International Immune Tolerance Study

**IMMUNE TOLERANCE INDUCTION STUDY IN PATIENTS WITH SEVERE TYPE A HAEMOPHILIA WITH INHIBITOR AFTER FAILURE OF A PREVIOUS INDUCTION OF IMMUNE TOLERANCE WITH FVIII CONCENTRATES WITHOUT VON WILLEBRAND FACTOR**

**REScue Immunotolerance Study**

*In ITI-Experienced Patients*

Acronym: **RES.I.ST.** EXPERIENCED

Final Version –2.0

July 17, 2013
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Background</td>
<td>7</td>
</tr>
<tr>
<td>2. Aim of the study</td>
<td>11</td>
</tr>
<tr>
<td>3. Study design</td>
<td>11</td>
</tr>
<tr>
<td>4. Population</td>
<td>13</td>
</tr>
<tr>
<td>5. Treatment</td>
<td>14</td>
</tr>
<tr>
<td>6. Baseline evaluation and follow-up</td>
<td>15</td>
</tr>
<tr>
<td>7. Study procedures</td>
<td>16</td>
</tr>
<tr>
<td>8. Additional Laboratory Investigations</td>
<td>22</td>
</tr>
<tr>
<td>9. Statistical Analysis</td>
<td>23</td>
</tr>
<tr>
<td>10. Ethics</td>
<td>23</td>
</tr>
<tr>
<td>11. Data Safety Monitoring</td>
<td>24</td>
</tr>
<tr>
<td>12. Publication Policy</td>
<td>28</td>
</tr>
</tbody>
</table>
1. **BACKGROUND**

In vitro\(^1\) and retrospective clinical studies\(^2,3\) suggest that FVIII/VWF complex concentrates may have less immunogenicity with respect to those plasma-derived concentrates purified with monoclonal antibodies (MABs), and recombinant DNA factor VIII concentrates (rFVIII), in both which the von Willebrand factor (VWF) is absent. Based on these findings, some authors advocated that the VWF may actually protect against inhibitor development by reducing the immunogenicity of factor VIII\(^4\). Even still to be demonstrated by large scale trials, this may be clinically mirrored by a lower incidence of inhibitors reported either in prospective\(^5,6\) and in retrospective studies\(^7\).

Recently published in vitro studies\(^8,9,10,11\) showed that FVIII/VWF complex concentrates presented less reactivity with FVIII-inhibitor antibodies, with respect to VWF devoid FVIII concentrates (MABs purified plasma-derivatives and rFVIIIs). These results were consistent with a previous report\(^12\) in which a better in vivo recovery and clinical response was observed in a patient with inhibitors when switched to VWF/FVIII complex concentrate. All these findings point to a potential role of VWF in the management of bleeding episodes in patients with hemophilia A and inhibitors.

In a recently reported prospective series 8 of 10 patients non responsive to previous immune tolerance treatment with VWF-devoid FVIII concentrates, succeeded in achieving inhibitor remission when switched to plasma-derived VWF/FVIII complex concentrates\(^13\), confirming the results of an earlier report from the same group\(^14\).

Immune tolerance induction (ITI) showed to be effective in about 70% of hemophiliacs with inhibitors. Poor prognosis factors have been identified by different Registries: age ≥ 6 years, ITI started >1 year from inhibitor development, inhibitor peaks >200 BU, inhibitor titer >10 BU at the start of ITI and previously failed ITI.
Immune tolerance induction with isolated FVIII vs. FVIII/VWF concentrates. Single Center experience (Kreutz et al. Haematologica 2001; 86 (S4): 16-20)

<table>
<thead>
<tr>
<th>Type of FVIII concentrate</th>
<th>1979-93</th>
<th>1993-00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FVIII/vWF</td>
<td>Isolated FVIII</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>LR</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Success rate (%)</td>
<td>91</td>
<td>28</td>
</tr>
<tr>
<td>LR (% , n/n)</td>
<td>100 (5/5)</td>
<td></td>
</tr>
<tr>
<td>HR (% , n/n)</td>
<td>88 (14/16)</td>
<td>28 (4/14)</td>
</tr>
</tbody>
</table>

Median time (range) of ITI achievement (months)

| LR | 1.5 (0.5-3 ) | ---- | 1.5 |
| HR | 4 ( 0.5-42 ) | 3 (2-7) | 3   |

**Keys to table:** HR High responders; LR = Low responders; * Coming from not successful ITI with isolated FVIII concentrates.

