SUMMARY OF PASS CLAIRYG® STUDY RESULTS

Study 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)**
Studied product	CLAIRYG® (IVIg) 50 mg/mL, solution for IV infusion. CLAIRYG® is a 5% (50 mg/mL) concentrated, liquid, ready to use preparation of polyvalent human normal immunoglobulins (IVIg), to be administered intravenously. At least ninety-five percent (95%) of the total proteins are IgG. Marketing authorisation (MA) was obtained for CLAIRYG® in France by LFB BIOMEDICAMENTS in December 2009, and it was first sold in August 2010.
Study objectives	In accordance with the regulations, LFB has made a commitment to the European Medicines Agency to conduct a follow-up study on the use of CLAIRYG® in current medical practice in children to confirm its good tolerance. The aim of this study was to document the safety of the product in real-world conditions during the 12 months study period in patients under 12 years of age in the following indications: • PID: for replacement therapy • ITP: for immunomodulation therapy The secondary objectives were the description of the conditions of use of CLAIRYG® as part of common practice and the collection of efficacy data if available in order to document the benefit/risk ratio in the two pathologies studied, PID and ITP in children under 12 years.
Methodology	Prospective, observational, multicenter, PASS. All procedures were performed, and the products used based on local standard of care, without any additional or unusual diagnostic or monitoring procedures of the hospitals in which patients were followed. Included children had to be under 12 and be treated with CLAIRYG® for PID or ITP. The duration of their participation in the study was a maximum of 12 months. This study contains 2 cohorts, including either children with PID or children with ITP. In this document, study results are presented for each cohort.

	PID COHORT RESULTS
Number of patients and centres	Thirty-two (32) children under 12 with PID were included in 7 French hospitals. Patients' recruitment occurred from October 2015 to March 2016. The last patient left the study in March 2017.
PID population	A total of 32 children with PID were included in this cohort, 9 girls (28.1%) and 23 boys (71.9%), with an average age of 6.4 years (ranging from 0.7 to 11.9 years), including 6 children (18.8%) under 4 years, 16 children (50%) above 4 and under 8 years and 10 children (31.3%) above 8 and under 12 years. The types of deficiencies treated were very heterogeneous. The most represented were: - Bruton's agammaglobulinemia (X-linked) (5 patients), - Wiskott Aldrich syndrome/XLT (4 patients), - and predominantly humoral PID not elucidated at the molecular level (8 patients, 4 of whom were assimilated in the study to common variable immunodeficiency type and 4 to hypogammaglobulinemia without further precision). In total, only 1 child had never been treated with Immunoglobulins before participating in the study, the others had already received either IVIg (30 children) or subcutaneous Ig (SCIg, 1 child). Among them, 19 (59.4%) children had complications due to their deficiency whatever their PID type. Their median duration of participation in the study was 11.99 months [with a duration ranging from 10 days to 12.7 months, depending on the children].
Key results	Conditions of use of CLAIRYG® during the 12 months of children follow-up were broadly in line with the Summary of Product Characteristics (SPC) recommendations: • The 32 patients received a total of 464 infusions with a median number per patient of 17.5 infusions with extremes ranging from 1 to 23. The median time between 2 infusions per patient was 3.1 weeks [from 2.4 to 6.0 weeks]. • The IVIg dose given per infusion was consistent with the recommended dose for all children, with a median value of 0.4 g/kg [range 0.2 to 0.9 g/kg] The median infusion time was of 3.3 hours [ranging from 0.2 to 8 hours depending on the child], only the recommendation to administer the product at progressively faster infusion rates was not always followed at participating centres. 51.9% of infusions (241/464 infusions in 23 patients) were administered without rate levels. • Premedication prior to CLAIRYG® infusion was observed for 58.7% of infusions (in 21 patients). The main types of treatment used for this premedication were: acetaminophen, antihistamines, systemic or local anaesthetics, glucocorticoids, or parental solutions for pre-hydration. • During the study, 30/32 children (93.8%) experienced in total 171 infections that occurred on a median time of 18.5 days [1 to 141 days] after a CLAIRYG® infusion. Eight (8) were serious infections in 6/32 children (18.7%). These included 1 pulmonary and meningeal sepsis, 2 ear infections, 1 acute otitis media, 1 bronchiolitis, 1 febrile bronchitis, 1 exacerbation of chronic bronchopathy and 1 eczematous dermatitis. Thus, the annualized number of infections per patient was 6.20 infections/year and 0.11 serious bacterial infections/year. • Most children received prophylactic anti-infective treatment (84.4%) and 68.8% used curative anti-infective treatment during the study.

