Post-Authorisation Safety Study (PASS) of CLAIRYG® (Human normal immunoglobulin for intravenous use) in children under 12 years treated for primary immunodeficiency (PID) or immune thrombocytopenic purpura (ITP)

PROTOCOL

Version No. and Protocol date	3.0 dated 27/01/2015
SPONSOR	**LFB BIOMEDICAMENTS** 3, avenue des Tropiques BP 305 – Les ULIS 91958 COURTABOEUF Cedex – France
Name of the study drug	CLAIRYG® (IVIg) 50 mg/ml, solution for IV infusion
Indication(s) studied	Primary Immunodeficiencies (PID) Immune Thrombocytopenic Purpura (ITP)
Clinical phase	IV
DIRECTOR OF MEDICAL AFFAIRS LFB BIOMEDICAMENTS	[redacted]
SCIENTIFIC COMMITTEE	
- Coordinating expert	[redacted]
- Coordinating expert	[redacted]
- Methodology/Statistics expert	[redacted]
CLINICAL PROJECT MANAGER LFB BIOMEDICAMENTS	[redacted]

HEAD OF CLINICAL OPERATIONS
LFB BIOMEDICAMENTS

EU QPPV
Pharmaceutical Affairs and Quality Department
LFB Group

SERVICE PROVIDER RESPONSIBLE FOR DATA COLLECTION AND PROCESSING

Study ID	**CLAIRYG® PAEDIATRIC PASS**
Title	**Post-Authorisation Safety Study (PASS) of CLAIRYG® (Human normal immunoglobulin for intravenous use) in children under 12 years treated for primary immunodeficiency (PID) or immune thrombocytopenic purpura (ITP)**
Protocol version number	3.0
Date of last protocol version	27/01/2015
EU PAS Register No.	Study not registered
Active substance	Pharmacotherapeutic group: immune sera and immunoglobulins: human normal immunoglobulin for intravenous use ATC code: J06BA02
Product name	CLAIRYG® 50 mg/ml (5%), solution for IV infusion
Product reference No. (MA No.)	3400957618674, 3400957618735, 3400957618964, 3400957619046, 3400957619107
Procedure number	Not applicable
MA holder	LFB BIOMEDICAMENTS
Joint PASS	No
Question asked and primary objectives	The primary objective is to evaluate the safety of CLAIRYG® administered as part of common practice in children under 12 years treated for PIDs or ITP over a follow-up period of 12 months. The secondary objectives are as follows: - To describe the conditions of use of CLAIRYG® as part of common practice in children under 12 years, - And to collect efficacy data to better document the benefit/risk ratio in the two pathologies studied: PIDs and ITP
Country where the study is conducted	France
Authors	[redacted]
Director of Medical Affairs **LFB BIOMEDICAMENTS**	[redacted]

LFB BIOMÉDICAMENTS

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2 ABBREVIATIONS

ANSM	*Agence Nationale de Sécurité du médicament et des Produits de Santé* (National Agency of Medicine and Health Product Safety)
CRA	Clinical Research Associate
CCTIRS	*Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (Advisory Committee for the Treatment of Health Research Data)
CNIL	*Commission Nationale de l'Informatique et des Libertés* (French Data Protection Committee)
CNOM	*Conseil National de l'Ordre des Médecins* (French National Board of Physicians)
CPP	*Comité de Protection des Personnes* (Committee for the Protection of Persons involved in Biomedical Research - Ethics Committee)
CRF	Case Report Form
CRPV	*Centre Régional de PharmacoVigilance* (Regional Pharmacovigilance Centre)
CV	Curriculum vitae
CVID	Common Variable ImmunoDeficiency
PID	Primary ImmunoDeficiency
AE, SAE	Adverse Event, Serious Adverse Event
EMA	European Medicines Agency
i.e.	Id est (that is to say)
IgG	Type G immunoglobulin
IVIg	Human immunoglobulins for intravenous use
SCIg	Human immunoglobulins for subcutaneous use
LFB	Laboratoire français du Fractionnement et des Biotechnologies
LLT	Lowest Level Term
PASS	Post-Authorisation Safety Study
PDCO	Paediatric Committee (of the EMA)
PSUR	Periodical Safety Update Report
PT	Preferred Terms (PT)
ITP	Immune Thrombocytopenic Purpura
PV	Pharmacovigilance
SPC	Summary of Product Characteristics
SOC	System Organ Class

CTT	Clinical Trial Technician
TMF	Trial Master File

3 RESPONSIBLE PARTIES

3.1 Responsibility of the investigator

The study will be conducted in accordance with the principles of Good Pharmacovigilance Practice (Guideline on good pharmacovigilance practice (GVP) Module VIII – Post-authorisation safety studies – EMA/813938/2011 Rev.1 - 2013), Good Clinical Practice (ICH-E6) and regulatory requirements in force.

3.1.1 Provisional list of investigators

The provisional list of investigators who were contacted to take part in this study is shown in appendix I of the documents not included.

3.1.2 Information and collection of consent and assent

Once a child with a PID or ITP is treated with CLAIRYG®, the investigator at the site participating in the study will propose to the holder(s) of parental authority or the legal representative(s) and to the child (if he/she is able to understand) to participate in this study.

The holder(s) of parental authority or the legal representative(s) and the child will be provided with information and their consent and assent will be collected as described in section 9.2.3.1.

At the end of the study, in application of the law on patient rights (Law no. 2002-303 of 4 March 2002), the investigator may provide, at the request of the person who participated or his/her legal representative(s), information concerning the overall results of this study.

The Sponsor will provide this information beforehand in the form of a short summary of the main results of the study. If applicable, the investigator will document how the information was provided in the patient's source file.

3.1.3 Reporting of adverse events

The investigator will be responsible for reporting adverse events (AEs) observed in the children participating in the study within 24 hours after he/she learns of them. For this, he/she will complete the AE section of the electronic case report form (e-CRF), as described in section 11.1.

The Pharmacovigilance Unit, the project managers of LFB BIOMEDICAMENTS and the service provider responsible for managing the study will be notified of them automatically through an e-mail alert, as described in section 11.2.

3.1.4 Collecting data in the electronic case report form (e-CRF)

The investigator will be responsible for the collection, validity, completeness and accuracy of the data reported in the electronic case report form. If the investigator would like to delegate completion of the case report forms to a Clinical Trial Technician (CTT), he/she shall remain responsible for the accuracy of the data entered into the e-CRF. The CTTs will need to make sure that a consent form was indeed signed before filling out the case report form.
The CTTs will be able to access the medical files under the responsibility and supervision of the investigator.

3.1.5 Retention of the study documents

The investigator will be responsible for keeping the study documents (40 years) and allowing rapid access to the medical file of the children participating in the study in the event of an audit by the Sponsor or any inspection by Authorities.

3.1.6 Availability for monitoring and quality control

The investigator and the members of his/her team involved in the study will need to be available for monitoring visits made by the Clinical Research Associates (CRAs) and for audits and inspections. The investigator will be responsible for guaranteeing that the Sponsor and Competent authorities have direct access to the source documents.

3.2 Responsibility of the Scientific Committee

3.2.1 Composition of the Scientific Committee

The scientific committee will be composed of 2 coordinating experts and one methodology expert:

Names	Role and Area of expertise	Affiliation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3.2.2 Roles and Responsibilities

The principal mission of the Scientific Committee will be to provide medical, scientific and methodological advice during preparation for the study, while it is underway and during data analysis and writing of the end-of-study reports and publications. This will mainly consist of the following:

- Participating in review and validation of the key study documents (protocol, case report forms for the 2 Primary Immunodeficiency (PID) and Immune Thrombocytopenic Purpura (ITP) cohorts, information and consent forms for the holders of parental authority or legal representatives, information documents for the children or pre-adolescents),
- Advising the Sponsor during preparation of the provisional list of investigational sites for the study,
- Participating in review and validation of the statistical analysis plan,
- Participating in the data review meeting for the 2 cohorts (PIDs and ITP),
- Participating in review and validation of the study report,
- Contributing to writing the scientific publication of the data.

The Sponsor will responsible for correspondence and coordination of the Scientific Committee meetings.

The frequency of correspondence and/or meetings with each of the Committee members and of the meetings will be adapted to the events and progress of the study.

3.3 Responsibilities of the Sponsor

3.3.1 Regulatory aspects

LFB BIOMEDICAMENTS, Sponsor of the study, has the following responsibilities:

- To submit:
  - The study protocol to the National Agency of Medicine and Health Product Safety (ANSM) for information
  - The request for an opinion to the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (CCTIRS - Advisory Committee for the Treatment of Health Research Data).
  - The request for authorisation to the *Commission Nationale de l'Informatique et des Libertés* (CNIL - French Data Protection Committee)
  - The submission to a *Comité de Protection des Personnes* (CPP - Ethics Committee) (for publication of the results in a scientific journal),
  - The request for an opinion to the *Conseil National de l'Ordre des Médecins* (CNOM - French National Board of Physicians) on the contracts of the investigators and coordinating experts for the study,
  - The final study report to the ANSM and the Paediatric Committee (PDCO) of the EMA.
- To guarantee publication of the results of the study in a peer-reviewed scientific journal in collaboration with the coordinating experts of the study.
- To provide the investigators with the overall results at the end of the study as well as a comprehensible overview intended for the holder(s) of parental authority or the legal representative(s) of the child.

3.3.2 Management of the study

LFB BIOMEDICAMENTS will subcontract management of the study to a Service Provider, including for the start-up, monitoring and quality control of the study.

