



Final Appraisal Report:

Mecasermin (Increlex[®]▼)

Ipsen Limited

Advice No: 1709 - October 2009

Recommendation of AWMSG

Mecasermin (Increlex[®]) is recommended for use within NHS Wales for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency.

Treatment should be initiated and monitored by physicians who are experienced in the diagnosis and management of patients with growth disorders

AWMSG is of the opinion that mecasermin (Increlex[®]▼) is not suitable for shared care within NHS Wales.

Statement of use:

No part of this advice may be used without the whole of the advice being quoted in full.

This report should be cited as:

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BMI	Body Mass Index
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GH	Growth Hormone
GHIS	Growth Hormone Insensitivity Syndrome
GHR	Growth Hormone Receptor
ICER	Incremental cost effectiveness ratio
IGF-I	Insulin-like growth factor-I
IGFD	Insulin-like growth factor-1 deficiency
NHS	National Health Service
NMG	New Medicines Group
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
rhIGF-I	Recombinant human insulin-like growth factor-I
SPC	Summary of Product Characteristics
SPIGFD	Severe primary insulin-like growth factor-I deficiency
WHO	World Health Organisation
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 14th October 2009

Recommendation of AWMSG is:

Mecasermin (Increlex[®]▼) is recommended for use within NHS Wales for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency

Treatment should be initiated and monitored by physicians who are experienced in the diagnosis and management of patients with growth disorders.

AWMSG is of the opinion that mecasermin (Increlex[®]▼) is not suitable for shared care within NHS Wales.

Additional notes:

- AWMSG considers that mecasermin (Increlex[®]▼) meets the AWMSG criteria for ultra orphan drug status.
- AWMSG recommends that there should be careful monitoring of the long term effects of mecasermin (Increlex[®]▼) treatment and that information should be collated and included in the already-established European Registry.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Mecasermin (Increlex[®]▼) is licensed for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (SPIGFD)¹.

SPIGFD is defined by¹:

- height standard deviation score ≤ -3.0
- basal insulin-like growth factor-I (IGF-1) levels below the 2.5th percentile for age and gender and
- growth hormone sufficiency
- exclusion of secondary forms of IGF-1 deficiency (IGFD), such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

It is recommended to confirm the diagnosis by conducting an IGF-1 generation test¹.

2.2 Dosing

The dose should be individualised for each patient. The recommended starting dose of mecasermin is 40 micrograms/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 40 micrograms/kg to the maximum dose of 120 micrograms/kg given twice daily. Doses greater than 120 micrograms/kg given twice daily have not been evaluated in children with SPIGFD¹. Further details regarding dosing be found in the Summary of Product Characteristics (SPC)¹.

2.3 Market authorisation date

3rd August 2007²

2.4 UK Launch date

10th September 2007²

3.0 DECISION CONTEXT

Primary IGFD or Laron syndrome results typically from a defect in the growth hormone receptor (GHR). Dysfunction of GHR is characterised by symptoms suggestive of growth hormone deficiency: short stature, delayed bone age, and occasionally blue sclerae and hip degeneration. Additional features include delayed bone maturation in the absence of bone dysplasia and chronic diseases which would suggest secondary causes³. Most of the growth-promoting effects of growth hormone are due to stimulation of IGF-1 in the liver and other tissues⁴. IGFD associated with growth hormone deficiency has been recognised as a potential cause of growth failure for many years, and growth hormone replacement has been used successfully in these patients for decades to stimulate endogenous production of IGF-1 and consequently stimulate statural growth⁵. However, the cause of IGFD in some children is growth hormone insensitivity rather than growth hormone deficiency^{4,5}. Patients with this condition have low IGF-1 despite normal or increased levels of growth hormone³. SPIGFD includes patients with mutations in the GHR, post-GHR signalling pathway, and IGF-1 gene defects; they are not growth hormone deficient, and therefore, they cannot be expected to respond adequately to exogenous growth hormone treatment^{1,4}.

Mecasermin is a recombinant human insulin-like growth factor-1 (rhIGH-1) designed for use as replacement therapy in SPIGFD^{1,4}. It is the first therapy in the European Union (EU) licensed for the treatment of SPIGFD. It is likely to meet the AWMSG criterion for ultra-orphan status, as WMP-sought expert opinion suggests the prevalence of the condition is less than one case per 50,000 persons in the UK. Currently, there are no patients receiving treatment with mecasermin in Wales, possibly one or two patients may be eligible for treatment, with perhaps one new case in each of the next five years.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Evidence presented in the company submission includes five studies (F0206s, F0375g, F0632g, F0671g, and study 1419) which have been conducted to evaluate the long-term safety and efficacy of mecasermin (rhIGF-I) in 76 children with SPIGFD. Of these studies, only one (F0375g) was randomised, double-blind and placebo-controlled, the other four were uncontrolled. Study 1419 (an integrated analysis of all five studies) remains ongoing and provides primary efficacy analysis in 62 patients who had completed one year of therapy at the cut-off date. Study outcome measures included height velocity standardised deviation scores, height standardised deviation scores, and bone age. In study 1419 height velocity (in treatment naive patients) was the primary efficacy endpoint. Results from study 1419 show mecasermin to have a statistically significant effect on height velocity from pre-treatment values through to year six of treatment.

All patients enrolled in study 1419 have been included in the safety analysis (n=76). Hypoglycaemia was the most frequently reported adverse drug reaction. Symptomatic hypoglycaemia however was generally avoided when a meal or snack was consumed either shortly before or after the administration of the study drug.

4.2 Review of the evidence on cost-effectiveness

The company's submission describes a cost utility analysis of mecasermin compared against no treatment in patients aged 2-4 years with SPIGFD. Short-term data from the open-label, non-comparative study 1419 has been used to model predicted height of patients undergoing treatment up to the point of treatment cessation (assumed to be age 14 years in girls, age 16 years in boys). In the base case analysis, the model estimates an incremental cost per quality adjusted life year (QALY) gained of £47,516. However, the gain in utility with increased height assumed in the base case analysis is subject to considerable uncertainty and sensitivity analyses indicate that the model is extremely sensitive to this parameter. An estimate of utility drawn from the literature on short stature in the general population results in an incremental cost effectiveness ratio (ICER) of £95,459 per QALY gained. There is no consideration given to any potential disutility associated with the incidence of treatment-related adverse events or the requirement for twice daily subcutaneous injections over the long term.

