International Immune Tolerance Study

**Randomised Study of First Time Immunotolerance Induction in Patients with Severe Type A Haemophilia with Inhibitor at High Risk of Failure:**
Comparison of Induction of Immune Tolerance with FVIII Concentrates with or without Von Willebrand Factor

**REScue Immunotolerance Study In ITI-Naïve Patients**
Acronym: **RES.I.ST.\textsubscript{NAÏVE}**

Final Version - 1.2.
May 04, 2009

**Steering Committee Members:**
Europe: Alessandro Gringeri, Claude Negrier
North America: Nadia Ewing, Keith Hoots, Margaret Kurth-Heisel

Website: www.itistudy-resist.com
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Background</td>
<td>3</td>
</tr>
<tr>
<td>2. Aim of the study</td>
<td>7</td>
</tr>
<tr>
<td>3. Study design</td>
<td>7</td>
</tr>
<tr>
<td>4. Population</td>
<td>9</td>
</tr>
<tr>
<td>5. Treatment</td>
<td>10</td>
</tr>
<tr>
<td>6. Randomization</td>
<td>11</td>
</tr>
<tr>
<td>7. Baseline evaluation and follow-up</td>
<td>11</td>
</tr>
<tr>
<td>8. Assessment of the response achievement/failure</td>
<td>13</td>
</tr>
<tr>
<td>9. Statistical Analysis</td>
<td>15</td>
</tr>
<tr>
<td>10. Ethics</td>
<td>16</td>
</tr>
<tr>
<td>11. Data Safety Monitoring Committee</td>
<td>17</td>
</tr>
<tr>
<td>12. Study procedures</td>
<td>18</td>
</tr>
<tr>
<td>13. Appendix</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 treatment was 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>
<th>FVIII/VWF</th>
<th>Isolated FVIII</th>
<th>FVIII/VWF</th>
<th>Switched after ITI failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>21</td>
<td>14</td>
<td>2</td>
<td>10*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>16</td>
<td>14</td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success rate (%)</td>
<td>91</td>
<td>28</td>
<td>100</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR (%, n/n)</td>
<td>100 (5/5)</td>
<td>----</td>
<td>100 (1/1)</td>
<td>----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (%, n/n)</td>
<td>88 (14/16)</td>
<td>28 (4/14)</td>
<td>100 (1/1)</td>
<td>80 (8/10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time (range) of ITI achievement (months)</td>
<td>1.5 (0.5-3 )</td>
<td>----</td>
<td>1.5</td>
<td>17 (5-36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR</td>
<td>4 (0.5-42 )</td>
<td>3 (2-7)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Coming from not successful ITI with isolated FVIII concentrates.

Another study\textsuperscript{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\textsuperscript{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, for ITI failure, such as ITI started >2 year from inhibitor development, inhibitor peaks >200 BU, inhibitor titre >10 BU at ITI initiation, previously failed ITI, were prospectively evaluated. Seventeen haemophiliacs (16 severe, 1 moderate), aged 4-54 years (median 23) were followed 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 results 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 with poor prognostic features

References

6 Aznar JA, Lorenzo I, Molina R, Haya S, Querol F, Dasi AM. Zero incidence of inhibitor dvelopment in previously treated haemophilia A, HIV negative patients


2. **AIM OF THE STUDY**

The study is aimed at evaluating whether FVIII/VWF concentrates can induce immune tolerance to FVIII in haemophilia A patients with high-responding inhibitors with poor prognostic features more frequently and rapidly than VWF-free FVIII concentrates.

3. **STUDY DESIGN**

The study is a prospective, controlled, randomized, open label study, aimed at comparing FVIII/VWF concentrates with FVIII concentrates in their ability to induce immune tolerance in hemophilia A patients with high responding inhibitors and poor prognosis for success.

The design foresees randomisation to either VWF-free FVIII or a FVIII/VWF concentrates at 200 IU/Kg daily.

3.1. **End points**

3.1.1. **Primary end point**

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

**I. Complete success**

Complete 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.

This determination will be made only among subjects who have competed 33 months of ITI but who do not fulfil the criteria for success.

III.  Treatment failure:

Failure to fulfil the criteria for full 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 partial or complete success as defined in this section of the protocol (either complete and/or partial)

III. Safety - compliance to treatment

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

IV. Cost of care
Direct costs will be calculated.

3.1.3. **Main variables**

The following variables will be evaluated:

- Rate of success (complete or partial)
- Time to success
- 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 characterisation, epitope mapping, peak titre of inhibitor, trough titre of inhibitor, inhibitor titre at rescue ITI start-up, age at start of ITI, previous ITI attempt, influence of line infection on outcome).

4. **POPULATION**

Subjects will be patients with severe haemophilia A with a high responding inhibitor (>5 BU/ml).

In order to have a power of 80% to discriminate a difference of 20% (p<0.05), we need 74 patients per arm, expecting 60% success in the recombinant arm (and 80% in the von Willebrand arm). This number increases with a lower success rate in the recombinant arm (with the same 20% difference, i.e. 50% in recombinant arm vs. 70% success rate in the VWF arm, we need 83 patients) and decreases with a higher success rate in the recombinant arm (with 20% difference, i.e. 70% vs. 90% respectively, 58 patients).
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. any inhibitor level at study enrolment;

e. ability and willingness to participate in to the study;

f. no concomitant systemic treatment with drugs with immunosuppressive side effects (eg. Corticosteroids, if used more than 5 days every iii 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. no concomitant experimental treatment;

h. at least one of the following risk factors for ITI failure:

   i. peak inhibitor titer > 200 BU
   
   ii. titer at ITI start > 10 BU
   
   iii. age > 7 years
   
   iv. time between inhibitor occurrence and ITI > 2 years

i. no previous ITI attempt.

j. no previous history of myocardial infarction and/or cerebral stroke.

k. absence of high risk of cardiovascular, cerebrovascular or other thromboembolic events as judged by the treater in charge of the patient treatment.
5. **TREATMENT**

Patients will be centrally randomized to receive a von Willebrand factor-free FVIII concentrate (recombinant or plasma-derived, monoclonally-purified) or a FVIII/VWF concentrate, both at the same dose of 200 IU/Kg by one or two bolus injections daily.

The choice of the product within the class of product to which the patient has been randomized will be based on physician / patients preferences.

After success confirmation the dose will be tailed off until discontinuation or institution of prophylaxis according to physician or patient preference (see Paragraph 12.7: “Tailing Off Procedure and Prophylaxis” of STUDY PROCEDURES).

6. **RANDOMIZATION**

The computerized randomization will be conducted using the minimization method. Randomization will be carried out using a computerized system, minimizing for major factors, such as age at start of ITI (age ≤ or > 7 years of age), historical peak inhibitor level (≤ or > 200 BU/ml), inhibitor titre at ITI start (≤ or > 10 BU/ml).

7. **BASELINE EVALUATION AND FOLLOW-UP**

Patients will have monthly medical visits through the treatment period, unless the end point 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 tests to be carried out at any time during the study is displayed in the following table.
### Clinical Evaluation
- Height, weight, complete blood count, concomitant chronic diseases

### Inhibitor Determination
- 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 assay and the final assay 12 months after the end if ITI will be confirmed centrally.

### In vivo Recovery
- Estimated from body weight and FVIII taken pre and 15-30 minutes post-infusion of approximately 50 IU/Kg FVIII.

