Clinical Study Protocol

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 3.0, 28 February 2023

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INTERVENTIONAL STUDY WITH MINIMAL RISKS AND CONSTRAINTS

PROTOCOL TAK-660-4013

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 Short Title: **DoL-x Poc**

Protocol Version and Date TAK-660-4013, Version 3.0, 28 February 2023

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Medicinal Product: Not applicable

Product Reference: Not applicable

Sponsor
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Country of Study: France

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PROTOCOL SIGNATURE PAGE – TAKEDA STUDY LEAD

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[redacted] [redacted] Rare Diseases Takeda, France	04-mars-2023 [redacted]

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

Investigator Acknowledgement

I have read this protocol for Takeda Study (protocol number: TAK-660-4013).

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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, Good Clinical Practice and with the applicable regulatory requirements, including the reference method MR-001.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: **Dr.** [redacted]

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France

Signature: _____ **Date:** 03-mars-2023

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STUDY SYNOPSIS

FOR INTERVENTIONAL STUDY WITH MINIMAL RISKS AND CONSTRAINTS

Protocol Number, Version and Date:

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

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 Short Title: DoL-x Poc

Duration of Study (planned):

- Test phase of the study (to validate the proper functioning of the hardware and software solution, and its appropriation by patients and caregivers): 6 months
- Clinical study itself: 7 months (inclusions: 6 months; patient follow-up: 4 weeks)

Background and Rationale

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.

Research Question

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.

Objectives

Primary objective

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

Secondary objectives

- 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

Exploratory objective

To describe the evolution of drug therapies used by patients for pain and anxiety, under the virtual-reality based solution

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:

- A mobile phone application including explanation on the different steps to be followed to perform 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
    - Simulation of infusions themselves (before infusion)
    - 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 be in charge of the infusions when not performed by the healthcare professional (patient or family).

Before the clinical study itself, a test phase will be 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 will be 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).

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 at 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).

Study Population (clinical study)

Haemophilia patients over the age of 6 years, receiving prophylactic Factor VIII or Factor IX infusions, included by 6 French haemophilia treatment centres (Lyon Reference Centre; Clermont Ferrand, Bordeaux, Toulouse, Nantes, and Strasbourg)

Two groups of patients will be defined according to their autonomy with Factor VIII or Factor IX infusions according to physician opinion

- Autonomy acquired or in the process of being acquired
- Non-autonomy

Patient Inclusion / Exclusion Criteria (clinical study)

Inclusion criteria

- Male patient over the age of 6 years, with diagnosed Congenital Haemophilia A or B, whatever the severity is
- Patient under long-term prophylaxis with intravenous Factor VIII or Factor IX infusions
- Patient (or the legal guardians if patient age <18 years) able and willing to give written informed consent and to comply with the requirements of the study protocol
- Patient affiliated to the national social security or beneficiary to such insurance.

Exclusion criteria

- Patient with known or suspected hypersensitivity to virtual-reality based tools
- Patient with central venous line for the administration of Factor VIII or Factor IX
- Patient (and the legal guardians if patient age <18 years) with history of unreliability or non-cooperation (including for completion of self-reported questionnaires)
- Patient (and the legal guardians if patient age <18 years) with insufficient comprehension of French language
- Patient participating in another clinical trial
- Patient deprived of his liberty by judicial or administrative order

NB: patients with haemophilia A having participated in the test phase of the study could be included in the clinical study itself after a 4-month period with no use of the virtual-reality based solution.

Data Sources / Data Collection

Visit data when available as documented in patients' records will be entered by investigators in the eCRF (patient and disease characteristics, drugs taken for pain and anxiety).

Data related to treatment burden over time and satisfaction with the virtual-reality based solution will be entered by patients and/or relatives

- On paper questionnaires at the inclusion and Week 4 visits
- On a specific module of the virtual-reality based solution at the time of each Factor VIII or Factor IX infusion between the inclusion and Week 4 visits.

Variables (Exposures, Outcomes and/or Endpoints)

Related to Primary objective

Before 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
- 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

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.

Related to secondary objectives:

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
- 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

Related to exploratory objective

Drug therapies used by patients for pain and anxiety at inclusion and end of follow-up

Sample size:

Test phase of the study

A total of 8 patients (2 patients in each of the 4 following subgroups: autonomous children, autonomous adults, non-autonomous children, and non-autonomous adults) are required to test the hardware and software solution.

Study part two (clinical study itself)

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 considered to be a medium effect size. Power is set at 80% and the significance level at 5% two-sided. As an example, the study has a 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 (i.e.,50% of the total population for each subgroup) and the same hypotheses, the effect size is expected to increase from 0.5 to 0.7.

Data Analysis

Means absolute variation before and after the virtual-reality based solution will be described using an analysis of covariance adjusted on baseline value and group (acquired autonomy or without autonomy). This model will estimate the LSMeans with the associated two-sided 95% confidence interval and p value. 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.

The percentage of responder patients for each scale (pain, anxiety, depression, quality of life, adherence to treatment, satisfaction, willingness to continue and preference) will be presented with the associated 95% two-sided exact confidence interval.

Patient and disease characteristics will be described at inclusion: 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 infusions [age at first infusion, inhibitors' history, immune tolerance (yes/no, success or failure), current number of weekly

infusions], daily use of analgesics and/or NSAIDs for at least 3 months, socio-professional activity and education level of patients (or parents).

Study Limitations and Potential Sources of Bias

For this proof-of-concept study, no representativeness of the studied population is required. After the test phase conducted in 8 patients, only a limited number of 34 eligible patients will be included (17 patients with acquired autonomy and 17 patients without autonomy). No handling for multiplicity is considered for the analysis of the different endpoints.

However,

- The 6 participating centres, fully involved in the management of haemophilia patients and prophylactic Factor VIII or Factor IX infusions, will be in different French areas (Lyon Reference Centre; Clermont Ferrand, Bordeaux, Toulouse, Nantes, and Strasbourg)
- Physicians will be asked to include consecutive eligible patients from the study implementation.

Safety Monitoring

Potential adverse events related to the virtual-reality based solution are, for example, nausea, headaches, or visual disturbances.

