**Official Title:** A Multicenter, Non-Interventional Study to Evaluate Physical Activity, Bleeding Incidence and Health Related Quality of Life, in Patients With Haemophilia A Without Inhibitors Receiving Standard Of Care Treatment

**NCT Number:** NCT04165135

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# STATISTICAL ANALYSIS PLAN

**TITLE:** A MULTICENTER, NON-INTERVENTIONAL STUDY TO EVALUATE PHYSICAL ACTIVITY, BLEEDING INCIDENCE AND HEALTH RELATED QUALITY OF LIFE, IN PATIENTS WITH HAEMOPHILIA A WITHOUT INHIBITORS RECEIVING STANDARD OF CARE TREATMENT

**PROTOCOL NUMBER:** ML40983

**STUDY DRUG:** na

**VERSION NUMBER:** Final 2.0

**SPONSOR:** Roche S.p.A

**PLAN PREPARED BY:** [redacted] Biostatistician, CROS-NT

**DATE FINAL:** 15 July 2022

## STATISTICAL ANALYSIS PLAN APPROVAL

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## STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

**Amendment 1.1: 02 February 2022:**

All the co-primary endpoints presented in Section 2.2.1, i.e.:

- active minutes:
    - heart zone minutes (overall, fat-burn minutes, cardio minutes, peak minutes)
    - active zone minutes (overall, lightly active minutes, fairly active minutes, very active minutes)
    - MVPA minutes
- METs
- number of steps

will be summarized at subject level as median per day (i.e. the median of each parameter will be calculated by using all the valid days collected during the observational period). In this way it is possible to obtain a more robust measurement that is not affected by the presence of outliers related to scattered peak of physical activity or errors in the measurement related to the fitness tracker.

**Amendment 1.2: 08 June 2022:**

The changes done in this amendment mainly regard the definition of the evaluable population. The following section have been changed:

- Section 4.1.2: the definition of the Evaluable population has been updated by including a condition on the compliance to the use of the fitness tracker in addition to the presence of a valid period defined by an exposure of at least 180 days (6 months)
- Section 4.3.2.1: a definition of the compliance to the use of fitness tracker relatively to the period defined by the extent of exposure (from the first valid day to the last valid day, extremes included) has been added.

Moreover, the following sentence has been added in Section 4.0:

*With reference to the ePROs* and *physical activity data (i.e. all data derived from ePRO app and the fitness tracker), only data collected between the informed consent date and Date of patient completion or withdrawal (extremes included) will be analyzed. For the interim analysis, the minimum between Date of patient completion or withdrawal and the cut-off date will be considered as upper bound.*

**Amendment 2.0: 15 July 2022:**

In section 2.2.1 the types of physical activities identified by the fitness tracker have been listed.

In Section 4.1.4, the definition of SWITCH population has been added along with the classification of subjects who switch to a replacement or non-replacement therapy.

In Section 4.2.3, the time to discontinuation will be analyzed even if less than 30% of subjects will discontinue the study in order to provide an estimate of the median follow-up time.

In Section 4.4.2, the following changes have been done:

- Treatment regiment for bleeding: number and proportion of bleeding with adherence to treatment regiment in the week preceding the bleeding will be shown.
- HRQoL measured using the EQ-5D-5L will be analyzed monthly instead of every 3 months, deriving the timepoint from the date in which the questionnaire is recorded in the ePRO.
- Annualized Bleeding Rate: Number and proportion of subjects with at least one bleeding will be also shown.
- The analysis to explore the relationship between bleedings and physical activity has been explained better.

In Section 4.4.4, the following changes have been done:

- the definition of subgroups accordingly to the start of any newly approved drug for haemophilia has been updated.
- the analysis by month to observe the impact of COVID-19 has been added.

## TABLE OF CONTENTS

# 1. BACKGROUND

This document outlines the statistical methods to be implemented in the analysis of the data of ML40983 Clinical Study. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol (1) or electronic Case Report Form (eCRF) (2) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.

All final study data will be considered for the analysis regulated by this SAP.

# 2. STUDY DESIGN

This is a multicenter, non-interventional, prospective study. The study will be conducted according to the scheme shown in Table 1 and includes two phases: baseline and observational period.

This study will include patients aged ≥ 12 years and ≤ 50 years with severe (FVIII < 1%) or moderate (FVIII ≥ 1 and ≤ 2%, i.e., in the higher range of severity) Haemophilia A without inhibitors against FVIII.

**Table 1: Study scheme**

| | **Observational period** | |
|---|---|---|
| **Baseline** | Standard observational period for all observed patients | Prolonged observational period if patients start newly approved drugs between Month 6 and Month 12 |
| | Month 0 to Month 12 | 6 months after the start of new therapy (e.g., max observation period of 18 months if patients start the newly approved drugs during the last month of standard observational period). |

The entire observational period will last 12 months. Patients that will start treatment with any newly approved drugs between Month 6 and Month 12 will complete a 6-month observational period after the switch, and therefore the entire observational period in these patients may be prolonged up to a maximum of 18 months. In the context of this study, newly approved drugs are considered all those newly approved

during the study and commercially available for prophylaxis treatment in patients with Haemophilia A without inhibitors.

## 2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

For additional details on the Visit Schedule and Visit Windows, see the Schedule of Assessments in Appendix 2.

## 2.2 OUTCOME MEASURES

The co-primary outcome measures are given by the physical activity data collected through a wearable device (i.e., fitness tracker) in terms of active minute, METs and steps count.

According to the protocol (see Study protocol, Section 6.1.1), a valid day of monitoring is defined as at least 10 wearing hours per day. Only data from days in which the fitness tracker was worn for at least 10 hours will be included in the statistical analysis (see Appendix 3 for the derivation of the wearing time).

The minutes are saved in two different sets of data collected by the fitness tracker. For each set, minutes are categorized by intensity of the activity done.

The first set is comprised of the minutes categorized accordingly to the time collected in each heart zones (following referred as “heart zone minutes”):

- fat-burn minutes,
- cardio minutes,
- peak minutes.

The second set is comprised of the minutes categorized accordingly to the active zones (following referred as “active zone minutes”):

- lightly active minutes,
- fairly active minutes,
- very active minutes.

The conversion from heart zones to active zones is not shared by the owner of the fitness tracker but it is known that it is based on the METs (Metabolic Equivalent of Task). The MET is the objective measure of the ratio of the rate at which a person expends energy, relative to the mass of that person, while performing some specific physical activity compared to a reference. METs calculated by the fitness tracker are not directly available but must be derived.

In our analysis, the METs will be derived by using the following formula:

$$1\ MET = \frac{kcal}{kg * h}$$

where:

- $kcal$ will be given by the sum of calories collected by the fitness tracker during the time spent in fat-burn, cardio and peak heart zones, respectively.
- $kg$ will be given by the weight collected in the eCRF at baseline and every 3 months when the observation visit is conducted and the weigh is collected (the weight is assumed constant between each visit and the subsequent, in case of missing assessment, the last available value will be carried forward).
- $h$ is the time that will be derived as sum of fat-burn minutes, cardio minutes, and peak minutes.

The minutes will be also analyzed in terms of overall sum:

$$overall\ heart\ zone\ minutes = \\ = fatburn\ minutes\ +\ cardio\ minutes\ +\ peak\ minutes$$

$$overall\ active\ minutes = \\ = lightly\ active\ minutes\ +\ fairly\ active\ minutes\ +\ very\ active\ minutes$$

And of MVPA (Moderate-to-Vigorous Physical Activity) minutes:

$$MVPA\ minutes = \ fairly\ active\ minutes + very\ active\ minutes$$

### 2.2.1 Secondary Endpoints

- To document physical activity, particularly in terms of active minutes, by ages categories (12-17, 18-30 and 31-50 years), by type of physical activity and by intensity (as per fitness tracker default categorization)
    - The physical activities are categorized in the followings groups:
        - Exercises at intervals
        - Gymweights
        - Running
        - Swimming
        - Tapis roulant
        - Walk
        - General exercises: other types of physical activity identified by the fitness tracker that are not already included in the above-mentioned categories.
- To describe the observed population in terms of:
    - Number of patients who are adherent to World Health Organization (WHO) Guidelines (i.e., Global Recommendations on Physical Activity for Health) for the definition of physical activity.

      The adherence to WHO guidelines will be derived considering the measures derived as described in Section 4.1.