### Half-life
- Studied after 3-day treatment-free wash-out period after the 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.

### Central Laboratory
- Serum sample at –70° C for shipment to central laboratory

### EPITOPE MAPPING
- Yes

### IN VITRO REACTIVITY
- Yes

### GENETIC TESTING
- Any time if not yet available

---

*If not reaching earlier success or failure*

1. Clinical evaluation: height, weight, complete blood count, concomitant chronic diseases
2. Inhibitor determination: 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 assay and the final assay 12 months after the end if 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 3-day treatment-free wash-out period after the 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 serum sample at –70° C for shipment to central laboratory
6. Central laboratory (in case of unavailability at local Centre)

**A**: Total Blood Count only during the first visit
8. **ASSESSMENT OF THE RESPONSE ACHIEVEMENT/FAILURE**

8.1 **Inhibitor measurements**

Inhibitor determination will be performed on a monthly basis during the ITI course.

Inhibitor measurements will be conducted at each local laboratory using either the Bethesda assay or Nijmegen modification. A negative result will be a value < 0.6 BU/ml, for the Bethesda assay and <0.4 NBU/ml for the Nijmegen modification.

The loss of inhibitor will be confirmed by two consecutive negative determinations in one month apart and normalization of pharmacokinetic parameters.

8.2 **Pharmacokinetic assessment**

After two consecutive negative inhibitor determinations have been found in 1 month interval, the following procedure will be carried out to determine whether the inhibitor has disappeared:

I. **In vivo recovery**

   In vivo FVIII recovery (IVR) will be determined after single dose administration of 50 IU FVIII/kg administered at a maximum time interval from the last dose of concentrate allowed by the regimen.

   If the IVR is < 66% of the expected value ITI, will be continued for 33 months since ITI start-up or until the patient achieves the failure criteria, whichever occurs first.

   If the IVR is ≥ 66% of the expected value, the factor VIII half life will be estimated within two weeks, and after a 3-days washout period.

   The expected in vivo recovery for study product is 2 IU/dL/IU/Kg.

II. **Half-life**
A single dose (50 IU/kg) half life assessment must be carried out within two weeks, after at least 3 days wash out period.

Fifty IU/kg of study concentrate will be administered, assaying the FVIII:C plasmatic activity for PK plotting before infusion, at 15 min, 1 hour, 2hours, 4 hours (optional), 6 hours, 24 hours, and 48 hours (optional) after the infusion.

If the half life is still reduced (< 6hrs.) the patient will continue ITI for 33 months since ITI start-up.

Conversely when the factor VIII half-life and recovery will be both normalised (IVR > 66% than expected, half life ≥ 6hrs) ITI will be considered as completely successfully and the dose reduced to a prophylactic level.

8.3 Monitoring for Relapse

The patients will be monitored for early indicators of a relapse of their inhibitor during the 12 months follow-up after the inhibitor has disappeared.

Inhibitor titre and factor VIII recovery will be assayed. At month 1, 2, 3, 4, 6, 9, 12 of the follow-up period. At month 12, a Factor VIII half life will be re-assessed as well. If one of these tests indicates the possibility of a recurrence of an inhibitor it must be repeated within two weeks to confirm relapse. Two consecutively abnormal tests (presence of inhibitor and/or reduced factor VIII recovery and/or reduced half-life) are required to define a relapse.

8.4 Laboratory Investigations

Genetic testing

Blood withdrawal of 5mL for genetics test (to determine factors potentially associated to the response of the immunotolerance therapy) will be performed anytime during the follow up at the hospital laboratory

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; in addition an aliquot of 100µl of plasma is required at each time points already scheduled for inhibitor evaluation. Plasma sample will be stored at –70°C The Central Laboratory appointed for this purpose is located at JW Goethe University, Laboratory for mol Hemostasis and Immunodeficiency, attention to Dr. Christoph Königs, Dept. of Pediatrics, Hs32, Theodor-Stern-Kai 7 - 60596 Frankfurt - Germany

Reactivity toward concentrate panel (rich or devoid of VWF)

Patient plasma collected for epitope mapping will be also tested in the same lab against a panel of FVIII concentrates (rich and devoid of VWF) by modified Bethesda assay (Oxford method), in order to detect differences in antibody reactivity. Plasma samples will be tested against the following panel:

- Recombinant FVIII
- FVIII/VWF
- Porcine FVIII

9. **STATISTICAL ANALYSIS**

Sample size: *there is insufficient data on success rate in high risk patients for a precise sample size calculation.* With a power of 80% to discriminate a difference of 20% with a significance level of <0.05, 74 patients per arm should be enrolled, expecting 60% success in the recombinant arm (and consequently 80% in the von Willebrand arm) with a one-tail test. With 10% drop-out rate overall 164 patients should be enrolled. This number would increase assuming a lower success rate in the recombinant arm (with the same 20% difference, i.e. 50% success rate in the recombinant arm vs. 70% success rate in the FVIII/VWF arm, 83 patients per arm would be required) and decreases a bit with a higher success rate in the recombinant arm (with 20% difference, i.e. 70% success rate in the recombinant arm vs. 90% success rate in FVIII/VWF arm, 58 patients per arm would be required).
Descriptive statistics will be use to depict the study population and all the main variables. The main end-point, development of tolerance to FVIII, will be compared in the two treatment arms by Cox regression with an intent-to-treat-analysis. A per protocol analysis will be additionally carried out.

Association of primary and secondary end-points with predictive factors or other variables will be assessed by logistic regression.

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 (Appendix 1). A written informed consent will be obtained from each patient prior to enrollment in the study (Appendix 2).

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 and Adverse Events 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 COMMITTEE

11.1. Objectives 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 investigators and the Principal Investigators (PIs) of the recommendation(s) of the committee immediately, as to whether this is a related-to-drug or unrelated-to-drug event
- Guarantee quality of the study:
  - Ensure adherence to inclusion/exclusion criteria
  - Ensure adherence to dosage/schedule of treatment as per protocol
  - Ensure data/specimens collection as per protocol
- Evaluation of the endpoints put 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 a 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.

12. STUDY PROCEDURES

12.1. Centre Registration
Centres must first register for the study with Milan and obtain ethical approval from their Institutional Review Board. The study will be conducted according to the Declaration of Helsinki.
Upon receipt of a copy of the ethical approval letter, a copy of the local patient information sheet and a completed centre registration form, the centre will be issued 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](http://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.

12.2. Patient Recruitment
Patients who fulfill the entry criteria and express written consent will be recruited. The presence of their inhibitor titre will be confirmed locally, if this has not already taken place. The patient may be enrolled on-line by filling in the enrollment form on [www.itistudy-resist.com](http://www.itistudy-resist.com) using Internet Explorer 4 or 5. An easy to follow user’s manual to the electronic patient record (CRF) is also available at [www.itistudy-resist.com](http://www.itistudy-resist.com).
Alternatively, a completed enrollment form giving anonymous patient details may be sent either by fax (+39 02 5503.2072) or directly to the web site ([www.itistudy-resist.com](http://www.itistudy-resist.com)).