The Service Provider will be appointed to start-up the study at the sites and to train the investigators in completing the e-CRF.
Throughout the study, it will handle correspondence with the sites and will make sure that the data collected is accurate, including by sending out CRAs on site to perform monitoring visits.

At the sites that do not have internal CTTs, the Service Provider could send out a CTT on site, at the request of the investigator.

The CTTs and CRAs of the Service Provider appointed by LFB will be given access to the medical files of the patients:

- Under the responsibility and supervision of the investigator,
- Under terms of professional secrecy, according to the terms of articles 226-13 and 226-14 of the French Criminal Code.

3.3.3 Biometrics

LFB BIOMEDICAMENTS will subcontract processing of the data to a Service Provider. This will include the data management and statistical analyses.

The Service Provider will develop the technical e-CRF solution and will handle management and monitoring of the data until the database freeze. All of these services will be performed in accordance with Good Clinical Practice (GCP).

The subcontracted activities will remain under the joint responsibility of the Sponsor and the Service Provider, which will commit to the quality of the methodology and compliance with regulations in connection with Law No. 78-17 "Information Technology and Liberties" of 6 January 1978, as modified on 1 July 1994 and 6 August 2004.

3.3.4 Pharmacovigilance

LFB BIOMEDICAMENTS will train the Service Provider's staff involved in management of the clinical study in:

- The safety profile of the study drug, CLAIRYG®,
- The protocol and e-CRF,
- The procedures for handling serious or non-serious adverse events, as described in the protocol and "Safety plan" for the study,
- The procedures for completing the serious or non-serious adverse event reporting form,
- The procedures for reporting of serious or non-serious adverse events by the investigator, in accordance with the protocol, the "Safety plan" for the study and regulatory requirements.

The Project Manager or CRA of the Service Provider will train the investigators during the study start-up visits or the investigators meeting in:

- The protocol and e-CRF,
- The safety profile of CLAIRYG® (SPC),
- The procedures for completing the serious or non-serious adverse event reporting form,
- The procedures for reporting of serious or non-serious adverse events by the investigator, in accordance with the protocol and regulatory requirements.

4 SUMMARY

The protocol summary is a separate document listed in APPENDIX 1 to the protocol

5 AMENDMENTS AND UPDATES

Not applicable

6 MAIN MILESTONES

Milestones	Provisional dates
Start of data collection	Estimated 1st quarter of 2015
End of data collection	Estimated 1st quarter of 2017
Final report on the results of the study	Estimated 3rd quarter of 2017

7 RATIONALE FOR THE STUDY AND CURRENT KNOWLEDGE ON THE SAFETY OF THE STUDY DRUG

In general, when human normal intravenous immunoglobulins are administered, intolerance reactions such as chills, headache, feeling of dizziness, hyperthermia, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate lumbar pain may sometimes occur.
In rare cases, human normal immunoglobulins may cause a sudden drop in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administrations.
Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulins. Reversible haemolytic reactions have been observed in certain patients, and especially in those with blood groups A, B, and AB. More rarely, haemolytic anaemia requiring transfusion may develop after treatment with IVIgs.
Elevated plasma creatinine levels and/or acute renal insufficiency have been observed. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism or deep vein thromboses have been reported.

7.1 Study drug

CLAIRYG® is a liquid, ready-to-use preparation of human normal polyvalent intravenous immunoglobulins (IVIg) at a concentration of 5% (50 mg/ml). 95% of the total quantity of proteins are IgG.

The distribution of IgG subclasses (normal values) is as follows:

- IgG1: 55 - 67%
- IgG2: 29 - 37%
- IgG3: 1 - 4%
- IgG4: 1 - 3%

The maximum IgA concentration is 0.022 mg/ml.

The excipients are: mannitol, glycine, polysorbate 80, water for injections.

Clairyg is sold in France by LFB BIOMEDICAMENTS. Marketing authorisation (MA) for CLAIRYG® was obtained in France in December 2009 and it was first sold in France starting in August 2010.

CLAIRYG® is prescribed for the following indications:

REPLACEMENT THERAPY

- In primary immunodeficiencies such as: congenital agammaglubulinemia and hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott Aldrich syndrome,
- In secondary Immunodeficiencies: myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections, recurrent infections in HIV-infected children.

IMMUNOMODULATION TREATMENT

- Idiopathic thrombocytopenic purpura in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barré Syndrome.
- Kawasaki disease.

ALLOGENEIC BONE MARROW TRANSPLANT

- Treatment of infections and prevention of graft-versus-host disease
- Persistent lack of antibody production

The dose and posology are dependent on the indication:
In replacement therapy, the posology may need to be individualised for each patient depending on the pharmacokinetic and clinical response. The following posologies are given as a guideline.

Replacement therapy in cases of PIDs
The treatment should achieve a trough level of IgG (measured before the next administration of IVIg) of at least 4 to 6 g/l. In the presence of persistent infections, the trough level of IgG could be brought to 8 or even 10 g/l. Three to six months are required after the initiation of therapy to reach steady state. The recommended starting dose is 0.4 to 0.8 g/kg of body weight followed by at least 0.2 g/kg of body weight every three weeks.

The dose required to achieve a trough level of 6 g/l is in the range of 0.2-0.8 g/kg body weight per month. The interval between doses when steady state has been reached varies from 2 to 4 weeks. More frequent infusions can be required if the patient develops infections. Trough levels should be measured in order to adjust the dose and dosage interval.

Immunomodulatory treatment for ITP
For the treatment of an acute episode, 0.8-1 g/kg of body weight on day one, which may be repeated within three days, or 0.4 g/kg of body weight daily for 2 to 5 days. This treatment can be repeated if relapse occurs.

Complete information about the product is available in the SPC.

7.2 Rationale

In accordance with the European paediatric regulation, the application for Marketing Authorisation for CLAIRYG® required that a Paediatric Investigation Plan (PIP) be submitted to the "Paediatric Committee" (PDCO) of the European Medicines Agency (EMA). The PIP describes the development program designed for the medicinal product in order to provide data on the safety of CLAIRYG® administered to children under 12 years and to document its efficacy.

Given the absence of safety data for CLAIRYG® in the population under 12 years in the pivotal studies, the LFB group submitted a Paediatric Investigation Plan (PIP) to the PDCO on 8 February 2008. The PIP included the completion of a post-MA study to monitor safety in common medical practice, a so-called Post-Authorisation Safety Study (PASS). The primary objective of this study is to collect safety data in children under 12 years treated with CLAIRYG®, whether they suffer from a PID or ITP. As a reminder, children with ITP receive higher doses than those treated for a PID.
During evaluation of the dossier, the PDCO confirmed on 15 July 2011 (Opinion of the EMA/PDCO with number: EMA/PDCO/364595/2011) that the study could be limited to children under 12 years, as they estimated that adolescents between the ages of 12 and 19 years can be likened to adults. Furthermore, data have since been reported for this age group: safety data have

been reported in 6 adolescents aged 12 to 18 years as part of a pivotal post-MA monitoring study (IGNG 0629) and are presented below (cf. section 7.3.2).
In this context, LFB BIOMEDICAMENTS is organising a national (France), prospective, observational, multicentre, longitudinal study in the population of children under 12 years treated with CLAIRYG® in the following 2 indications:

- Replacement treatment of children with PIDs,
- And immunomodulatory treatment of children with ITP.

The primary objective of the study is to evaluate the safety of the product administered to children under 12 years and the secondary objectives are to collect information on how CLAIRYG® is used in common medical practice as well as any available information on its clinical efficacy.

7.3 Current knowledge on the safety of CLAIRYG®

7.3.1 Safety reported in interventional clinical trials in adults

The safety of CLAIRYG® was studied in 2 pivotal clinical studies which included 41 adult patients treated with this product. No patient under 18 years was included in these 2 studies.

- A prospective, controlled, open-label, multicentre study in France (IGNG 0612) which was held in 2 successive phases (treatment for 3 months with TEGELINE® followed by treatment for 6 months with CLAIRYG®) in 22 adult patients with PIDs. These patients received a total of 146 infusions of CLAIRYG® at a mean dose per infusion of 29.1 g (20 g to 45 g)
  - 15/22 received one infusion every 4 weeks, for a total of 6 infusions per patient,
  - 7/22 received one infusion every 3 weeks, for a total of 8 infusions per patient.
- A prospective, non-comparative, multicentre study (IGNG 0613) conducted in France in 19 adult patients with ITP. These patients received a total of 27 infusions of CLAIRYG® at a median dose of 1 g/kg [0.9-2.1]:
  - 11/19 (57.9%) received one single infusion,
  - 8/19 (42.1%) received two infusions of CLAIRYG® (on D1 and D3 for 7/19 and on D1 and D15 for 1 patient).

Safety observed in the PID patients included in the pivotal study (IGNG 0612) during the 2nd treatment phase (CLAIRYG®)

Forty-nine (49) adverse events (AEs) were reported in 17/22 patients with PIDs treated with CLAIRYG®, 3 of which were considered as SAEs in 3 patients. These were one moderate case of hepatitis C, one mild gastric ulcer and one moderate thrombocytopenia. None of the SAEs were related to CLAIRYG®.

Of these 49 reported AEs, 6 observed in 4 patients (18%) were considered by the investigators to be related to the administration of CLAIRYG®:

- Three (3) cases (13.6%) of transient lymphopenia, rated as with dubious causality for 2 and possible causality for 1,
- One (1) case (4.5%) of monocytopenia rated as dubious,
- One (1) case (4.5%) of erythematous rash rated as possible,
- One (1) case (4.5%) of headache rated as dubious.