	• Through plasma IgG levels observed in the study prior to CLAIRYG® infusions were a median of 9.5 g/L [ranging from 2.2 to 18.1 g/L]. • No lack of CLAIRYG® efficacy in the 32 treated children was reported by the investigators.
Safety	• A total of 100 adverse events (AEs) were observed in 25/32 children (78.1%). 4/100 were considered as serious in 3 children (9.4%) but were not related to CLAIRYG®. • Among the 96 non-serious AEs, 44 were related to the treatment CLAIRYG® in 15/32 children (46.9%). The main AEs were headache: 10 children (31.2%), vomiting: 4 children (12.5%), fever: 1 child (3.1%), migraine: 1 child (3.1%) and pollakiuria: 1 child (3.1%). They occurred predominantly (65.9%) on the day of the infusion, 22% on the second or third day after the infusion and 12.2% 3 days and more after the infusion [0 to 21 days]. • CLAIRYG® administration modalities had to be adapted for 6 treatment-related AEs which evolved favourably. It concerned: - a decreased infusion flow rate for 3 AEs (dizziness, hot flushes and headache) in 2 children, - and a temporary discontinuation of infusion for 3 other AEs (headache, cough and oedema) in 3 other children.
Conclusion	For this cohort of patients under 12 with PID treated with CLAIRYG®, all treatment-related adverse reactions were mild to moderate in intensity, none were serious, and they consisted primarily of headaches and vomiting. No new signal was detected. No thrombosis was observed. The local tolerance was satisfactory, though 1 extravasation at the infusion site occurred once in one patient. The annualized rates of infections (6.20 infections/year/patient) and serious bacterial infections (0.11 serious bacterial infections/year/patient) observed per patient were consistent with those reported in the literature. In total, this cohort contributes to documenting the risk management plan of CLAIRYG® and confirms that the benefit/risk balance of the product for this population of children under 12 with PID is favourable in view of the data collected.

	ITP COHORT RESULTS
Number of patients and centres	Twenty-seven (27) children under 12 with ITP were enrolled in 5 French hospitals. Patients' recruitment occurred from October 2015 to October 2016. The last child left the study in October 2017.
ITP population	A total of 27 children with ITP were included in this cohort, 12 girls (44.4%) and 15 boys (55.6%), with an average age of 4.4 years (ranging from 0.3 (3.6 months) to 11.7 years), including 16 children (59.3%) under 4 years, 7 children (25.9%) above 4 and under 8 years and 4 children (14.8%) above 8 and under 12 years. They were: • 17 children with acute ITP (diagnosed within 3 months) • 2 children with persistent ITP (diagnosed for 3 to 12 months) • 8 children with chronic ITP (diagnosed for more than 12 months) Given the small number of patients with persistent ITP and for descriptive analysis of this cohort, children were classified into 2 subgroups: • 1 subgroup of 17 (63%) children with acute ITP (newly diagnosed), • and another subgroup of 10 (37%) children with non-acute ITP (persistent or chronic ITP). The mean duration participation in the study for the 27 included children was 9.4 months with extremes ranging from 0.6 month (18 days) to 12.9 months. The causes (if reported) of the onset of ITP indicated by the investigators were mostly unknown (13/27 patients; 48.1%) or infectious (12/27 patients; 44%), for 2 patients (2/27; 7.4%) the cause seemed to be both infectious and drug-related (vaccines). Prior to be included in the study, 16/27 (59.3%) patients were treatment-naïve for the condition studied, including: • 15/17 (88.2%) acute ITP and • 1/10 (10 %) non-acute ITP. Children who have already received treatment for their ITP may have previously received 1 or more types of treatment such as corticosteroids, IVIg, anti-D immunoglobulins, vinca alkaloids, anti-CD20 monoclonal antibodies, immunosuppressive agents, thrombopoietin receptor agonists, purine analogues or steroid-sparing agents. At the time of inclusion in the study, the children's condition of their disease was as follows: • Of the 17 children with acute ITP: 17 had cutaneous bleeding, 13 had mucosal bleeding and 1 had urinary or genitourinary bleeding and the mean platelet count was 6.53 $x10^9$/L, • Among the 10 children with non-acute ITP: 9 had cutaneous bleeding and 6 had mucosal bleeding and the mean platelet count was 26.20 $x10^9$/L.
Key results	The conditions of use of CLAIRYG® during the 12 months of follow-up of the children were broadly in line with the SPC recommendations. For all 27 children, a total of 85 infusions of CLAIRYG® were administered in the study: • 21 infusions to children with acute ITP, with a mean of 1.2 infusions received per child [ranging from 1 to 3], • And 64 infusions to children with non-acute ITP with a mean of 6.4 infusions received per child [ranging from 1 to 24]. The 85 infusions were administered over 84 courses (only 1 child with acute ITP received 2 infusions during one of his courses): • 20 courses in the 17 children with acute ITP with extreme values ranging from 1 to 3 courses received per child (only 2 children had more than one course, respectively 2 and 3 courses), • 64 courses for the 10 children with non-acute ITP with extreme values ranging from 1 to 24 courses per child.

