HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 June 2011

INCRELEX 10 mg/ml, solution for injection
B/1 vial of 4 ml (CIP code: 381 467-7)

Applicant: IPSEN PHARMA

Mecasermin
ATC code: H01AC03 (somatropin and somatropin agonists)

List I
Medicine for hospital prescription restricted to specialists in paediatrics or in endocrinology and metabolic diseases.
Medicine requiring special monitoring during treatment.
Orphan medicinal product.

Date of Marketing Authorisation: 13/08/2007
Centralised European Marketing Authorisation in exceptional circumstances (the SPC states that the EMA will review any new information which may become available every year and this SPC will be updated as necessary).

Reason for examination: Re-assessment in view of new data available in accordance with the request of the transparency Committee mentioned in the opinion on inclusion dated 05/12/2007.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Mecasermin

1.2. Background
First recombinant IGF-1.
Mecasermin is a recombinant DNA-derived human insulin-like growth factor-1 (IGF-1) produced in *Escherichia coli*.

1.3. Indication
"For the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (primary IGFD).

Severe primary IGFD is defined by:
• height standard deviation score (SDS) ≤ - 3.0 and
• basal IGF-1 levels below the 2.5th percentile for age and gender, and
• GH sufficiency, and
• exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

Severe primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signalling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. It is recommended to confirm the diagnosis by conducting an IGF-1 generation test."

1.4. Dosage
"Treatment with INCRELEX should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders.
The dosage should be individualised for each patient. The recommended starting dose of mecasermin is 0.04 mg/kg twice daily by subcutaneous injection. If no significant treatment-related adverse events occur for at least one week, the dose may be raised in increments of 0.04 mg/kg to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with severe primary IGFD.
If the recommended dose is not tolerated by the subject, treatment with a lower dosage can be considered. Treatment success should be evaluated based on height velocities. The lowest dosage that was associated with substantial growth increases on an individual basis was 0.04 mg/kg BID.
INCRELEX should be administered shortly before or after a meal or snack. If hypoglycaemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. If the patient is unable to eat, for any reason, INCRELEX should be withheld. The dose of INCRELEX should never be increased to make up for one or more omitted doses.
Injection sites should be rotated to a different site with each injection.
INCRELEX should be administered using sterile disposable syringes and injection needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.
INCRELEX is not recommended for use in children below age 2 years due to a lack of data on safety and efficacy."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification

H	Systemic hormonal preparations, excluding sex hormones and insulins
H01	Pituitary and hypothalamic hormones and analogues
H01A	Anterior pituitary lobe hormones and analogues
H01AC	Somatotropin and somatropin agonists
H01AC03	Mecasermin

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

There is no other medicinal product which is indicated in the management of severe primary IGF-1 deficiencies (primary IGFD).

3. REMINDER OF THE CONCLUSIONS OF PREVIOUS ASSESSMENTS

Opinion on inclusion of 5 December 2007

AB: The actual benefit of this proprietary medicinal product is substantial.

IAB: INCRELEX provides a moderate improvement in actual benefit (IAB III) in the management of children and adolescents (age 2 to 16 years) with growth failure due to a severe primary IGF-1 deficiency (primary IGFD).

4. ANALYSIS OF AVAILABLE DATA

In its opinion of 5 December 2007, the Committee stated that it wished to reassess this proprietary medicinal product every year in the light of the new data available. Data were first deposited in September 2009; the new data provided by the company were too fragmentary to allow this proprietary medicinal product to be reassessed. The company was then asked to submit all the data available.

4.1. Reminder of the data available on inclusion (5 December 2007)

"The efficacy and safety data for INCRELEX, in the treatment of growth failure in children and adolescents with primary IGFD, are taken from a double-blind study (F0375g), three open studies (F0206s, F0671g and F0632g) and a follow-up study (1419).

The results of these studies show that there is an improvement in the annual growth rate. The relevance of these results is difficult to assess in view of the "open" nature of three of these studies, the small number of patients included and a size of effect which differs from one study to another.

The open-label follow-up study in 75 patients (treated with doses of 100 to 120 µg/kg 2x/day) most of whom were included in the earlier studies shows a mean growth rate of 8 cm/year after the first year of treatment and 5 cm/year during years 2 to 8. This study is still in progress. Interim results observed after 8 years of treatment are available for only 14

patients. The impact of INCRELEX on the height reached in adulthood is known for only six patients (164.4 cm, 150.2 cm, 112 cm, 142 cm, 121.2 cm and 120.8 cm).

In these studies, the patients had, before treatment, a slow growth rate (rate of -3.3 SD ± 1.7) and a mean height of -6.7 ± 1.8 SDS, with a failure more severe than that defined by the indications of the marketing authorisation (height ≤ -3SD).

The main adverse effects are hypoglycaemia (47%), injection site hypertrophy (32%), tonsillar hypertrophy (16%) and ear and labyrinth disorders. In the absence of any sound data on the potential development of anti-IGF-1 antibodies, there is still some doubt about the longer-term maintenance of efficacy."