Another study\(^{15}\), which was part of the French ITI Study, carried out in a cohort of 8 patients treated with FVIII/VWF concentrates, showed complete success in seven patients in a very short period of time —a median of 8 months—, while a partial success was achieved in the remaining patient, who became a low responder. At the same time, in other seven patients treated with rFVIII, there was only one complete success, one partial success and one failure, while the remaining 4 patients have not been tolerised yet after 16-30 months.

Recently, a study was conducted in Italy and in Spain\(^{16}\) to assess the effectiveness of ITI using a high purity VWF/FVIII complex concentrate in inhibitor patients at high risk of failure [19]. Patients with severe or moderate haemophilia A and high responding inhibitors who had at least one poor prognostic factor, were prospectively evaluated. Seventeen haemophiliacs (16 severe, 1 moderate), aged 4-54 years (median 23) were followed-up for 6-71 months. Poor prognostic factors were: delayed-onset ITI (n=16), age >6 years (n=16), previously failed ITI (n=4), inhibitor peak >200 BU (n=2), inhibitor >10 BU when ITI was started (n=4). Complete success was obtained in 9 patients (53%) after 4-30 months of treatment (median 24), including 2 of 4 patients who had previously failed ITI. Seven patients achieved partial success, with sustained low inhibitor titres (median 1.5 BU, range 1.1-2.8) but abnormal recovery and/or half-life, while the remaining patient withdrew ITI after 12 months when the inhibitor titre was 70 BU. No patients relapsed, and response was maintained after ITI for a median follow up of 8 months (range 2 to 27 months). The positive clinical
response to ITI with a VWF/FVIII complex concentrate resulted in a significantly lower number of bleeding episodes and hospitalizations and by a discontinuation of bypassing agents.

All these findings suggest VWF/FVIII complex concentrates can be effective in ITI, even in patients at high risk of failure.

To explain these findings, a role for VWF (i.e. prolonged antigen exposure) has been hypothesized. Other possible explanations encompass the maintenance of the sterical conformation of FVIII while complexed with its natural carrier, i.e. VWF. This might result in a significant therapeutic benefit with respect to VWF-devoid factor VIII concentrates.

The purpose of this study is to assess the role of FVIII/vWF complex concentrates in successfully inducing immune tolerance in patients who have previously failed ITI with factor VIII concentrate devoid of VWF.

References


7 Smith MP Flora HK Savidge GF. Successful clinical use of a plasma derived, dual virus inactivated factor VIII concentrate incorporating solvent-detergent and


2. **AIM OF THE STUDY**

The study will evaluate whether FVIII/vWF concentrates successfully induce immune tolerance in patients who have already experienced and failed immune tolerance induction with VWF-free FVIII concentrates.

3. **STUDY DESIGN**

The study is designed as a prospective, open label, naturalistic study.

This study will assess a rescue treatment with a FVIII/vWF concentrate at high dosage (200 IU/Kg daily) in patients who failed a previous ITI attempt with a vWF-free FVIII concentrate (plasma-derived or recombinant).

3.1. **End points**

3.1.1. **Primary end point**

Primary end point is the success in inducing immune tolerance, defined as:

1. **Success**

   Success, is defined as the abolition of the inhibitor to < 0.6 BU within 33 months of ITI with a factor VIII recovery ≥ 66% and half-life ≥ 6 hrs, and measured after a 72-hour treatment-free washout period.

   In this case the dose of concentrate is gradually tapered off to regular prophylaxis.
II. **Partial response:**

A reduction in inhibitor titre to < 5 BU/ml with factor VIII recovery of <66% and half life of <6hrs associated with clinical response to factor VIII therapy, and not followed by a treatment limiting anamnestic rise in inhibitor to >5 BU/ml over a period of six months of on-demand treatment or 12 months of prophylaxis.