      A patient will be defined “adherent” to WHO guidelines if:

        - 12-17 years old:

- MVPA minutes per day ≥ 60 minutes

- 18-50 years old:
  - Fairly active (moderate) minutes per week ≥ 150 minutes OR
  - Very active (vigorous) minutes per week ≥ 75 minutes OR
  - An equivalent combination of fairly and very active minutes (i.e. considering 1 fairly active minute as 0.5 very active minutes)

A subgroup analysis will be done by severity of the disease (see Section 4.4.5 for subgroup definition).

A patient who will result adherent to the WHO guidelines according to the previous definition will be define as an “active patient”, otherwise as a “sedentary patient”.

- Number, sites and types of bleeds occurring during routine clinical practice and reported at any occurrence via the electronic Patient-Reported Outcome (ePRO) application.
- Treatment regimen for haemophilia A (prophylaxis, preventative treatment before physical activity, treatment for any episode of bleeds), in terms of type of regimen (on demand vs. prophylaxis), product used and dose.
- Health-Related Quality of Life (HRQoL) and health status reported during routine clinical practice, measured using the European Quality of Life-5 Dimensions (EQ-5D-5L) score (adults/adolescents).

  HRQol will be evaluated at baseline, every 3 monhts, and at the end of the study).

  The EQ-5D scale is composed of two main sections: in the first it is requested a subjective evaluation of five dimensions (mobility, selfcare, usual activity, pain discomfort, anxiety / depression), in the second an evaluation of the overall health status using a visual analogue scale (VAS) from 0 to 100. As for the first section, the original version of the scale (EQ-5D-3L) used a scoring system in 3 levels for each dimension, the most recent version a scoring system in 5 levels (1=no, 2=slight, 3=moderate, 4=severe, 5=extreme problems). An algorithm must be used to compute the synthetic index, commonly defined “EQ-5D Index Utility Score”, algorithm which assigns specific weights, defined “value set”, to each dimension of the health status. This value set is defined for a general population using techniques that are typical of the cost-utility analysis, following a protocol (EQ-VT) which has been developed by EuroQoL. This value set is Nation-specific. For Italy, the value set for the EQ-5D-5L is not yet available (validation is ongoing). However, a value set has been validated for the EQ-5D-3L (3). As recommended in the User’s Manual of the EQ-5D scale (4), it is possible to compute the so-called “crosswalk value set”, which allows to convert the value set of the 3-level scale (EQ-5d-3L) to the value set of the 5-level scale

(Eq-5d-5L) (5). In brief, using papers (3) and (5) it is possible to compute the Index Utility Score for Italy.

- Dose and frequency of concomitant medications taken to control pain (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], painkillers).

  The concomitant medications flagged as “for pain treatment” in the eCRF during the study will be considered for this purpose.

- Joint health status of enrolled patients, based on Haemophilia Joint Health Score (HJHS) questionnaire (evaluated at baseline, at six months, and at the end of the study).

  The HJHS is an instrument developed to measure joint health status and to identify early signs of joint disease in children. This tool assesses joints most commonly affected by bleeding (knees, ankles and elbows). Each of the 6 joints is assessed across 8 domains (swelling, duration of swelling, atrophy, crepitus, flexion loss, extension loss, pain and strength) and a Total Score is calculated as the sum of all joint domain scores. The instrument also includes a measure of Global Gait, which encompasses assessments of 4 skills: walking, climbing stairs, running and hopping on 1 leg.

- Body Mass Index (BMI) evaluated at baseline and every three months.

- Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period, evaluated through administration of questions (evaluated at baseline, every month, and at the end of the study).

- Number of hospitalization days (patient) during the observation period evaluated through administration of questions (evaluated at baseline, every month, at the end of the study).

- Pain intensity measured using a Visual Analogue Scale (VAS) (evaluated at baseline, every month and at the end of the study).

  The intensity of pain will be evaluated at baseline, every month and at the end of the study, as well as at each bleeding episode, by means of a 100 mm VAS and will be recorded through ePRO application. The left extreme of the horizontal line means “No pain = 0” while the right extreme means “Worst Pain Imaginable = 100”.

- To evaluate adherence to the treatment regimen: documented during planned visits according to source data (ePRO data) in electronic Case Report Forms (eCRF) by the investigator.

  The adherence to the treatment regimen will be analyzed as proportion of “Yes” and “My therapeutic plan does not include any treatment in the last week” on the total of week reported via the ePRO. Missing data for some weeks will be treated as “No”. The total number of weeks will be derived as:

  $$(\text{End of study date} - \text{Baseline date} + 1) / 7$$

- To describe the active vs. sedentary haemophiliac patients in terms of:
  - Severity of disease
  - Annualized bleeding rate (ABR)

The annualized bleeding rate will be derived as follows:

$$\frac{total\ number\ of\ bleeds}{sum\ of\ the\ individual\ study's\ durations}$$

where the individual study's duration will be given by

$$end\ of\ study\ date - baseline\ date + 1$$

- Pain and use of painkillers (as described above).
- Drug regimen adopted (as described above).
- HRQoL (as described above).
- Hospitalization/missed days at school (as described above).
- Joint Health Status (as described above).

- To describe severe vs moderate haemophiliac patients for the above mentioned items.

### 2.2.2 Other Exploratory Endpoints

- To evaluate the relationship between physical activity (type and intensity) and bleedings
- To evaluate the sleep duration and sleep stage in participant patients.
- Sleep duration (overall) and sleep stage duration (Wake, REM, Light, Deep) collected through a wearable device (i.e., fitness tracker). Sleep duration (overall and by stage) will be analyzed for the valid days of monitoring (i.e., defined as at least 10 wearing hours per day).
- To observe patients, on primary and secondary objectives, for additional 6 months if new therapies become commercially available for patients with Haemophilia A without inhibitors against FVIII, during the course of the study and if patient will start such treatments during the observation period
- Physical examination at baseline and every three months.
- Vital signs at baseline and every three months.

## 2.3 DETERMINATION OF SAMPLE SIZE

Given the exploratory nature and the objectives of this non-interventional study, rather than testing a formal hypothesis, a justification based on epidemiologic data from the Italian registry of congenital bleeding disorders (Giampaolo et al. 2017) was considered more appropriate than a power calculation in the traditional fashion or using an estimation approach through the precision of confidence intervals.

The total sample size planned is approximately 150 patients overall, 125 patients with severe Haemophilia A and 25 patients with moderate Haemophilia A.

Based on data collected from the 54 Haemophilia Treatment Centers, members of the Italian Association of Haemophilia Centres (AICE), it is estimated that this planned number

of participants will represent approximately 10-15% of patients with Haemophilia A in Italy, in the same age range and category of severity planned for this study.

The estimated sample size (150 subjects) allows to obtain 95% confidence intervals with half-width (i.e., precision) less than or equal to 17% of the standard deviation with a probability of over 80%.

### 2.3.1 Change in sample size.

The enrolment was interrupted on 30 April 2021 due to difficulties associated with the SARS-COV-2 pandemic that limited the participation of potential patients in the study within the acceptable enrolment period.. Of the anticipated 150 patients, 107 (71.3%) were included in the study. The reduction of the sample size to 107 patients involves a slight reduction in precision, i.e., an increase in the half-width that will be observed to be less than or equal to 20% (instead of 17% reported in the original protocol) of the standard deviation with an 80% probability. Hence, the reduction of the sample size due to the early interruption of the enrolment does not cause a significant deviation from the planned precision of the estimates.

## 2.4 ANALYSIS TIMING

One interim analysis is planned, when all enrolled patients have completed 6 months of observation, to have a preliminary evaluation of results.

Due to the observational nature of this study, no adjustments will be done for the derivation of the p-values of the proposed statistical tests.

The final analysis will be done the last enrolled subject will have finished the planned observational period of 12 months, or in case of starting a new therapy, when all applicable patients have completed the 6 months of observation after the first new therapy administration. See Table 1 for further details.

# 3. STUDY CONDUCT

## 3.1 RANDOMIZATION

NA

## 3.2 INDEPENDENT REVIEW FACILITY

NA

## 3.3 DATA MONITORING

NA

## 3.4 DATA REVIEW MEETING

Once the study database is considered clean and before database lock, a data review meeting will be performed. During this meeting the study data will be reviewed to identify potential issues and document decisions taken to address them before the database is locked and the analysis of the data starts.

# 4. STATISTICAL METHODS

Appropriate descriptive statistics will be produced, according to the variable. For continuous data n, mean, standard deviation (SD), median, I and III quartile, and range (minimum and maximum) will be presented. For categorical data, frequency distributions and percentages will be presented.

Unless otherwise specified, hypothesis testing (exploratory in nature) will be carried out at the alpha = 0.050 level (two-sided). For all inferential analyses, the p-values will be rounded to three decimal places. Due to the exploratory nature of this study, no adjustment for multiplicity will be made.

