2 SYNOPSIS

Name of Sponsor/Company: IPSEN Name of Finished Product: Increlex®	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Active Ingredient(s): Mecasermin	Volume: Page:	
Title of study: Global Patient Registry to Monitor Long-Term Safety and Effectiveness of Increlex® in children and adolescents with Severe Primary Insulin-Like Growth Factor-1 deficiency (SPIGFD) Study number: 2-79-52800-002		
Investigators: A Principal Investigator at each site was responsible for the conduct of the study at that site. A Data Monitoring Committee composed of three external experts in paediatric endocrinology, paediatric oncology and statistics, is regularly consulted.		
Study centres: 131 participating sites (123 active sites enrolled at least one participant in the scope of analysis) in 11 European countries: Austria, Belgium, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden, United Kingdom (UK) and the United States (US). The Global Registry is conducted in eight European countries and the USA. Two of the European countries previously involved in the European Increlex® Growth Forum Database (EU-IGFD) (Belgium and The Netherlands) have been closed.		
Publication (reference): Not applicable.		
Studied period (years): Date of first enrolment: 09 December 2008 Date of last completed: cut-off date for this interim report: 20 April 2023		Phase of development: 4
Objectives: The primary objective is to collect safety data in children and adolescents receiving Increlex® for the treatment of SPIGFD. The secondary objectives are: • To describe long-term safety data, for at least 5 years after the end of Increlex® therapy, in children and adolescents who have received Increlex® therapy, regardless of treatment duration and adult height. • To describe long-term safety data at 2 and 5 years after the end of Increlex® therapy, for a subset of children and adolescents who have been exposed to Increlex® therapy for at least three cumulative years excluding interruptions, regardless of adult height. • To describe Increlex® effectiveness throughout the study until the participant reaches adult height.		

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- To identify predictive factors of the main effectiveness parameters by modelisation of height velocity (HV), final adult height (FAH), height standard deviation score (SDS) change, timing and progression of puberty and bone age development.
- To evaluate Increlex® therapy exposure (dose and '; duration) and compliance.
- To determine the lowest effective dose of Increlex® defined as the cut-off dose under which there is no further effect on the HV anymore (short-term evaluation: 1-Year HV).
- To assess quality of life (QoL) during Increlex® therapy and in the Post-Treatment period (using EQ-5D version EQ-5D-Y (paediatric questionnaire)).
- To describe the timeframe of the occurrence of neoplasia (benign and malignant) and hypoglycaemia.

Methodology:

The Global Registry is an ongoing, multicentre, global, prospective, non-interventional, observational, open-ended, post-authorisation safety surveillance Registry implemented since the end of 2008 by Ipsen in ten European countries with European Marketing Authorisation (MA) for Increlex®. The EU-IGFD Registry has been substantially amended to a Global Registry which is ongoing since December 2021 (Protocol Amendment #8). This Global Registry is designed to collect safety and effectiveness data on the use of Increlex® in children and adolescents with SPIGFD. The Global Registry is conducted in eight European countries and the USA. Participants with confirmed SPIGFD, for which Increlex® was indicated and who were initiating or already receiving therapy with Increlex®, were enrolled into the study and followed throughout their course of treatment. Data on safety, effectiveness, treatment exposure, compliance and QoL of participants were collected, as available. As this is a noninterventional study, the decision to prescribe Increlex® was to be taken prior to and independently from, the decision to enrol the participant. Prescribing of Increlex® was to be made by Investigator according to his/her judgement on the basis of the clinical needs of the participant and according to the locally approved product information. The Investigators were free to choose the dose and administration schedule, which were to be individualised for each participant.

Study visits included the enrolment visit, the baseline visit and the follow-up visits during the Treatment and Post-Treatment periods. All of the procedures performed at these visits were in accordance with routine clinical practice.

During the enrolment visit, the Investigator had to check the inclusion and exclusion criteria and to obtain the Informed Consent Form (ICF) signed by both parents or the liable parent or the legal guardian of the participant (and the participant him/herself according to his/her

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age), before any further data collection. Data were collected into the electronic Case Report Form (eCRF) at the enrolment visit.