Adverse events/ incidents will be collected and securely reported according to the usual reporting process provided by current regulations:

- To be reported to Takeda France Pharmacovigilance:
  - Adverse effects that may be related to the infusions of Factor VIII or Factor IX (whatever the drug is)
  - Adverse effects that may be related to the VR-based solution
  - All serious adverse events (related or not related to the infusions of Factor VIII or Factor IX, or VR-based solution)
- To be reported to Deepsen:
  - Incidents that may be related to the mobile phone application or 3D mask device incidents

Consent, Protection, and Ethics

Before inclusion in each study step, patients (and/or the legal guardians) will be informed about the content of the study, and sign a written informed consent provided by investigators. Several Consent Forms are defined according to the age classes of patients, for each phase of the study: 6-18 et ≥18 years for the test phase; 6-12, 12-18 et ≥18 years for the clinical study itself.

Only identifying numbers of the patient and the virtual-reality based solution provided will appear on eCRF and self-reported questionnaires. Physicians will keep a list of codes to identify patients and their medical files. This list will never be conveyed to the sponsor.

Indirect personal data on patients collected on the virtual-reality based solution during the study will be securely transferred to the CRO mandated by the Sponsor (daily automated transfer).

According to French relevant regulations, the sponsor will submit the study protocol and any accompanying material to be provided to the subject / legal guardians (such as patient written informed consent) to an independent Medical Ethics Committee which will be randomly assigned. According to French regulation, this study is interventional research at minimal risks which contains only minimal risks and constraints. This category was formerly called “common care research”.

No data will be conveyed outside the European Union.

Data Management

An electronic data capture (EDC) system will be used for the study:

- eCRF to collect data from investigators
- ePRO developed as a specific module of the virtual-reality based solution to collect subject’s data between the inclusion and Week 4 visits.

At inclusion and Week 4 visits, paper self-reported questionnaires will be completed by patients and/or relatives.

To ensure confidentiality and security of the data, personal logins and passwords will be used. This process allows the restriction of system access to authorized personnel only. The list of authorized personnel will be documented. The system will ensure a traceability of any data modified, the date of modification, the reason for modification and identification of the corresponding user via the audit-trail. Each confirmation or correction of data must be performed by authorized site staff on the eCRF with the reason of correction.

After completion and cleaning process of data and before database lock, each eCRF will be signed by the investigator using electronic signature function available on the eCRF (entering login and password). This action will ensure that the investigator confirm the accuracy, completeness, legibility of the data collected on the eCRF.

To ensure confidentiality and security of the data, personal logins will be used by patients on the virtual-reality based solution. Collection of patient indirect personal data between the inclusion and Week 4 visits will be transferred (encrypted cvs file) by Deepsen to the CRO in charge of biometry at the end of the study

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data handling plan/ data management plan together with a description of the personnel responsible for data entry.

AMENDMENTS AND UPDATES

Summary of Changes from Previous Version

Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **28 February 2023**	**Section of Study Protocol**
Description of Changes		**Section(s) Affected by Change**
Considering the increasing proportion of haemophilia patients currently treated with subcutaneous injections of emicizumab, the following changes are implemented to allow reaching the number of included patients requested in the clinical study itself		
- inclusion of patients with haemophilia B (treated with infusions of Factor IX)		Study title (Title page and Protocol Signature page) Sections 2.3, 3.2.1, 4.1, 4.2.3.1, 4.3.2, 4.4.2, 4.6, 4.7, and 7.1.1
- Inclusion of patients having participated in the test phase of the study (after a 4-month-period minimum with no use of the virtual-reality based solution)		Sections 4.1 and 4.7
- New investigator centres		Sections 4.2.2 and 4.7
Since responses to the anxiety and pain VAS completed by patients between the inclusion and Week4 visits will be collected at the end of follow-up (when patients will return the mask to the centre at Week4), the inclusion criterion related to the need for patient web connexion is deleted		Sections 4.2.3.1
Considering the increased duration of the test phase of the study already performed in the coordinator centre (from 4 to 6 months), the study duration is updated		Section 4.1
On the basis of the recommendations of the author of the MMAS-4 (to describe the adherence to the VR-based solution and infusions of coagulation factors), this endpoint is amended		Section 4.4.2

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ADDITIONAL DOCUMENTS

- Detailed description of the VR-based solution
- Simplified user guide regarding the VR-based solution (to be provided to patients at inclusion)
- Instructions regarding the most current problems potentially encountered when using the VR-based solution (to be provided to patients at inclusion)

1 ABBREVIATIONS

3D	Three-dimensional
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
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

STAI-Y	State-Trait Anxiety Inventory
VAS	Visual analogue scale
VR	Virtual reality

2 BACKGROUND AND RATIONALE

2.1 Epidemiology and Natural History of Haemophilia

Haemophilia is a rare X-linked bleeding recessive disorder caused by a deficiency of coagulation Factor VIII (in haemophilia A) or Factor IX (in haemophilia B). It is commonly observed in males, but may be rarely seen in females as a consequence of homozygosity, double heterozygous mutation or unbalanced lyonization (Manucci 2001). On the basis of clotting factor concentrations, the disease can be severe (factor deficiency <1%), moderate (1-5%), or mild (between 6% and 40%) (PNDS Hémophilie 2019). Patients with severe haemophilia represent approximately half of the diagnosed cases (Srivastava 2015).

Based on recent data, the prevalence of haemophilia appears to be higher than previously estimated (Stonebraker 2020). A recent study showed that the expected number of patients with haemophilia worldwide is 1 125 000, of whom 418 000 should have severe disease (Iorio 2019). Haemophilia A accounts for 80-85% of all haemophilia cases (World Federation of Hemophilia 2018). The prevalence of haemophilia A (per 100 000 males) is 17.1 cases for all severities of the disease, and 6.0 cases for severe haemophilia A. In addition, incidence at birth (per 100 000 males) is 24.6 cases for all severities of haemophilia A, and 9.5 cases for severe haemophilia A. In France, a total or approximately 7 000 haemophilia patients are estimated (World Federation of Hemophilia 2018).

Depending on the level of coagulation factor activity, patients with haemophilia may present with easy bruising, inadequate clotting of traumatic or even mild injury, or, in the case of severe haemophilia, spontaneous haemorrhage (PNDS Hémophilie 2019). The frequency of bleeding depends on the site: joints (70-80%), muscle (10-20%), other sites (major bleeds; 5-10%), and central nervous system (< 5%) (Srivastava 2015). Severe and/or repeated bleeds may lead to chronic synovitis, resulting in chronic, painful, arthropathy and disability.