Any unplanned analyses as well as deviations from the original SAP will be clearly documented in the Clinical Study Report.

All the data collected and derived in the study will be presented in subject data listings.

With reference to the ePROs and physical activity data (i.e. all data derived from ePRO app and the fitness tracker), only data collected between the informed consent date and Date of patient completion or withdrawal (extremes included) will be analyzed. For the interim analysis, the minimum between Date of patient completion or withdrawal and the cut-off date will be considered as upper bound.

## 4.1 ANALYSIS POPULATIONS

### 4.1.1 Enrolled Population (ENR)

The Enrolled Population will consist of all patients for whom the inclusion/exclusion criteria have been verified and met.

### 4.1.2 Evaluable population

The evaluable population will consist of all enrolled patients with at least 6 valid months of physical activity evaluations during the study.

The patients with 6 valid months of physical activity will be defined by the presence of the two following conditions:

- an Extent of Exposure to the fitness tracker of at least 6 months (180 days) (see Section 4.3.1 for the definition of Exposure).

  AND

- a compliance to the use of the fitness tracker of at least 50% in the period defined by the extent of exposure (see Section 4.3.2.1 for the definition of the compliance respect to the exposure).

### 4.1.3 Intention-to-treat Population (ITT)

The Intention-To-Treat Population will consist of all enrolled patients who received the ePRO application and the fitness tracker.

All objectives will be evaluated both on the Evaluable population and on the ITT population. In case that the Evaluable population will consist of less the 50% (< 50%) of the ENR populations, only the primary endpoint and the secondary endpoint on the type of physical activity will be assessed on the Evaluable populations while all endpoints will be assessed on the ITT population.

### 4.1.4 SWITCH - ITT Population (ITT)

The SWITCH population will consist of all enrolled patients who received the ePRO application and the fitness tracker and who switch to any newly approved drug for haemophilia during the observational period.

Subjects who switch to any newly approved drug for haemophilia A are divided in two subgroups:

- Subjects who switch to a replacement therapy
- Subjects who switch to a non-replacement therapy

This population will be used for one of the exploratory objectives.

## 4.2 ANALYSIS OF STUDY CONDUCT

### 4.2.1 Subject enrolment and disposition

For describing the subject disposition, the following populations will be summarized:

- Subjects enrolled (overall).
- Subjects enrolled but who did not receive the ePRO and wearable device and reasons for no dispensation.
- Subjects in the Evaluable population.
- Subjects in the ITT population.

For the overall report, the percentage denominator will be the number of the subjects in the related population.

### 4.2.2 Protocol violations

All the protocol violations will be discussed case by case before database lock with the clinical team during the DRM and described in the DRM Report.

Number of occurrences and of subjects with at least one major and minor protocol violations will be summarized.

Protocol violations will be also shown by start of any newly approved drug for haemophilia.

### 4.2.3 Study discontinuations

Number and proportion of study completers will be shown.

The distribution of the time from baseline to discontinuation will be summarized using time-to-event method. In this case, Kaplan-Meier estimates and plots will be provided with 95% confidence interval bounds calculated per Greenwood method. Subjects who have not prematurely discontinued the trial will be censored at study termination.

### 4.2.4 Demographics and baseline characteristics

The baseline demographic characteristics will be summarized by means of descriptive statistics.

The following demographic characteristics will be reported for this study:

- Age (years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Demographics and baseline characteristics will be show overall, by age group and by start of any newly approved drug for haemophilia (see Section 4.4.4 for the subgroup definition).

### 4.2.5 Medical or Surgical History and/or Concomitant Diseases

A disease is considered as medical history if it is not ongoing at baseline visit (“ongoing” box is not ticked).

A disease is considered as concomitant disease if it is ongoing at baseline visit (“ongoing” box is ticked as “Yes”).

Medical history and concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary and frequency distributions and percentages will be summarized in the Evaluable population by System Organ Class (SOC), and Preferred Term (PT).

Medical history and concomitant diseases will be analyzed separately. Frequency distributions and percentages will be given for both SOC and PT by subject. Subjects experiencing more than one past/concomitant disease event will be counted only once within each SOC and PT.

### 4.2.6 Prior and concomitant medications

Medications will be coded using World Health Organization Drug Dictionary (WHO DD).

A medication is considered as prior medication if it is not ongoing at screening visit (“ongoing” box is not ticked).

A medication is considered as concomitant medication if it is ongoing at screening visit ("ongoing" box is ticked as "Yes").

Prior and concomitant medications will be summarized separately. Frequency distributions and percentages will be summarized in the Evaluable population by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

Subjects taking more than one medication classified in the same category (prior medications or concomitant medications) within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

### 4.2.7 Other baseline characteristics

History of Physical Activity

The history of Physical Activity will be presented by age group. The following information collected in the eCRF at baseline will be summarized:

- Only for patients that are 12-17 years old:
    - Number and proportion of patients who regularly play activities, entertainment, fun that involve a physical commitment.
    - Number and proportion of patients who practice a sport discipline regularly, albeit at an amateur level, or participate to the school sessions of physical education.
    - Type of sport disciplines.
    - Number and proportion of patients who exercise aerobic activities including low/medium physical intensity (e.g., walking, cycling, swimming) in the context of family, community or school activities.
    - Number and proportion of patients who spend most of the day for the conduct of sedentary activities (e.g., study, videogames, use of electronic devices).
    - Number and proportion of patients who are reluctant to use active means of transport (e.g., walking, cycling or climbing stairs).
- Only for patients that are 18-50 years old:
    - Number and proportion of patients who regularly exercise in their free time, for fun or leisure.
    - Number and proportion of patients who practice a sport discipline or physical exercises planned, albeit on an amateur level.
    - Type of sport disciplines.
    - Number and proportion of patients who exercise aerobic activities also of average physical intensity (e.g., dynamic work, walk to make orders, carry out housework) in the context of daily, family or community.

- Number and proportion of patients who spend most of the day for the conduct of sedentary activities (e.g., working on the PC, driving a vehicle or using electronic devices).
- Number and proportion of patients who are reluctant to use active means of transport (e.g., walking, cycling, or climbing stairs).

History of Haemophilia

The following information collected in the eCRF at baseline will be summarized:

- Confirmation of Haemophilia A diagnosis (Yes/No).
- Time from diagnosis (years).
- Disease severity (Moderate/Severe Haemophilia).
- History of positive inhibitor against FVIII (Yes/No) and time since the inhibitor was eradicated (years).
- History of known thrombophilia (Yes/No).
- History of anaphylaxis (Yes/No).
- Number of bleeds during 24 weeks prior to baseline (0, 1/2, 3/4, 5/6, >6, Unknown).
- Number of school/work days missed during 24 weeks prior to baseline (for the patient) (0, 1/2, 3/4, 5/6, >6, Unknown).
- Number of days hospitalized during 24 weeks prior to baseline (for the patient) (0, 1/2, 3/4, 5/6, >6, Unknown).
- Number of school/work days missed during 24 weeks prior to baseline (for the caregiver) (0, 1/2, 3/4, 5/6, >6, Unknown).
- Age of possible early retirement (for parent or caregiver).

All parameters related to the history of haemophilia will be shown overall, by age group and by start of any newly approved drug for haemophilia (see Section 4.4.4 for the subgroup definition). Moreover, the disease severity will also be summarized by frequency of physical activity.

## 4.3 EVALUATION OF COMPLIANCE AND EXPOSURE

### 4.3.1 Exposure to use of the fitness tracker

On a per patient basis, the evaluation of the exposure to the use of the fitness tracker will be done using the following formula:

$$Exposure\ (days) = \ date\ of\ the\ last\ valid\ day - \ date\ of\ first\ valid\ day + 1$$

where a “valid day” is defined as a day in which the fitness tracker is worn for at least 10 hours. The wearing time derivation is presented in the Appendix 3.

### 4.3.2 Compliance to use of the fitness tracker

On a per patient basis, the evaluation of the compliance during the overall study period will be done using the following formula:

$$Compliance\ (\%) = \frac{total\ number\ of\ valid\ days\ during\ the\ observational\ period}{end\ of\ study\ date - baseline\ date + 1} \times 100$$

where a "valid day" is defined as a day in which the fitness tracker is worn for at least 10 hours. The wearing time derivation is presented in the Appendix 3.

Compliance will be summarized by means of summary statistics on the overall sample and by age group.

Compliance to the use of fitness tracker will also be summarize by start of any newly approved drug for haemophilia (see Section 4.4.4 for the subgroup definition).