Furthermore, among these 49 AEs, 13 were considered as temporally related to the study drug according to the Note for Guidance for IVIg (EMA/CHMP/BPWP/94033/2007 rev.2; i.e. AEs

occurring during or within the 48 hours following the infusion): 3 lymphopenias, 1 monocytopenia, 1 erythematous rash, 1 abdominal pain, 1 cough, 1 epistaxis and crepitant rales
They were reported in 8/22 patients (36.4%). Twelve (12) of these AEs were observed during or within the hour following the infusion.

Safety observed in the patients with ITP included in the pivotal study (IGNG 0613)

Forty-five (45) AEs were reported in 17/19 patients (89.5%) treated with CLAIRYG®, 6 of which (13.3%) were considered as SAEs in 5 patients (26.3%). 1 SAE was hospitalisation for aggravation of arterial hypertension and the others were relapses of thrombocytopenia. None of the SAEs were related to CLAIRYG®.

Of the 45 reported AEs, 16 (35.6%) observed in 13 patients (68.9%) were considered by the investigators to be related to the administration of CLAIRYG®:

- Five (5) cases (26.3%) of headache, rated as with dubious causality for 2 and possible/probable causality for 3,
- Five (5) cases (26.3%) of fever rated as possible/probable,
- Two (2) cases (10.6%) of aggravation of arterial hypertension rated as possible/probable,
- Two (2) cases (10.6%) of nausea rated as possible/probable,
- One (1) case (5.3%) of chills rated as possible/probable,
- One (1) case (5.3%) elevated plasma creatinine rated as possible/probable.

Furthermore, twenty-nine (29) AEs reported in 17 patients (89.5%) (corresponding to 15 related AEs and 14 unrelated AEs according to the investigators) were considered as temporally related to the study drug according to the Note for Guidance for IVIg (i.e. AE occurring during or within 48 hours following the infusion):

- Episodes of fever (8) which occurred in 6 patients (31.6%),
- Headaches (5) in 5 patients (26.3%),
- Arterial hypertension (5) in 5 patients (26.3%)
- Nausea (2) in 2 patients (10.5%),
- Insomnia (2) in 2 patients (10.5%),
- Iron-deficiency anaemia, abdominal pain, chills, malaise, muscle pain, vagal reaction and bronchospasm which each occurred in 1 patient (5.3%).

15 other AEs were considered as not related by the investigators and had not occurred in the 48 hours following the infusion. These included: thrombocytopenia in 6 patients, asthenia in 2 patients, diarrhoea, fever, flu syndrome, inguinal hernia, weight loss, hypertension and elevated transaminases, each in 1 patient.

The outcome of all of the AEs related to CLAIRYG® was favourable, without sequelae. For 2 unrelated AEs, the outcome was not reported (weight loss and elevated transaminases) and healing was not achieved in one case (inguinal hernia).
All of the AEs related to the study drug are known and classically reported after the administration of IVIg; the safety profile of CLAIRYG® is thus conforming to that which can be expected for an IVIg preparation.

Safety reported during long-term safety and efficacy follow-up in patients (adults and adolescents) with PIDs (Study IGNG 0629)

This study allowed the patients in the pivotal study (IGNG-0629) to continue using the product until its commercialisation of CLAIRYG® and also served to collect additional safety and efficacy data during common medical practice, over a longer period of time (31.9 months on average). 23 patients over 12 years (adults and adolescents) with PIDs were monitored. These were 17 adult patients, 11 of which came from the previous pivotal study, and 6 adolescents between the ages of 12 and 18 years.

All of the patients received CLAIRYG® for at least one year, with the exception of one 15-year-old adolescent patient who was withdrawn from the study prematurely following anaphylactic shock that occurred after 108 treatment days.

For a total of 849 infusions administered, 333 AEs were observed.

Of the 333 reported AEs, 65 (19.5%) observed in 14 patients were considered by the investigators to be related to the administration of CLAIRYG®:

- Eight (8) cases judged to have dubious causality: asthenia, arterial hypertension, elevated gamma-glutamyl transferases, nephropathy, elevated blood pressure, dyspnoea, pulmonary hypertension and chronic renal insufficiency.
- Fifty-seven (57) cases judged to have possible/probable causality: 1 case of abdominal pain, 1 anaphylactic shock, 9 cases of arthralgia, 6 cases of asthenia, 1 case of back pain, 2 cases of chills, 1 positive indirect Coombs test, 1 case of cough, 1 sensation of discomfort, 2 sensations of cold, 4 cases of headache, 2 cases of hyperthermia, 1 case of arterial hypotension, 7 cases of pain at the injection site, 14 cases of pain, 2 cases of pain in the extremities, 1 case of pharyngolaryngeal pain and 1 case of vomiting.

Thirty-five (35) SAEs were reported in 11 patients and 3 of these SAEs which occurred in 3 patients were considered as related to the administration of CLAIRYG®. In 2 cases, the link was evaluated as dubious (pulmonary arterial hypertension and chronic renal insufficiency) and, in one case of anaphylactic shock that occurred shortly after the end of the infusion (disappeared without sequelae after interruption of the infusion), the link as considered as probable.

Detailed presentation of the SAEs observed in the 6 adolescents included (12 to 18 years)

Six (6) adolescents were included in this study at 3 different paediatric sites. They were followed between 108 and 969 days and received between 6 and 46 infusions (cf. table 3 below).

They presented a total of 47 AEs during the study (from 1 to 22 AEs per patient):

- 10 AEs related to CLAIRYG® occurring in 2/6 adolescents:
  - 1 anaphylactic shock (SAE) in 1 patient,
  - Pain at the injection site (7 non-serious adverse events (NSAEs)), abdominal pain (1 NSAE) and pharyngeal pain (1 NSAE) in the 2nd patient.
- 9 SAEs occurring in 4/6 adolescents:
  - 1 SAE related to the product: anaphylactic shock,
  - 8 SAEs not related to the product: bronchiectasis (2), abdominal pain (1), eardrum superinfection (1), mastoiditis (1), left purulent lymphadenitis (1), implant infection (1) and superinfection of a molluscum (1).

Description of the serious adverse event related to the product: Anaphylactic shock

This was a 15-year-old adolescent with a congenital humoral immunodeficiency associated with a lymphoproliferative syndrome with splenomegaly, lymphadenopathies, benign pulmonary nodules and IgA deficiency (0.1 g/l). The patient began treatment with CLAIRYG® at a mean posology of 572.9 mg/kg every 3 weeks.

Shortly before the end of the 6th infusion of CLAIRYG®, the patient suddenly presented with malaise in association with a drop of blood pressure to 80/50 mmHg, mottling, urticarial rash, a 39°C fever, chills and pallor. The infusion, administered at a rate of 1.04 ml/kg/h for the first 45 minutes and then increased to 4.16 ml/kg/h, was stopped. The symptoms subsided within 1 hour following discontinuation of the infusion and initiation of treatment with Polaramine® (dexchlopheniramine) 10 mg in combination with hydrocortisone (50 mg x 2 by intravenous route). The fever was treated with an intravenous injection of 2.5 g of Rocephine® (ceftriaxone) according to common practice at the site at the appearance of an undocumented fever. The treatment with CLAIRYG® was never resumed and the patient was withdrawn from the study prematurely due to this SAE.

Anti-IgA alloimmunisation associated with anaphylactic reactions in patients with IgA deficiencies are reactions which have already been described with IVIg. In this type of patient, IVIg preparations containing low IgA levels must be used. This is mentioned in the SPC of CLAIRYG®.

LFB BIOMÉDICAMENTS

TABLE 1 - DESCRIPTION OF THE 6 ADOLESCENTS INCLUDED IN STUDY IGNG-0629: INFECTION AND AE RATES

Age at inclusion, Diagnosis	Follow-up time (months)	Number of infusions administered	Mean dose per infusion (mg/kg)	Mean trough IgG levels during the study (g/l)	Number of infections (annual rate)	Number of AEs	Number of AEs related to CLAIRYG	Number of SAEs
14.4 Agammaglobulinemia	33.1	46	439.6	10.2	4 (1.51)	6	0	1 not related (bronchiectasis)
17.6 CVID	29.4	29	330.8	8.8	9 (4.21)	3	0	0
15 Hyper IgM	15	21	624.7	12.9	4 (3.38)	1	0	0
15.1 Hyper IgM	4.9	6	572.9	6.43	1 (3.38)	3	1	1 probably related (anaphylactic shock)
16.9 Agammaglobulinemia	31.1	44	512.5	10.4	2 (0.81)	12	0	2 not related (abdominal pain and bronchiectasis)
12.1 CVID	18.2	18	421.7	12.9	17 (11.72)	22	9	5 not related (eardrum superinfection, mastoiditis, left purulent lymphadenitis, implant infection, superinfection of a molluscum)

***Patients on anti-infection prophylaxis**

7.3.2 Safety reported in children under 12 years during post-registration exposure

Since the marketing of CLAIRYG®, on 30 August 2010, and until 31 March 2013 (date of the end of the period of the last PSUR), 162 individual pharmacovigilance cases with adverse event(s) were received by the LFB Pharmacovigilance Unit. Among these cases, 21 (13%) were reported in children under 12 years. The reports concerned neonates (2 days) in 2 cases, children (3-10 years) in 17 cases. The age was not specified in 2 cases.

