on PHQ-9: 0-5 (none) 5-10 (mild) 10-15 (moderate) 15-20 (moderately severe) 20-27 (severe).

4.1.2.7. Adherence to infusions using MMAS-4

Absolute variation and changes in classes (0-1: low adherence; 2-3: medium adherence; 4: high adherence) will be provided. The number of patients with a Score at 4 (high adherence) at the end of follow-up will be described with the associated 95% two-sided exact confidence interval.

4.1.2.8. Adherence to virtual reality-based solution

Adherence to virtual-reality based solution at the end of follow-up using MMAS-4. The score in classes (0-1: low adherence; 2-3: medium adherence; 4: high adherence) at the end of follow-up will be described with the associated 95% two-sided exact confidence interval.

The global Impression of Change (GIC) Scale at the end of follow-up (patients, relatives, and caregivers) will be described. The number of patients with a Score at 3 or more at the end of follow-up will be described with the associated 95% two-sided exact confidence interval.

4.1.3. Sensitivity analysis

For all the ANCOVA models Wilcoxon signed rank test will be also provided in the Tables.

4.1.4. Supplementary analysis

As additional analysis to explore the adherence to virtual-reality based solution, the expected number of VAS for anxiety (A-VAS) will be calculated using the real date of baseline and week4 visits and the number of perfusions per week provided at the inclusion visit. As an example, for a 4-week period and 3 perfusions per week the expected number of VAS is 12.

The adherence to virtual-reality based solution will be the ratio between observed number of VAS for anxiety (A-VAS) and expected number of VAS for anxiety (A-VAS). The adherence at the end of follow-up will be described. The number of patients with an adherence higher than 80% at the end of follow-up will be described with the associated 95% two-sided exact confidence interval.

Same analysis will be provided for P-VAS.

5. Analyses Supporting Secondary Objective(s)

- To describe the satisfaction of patients, relatives, and health care professionals with the virtual reality-based solution
- To describe the tolerance of the virtual reality-based solution (described in section 7).

5.1. Analyses Supporting Satisfaction

5.1.1. Secondary Endpoints

5.1.1.1. Definition of Endpoint(s)

At the end of follow-up (week 4)

- Satisfaction, Willingness to Continue the virtual-reality based solution: Patient, Caregiver and relatives using a 4-point Likert scale
- Score at 3 or 4 (satisfied or very satisfied)

Preference for the virtual reality-based solution: Patient Caregiver and relatives using a binary question: Preference for the virtual-reality based solution versus no virtual-reality based solution

5.1.1.2. Main Analytical Approach

The satisfaction at the end of follow-up using Likert scale will be described. The number of individuals with a Score at 3 or more at the end of follow-up will be described with the associated 95% two-sided exact confidence interval.

The preference at the end of follow-up using binary variable will be described. The number of individuals with a Preference for the virtual reality-based solution at the end of follow-up will be described with the associated 95% two-sided exact confidence interval.

5.1.1.3. Sensitivity analyses

Not applicable.

5.1.1.4. Supplementary analysis

Not applicable.

5.1.2. Supportive Secondary endpoints

Not applicable.

6. Analyses Supporting Exploratory Objective

Drug therapies used by patients for pain and anxiety will be coded using the WHO Drug dictionary. Results will be presented on FAS overall and by subgroup.

Drug therapies used by patients for pain and anxiety will be described as follows:

- Number and percentage of patients with at least one drug therapy for pain and/or anxiety.
- For each indication, number, and percentage of patients with at least one drug therapy for pain and/or anxiety.
- Drug therapy for pain and anxiety will also be tabulated by the fourth level of the Anatomic Therapeutic Class (ATC4) and Preferred-Term (PT)

7. Safety Analyses

7.1. Extent of Exposure

Not applicable

7.2. Adverse Events

AE term will be assigned to the lowest level term (LLT), and a preferred term (PT) will be classified by a high-level term (HLT), a high-level group term (HLGT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus in force. The last available version at the time of database lock of MedDRA will be used.

A listing of adverse events sorted by SOC will be provided with the overall information including relation to a drug or to the medical device.

7.3. Additional Safety Assessments

A listing of technical incidents will be provided with the overall information.

8. Other Analyses

Not applicable.

8.1. Other Variables and/or Parameters

Patient and disease characteristics

Patient and disease characteristics will be described at inclusion overall and per subgroup (autonomous/ non autonomous) in the IS and FAS: patient age at diagnosis and inclusion, haemophilia severity according to the residual level of Factor VIII or Factor IX, disease complications over the last 12 months (haemorrhagic events, synovitis, chronic arthritis), factor VIII or Factor IX perfusions [age at first perfusion, inhibitors' history, immune tolerance (yes/no, success or failure), current number of weekly perfusions], daily use of analgesics NSAIDs, and/or anxiolytics for at least 3 months, socio-professional activity and education level of patients (or parents). If non autonomous, the type of relative (family/study nurse) will be provided.