5.0 LIMITATIONS OF DECISION CONTEXT

- Mecasermin meets the AWMSG criteria for ultra-orphan drug status. The company reports that, currently, there are no known patients with SPIGFD in Wales.
- There are significant uncertainties in the assumed utility values in the economic model, which leads to significant uncertainty in the estimates of cost effectiveness.
- Mecasermin is not recommended for use in children below two years of age due to a lack of data on safety and efficacy¹.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

Evidence presented in the company submission includes five studies which have been conducted to evaluate the long-term safety and efficacy of mecasermin (rhIGF-I) in 76 children with SPIGFD⁵. Four of the studies have been completed, including one phase II (F0206s) and three phase III (F0375g, F0632g, and F0671g) trials. The remaining study (1419) is a long-term, open-label, extension study which is an integrated analysis of all five studies and is ongoing. Only F0375g was randomised, double-blind and placebo-controlled, the other four trials were single-arm uncontrolled. As study 1419 remains ongoing, only those subjects who completed one year of therapy have been included in the primary efficacy analysis (n=62), whereas all subjects enrolled in the study have been included in the safety analysis (n=76)³. It should be noted that in the late 1980s rhIGF-1 was manufactured by a number of companies⁵, and until March 2007 there were two formulations of rhIGF-1 in the US⁴. Some of the patients in the integrated analysis (Study 1419) have therefore received different rhIGF-1 materials. Outcomes from the studies are reported as they are described in the European Public Assessment Report (EPAR), Summary of Product Characteristics (SPC), the published papers and the company submission. Different terminology has been used, therefore a guide to the terms can be found in the glossary.

6.1 Clinical efficacy

Study F0632g (the only dose-response study) was carried out to determine whether a lower dose of mecasermin than had been administered previously (60 micrograms/kg given subcutaneously twice daily) could be efficacious. A total of six naïve-to treatment patients received this dose for one year; however results showed that this lower dose of mecasermin was not sufficient in the treatment of primary IGFD³. The four main efficacy studies are discussed in further detail below. Participants in these four studies were enrolled in the US and from 21 other countries and had growth failure due to SPGFD associated with either GHR defects or growth hormone gene-deletion defects, and anti growth hormone antibodies³. The main primary enrolment criteria and also the exclusion criteria were similar for all studies and can be found in Table 1, Appendix 1.

6.1.1 Study F0375g³

This was a phase III randomised, double-blind, placebo-controlled, crossover, multi-centre study of children with short stature due to growth hormone insensitivity syndrome (GHIS). A total of eight patients (gender and mean age remain confidential⁶) were enrolled and received open-label mecasermin initiated at 80 micrograms/kg and increased to 120 micrograms/kg, given subcutaneously twice daily. If the patient experienced symptoms of hypoglycaemia at either of these dose levels, the dose was decreased by 20 micrograms/kg.

The study consisted of three periods. Each patient was randomised to receive either placebo or mecasermin for six months (period A); then study medication was discontinued for a three-month washout (period B). Patients were then subsequently

crossed over to the alternative treatment for a further six months (period C). On completion of the 15-month blinded study, subjects received open-label mecasermin at their patient-appropriate dose for an additional year.

The primary efficacy endpoint was linear growth rate. The secondary efficacy endpoint was the change in standardised height (also known as the height standardised deviation score). The mean annualised growth rate for the six months prior to study entry for these children was 3.4cm/year (range: 1.0 to 5.6 cm/year). The mean height standardised deviation score at baseline was - 6.5 (range: - 9.6 to - 2.9). Only four out of the eight patients enrolled completed the trial. The definition of clinically meaningful in this context has not been defined. One of these four patients showed similar growth rate both during placebo and mecasermin treatment.

6.1.2 Study F0206s⁷

This was a phase II, open-label, single centre study of prolonged treatment (24 months [36 months in one patient]) with mecasermin in eight patients (six boys and two girls) with GHIS, whose ages ranged from 2.3 years to 11 years at enrolment⁸. They all received mecasermin at a starting dose of 40 micrograms/kg subcutaneously twice daily; increased to 120 micrograms/kg twice daily. Six patients continued to receive prolonged treatment at this dose, however in one patient the dose was reduced to 80 micrograms/kg twice daily after one month due to hypoglycaemia, and then subsequently increased to 100 micrograms/kg. The other patient also developed symptomatic hypoglycaemia at the higher dose and was initially treated with 80 micrograms/kg for the first six months, but was able to tolerate the 120 micrograms/kg dose thereafter.

The primary efficacy endpoint was growth rate. Changes in height standard deviations, weight, pubertal stage, bone age, and bone mineral density were also examined. During the first year of mecasermin therapy, mean height velocity increased 2.4-fold for the group to 9.3 cm/year (mean height velocity SD score, + 3.8). During the second year of therapy, mean height velocity decreased to 6.2 cm/year (mean height velocity SD score, + 0.5). The one subject treated for three years grew at nearly the same rate in the third year as in the second year. The average change in height standardised deviation score after two (or three) years of therapy was + 1.2 (range 2.1 to - 0.3)³.

6.1.3 Study F0671g³

This was a phase III, open-label, multicentre study conducted over 24 months in order to determine if replacement therapy with mecasermin continued to be safe and effective in improving statural growth in children with GHIS. This study was terminated prematurely due to the discontinuation of the rhIGF-I programme by the previous market authorisation holder. A total of 23 patients had been enrolled and received mecasermin therapy at this time (21 from prior studies [F0206s, F0375g and F0632g] and two patients naïve-to treatment). Patients received one of three doses of mecasermin therapy based on tolerability and received this dose for two years, unless no benefit was seen (annualised growth rate of <2.5cm/year over baseline based on measurements at six-month intervals) or an adverse event required discontinuation. Patients received 80 micrograms/kg, 100 micrograms/kg or 120 micrograms/kg twice daily. The number of patients receiving each dose remains confidential⁵.

The primary measure of efficacy was annual growth rate over the first and second years of treatment. Overall, patients' heights increased by 10.8 ± 2.8cm over 24 months. A total of 21 out of 23 participants had been treated with mecasermin for six months to several years prior to enrolment in study F0671g. Growth increments in this study were reported to be consistent with that expected in a group of subjects previously treated with mecasermin.

Two publications based on this study were highlighted by the company in their submission^{8,9}. Backeljauw and colleagues presented data on a subset of the 23 patients who participated in Study F0671g. Eight of these patients originally completed study F0206s and were treated with mecasermin for a total of 6.5 to 7.5 years. During the subsequent years, height velocity remained slightly below that achieved in the first two years at mean height velocities of 5.4, 5.5, 5.2 and 4.8 cm/year during years three to six, respectively⁹.

6.1.4 Study 1419 (integrated efficacy analysis)¹⁰

This is an ongoing open-label, multicentre study to evaluate the efficacy and safety of mecasermin replacement in 76 children with SPIGFD, and is designed to follow patients to adult height⁵. A total of 22 out of the 23 children from study F0671g, and an additional 53 patients (44 who were naïve-to treatment) were enrolled in this study³. On average, the patients were treated for 4.4 years $\pm$ 3.1 years, at the time of cut-off, representing a total exposure of 321 patient-years⁵. The starting treatment dose was low and then titrated up to 120 micrograms/kg subcutaneously twice daily. Additional confidential data on drug exposure in the analysis population¹¹ was provided to AWMMSG.