III. **Treatment failure:**

Failure to fulfil the criteria for **success** or partial success within 33 months

or

a less than 20% reduction in inhibitor titre, relative to the peak inhibitor titre on ITI, over any six-months period after the first three months of treatment. This implies that 9 months is the minimum treatment period and 33 months the maximum possible duration of unsuccessful ITI

or

withdrawal from the study for any other reason.

3.1.2. **Secondary end points**

Secondary end points will be:

I. **Maintenance of immune tolerance**

Defined as absence of relapse, assayed up to 12 months after the achievement of tolerance

II. **Time to achieve success**

Referring to either success or partial-success as defined in this section of the protocol

III. **Safety / Compliance to treatment**

It includes assessment and evaluation of the adverse events occurring through treatment and the compliance with a lengthy regimen

IV. **Cost of care**

Direct costs will be calculated.
3.1.3. Main variables

The following variables will be evaluated:

- Rate of success (or partial success)
- Time to achieve primary end points
- Maintenance of response, defined as absence of relapse (see methods section)
- Number of breakthrough bleeding events
- Occurrence of adverse events
- Requirement for central venous device
- Treatment compliance
- Treatment-related direct costs
- Predictive factors (genetic defect, epitope mapping, age at start of previous ITI, peak inhibitor titre during previous ITI, line infections, inhibitor titre at rescue ITI start-up, age at start of rescue ITI, peak inhibitor titre during rescue ITI).

4. POPULATION

50 Subjects with severe haemophilia A with a high responding inhibitor who previously failed ITI with a concentrate containing FVIII alone. (See enrollment criteria 4.1).

4.1. ENROLLMENT CRITERIA

Patients will be eligible when meeting the following criteria:

a. severe hemophilia A (FVIII<1%)  
b. male patients, any age;  
c. high responders (peak inhibitor levels > 5 BU);  
d. with any inhibitor level at study enrolment;  
e. with ability and willingness to participate in the study;
f. with no concomitant systemic treatment with immunosuppressive drugs (eg. Corticosteroids, if used more than 5 days every 3 months and/or at a dose of > 2mg/kg or 60 mg/day), azathioprine, cyclophosphamide, high-dose immunoglobulin as well as the use of a protein A column or plasmapheresis; interferons);

g. with no concomitant experimental treatment.

h. previous ITI course of at least 9 months with a VWF-free FVIII concentrate at any dosage, such as recombinant FVIII and/or monoclonally purified FVIII.

i. patients who initially succeeded in clearing the inhibitor and then relapsed may be included.

j. absence of high risk of cardiovascular, cerebrovascular or other thromboembolic events, as deemed by the treating physician.

5. **TREATMENT**

Patients will be given a VWF/FVIII concentrate, 200 IU/Kg by one or two bolus injections daily **beginning on Day 0**. The product will be chosen according to physician / patients preferences.

After success confirmation the dose will be tailed off progressively until discontinuation or until institution of prophylaxis according to physician and patient preference (see Section 7.7. “Tailing Off Procedure and Prophylaxis” of STUDY PROCEDURES).

Subjects may be treated with FVIII bypassing agents on demand or on prophylaxis, but bypassing agents prophylaxis should be avoided when the inhibitor level drops to ≤ 2BU due to potential risk for thrombosis. Bypassing agents should not be infused at the same time as FVIII concentrates when the inhibitor titre is equal to or less than 5 BU (≤5BU).
6. **BASELINE EVALUATION AND FOLLOW-UP**

Patients will have monthly medical visits through the treatment period, until the endpoint is reached or treatment is withdrawn for early failure.

Patients achieving a response will be monitored for relapse with follow up visits up to 12 months after immune tolerance achievement at a defined time schedule.