#### 4.3.2.1 Compliance to use of the fitness tracker (respect to the exposure)

On a per patient basis, the evaluation of the compliance during the period defined by the exposure will be done using the following formula:

$$Compliance\ (\%) = \frac{\begin{matrix} total\ number\ of\ valid\ days \\ between\ the\ first\ and\ last\ valid\ days \end{matrix}}{Exposure\ to\ the\ fitness\ tracker} \times 100$$

where a "valid day" is defined as a day in which the fitness tracker is worn for at least 10 hours. The wearing time derivation is presented in the Appendix 3.

This definition of compliance will be used to define the Evaluable population.

## 4.4 EFFICACY ANALYSIS

### 4.4.1 Co-primary Endpoints

All the co-primary endpoints presented in Section 2.2.1, i.e.:

- active minutes:
    - heart zone minutes (overall, fat-burn minutes, cardio minutes, peak minutes)
    - active zone minutes (overall, lightly active minutes, fairly active minutes, very active minutes)
    - MVPA minutes
- METs
- number of steps

will be summarized at subject level as median per day (i.e. the median of each parameter will be calculated by using all the valid days collected during the observational period for each subject). Each parameter, derived as median per day at subject level, will be analyzed by means of descriptive statistics as described in Section 4. The 95% confidence interval for the mean will be also displayed.

The statistics will be shown overall and by age groups (12-17, 18-30 and 31-50). The comparison among the age groups will be performed by means of a one-way ANOVA or, if assumptions of normality is not confirmed (by a visual inspection: histogram and qq-plot), by means of a Kruskal-Wallis test.

Daily physical activity will also be summarized:

- by start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).
- by COVID-19 period on the EVL population (see Section 4.4.4 for subgroup definition).
- by month through the entire observational period on the EVL to observe the impact of COVID-19.

Data will be summarized at subject level considering data collected in each period above-mentioned.

### 4.4.2 Secondary and Exploratory Endpoints

The endpoints assessed via the ePRO application that require to be evaluated at specific timepoint need to be "remapped" at each time point by deriving from the date the corresponding week/month starting from the baseline date. In case that more than one observation occurs within the same week/month, the mean among the two observations will be used.

**To document physical activity, particularly in terms of active minutes, by ages categories (12-17, 18-30 and 31-50 years), by type of physical activity and by intensity (as per fitness tracker default categorization)**

Data will be analyzed as for the primary endpoint described in Section 4.4.1 but they will analyzed at activity level (instead of a daily level).

For example, if we consider "Bike", the active minutes and METs will be derived as median of the active minutes (heart zone minutes, active zone minutes and MVPA minutes) for single activity (i.e. if Bike is reported twice, the active minutes for Bike will be derived as median of the values reported for each of two activities done).

Moreover, the activity rate will be derived as follow (in the example for "Bike"):

$$Bike\ weekly\ rate = \frac{number\ of\ times\ that\ Bike\ is\ reported\ on\ the\ fitness\ tracker}{end\ of\ study\ date - baseline\ date + 1} \times 7$$

For each type of activity, the statistics will be shown overall and by age groups (12-17, 18-30 and 31-50). The comparison among the age groups will be performed by means of a one-way ANOVA or, if assumptions of normality is not confirmed (by a visual inspection: histogram and qq-plot), by means of a Kruskal-Wallis test.

Daily physical activity will also be summarized:

- by start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).
- by COVID-19 period on the EVL population (see Section 4.4.4 for subgroup definition).
- by month through the entire observational period on the EVL to observe the impact of COVID-19.

Data will be summarized at activity level considering data collected in each period above-mentioned.

**Number of patients who are adherent to WHO Guidelines for the definition of physical activity**

Number and proportion along with the 95%CI (Clopper-Pearson's formula) of subjects who are adherent to World Health Organization Guidelines for the definition of physical activity will be calculated in the whole sample and compared by age group.

Adherence to WHO guidelines will also be summarized:

- by start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).
- by COVID-19 period on the EVL population (see Section 4.4.4 for subgroup definition).
- by month through the entire observational period on the EVL to observe the impact of COVID-19.

The adherence will be summarized considering data collected in each period above-mentioned.

Other subgroup analyzes: severity of the disease (see Section 4.4.4 for subgroup definition).

**Number, sites and types of bleeds occurring during routine clinical practice and reported at any occurrence via the electronic Patient-Reported Outcome (ePRO) application**

The overall number of bleeds per patients will be analyzed by means of descriptive statistics as described in Section 4. Data will be shown overall and by age group.

Bleeds that occur the same day but in different body site will be counted separately. Number and proportion of patients with no bleeds and 1 or more bleeds will also be shown.

The bleeds will be analyzed overall, by body site (Joint bleeds, Muscle bleeds, Other bleeds) and type (Spontaneous bleeds, Traumatic bleeds, Bleeds related to procedure/surgery).

The 95%CI for the mean number of bleeds will also be shown.

Number, sites and types of bleeds will also be summarized:

- by start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).
- by COVID-19 period (see Section 4.4.4 for subgroup definition).
- by month through the entire observational period to observe the impact of COVID-19.

Other subgroup analyzes: frequency of physical activity, severity of the disease.

**Treatment regimen for haemophilia A (prophylaxis, preventive treatment before physical activity, treatment for any episode of bleeds), in terms of type of regimen (demand vs. prophylaxis), product used and dose.**

*Treatment regimen for Haemophilia A*

Only concomitant medication for haemophilia will be displayed. Prophylaxis and "on demand" treatment for haemophilia will be summarized separately. Frequency distributions and percentages will be summarized in the Evaluable population by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

Subjects taking more than one medication classified in the same category (prior medications or concomitant medications) within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

Number and proportion of subjects who take prophylaxis and "on demand" treatment for haemophilia during the study will be also shown.

A detailed listing with the concomitant treatments for haemophilia, regimen (prophylaxis, on demand) dose and frequency will be generated.

Moreover, number and proportion of patients who start treatment with any newly approved drugs during the study for prophylaxis treatment in patients with haemophilia A without inhibitors will be presented.

Other subgroup analyzes: frequency of physical activity, severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

*Treatment regimen for bleeding*

The following information collected in the eCRF will be shown to describe the treatment for bleeding:

- number and proportion of treated bleedings
- number and proportion of bleeds treated with each type of treatment for bleeding (haemostatic treatment, treatment for pain)
- duration of treatment for bleed (hours)
- number and proportion of bleeds treated with each route of administration

- number and proportion of bleeds which needed to receive a transfusion
- number and proportion of bleeds which needed to administer an additional hemostatic therapy
- number and proportion of bleeds which with adherence to the treatment regimen in the week preceding the bleeding.

A listing with complete information on each bleed and its treatment will be also provided.

Treatment regimen for bleed will also be analyzed by the intensity of physical activity done in the 2 days preceding the day of bleeding. Intensity of physical activity will be defined considering the MVPA done in the 2 days before the bleeding. MVPA minutes will be summarized as median of the values recorded in the 2 valid days before the bleeding. A median greater than 0 minutes will mean an intense physical activity (in case of only one valid day, that value will be used to summarize the physical activity preceding the bleeding).

Other subgroup analyzes: severity of the disease (see Section 4.4.5 for subgroup definition).

**Health-Related Quality of Life (HRQoL) and health status reported during routine clinical practice, measured using the European Quality of Life-5 Dimensions (EQ-5D-5L) score**

The EQ-5D-5L score will be analyzed at baseline and monthly up to the end of the observational period. The month will be derived as: rounded[(reference date – baseline date + 1) /30.4375].

The EQ-5D Index Utility Score as well as the EQ VAS Score will be analyzed according to their continuous nature. The change from baseline will also be shown. The 95%CIs for the mean and for the mean change from the baseline will also be calculated.

Moreover, the score related to each dimension (mobility, selfcare, usual activity, pain/discomfort and anxiety/depression) will be analyzed according to its categorical nature in the overall sample. Number and proportion of patients in each category will be displayed (No problems, Slight problems, Moderate problems, Severe problems, Extreme problems).

Data will also be summarized:

- by start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).
- by COVID-19 period (see Section 4.4.4 for subgroup definition).
- by month through the entire observational period to observe the impact of COVID-19.

In case of more than 1 value for each subject in each period, the continuous variable will be replaced by using the mean of the value for each subjects, the qualitative variables (e.g. the score domain) will be replaced by the worst value.

Other subgroup analyzes: frequency of physical activity, severity of the disease (see Section 4.4.4 for subgroup definition).