The indication of CLAIRYG® for these 21 cases was:

- Immunodeficiency for 4 patients,
- Immunomodulation for 9 patients (idiopathic thrombocytopenic purpura (8) and Kawasaki disease (1)),
- Non-MA indication for 5 patients (Chylothorax (1), Chronic Inflammatory Demyelinating Polyradiculoneuropathy (1), immunodeficiency secondary to plasmapheresis (1), severe haemolytic anaemia in a context of Rhesus incompatibility (1), cervical myelitis (1)),
- Unspecified for 3 patients.

Of these 21 cases, 17 were serious and 4 were non-serious (including 2 cases of extravasation without complications). The outcome was favourable in 15 cases and was not specified in 6 cases.

These cases reported the following adverse events (1 case may correspond to several adverse events:

- Nervous system disorder (headache, meningeal disorders, suspected intracranial hypertension) in 9 cases,
- General disorders and administration site abnormalities (fever, chills, extravasation) in 5 cases,
- Skin and subcutaneous tissue disorders (rash, photosensitivity) in 2 cases,
- Vomiting in 2 cases,
- Aseptic meningitis in 3 cases,
- Anaphylactic reaction in 1 case,
- Hypotension in 1 case,
- Probable iatrogenic renal insufficiency in 1 case.

Most of these adverse events reported in children are effects which are already known with intravenous immunoglobulins.

Experience in children under 12 years is limited and few cases of adverse events have been received. Analysis of the available data does not reveal any particularity in the safety profile of CLARYG® in this population.

7.3.3 Safety reported with CLAIRYG® to date

The safety of CLAIRYG was studied in specific in the 3 clinical trials cited above (sections 7.3.1 and 7.3.2) which included 53 adult patients exposed to CLAIRYG.
The adverse events reported in the largest number of patients were fever and headache. Fever occurred most often during the administration of CLAIRYG while the headaches mainly occurred within 24 hours after the infusion.
The adverse events reported in these studies and considered as at least possibly related to the treatment as well as the adverse events observed since marketing of the product are listed in table 2 below, which is taken from the SPC which is currently under evaluation by the ANSM.

Table 2 is presented is according to the MedDRA classification (System Organ Class (SOC) and Preferred Term Level).

TABLE 2 – ADVERSE EVENTS OBSERVED WITH CLAIRYG®

MedDRA System Organ Class (SOC)	Adverse reactions	Frequency*
Blood and lymphatic system disorders	Lymphopenia	Rare
Immune system disorders	Anaphylactic shock	Rare
	Hypersensitivity reaction (possibly leading to general disorders (malaise, chills, hyperthermia), skin disorders (rash, erythema, eczema, urticaria, pruritus), respiratory disorders (bronchospasm, respiratory distress) and injection site reactions)	Not known
Nervous system disorders	Aseptic meningitis, meningism, meningeal disorders	Not known
	Headache	Uncommon
Vascular disorders	Thromboembolic events (pulmonary embolism, venous thrombosis)	Not known
	Hypertension	Uncommon
	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Cough	Rare
	Pharyngeal pain	Rare
Gastrointestinal disorders	Nausea	Uncommon
	Vomiting	Rare
	Abdominal pain	Rare
Skin and subcutaneous tissue disorders	Erythematous rash	Rare
Musculoskeletal and systemic disorders	Joint pain	Uncommon
	Pain in the extremities	Uncommon
	Lumbar pain	Rare
General disorders and administration site conditions	Fever	Uncommon
	Hyperthermia	Uncommon
	Chills	Uncommon
	Asthenia	Uncommon
	Pain**	Common**
	Pain at the administration site	Uncommon
	Sensation of cold	Uncommon
	Discomfort	Rare
Investigations	Slight reversible, transient increase in plasma creatinine without clinical consequences	Rare
	Positive indirect Coombs test	Rare

** Absence of detail on the site and type of pain; effect presented by one single patient during 14 infusions.

*The frequencies were calculated with respect to a total of 1,021 infusions administered in a total of 53 patients exposed to the product in the 3 clinical studies, and are defined as follows: very common (≥1/10), common (≥1/100 <1/10), uncommon (≥1/1,000 <1/100), rare (≥1/10,000 <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). For each frequency, the adverse reactions are shown by decreasing order of seriousness.

7.3.4 Safety in children with PIDs or ITP treated with IVIg as reported in publications

Analysis of the literature over a period of about 25 years provides available information about the safety of IVIg in the following paediatric population:

For children with PIDs

Out of 36 identified publications [1988-2013] concerning patients with PIDs treated with IVIg and including children, only 10 presented adverse events that occurred specifically in the paediatric population (1 month to 18 years). These publications described different types of studies: retrospective (2), prospective (4), case-control studies (3). The type of study was not specified in one case (1).

The main adverse effects described are known with IVIgs based on the Core SPC for IVIg (CPMP/BPWG/859/95 rev.2): headache, fever, nausea, vomiting, chills, fatigue, arterial hypotension, gastric discomfort and diarrhoea.

In 3 children between 7 and 10 years of age, an increased hyperactivity score was reported after infusion [1].

In one 11-year-old child, a thrombosis of the cerebral sinuses was observed 1 month after the 29th infusion of IVIg given at the dose of 400 mg/kg/month [2].

Two patients aged 7 and 9 years presented with angioedema of the hands after infusion [3].

One aseptic meningitis was reported in a 9-year-old patient, without specification of the dose received [4]. Lastly, one vasculitis and one retinal uveitis were observed, again in a 9-year-old child 3 months after a dose increase from 200 to 400 mg/kg every 2 weeks [5].

For children with ITP

Out of 56 identified publications [1985-2013] concerning patients with ITP treated with IVIg and including children, most (50/56) reported adverse events that occurred specifically in the paediatric population (1 month to 18 years). These publications described different types of studies: retrospective (11), prospective (3), prospective randomised (20) or clinical cases (17).

The main adverse events described are known effects associated with IVIg: headache, fever, nausea, vomiting, chills, fatigue, hypotension, redness and vertigo.

The retrospective studies revealed the following other effects:

- Drop in neutrophils (<1500/µl) in 28% of 64 patients under IVIg [6] and in 36% of 14 patients (5 patients < 2000/µl) after a first infusion of IVIg [7],
- Case of aseptic meningitis in 4/125 (3%) children treated at the dose of 1 to 2g/kg [8],
- Mainly neurological complications with severity from grade 1 to 4 in 27/89 children (30%) treated at the dose of 1 to 2 g/kg of IVIg [9], including headache, vomiting and fever (grade 3) in 8/27 children and one aseptic meningitis (grade 4) in 4 children.
- Thirteen (13) case reports of the 17 found reported aseptic meningitis in 15 children aged 2 to 11 years, appearing in 1 hour to 4 days after the infusion [10-22].
- Two (2) case reports reported haemolytic anaemia:
  - Occurring 3 or 4 days after the start of the infusion in two 7-year-old children treated at 400 mg/kg/day for 3 to 5 days.

The presence of anti-A and anti-B erythrocyte antibodies for the 1st child and of anti-A antibodies for the 2nd in the batches of IVIg administered could account for the haemolysis observed [23].

- Occurring in one 4-year-old child treated with high-dose immunoglobulins and in whom alloantibodies were detected in a blood sample [24].

- Lastly, 1 case report describes the onset 9 days after the start of treatment with 2 doses of IVIg at 1g/kg over 2 days of multiple bilateral ischaemic infarctions in a 3-year-old child presenting with an intracranial haemorrhage [25].

This review of the literature found known AEs in connection with IVIgs. It did not show any apparent specificities of the AEs observed in children after the administration of IVIg.

In conclusion, the adverse events reported with CLAIRYG® in children under 12 years are effects described in the Core SPC for IVIg (CPMP/BPWG/859/95 rev.2) and are similar to those published in the literature in association with other IVIg.

The relatively limited experience with CLAIRYG® justifies extending the observation by conducting a prospective study in the paediatric population under 12 years treated for PIDs (representative of immunoreplacement therapy) and collecting data in ITP used as the representative pathology of the immunomodulatory side of IVIg treatment.

8 STUDY OBJECTIVES

8.1 Context

This is a post-authorisation safety study (PASS) conducted in France to evaluate the safety of CLAIRYG® in common practice as replacement therapy for PIDs in children under 12 years, over a period of 12 months.

The children with ITP treated at the same sites as the children with PIDs will also be included in the study in order to collected safety data in children receiving higher doses for immunomodulatory treatment. The follow-up time of the children in the study will depend on clinical progression of each child with ITP and on the practice of the investigator at each site; it will be a maximum of 12 months.

This study will collect all serious and non-serious adverse events, whether or not they are related to the administration of CLAIRYG® occurring in the children treated with CLAIRYG® during the period of their follow-up, in order to document the product's safety in real conditions of use.

Efficacy data will also be collected when available during the follow-up period in order to continue documenting the benefit/risk ratio of the product for the two indications studied (PID and ITP) in common medical practice.

8.2 Study objectives

8.2.1 Primary objective

The primary objective of this study is to evaluate the safety of CLAIRYG® administered as part of common practice in children under 12 years treated for PIDs or ITP over a maximum follow-up period of 12 months.

8.2.2 Secondary objectives

The secondary objectives are as follows:

- To describe the conditions of use of CLAIRYG® as part of common practice,
- To collect efficacy data to better document the benefit/risk ratio in the two pathologies studied, PIDs and ITP in children under 12 years.

9 METHODOLOGY

9.1 Study design

This is a prospective, observational, non-comparative, longitudinal, multicentre, post-authorisation safety study (PASS) in France to evaluate the safety of use of CLAIRYG® in common medical practice in children under 12 years with PIDs or ITP.