After the enrolment visit was performed, Increlex® was started or continued if the participant was already receiving Increlex® treatment. The study follow-up visits during the Treatment period were thereafter conducted as per routine medical practice.

After the end of treatment, study Post-Treatment visits were conducted and included effectiveness and safety parameters.

For each participant, the treatment duration was at the discretion of the Investigator according to his/her judgement on the basis of clinical needs of the participant and according to the locally approved product information. Participants could be followed and monitored for safety throughout their course of treatment and for a Post-Treatment follow-up period of at least 5 years in addition to the Treatment period. If the participant had not reached FAH at the end of the 5-Year Post-Treatment period, the follow-up period was extended until FAH was achieved.

Number of participants (planned and analysed):

The study aims at screening all Increlex®-treated patients with SPIGFD at each participating site of the participating countries with the aim of enrolling as many participants as possible. At the cut-off date for this report (20 April 2023), 324 participants were enrolled; 312 participants who were treated with Increlex® and had at least one follow-up visit or Post-Treatment visit were in the Registry Population and 322 participants were included in the Safety Population.

Diagnosis and criteria for inclusion:

Participants were eligible for participation in the study after Protocol Amendemnt#8 if they met the following criteria. These were slightly different for the participants who were part of the EU-IGFD Registry as per previous protocol requirements. The participants enrolled in the EU-IGFD Registry had to re-consent and sign a new ICF.

- Children and adolescents from 2 to 18 years:
  - For the USA, participants starting or planning to start or currently receiving treatment with Increlex® therapy for SPIGFD as defined by the USA Increlex® prescribing information or for growth hormone (GH) gene deletion who had developed neutralizing antibodies to GH.
  - For Europe, participants starting or planning to start or currently receiving treatment with Increlex® therapy according to the locally approved product information.

    Note: not applicable for participants enrolled in the EU-IGFD Registry and entering or currently in the Post-Treatment period

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- Signed informed consent as per local regulations needs to be obtained. Parents or legally authorised representatives if applicable must give signed informed consent before any Registry-related activities are conducted. Assent from the participant should also be obtained as appropriate.

Test product, dose and mode of administration:

The decision to prescribe Increlex® 10 mg/mL was made as per local clinical practice and local product information, prior to and independently from the decision to enrol the participant in this noninterventional study.

The drug was administered by subcutaneous injection and the injection site changed with each injection; the recommended dose and administration schedule were individualised for each participant.

The recommended starting dose was 0.04 mg per kilogram body weight twice a day (BID). The dose was to be tailored individually for each participant according to the effectiveness and tolerance. The maximum dose was 0.12 mg per kilogram BID.

Duration of treatment:

Treatment duration was to be individualised for each participant.

Criteria for evaluation:

Effectiveness:

Primary endpoints:

- Height SDS and height velocity

Secondary endpoints:

- Height (cm)
- Weight (kg and SDS)
- Body mass index (BMI) (kg/m² and SDS)
- Bone age
- Difference between bone age and chronological age
- Final adult height (FAH)
- Tanner stage
- Quality of life using EQ-5D-Y paediatric questionnaire

Safety:

Primary endpoints:

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- Incidence of serious adverse events (AEs) (SAEs) (including AE of special interest [AESI] of neoplasia), targeted Treatment Emergent AEs (TEAEs), all TEAEs, deaths and withdrawals due to TEAEs during Increlex® treatment.

Secondary endpoints:

- Incidence of SAEs (including AESI of neoplasia), targeted AEs, all AEs, deaths, withdrawals due to AEs, special situations and concomitant medications within the 5 year Post-Treatment period, overall and in the subset of children and adolescents exposed to Increlex® for at least three cumulative years excluding interruptions.
- Incidence of special situations and concomitant medications during Increlex® treatment.
- Description of neoplasia (benign and malignant) and hypoglycaemia according to the timeframe of occurrence (e.g. within the first 3 years after start of treatment, between 3 and 5 years and over 5 years).