12.3. Product type
The brand and type of FVIII/VWF complex concentrate or VWF-free FVIII concentrate to be used for ITI (according to randomisation) will be at the discretion of the managing clinician.
A major switch in product type during ITI will be a reason for withdrawal from the trial.
A major switch in product type refers to changes made across the major product categories: 1) recombinant/monoclonal; 2) von Willebrand factor containing concentrate; 3) other FVIII concentrates.

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 major product categories.

A change of FVIII dosage/regimen will be cause for patient withdrawal from the study.

12.4. 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 to confound the dose comparison. All treatment for bleeding will be recorded in the CRF and will be used for cost-effective analysis and analysis of morbidity.

12.5. 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 far 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.

12.6. Procedures for determining if the inhibitor has disappeared
- 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. 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. Two negative inhibitor titres must be obtained within a two-month period prior to initiating recovery/half life studies.

- When the factor VIII recovery is found to have normalized (≥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 level (see Tailing Off Procedure and Prophylaxis, below).
- Inhibitor disappearance is defined as: negative inhibitor titre, as defined in paragraph 8.1, a normal factor VIII half-life (≥ 6 hrs) and recovery measurement (> 66%) assessed after a 72-hour, treatment free, and washout period.

12.7. **Tailing Off Procedure and Prophylaxis**

- Patients will tail off dose of factor VIII over three months, starting when the patient is judged to be inhibitor-free. They will use:
  - 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
- 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 in both treatment-arms during this period (see table in section Monitoring for Relapse, page 21).

12.8. **Monitoring for Relapse**

During the 12-month period of tailing off and prophylaxis following inhibitor disappearance, the patients will be monitored for early indicators of a recurrence of their inhibitor. The Bethesda assay and factor VIII recovery measurements will be used and, at the end of the study, a factor VIII half-life study will be done. In
each case, recovery of half life will be estimated following the administration of 50 IU/kg factor VIIIc. Inhibitor and recovery measurements should be taken at the longest possible interval following the previous dose of factor VIII on the treatment regimen, and the half-life estimation will be conducted after a 72-hour treatment-free washout period.

If any of these tests indicate possibility of a recurrence of an inhibitor at any time within 12 months after ITI finishes and tailing off or prophylaxis starts, 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.

**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)

**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.

**12.9. The end of the 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 parents or physician to stop ITI.

12.10. Success, treatment-failure, and partial response

- **Success is defined as:**
  The abolition of the inhibitor within 33 months of ITI as defined by inhibitor titre <0.6 Bethesda Assay or < 0.4 Nijmegen modification, a factor VIII recovery ≥ 66% and half-life ≥ 6 hrs, and measured after a 72-hour treatment-free washout period.

- **Treatment failure is defined for the purpose of this study as:**
  Failure to fulfil the criteria for full 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-month 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.

- **Partial success is defined at the end of study as:**
  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.
  This determination will be made only among subject who have competed 33 months of ITI but who do not fulfil the criteria for success.
12.11. Withdrawal from the study

If ITI continues off protocol, these data should continue to be recorded for the duration of the study period since these data form the basis for a further sub-analysis.

It is recognized that patients requiring central venous access devices may suffer 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 wherever possible. However, if otherwise unavailable, some interruption will be accepted so long as the ITI is not interrupted for longer than two weeks. Patients will, therefore, 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.

12.12. Record Keeping

The central fileserver in Manchester will monitor the progress of each patient and automatically issue reminders for outstanding data and instructions on 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 finishing the study or at time of patient withdrawal. Reminders will be issued centrally every three months.

The data collected on study should permit an analysis of the relative efficacy of the two arms and of their cost effectiveness and associated morbidity. These details may be summarized as follows: entry details; details of factor VIII administered for ITI; treatment for intercurrent bleeding; and inhibitor titres, factor VIII recovery and factor VIII half-life determinations. A record of concomitant treatments capable of affecting the immune system, intravenous catheter
insertions and infections and non- catheter related infections will also be noted. The number of hospital in-patient days during the study will be also recorded.

12.13. **Laboratory Monitoring**

**Pre Study Monitoring**
The following will be measured before starting:

- Height and weight
- VIIIC (1-stage, IU/ml)
- Inhibitor titre (BU) x 2
- Total blood count

**On study monitoring**

**Inhibitor Titres (Bethesda Assays)**
The inhibitor titre will be measured on site at the participating institution at weeks 0, 2, and 4 weeks after initiating ITI, and every four weeks thereafter until the factor VIII recovery and half-life are normal and the dose of factor VIII has been tailed down to a prophylactic dose. The inhibitor titre will then be measured every 3 months until the end of the study. Negative Bethesda titre prior to initiating recovery and half-life studies must be confirmed once.

Inhibitor measurements will be conducted using the standard Bethesda method or the Nijmegen modification of the Bethesda assay. A negative assay is usually taken as <0.6 BU/ml for standard Bethesda assay and < 0.4 NBU/ml for the Bethesda assay with the Nijmegen modification.

Central confirmation of key inhibitor measurements is essential. The initial pre-ITI inhibitor, the first two “negative” assays on ITI and the final assay 12 months after the end of ITI will be confirmed centrally.

Plasma samples from European and Asiatic centres for central testing will be stored at -70 °C and sent to the central lab of Dr. Alessandro Gringeri at the ABB Haemophilia and Thrombosis Centre, University of Milan, Via Pace 9, 20122 Milan (Italy) on dry ice in a batch when the patient has finished the study. In the US, these samples will be sent to Dr. Nadia Ewing, City of Hope, 1500 East Duarte Road, Research Processing Lab/Biospecimen Repository, Northwest
Bldg 2nd floor, Room 2234, Duarte, CA 91010-3000, and stored in a central repository for bulk shipment to the central laboratory.


<table>
<thead>
<tr>
<th>Time</th>
<th>VIIIC</th>
<th>Inhibitor BU/ml</th>
<th>VIIIC Recovery</th>
<th>VIIIC Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>X</td>
<td>X* (done twice)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 4 weeks to negative BU#</td>
<td></td>
<td>X* (done twice)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 4 weeks to recovery normal</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Every 3 months to normal half-life</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3, 6, 9 and 12 months after ITI##</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months after ITI</td>
<td></td>
<td>X*</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Plasma samples saved for central lab confirmation of inhibitor titres.
# When the Bethesda assay becomes negative, follow the procedure for determining if the inhibitor has disappeared on page 19.
## The inhibitor titre and factor VIII recovery are also determined four weeks after each dose reduction, when tailing off treatment after tolerance has been achieved. For a detailed timetable of testing after tolerance has been achieved see page 21 in section entitled, Monitoring Relapse.

12.15. Factor VIII Recovery

Relative incremental factor VIII recovery will be estimated from body weight 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.

**NB:** if recombinant B - domainless rVIII:SQ is used in the ITI RESIST study, all recovery or half – life estimations must be conducted using the chromogenic factor VIII assay or using the rVIII:SQ standard from the NIBSC for use with the one stage clotting factor VIII assay. The use of the usual one-stage assay without an appropriate standard may cause the recovery and half – life of this product to be seriously underestimated.

A normal recovery will be taken as greater than or equal to 66% of expected rise in post-infusion factor VIII level is 0,02 IU/ml (2%) per IU/kg infused.
12.16. Factor VIII half-life studies

The ultimate disappearance of the inhibitor will be confirmed by demonstrating that the factor VIII half-life has normalised following a **72-hour treatment-free washout period**. This estimation should be made after the administration of 50 IU/kg VIIIIC. Assay will be conducted locally. Note that if rVIII:SQ is used for ITI, factor VIII assays will have to be conducted using a chromogenic method or using an appropriate rVIII:SQ standard provided by NIBSC.