Diagnosis of haemophilia is commonly made in the case of bleeding symptoms or family history in patients with severe disease, and frequently on the basis of haemostasis tests for patients with a mild or moderate form of haemophilia (Réseau FranceCoag 2005, PNDS Hémophilie 2019).

2.2 Prophylaxis with Anti-Haemophilic Factors

The standard of care, which is to offer primary prophylactic infusions with anti-haemophilic factors to patients with severe haemophilia, has led to dramatic increase in the quality of life for these patients (Coppola 2010). Regular infusion of factor concentrates (primary prophylaxis) significantly contributed to prevent bleeding and subsequent joint damage.

Current recommendations promote early treatment of children with haemophilia (Manco-Johnson 2007, Fisher 2016, Feldman 2018, Manco-Johnson 2018). Primary prophylaxis should start before the age of 3 and even before reports of joint bleeds, secondary prophylaxis included all other situations (World Federation of Hemophilia 2020).

In France, since the recommendations of the CoMETH (Coordination médicale pour l'étude et le traitement des maladies hémorragiques constitutionnelles), progressively intensive prophylaxis is favoured, according to the Canadian model (Meunier 2009). This regimen aims to increase adherence to treatment by children and parents, initially and for long-time, and to limit venous access problems (Feldman 2006, Meunier 2009).

Primary long-term prophylaxis consists of starting - at the latest at the 2nd hemarthrosis (whether spontaneous or post-traumatic) or before the age of 3 years - intravenous preventive therapy with anti-haemophilic factor in severe or moderate haemophilia patients meeting these criteria. Implementation of secondary prophylaxis (after more than 2 hemarthroses or beyond 3 years) or tertiary (after arthropathy occurrence) (Manco-Johnson 2007) concerns all persons with severe haemophilia who did not receive primary prophylaxis.

Long-term prophylaxis therapy of haemophilia required several infusions of anti-haemophilic factor per week that may lead to a real treatment burden for patients (pain, anxiety, decrease in quality of life…) and relatives. Despite the medical advantages of such a continuous therapy, this treatment burden could lead to treatment avoidance and poor adherence and then contribute to poor medical outcomes.

2.3 Study Rationale

Virtual reality (VR) technology enables people to become immersed in a computer-simulated, three-dimensional (3D) environment. The potential use of VR in the medical field has recently been explored.

Based on pain-rating (visual analogue or graphic scales), VR distraction was notably shown to be effective for reducing pain during medical procedures (Hoffman 2001, Malloy 2010, Hoffman 2011, Arane 2017, Le Du 2021). It was also shown that immersive VR reduced pain ratings and pain-related brain activity assessed by functional magnetic resonance imaging (Hoffman 2011).

Overall, VR's immersive, entertaining effects are useful for redirecting the patient's attention away from painful treatment experiences and reducing anxiety, discomfort, or unpleasantness (Wiederhold 2007, Dascal 2017).

If distraction is a common non-pharmacologic technique used by health care professionals to manage and attenuate anxiety, and possibly pain, during painful procedures in paediatric patients (Koller 2012), VR might offer even more distraction, as it completely immerses the patient in another world and involves multiple senses (Malloy 2010). A recent interventional study showed that a VR environment could be developed and safely used during paediatric haemophilia care for distraction during IV interventions, with the potential to improve patient experience during medical procedures (Dun 2019).

In this context, it is of interest to explore the concrete interest and potential of a VR-based solution specifically developed and adapted to haemophilia patients. To answer to this question, a proof-of-concept (POC) study appears to be the best design (see some examples of POC

studies provided by the National Institute of Health Research, https://www.nihr.ac.uk/documents/proof-of-concept/19909).

Deepsen, a French company specialized in e-health solutions to reduce pain, has developed a medical device CE marked, VR-based solution specifically adapted to haemophilia patients receiving frequent anti-haemophilic factor infusions.

This VR-based solution comprises:

- A mobile phone application including explanation on the different steps to be followed to perform infusions in satisfactory conditions, notably as regards safety, as well as VAS for pain and anxiety to be completed at each Factor VIII or Factor IX infusion between inclusion and the Week 4 visit
- A 3D mask (to be used before or during infusions) including
    - Simulation of the infusions themselves (before infusion)
    - A relaxing and distracting content (during and after infusions).

More details on this VR-based solution are provided in section 10.1 and in additional documents.

Takeda is fully involved in the prophylactic treatment of haemophilia, notably through providing a recombinant Factor VIII (Advate®, octocog alfa) or Factor IX (Rixubis®, nonacog gamma).

In this context, Takeda proposes to conduct a proof-of-concept study designed to assess the ability of this VR-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. Patients with haemophilia A or B will be enrolled.

3 RESEARCH QUESTION AND OBJECTIVES

3.1 Research Question

Haemophilia patients with long-term prophylaxis therapy experience a real burden related to repetitive intravenous perfusions which could lead to treatment avoidance and poor adherence and then contribute to poor medical outcomes.

In this context, this proof-of-concept 4-week study mainly aim to assess the impact of a specific VR-based solution to be used in infusions 'environment on the different aspects of the treatment burden (pain, anxiety, depression, quality of life). Adherence and satisfaction to the VR-based solution will be also assessed, and the evolution of drug therapies used by patients for pain and anxiety. Adverse events (AEs) related to the VR-based solution will be collected.

3.2 Objectives

3.2.1 Primary objective

- 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

3.2.2 Secondary objectives

- 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

3.2.3 Exploratory objective

- To describe the evolution of drug therapies used by patients for pain and anxiety, under the virtual-reality based solution.

4 RESEARCH METHODS

4.1 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 VR-based solution, as well as for patient relatives and health care professionals.

The VR-based solution to be studied is a medical device CE marked (class I) and specifically developed by Deepsen, a French company specialized in e-health solutions to reduce pain. It includes both a mobile phone application (for explanation on infusions) and a 3D mask to be used during infusions.

Whatever the step of the study is, nurses and investigators will be specifically trained to the VR-based solution at the time of study implementation, during an on-site visit. In addition, enrolled patients will be trained by the nurses at inclusion, and a specific user guide will be provided to them.

The content of the different parts of the studied solution is adapted to the person who will be in charge of the infusions when not performed by the healthcare professional (patient or family). More details on this VR-based solution are provided in section 10.1.