The targeted AEs for the Global Registry were:

During Treatment Period: hypersensitivity; scoliosis, immunogenicity (presence of antibodies if available), slipped capital femoral epiphysis, headache, otitis media, papilloedema, hypoglycaemia (suspected or documented – documented means blood level glucose <50 mg/dL or 2.78 mmol/L), acromegalic facial changes, gynaecomastia, hearing loss, intracranial hypertension, lipohypertrophy at injection sites, sleep apnoea, tonsillar hypertrophy, cardiomegaly, oedema and myalgia.

During the Post-Treatment Period: All targeted AEs mentioned in the Treatment period except lipohypertrophy at injection sites.

Statistical methods:

The Safety Population included all participants who received at least one Increlex® injection and with at least one follow-up visit or presence of any post-study treatment safety data. The Safety Population was the primary population for safety analysis.

The Post-Treatment Safety Population included all participants who had taken the treatment at least once, who definitely ended therapy and with at least one Post-Treatment follow-up visit or presence of any safety data in the Post-Treatment period.

The Post-Treatment Safety Population 3-Year included all participants who had been exposed to Increlex® for at least 3 years, who definitely ended therapy with a follow-up visit at 2 and 5 years or at least 2 years (±6 months) after the end of therapy.

The Registry Population (effectiveness population) included all participants who completed at least one follow-up visit and who received at least one Increlex® injection. The effectiveness parameters were also described on the subgroup of treatment-naïve prepubertal

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participants, participants with Laron Syndrome (LS) and treatment-naïve prepubertal participants with LS.

Primary analyses:

An overall summary table of AEs during the Treatment period (up to 30 days after the last dose) including SAEs, AESI, targeted AEs, all AEs, AEs leading to death and AEs leading to withdrawal was presented with the number and proportion of participants and the number of events.

All treatment emergent AEs (TEAEs) were coded according to MedDRA and were classified by MedDRA primary system organ class (SOC) and preferred term (PT). The incidence of all TEAEs, SAEs, AESI, targeted AEs, AEs leading to death and AEs leading to withdrawal were tabulated by primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship were presented.

The most frequent AE, hypoglycaemia was described in terms of timeframe of occurrence, dose of Increlex®, age at hypoglycaemia or number of episodes of hypoglycaemia per participant. Prognostic factors such as age, pubertal status and dose were explored using logistic regression.

Secondary analyses:

Safety analyses

An overall summary table of AEs occurring during the Post-Treatment period (over 30 days after the last dose) including SAEs, AESI, targeted AEs, all AEs and AEs leading to death was presented with the number and proportion of participants and the number of events.

The incidence of all Post-Treatment AEs, SAEs, AESI, targeted AEs and AEs leading to death was tabulated by MedDRA primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship were presented.

The same analyses were performed in a subset of children and adolescents exposed to Increlex® for at least 3 years.

An overall summary table of special situations occurring during the Treatment and Post-Treatment periods was presented with the number and proportion of participants and the number of events. For the Post-Treatment period, the same analyses were performed in a subset of children and adolescents exposed to Increlex® for at least 3 years.

Concomitant medications during the Treatment and Post-Treatment periods were tabulated.

Incidence of neoplasia (benign and malignant) was presented according to the timeframe of occurrence (e.g. within the first 3 years after start of treatment, between 3 and 5 years and over 5 years).

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Effectiveness analyses

Primary endpoints

- Descriptive statistics of raw value and change from baseline for height SDS and HV.
- Multivariate linear regression analyses were performed on naïve prepubertal participants to identify predictive factors of change in height SDS from baseline at Year 1 and until Year 4, change in height SDS between Year 1 and Year 2 and HV at Year 1 and until Year 4. The covariates entered in the model are listed hereafter: gender, parental heights, LS, height SDS at baseline, weight SDS at baseline, insulin-like growth factor 1 (IGF-1) at baseline (ng/mL), average dose injected between the two evaluated timepoints, age at Increlex® intake, change between baseline and Year 1 (only for change in height SDS between consecutive years) and HV at Year X -1 (only for HV at Year X, with $X \geq 2$).