Number of weekly perfusions will be described according to haemophilia type (A or B).

Site characteristics

Site characteristics will be described with number of patients included by site overall and per subgroup in the IS and FAS. Number of study discontinuations per site will also be provided.

8.2. Subgroup analysis

All the analyses will be presented in the 2 subgroups: autonomy and without autonomy.

9. Interim Analysis

No interim analysis is planned for this study.

10. Changes to Protocol-planned Analyses

Not applicable

11. Sample Size Determination

This clinical study requires 34 subjects to detect an absolute difference (evolution between before and after the virtual reality-based solution) with an effect size of 0.5 (ratio difference/standard deviation) which is a medium effect size. Power is set at 80% and the significance level at 5% two-sided.

As an example, the study has sufficient power to detect a difference of 2±4 points on the anxiety or pain scales. With 17 patients in the acquired autonomy or without autonomy subgroups and the same hypotheses, the effect size is expected to increase from 0.5 to 0.7.

The final sample size after the end of inclusions in Jan2024 is 24 with 2 study discontinuations. With 22 subjects and the same hypotheses, the power decreases to 61%. With 22 patients, the study can detect an absolute difference (evolution between before and after the virtual reality-based solution) with an effect size of 0.63. Power is set at 80% and the significance level at 5% two-sided.

As an example, the study has sufficient power to detect a difference of 2±4 points on the anxiety or pain scales.

12. Supporting Documentation

- Participant disposition
- Baseline characteristics and demographics
- Protocol deviations
- Prior/concomitant/follow-up medications (including dictionary)
- Data derivation rules
- TFLs list

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Version Number	Date Issued
MMAS-4	Final	2021/09/20
EQ- 5D- 3L (or EQ- 5D- Y for youth)	1.2	2012
STAI-Y	NA	1977
PHQ-9	NA	
PGIC	1.0	2004/03/19

12.1. Tables Templates

Template 1:

Demographic and baseline characteristics	Acquired autonomy (N=XX)	Without autonomy (N=XX)	Total (N=XX)
Quantitative variable (unit)	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Q1 - Q3	XX.X- XX.X	XX.X- XX.X	XX.X- XX.X
Range	XX.X - XX.X	XX.X - XX.X	XX.X - XX.X
Missing data	XX	XX	XX
Qualitative variable	XX	XX	XX
Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Demographic and baseline characteristics	Acquired autonomy (N=XX)	Without autonomy (N=XX)	Total (N=XX)
Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
…	…	…	…
Missing data	XX	XX	XX

Template 2:

		Acquired autonomy (N=XX)	Without autonomy (N=XX)	Total (N=XX)
Number of participants with at least one medication		n (%)	n (%)	n (%)
ATC 1		n (%)	n (%)	n (%)
	Drug name 1	n (%)	n (%)	n (%)
	Drug name 2	n (%)	n (%)	n (%)
	Drug name 3	n (%)	n (%)	n (%)
	Drug name 4	n (%)	n (%)	n (%)
	…			
ATC 2		n (%)	n (%)	n (%)
	Drug name 1	n (%)	n (%)	n (%)
	Drug name 2	n (%)	n (%)	n (%)
	Drug name 3	n (%)	n (%)	n (%)
	Drug name 4	n (%)	n (%)	n (%)
	…			

ATC will be sorted by alphabetic order. Within an ATC, drug name will be sorted by descending frequency.

Template 3:

	Acquired autonomy (N=XX)	**Without autonomy (N=XX)**	**Total (N=XX)**
Number of patients with at least one AE	n (%)	n (%)	n (%)
System Organ Class 1	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)
Preferred Term 3	n (%)	n (%)	n (%)
Preferred Term 4	n (%)	n (%)	n (%)
…			
System Organ Class 2	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)
Preferred Term 3	n (%)	n (%)	n (%)
Preferred Term 4	n (%)	n (%)	n (%)
…			

System Organ Classes will be sorted by alphabetic order. Within a SOC, Preferred Terms will be sorted by descending frequency.

12.2. Individual Listings

All CRF data will be provided using individual data listings. All listings will include centre number, patient number, autonomy subgroup, inclusion date.

12.3. Tables, Figures and List

Tables, Figures and Listing	**Template**
14.1 Disposition of Patients, Demographics and Other Baseline Characteristics	
14.1.1 Disposition of Patients	
Table 14.1.1.1 Disposition of Patients	Consort

13. References

Arane K, Behboudi A, Goldman RD. Virtual reality for pain and anxiety management in children. Can Fam Physician 2017;63(12):932-4

Coppola A, Di Capua M, Di Minno MN, et al. Treatment of hemophilia: a review of current advances and ongoing issues. J Blood Med 2010;1:183-95.