This study will thus include two cohorts:

- One cohort including children with PIDs
- One cohort including children with the different forms of ITP: acute, persistent or chronic.

9.2 Framework for the study

9.2.1 Participating sites

The study will be proposed to paediatric sites using CLAIRYG® specialised in the management of children with PIDs and ITP. We estimate that at least 10 to 15 sites will need to participate.

9.2.2 Study population

9.2.2.1 Patients studied

The study population will be composed of children under 12 years with:

- a PID treated with CLAIRYG® in the paediatric units of French hospitals participating in the study,
- or an ITP treated with CLAIRYG® at the same sites.

In order to limit the bias that could be associated with screening of the patients, we will attempt to include all children treated with CLAIRYG® at each participating site.
Therefore, each site will propose the study all children followed at consultations there. The reasons for any non-inclusion of a child will be collected in a specific form.

Inclusion criteria

- Child under 12 years treated with CLAIRYG® for a PID or ITP,
- Collection of consent: holder(s) of parental authority or legal representative(s) of the child and the child if applicable who received the information about the study and signed a consent or assent form within the period stipulated by the protocol and any amendments.

Non-inclusion criteria

As this is a non-interventional safety study under real prescription conditions, there are no criteria for non-inclusion as long as holder(s) of parental authority or the legal representative(s) of the child and the child if applicable have accepted to participate in the study.

9.2.2.2 Population

The EMA recommendation (EMA/CHMP/BPWP/94033/2007 rev.2) for the pre-MA development of IVIg estimates that at least 40 PID patients, of which at least one half should be children and adolescents followed for at least 12 months, would be sufficient to evaluate the safety and efficacy for registration of a new immunoglobulin.

Therefore, for a post-MA study designed to increase the body of knowledge in a rare disease, the PID population to be included was set at 25 children, in order to obtain 20 evaluable files. No statistical calculation defines the population size because the analysis will be purely descriptive.

The study will also be proposed to all children with ITP treated with CLAIRYG® at the participating sites. The number of children with ITP to be included has not be set in advance, but the enrolment potential is estimated at 30 children, based on a feasibility study performed by LFB in 2010.

9.2.3 Study description

As this is an observational safety study of a medicinal product already sold on the market, no therapeutic strategy with treatment procedures was defined for this 2-cohort study. Moreover, one of its objectives is to describe the real procedures of use of the product in common practice.

Furthermore, pursuant to articles L. 1121-1 and R.1121-2 of the French Public Health Code, this study is defined as a non-interventional study, during which all procedures must be performed and the products must be used normally, without any additional or unusual diagnostic or monitoring procedure. The medical strategy designed for the children participating in this study is not defined in advance in the protocol and falls under common practice, based on the SPC. This study is not subject to the system applicable to biomedical research studies.

CLAIRYG® is prescribed or used as usual and in accordance with the marketing authorisation mentioned in article L. 5121-8. The decision to prescribe or use this medicinal product is independent of that to include the individual in the study.

The follow-up of the patients and the type of data collected are summarised in tables 3 and 4 below for each of the two cohorts.

9.2.3.1 Supply of information and collection of consent

In order to comply with legislation in force on the respect of patient rights, the holder(s) of parental authority or the legal representative(s) of the child or the child (if applicable) will be provided with information in the following manner:

- Information provided by posting in the units of the healthcare institutions where the investigators participating in the study practice, to inform the holder(s) of parental authority or the legal representative(s) of the child of the start-up of this study in the healthcare institution caring for their children,
- Information given individually to the holder(s) of parental authority or the legal representative(s) of the child or the child (if applicable) by the investigator.

The investigator will orally inform the holder(s) of parental authority or the legal representative(s) of the child of the aim of the study, how the data will be collected and what medical data will be collected.
He/she will also provide information on the efficacy and safety of the product and could provide the package leaflet for the product.
The investigator will provide the holder(s) of parental authority or the legal representative(s) with an information sheet and a consent form to sign.

Collection of written consent from at least one holder of parental authority or one legal representative of the child is a prerequisite for the child's participation in this study (cf. *Guide de rédaction documents information et consentement* (Guide on how to write information and consent documents), CCTIRS, January 2014, available at the site http://www.enseignementsup-recherche.gouv.fr)

If he/she deems appropriate, the investigator for the study will also orally inform the child that medical data concerning him/her will be collected. He/she will use words which are appropriate for the child's age, knowledge and ability to comprehend. The objective of the study and what it will involve will be explained to him/her using a document that he/she can understand. The investigator will collect his/her agreement (or assent) to participate in the study, if applicable. The child will have the right to refuse to participate if he/she exercise it and no data about him/her will be collected.

The investigator will inform the holder(s) of parental authority or the legal representative(s) that he/she/they have a right to access and correct the data concerning his/her/their child's medical data, and to object to the transmission of data covered by professional secrecy that could be used and processed during this study.

The investigator will need to document the following in the child's medical file:

- The procedures used to provide information to the holder(s) of parental authority or the legal representative(s) and the child, if applicable,
- Handing over of the information sheet and consent form to the holder(s) of parental authority or the legal representative(s),
- If applicable, handing over of the suitable information sheet and assent form to the child depending on his/her age and ability to comprehend (child or pre-adolescent),
- The date of collection of the consent(s) of the holder(s) of parental authority or the legal representative(s) and the asset of the child, if requested.

9.2.3.2 Description of the study procedures for the PID cohort

FIRST VISIT (V1)

The first visit will take place after an infusion of CLAIRYG®.
It will correspond to collection of the inclusion data and of data about the infusion of CLAIRYG®.

During this visit, the investigator will record the information about the child's health before his/her inclusion in the study in the e-CRF.

These include:

- Demographic data: date of birth, male or female sex,
- Medical and surgical history, any concomitant diseases,
- Disease history, including:
  - Organ failures and complications of the PID,
  - Date of diagnosis of the PID,
  - PID type (Hyper-IgM, X-linked agammaglobulinemia, CVID or other),
  - Plasma IgA, IgG and IgM immunoglobulin levels available at diagnosis,
  - Any ongoing infections.

- Any previous treatments received before inclusion:
  - Any antibiotics, antivirals, antifungals and antiparasitics received over a period of 30 days before inclusion,
  - All other treatments received over a period of 2 weeks before inclusion,
  - The type of immunoglobulins (Ig) (CLAIRYG®, other IVIg or SCIg), the date of the 1st administration of IV/SC immunoglobulins, the time between the last two administrations of IV/SCIg, the date of the last administration of IV/SCIg and the total dose administered, the plasma trough IgG level measured before that last administration.
- Abnormal biological values,
- the available plasma trough IgG level before the 1st infusion of CLAIRYG®.

The data on the first infusion of CLAIRYG® will be collected:

- The child's weight and height,
- The procedures used to administer the product: the total dose prescribed and administered, the infusion start and end dates and times, the infusion rates and the reasons for any modifications of the rate and dose,
- Any adverse events observed during the infusion,
- Any premedication received.

The number of visits made during the study will depend on the time between two infusions which can vary from one child to the next and change during the study for one same child. CLAIRYG® may be administered at a frequency of 2 to 4 weeks based on the SPC. The frequency of administration will be determined by the investigator based on his/her common practice and the child's needs.

Each child with a PID will be followed for 12 months in order to take seasonal infection variability into account.

INFUSION VISIT

At each new visit for infusion of CLAIRYG®, the investigator will record the following data in the e-CRF when they are available:

Before each infusion of CLAIRYG®:

- Any adverse events that occurred since the last visit,
- Concomitant treatments administered since the last visit (antibiotics, antivirals, antifungals, antiparasitics...),
- Any infectious episodes that occurred,
- Concomitant diseases (other than infections) and any surgeries performed,
- The immunology data (trough IgG levels) and any abnormal biological values.

During each infusion of CLAIRYG®:

- The child's weight and height,
- The procedures used to administer the product: the total dose prescribed and administered, the infusion start and end dates and times, the infusion rates and the reasons for any modifications of the doses and rates,
- Any adverse events observed during the infusion,

- Any premedication received.

PREMATURE STUDY WITHDRAWAL OR END-OF-STUDY VISIT (VFINAL)

The end-of-study visit will take place at the end of the 12 months of follow-up or earlier in the event of premature withdrawal of the child, for any reason.

A premature withdrawal is defined by discontinuation of the administration of CLAIRYG® and/or administration of another IV/SCIg or for other reasons such as: withdrawal of consent, child lost to follow-up, AE judged to be unacceptable. The investigator will document the reasons for withdrawal from the study for each child.
If the child is withdrawn prematurely from the study, he/she will be followed for a maximum of 4 weeks after the last infusion of CLAIRYG®.

The investigator will also specify whether a lack of efficacy of CLAIRYG® was observed during the follow-up period.

The following data will be collected when available:

- Any adverse events that occurred since the last visit,
- The child's clinical data, including:
  - Any infectious episodes that occurred,
  - Concomitant diseases (other than infections) and any surgeries performed.
- Concomitant treatments administered since the last visit (antibiotics, antivirals, antifungals, antiparasitics, ...,
- The immunology data (trough IgG levels) and abnormal biological values.