Secondary endpoints

- Descriptive statistics at different timepoints of raw value and change from baseline for the following effectiveness variables: height (cm), weight, BMI SDS, bone age development.
- Multiple regression analysis was performed to identify time between the first intake of treatment and the first visit date where puberty reached using a Cox Regression for naïve prepubertal participants. Gender, parental height, height (SDS) at baseline, weight (SDS) at baseline, IGF-1 at baseline (ng/mL), LS, average dose on the last 6 months before onset, age at Increlex® onset and whether the participant was previously treated with GH were entered as covariates.
- On participants who reached adult height, the difference between predictive adult height (PAH) and FAH was estimated as well as the height SDS gain from the first Increlex® intake.
- Description of effectiveness parameters (height SDS, HV) according to average dose received and according to dose ranges (e.g. 4 dose ranges (≤50, >50-80, >80-110, >110 µg/kg BID)). This analysis supports the description of the lowest effective dose.
- Description and evolution of QoL in participants aged 4 and over using EQ-5D version EQ-5D-Y including changes from baseline at year one, at end of treatment and at FAH.

For safety, analyses in the Treatment period were performed on the Safety Population and analyses in Post-Treatment periods were performed on Post-Treatment Safety Population and Post-Treatment Safety Population 3-Year.

Effectiveness analyses were performed on the Registry Population.

Summary - Conclusions:

Population:

At the cut-off date of 20 April 2023, a total of 324 participants were enrolled in 123 active sites, in 11 countries, mostly in Germany, France, Spain, UK and Italy. A total of 312 participants were in the Registry Population and 322 participants were in the Safety Population. One hundred and two (102) participants reached the adult height (Completed participants); 87 participants were currently in the Treatment period, 20 participants were currently in the Post-Treatment period and 216 participants had withdrawn from the Registry. Thirty one (31) participants were exposed to Increlex® for at least three years and were included in Post-Treatment Safety Population 3-Year.

The characteristics of the enrolled participants were consistent with the indications of Increlex® and similar to those reported in 2021. The primary diagnosis of SPIGFD was reported in 278 participants (85.8%). Other primary diagnosis was mostly Primary IGF I deficiency (PIGFD).

The population of enrolled participants (n=324) included a majority of boys (63.6%) and 193 participants (59.6%) were treatment-naïve prepubertal and 47 (14.5%) had LS. Mean age when starting Increlex® was 9.81±4.15 years for boys and 8.60±3.89 years for girls. Most participants (83.9%) were at pubertal stage 1 (i.e. prepubertal; no sexual development). Mean height±SD at first Increlex® intake was 116.2±21.6 cm for boys and 109.7±20.9 cm for girls. Mean height SDS±SD was -3.62±1.35 for boys and 3.86±1.41 for girls. Mean HV±SD was 4.75±2.73 cm/year for boys and 4.88±1.74 cm/year for girls.

The proportion of participants who had already received growth promoting therapy was stable compared with data reported in 2021 (31.0% in 2021 versus 29.9% in 2023). These participants were mostly treated with GH therapy (84.5% of the previously treated participants).

Two hundred and sixteen participants (66.9%) withdrew from the Registry. The main reason for discontinuation of therapy was the fact they attained adult height according to the Investigator. At the time of data cut-off, 90 participants (41.7%) withdrew from the Registry as they attained adult height.

Treatment exposure:

The median dose of Increlex® received at start of treatment was 40 µg/kg BID, ranging from 10 to 410 µg/kg BID (the participant who received an initial dose of 410 µg/kg BID was diagnosed with severe insulin resistance syndrome). Only two participants had a dose over 120 µg/kg BID at baseline. Median dose increased progressively up to 120 µg/kg BID (which is the maximum recommended dose) between Month 12 and Month 156, with a slight decrease (n=2) to 100 µg/kg BID at Month 156 and 80 µg/kg BID at Month 162.

In the Safety Population, the median (range) treatment duration was 1324 days i.e. 3.6 years (1;4924). Among the 192 participants who discontinued the treatment, the main reasons for discontinuation of therapy were attained adult height (21.9%), lack of effectiveness (19.7%) and other reasons (16.1%). On the Post-Treatment Safety Population 3-Year, the median (range) treatment duration was 1463 days i.e. 4 years (1085;3664), with 35.5% of participants treated five years or more. The main reason for discontinuation of therapy was attained adult height (33.3%).