Dascal J, Reid M, IsHak WW, et al. Virtual reality and medical inpatients: A systematic review of randomized, controlled trials. Innov Clin Neurosci 2017;14(1-2):14-21

Dunn A, Patterson J, Biega CF, et al. A novel clinician-orchestrated virtual reality platform for distraction during pediatric intravenous procedures in children with hemophilia: randomized controlled trial. JMIR Serious Games 2019;7(1):e10902

Feldman BM, Pai M, Rivard GE, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. J Thromb Haemost 2006;4(6):1228-36

Feldman BM, Rivard GE, Babyn P, et al. Tailored frequency-escalated primary prophylaxis for severe haemophilia A: results of the 16-year Canadian Hemophilia Prophylaxis Study longitudinal cohort. Lancet Haematol 2018;5(6):e252-e260

Fischer K, Collins PW, Ozelo MC, et al. When and how to start prophylaxis in boys with severe hemophilia without inhibitors: communication from the SSC of the ISTH. J Thromb Haemost 2016;14(5):1105-9.

Hoffman HG, Patterson DR, Carrougher GJ, et al. Effectiveness of virtual reality-based pain control with multiple treatments. Clin J Pain. 2001;17(3):229-35

Hoffman HG, Chambers GT, Meyer WJ 3rd, et al. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. Ann Behav Med 2011;41(2):183-91

Iorio A, Stonebraker JS, Chambost H, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: A meta-analytic approach using national registries. Ann Intern Med 2019;171(8):540-6

Koller D, Goldman RD. Distraction techniques for children undergoing procedures: a critical review of pediatric research. J Pediatr Nurs 2012;27(6):652-81

Le Du K, Septans AL, Maloisel F, et al. A new option in pain prevention with bliss, a therapeutic virtual reality solution in bone marrow biopsy context: Results of a French open-label multicenter randomized phase II/III study (REVEH Trial). Journal of Clinical Oncology 2021;39(15 Suppl):6573

Malloy KM, Milling LS. The effectiveness of virtual reality distraction for pain reduction: A systematic review. Clin Psychol Rev 2010;30(8):1011-8

Manco-Johnson M. Comparing prophylaxis with episodic treatment in haemophilia A: implications for clinical practice. Haemophilia 2007;13 Suppl 2:4-9

Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007;357(6):535-44

Manco-Johnson MJ, Lundin B, Funk S, et al. Effect of late prophylaxis in hemophilia on joint status: a randomized trial. J Thromb Haemost 2017;15(11):2115-2124

Manucci PM, Tuddenham EG. The hemophilias-from royal genes to gene therapy. N Engl J Med 2001;344(23):1773-9
Meunier S, Trossaert M, Berger C, et al. French guidelines. Long-term prophylaxis for severe haemophilia A and B children to prevent haemophiliac arthropathy. Arch Pediatr 2009;16(12):1571-8
PNDS Hémophilie. Centre de Référence Hémophilie et autres déficits constitutionnels en protéines de la oagulation. 2019, version 3. https://www.has-sante.fr/upload/docs/application/pdf/2019-10/pnds_hemophilie_argumentaire_10.10.19.pdf. Accessed 27 July 2021
Réseau FranceCoag. Cohorte française des patients atteints de maladies hémorragiques par déficits héréditaires en protéines de la coagulation. Données descriptives 2005. https://www.vie-publique.fr/sites/default/files/rapport/pdf/064000522.pdf. Accessed 27 July 2021
Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19(1):e1–47.
Stonebraker JS, Bolton-Maggs PHB, Brooker M, et al. The World Federation of Hemophilia Annual Global Survey 1999-2018. Haemophilia 2020;26(4):591-600
Wiederhold MD, Wiederhold BK. Virtual reality and interactive simulation for pain distraction. Pain Med.2007;8:182-8
World Federation of Hemophilia. Report of the Annual Global Survey. 2018. http://www1.wfh.org/publications/files/pdf-1731.pdf. Accessed 27 July 2021
World Federation of Hemophilia. WFH Guidelines for the Management of Hemophilia, 3rd edition. https://onlinelibrary.wiley.com/doi/10.1111/hae.14046. Accessed 27 July 2021

GUIDANCES

- Adjustment for baseline covariates in clinical trials (2015)
- Missing Data in Confirmatory Clinical Trials (2011)
- Multiplicity issues in clinical trials (2002)
- Guideline on the investigation of subgroups in confirmatory clinical trials (2019)
- Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biologics with Continuous Outcomes - Guidance for Industry (2019)
- Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products - Guidance for Industry (2023)
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and Food and Drug Administration Staff (2017)