This study will be conducted in two successive steps:

- A preliminary test phase will be 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 will be conducted at the National Reference Centre for Haemophilia and other rare inherited bleeding disorders (Lyon) 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)

- The 4-week clinical study itself will be conducted as follows for eligible patients:

    - At the inclusion visit, the Factor VIII or Factor IX infusion will be firstly performed at hospital as usual, with no use of the VR-based solution. After collection of baseline data collected from investigators, patients and relatives, patients (and/or relatives) will be trained with the VR-based solution by the

nurses or investigators of the centre. All patients with planned infusions at home will receive a dedicated VR-based solution with the application installed.

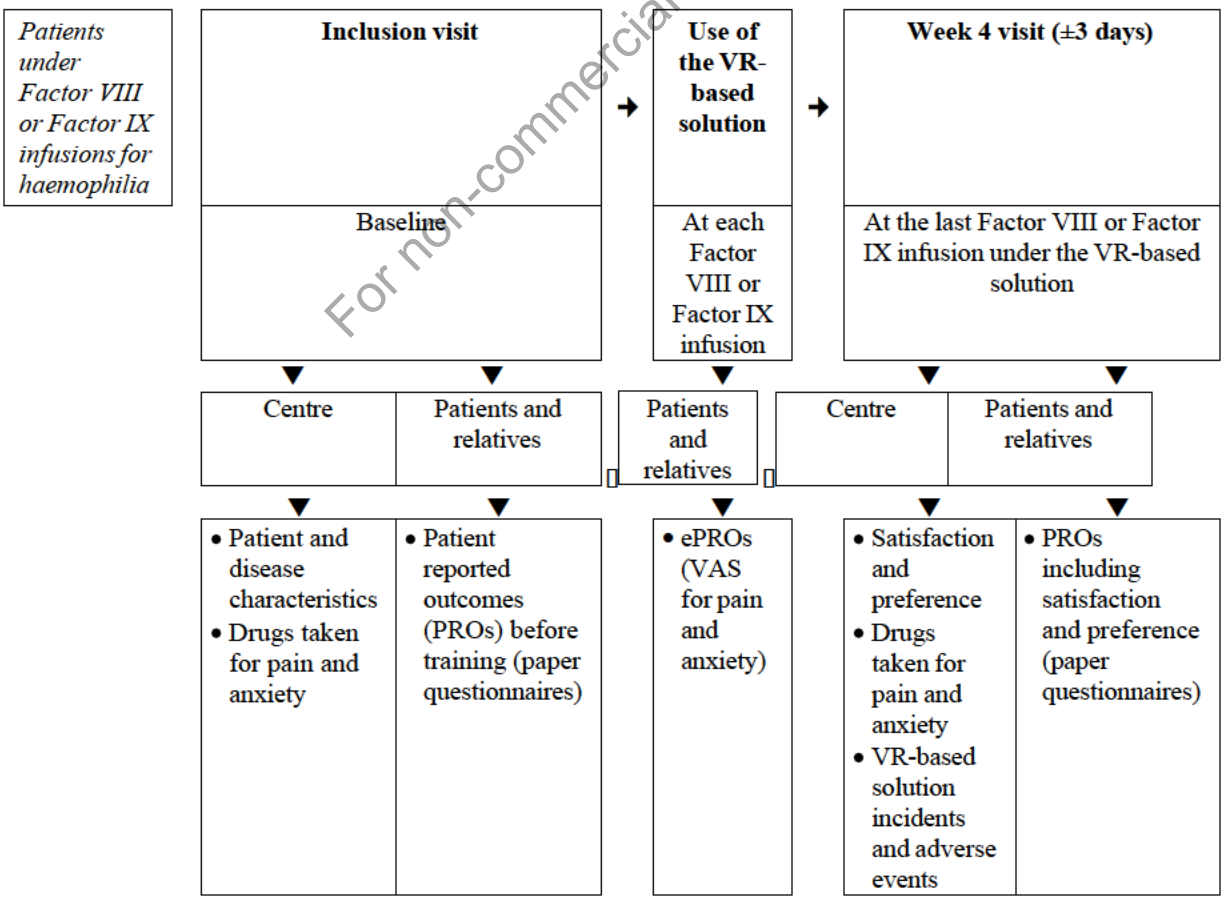
- At the time of each following infusion using the VR-based solution provided by the centre (at home with or without the help of a nurse, or at hospital), patients and relatives will be asked to fulfil self-reported questionnaires
- At the final visit at hospital (4 weeks after inclusion, at the time of the last infusion during follow-up, using the VR-based solution), data will be collected from caregivers, patients and relatives.

The duration of the test phase of the study will be limited to a single visit for each participant patient.

The duration of the clinical study will be 4 weeks for each patient enrolled. Considering the mean number of weekly Factor VIII or Factor IX infusions performed per Haemophilia patients, approximately 12 documented infusions are expected for each patient during follow-up.

A study design flow chart is presented in Figure 1 for the clinical study itself.

Figure 1: Study Design Flow Chart



Data to be collected at each study time-point are detailed in section 0.

Study duration

The total length of the study, from screening of the first patient for the test phase of the study to the end of the clinical study itself, is expected to be approximately 15 months:

- Test phase of the study (to validate the proper functioning of the hardware and software solution, and its appropriation by patients and caregivers): 6 months
- Clinical study itself: 7 months (inclusions: 6 months; follow-up: 4 weeks)

Reference method

The VR-based solution to be studied could lead clinicians to change the current management of haemophilia patients (e.g.: potential decrease in analgesics or anxiolytics). This study is therefore qualified as an interventional study with minimal risks and constraints as the intervention performed on the subjects are listed in the decree of April 12th, 2018; NOR: SSAP1810239A (JORF No 0089, dated on 2018, April 17).

In addition, this study is in accordance with the reference MR-001 method.

4.2 Study Setting and Study Population

4.2.1 Number and Type of Participants

For this French proof-of-concept study, no sampling method will be applied.

4.2.2 Sites, Regions and Countries

This study will be conducted in France in the following haemophilia treatment centres:

- For the test phase of the study, aiming to validate the proper functioning of the hardware and software solution, and its appropriation by patients and caregivers, patients will be enrolled by the National Reference Centre for Haemophilia and other rare inherited bleeding disorders (Lyon)
- For the clinical study itself, six haemophilia treatment centres will be involved (Lyon Reference Centre, Clermont Ferrand, Bordeaux, Toulouse, Nantes, and Strasbourg).

Details on participating centres are provided in Section 0.

4.2.3 Participant Selection Criteria

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), patients enrolled in the test-phase should have similar characteristics than those included in the second phase.