Effectiveness results:

After one year of treatment, mean HV was 6.94±2.24 cm/year (n=225) (the change from baseline to Year 1 was 2.08±3.30 cm/year; n=142) and mean height SDS was -3.41±1.39

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(n=262) (the change from baseline to Year 1 was 0.34±0.45; n=235) in the whole Registry Population.

In the same way after one year of treatment, mean HV was 7.22±2.09 cm/year (n=141) (the change from baseline to Year 1 was 2.63±2.61 cm/year; n=81) and mean height SDS was -3.36±1.43 (n=161) (the change from baseline to Year 1 was 0.40±0.43; n=144) in the treatment-naïve prepubertal participants with available data. Mean HV was 5.27±1.66 cm/year (n=46) at Year 5 but remained above baseline value until Month 96.

Similarly, after one year of treatment, mean HV was 7.00±2.65 cm/year (n=32) (the change from baseline to Year 1 was 0.43±5.68 cm/year; n=20) and mean height SDS was -4.27±1.66 (n=41) (the change from baseline to Year 1 was 0.46±0.56; n=34) in participants with LS. Mean HV decreased to 4.76±2.63 cm/year at Year 3.

A linear regression analysis of treatment-naïve prepubertal participants showed that HV at Year 1 was likely to be higher in female participants and that change from baseline in height SDS was likely to be higher in younger participants and in female participants.

In treatment-naïve prepubertal participants, after two years of treatment, mean HV was 6.32±1.58 cm/year (n=109) and mean height SDS was -3.09±1.43 (n=135). Pearson test showed a correlation coefficient of 0.28 (p=0.005), indicating a low association between HV at Year 1 and HV at Year 2.

A linear regression analysis of treatment-naïve prepubertal participants showed that HV at Year 2 was likely to be higher in participants with a higher HV at Year 1 and that change from baseline in height SDS was likely to be higher in participants with lower height SDS (growth retardation more severe) at baseline.

Forty-five (45) participants in treatment-naïve prepubertal subgroup reached FAH: the mean FAH was 161.3±14.1 cm in boys (-2.03±1.43 in terms of height SDS) and 148.5±9.0 cm in girls (-2.45±1.30 in terms of height SDS). The mean height SDS gain between FAH and height SDS at first Increlex® intake was 1.30 (0.84) in boys and 1.45 (1.20). Final adult height SDS gain was likely to be higher in participants with high PAH, high biological mother height and in participants with low height SDS at baseline.

Safety results:

At the cut-off date of 20 April 2023, 765 TEAEs had been reported in 206 participants (64.0%) since the start of the EU Registry in December 2008. These TEAEs were mostly of mild to moderate intensity and were considered possibly related to treatment by the Investigator in 169 participants (52.5%).

Overall, 410 targeted TEAEs were reported in 161 participants (50.0%) and 334 of them were considered as related to treatment by the Investigator. The most frequently reported targeted AEs were: hypoglycaemia (25.2% participants), lipohypertrophy (13.0% participants), headache (10.2% participants), tonsillar hypertrophy (8.7% participants) and

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otitis media (7.8% participants). The other targeted AEs reported were acromegalic facial changes (15 participants), hearing loss (PT: deafness) (seven [7] participants), injection site pain (eight (8) participants), sleep apnoea syndrome (seven (7) participants), injection site haematoma (seven (7) participants), myalgia (five (5) participants), injection site erythema (four (4) participants), gynaecomastia (four (4) participants), injection site reaction (three (3) participants), papilloedema (three(3) participants) oedema (four (4) participants) and all events of intracranial hypertension (PT: intracranial pressure increased), scoliosis, injection site bruising, atrophy, extravasation, hypersensitivity, induration, inflammation, irritation, pruritus, rash or swelling (between one (1) and two (2) participants).

Overall, nine (9) AESI (neoplasia) were reported in nine (9) participants (2.8%). Most of the AESI (six events) were reported within the first three years after start of treatment. Three AESI were assessed to be serious. The serious AESI reported were cartilage neoplasm, myelodysplastic syndrome and papillary thyroid cancer.