Once the factor VIII assays are available an half-life estimate may be obtained by entering the raw data on-line direct into the electronic CRF on [www.itistudy-resist.com](http://www.itistudy-resist.com) or by faxing the data to 39 02 5503.2072 Milan’s fax. 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>Assay Time</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>6 hrs</td>
</tr>
<tr>
<td>24 hrs</td>
<td>48 hrs*</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. The half-life must be obtained by faxing the data to Dr. Alessandro Gringeri or entering it directly on-line using the centre password.

12.17. Statistical Analysis

The computerized randomization will be conducted using the minimization method. Randomization will be carried out using a computerized system, minimizing for major factors, such as age at start of ITI (age ≤ or > 7 years of age), historical peak inhibitor level (≤ or > 200 BU/ml), inhibitor titre at ITI start (≤ or > 10 BU/ml).

Primary end-points will be analysed on an intent-to-treat basis and on a per-protocol basis. Descriptive statistics will be used to depict the study population and all the main variables. The significance of success rates of rescue treatment will be evaluated on the basis of 95% confidence interval of the rate achieved.
Association of primary and secondary end-points with predictive factors or other variables will be assessed by parametric and non-parametric tests, when appropriate, or cross-tabulation tests for frequencies.

12.18. 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 “RESISTNAÏVE study 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.
APPENDIX

Appendix 1: Declaration of Helsinki

Appendix 2: Patient Information Sheet and Informed Consent

Appendix 3: Monitoring Serious Adverse Events
WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy
volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
   • The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
   • Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.
Appendix 2
INFORMATION SHEET AND INFORMED CONSENT FOR PARTICIPATION IN THE RESISTNAÏVE STUDY
(REScue Immunotolerance STudy in ITI-Naïve patients)

Randomised study of first time Immunotolerance Induction in patients with severe type A haemophilia with inhibitor at high risk of failure: comparison of induction of immune tolerance with FVIII concentrates with or without Von Willebrand factor

You are invited to take part in a clinical trial organised by (insert the local institution)…., acting as administrative sponsor. You are free to accept or refuse, and may in any event stop participating in it at any time, with no requirement to give a reason. Your relationship with your doctor will not be affected in any way.

Before deciding whether or not to give your consent it is very important to understand why the study is being carried out and what it implies. Please take the time to carefully read the information below, and to ask for further information about anything that is not clear to you.

AIM OF THE STUDY

Your physician would like to invite you to participate in this study because you have severe haemophilia A with inhibitor. This inhibitor impedes the function of factor VIII (FVIII) and renders treatment very difficult. The appearance of an inhibitor is a serious and potentially very severe complication of haemophilia.

Children and adult patients with factor VIII inhibitors from 14 countries have been invited to take part in this study.

This immune tolerance induction study (RESISTNAÏVE) is organised by international investigators as a satellite study of the international Immune Tolerance Induction study (ITI study). The study is not organised by a manufacturer of factor VIII concentrates.

STUDY OBJECTIVES

Patients with factor VIII inhibitors are frequently treated with “immune tolerance induction”. Immune Tolerance (IT) means that the body can accept infused factor VIII and that factor VIII is again effective in controlling bleeds. Immune tolerance is obtained by administering high doses of factor VIII regularly, until the inhibitor disappears. Immune tolerance induction is not always effective, and in about 20% of patients the inhibitor persists.

There are 2 types of factor VIII concentrates: factor VIII concentrates derived from human plasma, which contain the Von Willebrand factor, and concentrates of plasma derived, or recombinant factor VIII which do not contain this other coagulation factor. These two classes of concentrates are commonly used to induce immune tolerance in patients with type A haemophilia.

It has been suggested that factor VIII concentrates obtained from donor plasma, containing the Von Willebrand factor, might improve the results of immune tolerance induction.

The principal aim of this study is to test whether or not this is true in a clinical trial, so as to improve the management of patients with severe type A haemophilia with inhibitor when undergoing immune tolerance induction treatment.

The patients who participate in this trial will be divided into 2 groups: one will use plasma factor VIII concentrates, and the other recombinant factor VIII concentrates without Von Willebrand Factor.
Patients will be assigned to a treatment type by a centralised draw (randomised) performed after their inclusion in the study. The patients in the 2 groups will receive the same treatment doses and will benefit from the same monitoring throughout the study.

HOW THE STUDY WILL BE CARRIED OUT

This study will observe if there is a difference in the ability of high doses (200 units/kg/day) of the different factor VIII concentrates to induce immune tolerance. Within each treatment group there are several commercial preparations of factor VIII concentrates. You and your doctor will decide what brand of product you will receive. This treatment will continue to the end of the study. The maximum duration of the immune tolerance induction treatment in this study is 33 months. After immune tolerance has been achieved, you will be followed-up for the subsequent 12 months to monitor the risk of relapse.

You will be examined by your doctor at the haemophilia centre once a month throughout the study; a blood sample (10 ml, 2 teaspoon) will also be taken at the beginning and the end of the study and a sample of 3.5 ml every month. Additionally, a genetic test, if not yet available will be performed anytime during the study. About 5 ml or 1 tsp of your child’s blood will be drawn to determine factors potentially associated with the response to immune tolerance therapy.

Once the inhibitor has disappeared, more detailed blood tests will be performed: a recovery test, with an injection of 50 units/kg and factor VIII assays 15 and 30 minutes (5 ml in each sample) after the injection and then, if the results are normal, a complete pharmacokinetics study, with FVIII assays in your blood for 48 hours (15 minutes after the injection and then at 1 hour, 2 hours, 4 hours, 6 hours, 24 hours and 48 hours.) For a total of 40 ml of blood. These same tests will be repeated in the year in which you are monitored for any relapses.

You will be administered questionnaires focusing on quality of life issues at the beginning of therapy, after 6 months, and at the end of the study. Each should take about 10 minutes to fill out.

POTENTIAL RISKS

All factor VIII/Von Willberand Factor concentrates used by the patients in this study are commercially available for use in the induction of immune tolerance. The method used to induce immune tolerance is also frequently used as a standard treatment modality.

Rare thromboembolic complications have been observed in patients at risk of thrombosis in presence of high levels of FVIII in the blood. Your physician has determined that you do not have an increased risk for thrombosis.

To enable you to administer daily injections of factor VIII for several months for a period of up to 33 months, your doctor may suggest to place a central venous catheter. This procedure is also a standard one, and depends primarily on the condition of your peripheral veins. Insertion of a central venous catheter is a surgical procedure performed under general anaesthetic and thus carries the risk of any surgery...

The principal risk is possible infection, which would require treatment with antibiotics or removal of the catheter, with the consequent need to insert a new one.

You may become tired from the amount of time (about 10 minutes) needed to fill out the questionnaires. The questionnaires will focus on Quality of Life (QoL) issues that could be related to your disease and/or your treatment and that could make you emotionally upset. If this occurs, you will be referred to your physician to determine how best to handle the concerns and issues. Support and counselling will be available to you from social workers and psychologists as needed.