Outcome measures included height velocity standardised deviation scores, height standardised deviation scores, and bone age. However, height velocity (in naïve-to treatment patients) was the primary efficacy endpoint. Of the study population, 62 patients had completed at least one year of mecasermin therapy. Of these, 53 (85%) had Laron syndrome-like syndrome phenotype; seven (11%) had growth hormone deletion, and one (2%) had neutralising antibodies to growth hormone. In total 38 (61%) patients were male and 49 (79%) were Caucasian. Most (90%) were pre-pubertal at baseline¹.

The effect of mecasermin on height velocity could be assessed in 59 patients who were naïve to treatment and also had a pre-treatment height velocity measurement. Mean height velocity rose from 2.8 cm/year pre-treatment, to 8.0 cm/year during the first year of treatment ($p < 0.0001$)¹. The patient numbers dropped throughout the duration of the study. The mean height velocities reported however for years 2 through 6 (5.8, 5.5, 4.7, 4.7, and 4.8 cm/year, respectively) remained statistically significantly greater than baseline ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$, $p = 0.0015$, and $p = 0.0009$, respectively)¹. There were positive trends for years seven and eight (mean height velocities were 4.6 cm/year [$n = 16$] and 4.5 cm/year [$n = 14$], respectively); mean change from baseline was not significant¹.

In their submission the company have highlighted a number of additional publications based on this study^{7-9, 12}.

6.1.5 Points to note from the studies:

- Many of the patients in these studies had been continuously treated with mecasermin for years, and have transferred from one study, when it ended, to another (i.e. all of the patients enrolled in studies F0206s, F0375g, and F0632g were later enrolled in study F0671g. All subjects [except one] enrolled in F0671g, were later enrolled in study 1419)³. The retrospective data from these other studies has been transferred over into Study 1419 for pooled analysis and follow up.
- Study 1419 contains the longest treatment data to date with mecasermin and illustrates the durable nature of the effect on height velocity, which is statistically significant from pre-treatment values through to year six of treatment.
- No quality of life data were included in any of the studies.
- The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) raised concerns on the efficacy and safety results in Study 1419 due to varying rhIGF-I materials used in the patient population and the fact that patients were collected from several studies. Further analysis carried out by the company demonstrated that the efficacy results for the 44 naive-to treatment patient cohort were similar to the cohort of 23 subjects enrolled prior to Study 1419. Adverse events were generally lower in the 44-patient cohort; suggesting no specific safety issue with the previous rhIGF-I materials⁵.
- In an attempt to achieve greater adult height by delaying puberty and prolonging the growth period, 14 children in Study 1419 received Lupron[®] (a gonadotropin releasing hormone analogue). Height velocity following initiation of Lupron[®] therapy was expected to be lower in these individuals; however no special adjustments were made for the analyses of height velocity or height standard deviation score¹⁰.
- According to the guidance from CHMP on products containing somatropin, change in height velocity standard deviation score from baseline is the recommended primary efficacy endpoint. However, in study 1419 height velocity was chosen as the primary endpoint because it is considered by the company to be more interpretable as an endpoint than either height velocity standard deviation score or height standard deviation score. An explanation is outlined in the company submission⁵.

6.2 Safety

An integrated safety database from clinical studies (reported under section 6.1) contains 76 subjects with SPIGFD treated for a mean duration of 4.4 years and representing 321 subject-years¹. The adverse events profile was considered by CHMP to be similar to that seen in several other rhIGF-1 treated SPIGFD cohorts³.

Hypoglycaemia is the most frequently reported adverse drug reaction. The thirty-six subjects (47%) who had one or more episodes of hypoglycaemia included four subjects who had hypoglycaemic seizure on one or more occasion. Of the 36 subjects, 12 (33%) had a history of hypoglycaemia prior to beginning treatment. The frequency of hypoglycaemia was highest in the first month of treatment, and episodes were more frequent in younger children. Symptomatic hypoglycaemia was generally avoided when a meal or snack was consumed either shortly before or after the administration of the study drug¹. Further details and advice can be found in the SPC¹.

Injection site hypertrophy occurred in 24 subjects (32%). This reaction was generally associated with lack of proper rotation of injections. When injections were properly dispersed, the condition resolved. Lymphoid tissue hypertrophy associated with hypoacusis (see glossary) and snoring occurred in approximately 22% of patients^{1,4}; snoring generally beginning in the first year of treatment¹. Tonsillar hypertrophy was

noted in 12 (16%) subjects, particularly in the first one to two years of therapy with lesser tonsillar growth in subsequent years. Intracranial hypertension occurred in three subjects (4%). In two subjects the events resolved without interruption of mecasermin therapy. Mecasermin treatment was discontinued in the third subject and resumed later at a lower dose without recurrence. Fourteen subjects (18%) had headache considered related to study drug. Changes in organ size and function were observed during clinical development. Nevertheless CHMP considered data at the time of market authorisation did not support a disproportionate growth in organ size and recommended that normal careful follow-up regarding renal and spleen growth in patients receiving mecasermin is sufficient. Follow-up of cardiac growth however by means of echocardiogram in these patients has been included in the SPC^{1,3}.

As with all protein pharmaceuticals, some patients may develop antibodies to mecasermin. Anti-IGF-1 antibodies were observed in approximately half (11 out of 23 children) with SPIGFD tested during the first year of therapy. However, no clinical consequences of these antibodies were observed (e.g., allergic reactions or attenuation of growth)¹.

CHMP commented in the European Public Assessment Report (EPAR) that the study population was small and methods used to assess anti-IGF-1 antibodies were not validated. CHMP have advised that since it remains unclear if the immunogenicity of the product is comparable to those manufactured previously, immunogenicity should be monitored³. The company advise in the SPC that antibody testing should be performed in individuals who after receiving mecasermin experience an allergic reaction, have unexpectedly high blood values of IGF-1 or fail to show a growth response¹.

As some of the side effects of mecasermin may take time to develop⁴, it has been proposed that the frequency of such events may increase over time during post marketing follow up. A condition of the Marketing Authorisation for Increlex[®]▼ is that the Marketing Authorisation Holder should perform one long-term safety study of mecasermin treatment, initiated in the early phase of childhood and continued to adulthood. This will investigate long-term toxicity in patients undergoing developmental changes and the possible occurrence of malignancies as well as other risks⁵.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Mecasermin is the first therapy in the EU licensed for the treatment of SPIGFD. Growth hormone treatment is not considered to be a viable option for these patients, as endogenous growth hormone function and levels are typically normal³. There are currently therefore no appropriate clinical comparators to mecasermin for the treatment of SPIGFD.