Schedule of visits and laboratory assessments to be carried out at any time during the study is displayed in the following table (see also STUDY PROCEDURES).
### TIME POINTS

<table>
<thead>
<tr>
<th>TIME POINTS</th>
<th>Enrollment</th>
<th>Start of ITI</th>
<th>Up to 33 months (#)</th>
<th>At Failure or Success Confirmation</th>
<th>MONITORING OF FOR RELAPSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL EVALUATION&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Each visit&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INHIBITOR DETERMINATION&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Each visit</td>
<td></td>
</tr>
<tr>
<td>IN VIVO RECOVERY&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>after 2 consecutive inhibitor det. &lt;0.6 BU or &lt;0.4 NBU</td>
<td>Each visit</td>
</tr>
<tr>
<td>HALF LIFE&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>after normalisation of IVR ≥ 66% expected value</td>
<td>Last visit (12&lt;sup&gt;th&lt;/sup&gt; month)</td>
</tr>
<tr>
<td>PATIENT SATISFACTION QUESTIONNAIRE</td>
<td>Yes</td>
<td></td>
<td>Every 6 months</td>
<td>In case of success or failure</td>
<td></td>
</tr>
<tr>
<td>EPITOPE MAPPING</td>
<td>Yes&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG Subclasses</td>
<td>Yes&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>Yes&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENETIC TESTING</td>
<td>any time if not yet available&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a**</sup> If not reaching earlier success or failure

1 Clinical evaluation: height, weight, concomitant illness, complete blood count at 1<sup>st</sup> visit only, Hct at monthly visits

2 Inhibitor determinations: the inhibitor level will be measured locally using the standard Bethesda method or the Nijmegen modification. The initial ITI inhibitor and the first 2 negative assays and the final assay 12 months after the end of ITI will be confirmed centrally.

3 In vivo recovery will be estimated from body weight and FVIII taken pre and 15-30 minutes post-infusion of approximately 50 IU/Kg FVIII.

4 Half-life will be studied after at least 72 hours treatment-free wash-out period following administration of 50 IU/Kg FVIII. To calculate half-life blood samples will be taken pre and 15 min, 1 hour, 2, 4, 6, 24 and 48 hours post-infusion (blood samples after 4 and 48 hours are optional). Weight, number of units infused, sample times and FVIII assays results are necessary for half-life calculation.

5 Central laboratory - store plasma sample at –70° C for shipment to central laboratory

6 Central laboratory (in case of unavailability at local Centre)

#1 Monthly visit begins 30 days (+/- 2 days) after Day 0

### 7. STUDY PROCEDURES

#### 7.1. Centre Registration

Centres in North America will register the study with City of Hope and obtain ethical approval from their Institutional Review Board. The study will be conducted according to the Declaration of Helsinki.
Once the IRB approval and approved consent form have been received, the centre will be issued with a password for access to the study website. Each password is unique to the centre and will permit secure access to the electronic clinical record form (CRF) on www.itistudy-resist.com for direct, interactive, electronic data entry. The website will also have a notice board, a summary of the protocol, and a printable CRF and protocol to be downloaded.

7.2. Patient Enrollment
Patients who fulfil the entry criteria, and express written consent will be enrolled. The presence of their inhibitor titre will be confirmed locally, if this has not already taken place. Patients may be enrolled on-line by filling in the enrolment form on www.itistudy-resist.com. An easy to follow user's manual to the electronic patient record (CRF) is also available at www.itistudy-resist.com.

7.3. Product type
The brand and type of FVIII/VWF complex concentrate to be used for ITI is at the discretion of the managing clinician.

A major switch in product type during ITI is a reason of withdrawal from the trial.

A major switch in product type refers to changes made across the major product categories: 1) von Willebrand factor containing FVIII concentrate; 2) other FVIII concentrates not containing von Willebrand Factor.

A minor switch in product type during ITI will be considered in the final analysis.

A minor switch in product types refers to changes made within the brands of FVIII/von Willebrand Factor concentrates.

A change of FVIII dosage/regimen will be cause for patient withdrawal from the study.
7.4. **Treatment of Intercurrent Bleeding**

PCCs, APCCs, rVIIa and human and porcine factor VIII can be used to treat active bleeding during immune tolerance induction as directed by the managing clinician. It is thought unlikely that sufficient factor VIII concentrate will be used for the treatment of bleeding episodes to confound the dose comparison. All treatment of bleeds will be recorded in the CRF and will be used for the cost-effect analysis and analysis of morbidity.