TABLE 3 - OVERVIEW OF FOLLOW-UP OF THE PID COHORT

	First Visit (V1)	Infusion Visit (V2 to N)	Premature study withdrawal or End-of-study visit (Vfinal)
	Inclusion / Infusion 1		
Information to holder(s) of parental authority/legal representative(s) + written consent If applicable, Information to/assent of the child	X		
Demographic data Medical and surgical history Concomitant diseases Disease history Previous treatments	X		
Concomitant treatments	X	X	X
Diseases (other than infection) and surgeries during the study		X	X
Weight, Height	X	X	
Infusion of CLAIRYG®: dose, rates, and infusion start and end dates, ...	X	X	

Collection of Adverse Events (AEs)	X	X	X
Recording of available infectious episodes	X	X	X
Recording of available immunology data (IgG)	X[1]	X[1]	X[1]
Collection of available abnormal biological values	X[1]	X	X

[1]: **recording of data before the infusion**

9.2.3.3 Description of the study procedures for the ITP cohort

FIRST VISIT

The first visit will take place after an infusion of CLAIRYG®.
It will correspond to collection of the inclusion data and of data about the infusion of CLAIRYG®.
The investigator will record the information about the child's health before his/her inclusion in the study in the e-CRF, if available:

- Demographic data: date of birth, male or female sex
- Disease history, including in particular:
  - Date of diagnosis of the ITP,
  - The possible causes of the ITP, when known,
  - The ITP phase (newly diagnosed or persistent or chronic),
  - The platelet count at diagnosis and at inclusion (if different),
  - Description of any bleeding events that occurred at diagnosis and at inclusion (if different) and the corresponding Buchanan scores [26],
- Medical and surgical history (including any splenectomy), any concomitant diseases,
- Previous and concomitant drug treatments:
  - All treatments for ITP received since the diagnosis will be recorded: corticosteroids, immunoglobulins and other (anti-CD20 monoclonal antibody, immunosuppressants, ...), with their posology and duration of administration,
  - Other previous treatments received during the last 2 weeks before inclusion and concomitant treatments.
- Any abnormal biological values observed at inclusion.

Data on the CLAIRYG® treatment session given at the first visit will be recorded in the e-CRF after inclusion:

- The child's weight and height
- The procedures used to administer CLAIRYG®: planned number of infusions per treatment session, total dose prescribed and administered,
  - For each infusion:
    - The dose and duration of the infusion (infusion start and end date and time), the infusion rates and the reasons for any modifications of these rates,
    - Any adverse events occurring during the infusion,
    - Premedication received.
- Between two infusions of one same treatment session:
  - Any adverse events occurring,
  - Any concomitant treatments received.
- At the end of the treatment session and before discharge from the hospital
  - The reasons for any differences between the dose of CLAIRYG® prescribed and that effectively received,
  - Available platelet counts,
  - Description of any bleeding events and the corresponding Buchanan score,
  - Date of discharge from the hospital.

ADDITIONAL CLAIRYG® TREATMENT SESSION (OPTIONAL)

Certain children could receive several treatment sessions of CLAIRYG® during the study; the investigator will determine whether or not an additional treatment session needs to be administered depending on his/her common practice and the child's needs.

At each new CLAIRYG® treatment session, the investigator will record the following data in the e-CRF when they are available:

- Since the last visit and before each infusion of CLAIRYG®
  - Any adverse events occurring,
  - Any concomitant treatments received,
  - Follow-up of ongoing diseases at inclusion,
  - Abnormal biological values,
  - Available platelet counts.
- During each CLAIRYG® treatment session
  - Description of any bleeding events and the corresponding Buchanan score.
  - The child's weight and height
  - The procedures used to administer CLAIRYG®: planned number of infusions per treatment session, total dose prescribed and administered,
    - For each infusion:
      - The dose and duration of the infusion (infusion start and end date and time), the infusion rates and the reasons for any modifications of these rates,
      - Any adverse events occurring during the infusion,
      - Premedication received.
    - Between two infusions of one same treatment session:
      - Any adverse events occurring,
      - Any concomitant treatments received.
- At the end of the treatment session and before discharge from the hospital
  - The reasons for any differences between the dose of CLAIRYG® prescribed and that effectively received,
  - Available platelet counts,
  - Description of any bleeding events and the corresponding Buchanan score,
  - Date of discharge from the hospital.

FOLLOW-UP

The follow-up time of the children with ITP as part of this study will depend on the investigator's practice and the child's needs. The maximum follow-up time will be 12 months.

The data from each check-up visit made to the hospital after a CLAIRYG® treatment session will be recorded in the e-CRF.

The investigator will collect the following data since the last infusion, when available:

- Any adverse events that occurred since the last infusion,
- Any concomitant treatments received,
- Follow-up of ongoing diseases at inclusion,
- Abnormal biological values,
- Available platelet counts,

- Any bleeding events observed at this visit, their description and the corresponding Buchanan score.

The investigator's medical evaluation of the child will be recorded and he/she may decide:

- To continue following the child,
- To continue following the child, with administration of an additional CLAIRYG® treatment session.
- To end follow-up of the child for the following reasons:
  - Remission of his/her disease,
  - Withdrawal of the consent of the holder of parental authority or legal representative,
  - Adverse event judged as unacceptable by the investigator,
  - Loss to follow-up,
  - Definitive discontinuation of CLAIRYG® and prescription of another immunoglobulin,
  - Definitive discontinuation of CLAIRYG® and initiation of another ITP treatment,
  - Other reasons to be specified.

LAST FOLLOW-UP VISIT

At the last follow-up visit, the investigator will record the following data in the e-CRF when they are available:

- Any adverse events that occurred since the last visit,
- Any concomitant treatments received,
- Available platelet counts,
- Any causes or diseases associated with ITP identified since inclusion,
- Any lack of efficacy of CLAIRYG® observed during follow-up,
- The ITP phase.

TABLE 4 - OVERVIEW OF FOLLOW-UP OF THE ITP COHORT

	First Visit (V1)	Additional CLAIRYG® treatment session	Follow-up visit (1 to N)	Last follow-up visit
	Inclusion / Treatment session 1			
Information to holder(s) of parental authority/legal representative(s) + written consent If applicable, Information to + assent of the child	X			
Demographic data Medical and surgical history Disease history Previous ITP treatments	X			
Concomitant treatments	X	X	X	X
Weight, Height	X	X		
CLAIRYG® treatment session (dose, number of infusions, infusion rates and durations, ...) Premedication	X	X		
Collection of Adverse Events (AEs)	X	X	X	X
Recording of available platelet counts	X	X	X	X
Description of bleeding episodes and Buchanan score	X	X	X	
Collection of abnormal biological values	X	X	X	

9.3 Endpoints

9.3.1 Treatment exposure endpoints

As this is a non-interventional study, the therapeutic strategy and treatment procedures are not defined as part of this study. The treatment will be administered according to the recommendations in the SPC and common practice at the site and of the prescriber.

The parameters used to evaluate exposure to the treatment for the two cohorts are as follows:

- Number of infusions (PID) / or treatment sessions (ITP) administered per child,
- Time between 2 infusions / or treatment sessions,
- Total dose prescribed per infusion / or treatment session (mg/kg and g/patient),
- Infusion time, rate (ml/kg/h) and any infusion increments

9.3.2 Safety endpoints

All serious or non-serious adverse events (AEs), whether or not they are related to CLAIRYG®, and whether they are expected or unexpected based on the SPC, will be collected throughout the duration of the study. Management and reporting of the AEs is described in section 11 of this protocol.

The following data will be recorded in the e-CRF:

- Description of the event, providing the diagnosis when known, or otherwise the clinical description of the signs observed,
- The start date corresponding to the date when the first sign/symptom appeared and the end date corresponding to the date when the last sign/symptom disappeared.
- Its seriousness (serious, non-serious) based on the definition given below,
- Its intensity (mild, moderate, severe),
- Its causal link with the treatment,
- Its outcome (recovery without sequelae, with sequelae, improvement, not healed, fatal, unknown),
- Action taken with respect to the study drug,
- Any symptomatic or curative treatments prescribed,
- Medical and surgical history deemed to be pertinent,
- Concomitant treatments.

9.3.2.1 Definition of adverse events and serious adverse events

An **adverse event** (AE) is "any noxious symptom in a patient or clinical trial participant treated with a medicinal product and which is not necessarily connected with that treatment".
An adverse event can thus be any noxious or undesired sign (including an abnormal laboratory test result), a symptom or disease that is concomitant to the use of a medicinal product, but not necessarily linked to the medicinal product.

Whether or not it is considered as related to the study treatment, an AE may be:

- Deterioration of a pre-existing chronic disease, aggravation of symptoms or a disease present at inclusion of the patient in the study,
- A symptom and/or disease discovered after the start of the study, even if they were probably present prior to inclusion of the patient in the study.
- Abnormal biological values when they are considered as clinically significant by the investigator.

A **serious adverse event** (SAE) is an adverse event that, at a given time, meets one or more of the following seriousness criteria:

- Death: the event led to the child's death,
- Life-threatening: the child is in danger of death at the time of the event. This does not refer to events that could have caused death if they were more severe,
- Hospitalisation or prolongation of hospitalisation: the occurrence of the event requires / required that the child be hospitalised or that his/her hospitalisation be prolonged. Hospitalisation means that the child was admitted to the hospital, which generally involves at least one overnight stay. A stay for less than 24 hours in the emergency department is not considered as hospitalisation,
- Significant or lasting disability or incapacity: the event is causing / caused major or prolonged perturbation of the child's ability to perform daily activities,
- Congenital abnormality or malformation: the event led to a congenital defect or malformation (not applicable for this study),
- Any other "medically-significant adverse event": This is a major medical event that is not immediately life-threatening for the child, which did not lead to death or hospitalisation, but

that, based on a suitable medical opinion, could evolve to one of the other cited seriousness criteria in the absence of medical intervention...