7.2 Comparative effectiveness

- The long-term study 1419 is single arm and therefore no comparisons have been made on projected height for patients not receiving therapy.
- Comprehensive data on the safety and efficacy of mecasermin is lacking.
- As the indication for mecasermin is encountered so rarely, the CHMP felt that the applicant could not reasonably be expected to provide comprehensive data on the efficacy and safety of the product at the time of market authorisation³. The product was granted a marketing authorisation under exceptional circumstances.
- The company comment in their submission that although children with confirmed growth hormone deficiency can have a greater increase in height velocity and height standard deviations in response to recombinant human growth hormone (rhGH) replacement therapy, this is not a meaningful comparison, as children with SPIGFD do not respond at all, or respond poorly, to rhGH⁵.
- Although the clinical trials included children and adolescents of various ages, expert opinion obtained by the company suggests that in Welsh clinical practice, subjects with SPIGFD will be diagnosed and commence treatment between the ages of 2-4 years⁵.
- The company have highlighted in their submission that the licensed indication in the US is broader than in the UK. In addition to patients with Laron-type SPIGFD, mecasermin is also indicated in the US for the treatment of growth failure in children with growth hormone gene deletion who have developed neutralising antibodies to growth hormone⁵.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for consideration

The key economic issues for AWMSG to consider are whether the additional benefits offered by mecasermin over the relevant comparator justify the additional costs and if so, whether the total budgetary impact of supporting the use of mecasermin is acceptable.

8.2 Description and critique of the company's submission

The company's submission describes a cost utility analysis of mecasermin compared against no treatment in patients with SPIGFD⁵. A simple decision analytic model has been developed, in which a cohort of patients aged 2 to 4 years receive treatment with mecasermin until epiphyseal plate closure (see glossary) (assumed to be at the age of 16 years in boys and 14 years in girls) or no treatment. The time horizon of the analysis is lifetime, on the basis that the benefits of treatment (increased adult height) are retained for the lifetime of the patient.

Short-term data from the open-label, non-comparative Study 1419 has been used to model predicted height of patients undergoing treatment up to the point of treatment cessation¹¹. Height standard deviation scores have been derived from Study 1419 and have been notionally used to estimate the health-related quality of life for patients undergoing treatment relative to untreated patients based on a study that used data from the adult general population taking part in the 2003 Health Survey for England¹³. However, the gain in utility with increasing height in that study has been doubled for the base case analysis, reportedly based on the opinion of company-sought clinical experts, and there is no consideration given to any potential disutility associated with the incidence of adverse events or the requirement for twice daily injections over the long term. Sensitivity analyses indicate that the model is very sensitive to the

assumptions of utility gain with increasing height and so the model outputs should be interpreted with caution. The model has been provided to WMP.

8.3 Population

The modelled patient cohort consists of children who initiate treatment at age two years (20%), three years (40%) or four years (40%). This is based on company sought expert opinion, which reportedly suggests that the full benefit of treatment would be achieved when treatment is started at an early age. The impact of age at initiation of treatment is explored in sensitivity analyses⁵.

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. A lifetime horizon has been used on the basis that any benefits from mecasermin treatment (increased height) would be retained throughout the lifetime of the patient⁵.

8.5 Comparator

There are no other treatments licensed specifically for primary IGFD. Growth hormone treatment is not considered to be a viable option for these patients, as endogenous growth hormone function and levels are typically normal³. The comparator of no treatment would, therefore, seem appropriate.

8.6 Clinical inputs

8.6.1 Efficacy data

8.6.1.1 Mecasermin treated patients

Short-term data from the open-label, non-comparative study 1419 has been used to model predicted height of patients undergoing treatment up to the point of treatment cessation (age 14 years in girls, age 16 years in boys)¹¹. The primary end point of study 1419 is height velocity. However, a study using data from the 2003 Health Survey for England, which involved height being measured and health-related quality of life being assessed using the EQ-5D questionnaire in a sample of the general adult population, links health-related quality of life and height standard deviation scores¹³. Therefore, height standard deviation scores, which are a measure of the height of patients compared to the height of age-matched members of the normal population, have been derived from the study 1419 data and have been used to estimate the health-related quality of life for patients undergoing treatment relative to those who are not (see section 8.6.3).

Height velocity data relating to over eight years of treatment with mecasermin are available from study 1419¹¹. However, a proportion of the modelled cohort may require treatment for up to 14 years. Additional confidential data on the number of patients that provide data over time was made available to AWMSG. Mean height velocity data for one to eight complete years of treatment are taken directly from study 1419 data. For treatment in years nine to 12, data from the very few patients who completed more than eight years of treatment are reportedly used (not verified from the references provided). It should be noted that the height velocities that are estimated for treatment during this period do not follow the general trend observed in the data in the preceding periods; the height velocities are greater than in the preceding periods⁵, which would have the effect of increasing the modelled height and reducing the height standard deviation scores compared with the untreated group. For treatment in years 13 to 14 (boys cohort only), it is assumed that height velocity would be comparable with that in the untreated group (see section 8.6.1.2), which the company feels is a conservative approach.

The height velocity data have then been used to predict the mean height of patients in each subsequent year for boys and girls aged two, three or four years at the start of treatment. Height standard deviation scores over time have then been derived for each of these cohorts by cross referencing their predicted heights with those obtained from World Health Organisation (WHO) growth charts for children aged 0-5 years¹⁴ and children aged five to 19 years¹⁵. It should be noted that the WHO growth charts are compiled using data collected from a wide range of countries, many of which are likely to differ from Wales.

8.6.1.2 Untreated patients

As study 1419 did not include a control arm, the expected height of patients who are untreated has been taken from growth curves that were derived from an earlier published study, which used anthropometric measurements from 24 patients with Laron syndrome (the cause of severe primary IGFD in 85% of the patients in study 1419) who were followed up from infancy to adulthood to determine growth patterns in untreated children¹⁶. As raw data from these patients with Laron syndrome were not available to the company, a software package has been used to extract data from the graphical representation of height by age. The height data were used to derive height standard deviation score for untreated patients as described in 8.6.1.1. The company considers that these data from patients with Laron syndrome adequately reflect all relevant patients with SPIGFD, as is suggested by the authors of the published study¹⁶.

SPIGFD is not considered to impact upon mortality. Welsh life tables have been used to model life expectancy of patients over the long term⁵.

8.6.2 Adverse events

Adverse events are considered only from a cost perspective⁵ (see section 8.7.2).

8.6.3 Utility weights

The company submission details literature searches that were undertaken to inform the model inputs. It is reported that there were no health-related quality of life data identified specifically in patients with SPIGFD, nor any appropriate published data related to patients with growth hormone deficiency⁵. Therefore, a study by Christensen et al that took data from the 2003 Health Survey for England, which involved height being measured and health-related quality of life being assessed using the EQ-5D questionnaire in a sample of the general adult population¹³, has notionally been used to inform estimates of the impact of short height on health-related quality of life.

This study reports that, in adults with a height standard deviation score of less than -2.0, and controlling for the confounding variables of age, gender, weight, social class and presence of chronic illness, an improvement of 1 height standard deviation score results in a significant change in the EQ-5D score of 0.061¹³. However, the company submission reports that, based on company-sought clinical opinion, the use of this change in utility score, which is derived from the general population, would underestimate the gains in utility for patients with SPIGFD⁵. Therefore, this utility gain associated with an improvement of 1 height standard deviation score has been doubled to 0.122 in the base case analysis. Utility gains associated with an increase in height are assumed to persist unchanged throughout the remainder of the patient's life.