7.5. **Interruption of ITI**

Interruptions of ITI should be avoided whenever possible since they are thought to have an adverse effect on the outcome of the ITI. If central venous access is temporarily lost because of line infection, ITI should continue through peripheral veins as long as possible until central venous access can be restored. If it proves impossible to continue ITI in this way, an interruption of a maximum of two weeks will be permitted.

7.6. **Procedures for determining if the inhibitor has disappeared**

7.6.1. **Factor VIII Recovery**

Within a month after the first negative inhibitor titre, the Bethesda assay is repeated. If this is still negative, the factor VIII recovery is determined locally after the administration of 50 IU/kg of factor VIII.

Relative incremental factor VIII recovery will be estimated from bodyweight and factor VIII assays taken pre and 15-30 minutes post-infusion of approximately 50 IU/kg factor VIII. Recovery should be estimated at the longest possible interval after the last dose of factor VIII concentrate permissible on the treatment regimen given for ITI, prophylaxis or intercurrent bleeding.

A normal FVIII recovery is defined as greater or equal to 66% of the expected rise in factor VIII activity level. (e.g. 2%-FVIII activity for each unit/kg of infused FVIII).
If factor VIII recovery is still < 66%, recovery is determined in the same way at monthly interval until ≥ 66%. Inhibitor and recovery measurements should be conducted at the longest possible interval after the previous factor VIII dose.

### 7.6.2. Factor VIII half-life

Assay will be conducted locally.

Once the factor VIII assays are available, a half-life estimate may be obtained by entering the raw data on-line directly into the electronic CRF on [www.itistudy-resist.com](http://www.itistudy-resist.com). The half-life will be calculated using a software package which calculates half-life using a model independent analysis by linear regression using the method of least squares. For this purpose, the following, relatively truncated, factor VIII half-life estimate is considered adequate. Blood samples will be taken for factor VIII estimation as follows:

<table>
<thead>
<tr>
<th>Time</th>
<th>Factor VIII Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-infusion</td>
<td>2 hrs</td>
</tr>
<tr>
<td>15 minutes</td>
<td>4 hrs(^{*})</td>
</tr>
<tr>
<td>1 hour</td>
<td>(*Optional)</td>
</tr>
</tbody>
</table>

The data required to calculate half-life includes the patient’s height, bodyweight and haematocrit; the number of factor VIII units infused; the factor VIII assay results; and the time of the infusion and sample times.

When the factor VIII recovery is found to have normalised (≥66%), the factor VIII half-life is estimated locally within one month, after a 72-hour washout period and using a dose of factor VIII of 50 IU/kg.

If the half-life is still reduced at this point (< 6 hrs) the patient will continue ITI and the half-life will be repeated every three months until normal (≥ 6 hrs).

When the factor VIII half-life and recovery are both normal, then ITI will be considered successful and the dose of factor VIII will be reduced to a prophylactic regimen. (see Tailing Off Procedure and Prophylaxis, below).
Inhibitor disappearance is defined as: a factor VIII inhibitor titer of < 0.6 BU, and normal factor VIII recovery (≥66%) and half-life (≥ 6 hours). Inhibitor and recovery measurements should be obtained at the longest possible interval following the previous dose of FVIII on the treatment regimen. Half-life studies should be conducted after a washout period of at least 72 hours.

7.7. Tailing Off Procedure and Prophylaxis

- Patients will gradually tail off the dose of factor VIII over three months at the discretion of the treating physician, starting when the patient is judged to be inhibitor-free. A recommended tapering schedule is as follows:
  a. 100 IU/kg/day for the first four weeks; then
  b. 50 IU/kg/day for the next 4 weeks; then
  c. 50 IU/kg every second day for the remaining four weeks; then
  d. Prophylactic dose regimen of 20-30 IU/kg, three times a week or every other day.

- The Bethesda titre and factor VIII recovery (using 50 IU/kg factor VIII) will be measured one month after each dose change and then every three months.