For the test phase of the study, different patient profiles are required in order to fully validate the proper functioning of the hardware and software solution, and its appropriation by patients and caregivers. Consequently, these 8 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, non-autonomous adults).

For the clinical study itself, investigators will be asked to include patients in rank order from the study implementation. In addition, two groups of patients will be defined according to their autonomy with Factor VIII or Factor IX infusions according to physician opinion: autonomy acquired or in the process of being acquired; non-autonomy. In each participant centre, investigators will be asked to include half of their patients in each group, in a consecutive way.

Whatever the step of the study is, only patients over the age of 6 years will be eligible as they are able to understand and fulfil (with parents' aid if useful) the scales to be used to assess their treatment burden over the study period.

Inclusion and exclusion criteria are detailed below.

4.2.3.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

- Male patient over the age of 6 years, with diagnosed Congenital Haemophilia A or B, whatever the severity is
- Patient under long-term prophylaxis with intravenous Factor VIII or Factor IX infusions
- Patient (or the legal guardians if patient age <18 years) able and willing to give written informed consent and to comply with the requirements of the study protocol
- Patient affiliated to the national social security or beneficiary to such insurance

4.2.3.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met:

- Patient with known or suspected hypersensitivity to virtual-reality based tools

- Patient with central venous line for the administration of Factor VIII or Factor IX
- Patient (and the legal guardians if patient age <18 years) with history of unreliability or non-cooperation (including for completion of self-reported questionnaires)
- Patient (and the legal guardians if patient age <18 years) with insufficient comprehension of French language
- Patient participating in another clinical trial
- Patient deprived of his liberty by judicial or administrative order.

NB: patients with haemophilia A having participated in the test phase of the study could be included in the clinical study itself after a period of 4 months minimum with no use of the virtual-reality based solution.

4.2.4 Discontinuation of Participants

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.3 Data Source/Data Collection

Before any study procedures, subjects have to be informed about the study objectives and content, how their data will be processed, and they should consent in written to take part in the test phase or in the clinical study itself.

No directly identifiable patient data will be collected in the CRF completed by investigators and the VR-based solution completed by patients (anxiety and pain VAS).

4.3.1 Test Phase

At the end of the single visit conducted at the Lyon centre (National Reference Centre for Bleeding disorders), patients (or relatives) will complete a paper qualitative questionnaire on learning agility, understanding of modules and objectives, and actions to be taken if technical problems. The eight completed questionnaires will be sent to Deepsen in order to perform adaptations if required.

In addition, in the event of adverse events related to the infusions of Factor VIII or VR-based solution, or incidents related to the medical device, they are to be reported to the Sponsor or Deepsen respectively, as specified in section 7.

4.3.2 Clinical Study

Data will be collected by investigators (or nurses involved in the study) at the inclusion and Week 4 visits, on the basis of patient medical files.

Patient reported outcomes will be collected by patients (and/or relatives) on self-reported questionnaires at the time of each Factor VIII or Factor IX infusion (at the inclusion visit with no use of the VR-based solution and at each of the following infusions with the use of the VR-based solution).

Data to be collected during the 4-week clinical study are detailed in the following table.

Table 1. Data Collection Schedule

	Enrolment Visit	At each Factor VIII or Factor IX infusion	Week 4 visit (or premature study withdrawal)
Data to be collected by investigators			
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Patient and disease characteristics[1]	X		
Drugs taken by patients for pain and anxiety[2]	X		X
Incidents with the VR-based solution, adverse events related to the infusions of Factor VIII or Factor IX, and VR-based solution, serious adverse events	←	———	→
Reasons for premature study withdrawal[3]			X
Data to be collected by patients			
VAS for pain and anxiety[4]	X	X	X
Adherence to Factor VIII or Factor IX infusions (MMAS-4)[5]	X		X
Adherence to VR-based solution (MMAS-4)[5]			X
Data to be collected by patients and relatives			
Quality of life, using the EQ- 5D- 3L (or EQ-5D- Y for youth)	X		X
Anxiety, using the STAI-Y	X		X
Depression, using the PHQ-9	X		X
Data to be collected by patients, relatives, and investigators or nurses			
Global Impression of Change (GIC)			X
Satisfaction and preference with the VR-based solution			X

1. Type of haemophilia (A or B), 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 infusions [age at first infusion, inhibitors' history, immune tolerance (yes/no, success or failure), current number of weekly infusions, place of Factor VIII or Factor IX infusion (at hospital, at home, at both places), autonomy with Factor VIII or Factor IX infusions (autonomy acquired or in the process of being acquired, non-autonomy, person in charge of infusions if non autonomy)], socio-professional activity and education level of patients (or parents).

2. Daily use of analgesics / NSAIDs and anxiolytics for at least 3 months (inclusion visit) and over the last week (Week 4 visit); drugs taken at the infusion of Factor VIII or Factor IX (at inclusion and Week 4 visits)
3. Patient no longer wants to participate in the study, moved home/changed medical team, patient's death, other
4. Pain VAS completed after each infusion of Factor VIII or Factor IX; Anxiety VAS completed before and after each infusion (without the VR-based solution at inclusion and using the VR-based solution for the following infusions)
5. Relatives will be asked to assess adherence to Factor VIII or Factor IX infusions and VR-based solution for non-autonomous patients

4.3.3 Data Collection Procedures

See above for data to be collected at each study visit (inclusion and Week 4) and by patients and/or relatives at each infusion of Factor VIII or Factor IX in the meantime (section 4.3).

4.3.4 Data Collection Instrument

Data collection by investigators (or nurses involved in the study) will be performed using a dedicated electronic case report form (eCRF).

Data collection by patients and relatives will be performed using:

- Paper self-reported questionnaires at the inclusion and Week 4 visits
- Dedicated electronic self-reported questionnaires (ePRO) at each factor VIII or Factor IX injection between inclusion and Week 4. These VAS for pain and anxiety will be implemented into the VR-based solution provided to patients at the inclusion visit.

4.4 Variables (Exposures, Outcomes and/or Endpoints and Other Study Variables)

4.4.1 Exposures

Not Applicable – No study treatment in this study.

