NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SAIZEN® solution for injection cartridge

Somatropin (rmc*), recombinant human growth hormone

6 mg/1.03 mL (5.83 mg/mL)

12 mg/1.5 mL (8 mg/mL)

20 mg/2.5 mL (8 mg/mL)

*recombinant mouse cell

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAIZEN is a recombinant human growth hormone (somatropin), which is prepared from genetically engineered mammalian cells (recombinant mouse cells – C127) transformed with a bovine papilloma virus vector containing the human growth hormone coding sequence. According to the European Pharmacopoeia, somatropin (rmc) 3 IU equals 1 mg somatropin (rmc) by weight. The dose in mg, set out below, is based on this equivalence.

Each cartridge contains somatropin (rmc) 6 mg/1.03 mL (5.83 mg/mL), 12 mg/1.5 mL (8 mg/mL) or 20 mg/2.5 mL (8 mg/mL).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SAIZEN solution for injection is a clear solution, free from visible particles. The solution should not be administered if it contains particles or is not clear.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

SAIZEN is indicated for:

Children and adolescents (≤ 18 years old):

1. Growth failure in children due to human growth hormone deficiency.

2. Growth failure in girls with gonadal dysgenesis (Turner Syndrome), confirmed by chromosomal analysis.

3. Growth disturbance (growth retardation) in pre-pubertal children due to chronic renal insufficiency (CRI).

Adults (> 18 years old):

4. SAIZEN is indicated for replacement therapy in adults (over 18 years old) with pronounced growth hormone deficiency as diagnosed in 2 different dynamic tests for growth hormone deficiency and defined by peak GH concentrations of less than 2.5 nanogram/mL. Adults must also fulfil the following criteria:

   Childhood onset:

   Patients who were diagnosed as growth hormone deficient during childhood, must be retested and their growth hormone deficiency confirmed before replacement therapy with SAIZEN is started.

   Adult onset:

   Patients must have growth hormone deficiency as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using growth hormone may begin.

4.2 Dose and method of administration

Dose

Paediatric population

Treatment should be discontinued when a satisfactory adult height has been reached or when epiphyses are closed.

The maximum recommended daily dose should not be exceeded.

1. Treatment of growth failure due to growth hormone deficiency in children

The recommended weekly dose is as follows:
0.2 mg/kg body weight
4 mg/m^2 BSA (Body Surface Area)

The weekly dose may be divided as shown below and is expressed per injection:

3 single doses	0.07 mg/kg body weight 1.3 mg/m^2 BSA
6 single doses	0.03 mg/kg body weight 0.7 mg/m^2 BSA
7 single doses	0.03 mg/kg body weight 0.6 mg/m^2 BSA

2. Treatment of growth failure in girls with gonadal dysgenesis (Turner Syndrome)

The recommended daily dose is:

0.045-0.05 mg/kg body weight 1.4 mg/m^2 BSA

3. Treatment of growth disturbance in children with chronic renal insufficiency

The recommended daily dose is:

0.045-0.05 mg/kg body weight 1.4 mg/m^2 BSA

Adults

4. Treatment of growth hormone deficiency in adults

At the start of somatropin therapy, low doses of 0.15 – 0.3 mg are recommended, given as a daily subcutaneous injection. The dose should be titrated carefully guided by IGF-1 age-adjusted normal values and on the basis of clinical effect and adverse events. The recommended final GH dose seldom exceeds 1.0 mg/day. In general the lowest efficacious dose should be administered. With men showing an increasing IGF-1 sensitivity over time, dose adjustment may be required for women, especially for those on oral oestrogen replacement. In older or overweight patients, lower doses may be necessary.

Method of administration

For medicine preparations intended for **self-administration by subcutaneous injection**, patients should be thoroughly instructed in the correct administration procedures. This is especially important if **injection devices** are used in combination with multidose medicine preparations. Before using the injection devices, patients should be thoroughly trained to ensure that they are competent in the operation of the device. Periodic monitoring/supervision are also advisable.