It should be noted that the economic model does not consider any impact upon health-related quality of life of the covariates that are included in the regression analysis presented by Christensen et al in relation to height⁵. Nor does it consider the impact of the adverse events of mecasermin treatment (see sections 6.2 and 8.7.2), or the impact of twice daily subcutaneous injection over up to 14 years of treatment for the modelled cohort, which are children and not adults as in the 2003 Health Survey for England. Overall, there would appear to be significant uncertainty in the assumed utility gains with mecasermin treatment, which may potentially bias the model in favour of mecasermin treatment. Sensitivity analyses indicate that the model is particularly sensitive to the assumptions of utility gains associated with mecasermin treatment, which warrants caution in the interpretation of the model outputs (see section 8.10).

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

The drug acquisition cost for mecasermin is based on patient weight and tolerability. The mean daily dose (223 micrograms/kg) used in the base case model is reportedly based on that observed in study 1419. It is assumed there would be no vial content wastage on the basis that vial contents can be used for up to 30 days⁵. The company acknowledges that vial content wastage may occur in patients of low body weight during the early dose titration phase⁵.

Although study 1419 recorded patient body weight, the patient weight that is used in the model to estimate total daily doses of mecasermin has reportedly been calculated from the relationship between body mass index (BMI), height and weight. Patients with SPIGFD are reported to have “normal” BMIs, therefore, using a software package, BMI data have been extracted from BMI graphs derived in a study of British children and young adults¹⁷ to reflect the BMI of Welsh patients. The height of treated patients is then used to derive patients’ weight in each year. The company has justified this approach on the basis that study 1419 was an international trial and the trial-reported body weights may not be representative of Welsh patients. Whether or not this approach actually results in a more appropriate estimate of patients’ body weights is unclear.

8.7.2 Adverse event costs

Adverse events that were considered in study 1419 to be related to mecasermin treatment and which company-sought clinical experts considered to be associated with resource use and costs are included in the model. These are severe hypoglycaemia, tonsillar hypertrophy, tonsillectomy, intracranial hypertension and ear tube placement. The rates of these as reportedly observed in study 1419 (unverified) are assumed, and unit cost data are applied to estimate the total costs of adverse events⁵.

It should be noted that the mean duration of treatment in study 1419 was around 4 years. Therefore, the incidence rates for these adverse events as reportedly observed for study 1419 may be underestimates for the modelled treatment duration of up to 14 years. Company-sought expert opinion is reported to indicate that adverse events are more likely to occur at the start of treatment, rather than at a constant rate throughout treatment. Sensitivity analysis has been conducted to explore the impact of increasing the assumed incidence of adverse events¹.

8.7.3 Other resource use and costs

Resource use associated with diagnostic and treatment pathways were based on the opinions of company-sought clinical experts, one from Scotland and one from Wales. It is assumed that there would be no incremental costs of diagnosis.

It is reported that, currently, there are no untreated patients with severe primary IGFD in Wales but, based on company-sought expert opinion, the likely management of such

patients would involve two or three paediatric endocrinology visits per year until final height has been reached.

Initiation of mecasermin treatment is assumed to involve a three-day hospital stay. Ongoing monitoring costs that are considered for treated patients include glucose monitoring, hand x-rays, paediatric endocrinologist visits, and annual one-day inpatient stays for sleep studies⁵. No specific mention is made regarding echocardiography, which is recommended in the SPC at the start of treatment and at the end of treatment¹, but the omission of costs associated with this is unlikely to significantly influence the model outputs, given the modelled difference in overall costs (see section 8.9.1).

Published unit cost data and list prices are used to estimate the costs associated with treatment initiation and monitoring in treated and untreated patients.

8.8 Discounting

Costs and outcomes in the base case analysis are discounted at 3.5% per annum⁵, which is the preferred discount rate. Rates of 0% and 6% are explored in sensitivity analyses⁵.

8.9 Results

8.9.1 Base-case analysis

The incremental cost per quality adjusted life year (QALY) gained for mecasermin compared with no treatment is estimated to be £47,516. This is based on additional costs of £179,686 (£183,053 versus £3,367) and a gain of 3.78 QALYs. As survival is not influenced by treatment, the QALY gains are a result of the assumed improvement in health-related quality of life associated with increased height as a result of mecasermin treatment.

8.10 Sensitivity/scenario analyses

8.10.1 One-way sensitivity/scenario analyses

Only one-way sensitivity analyses have been conducted. These test the impact on the incremental cost effectiveness ratio (ICER) of changing the discount rate, increasing unit costs, increasing adverse event rates, changing the start age of the modelled cohort, and changing the utility allocated to an increase in height standard deviation score.

The model was very sensitive to the assumed utility values allocated to an increase in height standard deviation score. In the base case analysis, a utility value that was double that observed in a study of the general population was used (0.122). When the utility value was reduced to that observed in the study (0.061), the ICER increased dramatically to £95,459 per QALY gained. Given that there are several areas of uncertainty in the assumed utility values used in this model (see section 8.6.3), this finding is important and highlights the need to interpret the base case analysis with caution.

The model is also sensitive to the application of discount rates due to the fact that utility gains are assumed to remain constant throughout the life time of the patient, whereas costs are applied only for the duration of mecasermin treatment (maximum of 14 years in boys). Results are as would be expected, with the lowest ICER being reported at a 0% discount rate (£23,991 per QALY gained). At a discount rate of 6% the ICER increases to £60,947 per QALY gained.

The model is relatively insensitive to the assumptions around the costs of diagnosis and treatment, and the costs of managing adverse events. A 3.3-fold increase in the incidence of adverse events and an increase in unit costs by 50% each only marginally changed the model outputs from those observed in the base case analysis. The age at treatment initiation also only marginally influenced the estimated ICER. When 100% of the cohort was assumed to start treatment at age two, three or four years the ICER was relatively unchanged from the base case scenario of 20% 2-years old, 40% 3-years old and 40% 4-years old. When treatment was assumed to be initiated at 5 years of age, the ICER increased to £52,350 per QALY gained.

8.10.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was not reported in the company submission, but the model provided by the company includes the outputs of PSA. It appears that BMIs, height velocities and dose intensities have been sampled using random draws from normal distributions. Utility values, to which the deterministic model was very sensitive, are not sampled within the PSA. From 2,000 simulations, the probability that mecasermin is cost effective compared with no treatment at a willingness to pay threshold of £30,000 per QALY is practically 0%. For a 50% probability of being cost effective, a willingness to pay around £47,000 per QALY is required. The probability of cost effectiveness approaches 100% at a willingness to pay value of around £60,000 per QALY.

This PSA does not appear to address the issue of the uncertainty associated with the assumed improvement in health-related quality of life with successful treatment.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of mecasermin in its licensed indication.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The company submission states that there are no known diagnosed cases of SPIGFD in Wales, and no direct epidemiological data to inform estimates of the incidence of the condition. Therefore, incidence rates of one patient per year have been used to represent the likely upper limit of cases over the next five years, based on company-sought Welsh expert opinion. The budget impact analysis considers the costs of drug acquisition and ongoing management, taken from the economic model. There appear to be some areas of uncertainty in the costs assumed for mecasermin, due to the method of estimating patient body weight for calculating dose requirements. The company estimates of the net budget impact are, therefore, subject to significant uncertainty.