4.2. Analysis of the new data available

4.2.1. Study 1419 (see Table 1 in the appendix)

This follow-up study is still in progress. Since 2007, 16 new treatment-naïve patients have been included, taking the total number of patients included to 91. After an additional two years of follow-up, the adult height is known for 23 of these 91 patients:

- The adult height reached by 13 patients with an IGF-1 deficiency with a variable height deficit was: 164.4 cm (SDS -1.5), 152.1 cm (SDS -1.7), 112 cm (SDS -7.8), 124.7 cm (SDS -6.5), 136.6 cm (SDS -4.1), 137.6 cm (SDS -3.8), 146.4 cm (SDS -4.1), 137.6 cm (SDS -3.9), 124 cm (SDS -6.7), 153 cm (SDS -2.9), 162.5 cm (SDS -2), 139 cm (SDS -4.9), 140.9 cm (SDS -4.8).
  On inclusion, the mean age of these patients was 6.3 years [2; 15.2] (eight patients ≤ 5 years, three patients about 9 years and two patients 15 years). The mean SDS for the height on inclusion was – 6.3 cm [-12.1; -3.4].
  In these 13 patients the mean adult height reached was 140.8 cm [112; 164.4], i.e. a mean SDS of -4.2 [-7.8; -1.5] (descriptive analysis).

- The adult height reached by five patients with deletion of the gene coding for GH (outside Marketing Authorisation) was: 142 cm (SDS -4.8), 121.2 cm (SDS -6.3), 120.8 cm (-6.4), 114.4 cm (SDS -8.5) and 128.8 cm (SDS -5.2).

- The adult height of five patients who had been treated with another IGF-1 (IGF-1 Pharmacia) before inclusion in study 1419 is not available.

Additional information about the duration of treatment, the initial height in cm and in SDS and the annual height velocity is given in Table 1 in the appendix.

As regards the other 68/91 patients, 58 left the study before reaching adult height for the following reasons: poor compliance (n = 4), lost to follow-up (n = 31), poor growth (n = 1), parental decision (n = 2), impossibility of administering the drug (n = 6), change of treatment for another marketed medicine (n = 14).[1] In total, **only 10/91 patients continue to be followed up** in this study as at 30 June 2010.

As regards the 31 lost to follow-up, after repeated requests by the Transparency Committee the company supplied the latest height data available[2] (see Table 3 in the appendix). Of these, 27 reached heights of ≤ -3 SDS of which 21 were <-5 SDS. Only one patient reached a height of >- 2 SDS.

1 The Transparency Committee is surprised to find that in this very rare disease, 1/3 of patients were lost to follow-up and that, despite the orphan drug status, patients were able to receive "another marketed treatment".

2 The heights given in the table correspond to the latest heights available for the patients; not all of them had reached adult height.

The data on the subgroup of 17 patients with primary IGFD and a height between -3 and -5 SDS are given in Table 4 (see appendix): 7 patients had a height of between -3 and -4 SDS and only 10 had a height of ≤- 4SDS. Of these 10 patients with a height of ≤ -4 SDS, the height reached was:

- > -3 SDS in 5/10 patients.
- between -3 and -4 SDS in 3/10 patients,
- <-4 SDS in 2/10 patients.

In these patients, the response was strongly age-related; a link between young age at the start of treatment and a favourable response seems to have been demonstrated.

4.2.2. Studies MS 301 and MS 308

The company reported two studies performed in pre-pubescent children with non-severe primary IGF-1 deficiency (height ≤ - 2SDS); since these patients do not correspond to the indication validated by the MA for INCRELEX (severe IGF-1 deficiency defined in the MA[3] by an SDS of ≤ -3), the results of these studies will not be presented in this Opinion.

4.2.3. Observational studies

American study MS 305: "INCRELEX Growth Forum database – IGFD Registry: a patient registry for monitoring long-term tolerance and efficacy of INCRELEX".

The aim of this open-label phase IV follow-up study conducted in the USA was to assess the efficacy and tolerance of INCRELEX in children and adolescents with severe IGF-1 deficiency or growth failure with deletion of the GH gene and anti-GH antibodies (indication not validated in France).

On 31 July 2008, 461 patients were included and an interim report on tolerance was prepared in December 2008 on the basis of the available data. A total of 365 patients were included in this interim analysis.

Before treatment, patients' mean age was 11 years, the mean height –2.5 SDS, the mean IGF 1 –1.8 SDS and 80% of patients had an IGF-1 deficiency.

In the patients analysed, the most common adverse events were hypoglycaemia (6.8%) and headaches (4.7%); these events are in accordance with those described in the SPC. A severe adverse event (major depression) was reported in a 15-year-old patient two months after starting treatment.

No efficacy data are available for this interim report; the first patients in this study should reach a height close to their adult height in 2016.

European observational study: "European INCRELEX Growth Forum database – A European subject registry long-term tolerance and efficacy monitoring of INCRELEX. EU-IGFD". (see Table 2 in the appendix)

The aim of this open-label follow-up study was to assess the efficacy and tolerance of INCRELEX in European children and adolescents.

The data collected in this registry are as follows:

- characteristics of the patients treated with INCRELEX,
- doses of INCRELEX at the start of treatment and their progression,
- the efficacy of INCRELEX assessed mainly using the following parameters: height, weight, age at puberty, final adult height,
- concomitant treatments administered,
- serious adverse events including all types of cancer,
- all types of adverse events linked to treatment,
- all abnormalities in laboratory tests.

3 Very severe deficiencies are defined by SDS for height of ≤ -6.

Two secondary analyses were added by amendments in January 2008 and February 2009:
- impact of treatment with INCRELEX on quality of life (in France only),
- record of predicted adult height and the height actually reached.

This study was started in 2009; only an estimated 19/42 patients treated with INCRELEX in France were included in this registry on 31 October 2010 (the interim data for these patients are presented for information purposes in Table 2 in the appendix).

4.2.4. Tolerance data

According to the SPC, the tolerance data collected in clinical studies cover 76 patients with severe primary IGFD and treated for a mean duration of 4.4 years, i.e. 321 patient-years.