	The mean total dose of CLAIRYG® administered per treatment course was 25.3 g with extremes ranging from 5 to 40 g. The mean dose relative to weight was 1 g/kg [0.4 to 2.1 g/kg]. The median duration of courses was 8.3 hours [0.5 (30 min) to 24.5 hours]: • 12.8 hours for children with acute ITP [5 to 24.5 hours], • And 6.9 hours for children with non-acute ITP [0.5 to 21 hours]. For the 85 infusions administered to the 27 patients, the median number of rate levels per infusion was 2 [1-4]. The median time between 2 courses was 14.0 days for children with non-acute ITP [11 to 126 days]. Nine (9) of the 27 children who participated in the study received premedication on at least one of their infusions. This premedication concerned 62.4% of infusions (53 of 85 infusions), including 19% of infusions for children with acute ITP and 76.6% of infusions for children with non-acute ITP. The main types of treatment used for this premedication were acetaminophen, antihistamines, systemic or local anaesthetics, glucocorticoids, or parental solutions for pre-hydration. An increase in platelet counts after CLAIRYG® infusions was observed overall for both ITP subgroups. Throughout the study and for the entire cohort, the median of mean platelet counts per patient was 108.4 x10^9/L [4 to 359 x10^9/L]. • For children with acute ITP: the median of mean platelet counts was 167.4 x10^9/L [23 to 359 x10^9/L]. • For children with non-acute ITP: the median of mean platelet counts was 47.8 x10^9/L [4 to 154 x10^9/L]. Bleedings occurred during the study were cutaneous in 20/27 children (74.1%), mucosal in 14/27 children (51.9%) and on a joint (haemarthrosis) in 1 child (3.7%). • Acute ITP: 10/17 children had cutaneous bleeding, 6/17 children had mucosal bleeding and only 1 child had 1 joint bleeding (haemarthrosis) • Non-acute ITP: 10/10 children had cutaneous bleeding and 8/10 mucosal bleeding. Eleven out of seventeen patients with acute ITP were evaluated by the experts of the scientific committee as being in remission at the end of their participation to the study. Only one investigator reported a lack of efficacy of CLAIRYG® in 1 child with non-acute ITP treated with 3 infusions of CLAIRYG® in this study.
Safety	For this cohort of ITP patients under 12 years of age treated with CLAIRYG®, it was observed: • A total of 69 AEs in 22/27 children (81.5%) with 65 (94.2%) as non-serious. • Four (4) serious AEs (SAE) in 3/27 children (11.1%) including only one was related to CLAIRYG®. It was an aseptic meningitis with severe frontal headache and repeated vomiting requiring hospitalization, occurring 3 days after administration of a dose of 1.05 g/kg in a 4.6-year-old child with chronic ITP, despite compliance with the product's precautions (maximum recommended dose being 1 g/kg), including premedication with appropriate hydration before the start of the infusion. The SAE recovered without sequelae after pain relievers and rehydration. • Among the 65 non-serious AEs, 31 (44.9%) were related to the treatment CLAIRYG® in 13/27 children (48.1%). These were mainly (AE with 2 or more episodes): fever (22.6%) in 6 patients (22.2%), headache (19.4%) in 5 patients (18.5%), vomiting (16.1%) in 5 patients (18.5%), asthenia (6.5%) in 2 patients (7.4%), pain in the extremities (12.9%) in 1 patient (3.7%), blood creatinine increased (6.5%) in 1 patient (3.7%). • Median time to onset of treatment-related AEs was 1 day after the last infusion of CLAIRYG® (i.e., the day after the infusion) with delays ranging from the same day of infusion (42.9%), less than 3 days after infusion (50%) to 3 days or more after infusion (7.1%).

Conclusion	This cohort described the real-life safety of CLAIRYG® in children under 12 years with ITP treated at immunomodulatory doses (approximately 1 g/kg), through careful and controlled collection of data, which helped to supplement the pharmacovigilance data obtained via spontaneous reports. No new risk or unexpected event related to CLAIRYG® was observed in this population. All treatment-related adverse events were known, and all were already listed in the SPC of CLAIRYG®. Most of them were of low to moderate intensity; only one AE was considered serious (aseptic meningitis) and non-serious related AEs were mainly characterized by fever, headache, and vomiting. Overall, this study confirms that the safety of CLAIRYG® for this population of children under 12 with ITP remains favourable in relation to the benefit provided.

LISTE OF ABBREVIATIONS

AE/SAE	Adverse Event/Serious Adverse Event
i.e.	that is (id est)
g	Gram
g/L	Gram/litre
IgG	Immunoglobulin G
ITP	Immune Thrombocytopenic Purpura
IV/IVIg	Intravenous/Intravenous Immunoglobulins
kg	Kilogram
LFB	Laboratoire français du Fractionnement et des Biotechnologies
MA	Marketing authorisation
mg	Milligram
mL	Millilitre
PASS	Post Authorisation Safety Study
PID	Primary ImmunoDeficiency
SC/SCIg	Subcutaneous/Subcutaneous Immunoglobulins
SPC	Summary of Product Characteristics