9.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over a five year period 2009-13⁵.

9.3 Data sources

9.3.1 Incident and prevalent cases

There are no known diagnosed cases of SPIGFD in Wales, and it is reported that there are no direct epidemiological data to inform estimates of the incidence of the condition. Company-sought Welsh expert opinion is reported to indicate that, due to the severity of the condition, any patients with the condition would have been identified. Therefore, it is assumed that there are currently no cases in Wales and it is assumed that a maximum of one patient may be newly diagnosed in each of the next five years. For the purposes of the budget impact analysis, it is assumed that this may be either a male or female patient (50:50 probability) aged three years old.

As a non-life threatening condition, it is assumed that there would be no deaths over this period, and so the prevalence is the same as the assumed incidence.

9.3.2 Projected rate of adoption and market share

It is assumed that all patients identified with SPIGFD would receive treatment with mecasermin.

9.3.3 Costs and resource use

The budget impact analysis considers the acquisition costs of mecasermin plus the ongoing management and monitoring costs as described for the economic model (see section 8.7).

9.4 Results

Based on the above assumptions, the company submission reports that the net cost impact of the use of mecasermin would be around £11,000 in 2009, rising to around £70,000 in 2013⁵.

This is considered to be the likely upper limit of the costs due to the assumption of one incident case per year in Wales, when currently there are not known to be any diagnosed patients in Wales. It is worth reflecting that a five year budget impact analysis based on patients starting treatment at age three years does not capture the ongoing costs of treatment as patients growth. Treatment is expected to continue until near adult height (assumed to be age 16 years in boys and 14 years in girls in the economic model), during which body weight, and hence the dose and costs of mecasermin, would increase substantially (see section 9.6).

9.5 Sensitivity analysis

No sensitivity analysis was conducted for the budget impact analysis.

9.6 Comparator costs

The annual acquisition cost of mecasermin is determined by patient weight and tolerability. The recommended starting dose is 40 micrograms/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 40 micrograms/kg to the maximum dose of 120 micrograms/kg given twice daily¹. The acquisition cost for a single 40mg vial is £605. Therefore, the crude annual cost for a child weighing 15kg, stabilised on a dose of 80 micrograms/kg twice daily, would be around £13,300 per annum. This increases to £22,400 per annum for an older child of 25kg requiring the same daily dose.

There are no other relevant comparators for patients with severe primary IGFD (see section 7.1).

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- A condition of the Marketing Authorisation for mecasermin is that the company should perform one long-term safety study of mecasermin treatment, initiated in the early phase of childhood and continued to adulthood. The aim of this study would be to investigate long-term toxicity in patients undergoing developmental changes and the possible occurrence of malignancies as well as other risks. In order to address this requirement, the company have set up a European registry along the same principles as the Increlex Growth Forum Database Registry already established in the US. The aim of the registry is to obtain data on patients treated with mecasermin beyond the data from the clinical studies described under Section 6.1. The registry in the US is a multi-centre, open-label, retrospective and prospective observational study; set up to monitor the safety and effectiveness of Increlex[®]▼. The first patient data was input into the European registry in January 2009⁵.
- Treatment with mecasermin should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders¹. AWMSG are of the opinion that mecasermin is not suitable for shared care.

10.2 Related advice

Currently, NICE are reviewing growth failure in children. The appraisal however focuses on conditions due to growth hormone deficiency, and the use of supplementary injections of synthetic growth hormone to help increase growth. The proposed appraisal is expected to be published in February 2010¹⁸.

10.3 Previous AWMSG/NICE advice

None

10.4 Ongoing studies

- In a recent presentation at the 13th International Congress of Endocrinology, Blethen and colleagues reported efficacy data from 86 prepubertal children enrolled in the US Registry who had received one year of Increlex[®]▼ treatment¹⁹. These patients however are not strictly comparable to those patients reported in Study 1419, as they generally have a less severe form of the disease. Midyett and colleagues recently reported safety data from this trial²⁰.

10.5 Patient organisation information

A patient organisation submission was not received.

10.6 Medical expert/Clinical expert summary

Medical/clinical expert views were provided to AWMSG members.

REFERENCES

- 1 Increlex[®] 10mg/ml solution for injection. Summary of Product Characteristics. Ipsen Limited. 4 Sep 2007. Available at: <http://www.emc.medicines.org.uk/>. Accessed 16 June 2009.
- 2 Ipsen Limited. Form A: Initial appraisal information. Increlex[®]. 15 May 2009.
- 3 European Medicines Agency. European Public Assessment Report: Increlex[®]. Aug 2008. Available at: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/increlex/H-704-en6.pdf>. Accessed 16 Jun 2009.
- 4 Collett-Solberg PF and Misra M on behalf of the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. The role of Recombinant Human Insulin-Like Growth Factor-1 in Treating Children with Short Stature. *J Clin Endocrinol Metab* 2008; 93:10-18.
- 5 Ipsen Limited. Form B: Detailed appraisal information. Increlex[®]. 15 May 2009.
- 6 Commercial in confidence data.
- 7 Backeljauw PF, Underwood LE and the GHIS Collaborative Group. Prolonged treatment with recombinant insulin-like growth factor-I in children with growth hormone insensitivity syndrome – a clinical research center study. *J Clin Endocrinol Metab* 1996;81(9):3312-17.
- 8 Underwood LE, Backeljauw P, Duncan V and the GHIS Collaborative Group. Effects of insulin-like growth factor-I treatment on statural growth, body composition and phenotype of children with growth hormone insensitivity syndrome. *Acta Paediatr Suppl.* 1999;88 (428):182-84.
- 9 Backeljauw PF, Underwood LE and the GHIS Collaborative Group. Therapy for 6.5–7.5 years with recombinant insulin-like growth factor-I in children with growth hormone insensitivity syndrome: A clinical research center study. *J Clin Endocrinol Metab* 2001;86(4):1504-10.
- 10 Chernausk SD, Backeljauw PF, Frane J, et al. Long-term treatment with recombinant insulin-like growth factor-I (IGF-I) in children with severe IGF-I deficiency due to growth hormone insensitivity. *J Clin Endocrinol Metab* 2007;92(3):902-10.
- 11 Commercial in confidence data.
- 12 Underwood LE, Backeljauw P. Therapy with recombinant human insulin-like growth factor 1 in children with insensitivity to growth hormone and in catabolic conditions. *J Intern Med* 1993;234(6):571-77.
- 13 Christensen TL, Djurhuus CB, Clayton P et al. An evaluation of the relationship between adult height and health-related quality of life in the general UK population. *Clin Endocrinol* 2007; 67: 407-12.
- 14 World Health Organisation. Child Growth Charts 0-5 years; 2006. Available at: http://www.who.int/childgrowth/standards/height_for_age/en/index.html. Accessed 25th May 2009.
- 15 World Health Organisation. Growth Reference Data for 5-19 years; 2007. Available at: http://www.who.int/growthref/who2007_height_for_age/en/index.html. Accessed 25th May 2009.
- 16 Laron Z, Lilos P, Klinger B. Growth curves for Laron syndrome. *Arch Dis Child* 1993; 68: 768-70.
- 17 Cole TJ, Freeman JV, Preece MA. Body Mass index reference curves for the UK, 1990. *Arch Dis Child* 1995; 73: 25-9.
- 18 National Institute for Health and Clinical Excellence. Final protocol. Growth Failure in Children. September 2008. Available at: <http://www.nice.org.uk/nicemedia/pdf/HGHFinalProtocol.pdf>. Accessed 27 June 2009.
- 19 Blethen S, Cohen AJ, Estrada E et al: Safety and efficacy of Increlex (mecasermin [rDNA origin] injection) treatment in the IGFD registry. Presentation at the 13th