The commonest adverse events (> 10%) are:
- hypoglycaemia (n = 36, 47%) including four convulsions,
- tonsillar hypertrophy (n = 12, 16%),
- snoring (n = 17, 22%),
- hypoacusis (n = 15, 20%),
- headache (n = 14, 18%)
- injection site hypertrophy (n = 24, 32%),
- thymus hypertrophy.

The company has supplied recent tolerance data.[4]
In the periodic safety update report (PSUR) for the period from 01/09/2008 to 28/02/2009, four serious adverse effects were reported: vitreous haemorrhage, hypoglycaemia, hypoglycaemic shock and headache and 40 unexpected non-serious effects were observed. These data did not give reason to call into question the tolerance profile of INCRELEX.

In the periodic safety update report (PSUR) for the period from 01/03/2009 to 31/08/2009, 75 serious and/or unexpected adverse effects were observed: This PSUR contained a cumulative analysis of the systemic and local hypersensitivity reactions; taking into account the data from this PSUR, the SPC for INCRELEX was updated (section 4.4 and 4.8) by including the systemic hypersensitivity events and the local allergic reactions.

3.2. Conclusions

In the opinion on the inclusion of INCRELEX of 5 December 2007, the efficacy and tolerance data in the treatment of growth failure in children and adolescents with primary IGFD are taken from a double-blind study (F0375g), three open-label studies (F0206s, F0671g and F0632g) and a follow-up study (1419).

The results of these studies showed an improvement in annual growth rate with very variable impacts on final heights. The relevance of these results is difficult to assess in view of the "open" nature of three of these studies, the small number of patients included and a size of effect which differs from one study to another.

The follow-up study (1419) is still in progress. Since 2007, 16 new treatment-naïve patients have been included, taking the total number of patients included to 91. After an additional two years of follow-up, the adult height is known for 23/91 of the patients included:
- 13 patients with an IGF-1 deficiency with a variable growth failure of between -1.5 and -6.7 SDS): on inclusion, the mean age of these patients was 6.3 years [2; 15.2] (eight patients ≤ 5 years, three patients about 9 years and two patients 15 years). In these 13 patients the mean adult height reached was 140.8 cm [112; 164.4], i.e. a mean SDS of -4.2 [-7.8; -1.5] (descriptive analysis).

4 Two PSURs covering the period from 01/09/2008 to 31/08/2009

- Five patients with deletion of the gene coding for GH (outside the MA): 142 cm (SDS -4.8), 121.2 cm (SDS -6.3), 120.8 cm (SDS -6.4), 114.4 cm (SDS -8.5) and 128.8 cm (SDS -5.2).
- Five patients who had been treated with another IGF-1-based proprietary medicinal product before inclusion in study 1419 for whom no data are available.

Out of the other 68/91 patients, 58 left the study before reaching adult height for the following reasons: poor compliance (n = 4), lost to follow-up (n = 31), poor growth (n = 1), parental decision (n = 2), impossibility of administering the drug (n = 6), change of treatment for another marketed medicine (n = 14). In total, only 10/91 patients continue to be followed up in this study on 30 June 2010.
As regards the 31 lost to follow-up, after repeated requests by the Transparency Committee the company supplied the latest height data available[5] (see Table 3 in the appendix). Of these, 27 reached heights of ≤ -3 SDS of which 21 were <-5 SDS. Only one patient reached a height of >- 2 SDS.

In study 1419, the data on the subgroup of 17 patients with primary IGFD and a height of between -3 and -5 SDS are given in Table 4 (see appendix): seven patients had a height of between -3 and -4 SDS and only 10 had a height of ≤- 4SDS. Of these 10 patients with a height of ≤ -4 SDS, the height reached was:

- > -3 SDS in 5/10 patients.
- between -3 and -4 SDS in 3/10 patients,
- <-4 SDS in 2/10 patients.

In these patients, the response was strongly age-related; a link between young age at the start of treatment and a favourable response seems to have been demonstrated.

In all these studies, the patients had a mean growth failure before treatment (height -6.7 ±1.8 SDS) which was more severe than that defined by the indications of the MA (height ≤ -3 SDS) and a slow growth rate (rate of -3.3 cm/year ±1,7 SDS).

The main adverse effects are hypoglycaemia (47%), injection site hypertrophy (32%), tonsillar hypertrophy (16%) and ear and labyrinth disorders. Systemic hypersensitivity manifestations and local allergic reactions have also been described since market launch.

The data on the potential development of anti-IGF-1 antibodies are limited.
The maintenance of efficacy in the long term is still uncertain.

The assessment of INCRELEX by the Transparency Committee was hindered by the lack of information about adult height for all the patients treated; this was not justified since these patients have a very rare disease which by definition requires close monitoring. Moreover, the Committee stresses the time it took to obtain the latest height data available or the adult heights for all the patients treated with INCRELEX during these studies (in particular patients who changed to another treatment and those lost to follow-up in study 1419, etc.) which had not been supplied initially.

5 The heights given in the table correspond to the latest heights available for the patients; not all of them had reached adult height.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Re-assessment of the actual benefit

Growth failure with a severe deficiency of IGF-1 is a rare and serious disease progressing to disability and a marked deterioration in quality of life.

This medicinal product is intended as replacement therapy.

This medicinal product is a first-line therapy

There is no alternative drug therapy.

In all the studies supplied by the company, patients had a growth velocity of -3.3 SD ±1.7 and a very severe mean growth failure before treatment of -6.7 ±1.8 SDS. On the basis of the available data, the efficacy/tolerance ratio of this medicinal product is substantial in children and adolescents with a severe primary deficiency in IGF-1 defined by very severe growth retardation ((SDS) for height ≥ - 4.0) for age and gender, normal or elevated GH levels.

