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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Increlex

MECASERMIN

Procedure no: EMEA/H/C/000704/P46/054.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Rapporteur's assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Increlex

International non-proprietary name: mecasermin

Procedure no.: EMEA/H/C/000704/P46/054.1 seq 0078

Marketing authorisation holder (MAH): Ipsen Pharma

Rapporteur:	**Dr. Outi Mäki-Ikola (FI)**
Start of the procedure:	**26.04.2015**
Date of this report:	**18.05.2015**
Deadline for Rapporteur's AR:	**26.05.2015**
Deadline for CHMP member's comments:	**10.06.2015**
Date of the Rapporteur's final report:	**15.06.2015**

Administrative information

Invented name of the medicinal product:	Increlex
INN (or common name) of the active substance(s):	MECASERMIN
MAH:	Ipsen Pharma
Currently approved Indication(s)	For the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor-1 deficiency (Primary IGFD). Severe Primary IGFD is defined by: · height standard deviation score £ –3.0 and · basal IGF-1 levels below the 2.5th percentile for age and gender and · GH sufficiency. · Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.
Pharmaco-therapeutic group (ATC Code):	H01AC03
Pharmaceutical form(s) and strength(s):	10 mg/ml solution for injection
Rapporteur:	**Name Dr. Outi Mäki-Ikola** Tel: + 358 29 522 3398 Email: Outi.Maki-Ikola@fimea.fi
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1. Introduction

On 6th October 2014 the MAH submitted a completed paediatric study (MS305) for Increlex, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the specific obligation SO 002.1 (Long term safety study).

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Increlex and that no consequential regulatory action is required. No amendments are introduced to the Product Information.

2. Scientific discussion

2.1. Information on the development program

The MAH states that Study MS305 is a stand-alone study.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a final report for: Increlex (Mecasermin (Rdna Origin) Injection) Growth Forum Database-IGFG Registry: A Patient Registry For Monitoring Long-Term Safety And Efficacy Of Increlex. Study number: W-TG-52800-010/MS305.

The United States Insulin-like Growth Factor-1 Deficiency (US-IGFD) Registry was a retrospective and prospective patient registry sponsored by Ipsen Biopharmaceuticals, Inc. In collaboration with participating health care practitioners, this observational study monitored the long term safety of patients treated with Increlex (mecasermin (rDNA) origin). The US-IGFD Registry was intended primarily to monitor the safety and efficacy of Increlex therapy in children with growth failure.

2.2.2. Clinical study

Study MS305: Increlex (Mecasermin (Rdna Origin) Injection) Growth Forum Database-IGDF Registry: A Patient Registry For Monitoring Long-Term Safety And Efficacy Of Increlex.

Description

This study was initiated voluntarily in 2006 by Tercica, Inc. after regulatory approval of Increlex in the US, as a noninterventional real world experience subject registry. The study was not initiated to fulfil any FDA post approval requirements, but to provide more data than was available in the NDA.

Due to the low number of patients meeting the key inclusion criteria relevant to provide meaningful efficacy results, the data from this study could not be analysed for efficacy. In addition, a very small number of subjects were treated with Increlex for the US labelled indication, although it should be noted that the US labelled indication is very similar to the EU one.

As a result, only baseline characteristics and safety data were analysed and presented herein. Consequently, this abbreviated Clinical Study Report (CSR) does not contain all the sections required by ICH E3 but does contain full safety data as requested by ICH. This is the final CSR of the US-IGFD Registry following its closure.

Methods

Objective(s)

The study objectives were:

• To obtain long term safety data for Increlex replacement therapy in children with growth failure

• To obtain long term efficacy data for Increlex replacement therapy in children with growth failure

Study design

This minimal risk, phase IV, multicentre, open label, observational study of the long term safety and efficacy of Increlex treatment was open ended with the duration of Increlex treatment determined at the investigator's discretion.

The US-IGFD Registry was initiated in May 2006 and closed on 23 May 2014. The protocol was a retrospective and prospective patient registry originally sponsored by Tercica, Inc. (a subsidiary of the Ipsen Group). In collaboration with participating healthcare providers, the US-IGFD Registry monitored the long term safety and efficacy of children with growth failure treated with Increlex in the US.

All data collected were from the patients' medical records, which were recorded as part of standard medical care. No additional patient procedures or activities were mandated or performed during this study. The data were captured using electronic Case Report Forms (eCRFs) via a secure website. Some data were mandatory for data transmission (e.g. Increlex dose, height, weight, and adverse events (AEs)) but other data were optional. Optional data were those considered useful to the data analysis but which, depending on the standard of care at each site, may or may not have been collected at each visit (e.g. serum IGF-1 levels), or may not be available to the investigator (e.g. gestational age at birth). The eCRF provided the opportunity to report the occurrence of targeted AEs, other important events considered to be related to Increlex administration and serious adverse events (SAEs).

Due to the low number of patients meeting the key inclusion criteria relevant to provide meaningful efficacy results, these data were not analysed and only baseline and safety data are presented.

Study population /Sample size

Patients entered into the US-IGFD Registry conformed to the following inclusion criteria:

• Parents or legally authorised representatives were required to give signed informed consent and must have given signed Authorisation to Use and Disclose Health Information before any Registry related activities were conducted. Assent from the patient was also to be obtained where appropriate.

• Patients receiving Increlex prescribed by a qualified practitioner were enrolled.

No exclusion criteria were specified.

This was a phase IV observational registry study. No formal sample size and power calculations were performed.

Treatments

Increlex was prescribed by a qualified physician according to the individual need of a patient.

Outcomes/endpoints

Safety assessments, performed at the follow up, end of therapy and post-treatment visits consisted of:

• Serious AEs

• All targeted AEs (asymptomatic papilloedema, acromegalic facial changes, oedema, gynecomastia, hearing loss, headache, hypoglycaemia, intracranial hypertension (other than asymptomatic papilloedema), lipohypertrophy at injection site, myalgia, otitis media, sleep apnoea, tonsillar hypertrophy, urticaria and injection site reaction)

• Other significant non serious AEs

• Non serious clinically significant laboratory abnormalities

• Increlex exposure

Targeted AEs were AEs of special interest based on clinical trials and research related to PIGFD and data were therefore sought proactively. The occurrence of each targeted AE, other significant nonserious AEs and nonserious clinically significant laboratory abnormalities were reported at each visit as 'yes/no.' No start or stop dates were collected for these AEs. Relationship to treatment, severity of the AE, outcome and action taken regarding Increlex treatment were only reported for SAEs. All targeted AEs were considered related to treatment.

Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in the US-IGFD Registry is documented in the Reporting and Analysis Plan (RAP) dated 20 May 2014.

All statistical analyses were performed by the biostatistics unit of a CRO contracted by the Sponsor using Statistical Analysis System (SAS®) software Version 9.2 or higher (SAS Institute Inc., Cary, North Carolina, US). The statistical analyses were performed in accordance with ICH E9 guidelines and were to be based on the pooled data from the individual US study sites, unless otherwise stated.

Demographics, the results of the IGF-1 generation test, GH concentrations, diagnoses, previous therapy and the results of genetic tests were summarised overall and by gender for the enrolled population.

For the primary endpoint, each type of AE (targeted AEs, other related significant nonserious AEs, nonserious clinically significant laboratory abnormalities and SAEs) were summarised with the number and proportion of subjects with at least one event classified by primary System Organ Class (SOC) and Preferred Term (PT). The number of occurrences was also presented. For each type of SAE, severity and causality were described.

Treatment emergent AEs (TEAEs) were defined as AEs with onset dates within 31 days following the last Increlex injection. Pretreatment AEs were those occurring before the first Increlex injection and post-treatment AEs were those occurring after 31 days of the last Increlex injection.

Data were summarised for the safety follow up population and the safety post-treatment population.

Results

Recruitment/ Number analysed

1377 subjects were enrolled from 114 active sites.

Among the enrolled population, 1342 (97.5%) subjects were included in the safety population (fewer in number than the enrolled population, as this population comprised enrolled subjects with at least one follow up visit or any safety data collected during treatment follow up), 1339 (97.2%) subjects had at least one follow up treatment visit (safety follow up population) and 164 (11.9%) subjects had post-treatment follow up data (safety post-treatment population).