The distinction must be made between severe and serious events. Severity is a measurement of the intensity, while seriousness is based on the outcome, as defined by the above criteria. For example, nausea that lasts for several hours could be considered as severe, but not as a serious adverse event. From another standpoint, a cardiovascular event that leads to a limited degree of incapacity can be considered as non-severe, but must be considered as a serious adverse event.

- Events initially reported as adverse events may become serious. For example, diarrhoea may become disabling and require hospitalisation or prolongation of hospitalisation and can then be considered as a serious adverse event.
- In this study, any transmission of a infectious agent through the study product will be considered as a serious adverse event.
- A surgical procedure is not considered as a serious adverse event, but the clinical condition requiring that surgery could be reported as a serious adverse event.
- If a medical situation known before the start of treatment with the study product requires hospitalisation for a scheduled surgical procedure, this should not be considered as an adverse event. However, that situation must be reported in the patient's medical history.
- Any overdose, misuse or addiction to the study product, with or without clinical signs or apparent symptoms, must be reported in the serious adverse event reporting form and notified to the Sponsor.

An **adverse event** is "any noxious, unintended response to a medicinal product, regardless of the dose administered".

A **serious adverse event** is an adverse event that, at a given time, meets one or more of the above seriousness criteria.

9.3.2.2 Specificity of the study

Due to their direct link with the pathology, the following events will not be considered as adverse events, but will be taken into account in the efficacy assessment:

- All infectious episodes for children with PIDs; these episodes will be reported in the "Infection" section of the e-CRF,
- Any bleeding episodes and thrombocytopenias related to the ITP of the children with ITP; these episodes will be reported in the section for recording bleeding events and platelet counts in the e-CRF.

Period of (serious) adverse event reporting

To ensure that all of the safety data are collected, all (S)AEs occurring during the study, meaning after the holder(s) of parental authority or the legal representative(s) of the child have signed the informed consent, must be collected, even if the study treatment has not been administered. This includes all (S)AEs that appear, reappear or deteriorate after the consent form has been signed. The observation period for the study extends:

- For the PID cohort: from the inclusion visit to the last CLAIRYG infusion visit, or a maximum of 12 months of follow-up or at least 4 weeks of follow-up after the last CLAIRYG® infusion.
- For the ITP cohort: from the inclusion visit to the last available follow-up visit, or a maximum of 12 months of follow-up or at least 4 weeks of follow-up after the last CLAIRYG® infusion.

If an investigator learns that an adverse event related to the treatment has occurred in a child who participated in the study, he/she must inform the Sponsor, even if data collection has been interrupted.

Follow-up of (Serious) Adverse Events

All (serious) adverse events considered as not related to the study product, including abnormal biological values or an abnormal clinical examination, must be followed until resolution of the event, stabilisation of the clinical condition or the last visit as part of the study.

(Serious) adverse events considered as related to the study product will be followed as long as necessary to allow for adequate evaluation of the product's safety, or until stabilisation of the event, or until loss of the patient to follow-up. If the event is considered as resolved, a resolution date must be given.

All information concerning complementary tests performed by the investigator to determine the nature and/or cause of the (S)AE, such as additional laboratory tests and paraclinical examinations, will be recorded in the "Adverse Event" appendix of the e-CRF.

In the event of premature withdrawal from the study, the investigator will need to make sure that it was not due to an AE. In the event of premature withdrawal from the study for safety reasons, the patient must be followed until resolution of the event or stabilisation of the patient's condition.

If no follow-up information can be provided despite all efforts and attempts, the investigator must document the outcome as "unknown" and provide a justification where possible.

9.3.3 Efficacy endpoints

The efficacy assessment is different for each pathology studied and will be based on the data available in the patients' medical files.

9.3.3.1 Efficacy endpoints for the children with PIDs

The assessment of the treatment's efficacy for the children with PIDs will be based on the following parameters, when available:

- Infectious episodes occurring during the 12-month study period:
  - Their nature, seriousness, the type of infection, the duration and the possible germ, any treatments received (type, duration, route of administration, frequency),
  - The frequency (number of infectious over a 12-month period).
- The trough IgG levels (g/l) if available,
- Possible observation of a lack of efficacy.

9.3.3.2 Endpoints for the response of the children with ITP

The response to treatment of the children with ITP will be assessed by the investigator based on the following parameters, when available:

- Available platelet counts reported,
- Any bleeding episodes observed:
  - Description of the bleeds,
  - Bleeding score assessed.
- Possible observation of a lack of efficacy.

9.3.4 Other endpoints

- The characteristics of the study population:
  - Demographic data: sex, age, weight, height,
  - Disease history,
  - Medical and surgical history,
  - Previous treatments:
    - Previous treatments for any infections in the children with PIDs (antibiotics, antifungals, antivirals and antiparasitics) will be collected over a period of 30 days before inclusion,
    - Previous treatments specific to the ITP (corticosteroids, immunosuppressants, ...) will be collected from the diagnosis of the disease to allow for documentation of the therapeutic drug strategies used in the child,
    - Other previous treatments will be collected over a period of 15 days before inclusion.
- Concomitant treatments received,
- Use of premedication,
- Abnormal biological values,
- Concomitant diseases.

9.4 Source data

The data collected will come from the children's medical files, including hospital reports, clinical examinations, nurses' notes and paraclinical explorations.
The procedures used to provide information to and obtain the consent of the holder(s) of parental authority or the legal representative(s) and the assent of the child, if requested, will be documented in the source file.

9.5 Data Management

9.5.1 Collecting information and managing the case report form

The two case report forms will be electronic (e-CRF).

Once the investigator has agreed to participate in the study and the study has been started up at his/her site, the investigator will have electronic access to complete the e-CRFs for the patients included.

9.5.2 Filling out the case report form

The data will be collected in the electronic case report form (e-CRF) under the responsibility of the investigator, based on the child's medical file.

If necessary, the investigator may be helped by a CTT for data entry into the e-CRFs.

The procedures used to fill out the form are described in the guide on how to complete the case report form. This guide will be provided and explained by the Service Provider during the study set-up meeting at the sites.

9.5.3 Treatment of missing data

As this is an observational study, some data will probably not be available in the source files. The missing data will be entered as "MD" and will be analysed as missing in the descriptive analyses. In the event of missing data, the CRA of the Service Provider will make sure that they are truly missing from the child's medical file. If they are present, requests for correction (RFCs) will be made.

9.5.4 Corrections to the e-CRFs

A coherency check of the data will be generated automatically by the computer application as the data are entered (alert system for illogicality).
Coherency checks of the dates will be performed and limits will be defined for all of the biological and medical values entered into the e-CRFs.

These checks serve to warn the person entering the information of possible errors during data entry.

Requests for correction of the data could be generated during the study, until freeze of the database.

9.5.5 Data processing and management software and procedures

The software used by the Service Provider to develop the e-CRFs is Clinsight.
Statistical analysis of the data will be performed by the Service Provider using the SAS (Statistical Analysis System, at least version 8) software.

9.5.6 Data review

A data review meeting will be held by LFB BIOMEDICAMENTS once all of the study data have been collected, entered and validated. That meeting will involve the Service Provider and the scientific committee for the study.
It will serve to review the population for analysis and to adapt the analyses planned in the Statistical Analysis Plan, if necessary.

9.6 Data analysis

All children for whom the holder(s) of parental authority or the legal representative(s) have given consent and who have received at least one infusion of CLAIRYG® will be evaluated.

A Statistical Analysis Plan will be prepared for each cohort before the e-CRFs are created.

For each cohort, a descriptive analysis will be performed on all of the data collected, if there are enough.

- The quantitative variables will be described by their number, mean, standard deviation, median, limit values and missing data.
- The qualitative variables will be described by their number, percentage and missing data. The 95% bilateral confidence intervals will only be given where applicable.

9.6.1 Analysis of the paediatric population treated with CLAIRYG®

The available demographic and clinical/biological characteristics will be analysed descriptively for each cohort.

This analysis will be based on the following in particular:

- Demographic data: age, sex, weight, height at inclusion,
- Pertinent medical and surgical history,
- Abnormal biological values available at inclusion,
- Concomitant diseases during the study and any concomitant treatments received,
- Disease history:
  - The child's age at diagnosis,
  - For the PID cohort:
    - Type of PID,
    - de DIP,
    - Previous treatments received before inclusion and concomitant treatments,
    - Date of the 1st administration of Ig (IV or SC) at diagnosis, and the last dose and type of Ig administered before inclusion,
    - Plasma trough IgG level at diagnosis and before the 1st infusion of CLAIRYG®
  - For the ITP cohort:
    - Date of diagnosis,
    - The ITP phase at inclusion (newly diagnosed ITP, persistent ITP or chronic ITP), and its possible causes
    - Available platelet counts at diagnosis and at inclusion,
    - Any bleeding episodes at diagnosis and at inclusion if this is not a newly diagnosed ITP,
    - Any previous treatments for ITP (corticosteroids, anti-CD20 monoclonal Ab, ...), splenectomy if any,

9.6.2 Analysis of exposure to CLAIRYG®

The mean doses (in g and g/kg) of CLAIRYG® administered per infusion (PID) or per treatment session (ITP) will be calculated and analysed.

For the PID cohort

The number of infusions administered during the study and the mean, standard deviation, median and limit values will be calculated. The mean time between two infusions will be evaluated over the 12-month follow-up period.
The times and rates of the infusions administered will be described. The reasons for any posology modifications during the study will be analysed.