7.8. Monitoring for Relapse

During the 12-month period of tailing off and prophylaxis following inhibitor disappearance, the patients will be monitored for indicators of a recurrence of their inhibitor. Subjects will have monthly Bethesda assays and FVIII recovery studies at months 1, 2, 3, 4, 6, 9, and 12. At month 12 a FVIII Survival study will be conducted as well.

Recovery studies and inhibitor assays (month 1, 2, 3, 4, 6, and 9) will be obtained at the longest possible interval following the previous dose of FVIII concentrate. The half-life study should be done after a washout period of at least 72 hours.

If any of these tests indicate possibility of a recurrence of an inhibitor at any time within 12 months after ITI completion, then the tests must be repeated within two weeks to confirm relapse. Two consecutive abnormal tests (positive inhibitor by
institutional criteria, reduced factor VIII recovery or half-life or any combination of these) are required for the patient to be judged to have relapsed.

Timetable for monitoring for relapse in the 12-month follow-up period after successful ITI:

<table>
<thead>
<tr>
<th>Months after successful ITI</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inhibitor, recovery</td>
</tr>
<tr>
<td>2</td>
<td>Inhibitor, recovery</td>
</tr>
<tr>
<td>3</td>
<td>Inhibitor, recovery</td>
</tr>
<tr>
<td>4</td>
<td>Inhibitor, recovery</td>
</tr>
<tr>
<td>6</td>
<td>Inhibitor, recovery</td>
</tr>
<tr>
<td>9</td>
<td>Inhibitor, recovery</td>
</tr>
<tr>
<td>12</td>
<td>Inhibitor*, recovery, Half-life</td>
</tr>
</tbody>
</table>

* Plasma saved for central laboratory confirmation of the inhibitor titre.

Relapse is defined as:

- A positive inhibitor assay according to institutional criteria and reduced factor VIII recovery (< 66%) x 2 within a two-week period at any time during the 12 months following cessation of immune tolerance induction
- Or a negative inhibitor according to institutional criteria, but a reduced factor VIII recovery x 2 within a two-week period at any stage during the 12 months following the cessation of immune tolerance
- Or a negative inhibitor titre according to institutional criteria, but a reduced factor VIII half-life that is confirmed within 2 weeks, 12 months after discontinuing ITI (end of study)

7.9. The End of study

The end of the study period will be:

a. Twelve months after the inhibitor has disappeared, or
b. The time that a patient is considered to have failed ITI, or
c. The time of relapse, or
d. The time that the patient is withdrawn for other reasons e.g. interruption of ITI > 2 weeks, desire of the patient, parents or physician to stop ITI.
7.10. Withdrawal from the study
If ITI continues off protocol, investigators are encouraged to continue collecting data so that this data may be used for future analysis.

It is recognised that patients requiring central venous access devices may develop line-infections, may require these lines to be replaced, and may suffer interruption of their ITI as a direct result. All possible steps must be taken to avoid interruption of therapy. Patients will be withdrawn from the study if a > 2 week continuous interruption in therapy occurs.

Patients may be removed from the study for other reasons, including failure to comply with the protocol or parental/physician wish to discontinue the study. These situations should be discussed with the study coordinators. Since the study will have an intention to treat analysis, all patients withdrawn from the study for any reason will be considered treatment failures.

7.11. Record Keeping
The central file server in Manchester will monitor the progress of each patient and automatically issue reminders for outstanding data and instructions on the further treatment of individual patients by e-mail or fax.
For investigators who do not wish to use the Internet in this way, a conventional paper system will also be available.

Top copies of CRF pages should be dispatched back to the central data-handling facility every three months, as well as at completion of the study or at the time of patient withdrawal. Reminders will be issued centrally every three months.

8. Additional Laboratory Investigations
Genetic testing
5mL of blood will be drawn for genetic-testing. Genetic testing may be performed anytime at a local laboratory or central laboratory if not already available.
Epitope mapping

Epitope mapping will be performed at baseline and at the conclusion of the achievement of success or failure. An aliquot of 2ml of plasma (corresponding to about 5 ml of blood) is required before ITI initiation. Plasma samples will be stored at –70°C and sent to City of Hope.