In patients with less severe growth retardation (-3 < SDS for height < -4), on the basis of the available data, the efficacy/adverse effect ratio for this medicinal product in these patients is low.

Public health benefit:

Growth failure with a severe primary IGF-1 deficiency is a serious clinical situation and a source of impaired quality of life with a psychosocial impact but a low public health burden because of its rarity.

Since the emergence of orphan medicinal products is regarded as an identified priority (GTNDO*****, Rare Diseases Plan), the treatment of this disorder is a public health need.

In view of the data available and taking account in particular of the inadequate quality of the effect demonstrated for INCRELEX on final height (adult height data available for only 17 patients) and the absence of data on these subjects' quality of life, the expected impact of this medicinal product in terms of morbidity and quality of life by comparison with the usual treatment is not quantifiable. That impact would at best be weak.

In addition, given the uncertainty about long-term *tolerance* and compliance with this INCRELEX treatment, the applicability of the results of the studies to clinical practice is not assured.

Consequently, it is not anticipated that there will be any public health benefit from INCRELEX in this indication.

*National Technical Group for the Definition of Objectives (DGS- 2003).

The actual benefit of this medicinal product:

- **remains substantial** in children and adolescents with a severe primary IGF-1 deficiency defined by very severe growth retardation (standard deviation (SDS) for height ≤ - 4.0) for age and gender, normal or elevated GH levels.
- **is low** in patients with less severe growth retardation (-4 < SDS for height < -3), given the small amount of data available and the uncertainty of the effect.

5.2. Re-assessment of the improvement in actual benefit

The small number of patients included and followed up in these studies and the variable size of the effect observed from one study to another make it difficult to interpret the results. In addition, the lack of information about a large number of the patients treated with INCRELEX (patients changing to other treatments, those lost to follow-up, etc.) is not acceptable since these patients are suffering from a very rare disease which by definition requires careful monitoring.

Consequently, the Transparency Committee does not think that INCRELEX provides any improvement in actual benefit (IAB V) in the management of these patients.

5.3. Therapeutic use [6,7]

Growth failure with a severe primary IGF-1deficiency (primary IGFD) is characterised by a IGF-1 deficiency combined with normal production of endogenous GH. Patients are characterised by reduced growth rate from childhood, the absence of a pubertal growth spurt and severe dwarfism in adulthood.

Severe primary IGF-1 deficiency covers genetic abnormalities not all of which have been documented. The severity and presence of each of the clinical symptoms and characteristics vary from one individual to another and it is difficult to make a link between patients' phenotype and genotype.

One of the forms of this deficiency is Laron syndrome, an autosomal recessive disorder characterised by severe dwarfism, dysfunction of the growth hormone receptors, an inability to produce IGF-1 in response to growth hormone and normal or elevated levels of growth hormone.

Laron syndrome results from a mutation of the GHR gene on chromosome 5.

These patients have no growth hormone deficiency and no satisfactory response to treatment with exogenous growth hormone is to be expected. It is recommended to confirm the diagnosis by carrying out a standardised IGF-1 generation test with growth hormone; molecular analysis of abnormalities in the GHR and GH1 genes is also recommended before initiating treatment with INCRELEX.

No treatment is currently available. INCRELEX is one option for recombinant substitution treatment for the management of these children and adolescents (2 to 16 years).

6 Orphanet – September 2002.

7 Woods KA, Dastot F, Preece MA, Clark AJ, Postel-Vinay MC, Chatelain PG, et al. Phenotype: genotype relationships in growth hormone insensitivity syndrome. J Clin Endocrinol Metab 1997; 82(11): 3529-35.

5.4. Target population[8]

The target population for INCRELEX corresponds to children and adolescents (age 2 to 16 years) with growth failure due to a severe primary IGF-1 deficiency (primary IGFD) when it is characterised by a combination:

- of height ≤ -3 SDS for age and gender,
- of a normal GH level (absence of deficiency response to the GH secretion test)
- and the exclusion of secondary forms of IGF-1 deficiency, linked for example to malnutrition, hypothyroidism, or chronic treatment with glucocorticoids in an antiinflammatory dose.

Given the very limited nature of the available epidemiological data, the target population for INCRELEX cannot be established with any real certainty. Nevertheless, the sparse data available and experts' opinions mean that the target population for INCRELEX can be estimated at about twenty patients.

5.5. Transparency Committee recommendations

The transparency Committee recommends maintaining inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication in the Marketing Authorisation.
However, the transparency Committee draws the attention of the CEPS to the inadequacy of the data provided by the company as regards updating.

5.5.1. Exceptional medicinal product:
The transparency Committee would like this product to keep its status as an exceptional medicinal product.

5.5.2. Packaging: Appropriate for the prescription conditions

5.5.3. Reimbursement rate: 100%

The Committee wishes to be informed of any new data on this medicinal product and particularly of the final results of study 1419 and the results of the European observational study.

8 Bryant et al. "Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation. Health technology assessment" NHS R&D HTA Programme 2002.