The number of subjects who discontinued and the reasons for treatment withdrawal are and summarised in Table 3. In total, 804 subjects discontinued from the US-IGFD Registry, with 40 (5.0%) of these due to AEs.

Table 3 Subject Disposition by Gender and Reason for Treatment Withdrawal (Enrolled Population)

Subjects/Reason for treatment withdrawal	Boys N (%)	Girls N (%)	Total N (%)
Subjects enrolled	1047 (100)	330 (100)	1377 (100)
Subjects with at least one follow up visit	985 (94.1)	306 (92.7)	1291 (93.8)
Subjects with at least one post treatment visit	108 (10.3)	52 (15.8)	160 (11.6)
Subjects discontinued	597 (57.0)	207 (62.7)	804 (58.4)
Reason for withdrawal			
Adverse event	25 (4.2)	15 (7.2)	40 (5.0)
Attained adult height	56 (9.4)	25 (12.1)	81 (10.1)
Lost to follow up	132 (22.1)	24 (11.6)	156 (19.4)
Financial/insurance	75 (12.6)	29 (14.0)	104 (12.9)
Subject/parent decision	140 (23.5)	51 (24.6)	191 (23.8)
Non compliance	41 (6.9)	14 (6.8)	55 (6.8)
Changed physician	28 (4.7)	5 (2.4)	33 (4.1)
Physician decision	57 (9.5)	27 (13.0)	84 (10.4)
Other	43 (7.2)	17 (8.2)	60 (7.5)
Missing [a]	3	1	4

Protocol Deviations

The major protocol violation that occurred during the conduct of the study was lack of documented informed consent in many subjects. Of the 1377 subjects enrolled, 678 (49.2%) lacked adequate documentation that signed informed consent had been obtained. Due to site closure ICFs could not be verified, and subjects from closed sites were counted as subjects lacking documented ICFs.

Baseline data

Demographic characteristics of subjects in the enrolled population are and summarised in Table 4.

There were more boys than girls (1047 (76.0%) and 330 (24.0%) subjects, respectively). The mean±SD age at first Increlex treatment was 11.0±3.6 years for boys and 9.8±3.5 years for girls.

Thus, boys tended to be older than girls at first Increlex intake.

At baseline (enrolment visit, Day 0), in boys, mean±SD height was 128.3±19.6 cm, mean±SD height SDS was -2.4±0.9 and mean±SD height velocity was 5.0±2.3 cm/year.

At baseline, in girls, mean±SD height was 120.6±19.3 cm, mean±SD height SDS was –2.6±1.1 and mean±SD height velocity was 5.2±2.2 cm/year.

At baseline, in boys, mean±SD weight was 29.0±11.8 kg and mean±SD weight SDS was -2.1±1.5.

At baseline, in girls, mean±SD weight was 25.5±11.7 kg and mean±SD weight SDS was -2.1±1.5.

With respect to Tanner stage, at baseline the majority of boys had pubic hair assessments indicating stages I (472 (74.8%) subjects) and II (95 (15.1%) subjects). The majority of girls had pubic hair assessments indicating Tanner stages I (146 (76.8%) subjects) and II (28 (14.7%) subjects).

Table 4. Summary of Demography and Subject Characteristics by Gender (Enrolled Population)

Measurement [a]	Boys N=1047	Girls N=330	Total N=1377
Birth weight (kg)			
n	**845**	**260**	**1105**
Mean (SD)	3.0 (0.8)	2.8 (0.8)	2.9 (0.8)
Median	3.1	2.9	3.1
Min/Max	0.5 /4.8	0.5/7.1	0.5/7.1
Birth length (cm)			
n	**447**	**136**	**583**
Mean (SD)	48.8 (4.3)	47.9 (4.6)	48.6 (4.4)
Median	48.5	48.3	48.3
Min/Max	27.9/58.4	29.2/54.6	27.9/58.4
Gestational age (weeks)			
n	**755**	**214**	**969**
Mean (SD)	38.1 (3.3)	37.9 (3.3)	38.0 (3.3)
Median	40.0	39.5	40.0
Min/Max	24.0/43.0	25.0/43.0	24.0/43.0
Age at first Increlex intake (years)			
n	**1047**	**330**	**1377**
Mean (SD)	11.04 (3.58)	9.75 (3.53)	10.73 (3.61)
Median	11.84	10.27	11.44
Min/Max	1.32/18.63	1.26/18.85	1.26/18.85
Bone age at baseline (years)			
n	**658**	**191**	**849**
Mean (SD)	9.5 (3.4)	8.2 (3.4)	9.2 (3.4)
Median	10.0	8.8	10.0
Min/Max	1.0/17.0	0.3/15.0	0.3/17.0
Height at baseline (cm)			
n	**909**	**285**	**1194**
Mean (SD)	128.3 (19.6)	120.6 (19.3)	126.4 (19.8)
Median	131.3	122.2	129.7
Min/Max	63.0/168.0	66.8/165.1	63.0/168.0
Height SDS at baseline			
n	**909**	**285**	**1194**
Mean (SD)	-2.4 (0.9)	-2.6 (1.1)	-2.5 (1.0)
Median	-2.4	-2.6	-2.4
Min/Max	-8.0/0.5	-8.2/0.9	-8.2/0.9
Height velocity at baseline			
n	378	125	503
Mean (SD)	5.0 (2.3)	5.2 (2.2)	5.1 (2.3)
Median	4.8	5.0	4.9
Min/Max	0.2/16.7	0.6/12.5	0.2/16.7
Weight at baseline (kg)			
n	**907**	**285**	**1192**
Mean (SD)	29.0 (11.8)	25.5 (11.7)	28.2 (11.9)

Median	28.4	23.2	27.3
Min/Max	5.4/92.4	6.7/90.0	5.4/92.4
Weight SDS at baseline			
n	**907**	**285**	**1192**
Mean (SD)	-2.1 (1.5)	-2.1 (1.5)	-2.1 (1.5)
Median	-2.0	-2.1	-2.0
Min/Max	-16.6/2.4	-6.9/3.4	-16.6/3.4
BMI at baseline (kg/m^2)			
n	**899**	**282**	**1181**
Mean (SD)	16.9 (3.0)	16.7 (3.7)	16.8 (3.2)
Median	16.3	15.7	16.2
Min/Max	6.7/35.8	12.2/39.3	6.7/39.3
BMI SDS at baseline			
n	**899**	**282**	**1181**
Mean (SD)	-0.7 (2.0)	-0.6 (1.3)	-0.7 (1.8)
Median	-0.6	-0.6	-0.6
Min/Max	-36.0/3.1	-4.2/2.9	-36.0/3.1
Tanner stage pubic hair at baseline			
n	**631**	**190**	**821**
I	472 (74.8)	146 (76.8)	618 (75.3)
II	95 (15.1)	28 (14.7)	123 (15.0)
III	41 (6.5)	13 (6.8)	54 (6.6)
IV	18 (2.9)	2 (1.1)	20 (2.4)
V	5 (0.8)	1 (0.5)	6 (0.7)
Measurement[a]	**Boys N=1047**	**Girls N=330**	**Total N=1377**
Missing	416	140	556

Parental Height and Target Height

Parental heights and target heights in the enrolled population are and summarised in Table 5. In this population, mean biological parents' heights were comparable between girls and boys. The means target mid parental heights were 173.5±6.1 cm for boys and 159.5±6.9 cm for girls.

Table 5. Parental Heights and Target Heights by Gender (Enrolled Population)

	Boys N=1047	**Girls N=330**	**Total N=1377**
Biological mother's height (cm)			
n	**849**	**235**	**1084**
Mean (SD)	159.8 (7.5)	159.3 (7.7)	159.7 (7.6)
Median	160.0	159.0	160.0
Min/Max	139.7/193.0	134.0/185.4	134.0/193.0
Biological father's height (cm)			
n	**824**	**225**	**1049**
Mean (SD)	174.2 (8.2)	172.7 (8.7)	173.9 (8.3)
Median	175.3	172.7	173.7
Min/Max	139.7/200.7	139.7/210.8	139.7/210.8
Mid parental target height (cm) [a]			
n	**821**	**224**	**1045**
Mean (SD)	173.5 (6.1)	159.5 (6.9)	170.5 (8.5)
Median	174.0	159.8	171.6
Min/Max	151.9/193.2	133.2/191.6	133.2/193.2

Baseline IGF-1 and GH

For subjects in the enrolled population, baseline IGF-1 and GH values are summarised in Table 6.