Overall, 131 serious TEAEs were reported in 66 participants (20.5%). The most frequent serious TEAEs reported were hypoglycaemia (8 participants), tonsillar hypertrophy (7 participants), gastroenteritis (4 participants) and adenoidal hypertrophy (4 participants). Most serious TEAEs had resolved (111) or were resolving (4) at the time of the report. Five (5) cases were ongoing and two serious events were fatal: myelodysplastic syndrome and severe complications of bone marrow transplant, both assessed as not related to treatment.

Fifty-nine (59) serious TEAEs were reported as related to Increlex® in 37 participants (11.5%). These serious TEAEs were mostly hypoglycaemia (eight (8) participants), tonsillar hypertrophy (seven (7) participants), gastroenteritis (four (4) participants) and adenoidal hypertrophy (four (4) participants). Angioedema was reported in two participants. All other serious related TEAEs were reported in one participant each.

Participants who experienced episodes of hypoglycaemia during the treatment had more frequently a past history of hypoglycaemia and were more often presenting with LS.

A multivariate analysis identified presence of LS and history of hypoglycaemia at treatment initiation as statistically significant predictive factors for hypoglycaemia.

Nineteen (19) participants (5.9%) had to stop the treatment due to TEAE. Twenty-two (22) TEAEs leading to Increlex® withdrawal in 17 participants (5.3%) were considered as treatment related based on the Investigator's judgement: hypersplenism, splenic infarction and splenomegaly in one participant, headache and ovarian enlargement in one participant, pain in extremity, drug intolerance and headache in one participant, lipohypertrophy in two participants, hypoglycaemic unconsciousness, injection site pain, hypoglycaemia in three participants, hypertrophy (nose soft tissue), aortic valve incompetence, thyroid mass, IGF increased in two participants, papilloedema and alopecia in one participant.

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Among the 236 participants who ended therapy, 31 participants were included in Post-Treatment Safety Population 3-Year. During the Post-Treatment period, eight (8) participants (25.8%) out of 31 participants included in the Post-Treatment Safety Population 3-Year experienced nine (9) AEs: three (3) SAEs (pertussis resolved after an unknown number of days, tonsillitis resolved after three days, cyclic vomiting syndrome not resolved when the participant left the Registry) three (3) nonserious targeted AEs (gynaecomastia, deafness and tonsillar hypertrophy) and three (3) other nonserious events ([blood thyroid stimulating hormone increased, thyroxine free decreased and Vitamin D decreased], one recovered, one ongoing and one with unknown outcome). These AEs collected in the Post-Treatment Safety Population 3-Year are similar to those collected during Treatment and Post-Treatment periods. All AEs, except for one event of gynaecomastia, were reported as not related to treatment by the Investigator.

Since the previous interim clinical study report (cut-off: 12 May 2021; submitted: 07 January 2022), there was no new safety findings which require further investigation.

Conclusion:

In conclusion, at the cut-off date of 20 April 2023, 18 additional participants have been enrolled and treated and 6 additional participants have entered into the long-term safety follow-up (Post-Treatment Safety Population 3-Year) since the previous interim report. The overall safety results are consistent with the previous interim report and with the known safety profile of Increlex®.

Increlex® continues to demonstrate clinical and meaningful effectiveness while there has been no new significant change in the safety profile. Long-term treatment, albeit in a small sample of participants, is consistent with the known safety profile of the product over short/medium term and no additional new safety risks have been identified. Therefore the data reported in the Global Registry does not change the positive benefit/risk profile of the use of Increlex®.

The Marketing Authorisation Holder (MAH) will continue to provide annual report of Specific Obligation (SO.002) as part of the annual reassessment (16th Annual reassessment submitted on 28 August 2023 and Committee for Medicinal Products for Human Use [CHMP] Opinion is expected by 14 December 2023) until European Medicines Agency (EMA) considers the Specific Obligation (SO.002) as fulfilled and that MA can be switched to a full MA.

The MAH will continue all actions ongoing to improve the recruitment in the Specific Obligation (SO.002) and will make all efforts to accelerate participant recruitment in the Global Registry.

Date of report: 06 December 2023