4.4.2 Endpoints

4.4.2.1 Endpoints Related to Primary Objective

- **Before each Factor VIII or Factor IX infusion**
    - Anxiety (patients and relatives) using an Anxiety VAS (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
  - Anxiety (patients and relatives) using an Anxiety VAS (A-VAS).
    - Absolute and relative variation
    - Decrease of 2 points out of 10 in the A-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**
  - Adherence to virtual-reality based solution at the end of follow-up using MMAS-4
    - Score ~~at 3 or 4~~ in classes (0-1: low adherence; 2-3: medium adherence; 4: high adherence)
  - Patients' Global Impression of Change (PGIC) Scale at the end of follow-up (patients, relatives and caregivers)
    - Value at 3 or more

4.4.2.2 Endpoints Related to the Secondary Objectives

- **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
  - Incidents with the VR-based solution, adverse events related to the infusions of Factor VIII or Factor IX, or VR-based solution, serious adverse events

4.4.2.3 Endpoints Related to the Exploratory Objective

Drug therapies used by patients for pain and anxiety at inclusion and end of follow-up.

4.4.3 Other Study Variables

Not applicable

4.5 Sample Size

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 considered to be a medium effect size. Power is set at 80% and the significance level at 5% two-sided.

As an example, the study has a 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.

4.6 Data Analysis

The statistical considerations and analysis plan are summarized below. A more detailed description of analyses will be provided in a Statistical Analysis Plan (SAP) that will be 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 the SAP using SAS® release 9.4 or higher. All computer programs and macros will be developed and validated according to eXYSTAT standard operating procedures. 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 be also 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 be also presented.

No interim analysis is planned for this study.

All the analyses will be presented in 3 columns according to subgroups: autonomy, without autonomy, and total.

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

The risk 1 error (α) will be set to 5% (two-sided).

Study populations

Included set (IS)

The full analysis set will include all included patients with or without assessment at the 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 of the week 4 visit is available.

Number and percentage of patients included in the FAS will be described with the reason for non-inclusion in the FAS. Number and percentage of patients prematurely discontinued with the reason for premature discontinuation will be also provided.

Patient and disease characteristics

Patient and disease characteristics will be described at inclusion overall and per subgroup 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).

Drug therapies used by patients for pain and anxiety

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 anxiety
- For each indication, number, and percentage of patients with at least one drug therapy for pain and anxiety
- Drug therapy for pain and anxiety will also be tabulated by the 4th level of the Anatomic Therapeutic Class (ATC4) and Preferred-Term (PT)

Study analysis

All analyses will be performed in the FAS population.

Quantitative paired variables will be compared to assess the change from baseline significance using the Wilcoxon signed rank test. Changes will be associated with their exact 95% two sided Clopper-Person confidence interval.

Then means absolute variation before and after the virtual-reality based solution will be described using an analysis of covariance adjusted on baseline value and group (acquired

autonomy or without autonomy). This model will estimate the LSMeans with the associated two-sided 95% confidence interval and p value.

The percentage of responder patients for each scale (pain, anxiety, depression, quality of life, adherence to treatment, satisfaction, willingness to continue and preference) will be presented with the associated 95% two-sided exact confidence interval.

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.

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. 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.

4.7 Limitations of the Research Methods

For this proof-of-concept study, no representativeness of the studied population is required. After the test phase conducted in 8 patients, only a limited number of 34 eligible patients will be included (17 patients with acquired autonomy and 17 patients without autonomy). No handling for multiplicity is considered for the analysis of the different endpoints.

However,

- The six participating centres, fully involved in the management of haemophilia patients and prophylactic Factor VIII or Factor IX infusions, will be located in different French areas (Lyon Reference Centre; Clermont Ferrand, Bordeaux, Toulouse, Nantes, and Strasbourg)

- Physicians will be asked to include consecutive eligible patients from the study implementation.

Patients with haemophilia having participated in the test phase of the study in the coordinator centre will be solicited to participate in the clinical study itself. To limit the bias related to their prior exposure to the VR-based solution during a single visit, a period of at least four months will be requested between the two phases of the study, with no use of the VR-based solution.

5 PROTECTION OF HUMAN SUBJECTS

5.1 Sponsor's Responsibilities

5.1.1 Compliance with Relevant Guidelines

The study will be conducted in full conformance with all relevant French, European and international regulations applicable to interventional researches including the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice.

The VR-based solution to be studied is a class I medical device and it is compliant with the Regulation (EU) 2017/745 applicable since 26 May 2021.

This VR-based solution could lead clinicians to changes in the current management of haemophilia patients (e.g.: potential decrease in analgesics or anxiolytics). In addition, the last study visit at Week 4 is required to assess the overall evolution of treatment burden, including for the hospital team. This study is therefore 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).

The sponsor will ensure that local regulatory authority requirements are met before the start of the study.

5.1.2 Insurance

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study.

5.1.3 Study Suspension, Termination and Completion

The sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to investigator(s)/sites(s), regulatory agencies, Ministries of Health (if required) and Institutional Review Boards/Ethics Committees (IRBs/ECs) in writing as applicable. Conversely, should the investigator/site decide to withdraw from execution of the study, they will communicate their intention immediately in writing to the sponsor. Additionally, the discontinuation of a registered study which has been posted to a designated public website will be updated accordingly.

5.2 Investigator's Responsibility

5.2.1 Compliance with Relevant Guidelines

The investigator must undertake to perform the study in accordance with applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licences and certifications necessary to demonstrate such qualification. Curriculum vitae for these individuals as well as the investigator are provided to the study sponsor (or designee) before starting the study.

5.2.2 Protocol Adherence and Investigator Agreement

The investigator must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those participants who have met protocol eligibility criteria. The investigator is required to sign the protocol signature page to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at the site, the investigator will promptly inform the sponsor and the IRBs/ECs and provide them with a detailed written explanation. Upon study completion, the sponsor will provide the investigator, IRB/EC, and Regulatory Agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable contract research organization (CRO), investigator, or for multicentre studies, the coordinating investigator according to national provisions, and will be documented in the investigator agreement.

5.2.3 Documentation and Retention of Records

5.2.3.1 Case Report Forms

eCRFs are to be completed through use of a Sponsor-designated EDC system. Centres will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format (PDF/A) that must be kept with the study records.

5.2.3.2 Recording, Access, and Retention of Sources of Data and Study Documents

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records.

Records and documents pertaining to the conduct of this study including eCRFs, electronic PRO data, Informed Consent Form, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last publication of the study results or until the signature of the final study report. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location, according to national regulations.

5.2.3.3 Audit/Inspection

Site visits may be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

5.3 Ethical Considerations

5.3.1 Informed Consent

The Sponsor's sample Informed Consent Form will be provided to each centre.