Table 6. Baseline IGF-1 and GH by Gender (Enrolled Population)

	Boys N=1047	**Girls N=330**	**Total N=1377**
Serum IGF-1 (ng/mL) [a]			
n	**910**	**281**	**1191**
Mean (SD)	147.6 (147.5)	177.9 (195.5)	154.7 (160.5)
Median	105.5	107.0	106.0
Min/Max	0.0/1565.0	1.9/1293.0	0.0/1565.0
Basal/random GH (ng/mL)			
n	**404**	**112**	**516**
Mean (SD)	4.4 (13.9)	4.5 (5.4)	4.5 (12.6)
Median	1.0	2.2	1.2
Min/Max	0.0/200.0	0.0/29.1	0.0/200.0
Highest stimulated GH (ng/mL)			
n	**637**	**187**	**824**
Mean (SD)	20.0 (12.8)	20.8 (14.5)	20.2 (13.2)
Median	17.0	17.0	17.0
Min/Max	0.1/131.0	0.8/107.6	0.1/131.0

With respect to IGF-1, in boys, the mean±SD serum concentration was 147.6±147.5 ng/mL (ranging from 0.0-1565.0 ng/mL, with 137 missing values); in girls, the mean±SD serum concentration was 177.9±195.5 ng/mL (ranging from 1.9-1293.0 ng/mL, with 49 missing values).

With respect to GH, in boys the mean±SD basal GH concentration was 4.4±13.9 ng/mL (ranging from 0.0-200.0 ng/mL with 643 missing values) and the mean±SD highest stimulated GH concentration was 20.0±12.8 ng/mL (ranging from 0.1-131.0 ng/mL, with 410 missing values).

In girls, the mean±SD basal GH concentration was 4.5±5.4 ng/mL (ranging from 0.0-29.1 ng/mL, with 218 missing values) and the mean±SD highest stimulated GH concentration was 20.8±14.5 ng/mL (ranging from 0.8-107.6 ng/mL, with 143 missing values).

The range of values was wide and there were a large number of missing values. It should be noted that GH and IGF-1 concentrations are dependent on age and pubertal status which could account for the wide range of concentrations obtained.

Diagnosis

The most common primary diagnosis was primary IGFD (769 (73.4%) boys and 218 (66.1%) girls). These data also indicated that Increlex was being prescribed for other primary diagnoses, the most common being idiopathic short stature (207 (19.8%) boys and 79 (23.9%) girls).

Measurements of Treatment Exposure

Treatment exposure was estimated by the physician/study coordinator based on parent/subject reports. The data are and summarised in Table 12.

Table 12. Treatment Compliance at Each Time Point (Enrolled Population)

Timepoint	Total N=1342	Dose of Increlex (µg/kg BID)		Number of subjects ending therapy at time point
	n	Mean (SD)	Median (min/max)	
Baseline	1322	72.5 (38.8)	42.1 (0.0/200.0)	-
Month 1	1288	86.1 (37.3)	104.1 (0.0/180.0)	10 (0.8)
Month 3	1267	93.0 (35.1)	115.0 (0.0/180.0)	65 (5.1)
Month 6	1187	98.8 (32.5)	119.2 (0.0/170.0)	90 (7.6)
Month 12	1071	103.4 (31.0)	120.0 (0.0/200.0)	148 (13.8)
Month 18	855	104.7 (30.9)	119.8 (0.0/200.0)	122 (14.2)
Month 24	669	105.8 (30.9)	119.9 (0.0/200.0)	87 (13.0)
Month 30	526	105.3 (31.6)	119.5 (0.0/200.0)	75 (14.3)
Month 36	374	104.9 (32.5)	119.2 (0.0/196.0)	75 (20.1)
Month 42	244	105.2 (34.2)	118.2 (0.0/195.1)	36 (14.8)
Month 48	170	104.7 (32.3)	116.4 (28.0/194.5)	19 (11.2)
Month 54	118	106.3 (36.9)	117.5 (0.0/195.1)	23 (19.5)
Month 60	71	108.7 (41.4)	119.0 (0.0/196.6)	11 (15.5)
Month 66	43	107.6 (41.8)	117.0 (8.4/200.0)	11 (25.6)
Month 72	13	101.9 (26.6)	107.4 (61.1/144.1)	2 (15.4)
Month 78	7	111.5 (33.5)	116.1 (61.1/151.3)	2 (28.6)

At baseline, the median dose of Increlex administered was 41.6 µg/kg twice daily (BID) in boys and 55.9 µg/kg BID in girls. The investigators took 3-6 months to bring subjects up to the maximum approved dose of Increlex (120 µg/kg given BID) instead of the recommended 2 weeks. A total of 804 (58.4%) subjects permanently discontinued the treatment.

Efficacy results

Due to the low number of patients meeting the key inclusion criteria relevant to provide meaningful efficacy results these data were not analysed and are not provided in this abbreviated report.

Safety results

Extent of Exposure

The extent of exposure to Increlex is summarised in Table 13. The mean±SD duration of treatment with Increlex was 25.4±16.9 months for boys and 23.6±17.4 months for girls, and was therefore comparable between the genders. The maximum duration of Increlex treatment was 80.1 months for boys and 76.2 months for girls. The sum of duration of treatment with Increlex expressed in terms of subject years was 2151.5 years for boys and 637.7 years for girls, which reflected the gender imbalance in this study.

Table 13. Treatment Duration (Safety Population)

	Boys N=1018	Girls N=324	Total N=1342
Number of subject years	2151.5	637.7	2789.2
Increlex treatment duration (months)			
n	1018	324	1342
Mean (SD)	25.4 (16.9)	23.6 (17.4)	24.9 (17.1)
95% CI (mean)	24.3, 26.4	21.7, 25.5	24.0, 25.9
Median	22.4	20.6	22.0

Q1, Q3	12.0, 36.4	10.6, 32.6	11.8, 35.7
Min, Max	0.0, 80.1	0.0, 76.2	0.0, 80.1

Adverse Events

The safety analysis is based on a safety follow up population of 1017 boys and 322 girls and a safety post-treatment population, which comprised 112 boys and 52 girls.

Treatment emergent AEs recorded in the safety follow up population are summarised in Table 14.

In the US-IGFD Registry, 371 (27.7%) subjects in the safety follow up population experienced a total of 1256 TEAEs, of which 83 (experienced by 46 (3.4%) subjects) were serious TEAEs. With respect to targeted TEAEs, 667 events were experienced by 251 (18.7%) subjects, of which 13 (experienced by 11 (0.8%) subjects) were serious targeted TEAEs.

Table 14. Overall Summary of TEAEs (Safety Follow Up Population)

	Events	**Subjects N (%)**
N	1256	1339 (100.0)
At least one TEAE	1256	371 (27.7)
At least one targeted TEAE	667	251 (18.7)
At least one serious targeted TEAE	13	11 (0.8)
At least one nonserious targeted TEAE	654	250 (18.7)
At least one serious TEAE	83	46 (3.4)
At least one related serious TEAE	39	24 (1.8)
At least one non related serious TEAE	44	26 (1.9)
At least one other significant nonserious TEAE	396	179 (13.4)
At least one nonserious clinically significant laboratory abnormality	102	50 (3.7)
At least one TEAE leading to treatment withdrawal	49	40 (3.0)

For the US-IGFD Registry, all TEAEs in the safety follow up population are summarised in Table 15.

Hypoglycaemia was the most frequently reported TEAE (249 events reported by 125 (9.3%) subjects). The other most frequent TEAEs (concerning more than 1% of subjects) were: headache (90 (6.7%) subjects), injection site reaction (26 (1.9%) subjects), otitis media (22 (1.6%) subjects), myalgia (20 (1.5%) subjects), tonsillar hypertrophy (17 (1.3%) subjects) and injection site hypertrophy (16 (1.2%) subjects).