- International Congress of Endocrinology (ICE), November 8-12, 2008, Rio de Janeiro, Brazil.
- 20 Midyett LK, Rogol AD, Frane J et al. Efficacy and safety of twice-daily rhIGF-1 treatment in pre-pubertal children with primary IGF-1 deficiency. Presentation at the 13th International Congress of Endocrinology (ICE), November 8-12, 2008, Rio de Janeiro, Brazil.
 - 21 Commercial in confidence data.
 - 22 Coggon, D, Rose G, Barker, DJP. Epidemiology for the uninitiated. Fourth Ed. British Medical Journal Publishing Group: 1997. Available at: <http://www.bmj.com/collections/epidem/epid.2.dtl> Accessed 6 July 2009.
 - 23 Stedman's Medical Dictionary. 28th Edition .Lippincott Williams & Wilkins. Baltimore Maryland USA; 2000.
 - 24 World Health Organization. The Z-score or standard deviation classification system. Available at: <http://www.who.int/nutgrowthdb/about/introduction/en/index4.html>. Accessed 6 July 2009.
 - 25 EuroQol Group. European Quality of Life questionnaire (EQ-5d). Available at: <http://www.euroqol.org/eq-5d/what-is-eq-5d/eq-5d-nomenclature.html>. Accessed 6 July 2009.

Glossary

- **Annualised growth rate:**

Linear growth/height velocity (rate) over 12 months

- **Ephyseal plate closure:**

Fusing of the growth plates at the end of the long bones of the body (which signifies that the subject has achieved final adult height)⁵

- **EQ-5D:**

This is a measure of health status for use in evaluating health and healthcare. It describes health status according to five dimensions, and provides a simple descriptive profile generating a single index for health status on which full health is assigned to a value of one and death a value of zero. It has been specifically designed to complement other quality of life measures²⁵.

- **Height standard deviation scores:**

See below under standardised deviation score

- **Height velocity standard deviation score:**

See below under standardised deviation score

- **Hypoacusis (SYN. hypacusis):**

Hearing impairment²³

- **Incidence:**

The rate at which new cases occur in a population during a specified period²².

- **Linear growth rate/height velocity (rate):**

Rate of growth from one point in time to another

- **Prevalence:**

The proportion of a population that are cases at a point in time²².

- **Standardised deviation score:**

The standard score indicates how many standard deviations an observation is above or below the mean: the SD is the unit measurement of the standard score (also known as the z score)²⁴.

standard deviation score²⁴ = $\frac{\text{observed value} - \text{median value of the reference population}}{\text{standard deviation value of the reference population}}$.

Therefore:

Height standard(ised) deviation scores are a measure of the height of patients compared to the height of age-matched members of the normal population.

Height velocity standard(ised) deviation scores are a measure of the growth rate of patients compared to the growth rate of age-matched members of the normal population.

- **Standardised height:**

See definition for height standardised deviation score.

Appendix 1. Additional Clinical Information

Table 1. Prospective studies of mecasermin (Increlex®[▼]) for the long-term treatment of growth failure in children and adolescents with SPIGFD

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Study F0375g ^{3,5,6}	Phase III randomised, double-blind, placebo-controlled, crossover, multicentre Blinded phase: 15 months Open-label phase: 12 months	8	Inclusion criteria: ▪ HSDS < -2 for age. ▪ Growth rate of < 50th percentile for age ≥ 6 months prior to study entry. ▪ Plasma IGF-I SD score < -2 for age. ▪ Evidence that short stature not treatable with GH³. ▪ Laron-type SPIGFD: GH level ≥10ng/mL and failure to increase plasma IGF-1 by 50ng/mL in response to GH ▪ GH gene-deletion type SPIGFD only: presence of GH antibodies to exogenous GH with a binding capacity of > 10mcg/mL. Exclusion criteria: ▪ Active malignancy or any history of malignancy. ▪ Growth failure due to genitourinary, cardiopulmonary, gastrointestinal, nervous system or other endocrine disorders, i.e. diabetes mellitus, nutritional/vitamin deficiencies, chondrodystrophies,. ▪ Treatment with any corticosteroids or other medications that influence growth. ▪ Treatment with any other investigational drug within 30 days of this study. ▪ Abnormal ECG or a history of cardiac arrhythmia.	Commercial in confidence data	rhIGF-I therapy 80 mcg/kg to 120 mcg/kg SC twice daily versus placebo Period A: 6 month double blind treatment with rhIGF-1 or placebo Period B: 3 month washout period Period C: 6 month crossover double blind period treatment rhIGF-1 or placebo Following the completion of the blinded period, open label rhIGF1 was continued for an additional 12 months	Commercial in confidence data

ECG: electrocardiogram; HSDS: height standardised deviation score; GH: Growth Hormone; mcg: micrograms; SC: subcutaneously; SD : Standard deviation; SPIGFD: Severe Primary Insulin-like Growth Factor Deficiency; IGFH-1= Insulin-like Growth factor Hormone -1.