Table 1: Height close to adult height in naïve patients who had completed their treatment (n=18) and comparison with historical data

Patient	**10-901**	**18-004***	**18-010***	**10-908***	**10-909**	**10-928**	**10-950***	**18-006**	**18-011**	**10-915**	**10-906***	**18-012***	**18-003***	***18-013****	***10-904***	***10-905***	***18-008***	***18-009***
Disorder	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	*GHGD*	*GHGD*	*GHGD*	*GHGD*	*GHGD*
Gender	M	F	F	M	F	F	M	F	M	M	M	M	M	*M*	*F*	*F*	*M*	*F*
Age at start of treatment (years)	9.6	5.0	15.2	2.3	3.1	9.1	15.2	2.0	4.2	9.8	2.6	2.3	1.7	*13.0*	*8.2*	*8.2*	*9.9*	*2.6*
Duration of treatment (years)	7.7	12.5	5.4	15.1	13.4	6.3	3.6	14.3	13.5	7.1	16.9	15.5	16.9	*8.4*	*6.6*	*6.6*	*10.7*	*13.2*
Chronological age at adult height (years)	17.4	17.5	20.6	17.4	16.5	15.4	18.8**	16.4	17.7	17.0	19.5	17.9	18.6	*21.4*	*14.8*	*14.8*	*20.6*	*15.8*
Bone age (at adult height)	15.6	17.0	15.0	17.0	15.0	14.9	17.0	15.8	18.0	17.3	16.0	16.5	18.0	*17.0*	*14.5*	*13.5*	*17.0*	*15.3*
Height before treatment (cm)	111.2	92.7	86.1	64.0	69.3	102.7	133.1	61.3	70.2	107.8	69.9	69.1	65.1	*99.4*	*85.1*	*92.7*	*80.9*	*68.2*
Adult height measured (cm)	164.4	152.1	112.0	124.7	136.6	137.6	146.4	137.6	124.0	153.0	162.5	139.0	140.9	*142.0*	*121.2*	*120.8*	*114.4*	*128.8*
Change in height measured DURING TREATMENT (cm)	53.2	59.4	25.9	60.7	67.3	34.9	13.3	76.3	53.8	45.2	92.6	69.8	75.8	*42.6*	*36.1*	*28.1*	*33.5*	*60.7*
Estimated change in height (cm) for age and gender WITHOUT TREATMENT[i]	30	44	3	54	52	24	11	56	48	28	57	55	60	*24*	*25*	*25*	*34*	*53*
Difference (cm) between the change in height observed with treatment and that estimated without treatment[ii]	23	15	23	7	16	11	2	20	6	17	36	15	16	*19*	*11*	*3*	*0*	*7*
Initial height (SDS)	-4.2	-3.4	-12.1	-7.7	-6.9	-5.5	-4.2	-6.9	-7.9	-4.9	-6.6	-5.9	-6.1	*-7.5*	*-9.1*	*-7.2*	*-9.9*	*-6.1*

Patient	**10-901**	**18-004***	**18-010***	**10-908***	**10-909**	**10-928**	**10-950***	**18-006**	**18-011**	**10-915**	**10-906***	**18-012***	**18-003***	***18-013****	***10-904***	***10-905***	***18-008***	***18-009***
Last height measured (SDS)	-1.5	-1.7	-7.8	-6.5	-4.1	-3.8	-4.1	-3.9	-6.7	-2.9	-2.0	-4.9	-4.8	*-4.8*	*-6.3*	*-6.4*	*-8.5*	*-5.2*
Growth velocity (cm/year)																		
Year 1	10.3	7.4	7.9	9.5	9.4	10.5	7.8	12.8	3.8	7.6	8.8	5.4	5.8	*8.4*	*8.8*	*5.8*	*2.4*	*4.5*
Year 2	7.8	5.4	7.7	5.6	6.3	6.1	3.4	5.3	6.0	5.5	4.6	5.8	4.7	*7.1*	*6.2*	*3.6*	*4.5*	*4.8*
Year 3	6.7	7.5	4.0	5.0	2.2	7.4	1.5	5.5	6.3	7.0	6.3	5.3	5.5	*5.2*	*5.7*	*3.2*	*3.2*	*4.4*
Year 4	5.6	6.5	3.2	2.0	2.5	5.2	--	4.4	3.9	6.6	7.2	3.9	5.0	*5.2*	*6.2*	*5.0*	*3.0*	*5.0*
Year 5	6.2	8.3	2.4	4.1	3.5	3.0	--	6.0	3.8	7.7	6.8	3.4	5.6	*5.0*	*4.9*	*5.0*	*2.9*	*4.9*
Year 6	6.7	8.5	--	4.4	4.8	2.7	--	6.5	3.8	6.6	7.1	3.6	4.9	*4.8*	*3.0*	*3.4*	*2.9*	*5.1*
Year 7	7.2	6.2	--	2.4	6.2	--	--	5.6	3.6	3.6	6.4	4.6	3.4	*3.7*	--	--	*3.4*	*5.4*
Year 8	--	3.8	--	3.0	6.5	--	--	4.5	4.6	--	5.6	3.4	5.8	*2.6*	--	--	*4.7*	*5.1*
Year 9	--	1.8	--	4.8	5.1	--	--	4.2	5.1	--	5.3	4.5	5.0	--	--	--	*3.2*	*3.5*
Year 10	--	2.0	--	4.2	5.8	--	--	5.4	6.0	--	5.9	5.0	4.5	--	--	--	*1.9*	*3.6*
Year 11	--	0.7	--	5.5	6.6	--	--	5.2	4.5	--	5.6	5.9	3.0	--	--	--	--	*4.8*
Year 12	--	0.7	--	4.1	5.1	--	--	5.3	1.8	--	5.3	5.8	4.3	--	--	--	--	*5.3*
Year 13	--	--	--	4.4	2.8	--	--	3.9	0.4	--	4.8	5.4	4.1	--	--	--	--	*3.3*
Year 14	--	--	--	0.9	--	--	--	1.1	--	--	3.5	3.7	4.0	--	--	--	--	--
Year 15	--	--	--	0.8	--	--	--	--	--	--	3.7	2.8	5.2	--	--	--	--	--
Year 16	--	--	--	--	--	--	--	--	--	--	3.3	--	4.0	--	--	--	--	--
Year 17	--	--	--	--	--	--	--	--	--	--	2.6	--	1.2	--	--	--	--	--
												--						

* patients also treated with leuprorelin; IGFDP: severe primary deficiency in IGF-I (indication in European MA); GHGD: deletion of the GH gene (therapeutic indication not registered in Europe)

: new patients compared to table submitted in June 2009 (4 patients), : updated data (1 patient)

[i] Laron Z, Lilos P, Klinger B. Growth curves for Laron syndrome. Arch Dis Child. 1993 Jun; 68(6): 768-70.