Table 15. Summary of TEAEs Occurring in ≥3 of Subjects (Safety Follow Up Population)

SOC PT	Events	Subjects N (%)
All TEAEs	1256	371 (27.7%)
Metabolism and nutrition disorders	259	128 (9.6%)
Hypoglycaemia	249	125 (9.3%)
Nervous system disorders	199	114 (8.5%)
Headache	148	90 (6.7%)
Intracranial pressure increased	10	6 (0.4%)
Dizziness	9	7 (0.5%)
Benign intracranial hypertension	9	6 (0.4%)
Convulsion	5	5 (0.4%)
General disorders and administration site conditions	121	73 (5.5%)
Injection site reaction	42	26 (1.9%)
Injection site hypertrophy	28	16 (1.2%)
Oedema	8	8 (0.6%)
Pyrexia	5	5 (0.4%)
Fatigue	3	3 (0.2%)
Injection site urticaria	3	3 (0.2%)
Investigations	106	53 (4.0%)
Insulin-like growth factor increased	11	11 (0.8%)
Insulin-like growth factor increased	11	11 (0.8%)
Blood thyroid stimulating hormone increased	8	4 (0.3%)
Glycosylated haemoglobin increased	5	3 (0.2%)
Thyroxine free decreased	4	4 (0.3%)
Aspartate aminotransferase increased	3	3 (0.2%)
Blood 25-hydroxycholecalciferol decreased	3	3 (0.2%)
Blood glucose decreased	3	3 (0.2%)
Blood testosterone decreased	3	3 (0.2%)
Musculoskeletal and connective tissue disorders	96	57 (4.3%)
Myalgia	31	20 (1.5%)
Arthralgia	15	12 (0.9%)
Pain in extremity	11	10 (0.7%)
Scoliosis	7	6 (0.4%)
Infections and infestations	88	58 (4.3%)
Otitis media	29	22 (1.6%)
Pharyngitis streptococcal	11	10 (0.7%)
Upper respiratory tract infection	7	5 (0.4%)
Pneumonia	6	6 (0.4%)
Gastroenteritis viral	3	3 (0.2%)
H1n1 influenza	3	3 (0.2%)
Influenza	3	3 (0.2%)
Respiratory, thoracic and mediastinal disorders	85	37 (2.8%)
Tonsillar hypertrophy	41	17 (1.3%)
Snoring	11	10 (0.7%)
Sleep apnoea syndrome	10	5 (0.4%)
Oropharyngeal pain	5	4 (0.3%)
Adenoidal hypertrophy	4	3 (0.2%)
Cough	3	3 (0.2%)
Skin and subcutaneous tissue disorders	51	37 (2.8%)
Urticaria	14	12 (0.9%)
Hair texture abnormal	10	7 (0.5%)
Night sweats	5	3 (0.2%)
Alopecia	3	3 (0.2%)

Gastrointestinal disorders	42	30 (2.2%)
Constipation	10	6 (0.4%)
Vomiting	6	5 (0.4%)
Abdominal pain	5	5 (0.4%)
Nausea	4	4 (0.3%)
Psychiatric disorders	30	22 (1.6%)
Anxiety	5	3 (0.2%)
Depression	4	4 (0.3%)
Anger	3	3 (0.2%)
Endocrine disorders	26	14 (1.0%)
Acromegalic facial features or facial dysmorphism	20	11 (0.8%)
Surgical and medical procedures	23	17 (1.3%)
Tonsillectomy	5	5 (0.4%)
Adenoidectomy	4	4 (0.3%)
Injury, poisoning and procedural complications	22	16 (1.2%)
Fall	5	5 (0.4%)
Reproductive system and breast disorders	21	16 (1.2%)
Gynaecomastia	18	13 (1.0%)
Eye disorders	15	11 (0.8%)
Papilloedema	8	4 (0.3%)
Congenital, familial and genetic disorders	13	11 (0.8%)
Cystic fibrosis	4	3 (0.2%)
Ear and labyrinth disorders	13	6 (0.4%)
Deafness	11	4 (0.3%)
Immune system disorders	13	9 (0.7%)
Hypersensitivity	9	6 (0.4%)
Drug hypersensitivity	4	3 (0.2%)

Targeted Adverse Events

All targeted TEAEs in the safety follow up population are summarised in Table 16.

Table 16 Summary of Targeted TEAEs and Serious Targeted TEAEs (Safety Follow Up Population)

PT	**All targeted TEAEs**		**Serious targeted TEAEs**	
	Events	**Subjects N (%)**	**Events**	**Subjects N (%)**
All	667	251 (18.7)	13	11 (0.8)
Hypoglycaemia	249	125 (9.3)	2	2 (0.1)
Headache	148	90 (6.7)	1	1 (<0.1)
Injection site reaction	42	26 (1.9)	0	0
Otitis media	29	22 (1.6)	2	2 (0.1)
Myalgia	31	20 (1.5)	0	0
Tonsillar hypertrophy	41	17 (1.3)	5	4 (0.3)
Injection site hypertrophy	28	16 (1.2)	0	0
Gynaecomastia	18	13 (1.0)	0	0
Urticaria	14	12 (0.9)	0	0
Acromegalic facial features or facial dysmorphism	20	11 (0.8)	0	0
Oedema	8	8 (0.6)	0	0
Intracranial pressure increased	10	6 (0.4)	2	2 (0.1)
Sleep apnoea syndrome	10	5 (0.4)	0	0
Deafness	11	4 (0.3)	0	0
Papilloedema	8	4 (0.3)	1	1 (<0.1)

In total, 667 targeted TEAEs were reported for 251 (18.7%) subjects. The most frequent targeted TEAEs (affecting more than 1% of the subjects) were: hypoglycaemia (125 (9.3%) subjects), headache (90 (6.7%) subjects), injection site reaction (26 (1.9%) subjects), otitis media (22 (1.6%) subjects), myalgia (20 (1.5%) subjects), tonsillar hypertrophy (17 (1.3%) subjects) and injection site hypertrophy (16 (1.2%) subjects). There were 13 serious targeted TEAEs in 11 (0.8%) subjects.

Serious targeted TEAEs comprised tonsillar hypertrophy (four (0.3%) subjects), hypoglycaemia (two (0.1%) subjects), otitis media (two (0.1%) subjects), intracranial pressure increased (two (0.1%) subjects), headache (one (<0.1%) subject) and papilloedema (one (<0.1%) subject).

Five serious Increlex related cases of tonsillar hypertrophy (two mild and three moderate) were reported in four subjects, with times to onset ranging from 111 to 1368 days after the start of Increlex treatment. These events were assessed as serious as they involved hospitalisation (two cases), were medically significant (two cases) or were both medically significant and involved hospitalisation (one case). In four cases, the drug was temporarily suspended. The events were all reported to have resolved in periods ranging from 1 to 129 days.

Two serious Increlex related cases of hypoglycaemia (one moderate and one mild) were reported in two subjects, with times to onset of 896 and 661 days after the start of Increlex treatment. These events were assessed as serious as they were both medically significant. In one case, the dose of Increlex was reduced as a result of the event, with no action taken in the other case. Both events were reported to have resolved.

Two serious Increlex unrelated cases of otitis media (both moderate in intensity) were reported in two subjects, with times to onset of 689 and 104 days after the start of Increlex treatment. These events were assessed as serious as they both involved hospitalisation. In one case, no action was taken with respect to the study drug; in the other case, the drug was temporarily suspended. Both events were reported to have resolved.

Two serious Increlex related events of intracranial pressure increased (one moderate and one severe) were reported in two subjects, with times to onset of 88 and 67 days. These events were assessed as serious as they involved hospitalisation (one case) or were both life threatening and involved hospitalisation (one case). Both of these events led to drug withdrawal and were reported resolved in 3 and 136 days.

One serious Increlex related case of headache (severe in intensity) was reported in one subject, with a time to onset of 207 days after the start of Increlex treatment. This event was assessed as serious as it was medically significant. The drug was temporarily suspended and the event resolved after 4 days.

One serious Increlex related event of papilloedema (severe in intensity) was reported in one subject, with a time to onset of 118 days. This event was assessed as serious as it involved hospitalisation. This event led to drug withdrawal and was reported resolved in 1 day.

Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Deaths

Two deaths were recorded during the study, both during follow up**.**

Subject 1162 (aged 20 years at the time of the event) experienced sudden unexpected death, recorded as possibly related to study drug. This male subject was aged 15.0 years at the start of Increlex intake and had been treated with Increlex for PIGFD for 2102 days before the onset of the

event. The subject's medical history included a familial risk factor of Laron syndrome, Type I diabetes and hypoglycaemic episodes. The subject was not taking any concomitant medications.

For Subject 2273 (aged 13 years at the time of the event), death was due to progression of sickle cell disease and recorded as being unrelated to study drug. This male subject was aged 11.7 years at the start of Increlex intake and had been treated with Increlex for idiopathic short stature for 1116 days before the onset of the event. The subject's concurrent conditions included sulphonamide allergy, asthma and sickle cell disease, while his past medical history included serious events of fever of unknown origin, hypoxia, Epstein Barr virus infection and infarcts.

Other Serious Adverse Events

In the US-IGFD Registry study, 46 (3.4%) subjects experienced a total of 83 serious TEAEs during the study period. These are summarised by SOC and PT for the safety follow up population in Table 17.

Table 17. Summary of All Serious TEAEs and Related Serious TEAEs (Safety Follow Up Population)

SOC PT	All serious TEAEs		Related serious TEAEs	
	Events	Subjects N (%)	Events	Subjects N (%)
All	83	46 (3.4)	39	24 (1.8)
Nervous system disorders	14	13 (1.0)	11	10 (0.7)
Benign intracranial hypertension	6	5 (0.4)	6	5 (0.4)
Convulsion	2	2 (0.1)	2	2 (0.1)
Intracranial pressure increased	2	2 (0.1)	2	2 (0.1)
Cerebrovascular accident	1	1 (<0.1)	0	0
Headache	1	1 (<0.1)	1	1 (<0.1)
Migraine	1	1 (<0.1)	0	0
Posttraumatic epilepsy	1	1 (<0.1)	0	0
Infections and infestations	14	12 (0.9)	0	0
Otitis media	2	2 (0.1)	0	0
Infective pulmonary exacerbation of cystic fibrosis	3	1 (<0.1)	0	0
Beta haemolytic streptococcal infection	1	1 (<0.1)	0	0
Epstein-Barr virus infection	1	1 (<0.1)	0	0
Gastroenteritis viral	1	1 (<0.1)	0	0
Mastoiditis	1	1 (<0.1)	0	0
Pharyngitis streptococcal	1	1 (<0.1)	0	0
Pharyngotonsillitis	1	1 (<0.1)	0	0
Pneumonia	1	1 (<0.1)	0	0
Pyelonephritis	1	1 (<0.1)	0	0
Respiratory syncytial virus infection	1	1 (<0.1)	0	0
Respiratory, thoracic and mediastinal disorders	11	6 (0.4)	10	5 (0.4)
Tonsillar hypertrophy	5	4 (0.3)	5	4 (0.3)
Adenoidal hypertrophy	4	3 (0.2)	4	3 (0.2)
Hypoxia	1	1 (<0.1)	0	0
Nasal oedema	1	1 (<0.1)	1	1 (<0.1)
Psychiatric disorders	5	5 (0.4)	1	1 (<0.1)
Anxiety	1	1 (<0.1)	0	0
Bipolar disorder	1	1 (<0.1)	0	0
Encopresis	1	1 (<0.1)	1	1 (<0.1)
Major depression	1	1 (<0.1)	0	0
Mental disorder	1	1 (<0.1)	0	0

Gastrointestinal disorders	9	3 (0.2)	5	1 (<0.1)
Constipation [a]	6	2 (0.1)	4	1 (<0.1)
Abdominal pain	1	1 (<0.1)	1	1 (<0.1)
Oesophageal ulcer	1	1 (<0.1)	0	0
Small intestine ulcer	1	1 (<0.1)	0	0

General disorders and administration site conditions	4	3 (0.2)	1	1 (<0.1)
Condition aggravated	2	2 (0.1)	0	0
Pyrexia	1	1 (<0.1)	0	0
Sudden death	1	1 (<0.1)	1	1 (<0.1)
Congenital, familial and genetic disorders	3	3 (0.2)	0	0
Cleft lip	1	1 (<0.1)	0	0
Sickle cell anaemia	1	1 (<0.1)	0	0
Tourette's disorder	1	1 (<0.1)	0	0
Injury, poisoning and procedural complications	3	3 (0.2)	0	0
Limb traumatic amputation	1	1 (<0.1)	0	0
Post procedural haemorrhage	1	1 (<0.1)	0	0
Suture related complication	1	1 (<0.1)	0	0
Metabolism and nutrition disorders	3	3 (0.2)	2	2 (0.1)
Hypoglycaemia	2	2 (0.1)	2	2 (0.1)
Hyperglycaemia	1	1 (<0.1)	0	0
Musculoskeletal and connective tissue disorders	3	3 (0.2)	3	3 (0.2)
Spinal column stenosis	2	2 (0.1)	2	2 (0.1)
Epiphysiolysis	1	1 (<0.1)	1	1 (<0.1)
Eye disorders	2	2 (0.1)	2	2 (0.1)
Eye swelling	1	1 (<0.1)	1	1 (<0.1)
Papilloedema	1	1 (<0.1)	1	1 (<0.1)
Immune system disorders	2	2 (0.1)	2	2 (0.1)
Drug hypersensitivity	1	1 (<0.1)	1	1 (<0.1)
Hypersensitivity	1	1 (<0.1)	1	1 (<0.1)
Renal and urinary disorders	2	2 (0.1)	1	1 (<0.1)
Haematuria	1	1 (<0.1)	1	1 (<0.1)
Iga nephropathy	1	1 (<0.1)	0	0
Cardiac disorders	2	1 (<0.1)	0	0
Atrial fibrillation	1	1 (<0.1)	0	0
Mitral valve incompetence	1	1 (<0.1)	0	0
Vascular disorders	2	1 (<0.1)	0	0
Arterial stenosis	1	1 (<0.1)	0	0
Secondary hypertension	1	1 (<0.1)	0	0
Blood and lymphatic system disorders	1	1 (<0.1)	0	0
Splenomegaly	1	1 (<0.1)	0	0
Hepatobiliary disorders	1	1 (<0.1)	0	0
Cholestasis	1	1 (<0.1)	0	0
Skin and subcutaneous tissue disorders	1	1 (<0.1)	1	1 (<0.1)
Skin reaction	1	1 (<0.1)	1	1 (<0.1)
Surgical and medical procedures	1	1 (<0.1)	0	0
Hernia repair	1	1 (<0.1)	0	0

Other Serious TEAEs (Related and Not Related)

The most common serious TEAEs were benign intracranial hypertension (six events experienced by five (0.4%) subjects), tonsillar hypertrophy (five events experienced by four (0.3%) subjects), adenoidal

hypertrophy (four events experienced by three (0.2%) subjects and constipation (six events experienced by two (0.1%) subjects).

A total of 83 serious TEAEs were experienced by 46 patients during treatment with Increlex. For five additional subjects, five SAEs of graft versus host disease, osteonecrosis, increased intracranial pressure, pancreatitis and hyperplasia were reported more than 31 days after the last Increlex intake (post-treatment). Of the 83 serious TEAEs, 49 (59.0%) were of mild or moderate intensity, 33 (39.8%) were of severe intensity and one (1.2%) was of unknown intensity. For 10 subjects, these serious TEAEs led to treatment withdrawal. Serious TEAEs that led to treatment withdrawal included major depression, beta haemolytic streptococcal infection, IgA nephropathy, benign intracranial hypertension (three serious TEAEs in three subjects), increased intracranial pressure (two serious TEAEs in two subjects), papilloedema, sickle cell anaemia, condition aggravated, hypersensitivity and convulsion.

Treatment interruption occurred in 21 subjects due to 34 serious TEAEs. Among all serious TEAEs, 39 (47.0%) reported in 24 subjects were considered related to treatment.

The most common treatment related serious TEAEs were benign intracranial hypertension (six events experienced by five (0.4%) subjects), tonsillar hypertrophy (five events experienced by four (0.3%) subjects), adenoidal hypertrophy (four events experienced by three (0.2%) subjects), hypoglycaemia (two events experienced by two (0.1%) subjects) and spinal column stenosis (two events experienced by two (0.1%) subjects). Most of the 83 serious TEAEs had an outcome of 'resolved.'