ALTERNATIVE TREATMENT
Immune tolerance induction is the standard treatment for patients who have developed a factor VIII inhibitor. At present there is no single procedure, but the general plan for immune tolerance induction and follow-up is always the same. Other studies are currently underway (particularly the ITI Study) to evaluate any improvements in the outcome different doses or frequency of FVIII infusions.

If you decide not to take part in the study, you may undergo immune tolerance induction as part of standard treatment.

Whether or not you participate in the study, should suffer active bleeding that is not controlled by treatment with FVIII concentrate, you will be treated with other coagulation factors whose activity bypasses the FVIII inhibitor.

POSSIBLE BENEFITS

It is impossible to promise you a direct benefit from your participation in this study. However, your participation will expand our understanding and hopefully improve the outcome of future patients who undergo immune tolerance induction.

RISK/BENEFITS RATIO

The risk/benefit ratio of this study that allows you to undergo immune tolerance induction with either plasma derived FVIII/ von Willebrand Factor concentrates or FVIII concentrates does not involve increased risk, compared to the standard treatment.

NOTIFICATION OF NEW INFORMATION

All new information related to this study that may affect your decision to continue to participate or not will be communicated to you, and you will be required to sign a new consent to participate. Equally, you will be informed of the overall results of the study once it has ended.

PARTICIPATION

Your participation in this study is entirely voluntary. Moreover, you have the right to withdraw from the study at any time, without having to provide any explanation. Refusal or interruption of your participation will not prejudice your relations with your doctor at the haemophilia centre.

The European, Italian, French and US healthcare regulatory authorities (EMEA, AIFA, AFSSAPS and FDA) and the administrative sponsor of this study (country, Institution) have stipulated insurance policy no. with company, in accordance with the legal regulations currently in force guaranteeing civil liability, and providing coverage for the participants in this clinical trial in case of damage linked to this study.

The group of doctors organising the study and those on the Data Safety Monitoring Committee (DSMB) or the ethics committee or your doctor at the haemophilia centre also have the right to stop the study without your consent if they consider it necessary in the interest of the patients or if the study is not carried out as planned. If such a decision is made, you will be promptly informed, and your subsequent care will be organised.

LEGAL PROVISIONS

The study will be carried out in accordance with Good Clinical Practice and the Helsinki Declaration.
All reasonable precautions will be adopted to guarantee your safety during this study. However, as administrative sponsor of this study in (country, Institution)…………………………………………………. have stipulated insurance policy no. (if necessary) ……………………… with ……………………………………… company, in accordance with the legal regulations currently in force (put the reference of the law related to this issue) ……………………… guaranteeing civil liability, and providing coverage for the participants in this clinical trial in case of damage linked to this study. In accordance with the legislation that regulates all aspects of the conduct of a clinical trial, the local ethics committee was asked to authorise the study and issued a favourable opinion on (insert the date) …………….

You will receive no payment for your participation in this study, which does not involve more expense than the treatment and monitoring of the immune tolerance induction performed outside this study. The costs of organising the study are the responsibility of the administrative sponsor of the study. However, to be able to participate in this study you must be a member or beneficiary of a social security scheme.

CONFIDENTIALITY OF THE INFORMATION COLLECTED

All your personal medical information collected during this study will be retained in a strictly confidential form. Your data will be identified by your haemophilia treatment centre in the study documents by an anonymous number and your initials. This also applies to information transmitted electronically (through the internet to the study coordination centre): data will be transmitted in encrypted format through a dedicated blocked internet connection that uses several encrypted codes and other specific security devices for the transmission of medical data. The study data thus collected will be entrusted to the organisers for analysis, thus fulfilling the study objective.

Representatives of the European Medicines Evaluation Agency (EMEA), the Italian Medicine Evaluation Agency (AIFA), or the (insert the nationality and the name of Organization for the Evaluation) …………… organisation for the safety of healthcare products or other competent authorities, the study administrative sponsor or its representatives may examine and copy the medical data needed for this study. The results will be included in study-related publications, but your identity will in no case be revealed. All these arrangements are in accordance with the recommendations of the (insert the Institution or the related law) ……………………………… concerning the law on information technology, records and freedoms.

You are also entitled to access, check and oppose transmission of privileged information that may be used as part of this study. These rights may be exercised through the doctor who is treating you as part of this study and who knows your identity.

CONTACTS

If you have any further questions about the study or your rights, or if problems should arise in relation to the study, you can contact the investigating doctors at your haemophilia treatment centre: Professor/Doctor ________________________, at the following telephone number: ______________________.

Your comments, questions and involvement are encouraged. Please do not hesitate to get in contact with the staff of the haemophilia centre for further information.

Contact details for your haemophilia treatment centre:

Full contact details for your haemophilia treatment centre:
INFORMED CONSENT TO PARTICIPATE IN THE RESISTNAÏVE STUDY
(REScue Immunotolerance STudy in ITI-Naïve patients)

Randomised study of first time Immunotolerance Induction in patients with severe type A haemophilia with inhibitor at high risk of failure: comparison of induction of immune tolerance with FVIII concentrates with or without Von Willebrand factor

1. I confirm that I have read and understood the information sheet on the study mentioned above and have been able to ask questions to the investigating doctor.

2. I understand that my participation is voluntary, and that I am free to withdraw my consent at any time, through the investigating doctor, for any reason, without compromising my medical care and legal rights.

3. I am aware that from my inclusion in the study, my medical data will be fully anonymized when processed. I authorise the personnel working on this study to access my data.

4. By signing the informed consent form, I agree to participate in the RESISTNAÏVE study. Two copies of these documents have been made, one for the study, and the other for me.

5. I agree/I disagree (choose the option) to allow my left over blood samples after the study is complete, to be saved for long term storage and future testing which may include genetic testing. I will be contacted for any future research to give or rescind my consent.
THE PATIENT:
The undersigned (LAST NAME, First Name ) _______________________, declare that I freely and voluntarily agree to participate in the study entitled RESIST\_NAIVE.

[Place] __________________________ Date (dd/mm/yy): ______________

Signature of Patient: __________________________________________

THE INVESTIGATING DOCTOR:
The undersigned Dr. (LAST NAME, First Name) _______________________,
attest that I have explained to the signatory patient the aim, methods and potential risks of this study, and have answered all the questions.

[Place] __________________________ Date (dd/mm/yy): ______________.

Doctor’s signature: __________________________________________
INFORMATION SHEET AND INFORMED CONSENT FOR
PARTICIPATION IN THE RESIST- Naïve STUDY FOR PERSONS WITH
PARENTAL RESPONSIBILITY FOR A MINOR
(REScue Immunotolerance STudy in ITI-Naïve patients)

Randomised study of first time immunotolerance induction in patients with
severe type A haemophilia with inhibitor not eligible for the ITI study

Your child is invited to take part in a clinical trial organised by (insert the local
institution)……………………………………………………………………, acting as local Coordinator. You are
free to accept or refuse, and may in any event stop participating in it at any time, with no requirement
to give a reason. Relations with the child’s doctor will not be affected in any way.

Before deciding whether or not to give your consent for the participation of your child it is very
important to understand why the study is being carried out and what it implies. Please take the time to
carefully read the information below, and to ask for further information about anything that is not clear
to you.