**Dose and frequency of concomitant medications taken to control pain**

Only concomitant medication for pain treatment will be displayed. Frequency distributions and percentages will be summarized in the Evaluable population by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

Subjects taking more than one medication classified in the same anatomical main group, chemical subgroup and preferred name will be counted only once.

Other subgroup analyzes: frequency of physical activity, severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

**Joint health status of enrolled patients, based on Haemophilia Joint Health Score (HJHS) questionnaire (evaluated at baseline, at six months, and at the end of the study)**

The HJHS will be analyzed according to its continuous nature. The statistics will be displayed at each timepoint (baseline, 6 months and 12 months) for the HJHS Total Score and for the Global Gait Score along with the 95%CIs for the mean. The change from the baseline values will also be analyzed.

The score related to each joint (elbow, knee and ankle, left and right side respectively) will be listed.

Other subgroup analyzes: frequency of physical activity, severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

**Body Mass Index (BMI) evaluated at baseline and every three months**

The BMI will be analyzed at each timepoint (baseline, every 3 months and at end of study) by means of the descriptive statistics for continuous variables. The change from the baseline value will be also derived and analyzed at each timepoint after the baseline.

The statistics will be displayed for the value and for the change from baseline along with the 95%CIs for the mean.

Other subgroup analyzes: severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

**Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period, evaluated through administration of questions (evaluated at baseline, every month, and at the end of the study)**

*Patients*

The number of days away from school or work (patient) will be analyzed every month as a continuous variable as well as number and proportion of patients who missed at least one day of school or work.

An overall measure of the days away from school and/or work in one year will be derived for each patient as proportion between the total number of days away from school and/or work and duration of the study (derived as end of study date – baseline date + 1) multiplied by 365.25. This parameter will be analyzed as a continuous variable and shown along with the 95%CI.

Other subgroup analyzes: severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

*Caregiver*

The number of days away from work will be analyzed every month as a continuous variable as well as number and proportion of patients who missed at least one day of work.

An overall measure of the days away from work of the parent/caregiver in one year will be derived for each patient as proportion between the total number of days away from work and duration of the study (derived as end of study date – baseline date + 1) multiplied by 365.25. This parameter will be analyzed as a continuous variable and shown along with the 95%CI.

Other subgroup analyzes: severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

*Age of possible early retirement (caregiver)*

The age of possible early retirement of the parent/caregiver will be analyzed at the end of the study as described in section 4 for continuous variables.

Other subgroup analyzes: severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

**Number of hospitalization days (patients) during the observation period evaluated through administration of questions (evaluated at baseline, every month, at the end of the study)**

The number of hospitalization days (related to haemophilia and collected via ePRO) will be analyzed at baseline, every month and at the end of the study as a continuous variable as well as number and proportion of patients who were hospitalized during the previous month.

An overall measure of the hospitalization days for one year will be derived for each patient as proportion between the total number of hospitalization days and the period defined as (end of study date – baseline date + 1) multiplied by 365.25. This parameter will be analyzed as a continuous variable and shown along with the 95%CI.

Other subgroup analyzes: frequency of physical activity, severity of the disease, start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).

**Pain intensity measured using a Visual Analogue Scale (VAS) (evaluated at baseline, every month, and at the end of the study)**

The pain intensity will be analyzed at baseline and monthly up to the end of the observational period. The month will be derived as: rounded[(reference date – baseline date + 1) /30.4375].

The VAS for pain score will be analyzed as value at each timepoint and as change from baseline.

The 95%CIs for the mean and for the mean change will be also displayed.

Pain intensity will also be summarized:

- by start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).
- by COVID-19 period (see Section 4.4.4 for subgroup definition).
- by month through the entire observational period to observe the impact of COVID-19.

Other subgroup analyzes: frequency of physical activity, severity of the disease (see Section 4.4.4 for subgroup definition).

**To evaluate adherence to the treatment regimen: documented during planned visits according to source data (ePRO data) in electronic Case Report Forms (eCRF) by the investigator.**

The adherence will be summarized as a continuous variable as described in the introduction of Section 4. Moreover, the number and proportion of subjects who have a compliance of at least 80% will be shown.

The adherence to the treatment regimen will be analyzed as proportion of “Yes” and “My therapeutic plan does not include any treatment in the last week” on the total of week reported via the ePRO. Missing data for some weeks will be treated as “No”. The total number of weeks will be derived as the ceil of (End of study date – Baseline date + 1) / 7.

The main reasons for no assumption, change of the dose or frequency will be listed.

Adherence to treatment regimen will also be summarized:

- by start of any newly approved drug for haemophilia (see Section 4.4.4 for subgroup definition).
- by COVID-19 period (see Section 4.4.4 for subgroup definition).
- by month through the entire observational period to observe the impact of COVID-19.

**To describe the active vs sedentary haemophiliac patients in terms of:**

*Severity of disease*

The severity of disease will be analyzed as described in Section 4.2.7.

*Annualized Bleeding Rate (ABR)*

The total number of bleeds (overall, by site and by type) and the total follow-up (person-years) will be displayed. The rate will be derived as ratio between the number of bleeds and total follow-up.

Number and proportion of subjects with at least one bleeding will be also shown.

The exact Poisson 95%CI for the rate will be calculated overall, by site and type.

Other subgroup analyzes: frequency of physical activity, severity of the disease (see Section 4.4.4 for subgroup definition).

*Pain and use of painkillers*

This endpoint will be analyzed as described above and considering the frequency of physical activity as a subgroup analysis.

*Drug regimen adopted*

This endpoint will be analyzed as described above and considering the frequency of physical activity as a subgroup analysis.

*HRQoL*

This endpoint will be analyzed as described above and considering the frequency of physical activity as a subgroup analysis.

*Hospitalization / missed days at school*

This endpoint will be analyzed as described above and considering the frequency of physical activity as a subgroup analysis.

*Joint Health Status*

This endpoint will be analyzed as described above and considering the frequency of physical activity as a subgroup analysis.

**To describe severe vs moderate haemophiliac patients for the above mentioned items.**

This endpoint will be assessed by analyzing each of the endpoints above mentioned and considering the severity of disease as a subgroup analysis.

**To evaluate sleep duration and sleep stages in participant patients.**

The analysis of sleep duration (overall and by stage) will be done as for the primary endpoints described in Section 4.4.1.

**Bleeding and daily physical activity.**

The relationship between bleedings and physical activity (daily and by type) will be done as described in Section 4.4.1 but considering only data collected by the fitness tracker in the two days preceding the day in which the bleeding occurs.

For the relationship with daily physical activity, only data in the valid days will be considered. For each bleeding, the data collected in the two valid days before the bleeding will be summarized by the median. In case only one valid day is available, those values will be used to summarize the activity done before that bleeding.

All the activities recorded in the two days before the bleeding will be used regardless they occur in a valid day.

**To observe patients, on primary and secondary objectives, for additional 6 months if new therapies become commercially available for patients with Haemophilia A without inhibitors against FVIII, during the course of the study and if patient will start such treatments during the observation period.**

All the analysis proposed in sections 4.4.1 and 4.4.2 (except for the subgroup analyses) will be repeated by considering the start of any newly approved drug for haemophilia A during the study. See Section 4.4.4 for more details on this subgroup analysis.

**Physical examination at baseline and every three months.**

Analysis of physical examination data will be performed in the whole sample at baseline and every 3 months.

For each timepoint, the following summaries will be provided:

- Summary tables showing for each parameter the frequency of patients reporting an abnormal (clinically or not clinically significant) value and the frequency of patients reporting a clinically significant value.
- Shift tables presenting the number and the percentage of patients in each bivariate category (baseline versus each post-baseline visit) with regards to investigator's interpretation (normal/abnormal/not done).

**Vital signs at baseline and every three months**

Summary statistics will be provided along with summary of the change from baseline at each timepoint for vital signs:

- Weight (Kg)
- Heart rate (beats/min)

### 4.4.3 Sensitivity Analyses

NA

### 4.4.4 Subgroup Analyses

The following subgroups will be defined:

- Age group: 12-17, 18-30, 31-50 years.
- Frequency of physical activity: Active vs Sedentary patients, as derived in Section 2.2.1.