Related Serious TEAEs

Six serious Increlex related cases of benign intracranial hypertension (one severe and five moderate in intensity) were reported by five subjects. The times to onset ranged from 42 to 602 days after the start of Increlex treatment. These events were assessed as serious as they were medically significant (five cases) or involved hospitalisation (one case). In three cases, the drug was temporarily suspended and in three cases, the drug was withdrawn. The events were all reported to have resolved in time periods ranging from 2 to 1217 days.

Four serious Increlex related cases of adenoidal hypertrophy (one mild and three moderate in intensity) were reported by three subjects. The times to onset ranged from 286 to 1368 days after the start of Increlex treatment. These events were assessed as serious as they were medically significant (two cases) or involved hospitalisation (two cases). In three cases, the drug was temporarily suspended. The events were all reported to have resolved in time periods ranging from 1 to 129 days.

Four serious Increlex related cases of constipation (all severe in intensity) were reported by one subject. The times to onset ranged from 1484 to 1641 days after the start of Increlex treatment. These events were assessed as serious as they involved hospitalisation. In one case, the drug was temporarily suspended, with no action taken in the other cases. The events were all reported to have resolved in time periods ranging from 2 to 3 days.

Two serious Increlex related cases of spinal column stenosis (one severe and one mild in intensity) were reported by two subjects. The times to onset were 1872 and 2077 days after the start of Increlex treatment. These events were assessed as serious as they were both medically significant. In one case, the drug was temporarily suspended. Both events were reported as ongoing.

Two serious Increlex related cases of convulsion (one moderate and one severe in intensity) were reported by two subjects. The times to onset were 21 and 645 days after the start of Increlex treatment. These events were assessed as serious as they both involved hospitalisation. In one case,

the drug was temporarily suspended; in the other case, the drug was withdrawn. Both events were reported to have resolved in 1 day.

Serious Increlex related cases (one each) of skin reactions, abdominal pain, encopresis, eye swelling, nasal oedema, epiphysiolysis, hypersensitivity, haematuria and drug hypersensitivity (ranging in intensity from mild to severe) were reported.

The times to onset ranged from 38 to 1641 days after the start of Increlex treatment.

These events were assessed as serious as they were medically significant (five cases), involved hospitalisation (three cases) or resulted in persistent significant disability (one case). In one case, the drug was withdrawn, in five cases, the drug was temporarily suspended and in three cases no action was taken. The events were all reported to have resolved in time periods ranging from 2 to 260 days.

Other Significant Adverse Events

Adverse Events Leading to Drug Withdrawal

In the US-IGFD Registry, 40 (3.0%) subjects in the safety follow up population experienced a total of 49 TEAEs that led to drug withdrawal.

Treatment emergent AEs leading to drug withdrawal experienced by more than one subject included hypoglycaemia (four events experienced by four (0.3%) subjects, with times to onset of between 31 and 1062 days after the start of Increlex treatment), intracranial pressure increased (four events experienced by three (0.2%) subjects, with times to onset of between 111 and 631 days after the start of Increlex treatment), hypersensitivity (three events experienced by three (0.2%) subjects, with times to onset of between 9 and 641 days after the start of Increlex treatment), benign intracranial hypertension (three events experienced by two (0.1%) subjects, with times to onset of between 43 and 196 days after the start of Increlex treatment), acromegalic facial features or facial dysmorphism: two events experienced by two (0.1%) subjects, with times to onset of 1786 and 1994 days after the start of Increlex treatment), headache (two events experienced by two (0.1%) subjects, with times to onset of 388 and 690 days after the start of Increlex treatment), injection site rash (two events experienced by two (0.1%) subjects, with times to onset of 59 and 69 days after the start of Increlex treatment) and pain in extremity (two events experienced by two (0.1%) subjects, with times to onset of 195 and 1608 days after the start of Increlex treatment).

Other Significant Nonserious Adverse Events

In the US-IGFD Registry, 179 (13.4%) subjects experienced a total of 396 significant nonserious TEAEs.

The most common significant nonserious TEAEs (reported in more than five subjects) included arthralgia (15 events experienced by 12 (0.9%) subjects), snoring (11 events experienced by 10 (0.7%) subjects), pharyngitis streptococcal (10 events experienced by 10 (0.7%) subjects), pain in extremity (nine events experienced by eight (0.6%) subjects), dizziness and abnormal hair texture (each nine events experienced by seven (0.5%) subjects) and scoliosis (six events experienced by six (0.4%) subjects).

Analysis and Discussion of Deaths, Other Serious Adverse Events and Other

Significant Adverse Events

Mortality

There were two deaths during the study. One was recorded as sudden, unexpected death, possibly related to the study drug and the other was due to progression of sickle cell disease and was not related to the study drug.

Serious Adverse Events

A total of 46 (3.4%) subjects in the safety follow up population experienced 83 serious TEAEs during the study period. The most common serious TEAEs were benign intracranial hypertension, tonsillar hypertrophy, adenoidal hypertrophy and constipation. For 10 subjects, these serious TEAEs led to treatment withdrawal. In total, 39 (47.0%) serious TEAEs reported in 24 subjects were considered related to treatment.

Other Significant Adverse Events

A total of 40 (3.0%) subjects experienced 49 TEAEs that led to drug withdrawal. The most common TEAEs leading to treatment withdrawal were hypoglycaemia, increased intracranial pressure, hypersensitivity and benign intracranial hypertension. Additionally, 179 (13.4%) subjects experienced a total of 396 significant nonserious TEAEs.

2.2.3. Discussion on clinical aspects

MAH conclusion

The US-IGFD Registry was a retrospective and prospective patient registry program sponsored by Ipsen Biopharmaceuticals, Inc. This observational registry was initiated in the US in May 2006 to monitor the long term safety and efficacy of Increlex in the treatment of children with growth failure. The US-IGFD Registry was closed on 23 May 2014.

Efficacy analyses were not performed due to the low number of patients meeting the key inclusion criteria relevant to provide meaningful efficacy results Only safety and baseline data have been presented.

This US-IGFD Registry study included 1377 patients enrolled in 114 sites (enrolled population), with the mean age at initiation of Increlex intake being 11.0±3.6 years for boys and 9.8±3.5 years for girls. Over 90% of patients had a diagnosis of either PIGFD or idiopathic short stature. Overall, 27.2% of patients had previously received growth promoting therapy.

Overall, 667 targeted TEAEs were experienced by 251 (18.7%) patients, of which 13 were serious targeted TEAEs. The most frequently reported targeted TEAEs were hypoglycaemia, headache, injection site reaction, otitis media, myalgia, tonsillar hypertrophy and injection site hypertrophy. The serious targeted TEAEs comprised tonsillar hypertrophy, hypoglycaemia, otitis media, increased intracranial pressure, headache and papilloedema. Increlex was generally well tolerated, with only 40 (3.0%) patients having to stop treatment due to AEs.

A total of 83 serious TEAEs were experienced by 46 patients during treatment with Increlex. These led to treatment interruption in 21 patients and treatment withdrawal in 10 patients. Of the serious TEAEs, 39 were recorded as being related to Increlex treatment. More than half (59.0%) of the serious TEAEs were mild or moderate in intensity and most resolved. In addition, five SAEs were reported during the post-treatment period.

Overall, 179 (13.4%) patients experienced a total of 396 significant nonserious TEAEs. The most common significant nonserious TEAEs included arthralgia, snoring, pharyngitis streptococcal, pain in extremity, dizziness, abnormal hair texture and scoliosis.

Two deaths occurred during the study; one (sudden, unexplained death) was recorded as being possibly related to study treatment.

The overall AE profile observed in this population is consistent with the known safety profile of Increlex and the known pharmacology of the drug. No new safety signals or changes in Risk Benefit were identified after review of the safety data

Rapporteur's discussion on clinical aspects

Increlex was granted the marketing authorisation under Exceptional Circumstances on 3 August 2007 for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (Primary IGFD). At the time of the granting of the initial marketing authorisation, it was not possible for the MAH to provide complete information on this medicinal product. Several post-authorisation commitments were agreed with the CHMP for data to be provided as Specific Obligations (SOs) and Post-Authorisation measures.