AIM OF THE STUDY

Your child’s physician would like to invite your child participate in this study because he has severe
haemophilia A with inhibitor. This inhibitor impedes the function of factor VIII (FVIII) and so
renders treatment very difficult. The appearance of an inhibitor is a serious and potentially very severe
complication of haemophilia. It must be treated as soon as possible to return the patient’s immune
system to a state in which it again accepts treatments with FVIII concentrates. This is called immune
tolerance.

Children and adult patients with factor VIII inhibitors from 14 countries have been invited to take part
in this study.

This immune tolerance induction study (RESIST-Naïve) is organised by international investigators as
a satellite study of the international Immune Tolerance Induction study (ITI study). The study is not
organised by a manufacturer of factor VIII concentrates.

STUDY OBJECTIVES

Patients with factor VIII inhibitors are frequently treated with “immune tolerance induction”. Immune Tolerance (IT) means that the body can accept infused factor VIII and that factor VIII is again
effective in controlling bleeds. Immune tolerance is obtained by administering high doses of factor
VIII regularly, until the inhibitor disappears. Immune tolerance induction is not always effective, and in about 20% of patients the inhibitor persists.

There are 2 types of factor VIII concentrates: factor VIII concentrates derived from human plasma,
which contain the Von Willebrand factor, and concentrates of plasma derived, or recombinant factor
VIII which do not contain this other coagulation factor. These two classes of concentrates are
commonly used to induce immune tolerance in patients with type A haemophilia.

It has been suggested that factor VIII concentrates obtained from donor plasma, containing the Von
Willebrand factor, might improve the results of immune tolerance induction.

The principal aim of this study is to test whether or not this is true in a scientific study, so as to
improve the management of patients with severe type A haemophilia with an inhibitor when
undergoing immune tolerance induction treatment.
The patients who participate in this trial will be divided into 2 groups: one will use plasma factor VIII concentrates, and the other recombinant factor VIII concentrates without Von Willebrand Factor. Patients will be assigned to a treatment type by a centralised draw (randomised) performed after their inclusion in the study. The patients in the 2 groups will receive the same treatment doses and will benefit from the same monitoring throughout the study.

HOW THE STUDY WILL BE CARRIED OUT

This study will observe if there is a difference in the ability of high doses (200 units/kg/day) of the different factor VIII concentrates to induce immune tolerance. Within each treatment group there are several commercial preparations of factor VIII concentrates. The brand of product your child will receive will be decided by his doctor, with your agreement. This treatment will continue to the end of the study.

The maximum duration of the immune tolerance induction treatment in this study is 33 months. After immune tolerance has been achieved, your child will be followed-up for the subsequent 12 months to monitor the risk of relapse.

Your child will be examined by his doctor at the haemophilia centre once a month throughout the study; a blood sample (7 ml, 1 1/2 tsp) will also be taken at the beginning and the end of the study and a sample of 3.5 ml every month. (please confirm, should this be changed to 10 ml?)

Additionally, a genetic test, if not yet available, will be performed anytime during the study. About 5 ml or 1 tsp of your child’s blood will be drawn to determine factors potentially associated with the response to immune tolerance therapy.

Once the inhibitor has disappeared, more detailed blood tests will be performed: a recovery test, with an injection of 50 units/kg and factor VIII assays, 15 and 30 minutes (5 ml in each sample) after the injection and then, if the results are normal, a pharmacokinetics study, with FVIII assays for 48 hours (15 minutes after the injection and then at 1 hour, 2 hours, 4 hours, 6 hours, 24 hours and 48 hours.) For a total of 40 ml of blood.

These same tests will be repeated in the year in which the child is monitored for any relapses. Your child will also be administered questionnaires on quality of life issues at the beginning of therapy, after 6 months and at the end of the study. Each will take about 10 minutes.

POTENTIAL RISKS

All factor VIII and Factor VIII/Von Willebrand concentrates used by the patients in this study are commercially available for use in the induction of immune tolerance. The method used to induce immune tolerance is also frequently used as a standard treatment modality.

Rare thromboembolic complications have been observed in patients at risk of thrombosis in presence of high levels of FVIII in the blood. Your child’s physician has determined that your child does not have an increased risk for thrombosis.

To enable your child to administer daily injections of factor VIII for several months for a period of up to 33 months, your child’s doctor may suggest placing a central venous catheter. This procedure is also a standard one, and depends primarily on the condition of your child’s peripheral veins.

Insertion of a central venous catheter is a surgical procedure performed under general anaesthetic and thus carries the risk of any surgery.

The principal risk is possible infection, which would require treatment with antibiotics or removal of the catheter, with the consequent need to insert a new one.

Your child may become tired from the amount of time (about 10 minutes) needed to fill out the questionnaires. The questionnaires will focus on Quality of Life (QoL) issues that could be related to your child’s disease and/or your child’s treatment and that could make him emotionally upset. If this occurs, your child will be referred to his physician to determine how best to handle the concerns and issues. Support and counselling will be available to your child from social workers and psychologists as needed.
ALTERNATIVE TREATMENT

Immune tolerance induction is the standard treatment for patients who have developed a factor VIII inhibitor. At present there is no single procedure, but the general plan for immune tolerance induction and follow-up is always the same. Other studies are currently underway (particularly the ITI Study) to evaluate any improvements in the outcome with different doses and frequency of FVIII infusions.

If you decide, your child should not take part in this study, he may undergo immune tolerance induction as part of standard treatment.

Whether or your child participates in the study, should he suffer active bleeding that is not controlled by treatment with FVIII concentrate, he will be treated with other coagulation factors whose activity bypasses the FVIII inhibitor.

POSSIBLE BENEFITS

It is impossible to promise your child a direct benefit from participating in this study. However, your child’s participation will expand our understanding and hopefully improve the outcome of future patients who undergo immune tolerance induction.

RISK/BENEFITS RATIO

The risk/benefit ratio of this study that allows your child to undergo immune tolerance induction with either plasma derived FVIII Von Willebrand Factor concentrates or FVIII concentrates does not involve increased risk, compared to the standard treatment.

NOTIFICATION OF NEW INFORMATION

All new information related to this study that may affect your decision to continue to participate or not will be communicated to you, and you will be required to sign a new consent form.
PARTICIPATION

Your child’s participation in this study is entirely voluntary. Moreover, you have the right to withdraw your child from this study at any time, without having to provide any explanation. Refusal or interruption of your child’s participation will not prejudice relations with your child’s doctor at the haemophilia centre.

The European, Italian, French and US healthcare regulatory authorities (EMEA, AIFA, AFSSAPS and FDA) and the administrative sponsor of this study (country, Institution)…………………………………… have stipulated insurance policy no. ……………………………………… company, in accordance with the legal regulations currently in force (put the reference of the law related to this issue) …………………. guaranteeing civil liability, and providing coverage for the participants in this clinical trial in case of damage linked to this study.

The group of doctors organising the study and those on the Data Safety Monitoring Committee (DSMB) or the ethics committee or the doctor at the haemophilia centre also have the right to stop the study without your consent if they consider it necessary in the interest of the patients or if the study is not carried out as planned. If such a decision is made, you will be promptly informed, and your subsequent care will be organised.