For the ITP cohort

The number of treatment sessions administered/patient during the follow-up period and the number of infusions per treatment session will be described. The mean, standard deviation, median and limit values will be calculated.

9.6.3 Analysis of the safety data

The adverse events occurring throughout the study will be analysed for each cohort. The infections occurring in the children with PIDs and the bleeding events and thrombocytopenias observed in the children with ITP will not be analysed as adverse events. They will be evaluated under the secondary objective concerning the product's efficacy.

The adverse events will be coded using the MedDRA dictionary classification. The version used will be that in force at the time of the report. All adverse events will be listed by System Organ Class (SOC), Lowest Level Term (LLT) and Preferred Terms (PT).
The number and frequency of these events will be described by LLT, PT and SOC.

The number of patients with at least one adverse reaction and the number of adverse events will also be described.

All of the adverse events observed will be described by type, seriousness, intensity/severity, causality, outcome/resolution and other relevant parameters.

The numbers of cases where a treatment was administered to correct an adverse event will be analysed.

The duration of the events and time between the start of administration of CLAIRYG® and their onset will be calculated.

The percentage of children who have at least one adverse event during the follow-up period will be estimated.

The most common adverse events will be described and their frequencies of onset will be estimated.

The percentages of patients who stopped the treatment due to an adverse event will be given. The serious adverse events will be described.

At the request of the PDCO, any thromboses observed and the local tolerance will be described in a specific section.

9.6.4 Analysis of efficacy

An efficacy analysis will be performed for each cohort.

For the PID cohort

- Infectious episodes occurring during the study will be described
  - The number of infectious episodes per child will be calculated for the 12-month follow-up period,
  - The type of infection (bacterial, fungal, parasitic and viral) and the germ, if it is identified,
  - The seriousness based on the following criteria: death, life-threatening, hospitalisation or prolongation, disability or incapacity and any medically-significant event,
  - The duration of the infection and its resolution,
  - The time between last infusion and the onset of an infection,
  - The use of treatments (antibiotics, antivirals, antifungals, antiparasitics, ...).
- The serum trough IgG levels (g/l) available for the 12 months of follow-up will be described and the mean, median, minimum and maximum levels will be calculated.

- Any lack of efficacy reported.

For the ITP cohort

- The available platelet counts will be analysed.
- The clinical symptoms observed will be described:
  - The bleeding events occurring throughout the study: the number of children with at least one bleeding episode, the number and type of bleeding episodes, the time between the last infusion and the onset of bleeding,
  - The severity of the bleeding events evaluated using the reported Buchanan scores.
- The outcome of the ITP during the follow-up period will be reported:
  - Any use of other treatments for ITP (switch to IVIg, corticosteroids, immunosuppressants or other): drug class, route of administration, number of days of treatment,
  - Use of therapies or invasive procedures,
  - The number of children considered by the investigators as in remission during their follow-up.
- Any lack of efficacy reported.

9.7 Quality Control

A quality control of 100% of the data collected compared with the source data will be performed at all of the participating sites by the CRAs of the Service Provider appointed for this purpose. In the event that discrepancies or incoherencies are observed, requests for correction will be issued.

The CRAs will first make sure that written consent dated and signed by the legal representative(s) is present in the medical files of each child included.

The CRAs of the Service Provider are appointed by the Sponsor for quality control purposes and are bound by professional secrecy.

10 PATIENT PROTECTION

10.1 Applicable texts

The study will be conducted in accordance with the principles of:

- Articles L.1121-1, L.5121-8 and R.1121-2 of the French Public Health Code,
- Data privacy: law 78-17 of 6 January 1978 on information technology, files and liberties, as modified on 6 August 2004, and its enforcement orders,
- "Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products" EMA/873138/2011 – 2012. Available online: http://www.ema.europa.eu
- "Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies" EMA/813938/2011 Rev.1 – 2013. Available online: http://www.ema.europa.eu

- "Guide on Methodological Standards in Pharmacoepidemiology" EMA/95098/2010 Rev.2 The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) – June 2013. Available online: http://www.encepp.eu/standards_and_guidances
- "Les études post-inscription sur les technologies de santé, Principe et Méthode" (*Post-registration studies of healthcare technologies*) – HAS (High Health Authority) – November 2011. Available online: http://www.has-sante.fr
- "*Les recommandations de Déontologie et Bonnes Pratiques en Epidémiologie*" (Recommendations on Deontology and Good Epidemiology Practice) - ADELF, ADEREST, AEEMA, EPITER - France version – 2007. Available online: http://adelf.isped.u-bordeaux2.fr
- "Guidelines for Good Pharmacoepidemiology Practices (GPP)" - ISPE - April 2007. Available online: https://www.pharmacoepi.org

10.2 Competent authorities

LFB BIOMEDICAMENTS will send the protocol to the ANSM for information before starting-up the study.

10.2.1 CCTIRS

LFB BIOMEDICAMENTS will submit the protocol, synopsis and information sheet for the legal representatives and the assents for the children to the CCTIRS for its opinion.

10.2.2 CNIL

LFB BIOMEDICAMENTS is held to respect the rights of subjects with regard to the processing of their personal data, pursuant to the terms of Law 78-17 of 6 January 1978 on information technology and liberties, as modified on 1 July 1994 and 6 August 2004 and will take care of the administrative procedures with the CNIL.

LFB BIOMEDICAMENTS will submit the protocol, synopsis and information sheet for the legal representatives and the assents for the children to the CNIL for authorisation of implementation of the study.

10.2.3 CPP

The Sponsor will submit the protocol to a local ethics committee for publication of the results in a scientific journal.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/EFFECTS

11.1 Reporting and transmission of adverse events

As this is a post-authorisation safety study (PASS), all serious or non-serious adverse events, whether they are related or not related to the treatment with CLAIRYG®, that occur during the study will be reported by the investigator, with the exception of those described in section 9.3.2.2 "Specificity of the study".

During the study, the investigator will complete the adverse event (AE) reporting form included in the e-CRF within 24 hours after he/she learns of an AE.

The Pharmacovigilance Unit of LFB BIOMEDICAMENTS, the project manager of LFB BIOMEDICAMENTS and the Service Provider will be informed of the AE immediately through an e-mail alert. They will then be able to view the completed reporting form via a secure platform.

The Pharmacovigilance Unit of the LFB Group will be responsible for reporting the AEs to health authorities in accordance with regulations in force.

11.2 Follow-up of Adverse Events

In order to document the adverse events, the Pharmacovigilance Unit of LFB BIOMEDICAMENTS may ask the investigator for complementary information through the Project Manager of LFB BIOMEDICAMENTS or the Service Provider.

If the investigator has additional information or new information concerning a previously reported adverse event, he/she will complete the adverse event reporting form in the e-CRF, specifying that this is a follow-up and stating the number given to the initial AE.
During their visits, the CRAs of the Service Provider will make sure that all related or unrelated, serious or non-serious adverse events have been sent to LFB BIOMEDICAMENTS. If a related or unrelated, serious or non-serious adverse event that occurred during the study has not been sent, the CRA will ask the investigator to report it immediately.

12 AUDITS AND INSPECTIONS

An audit may be carried out by the staff of the Sponsor or by subcontracted auditors to ensure that the study is conducted in accordance with the protocol and regulatory requirements, and to ensure that the data is valid.

An inspection may be carried out by representatives of the ANSM to ensure that the study is conducted in accordance with the protocol and regulatory requirements, and to ensure that the data is valid.

Participation in this study by healthcare staff means that they accept to cooperate in any audits or inspections and that they must make themselves available for any audits or inspections.

The audit or inspection may include inspection of the facilities and equipment and verification of the study documents and data.

The audit or inspection may take place during and after the end of the study.

13 PLANS FOR DISCLOSURE AND COMMUNICATION OF THE RESULTS OF THE STUDY

13.1 Final report

A final report will be written by LFB BIOMEDICAMENTS, in accordance with current standards in force. It will be validated by the scientific committee for the study.

The Sponsor will provide the final study report to the ANSM and the EMA.

13.2 Summary of the overall results of the study

The sponsor will send the summary of the overall results of the study to all of the investigators who took part in the study. The investigator may provide those results to the legal representative or holder of parental authority if they so request.

13.3 Publications

All information and scientific data concerning the product and collected as part of this study are the exclusive property of LFB BIOMEDICAMENTS. They must be published in collaboration with the coordinating experts for the study.

In accordance with chapter VIII.B.7 of the "Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies" (EMA/813938/2011 Rev.1 – 2013), LFB BIOMEDICAMENTS will define the procedures for publication of the results of the study, in collaboration with the investigators for the study.

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APPENDIX 1. LIST OF DOCUMENTS NOT INCLUDED

Number	Document version number	Version date	Document title
1	2.0	25/07/2014	List of sites contacted
2	2.0	31/07/2014	Protocol summary
3	8.0	June 2013	Summary of Product Characteristics
4	3.0	27/01/2015	Information sheet and consent form for parental authority and legal representative - ITP
5	3.0	27/01/2015	Information sheet and consent form for parental authority and legal representative - PID
6	2.0	23/07/2014	Pre-adolescent assent
7	2.0	23/07/2014	Child assent
8	2.0	29/07/2014	Information sheet for posting concerning the Observational study to evaluate the safety of CLAIRYG® in children under 12 years treated for primary immunodeficiency (PID) or immune thrombocytopenic purpura (ITP)