In order to get more safety and efficacy data SO 002 was established:

The MAH should perform one long-term safety study where mecasermin treatment is initiated in early phase of childhood and continued to adulthood in order to investigate:

- long-term toxicity in patients undergoing developmental changes
- to evaluate possible occurrence of malignancies as well as other risks

At that stage, the US-IGFD Registry was already initiated (May 2006) to monitor the long term safety and efficacy of children with growth failure treated with Increlex in the US.

To fulfil this SO and in order fulfil the regulatory requirements in EU the MAH established an EU registry (EU-IGFD) in 2007.

During the 6th annual re-assessment (2013) the MAH stated that there were no patients, neither in the EU nor in the US registry, who meet all of the previous inclusion criteria.

At the same time MAH proposed several amendments to the original SO 002 which were agreed with CHMP:

- Obligation redefined to end when 100 patients with at least 3 years' instead of 5 years' exposure to Increlex have been followed-up for 5 years since completing treatment, irrespective of final height
- Long-term follow up of patients completing Increlex treatment in EU-IGFD only.

In addition, during the 6th annual re-assessment the MAH informed EMA the decision to close the US Registry (20 MAY 2014). Partly due to this the finalisation of this SO is estimated by 2023 at the earliest.

The MAH has now submitted the results from the closed US-IGFD Registry.

Due to the low number of patients meeting the key inclusion criteria relevant to provide meaningful efficacy results these data were not analysed and only baseline and safety data are presented. However, in 71.7% of the patie

nts the primary diagnosis was primary IGF-1 deficiency. The MAH is asked to clarify the number of these 987 subjects who fulfilled the EU indication for Increlex and the possibility to get efficacy data derived from this population.

Regarding safety, no new safety concerns were found.

371 (27.7%) subjects in the safety follow up population experienced a total of 1256 TEAEs, of which 83 (experienced by 46 (3.4%) subjects) were serious TEAEs. The TEAEs in the safety follow up population are in line with the known safety profile of Increlex: hypoglycaemia was the most frequently reported TEAE (9.3%) and the other most frequent TEAEs included headache (6.7%) injection site reaction (1.9%), otitis media (1.6%), myalgia (1.5%) subjects), tonsillar hypertrophy (1.3%) and injection site hypertrophy (1.2%). These AEs are all also targeted AEs associated with the use of Increlex and mentioned in the Increlex-SPC.

The related serious TEAEs included six cases of benign intracranial hypertension, four cases of adenoidal hypertrophy, four cases of constipation, two cases of spinal column stenosis, two cases of convulsion. These serious TEAEs are also associated with the known safety profile of Increlex and mentioned in the Increlex-SPC (all expect constipation, however this AE is considered to be covered with AE ”abdominal pain”) .

Two deaths were recorded during the study, both during follow up. The first subject experienced sudden unexpected death, recorded as possibly related to study drug. It seems that autopsy has been performed but the outcome of it has not been reported by the MAH. The MAH is asked to provide further clarification of the reason behind this death since at the moment it is not possible to exclude whether this death is related to use of the study drug or not. The other death was due to progression of sickle cell disease and thus unrelated to study drug.

In general, there were no new, unexpected TEAEs.

3. Rapporteur’s overall conclusion and recommendation

Overall conclusion

The MAH has submitted the current MS305 study to EMA in accordance with the Article 46 of the Regulation (EC) No 1901/2006, as amended. The study was carried out as a stand-alone study and provided long-term safety information from the US-IGFD-registry. Unfortunately, long-term efficacy data were not analysed and therefore not presented for evaluation. Since this US-IGFD-registry has been closed the data presented is the final data from this registry.

Children were treated with Increlex prescribed by a qualified physician according to the individual need of a patient.

The safety profile of Increlex in this study is in line with previous experience with Increlex and in line with Increlex SPC.

This study does not have any impact on the benefit-risk balance of Increlex in its current approved EU-indication. Thus, the benefit-risk balance of Increlex remains positive.

Recommendation

☐ **Fulfilled:**

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional clarifications related both efficacy and safety aspects of the study 305 as part of this procedure. (see section IV "Additional clarifications requested")

Additional clarifications requested

1. Due to the low number of patients meeting the key inclusion criteria relevant to provide meaningful efficacy results these closure, efficacy data were not analysed and only baseline and safety data are presented. However, in 71.7% of the patients the primary diagnosis was primary IGF-1 deficiency. The MAH is asked to clarify the number of these 987 subjects who fulfilled the EU indication for Increlex and the possibility to get efficacy data derived from this population.
2. Two deaths were recorded during the study, both during follow up. The first subject experienced sudden unexpected death, recorded as possibly related to study drug. It seems that autopsy has been performed but the outcome of it has not been reported by the MAH. The MAH is asked to provide further clarification of the reason behind this death since at the moment it is not possible to exclude whether this death is related to use of the study drug or not.

MAH`s reply to the additional clarifications:

Question 1 - Summary of the MAH's response

Efficacy analysis in patients enrolled in study W-TG-52800-010/MS305 was not provided primarily because of the low number of patients meeting the key inclusion criteria relevant to provide meaningful efficacy data. The low number of patients was related to 2 main factors: the first one is related to problems with the informed consent procedure and the second one is related to the very small number of subjects treated in accordance with the US labelled indication*. It should be noted that the US labelled indication is more restricted but very similar to the EU label**. In the EU label, the threshold of IGF-1 is -2SDS (equivalent to 2.5 percentile) instead of -3SDS for US label.

In study W-TG-52800-010/MS305, 987 patients have been enrolled with the primary diagnostic of primary IGF-1 deficiency.

As requested in the Rapporteur's Preliminary Assessment Report (PAR), the MAH has clarified the status of these 987 patients by selecting patients potentially eligible for efficacy analysis with the following criteria: patients who fulfilled the EU indication for Increlex and had signed off the informed consent. To be in line with the efficacy results of EU-IGF registry (study 2-79-52800-002), the subgroup of naïve pre-pubertal patients was also selected among the 987 patients. This subgroup is of particular interest for efficacy to have unbiased efficacy data (assessment of height could be biased on patients who started puberty and who were previously treated for short stature).

The results of the research were as follows:

- Over 987 patients, only 70 patients responded to selection criteria at baseline (patients fulfilling the EU indication for Increlex and with a signed off informed consent), including 39 patients naïve pre pubertal. At one and two year, the number of evaluable patients were 56 and 38 patients respectively (33 and 22 for naïve pre-pubertal) as shown in table below.

Follow-up	Overall (N=70)	Naive pre-pubertal (N=39)
Baseline	**70**	**39**
6 months	54	30
12 months	**56**	**33**
18 months	50	28
24 months	**38**	**22**
30 months	31	18
36 months	24	13
42 months	18	10
48 months	14	7

- Among the 917 patients non eligible for efficacy analysis,
  - 451 (49%) had not signed the informed consent,
  - 895 (98%) did not fullfill EU Increlex Label:

    - Some of them presented only primary IGF1 deficiency and not severe primary IGFD (with height ≤ -3SDS and IGF1 < 2,5 percentile): 576 patients were not compliant with height SDS (<-3 SDS, n=521) and/or with IGF-1 SDS (<-2 SDS,n=275). Only few patients (41) had GH deficiency.

    - For some other patients the data to classify the patients were missing: 319 patients have at least one missing data (mainly missing data on GH stimulation test to identify GH sufficiency). The efficacy analysis in the EU IGF-1 registry (last report submitted in November 2013) was performed in a patient sample of 172 subjects (registry population) including 96 naïve pre pubertal patients. Efficacy data at year 1 and 2 were presented for 138 and 88 patients respectively (62 and 36 naive prepubertal).

Taking into account the number of patients in the analysis previously performed in the EU IGF-1 registry overall (172, 138, 88) and in naïve pre-pubertal patients (96, 62, 36), the MAH estimates that the sample size of patients eligible for efficacy analysis in study W-TG-52800-010/MS305 overall (70, 56, 38) and in naïve pre pubertal (39, 33, 22) is too small to provide relevant effectiveness conclusions.