IgG Subclasses

Patient plasma will be tested for IgG Subclasses monthly. An aliquot of 100μl will be requested at each time point already scheduled for inhibitor evaluation and be sent to the Central Laboratory at City of Hope. IgG Subclass will be assessed by Christoph Königs, M.D. at JW Goethe University, Laboratory for mol Hemostasis and Immunodeficiency, Dept. of Pediatrics, Hs32, Theodor-Stern-Kai 7 - 60596 Frankfurt – Germany. Specimens will be sent directly from City of Hope to Dr. Königs.

9. STATISTICAL ANALYSIS

Sample size cannot be defined a priori. There are no available data about the rate of success in previously ITI-unresponsive patients. The rate of success for rescue treatments with FVIII/VWF concentrates was about 60-80% in previous retrospective reports. The power of the study will be calculated ex post.

Primary end-points will be analysed on an intent-to-treat basis. The significance of success rates of rescue treatment will be evaluated on the basis of 95% confidence interval of the rate achieved.

Descriptive statistics will be used to depict the study population and all the main variables. Association of primary and secondary end-points with predictive factors or other variables will be assessed.

10. ETHICS

The study is an investigator-originated proposal.
The study protocol and the informed consent form will be submitted for approval to the Independent Ethics Committee (IEC) of each participating institution prior to the initiation of the study, according to the local regulations.

The study will be conducted in accordance with national regulatory requirements, International Conference on Harmonization (ICH) Guidelines for GCP, and the Declaration of Helsinki. A written informed consent will be obtained from each patient prior to enrolment in the study.

IEC’s approval includes all necessary authorizations, specifically including patient consents, needed for disclosure of personal health information for use as appropriate.

All Serious Adverse Events (SAE’s) and Adverse Events (AE’s) involving the product used will be reported to regulatory and health authorities according to all applicable regulations, and to an independent Data Safety Monitoring Board (DSMB) (Appendix 3).

11. **DATA SAFETY MONITORING**

11.1. Functions of the Monitoring Committee

- Guarantee safety for participating patients:
  - Monitor all reported adverse events
  - Review and evaluate expeditiously all adverse events
  - Inform the coordinating center as to whether they are AE’S, SAE’s, study/drug related or not.

- Guarantee quality of the study:
  - Ensure respect of inclusion/exclusion criteria.
  - Ensure adherence to dosage/schedule of treatment as per protocol.
  - Ensure data/specimens collection as per protocol.

- Evaluation of the endpoints set forth by the study.
11.2. Authority of Monitoring Committee

- The Committee has the authority to ensure that Investigators respect the protocol and sanction them if they fail to comply.

- The Committee has the responsibility and the authority to recommend termination of either the participation of an individual centre or close the study prematurely, for reason of safety, protocol violations, or having reached significant success or failure.

- Recommendations will be based on majority vote.

- The Committee should meet at least once a year or as often as considered necessary by the Chair. This can be either in person or by teleconference. At each meeting, minutes will be prepared and a copy forwarded to the PIs and to the central file of the Study Coordinating Center.

11.3. Monitoring Serious Adverse Events

11.3.1. Definitions

**Adverse Event (AE)**

Any harmful clinical event appearing in a patient or subject involve in a clinical trial who has been administered a medicinal specialty, and which does not necessarily have a causal relationship with the treatment (GCP – European Directive 2001/20/CE; DL 211). A laboratory test abnormality considered clinically relevant, eg, causing the subject to withdraw from the study, requiring treatment, or causing apparent clinical manifestations, or judged relevant by the Investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

**Adverse Reaction (AR)**

Any harmful and undesired reaction to an experimental medicinal specialty, regardless of the administered dose (GCP – European Directive 2001/20/CE; DL 211).