- Severity of the disease: Moderate vs Severe Haemophilia, as derived by the data collected by the fitness tracker (see Section 4.2.7 “History of Haemophilia”)
- Patients that started any newly approved drugs for haemophilia A during the study: patients who start any newly approved drugs will be analyzed accordingly to the following characteristics:
    - Period of analysis: before and after the switch. In the second period, a new baseline measurement will be defined
        - For data collected in the eCRF: baseline values for the period after switch will be defined by the data collected in the first form in which the answer to the question “Will the patient start treatment with any newly approved drugs? Yes □ No □” is “Yes”
        - For data collected by fitness tracker or ePRO: baseline values for the period after switch will be defined by the data collected in the last visit before the date of start any newly approved drug for haemophilia (date coming from the prior and concomitant medications form).
    - Type of therapy: replacement vs non-replacement therapy.
- Lockdown period due to COVID-19 Pandemic: three subgroups will be defined as:
    - Lock down period = “First period”, from 1st March 2020 to 4th May 2020
    - Lock down period = “Second period”, from 13th October 2020 to 31st December 2020 (extremes included)
    - Lock down period = No lockdown, otherwise.

  Values and changes versus the period out of the lockdown will be analyzed.
- Month of observation during the entire observational period to observe the impact of COVID-19. Only the values for each month will be shown, no changes will be calculated.

For which endpoints the subgroup analysis will be provided is listed in Section 4.4.

## 4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

NA

## 4.6 SAFETY ANALYSES

NA

## 4.7 MISSING DATA

The number of patients with missing data will be presented under the “Missing” category, if present. Missing values will not be included in the denominator count when computing percentages. Similarly, only the non-missing values will be evaluated for computing summary statistics for continuous endpoint, without any imputation for missing data. Any exception will be clarified as a note in the related tables.

## 4.8 INTERIM ANALYSES

One interim analysis is planned, when all enrolled patients have completed 6 months of observation, to have a preliminary evaluation of results and to assess if some parameters need to be analyzed more or less in depth.

Due to the observational nature of this study, no adjustments will be done for the derivation of the p-values of the proposed statistical tests.

This SAP could be update after the interim analysis.

# 5. CHINA SUBGROUP ANALYSIS

NA

## 6. REFERENCES


1. Study protocol version 3.0 – 26 Jul 2019.

2. CRF version 2.0 – 5 May 2020.

3. Scalone L et al. Italian Population-Based Values of EQ-5D Health States. Value in Health 2013;16:814-822.

4. EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument, version 3, September 2019.

5. van Hout B et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012;15: 708-715.

# 7. APPENDIX 1: PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | A multicenter, non-interventional study to evaluate physical activity, bleeding incidence and health related quality of life, in patients with haemophilia A without inhibitors receiving standard of care treatment |
| **PROTOCOL NUMBER:** | ML40983 |
| **VERSION NUMBER:** | 3.0 |
| **DATE OF SYNOPSIS:** | 26 Jul 2019 |
| **STUDIED MEDICINAL: PRODUCT:** | None |
| **INDICATION** | Haemophilia A without inhibitors |
| **STUDIED INITIATOR:** | Roche S.p.A.<br>Viale G.B. Stucchi,110<br>20900 MONZA, MB (Italy) |
| **MAIN AUTHOR:** | [redacted] |

## Research Question and Objectives

### Objectives

The primary objective for this study is to document physical activity, particularly in terms of active minutes, steps count and Metabolic Equivalent of Tasks (MET) over the 12 months period, by age categories (12-17, 18-30 and 31-50 years) in patients with haemophilia A without inhibitors receiving standard of care treatment.

The secondary objectives for this study are as follows:

- To document physical activity, particularly in terms of active minutes, by ages categories (12-17, 18-30 and 31-50 years), by type of physical activity and by intensity (as per fitness tracker default categorization);
- To describe the observed population in terms of:
    - Number of patients who are adherent to World Health Organization (WHO) Guidelines (*i.e.*, Global Recommendations on Physical Activity for Health) for the definition of physical activity;
    - Number and type of bleeds occurring during routine clinical practice and reported at any occurrence via the electronic Patient-Reported Outcome (ePRO) application;
    - Treatment regimen for haemophilia A (prophylaxis, preventative treatment before physical activity, treatment for any episode of bleeds), in terms of type of regimen (on-demand vs. prophylaxis), product used and dose;
    - Health-Related Quality of Life (HRQoL) and health status (evaluated at baseline, every three months, and at the end of the study) reported during routine clinical practice, measured using the European Quality of Life-5 Dimensions (EQ-5D-5L) score (adults/adolescents);
    - Dose and frequency of concomitant medications taken to control pain (*e.g.*, nonsteroidal anti-inflammatory drugs [NSAIDs], painkillers);

- Joint health status of enrolled patients, based on Haemophilia Joint Health Score (HJHS) questionnaire (evaluated at baseline, at six months, and at the end of the study);
- Body Mass Index (BMI) evaluated at baseline and every three months;
- Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period, evaluated through administration of questions (evaluated at baseline, every month, and at the end of the study);
- Number of hospitalization days (patient) during the observation period evaluated through administration of questions (evaluated at baseline, every month, at the end of the study);
- Pain intensity measured using a Visual Analogue Scale (VAS) (evaluated at baseline, every month, and at the end of the study);

- To evaluate adherence to the treatment regimen:
  - Documented during planned visits according to source data (ePRO data) in electronic Case Report Forms (eCRF) by the Investigator;
- To describe the active vs. sedentary haemophiliac patients in terms of:
  - Severity of disease;
  - Annualized Bleeding Rate (ABR);
  - Pain and use of painkillers;
  - Drug regimen adopted;
  - HRQoL;
  - Hospitalization/missed days at school; - Joint Health Status.
  - To describe severe vs. moderate haemophiliac patients for the above mentioned items.

## Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the relationship between physical activity (type and intensity) and bleedings;
- To evaluate the sleep duration and sleep stage in participant patients;
- To observe patients, on primary and secondary objectives, for additional 6 months if new therapies become commercially available for patients with Haemophilia A without inhibitors against FVIII, during the course of the study and if patient will start such treatments during the observation period In the context of this study, newly approved drugs are considered all those newly approved during the course of the study and commercially available for prophylaxis treatment in patients with haemophilia A without inhibitors (See section 4.1).

## Study Design

This is a multicenter, non-interventional, prospective study. The study will be conducted according to the following scheme:

| | **Observational period** | |
|---|---|---|
| | **Standard observational period for all observed patients** | Month 0 to Month 12 |

| | | |
|---|---|---|
| **Baseline** | **Prolonged observational period If patients start newly approved drugs between Month 6 and Month 12** | 6 Months after the start of new therapy (*e.g.*, max observation period of 18 months if patients start the newly approved drugs during the last month of standard observational period) |

This study will include patients aged ≥ 12 years and ≤ 50 years with severe (FVIII < 1%) or moderate (FVIII ≥ 1 and ≤ 2%, i.e. in the higher range of severity) Haemophilia A without inhibitors against FVIII receiving standard of care treatment. During the study, HRQoL, health status and joint health status will be reported on a pre-determined frequency for 12-18 months, as shown in the Data Collection Overview (Appendix 2). Physical activity data will be collected daily using a fitness tracker.

Approximately 150 patients overall, 125 patients with severe haemophilia A and 25 patients with moderate haemophilia A without inhibitors against FVIII are planned to be enrolled.

Additionally, patients (or patient's legally authorized representative) will be reminded on a monthly basis to report via the ePRO application whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a further bleed has been given. When a bleed occurs, the patient (or patient's legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (date, time of start and time of end), symptoms of bleed, and treatment for bleed.

Physical activity will be measured daily by wearing a fitness tracker continuously during study participation. Patients will be reminded to wear the device daily. A valid day of monitoring is defined as at least 10 wear hours per day. Wear time will be derived through data collected by the fitness tracker.

The reason for the use of coagulation products will be documented by Investigator in source data and reported in the eCRF (*e.g.*, bleeding, prophylaxis, pain, etc.). The reason for the use of coagulation products for bleeding treatment, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed, will be recorded by patients in the ePRO application and will be then transmitted to the eCRF.

Therapy will be recorded by the investigator at baseline visit and it will afterwards be confirmed by the patient in ePRO application. If there are changes to the assigned therapy, the patient will enter therapy variations in ePRO (*e.g.*, dose, frequency, drug name etc.) and data will be then transmitted to the eCRF.

Demographics and results from physical examinations, and vital sign assessments, will only be collected if available from routine clinical practice. No additional diagnostic or monitoring procedures will be applied to the patients outside of routine clinical practice.

The usage of ePROs is considered non-interventional according to local regulation.

## Start Date of Study:

The study start date will be the date of the signing of informed consent of the first patient (or caregiver). The planned start date is October 2019.

## End of Study

The end of the study will be the date on which the last patient performs the last visit. This is expected when:

- The last patient completes the 12-month observation period (and patients that start treatment with any newly approved drugs between Month 6 and Month 12 complete a 6 months observational period after the start of therapy), or
- The last patient has lost to follow up, withdraws consent or died whichever occurs first, or

- The study has been terminated by the Sponsor, if earlier.