*: US Increlex indication: long-term treatment of growth failure in children with severe primary IGF-I deficiency, defined as height and IGF-I SDS ≤ - 3, with normal/elevated GH or with GH gene deletion who have developed neutralizing antibodies to GH

**: EU Increlex indication: severe primary IGF-I deficiency, defined as a height SDS ≤ -3 and basal IGF-I concentrations < 2.5th percentile, with GH sufficiency and exclusion of secondary forms of IGF-I deficiency

Assessment of the MAH's response

The MAH has provided the efficacy analysis in patients enrolled in study MS305. Only 70 patients responded to selection criteria at baseline (patients fulfilling the EU indication for Increlex and with a signed off informed consent), including 39 patients naïve pre pubertal.

The main reason for such a low number of patients (70/987) that fulfilled the selection criteria is the fact that patients who did not have signed informed consent were excluded. This is still considered unfortunate. Therefore the "real" number of patients who fulfilled the selection criteria remains unclear. The MAH has previously stated that it is not possible to get missing informed consents any longer afterwards. If this is the case, it is not possible to draw any meaningful efficacy conclusions from this US-registry-study.

The MAH concludes that the sample size of patients eligible for efficacy analysis in study /MS305 overall (70, 56, 38) and in naïve pre pubertal (39, 33, 22) is too small to provide relevant effectiveness conclusions. Because of the above mentioned reasons this reasoning is acceptable, although with some hesitance and caution.

Conclusion

Point is solved.

Question 2 - Summary of the MAH's response

A complete case narrative for subject 1219-1162 is provided in Section 14 of the Clinical Study Report (pages 384 – 386). The narrative is provided below, with additional information obtained from review of the subject line listings and final amended autopsy report. In addition, the dosing regime has been tabulated for clarity.

The final amended autopsy report states the immediate cause of death as 'Sudden unexpected death', with other significant conditions 'IGF-1 deficiency and complications'. No specific anatomical, microscopic or toxicological abnormalities sufficient to explain death were found at autopsy.

SUBJECT US 1219-1162: Spinal column stenosis, Sudden death

This 20 year old male subject with PIGFD was enrolled in the US-IGFD Registry on 10 Oct 2006, at age 15 years old. The patient's birth weight was 4.08 kg, and birth length was 44.5 cm. Baseline height was 106.1 cm, with SDS -6.34; baseline BMI was 17.14, with SDS -1.23. Genetic testing confirmed Laron dwarfism.

The subject's medical history included a familial risk factor of Laron syndrome, insulin dependent diabetes and hypoglycaemic episodes. The subject was not taking any concomitant medications at enrolment, but was taking 'agents to block puberty' at the follow-up visits (12 Jan 2007 through 30 Mar 2011).

On 01 Nov 2006, the subject started treatment with Increlex at a dose of 120 mcg/kg BID administered via a subcutaneous route, for the indication of severe IGF-1 deficiency associated with Laron syndrome.

The following dosing regimen was received by the subject:

Dosing Dates	Increlex Dose received
20 Mar 2007 to 04 Jun 2007	121 mcg/kg, BID
05 Jun 2007 to 30 Aug 2007	123 mcg/kg, BID
31 Aug 2007	Dose reduced to 120 mcg/kg BID due to weight changes
29 Nov 2007 to 25 Feb 2008	150 mcg/kg, BID
26 Feb 2008 to 26 May 2008	180 mcg/kg, BID
27 May 2008	Dose was reduced to 165 mcg/kg, BID due to lab results and 'comfort' with the dose level
05 Sep 2008 to 09 Mar 2009	168 mcg/kg, BID
10 Mar 2009 to 25 May 2009	183 mcg/kg, BID
26 May 2009	Dose was reduced to 173 mcg/kg, BID due to 'comfort' with the dose level.
25 Aug 2009 to 26 Apr 2010	185 mcg/kg, BID
27 Apr 2010	Dose was reduced to 170 mcg/kg BID due to weight changes
12 Oct 2010	Dose was reduced to 167 mcg/kg BID due to weight changes
04 Jan 2011 to 19 Sep 2011	181 mcg/kg, BID
20 Sep 2011 to 16 Jan 2012	206 mcg/kg, BID

On 12 Jan 2007 and 20 Mar 2007, the patient experienced non-serious adverse events hypoglycaemia and headache (both events on each date).

On 05 Jun 2007, the patient experienced non-serious adverse event hypoglycaemia.

On 12 Oct 2010, the patient experienced non-serious adverse event injection site reaction.

On 20 Sep 2011, the patient experienced non-serious adverse events headache and injection site reaction.

On 28 Nov 2011, the subject underwent a tonsillectomy due to airway obstruction associated with snoring. Following surgery the subject was required to use a positive pressure mask. It was reported that the subject skipped two doses of Increlex as he was not eating. The reporter assessed this as possibly related to Increlex as lymphoid hyperplasia has been reported with Increlex use.

On 17 Jan 2012, the Increlex dose was increased to 218 mcg/kg BID. From 08 Mar 2012 to 13 Jun 2012, the subject received 11 mg Increlex BID.

On 08 Mar 2012, the patient experienced non-serious adverse event headache.

On 14 Jun 2012, the subject developed hypoglycaemia after injecting himself at 7 am without eating a full breakfast. The subject became confused and had a headache. The subject received treatment with intravenous glucose in response to the event. Following treatment, the subject went home and rested and the symptoms resolved.

On 14 Jun 2012, the dose of Increlex was increased to 12 mg, BID.

On 09 Jul 2012, the subject underwent a lumbar MRI and was diagnosed with asymptomatic spinal stenosis. The physician did not provide any cause of spinal stenosis. However, stated that spinal stenosis has been reported in subjects with Laron syndrome. No corrective treatment was reported.

On 02 Aug 2012, the subject took his latest dose of Increlex at 9 pm and it was reported that he ate a normal meal, but later than the usual time. On 03 Aug 2012, at 5:30 am, the subject's room mate found the subject unresponsive and purple. The paramedics and police were called and cardiopulmonary resuscitation was performed, however, the subject could not be revived.

The autopsy examination was inconclusive in regards to the immediate cause of death. The post mortem vitreous glucose level was noted to be 10 mg/dL. The subject's underlying history of IGF-1 deficiency and any associated complications may have contributed as well to the fatal outcome. No evidence of injury, intoxication, infection or other pathological process was found. The final amended autopsy report states the immediate cause of death as 'Sudden unexpected death', with other significant conditions 'IGF-1 deficiency and complications'. No specific anatomical, microscopic or toxicological abnormalities sufficient to explain death were found at autopsy.

The reporting physician considered the event 'sudden unexpected death' as severe.

The reporting physician considered the events spinal stenosis, hypoglycaemia and airways obstruction associated with snoring to be related and the event sudden unexpected death to be possibly related to Increlex.

The events of sudden unexpected death, airway obstruction associated with snoring and hypoglycaemia were assessed by Ipsen as related to therapy with Increlex. The company commented that the autopsy examination was inconclusive with regards to the immediate cause of death. The post mortem vitreous glucose level was noted to be 10 mg/dL. The subject's underlying history of IGF-1 deficiency and associated complications may have contributed to the fatal outcome. Since hypoglycaemia is listed, a causal relationship could not be absolutely excluded. Snoring with associated airway obstruction is listed. The event of spinal stenosis was assessed by Ipsen as not related to therapy with Increlex. The company commented that this condition is seen in people suffering from Laron syndrome.

Assessment of the MAH's response

The MAH has provided final amended autopsy report as requested by the CHMP. In addition, the MAH has also provided updated case narrative for subject 1219-1162.

The MAH concludes that the autopsy examination was inconclusive with regards to the immediate cause of death and since hypoglycaemia is listed, a causal relationship could not be absolutely excluded.

MAH`s reasoning is acceptable. Although sudden unexpected death is always considered severe serious event, the inconclusive result of the autopsy does not confirm nor exclude the possible relationship of this death to use of the study drug.

Conclusion

Point is solved.

Rapporteur's updated overall conclusion

This study has no impact on the benefit-risk balance of Increlex in its current approved EU-indication. Thus, the benefit-risk balance of Increlex remains positive.

Recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**