LEGAL PROVISIONS

The study will be carried out in accordance with Good Clinical Practice and the Helsinki Declaration. All reasonable precautions will be adopted to guarantee your safety during this study. However, as administrative sponsor of this study in (country, Institution)…………………………………… have stipulated insurance policy no. (if necessary) ……………………………………… company, in accordance with the legal regulations currently in force (put the reference of the law related to this issue) …………………. guaranteeing civil liability, and providing coverage for the participants in this clinical trial in case of damage linked to this study. In accordance with the legislation that regulates all aspects of the conduct of a clinical trial, the local ethics committee was asked to authorised the study and issued a favourable opinion on (insert the date) ……….

In accordance with the legislation that regulates all aspects of the conduct of a biomedical study, the local ethics committee was asked to authorised the study and issued a favourable opinion on ……….

You will receive no payment for your child’s participation in this study, which does not involve more expenses than the treatment and monitoring of the immune tolerance induction performed outside this study. The costs of organising the study are the responsibility of the administrative sponsor of the study.

However, for your child to participate in this study your child must be a member or beneficiary of a social security scheme.

CONFIDENTIALITY OF THE INFORMATION COLLECTED

All the personal medical information of your child collected during this study will be retained in a strictly confidential form. Your child’s data will be identified by your haemophilia treatment centre in the study documents by an anonymous number and your initials.

This also applies to information transmitted electronically (through the internet to the study coordination centre): data will be transmitted in encrypted format through a dedicated blocked internet connection that uses several encrypted codes and other specific security devices for the transmission of medical data.
The study data thus collected will be entrusted to the organisers for analysis, thus fulfilling the study objective. Representatives of the European Medicines Evaluation Agency (EMEA), the Italian Medicine Evaluation Agency (AIFA), or the (insert the nationality and the name of Organization for the Evaluation) organisation for the safety of healthcare products or other competent authorities, the study administrative sponsor or its representatives may examine and copy the medical data needed for this study. The results will be included in study-related publications, but your identity will in no case be revealed. All these arrangements are in accordance with the recommendations of the (insert the Institution or the related law) concerning the law on information technology, records and freedoms. You are also entitled to access, check and oppose transmission of privileged information that may be used as part of this study. These rights may be exercised through the doctor who is treating your child as part of this study and who knows your child’s identity.

CONTACTS

If you or your child have any further questions about the study or your child’s rights, or if problems should arise in relation to the study, you can contact the investigating doctors at the child’s haemophilia treatment centre: Professor/Doctor _____________________, at the following telephone number: ____________________.

Your comments, questions and involvement are encouraged. Please do not hesitate to contact the staff of the haemophilia centre for further information.

Contact details for the child’s haemophilia treatment centre:
INFORMED CONSENT TO PARTICIPATE IN THE RESIST- NAÏVE STUDY FOR PERSONS WITH PARENTAL RESPONSIBILITY FOR A MINOR
(REScue Immunotolerance STudy in ITI-Naïve patients)

Randomised study of first time immunotolerance induction in patients with severe type A haemophilia with inhibitor not eligible for the ITI study

1. I confirm that I have read and understood the information sheet on the study mentioned above and have been able to ask questions to the investigating doctor.

2. I understand that the participation of my child is voluntary, and that I am free to withdraw my consent at any time, through the investigating doctor, for any reason, without compromising my child’s medical care and legal rights.

3. I am aware that from my child’s inclusion in the study, his medical data will be fully anonymized when processed. I authorise the personnel working on this study to access his data.

4. By signing the informed consent form, I agree that my child will participate in the RESIST- Naïve study.
Two copies of these documents have been made, one for the study, and the other for me.

5. I AGREE / I DISAGREE (choose the option) to allow my child’s left over blood samples after the study is complete, to be saved for long term storage and future testing which may include genetic testing. I will be contacted for any future research To give or rescind my consent.

HOLDERS OF PARENTAL RESPONSIBILITY: father, mother, guardian (cancel inapplicable terms)

The undersigned (LAST NAME, First Name ) ___________________________, declare that I freely and voluntarily agree to allow my child to participate in the study entitled RESIST- Naïve.

[Place] ___________________________ Date (dd/mm/yy): __________________
Signature: ____________________________________________________________

HOLDERS OF PARENTAL RESPONSIBILITY: father, mother, guardian (cancel inapplicable terms)

The undersigned (LAST NAME, First Name ) ___________________________, declare that I freely and voluntarily agree to allow my child to participate in the study entitled RESIST-. Naïve

[Place] ___________________________ Date (dd/mm/yy): __________________
Signature:
## INFORMED CONSENT TO PARTICIPATE
### IN THE RESIST- Naïve STUDY FOR PERSONS WITH PARENTAL RESPONSIBILITY FOR A MINOR
(REScue Immunotolerance STudy in ITI-Naïve patients)

<table>
<thead>
<tr>
<th>THE PATIENT</th>
<th>age: must agree, if he is capable of expressing his will. Your child’s refusal or withdrawal of consent cannot be ignored.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, LAST NAME, First Name __________________________, declare that I freely and voluntarily agree to participate in the study entitled RESIST- Naïve.</td>
<td></td>
</tr>
<tr>
<td>[Place] __________________________ Date (dd/mm/yy): __________</td>
<td></td>
</tr>
<tr>
<td>Signature of Patient</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>THE INVESTIGATING DOCTOR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The undersigned Dr. (LAST NAME, First Name) __________________________, attest that I have explained the aim, methods and potential risks of this study to the patient’s parents or legal guardians and have encouraged and answered their questions.</td>
</tr>
<tr>
<td>[Place] __________________________ Date (dd/mm/yy): __________</td>
</tr>
<tr>
<td>Doctor’s signature: __________________________________________</td>
</tr>
</tbody>
</table>
INFORMED CONSENT TO PARTICIPATE IN THE
RESIST- NAÏVE
(REScue Immunotolerance Study in ITI- Naïve Patients)
Minor-Adolescents

Randomized Study ITI in Patients with Severe Hemophilia A with Inhibitor-Ineligible for Enrollment in the International Immune Tolerance Induction Study

Principal Investigator: Prof. Alessandro Gringeri

Dear __________.

I would like to invite you to participate in a research project organized by the Hemophilia Center Angelo Bianchi Bonomi, Department of Medicine & Medical Specialties, IRCCS Fondazione Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, Via Pace, 9 Milano.

Before you decide as to whether to participate in this study, it is very important that you understand this project. Carefully read the following description and ask questions on anything that is not clear.

**Study Aims**
Your physician would like for you to participate in this study because you have severe Hemophilia A with an inhibitor. The presence of an inhibitor is a serious complication in Hemophilia; it should be treated as soon as possible to enable your immune system to accept treatment with Factor VIII concentrates and to enable you to better control your hemorrhages.

**Study Objective**
Conventional treatment of patients who, like you, have inhibitors is called Immune Tolerance Induction. Immune Tolerance (IT) means that the body can accept infused Factor VIII and that Factor VIII is again effective in controlling bleeds. Immune tolerance is achieved by daily infusions of high doses of Factor VIII until the inhibitor disappears.
There are 2 main types of Factor VIII concentrates: those which are plasma derived and contain Von Willebrand factor, and plasma derived or recombinant Factor VIII products with out Von Willebrand factor.