## Length of Study

This study will last approximately 24 months (approximately 6 months for enrolment, 12 months of observational period and up to 6 months of observation for patients that will start treatment with any newly approved drugs between Month 6 and Month 12).
Patients that will start treatment with any newly approved drugs between Month 6 and Month 12 will complete a 6-month observational period after the start of therapy, and therefore the entire observational period in these patients may be prolonged up to a maximum of 18 months. Visits at the clinic will be performed according to Investigator's judgment and local clinical practice: it is estimated that visits will take place approximately every three months, with some degree of flexibility (*e.g.*, ± 1 month or higher) according to local standard of care.

## Target Population

Patients aged ≥12 years and ≤ 50 years with severe or moderate haemophilia A without inhibitors against FVIII receiving standard of care treatment.
Patients must meet the following criteria for study entry:

1. Signed informed consent
   - Consent/assent will be taken as appropriate from patient, parent or legal guardian, according to age and applicable regulations.
2. Must own a device compatible with the ePRO application and with the fitness tracker that will be provided to the patient (Fitbit Versa model); please refer to appendix 6 for an exhaustive list of acceptable devices.
3. Must have on his/her own device a data traffic availability of at least 2 GB in total per month intended only for use of study applications and data transfer. If the data traffic plan is exhausted, the patient must be able to connect to a wi-fi network at least once every day in order to transfer the data collected for the study purpose.
4. Must accept to run on his/her own device the ePRO application and the fitness tracker application.
5. Must be available to turned on daily the bluetooth connection of his/her own device in order to allow the synchronization with the fitness tracker.
6. Ability and willingness to comply with all aspects of the protocol, including completion of questions on the ePRO application (for underage population, ePRO questions can be answered by legally authorized representative if deemed necessary).
7. Ability and willingness to wear the activity tracking device as indicated.
8. Patients aged ≥12 years and ≤ 50 years at time of informed consent.
9. Diagnosis of severe (FVIII < 1%) or moderate (FVIII ≥ 1 and ≤ 2%) congenital haemophilia A.
10. No prior history of a positive inhibitor against FVIII. If patient has a previous history of inhibitor development, the patient must have successfully eradicated inhibitors since 3 years.
11. At least 150 exposure days of FVIII prior to enrolment.

Patients who meet any of the following criteria will be excluded from study entry:

1. Bleeding disorder other than congenital haemophilia A.
2. Ongoing (or planned during the study) immune tolerance induction or FVIII prophylaxis if the patient has currently low title of inhibitors or had inhibitors in the past three years
3. Previous or concomitant autoimmune or connective tissue disease.
4. History of or suspected allergy or intolerance to any of the component of the fitness device (*e.g.*, aluminium anodised).

5. History of clinically significant hypersensitivity associated with monoclonal antibody
6. Obesity (BMI ≥ 30 kg/m$^2$).
7. Clinically important cardiovascular, metabolic, endocrine disorders or any other concomitant diseases or conditions that could limit the mobility of patients or could represent any risk according to the Investigator's judgment, or that could interfere with the study evaluation parameters.
8. Participation in any other interventional clinical trial, including Roche sponsored studies, or in any other support program that may include drug administration other than standard clinical practice (*e.g.*, compassionate use, use not in agreement with the authorized indications, patient support programs, etc.).

## Variables

Only data obtained during routine clinical practice and in compliance with the study objectives will be documented in this study.

### Primary Variable

The primary variable for this study is:

- Physical activity data collected through a wearable device (*i.e.*, fitness tracker) in terms of active minutes, METs and step counts.

### Secondary Variables

The secondary variables for this study are:

- Adherence to WHO Guidelines for the definition of physical activity;
- Date and time of bleed start and end;
- Sites of bleed;
- Types of bleed (spontaneous, traumatic);
- Treatment for bleed (episodic or prophylaxis agent and/ or other agent used, dose, route, start date and time of treatment used);
- Treatment regimen for Haemophilia A (episodic, prophylaxis, preventative treatment before physical activity), in terms of type of regimen (on-demand vs. prophylaxis), product used and dose, and adherence to treatment regimen;
- HRQoL through EQ-5D-5L and health status;
- Dose and frequency of concomitant medications taken to control pain (e.g., NSAIDs, painkillers);
- Joint health status based on HJHS questionnaire;
- BMI;
- Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period;
- Number of hospitalization days (patients) during the observation period;
- Pain intensity measured using a VAS;
- Engagement in physical activity (i.e. Active/Sedentary);
- Severity of disease.

### Other Variables of Interest

- Newly approved drugs, if patients will start such therapies during the observation period;
- Sleep duration and stages collected through a wearable device (i.e., fitness tracker).

All data will be recorded on eCRFs. The degree of detail and completeness of data collected will be dependent on local clinical practice. Data from source documents should be entered on the eCRF as soon as they become available. Daily physical activity data will be collected continuously via the wearable device (*i.e.*, fitness tracker). HRQoL, VAS for pain, missed days at school (patient) and/or work (patient and caregiver), age of possible early retirement (caregiver), number of hospitalization days (patients), bleeding information and drugs administered to treat Haemophilia (treatment for bleeds, episodic or prophylactic treatments, preventative treatment before physical activity) will be recorded by the patient through ePRO application according to protocol requirements (refer to Appendix 2, Data Collection).

## Data Source

All data will be recorded on electronic case report forms (eCRFs). The degree of detail and completeness of data collected will be dependent on local clinical practice. Data from source documents should be entered on the eCRF as soon as they become available. Daily physical activity data will be collected continuously via the wearable device (*i.e.*, fitness tracker). HRQoL, VAS for pain, missed days at school (patient) and/or work (patient andcaregiver), age of possible early retirement (caregiver), number of hospitalization days (patients), bleeding information and drugs administered to treat Haemophilia (treatment for bleeds, episodic or prophylactic treatments, and preventative treatment before physical activity) will be recorded by the patient through ePRO application according to protocol requirements (refer to Appendix 2, Data Collection).

## Data Analysis

The appointed Contract Research Organization (CRO) will be responsible for the statistical analysis of the study.

All statistical analyses and data processing will be performed using The Statistical Analysis Software (SAS), release 9.4 or later, under Windows 7 or Windows 10 Pro operating system.

The statistical methods planned in this study protocol (see below) will be detailed, agreed and approved in a statistical analysis plan (SAP) which will be finalized before database lock.

One interim analysis is planned, when all enrolled patients have completed 6 months of observation. Details of this analysis will be provided in the SAP.

Descriptive statistics will be provided in summary tables according to the type of the variable. Continuous variables will be summarized by using number of cases, mean, and standard deviation, median, quartiles and range (i.e. minimum and maximum). Categorical variables will be summarized by using frequency and percent distribution.

Primary variables (*i.e.*, daily evaluations of active minutes, step counts and METs) will be analyzed over the 12 months' observational period by means of descriptive statistics (e.g. weekly/monthly). The 95% confidence interval (CI) of the mean will be also presented. Moreover, results will be also shown graphically, if deemed necessary.

Analyses on primary variables will be conducted on patients with established valid measurements from the fitness tracker.

A sensitivity analysis could also be performed evaluating the relationship of primary variables with baseline, demographic or other clinically relevant variables which will be detailed and described in the SAP.

Secondary variables will be summarized by using descriptive statistics as indicated in general methodology section, according to the type of variable analyzed, at any given time point (where applicable). The 95% CI of the mean change could be also presented.

Particularly, the proportion of patients who will meet WHO recommendations for physical activity will be summarized using descriptive statistics and 95% CIs as well.

The same analysis will be performed on active/sedentary patients and severe/moderate patients.

A further exploratory analysis will be performed in patients that will start treatment with any newly approved drugs during the study. An intra-patients comparison will be performed on pre and post treatment start primary and secondary variables evaluations, through means of descriptive statistics.

Due to the exploratory nature of this study, no adjustment for multiplicity will be made.

## Study Size/Determination of Sample Size

Given the exploratory nature and the objectives of this non-interventional study, rather than testing a formal hypothesis, a justification based on epidemiologic data from the Italian registry of congenital bleeding disorders (*Giampaolo et al. 2017*) was considered more appropriate than a power calculation in the traditional fashion or using an estimation approach through the precision of confidence intervals.

Based on data collected from the 54 Hemophilia Treatment Centers, members of the Italian Association of Hemophilia Centres (AICE), it is estimated that the planned number of participants in this study will represent approximately 10-15% of patients with Haemophilia A in Italy in the same age range and category of severity planned for this study. The total sample size planned is approximately 150 patients overall, 125 patients with severe Haemophilia A and 25 patients with moderate Haemophilia A.