**Serious Adverse Event or Serious Adverse Reaction (SAE, SADR)**
A serious adverse event (SAE) or serious adverse drug reaction (SADR) is any untoward medical occurrence that at any dose of the drug results in death, is life threatening (life threatening refers to an event as a result of which the patient was at risk of death at the time of the event), require hospitalization or prolongation, results in persistent or significant disability/incapacity, or causes a congenital anomaly (birth defect). (GCP – Directive 2001/20/CE; DL 211)

The term “life-threatening” in the definition of “serious” refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission results in a hospital stay of less than 12 hours. OR
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study). OR
- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of “medically important” and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Important Medical Event

Important medical event is any adverse event considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the “WHO Adverse Reaction Terminology – Critical Terms List”. These terms either refer to or might be indicative of a serious disease state.
Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

13.3.2. Serious and Unexpected Adverse Reaction (SUSAR)

An adverse reaction whose nature or seriousness is unforeseeable on the basis of the information relating to the product (Investigator’s Dossier / Summary of product characteristics) (GCP – Directive 2001/20/CE; DL 211).

13.3.3 Reporting Procedure

Adverse Events (AE) and Adverse Reactions (AR)

All adverse events and adverse reactions occurring after the subject has signed the informed consent must be fully recorded in the subject’s case record form.

Serious Adverse Events (SAE) and Serious and Unexpected Reactions (SUSAR)

All SAEs, including laboratory test abnormalities, fulfilling the definition of serious, occurring during the study and after the period of 30 days following the last administration of study drug must be immediately (within 24 hours of the investigator’s awareness) be reported to the City of Hope at Phone: 626/256-4673, extension 64350, or E-mail: newing@coh.org or cdeguzman@coh.org.

Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the designated person.

The investigator is responsible for defining and reporting the possible causal relationship between the trial drug and serious adverse event, in accordance with the considerations and definitions below:

<table>
<thead>
<tr>
<th>Causal Nexus</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>• There is no evidence of a causal relationship of any kind.</td>
</tr>
</tbody>
</table>
| IMPROBABLY   | • It does not follow a reasonable temporal sequence after the administration of the drug  
               • It could easily be due to the known characteristics fo the clinical status of the patient, to environmental or toxic factors, or to other therapies administered to the patient  
               • It does not follow a known course of response to the suspected drug  
               • It does not reappear or worsen when the administration of the drug is resumed. |
<table>
<thead>
<tr>
<th>Causal Nexus</th>
<th>Description</th>
</tr>
</thead>
</table>
| POSSIBLE     | • The event follows a reasonable temporal sequence after the administration of the drug.  
• The known characteristics of the clinical status of the patient, environmental or toxic factors, or to other therapies administered to the patient could have contributed.  
• It follows a known course of response to the suspected drug. |
| PROBABLE     | • The event follows a reasonable temporal sequence after the administration of the drug.  
• It cannot be reasonably explained only by considering the known characteristics of the clinical status of the patient, to environmental or toxic factors, or to other therapies administered to the patient.  
• It follows a known course of response to the suspected drug. |
| CERTAIN      | • There is clear evidence of a causal relationship between the treatment and the adverse event, and the role of other factors can be absolutely excluded. |
| UNEVALUABLE  | • There is insufficient information for clinically defining a causal nexus between the event and the administration of the drug. |

Give details in the SAE form.

If notified of the decease of a subject, in addition to the Sponsor, the investigator must also inform the local Ethics Committee, providing all of the additional information requested.

The Pharmacovigilance Responsible will arrange for the forwarding of all SUSARs to the Regulatory Authority, Principal Investigator and Ethics Committee with 7 days of receipt in the case of death or a life threatening, and within 15 days in all other cases (DL 211)

12. Publication Policy

The raw data shall remain the property of the steering committee at all times and will not be given to any of the sponsors. A report will be prepared, upon which the principal publication is to be based, and will be given to each of the sponsors when the statistical analysis is complete. The content of this report is to be agreed upon by the principal investigators.

The results, or any part of the results, are not to be presented or published separately without the consent of the steering committee.
The authorship of all resulting publications will be decided by the steering committee. It is anticipated that all members of the steering committee will be co-authors of the principal publications. All participants will be acknowledged in all resulting publications (other than abstracts) in an alphabetical list as members of the “RESIST_EXP group”. Although individual centres may publish their personal experience separately, the final analysis of the main study should only be published by, and with the consent of the steering group.