Table 1 Continued

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Study F0206s ^{3,5,7}	Phase III open-label, single centre Treatment duration: 24 months	8	Inclusion criteria^{3,7}: ▪ HSDS < -2 for age. ▪ Growth rate of < 50th percentile for at least one year prior to study entry. ▪ Plasma IGF-I SD score < -2 for age, and failure to increase after administration of GH at a dose of 100 micrograms/kg daily for four consecutive days. ▪ No other reason for growth failure ▪ Open epiphyses ▪ Age >2 years. ▪ Laron-type SPIGFD only; basal serum GH >5 nanograms/mL, with additional increases after provocative testing Exclusion criteria^{3,7}: ▪ Active malignancy or any history of malignancy. ▪ Growth failure due to genitourinary, cardiopulmonary, gastrointestinal, nervous system; or other endocrine disorders, i.e. diabetes mellitus, nutritional/vitamin deficiencies, chondrodystrophies. ▪ Treatment with any corticosteroids or other medications that influence growth. ▪ Treatment with any other investigational drug within 30 days of this study. ▪ Abnormal ECG or a history of cardiac arrhythmia.	Laron-type SPIGFD (n=5) GH gene deletion defects (n=3). Female (n=2) Male (n=6) Mean age: 6.7 years (range:2.3 years to 11 years) ⁷ Mean (±SD) annualised growth rate prior to study: 3.9cm/year (range:-2.1-5.1 cm/year) ⁷ . Mean HSDS at baseline: - 5.6 (range: - 7.0 to - 3.4).	rhIGF-I starting dose of 40 mcg/kg SC twice daily increased over two days to 120 mcg/kg when tolerated.	Primary efficacy endpoint (n=8): Annualised growth rate over the first and second year of treatment (cm/year): First-year: Mean (SD) height velocity (cm/year) = 9.3 (3.8) Second year: Mean (SD) height velocity (cm/year) = 6.2 (0.5) Secondary efficacy endpoint: Mean change HSDS (range) after two years: +1.2 (-0.6 to +2.1)
ECG: electrocardiogram; HSDS: height standardised deviation score; GH: Growth Hormone; mcg: micrograms; SC: subcutaneously; SD: Standard deviation; SPIGFD: Severe Primary Insulin-like Growth Factor Deficiency; IGFH-1: Insulin-like Growth factor Hormone -1.						

Table 1 Continued

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Study F0671g ^{3, 21}	Phase III open-label, multi-centre Treatment duration: 24 months	23	Inclusion criteria: ▪ HSDS < -2 for age ▪ Growth rate of < 50th percentile for age ≥ 6 months prior to study entry. ▪ Plasma IGF-I SD score < -2 for ▪ Evidence that short stature not treatable with GH³. Exclusion criteria: ▪ Active malignancy or any history of malignancy. ▪ Growth failure due to genitourinary, cardiopulmonary, gastrointestinal, nervous system; or other endocrine disorders, i.e. diabetes mellitus, nutritional/vitamin deficiencies, chondrodystrophies ▪ Treatment with any corticosteroids or other medications that influence growth. ▪ Treatment with any other investigational drug within 30 days of this study. ▪ Abnormal ECG or a history of cardiac arrhythmia. NB: Additional commercial in confidence data was made available to AWMSG²¹.	Commercial in confidence data ²¹	rhIGF-I therapy 80 mcg/kg to 120 mcg/kg SC twice daily	Commercial in confidence data ²¹
ECG: electrocardiogram; HSDS=height standard deviations; GH=Growth Hormone; mcg: micrograms; SC: subcutaneously; SD =Standard deviation; SPIGFD= Severe Primary Insulin-like Growth Factor Deficiency; IGFH-1= Insulin-like Growth factor Hormone -1.						

Table 1 Continued

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Study 1419 ^{1,10}	Ongoing open-label, multicentre (intergrated study analysis) The mean duration of treatment was 4.4 ± 3.1 years, representing a total of 321 subject-years of therapy. Study 1419 is ongoing.	76	Inclusion criteria: ▪ HSDS < - 2 for age and sex. ▪ Height velocity < 50th percentile for age and sex. ▪ IGF-I SD score < - 2 for age and sex. ▪ Age > 2 years. ▪ Failure to increase serum IGF-I concentrations by 50 ng/mL in response to exogenous recombinant human GH at a dose of 100 micrograms/kg/day, except for subjects with GH gene deletions. ▪ Random or stimulated GH concentration ≥ 10 ng/mL except for subjects with GH gene deletions. ▪ For subjects with GH gene deletions, presence of anti-GH antibodies with a binding capacity > 10 mcg/mL. Exclusion criteria: ▪ Active malignancy or any history of malignancy. ▪ Growth failure due to other disorders of genitourinary, cardiopulmonary, gastrointestinal, or nervous system; other endocrine disorders, including diabetes mellitus, nutritional/vitamin deficiencies, chondrodystrophies, or a known dysmorphic syndrome. ▪ Treatment with any corticosteroids or other medications that influence growth. ▪ Clinically significant abnormal electrocardiogram (ECG) or a clinically significant history of cardiac arrhythmia³.	Male (n=38;61%) 56 (90%) of the children were pre-pubertal at baseline Mean ± SD age (years): 6.8 ± 3.8 ¹ Mean ±SD height velocity (cm/year): 2.8 ± 1.8 ¹ Mean HSDS at baseline: - 6.7 ± 1.8 ¹	rhIGF-I therapy 80 micrograms/kg to 120 micrograms/kg subcutaneously twice daily versus placebo NB: Additional commercial in confidence data was made available to AWMMSG.	Please refer to Table 1B, Appendix 1 for the results of height velocity (cm/year), height velocity SDS, and height SDS from year one through to year eight.
HSDS=height standard deviation score; GH=Growth Hormone; mcg =micrograms; ng=nanograms; SD =Standard deviation; SPIGFD= Severe Primary Insulin-like Growth Factor Deficiency; IGFH-1= Insulin-like Growth factor Hormone -1. BID= Twice daily						

Table 1B: Annual height results by number of years treated with Increlex[®]▼¹

	Pre-Tx	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Height Velocity (cm/yr)									
N	59	59	54	48	39	21	20	16	14
Mean (SD)	2.8 (1.8)	8.0 (2.2)	5.8 (1.4)	5.5 (1.9)	4.7 (1.4)	4.7 (1.6)	4.8 (1.5)	4.6 (1.5)	4.5 (1.2)
Mean (SD) for change from pre-Tx		+5.2 (2.6)	+3.0 (2.3)	+2.6 (2.3)	+1.6 (2.1)	+1.5 (1.8)	+1.5 (1.7)	+1.0 (2.1)	+0.9 (2.4)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	0.0015	0.0009	0.0897	0.2135
Height Velocity SDS									
N	59	59	53	47	38	19	18	15	12
Mean (SD)	-3.3 (1.7)	1.9 (2.9)	-0.2 (1.6)	-0.3 (2.0)	-0.7 (1.9)	-0.6 (2.1)	-0.4 (1.4)	-0.4 (1.9)	-0.3 (1.8)
Mean (SD) for change from pre-Tx		+5.1 (3.1)	+3.2 (2.2)	+3.1 (2.4)	+2.5 (2.1)	+2.5 (2.2)	+2.7 (1.7)	+2.5 (2.1)	+2.8 (2.7)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.0003	0.0041
Height SDS									
N	62	62	57	51	41	22	20	16	14
Mean (SD)	-6.7 (1.8)	-5.9 (1.7)	-5.6 (1.8)	-5.3 (1.8)	-5.3 (1.8)	-5.5 (1.8)	-5.4 (1.8)	-5.2 (2.0)	-5.2 (1.9)
Mean (SD) for change from pre-Tx		+0.8 (0.5)	+1.1 (0.8)	+1.4 (1.0)	+1.4 (1.1)	+1.4 (1.3)	+1.4 (1.2)	+1.4 (1.1)	+1.6 (1.1)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001

Pre-Tx = Pre-treatment; SD = Standard Deviation; SDS = Standard Deviation Score[1] P-values for comparison versus pre-Tx values were computed using paired t-tests.