SAIZEN is administered by subcutaneous injection, preferably in the evening. The injection site should be alternated to prevent localised lipoatrophy.

SAIZEN solution for injection must be administered with the dedicated autoinjector devices (electronic and/or manual) provided separately. For administration, refer to the instructions provided with the device.

4.3 Contraindications

SAIZEN should not be used for growth promotion in children/patients with closed epiphyses.

SAIZEN should not be used in patients with hypersensitivity to any constituent of the product (See **Presentation**).

SAIZEN is contraindicated where there is evidence of an active intracranial lesion. Intracranial lesions must be inactive for 12 months prior to instituting therapy and SAIZEN should be discontinued if there is any evidence of recurrent activity.

SAIZEN is contraindicated in patients with active neoplasia (either newly diagnosed or current). Any pre-existing neoplasia should be inactive and any anti-tumour activity must be completed prior to starting treatment with somatropin. SAIZEN should be discontinued if there is evidence of tumour growth.

Somatropin is contraindicated in patients with proliferative or preproliferative diabetic retinopathy.

SAIZEN should not be initiated to treat patients with acute critical illness due to complications following open heart surgery or abdominal surgery, multiple accident trauma, to patients having acute respiratory failure or patients with similar conditions (see **Warnings and Precautions**).

In children with chronic renal disease, treatment with somatropin must be discontinued at the time of renal transplantation.

4.4 Special warnings and precautions for use

SAIZEN therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of growth hormone deficiency.

When somatropin is administered subcutaneously at the same site over a long period, localised lipoatrophy may result. This can be avoided by frequent rotation of the injection site.

Fluid retention

Fluid retention is expected during growth hormone replacement therapy in adults. In case of persistent oedema or severe paraesthesis, the dosage should be decreased in order to avoid the development of carpal tunnel syndrome. Adult growth hormone deficiency is a lifelong condition. However, caution should be exercised because experience with prolonged treatment in adults is limited. Other hormonal deficiencies found in hypothalamic disease or pituitary disease should be treated with adequate replacement therapy before SAIZEN therapy is instituted.

Critically ill patients

The effects of *E-coli* derived growth hormone on recovery were studied in two placebo-controlled clinical trials involving 522 adult patients who were critically ill due to complications following open heart or abdominal surgery, multiple accident trauma, or who were having acute respiratory failure. Mortality was higher (41.9% vs 19.3%) among growth hormone treated patients (doses 5.3 - 8 mg/day) than among those receiving placebo. Based on this information, these patients must not be treated with somatropin (see **Contraindications**). The safety of continuing growth hormone in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation in patients having acute critical illness should be weighed against the potential risk.

Hypothyroidism

The possible appearance of hypothyroidism in the course of therapy with SAIZEN should be corrected with thyroid hormone in order to obtain a satisfactory growth response. Thyroid assessment, by thyroid hormone level measurements, should be undertaken before starting SAIZEN therapy and not less frequently than annually.

Insulin resistance

Because somatropin can decrease insulin sensitivity, patients treated with growth hormone should be monitored for evidence of glucose intolerance. SAIZEN should be used with caution in patients with diabetes mellitus or with a family history of diabetes mellitus. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted.

Growth hormone administration is followed by a transient phase of hypoglycaemia of approximately 2 hours, then from 2-4 hours onward by an increase in blood glucose levels despite high insulin concentrations. Somatropin may induce a state of insulin resistance which can result in hyperinsulinism and in some patients in hyperglycaemia. To detect an insulin resistance, patients should be monitored for evidence of glucose intolerance. Patients

with diabetes mellitus or glucose intolerance should be monitored closely during SAIZEN therapy.

Prader-Willi Syndrome
While Saizen is not indicated for the treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi Syndrome, it should be noted that there have been reports of sleep apnoea and sudden death after initiating therapy with growth hormone in paediatric patients with Prader-Willi Syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

Haematological neoplasms
An increased incidence of leukaemia in growth hormone deficient children has been observed. A causal relationship to growth hormone therapy has not been established.