# 8. APPENDIX 2: SCHEDULE OF ASSESSMENTS

Assessments and study visits will be performed as listed in the Table 2.

Visits at the clinic will be performed approximately every three months, but some degree of flexibility (e.g., ± 1 month or higher) will be considered according to Investigator's judgment and local clinical practice.

During the study, HRQoL, health status, joint health status will be reported on a pre-determined frequency for 12 months. Physical activity data will be collected daily using a fitness tracker.

Additionally, patients (or patient's legally authorized representative) will be reminded on a monthly basis to report via their ePRO application whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a further bleed has been given. When a bleed occurs, the patient (or patient's legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (date, time of start and time of end), symptoms of bleed, and treatment for bleed.

Health status will be captured in ePRO via the visual analogue scale (VAS) component of the EQ-5D-5L at baseline, every 12 weeks and at the end of study.

Physical activity will be measured daily by wearing a fitness tracker continuously during study participation. Patients will be daily reminded to wear the device. A valid day of monitoring is defined as at least 10 wear hours per day. Wear time will be derived through data collected by the fitness tracker.

The reason for the use of coagulation products (e.g., bleeding, prophylaxis, pain, etc.) will be documented by the Investigator in the source data and reported in the e-CRF. The reason for the use of coagulation products for bleeding treatment, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed, will be recorded by patients in the ePRO application and will be then transmitted to the eCRF.

Therapy will be recorded by the investigator at baseline visit and it will afterwards be confirmed by the patient in ePRO application. If there are changes to the assigned therapy, the patient will enter therapy variations in ePRO (e.g., dose, frequency, drug name etc.) and data will be then transmitted to the eCRF.

Demographics and results from physical examinations, and vital sign assessments will only be collected if available from routine clinical practice. No additional diagnostic or monitoring procedures will be applied to the patients outside of routine clinical practice.

End of study

The end of the study will be the date on which the last patient performs the last visit. This is expected when:

- The last patient completes the 12-month observation period (and patients that start treatment with any newly approved drugs complete a 6-month observational period after the switch)

OR

- The last patient has died, withdraws consent, or is lost to follow up, whichever occurs first

OR

- The study has been terminated by the Sponsor, if earlier.

**Table 2: Data collection overview**

| | Baseline | Observational period | | | Study Completion/ Early Termination Visit[1] | Patients starting any newly approved drugs between month 6 and month 12[2] | | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | | | |
| **Time (months)*** | **0** | **3** | **6** | **9** | **12** | **Start of therapy** | **3 post-start** | **6 post-start** |
| Informed consent[3] | X | | | | | | | |
| Demographic data | X | | | | | | | |
| History of physical activity | X | | | | | | | |
| Medical history and history of Haemophilia (including history of anaphylaxis or known thrombophilia) | X | | | | | | | |
| Number of bleeds, number of school/work days missed and number of days hospitalized during 24 weeks prior baseline | X | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | |
| Treatment for Haemophilia (including start of treatment with newly approved drugs) | X | X | X | X | X | X | X | X |
| Prior (in the 24 weeks before baseline) and Concomitant medications, including coagulation products | X | X | X | X | X | X | X | X |
| Physical examination[4] | X | X | X | X | X | | X | X |
| Vital signs (including height (at baseline only), weight and BMI (at baseline and every 3 months) | X | X | X | X | X | | X | X |
| Downloading of ePRO application and training in its use[5] | X | | | | | | | |
| Dispensing of fitness tracker and downloading of related application | | | | | | | | |
| Physical activity[6] | X | ← daily → | | | | ← daily → | | |
| Bleeding and treatments for bleeding (via ePRO)[7] | X | ← when bleeding occurs → | | | | ← when bleeding occurs → | | |
| VAS for pain (via ePRO)[8] | X | ← monthly → | | | | ← monthly → | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| EQ-5D-5L (via ePRO) [9] | X | X | X | X | X | | X | X |
| Joint health status (HJHS) [12] | X | | X | | X | | | X |
| Days away from school (patients) or work (patients and/or caregivers), age of possible early retirement (caregiver), (via ePRO)[10] | | ← monthly → | | | | ← monthly → | | |
| Days of hospitalization related to haemophilia (patients) (via ePRO) | | ← monthly → | | | | ← monthly → | | |
| Evaluation of start a newly approved drug therapy | | X | X | X | X | | | |
| Any relevant surgeries or procedures | | X | X | X | X | X | X | X |

* Visits at the clinic will be performed approximately every three months, but some degree of flexibility (e.g. ± 1 month) will be considered according to Investigator's judgment and local clinical practice.

[1]In case of early study discontinuation (for any reason), procedures will be those scheduled for Visit 5 (study completion visit)

[2]Patients who will start treatment with any newly approved drugs (see Study Protocol, Section 2 exploratory objectives), between Month 6 and Month 12 will complete a 6-month observational period after the switch, and therefore the entire observational period in these patients may be prolonged up to 18 months. They will also perform the Study Completion/ Early Termination Visit as their last visit.

[3]The Consent Forms must be signed and dated by the patient (if aged ≥18 years) and by parent/caregiver (for patient aged 12-17 years) before start of documentation of his/her data in the eCRF.

[4]A complete physical examination will be performed at baseline (if planned as per standard routine of care) and at least targeted physical examinations will be performed at all follow-up visits

[5]The ePRO application downloaded on the patient's own device) will be used by patients to record data on bleeds, bleeds treatment, HRQoL, number of days away from school (patients) or work (patients and/or caregivers), age of possible early retirement (caregiver), number of hospitalization days (patients) and VAS for pain. In patients who will start treatment with any other newly approved drugs (see Study Protocol, Section 2 exploratory objectives), measurements of the parameters listed above through ePRO application will be also performed at the time of start of treatment with any newly approved drugs, and for at least 6 months following the start of treatment.

[6]Physical activities will be measured by wearing a study device continuously during study participation. At baseline, information about physical activity in the previous 24 weeks will be collected if available.

[7]Bleeding and treatments for bleeds will be reported in a continuous manner, during study participation. Patients will be prompted electronically on a monthly basis to report any bleeds. In case of bleeds, patients will report bleed information, including site of bleed, type of bleed, time of each individual bleed (date, start time and end time), symptoms of bleed, treatment for bleed and health status information. The following information on treatments for bleeds will be reported: agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. At baseline, information about any bleedings which occurred in the previous 24 weeks will be collected.

[8]VAS for pain will be evaluated at baseline, monthly and at the end of study.

[9]EQ-5D-5L for pain will be evaluated at baseline, every 3 months and at the end of study

[10]Evaluated at baseline, monthly and at the end of the study

[11]HJHS will be evaluated at baseline, at 6 months and at the end of the study. HJHS will be also performed at the time of start of treatment with any newly approved drugs, and at 6 months following the start of treatment drugs.

# 9. APPENDIX 3: WEARING TIME ESTIMATION

The derivation of the Wearing time is reported in the following document attached to this SAP: Wearing Time Report_final 2.0_211102.pdf

# 10. APPENDIX 4: TABLES , LISTINGS AND FIGURES.

All tables/figures/listings will be presented in landscape format.

The standard font size is 9 points Arial for all tables. Listings will be presented with an 8 or 7 points Arial.

Titles will be center-aligned; footnotes will be left-aligned.

Each table/figure/listing will have 2 titles:

- The 1st title will be the table/figure/listing number with the description of the table/figure/listing;
- The 2nd title will be a description of the study set presented in the table/figure/listing.

Some tables will have a third title (before 2nd title) with a description of the statistical method used in those tables.

Any footnote added to explain the table/listing/figure contents will be presented in the following format:

Note 1: Percentages are calculated on the number of patients (N).

Note 2: A serious adverse event is an ....

Note 3: …….

The last two footnotes of each table/figure will be footers indicating:

- the reference listing of the data;
- the program name, the date and time of generation and the SAS® version used.

The last footnote of each listing will be a footer indicating the program name, the date and time of generation and the SAS® version used.

Listings will be presented on the enrolled population. A flag will define the evaluable patients.

The derived variables will be identified in the listings with a flag (*).

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes. Numeric variables will be listed generally with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- Min, max: same as actual data;

- Mean and its confidence limits (unadjusted and adjusted), adjusted difference between means and its confidence limits, SD, median: actual data + 1 decimal;
- Percentage: 1 decimal place;
- P-value: 3 decimal places.

The mock shells will be contained in an attached document.