The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason.

The Consent Form must be signed and dated by the patient (or his legal guardians if <18 years) before his/her participation in the study. Consent Forms are adapted according to the age of patients:

- For the test phase, two Consent Form are available: for children between 6 and 18 years, and for adults (≥18 years)
- For the clinical study itself, three Consent Forms are available: for children between 6 and 12 years, for children between 12 and 18 years, and for adults (≥18 years).

The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Form should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Form must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Form for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient his legal guardians if <18 years. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

5.3.2 Institutional Review Board or Ethics Committee

This protocol, the Informed Consent Form, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Sponsor and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC. Approval by the IRB/EC will be provided to the ANSM with the study synopsis.

The Sponsor is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. The Sponsor is also responsible for promptly informing the IRB/EC of any protocol amendments.

5.3.3 Privacy and Confidentiality

The privacy rights of individuals and the confidentiality of medical records will be protected in accordance with all applicable laws, regulations and guidelines.

Sites and laboratories or entities providing support for this study, which process personal data relating to EU-based subjects, must comply with the EU General Data Protection Regulation and with the French law called "Loi Informatique et Libertés" in performing all their processing activities in connection with this study.

After subjects have been informed about how their data will be processed and have consented in written to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations and guidelines to maintain the confidentiality of subjects' identities.

No directly identifiable patient data will be collected in the CRF completed by investigators and the VR-based solution (VAS for pain an anxiety completed by patients or relatives). Subjects are assigned a unique identifying number and the number of the virtual-reality based solution provided to patients at the inclusion visit. However, their year of birth will also be collected. Investigators will keep a list of codes to identify enrolled patients and their medical files. This list will never be conveyed to the Sponsor.

The results of studies – containing subjects' unique identifying numbers, relevant medical records and year of birth – will be recorded.

The sponsor may transfer data collected in this study to its affiliates, collaborators, licensees and other companies and organizations working with or for the sponsor in connection with these purposes. No data will be conveyed outside the European Union.

6 DATA MANAGEMENT AND QUALITY CONTROL

6.1 Data Management

Data management of this study will be performed by the contract research organization (CRO) eXYSTAT, under the supervision of the Sponsor. Data management notably includes quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Centres will be responsible for data entry into the EDC system. In the event of discrepant data, eXYSTAT will request data clarification from the centres, which the centres will resolve electronically in the EDC system.

In addition, an ePRO will be developed as a specific module of the VR-based solution to collect subject's data. At the end of the data collection, patient data on the virtual-reality based solution during the study will be transferred (encrypted cvs file) by Deepsen to the CRO in charge of biometry.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data management plan/data validation plan together with a description of the personnel responsible for data entry.

The Sponsor will perform oversight of the data management of this study, including approval of eXYSTAT's data management plans and specifications. Collection of patient indirect personal data between the inclusion and Week 4 visits will be transferred (encrypted cvs files) by Deepsen to the CRO in charge of biometry at the end of the study, and then from eXYSTAT to the Sponsor at the final locked version of the database. eXYSTAT standard procedures will be used to handle and process the electronic transfer of these data.

A validated, electronic database will be employed from the EDC system. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.

System backups for data and records retention for the study data will be consistent with the eXYSTAT's standard procedures. Electronic Case Report Forms (eCRF)/ Electronic Patient Reported Outcomes (e-PRO)

eCRFs are to be completed through use of the EDC system. Centres will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

ePROs are to be completed through use of the dedicated part of the VR-based solution by subjects. To ensure confidentiality and security of the data, personal logins will be used by patients on the virtual-reality based solution.

To ensure confidentiality, security of the data personal logins and passwords will be used. This process allows the restriction of system access to authorized personnel only. The list of authorized personnel for centres and study team will be documented. The system will ensure a traceability of any data modified, the date of modification, the reason for modification and identification of the corresponding user via the audit-trail. Each confirmation or correction of data must be performed by authorized site staff on the eCRF with the reason of correction.

After completion and cleaning process of data and before database lock, each eCRF will be signed by the investigator using electronic signature function available on the eCRF (entering login and password). This action will ensure that the investigator confirms the accuracy, completeness, and legibility of the data collected on the eCRF.

At the end of the study, the investigator will receive patient data for his or her site in a readable format (PDF/A) on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

6.2 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP. The MedDRA dictionary will be used for coding of AEs. Concomitant medication will be coded using the World Health Organization Drug Dictionary Anatomical Therapeutic Chemical code.

6.2.1 Deviations from the Protocol

Deviations from the protocol will be judged during the study and/or during the Data review will classify protocol deviations (major/minor) for statistical analysis.

6.2.2 Data Quality Assurance

Throughout the study, remote monitoring will be performed by eXYSTAT (regular contacts with the investigators/nurses) to ensure an ongoing quality control (adherence to the protocol, completeness, consistency, and accuracy of the data being entered on the eCRF). Remote monitoring will not include access to nominative data on patients. Investigators agree to cooperate to ensure that any problems detected in the course of these remote activities are resolved.

A study monitor may visit centres in accordance with the monitoring plan and review the CRF/eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF/eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is enrolled, it is expected that site personnel will complete the CRF/eCRF entry within approximately 3 business days of the subject's routine consultation/observation.

6.3 Database Archiving and Study Document Retention

All research documents, including all source data, and analytical data sets, all protocol versions, correspondence pertaining to the study (i.e. between sponsor, investigators, suppliers, regulators and scientific community), standard operating procedures, quality control, monitoring or audit reports, informed consent releases, copies of signed IRB/EC and other external reviewer reports, data analysis plan, computer programs, statistical outputs and study report and/or publications, shall be securely stored and archived after completion of the study. The archival material should be sufficiently detailed to permit re-editing and re-analysis.

7 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS AND VR-BASED SOLUTION INCIDENTS

7.1 Adverse Events/ Adverse Reactions

7.1.1 Adverse Events to be Collected

Only AEs related to the Factor VIII or Factor IX perfusions and to the VR-based solution, and all SAEs must be reported in this study. Consequently, non-serious AEs not related to the Factor VIII or Factor IX perfusions and to the VR-based solution will be not reported. Indeed, no drugs are to be studied in this interventional study.

The healthcare professional or patient shall be informed of the possibility to report direct to the relevant Takeda Pharmacovigilance department or national pharmacovigilance reporting system any adverse reactions not being collected as part of the study. These will be treated as spontaneous reports and independent of the study.