[ii] Laron Z, Lilos P, Klinger B. Growth curves for Laron syndrome. Arch Dis Child. 1993 Jun; 68(6): 768-70.

Table 2: Interim data for 19 French patients included in observational study Eu-IGFD: before treatment and on follow-up (at October 2010)

Subject	FR011-001	FR012-001	FR012-002	FR012-003	FR012-004	FR012-005	FR013-001	FR013-003	FR014-001
Etiology	SPIGFD	SPIGFD	PIGFD	MORQUIO DISEASE	SPIGFD	SPIGFD	SPIGFD	SPIGFD	PIGFD + small for gestational age
Gender	F	M	F	M	M	M	F	F	F
Age at Increlex start	8.3	12.3	3.6	9.2	7.9	11.4	8.3	11.9	10.2
Tanner stage at enrollment	1	1	1	1	1	1	1	1	1
Previous GH treatment									Yes
Duration (years) from beginning of treatment to last measured height							0.6	0.6	0.4
Chronological age (years) at last measured height							8.9	12.5	10.5
Estimated bone age (years) at last measured height	.	.	.	.	.	.	.	.	.
Height at beginning of treatment (cm)	80.0	125.8	84.4	98.5	109.0	121.3	110.0	129.0	112.0
Last measured height(cm)		.	.	.	.	.	116.0	135.2	112.5
Change of height from beginning of treatment (cm)		.	.	.	.	.	6.0	6.2	0.5
SDS for height at baseline (beginning of treatment)	-9.4	-3.4	-3.7	-6.2	-3.1	-3.6	-3.2	-2.9	-4.5
SDS for last measured height		.	.	.	.	.	-2.6	-2.6	-4.7
Annualized height velocity (cm/year) Month 3 Month 6 Month 12 Month 18 Month 24 Month 6 post treatment							 10.2	 9.7	 2.9

SPIGFD : Severe Primary IGF-I Deficiency ; PIGFD : Primary IGF-I Deficiency; ^{PT} Post treatment

Subject	FR011-001	FR012-001	FR012-002	FR012-003	FR012-004	FR012-005	FR013-001	FR013-003	FR014-001
Etiology	SPIGFD	SPIGFD	PIGFD	MORQUIO DISEASE	SPIGFD	SPIGFD	SPIGFD	SPIGFD	PIGFD + small for gestational age
Gender	F	M	F	M	M	M	F	F	F
Age at Increlex start	8.3	12.3	3.6	9.2	7.9	11.4	8.3	11.9	10.2
Tanner stage at enrollment	1	1	1	1	1	1	1	1	1
Previous GH treatment									Yes
Duration (years) from beginning of treatment to last measured height							0.6	0.6	0.4
Chronological age (years) at last measured height							8.9	12.5	10.5
Estimated bone age (years) at last measured height	.	.	.	.	.	.	.	.	.
Height at beginning of treatment (cm)	80.0	125.8	84.4	98.5	109.0	121.3	110.0	129.0	112.0
Last measured height(cm)		.	.	.	.	.	116.0	135.2	112.5
Change of height from beginning of treatment (cm)		.	.	.	.	.	6.0	6.2	0.5
SDS for height at baseline (beginning of treatment)	-9.4	-3.4	-3.7	-6.2	-3.1	-3.6	-3.2	-2.9	-4.5
SDS for last measured height		.	.	.	.	.	-2.6	-2.6	-4.7
Annualized height velocity (cm/year) Month 3 Month 6 Month 12 Month 18 Month 24 Month 6 post treatment							 10.2	 9.7	 2.9

SPIGFD : Severe Primary IGF-I Deficiency ; PIGFD : Primary IGF-I Deficiency; ^{PT} Post treatment

Table 3: Last data available for the 31 patients lost to follow-up from study 1419 (1/2)

Subject	10-938	10-907	10-903	10-911 *	10-920	10-927	10-929	10-930	10-931	10-932	10-933	10-934	10-935	10-936	10-937	10-939
Aetiology	GH Antibo	GHGD **	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP
Gender	Female	Male	Male	Male	Female	Female	Female	Male	Male	Male	Male	Male	Male	Male	Female	Male
Age (years) at beginning of treatment	6.5	6.1	11.0	14.8	5.8	4,9	2.2	6.3	6.0	3.3	13.6	9.2	6.2	3.4	3.0	12.1
Duration (years) from beginning of treatment to last measured height near-adult height	6.1	6.5	7.8	6.8	2.5	6,6	6.1	5.9	5.9	5.9	4.4	6.1	6.1	6.1	6.0	5.5
Chronological age (years) at last measured height	12.6	12.6	18.7	21.6	8.2	11,5	8.3	12.2	11.9	9.2	18.0	15.3	12.3	9.5	9.0	17.7
Estimated bone age (at last measured height, years)	12.0	12.6	15.6	14.3	6.0	11,4	8.6	9.7	12.4	9.4	15.4	14.0	12.8	8.3	8.5	14.3
Height at beginning of treatment (cm)	74.8	83.1	104.5	115.8	77.1	80,8	67.0	95.0	76.0	71.5	106.0	98.6	89.2	81.6	63.5	90.0
Last measured height (cm)	101.5	132.8	148.7	154.9	86.0	115,1	102.0	128.9	110.0	108.0	133.7	136.6	132.5	124.3	97.7	124.0
Change of height from beginning of treatment (cm)	26.7	49.7	44.2	39.1	8.9	34,3	35.0	33.9	34.0	36.5	27.7	38.0	43.3	42.7	34.2	34.0
Change in mean height (cm) estimated without treatment	27	24	27	15	11	29	27	21	21	19	16	23	22	20	27	21
Difference between height increase measured with treatment and height increase estimated without treatment (cm)	-0	26	17	24	-2	5	8	13	13	18	12	15	21	23	8	13
SDS for height at baseline (beginning of treatment)	-10.7	-6.4	-6.0	-5.5	-8.9	-6,4	-5.6	-4.3	-7.6	-7.6	-6.5	-6.3	-5.3	-4.4	-8.4	-9.2
SDS for last measured height	-7.0	-2.7	-3.8	-3.0	-8.9	-4,3	-5.2	-2.9	-5.7	-4.5	-5.6	-3.9	-2.5	-1.9	-6.5	-6.7