It is thought, but not proven that concentrates containing Von Willebrand Factor may be more successful in inducing tolerance to Factor VIII. You will be randomized (chosen by chance) to receive one of these products, either with or without Von Willebrand Factor. Therefore, the main objective of this study will be to assess which of these two classes of products is more effective in getting rid of the inhibitor.
**How the Study Will Be Conducted**
Your physician and you will choose one of the many brands of plasma derived concentrate containing Von Willebrand Factor or a factor VIII product without Von Willebrand Factor. You will continue with this product for the duration of the study.
- The maximum length of treatment is 33 months.
- Once you achieve tolerance, you will undergo a follow up period of another 12 months to assess for any possible inhibitor recurrence.
- You will be seen by your doctor at your Hemophilia center once a month for the duration of the study, and for the additional observation period.

**Potential Risks**
It is possible that your doctor may recommend insertion of a central venous catheter (port) in order to facilitate daily factor infusions. Insertion of a port is not an unusual procedure, but it will require a surgical operation under general anesthesia. The most common complication of having a catheter is infection, which will require treatment with intravenous antibiotics, possible removal of the catheter, and reinsertion after the infection has cleared from your bloodstream.

**Alternative Treatment**
Immune Tolerance Induction has become the standard treatment for patients who develop inhibitors. In the event you choose not to participate in this study, you may still undergo Immune Tolerance Induction (off study, in a non randomized fashion- i.e. selecting which class of treatment product). Whether on study or not, if you have a bleed, you be treated with a Factor VIII bypassing product (FEIBA or NOVO SEVEN).

**Possible Benefits**
It is impossible to promise you a direct benefit from participating in this study. However, what we learn from this study will expand our understanding and improve treatment of patients who need to undergo Immune Tolerance Induction.

**Study Amendment Information**
In case of any changes in this study that may influence your desire to continue on this protocol or not, you will be asked to sign a new informed consent. Also, you will be informed of any global results, once the study has been completed.
Participation
Your participation in this study is strictly voluntary. Furthermore you may withdraw from the study at anytime. Your refusal to participate or withdrawal from the study will not change your relationship with your physician at the Hemophilia center who will continue to take care of you as usual.

Legal Terms
This study will be conducted according to the standard of Good Clinical Practice as defined internationally, and according to the ethical principles based on the Declaration of Helsinki.

Confidentiality
Your medical data will be kept strictly confidential in order to guarantee anonymity. All study documents from your center will be identified by number and initials only.

Contacts
If you have any questions regarding this study, your rights or any problems regarding this study, contact the Principal Investigator Dr. __________ at extension __________. We will be happy to address any comments, questions, or any requests. For major information do not hesitate to contact the staff at the Hemophilia treatment center or Professor Gringeri.
INFORMED CONSENT TO PARTICIPATE IN THE
RESIST- NAÏVE
Minors and Adolescents
(REScue Immunotolerance STudy in ITI- Naïve Patients)

Randomized Study ITI in Patients with Severe Hemophilia A Complicated by an Inhibitor at High Risk of Failure

1. I confirm that I have read and understand the given information provided on this study, and was given the opportunity to ask Dr. _______ questions.
2. I understand that my participation is voluntary and that I am free to retract my consent at anytime for any reason, without compromising my medical care and my legal rights.
3. I am aware that my clinical data will be strictly anonymous. I authorize access to this data only to the Investigators.
4. By my signature I accept participation in the RESIST- Naïve Study.

These documents are in duplicate- one for the study and one for me to keep.

INFORMED CONSENT TO PARTICIPATE IN THE STUDY
RESIST- NAÏVE
Minors and Adolescents

(REScue Immunotolerance STudy in ITI- Naïve Patients)

THE PATIENT:
Name and Surname _____________________________, age ____ accepts participation freely and voluntarily in the RESIST- Naïve Study.

City ________________________ Date (Month/Date/Year): ______________

Patient Signature: __________________________________________________

PRINCIPAL INVESTIGATOR:
I Dr. Name and Surname have explained to the subject and his/ her parent(s) the purpose, method, risk and benefits of the study and answered all questions presented to me.

City ________________________ Date (Month/Date/Year): ______________

Patient Signature: __________________________________________________
INFORMED CONSENT TO PARTICIPATE IN THE
RESIST- NAÏVE
(REScue Immunotolerance STudy in ITI- Naïve Patients)
Minor- Child

Randomized Study ITI in Patients with Severe Hemophilia A with Inhibitor- Ineligible for Enrollment in the International Immune Tolerance Induction Study

Principal Investigator: Prof. Alessandro Gringeri

This paper has been written for children, who, like you, lack a factor that helps your blood clot, Factor VIII. Lack of Factor VIII is a condition called Hemophilia. Furthermore, your blood has some substances called antibodies (or inhibitors), which destroy the Factor VIII that you receive with your shots. For this reason it is necessary to treat you promptly and find a way to remedy this situation.

We are asking you, and other children like you to participate in this research in which we want to see if we can get rid of these antibodies that prevent Factor VIII to stop your bleeds. In this research, in order to get rid of your antibodies, you will have to have a shot everyday, possibly for many months. This treatment is fairly common, but we shall use one of two kinds of medicines both capable of getting rid of inhibitors. It is very important that these medicines are given according to the instructions given by your Doctor in the Hemophilia treatment center.

If you do not wish to participate in this study, we will still take good care of you, and it is possible that you may still need to receive daily shots. If you decide to be in this study, you will need to come for checkups several times, accompanied by your parent(s) or your caretaker. We will need to make sure that you are ok, check if the medicine is working without causing any problems.

If you feel that the medicine is causing any problems, you will need to tell your parent(s) immediately, and your Doctor who will tell you what to do.

During your medical checkups, the Doctor will ask you how you are doing, if you are having any problems and if you have taken your Factor everyday. During some of these visits, we will also take small amounts of blood to check if the medicine is working.

It is very important for you to know that you are free to choose whether to participate or not in this research. If you don’t want to participate we will continue to take good care of you regardless. Furthermore, if you decide
to quit the study, your parent(s) and your Doctor will not be mad at you. You should think about it before deciding. If you do not know what to do, ask your Doctor or parent(s) to explain the study some more and help you decide.

If you decide to be in the study, your Doctor will ask you to sign this paper. We will explain this study to your parent(s) (caretaker) as well, if they believe that it is good for you to participate, they will be asked to sign a paper as well.

I agree to participate in this study

_________________________________________  ________________________
Signature       Date
Appendix 3
Monitoring Serious Adverse Events

Definitions

Adverse event (AE)
Any harmful clinical event appearing in a patient or subject involved 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 drug reaction (SAE, SADR)
An 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 hospitalisation 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 (eg, social hospitalization for purposes of respite care).

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

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

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.

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).

Reporting procedure
Adverse events (AEs) and adverse reactions (ARs)
All adverse events and adverse reaction occurring after the subject has signed the informed consent must be fully recorded in the subject’s case record form.

Serious adverse events (SAEs) and serious and unexpected reactions (SUSARs)
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 immediately (within 24 hours of the investigator’s awareness) be reported to CENTRO DI EMOFILIA “ANGELO BIANCHI BONOMI”, phone +39 0255035290; fax +39 0255032072.

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>
| IMPROBABLE | - It does not follow a reasonable temporal sequence after the administration of the drug.  
- It could easily be due to the known characteristics of 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. |
| 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 disappears or diminishes when the drug is stopped or the dose reduced.  
- 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 within 7 days of receipt in the case of death or a life threatening, and within 15 days in all other cases (DL 211).