Tumour occurrence and recurrence
There are only limited data available in regard to the risk of tumour development under treatment with growth hormone. Therefore, patients treated with growth hormone should be carefully monitored.

In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with growth hormones.

Treatment in growth hormone deficient adults should be attempted only after definitive treatment of pituitary tumour (if present) is completed and all other pituitary hormone deficiencies are corrected as clinically needed.

Patients with growth hormone deficiency secondary to an intracranial tumour or other lesion should be examined frequently for progression or recurrence of the underlying disease process.

Pancreatitis
Pancreatitis should be considered in somatropin-treated patients, especially children, who develop abdominal pain.

Scoliosis
Scoliosis is known to be more frequent in some of the patient groups treated with somatropin, for example Turner syndrome. In addition, rapid growth in any child can cause progression of scoliosis. Somatropin has not been shown to increase the incidence or severity of scoliosis. Signs of scoliosis should be monitored during treatment.

Slipped capital femoral epiphysis
Patients receiving growth hormone therapy should be observed for the possible onset of a limp, or complaints of hip or knee pain, as this may indicate the development of slipped capital femoral epiphysis.

Patients with growth retardation due to chronic renal insufficiency should be regularly examined and monitored for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular necrosis of the femoral head may occur in children with advanced renal osteodystrophy and it is uncertain whether these complications are affected by growth hormone therapy. Assessment of the hip should be obtained prior to initiating therapy and at regular intervals upon discretion of the physician.

Idiopathic intracranial hypertension
Fundoscopic examination should be performed routinely before initiating treatment with SAIZEN to exclude pre-existent papilloedema and repeated if there is any clinical suspicion. In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a

fundoscopy for papilloedema is recommended. If papilloedema is confirmed by fundoscopy, a diagnosis of idiopathic intracranial hypertension should be considered and if appropriate, the growth hormone treatment should be discontinued.

At present there is insufficient evidence to guide clinical decision-making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Antibodies
As with all somatropin-containing products, a small percentage of patients may develop antibodies to SAIZEN. The binding capacity of these antibodies is low and there is no effect on growth rate. Testing for antibodies to somatropin should be carried out in any patient who fails to respond to therapy (also see **Adverse Effects**).

Chronic renal insufficiency
In children with chronic renal insufficiency, renal function should have decreased to below 50% of normal before therapy is instituted. To verify the growth disturbance, growth should have been followed for a year or upon physician discretion (for example not less than 6 months in the older children) before institution of therapy. Conservative treatment for renal insufficiency should have been established and should be maintained during treatment. Treatment should be discontinued at the time of renal transplantation.

Renal insufficiency
Somatropin clearance is known to be reduced in patients with renal impairment. However, based on clinical data there is no need for dosage adjustment.

Hepatic insufficiency
Somatropin clearance is known to be reduced in patients with hepatic impairment. However, as SAIZEN has not been studied in patients with hepatic impairment, the clinical significance of this finding is unknown.

Use in the elderly
Experience in patients over 60 years is limited.

Carcinogenicity
Associations between elevated serum IGF-1 concentrations and risk of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known.

Genotoxicity
There was no evidence of genotoxicity in assays for gene mutation in bacteria, chromosomal damage in human lymphocytes and rat bone marrow cells, gene conversions in yeast or unscheduled DNA synthesis in human carcinoma cells.

4.5 Interaction with other medicines and other forms of interaction

Concomitant corticosteroid therapy may inhibit the response to SAIZEN. If glucocorticoid replacement is required, the dose of somatropin should be carefully adjusted.