7.1.2 Definitions

7.1.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- a laboratory test result that meets the criteria for a serious adverse event (SAE)
- a laboratory test result that requires the subject/patient to receive specific corrective therapy
- a laboratory abnormality that leads to discontinuation of therapy
- a laboratory abnormality that the healthcare provider considers to be clinically significant.

7.1.2.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded
- in the view of the healthcare provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- any other medically important event that, in the opinion of the healthcare provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

7.1.2.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

7.1.2.4 Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labelling, or design of the product.

7.1.2.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- pregnancy: any case in which a pregnant patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure
- breastfeeding: infant exposure from breast milk
- overdose: all information of any accidental or intentional overdose
- drug abuse, misuse or medication error: all information on medicinal product abuse, misuse or medication error (potential or actual)

- suspected transmission of an infectious agent: suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product
- lack of efficacy of Takeda Product
- accidental/occupational exposure
- use outside the terms of the marketing authorization, also known as “off-label”
- use of falsified medicinal product
- use of counterfeit medicinal product
- drug–drug interactions and drug–food interactions
- inadvertent or accidental exposure with or without an AE
- unintended benefit.

A SSR should be reported even if there is no associated AE.

7.1.2.6 Relationship of an Adverse Event to Studied Drug(s)

The assessment of the relationship of an AE to the drug(s) and VR-based solution is based on the consideration of all available information about the event, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility and alternative aetiology (e.g., underlying illness, concurrent conditions, concomitant treatments).

- Related (yes): an AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), and for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also have contributed.

- Not related (no): an AE that does not follow a reasonable temporal sequence from administration of the medication, vaccine or device and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments.

7.1.3 Reporting

7.1.3.1 Collection and Recording of Adverse Events, Special Situation Reports (SSRs) and

Product Quality Issues (PQIs)

Collection and recording of SAEs, AEs, SSRs and PQIs will commence once the study participant has provided informed consent.

The investigator should notify Takeda within 1 working day of becoming aware of a fatal or life-threatening SAE, and other SAEs, and within 7 calendar days for all other events/issues. This is typically achieved by the investigator completing the AE report pages of an eCRF or by submitting an AE Report Form to Takeda.

The investigator may be contacted by Takeda to obtain additional information on the event or for data clarification. The investigator shall make best effort to obtain the requested additional information and will notify Takeda within 1 working day of obtaining the additional information for a fatal or life-threatening SAE, and other SAEs, and within 7 calendar days for all other events/issues.

7.1.3.2 Reporting of Adverse Drug Reactions to Regulatory Agencies and IRB/EC

Takeda is responsible for reporting serious and non-serious ADRs suspected of being related to Takeda products to regulatory authorities. The investigator is responsible for reporting ADRs to the IRB/EC, if required by national law or regulation. The investigator shall maintain records of all such submissions.

7.2 VR-Based Solution Incidents

7.2.1 Definition of Incidents

An incident is a minor hardware and/or software event that prevents the correct use of the solution in its context. The incidents are mainly associated with misuse by the user of the solution or with a software and/or hardware failure.

7.2.2 Reporting of Incidents

A specific document with solutions for the most current problems potentially encountered when using the VR-based solution will be provided by investigators to patients at inclusion (see additional documents).

For other incidents, patients will be asked to inform as soon as possible the investigator in order to receive another material.

8 PLAN FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

8.1 Public Posting and Disclosure of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites as required by regional regulatory requirement(s).

8.2 Study Results/Publications

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

After the research data are finalized and become available, the scope, planning and development of the publication(s), and how such publication(s) will be reviewed and amended is all in accordance with The International Society for Medical Publication Professionals (ISMPP) Good Publications Practice (GPP3). Unless otherwise required by the scientific journal to which the publication is submitted, or the forum in which it is presented, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

8.3 Submission of Summary of Final Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the final study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s), as appropriate. The sponsor will provide the ECs with a copy of the same summary.

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10 APPENDICES

10.1 Studied VR-Based Solution

The VR-based solution has been designed to provide haemophilia patients and accompanying persons (caregivers / family) with a digital tool able to help them reduce the burden of disease and treatment. With the use of a VR headset or a smartphone, patients and accompanying persons have access to 3 therapeutic modules, each designed to respond to a specific use in the care protocol:

10.1.1 Game Module

This module is a therapeutic game designed to distract and relax patients, during their regular medical cares related to their haemophilia problems. Busy playing, patients feel less pain related to this procedure. The game is based on a hypnotherapeutic speech, inviting the player to transform / make disappear his stress and/or pain. This speech, transposed into the game mechanics, is carried by a voice-over. We distinguish the following 4 phases of play:

- Observation game (tutorial): the player is asked to identify the objects to be transformed.
- Shooting game: the player transforms / makes disappear objects.
- Painting game: the player repopulates the environment.
- Shooting game: the player shoots bubbles, haemoglobin cells that he loads with clotting factor.

This module is started by the accompanying person. It has an indefinite duration, allowing to manage the time of the session. An end-of-game button, on the tablet, allows the caregiver to activate it once the injection is over.

10.1.2 Relaxation Module

This module consists of reducing the stress and the anxiety of parents and/or children in the moments preceding the prophylaxis cares. Parents in the phase of learning to inject the clotting factor to their child, go through great phases of anxiety. We offer 20-minutes sessions for parents to reduce their stress and anxiety, with a 360 audio-visual immersive bubble to drive them out of their stress zone. These sessions are structured as follows: 7 minutes of guided cardiac coherence type respiratory exercise (10-second cycle). 13 minutes of hypnotic relaxation

10.1.3 Learning Module

The objective of this module is to serve as a reassurance support for patients or parents in the learning phase of intravenous injection of clotting factor. Whether to inject or self-inject the

clotting factor, VR simulation allows Patient or parents to relive at their own tempo, and as many times as necessary, the different stages of the care protocol to make it a routine.

10.2 Participating Centres

Centre	Address	Telephone number	Investigator	Nurse
[redacted] (Coordinator centre)	[redacted]	[redacted]	Dr [redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Dr [redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Dr [redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Centre	Address	Telephone number	Investigator	Nurse
[redacted]	[redacted]	[redacted]	Dr. [redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Dr. [redacted]	[redacted]

10.3 Questionnaires/Scales Used for Assessments

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

A separate master file containing each scale/assessment listed above will be provided to the centre.