Height velocity (cm/year)																
Year 1	7.7	11.3	9.8	10.2	6.6	7.1	11.3	8.6	8.7	6.8	7.7	8.9	10.6	9.2	9.4	9.6
Year 2	4.6	8.2	7.2	7.8	1.3	5.8	6.3	4.9	6.6	5.9	4.8	5.0	7.0	6.6	6.0	3.9
Year 3	4.7	7.0	4.5	7.8		6.9	6.4	5.5	6.9	10.8	5.9	6.9	8.8	7.5	4.2	6.8
Year 4	3.8	7.7	5.2	4.2		2.9	4.6	5.2	4.5	4.2	6.9	6.4	5.3	5.6	4.3	5.4
Year 5	2.3	6.4	5.5	3.7		4.2	3.0	4.9	4.9	5.1		5.1	6.2	7.2	4.5	5.1
Year 6	3.7	6.3	5.0	2.5		4.8	3.6	5.5	3.5	4.6		5.1	5.1	6.1	5.9	
Year 7			3.6	3.4												
Year 8			4.2													
Year 9																
Year 10																
Year 11																
Year 12																
Year 13																
Year 14																
Year 15																
Year 16																
Year 17																

Table 3: Latest data available for the 31 patients lost to follow-up in study 1419 (2/2)

Subject	10-940	10-941	10-942	10-943	10-965	10-966	10-967	10-968	10-969	10-970	10-971	10-972	10-973	18-002	18-005
Aetiology	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP	IGFDP
Gender	Male	Female	Male	Male	Male	Female	Female	Male	Female	Female	Female	Female	Female	Male	Male
Age (years) at beginning of treatment	10.6	3.2	1.7	11.3	4.5	6.7	3.0	3.3	4.8	3.8	5.9	4.7	4.5	13.5	4.6
Duration (years) from beginning of treatment to last measured height near-adult height	5.5	6.0	5.2	0.7	0.9	0.9	0.9	1.5	1.5	0.9	0.8	0.9	1.0	6.6	8.6
Chronological age (years) at last measured height	16.1	9.2	6.9	11.9	5.4	7.6	3.9	4.8	6.3	4.7	6.7	5.6	5.5	20.1	13.2
Estimated bone age (at last measured height, years)	12.8	9.2	6.1	4.2	2.9	5.9	3.9	3.0	3.5	2.4	4.8	2.1	3.5	13.0	7.0
Height at beginning of treatment (cm)	87.8	67.0	66.7	96.2	68.0	84.5	59.7	67.7	67.0	67.0	88.5	74.0	78.6	97.8	69.0
Last measured height (cm)	118.0	104.0	100.5	100.0	74.2	94.0	71.0	74.0	76.0	71.5	93.5	82.0	87.0	132.7	97.8
Change of height from beginning of treatment (cm)	30.2	37.0	33.8	3.8	6.2	9.5	11.3	6.3	9.0	4.5	5.0	8.0	8.5	34.9	28.8
Change in mean height (cm) estimated without treatment	22	27	18	3	3	4	4	5	7	4	3	4	4	20	30
Difference between height increase measured with treatment and height increase estimated without treatment (cm)	9	10	16	1	3	5	7	1	2	1	2	4	4	15	-1
SDS for height at baseline (beginning of treatment)	-8.7	-7.7	-5.5	-7.6	-8.3	-8.0	-9.6	-8.9	-10.5	-8.7	-5.8	-8.1	-6.4	-7.4	-8.1
SDS for last measured height	-6.2	-5.3	-3.9	-7.3	-7.4	-6.4	-7.6	-7.1	-10.0	-8.9	-5,5	-7.2	-5.7	-6.0	-7.7

Height velocity (cm/year)														
Year 1	6.8	6.4	9.2	6.9	10.5	12.7	3.2	4.9	5.0	6.4	9.2	8.3	5.5	5.4
Year 2	5.2	7.8	6.8										6.4	3.7
Year 3	4.7	6.9	6.5										5.8	2.8
Year 4	4.9	5.8	4.8										6.2	4.2
Year 5	4.3	4.8	5.8										4.6	2.9
Year 6		5.3											4.3	2.7
Year 7														2.7
Year 8														2.7
Year 9														
Year 10														
Year 11														
Year 12														
Year 13														
Year 14														
Year 15														
Year 16														
Year 17														

Table 4: Latest data on patients with a height between -3 and -5 SDS

Patients	**10-901**	**10-915**	**10-916**	**10-918**	**10-919**	**10-926**	**10-930**	**10-936**	10-950 *	10-956 *	**18-004 ***	18-014 *	10-947	10-948 *	10-955	10-961 *	10-962 *
Aetiology	**IGFDP**	**IGFDP**	**IGFDP**	**IGFDP**	**IGFDP**	**IGFDP**	**IGFDP**	**IGFDP**	IGFDP	IGFDP	**IGFDP**	IGFDP	IGFDP #	IGFDP #	IGFDP #	IGFDP #	IGFDP #
Gender	**M**	**M**	**M**	**F**	**F**	**F**	**M**	**M**	M	M	**F**	F	F	F	M	M	M
Age (years) at the start of treatment	**9.7**	**9.8**	**8.6**	**3.7**	**2.4**	**6.6**	**6.3**	**3.4**	15.2	17.5	**5.0**	12.2	12.2	11.6	17.1	13.6	15.8
Duration (years) from the start of treatment to the last height measured	**7.7**	**7.1**	**5.1**	**4.8**	**4.8**	**5.6**	**5.9**	**6.1**	3.6	0.7	**12.5**	4.3	4.7	5.2	0.5	3.3	3.3
Chronological age (years) at the last meaurement of height	**17.4**	**17.0**	**13.6**	**8.5**	**7.3**	**12.2**	**12.2**	**9.5**	18.8	18.2	**17.5**	16.5	16.9	16.8	17.7	16.9	19.1
Estimated bone age (years) at the last measurement of height	**15.6**	**17.3**	**12.6**	**8.9**	**7.9**	**11.5**	**9.7**	**8.3**	17.0	11.9	**17.0**	14.0	16.2	16.0	13.5	15.4	15.7
Height at beginning of treatment (cm)	**111.2**	**107.8**	**104.2**	**83.0**	**77.5**	**97.6**	**95.0**	**81.6**	133.1	145.2	**92.7**	125.4	126.4	114.2	151.3	130.7	136.1
Last measured height (cm)	**164.4**	**153.0**	**135.0**	**118.1**	**117.0**	**130.9**	**128.9**	**124.3**	146.4	151.7	**152.1**	145.8	134.0	130.7	154.6	147.6	154.3
Change in height at the start of treatment (cm)	**53.1**	**45.2**	**30.8**	**35.1**	**39.5**	**33.3**	**33.9**	**42,7**	13.3	6.5	**59.4**	20.4	7.6	16.5	3.3	16.9	18.2
Estimated change in height (cm) without treatment	**30**	**28**	**19**	**22**	**22**	**25**	**21**	**20**	11	2	**44**	11	12	14	1	13	9
Difference between the increase in height measured with treatment and the estimated increase without treatment (cm)	**23**	**17**	**12**	**14**	**18**	**9**	**13**	**23**	2	5	**15**	9	-4	2	2	4	9
SDS for height before treatment	**-4.2**	**-4.9**	**-4.8**	**-3.9**	**-3.2**	**-4.5**	**-4.3**	**-4.4**	-4.2	-4.0	**-3.4**	-3.6	-3.5	-4.5	-3.2	-3.6	-4.2
SDS for the last measured height	**-1.5**	**-2.9**	**-3.2**	**-2.2**	**-1.1**	**-2.9**	**-2.9**	**-1.9**	-4.1	-3.3	**-1.7**	-2.6	-4.5	-5.0	-2.9	-3.5	-3.1
Status	**Height close to adult height reached and left study**	**Height close to adult height reached and left study**	**Left study before reach-ing height close to adult height**	**Left study before reach-ing height close to adult height**	**Left study before reach-ing height close to adult height**	**Left study before reach-ing height close to adult height**	**Left study before reach-ing height close to adult height**	**Left study before reach-ing height close to adult height**	Height close to adult height reached and left study	Left study before reach-ing height close to adult height	**Height close to adult height reached and left study**	Still included in the study	Height close to adult height reached and left study	Height close to adult height reached and left study	Left study before reach-ing height close to adult height	Left study before reach-ing height close to adult height	Left study before reach-ing height close to adult height

Growth velocity (cm/year)																	
Year 1																	
Year 2																	
Year 3	**10.3**	**7.6**	**9.4**	**9.5**	**8.8**	**6.9**	**8.6**	**9.2**	7.8		**7.4**	6.8	4.7	5.8		5.5	5.3
Year 4	**7.8**	**5.5**	**6.7**	**7.5**	**8.5**	**6.4**	**4.9**	**6.6**	3.4		**5.4**	6.6	0.5	2.3		5.1	6.8
Year 5	**6.7**	**7.0**	**4.0**	**6.4**	**8.3**	**4.7**	**5.5**	**7.5**	1.5		**7.5**	4.3	1.1	4.5		4.5	4.9
Year 6	**5.6**	**6.6**	**4.1**	**6.1**	**7.8**	**5.8**	**5.2**	**5.6**			**6.5**	1.9	0.8	2.4			
Year 7	**6.2**	**7.7**	**6.1**	**6.6**	**7.1**	**6.3**	**4.9**	**7.2**			**8.3**			1.5			
Year 8	**6.7**	**6.6**					**5.5**	**6.1**			**8.5**						
Year 9	**7.2**	**3.6**									**6.2**						
Year 10											**3.8**						
Year 11											**1.8**						
Year 12											**2.0**						
Year 13											**0.7**						
Year 14											**0.7**						
Year 15																	
Year16																	
Year 17																	

Date: July 2010
* Patients treated with leuprorelin
# Patients previously treated with rhIGF-1
In bold: patients under 10 years of age on the initiation of treatment