In addition, initiation of growth hormone replacement may unmask secondary adrenal insufficiency in some patients by reducing the activity of 11β-hydroxysteroid dehydrogenase, type 1 (11β-HSD1), an enzyme converting inactive cortisone to cortisol. Initiation of somatropin in patients receiving glucocorticoid replacement therapy may lead to manifestation of cortisol deficiency. Adjustment of glucocorticoid dose may be required.

Because oral oestrogens may reduce the serum IGF-1 response to somatropin treatment, patients receiving oral oestrogen replacement may require dosage adjustment of somatropin. If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be adjusted to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral oestrogen therapy, the dose of somatropin may need to be adjusted to avoid excess of growth hormone and/or side effects.
Published *in vitro* data indicate that growth hormone may be an inducer of cytochrome P450 3A4. The clinical significance of this observation is unknown. However, when somatropin is administered in combination with medicines known to be metabolised by CYP450 3A4 hepatic enzymes, it is advisable to monitor clinical effectiveness of such medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category B1)

Somatropin was not teratogenic in rats or rabbits at respective doses of up to 14 and 22 times the maximum recommended clinical dose (4.3 IU or 1.4 mg/m^2/day), based on body surface area. In rats, somatropin administered from late gestation to weaning, at 14 times the clinical dose based on body surface area, was associated with increased body weight of pups at birth and postnatally. There are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

Breast-feeding

There have been no clinical studies conducted with somatropin in breastfeeding women. It is not known whether somatropin is excreted in human milk. Therefore, caution should be exercised when SAIZEN is administered to breastfeeding women.

Following subcutaneous administration of radiolabelled somatropin to lactating rats, radioactivity was transferred to milk reaching four times the concentration found in maternal plasma. However, absorption of the intact protein in the gastrointestinal tract of the infant is extremely unlikely.

Fertility

In *E-coli* derived growth hormone studies, reproduction was inhibited in male and female rats at doses of 3 IU/kg/day (1 mg/kg/day) or more, with reduced copulation and conception rates, lengthened or absent oestrus cycles, and at 10 IU/kg/day (3.3 mg/kg/day), a lack of responsiveness of females to males, and slight reductions in sperm motility and survival. Rat reproduction was unaffected by (0.3 mg/kg/day) somatropin, which resulted in a systemic exposure (based on body surface area) of approximately twice that anticipated at the maximum clinical dose.

In reproduction studies using recombinant mouse cell derived somatropin, no effects on female fertility were observed in rats treated with somatropin at subcutaneous doses of up to 10 IU/kg/day (equivalent to 20 mg/m^2/day, about 14 times the maximum clinical dose on a body surface area basis).

4.7 Effects on ability to drive and use machines

Due to its pharmacological profile somatropin is unlikely to impair the patient's ability to drive or to operate machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

The adverse reactions reported below are classified according to frequency of occurrence as follows:

Very Common	≥ 1/10
Common	> 1/100 - < 1/10
Uncommon	> 1/1000 - < 1/100
Rare	> 1/10000 - < 1/1000
Very rare	≤ 1/10000

Application site disorders

Common: Injection site reactions (pain, numbness, redness, swelling), localized lipoatrophy, which can be avoided by varying the site of injection

Body as a whole – General disorders

Common (in adults) Uncommon (in children): Fluid retention: peripheral oedema, stiffness, arthralgia, myalgia, paresthesia.

Nervous System Disorders

Common: Headache, carpal tunnel syndrome (in adults)

Uncommon: Idiopathic intracranial hypertension (benign intracranial hypertension), carpal tunnel syndrome (in children)

Endocrine Disorders

Very rare: Hypothyroidism

Gastrointestinal disorders

Frequency not known: Pancreatitis

Immune system disorders

Frequency not known: localised and generalised hypersensitivity reactions

Reproductive system and breast disorders

Uncommon: Gynaecomastia

Musculo-skeletal disorders

Very rare: Slipped capital femoral epiphysis (epiphysiolysis capitis femoris)

Metabolism disorders

Frequency not known: Hyperglycaemia, hyperinsulinism, insulin resistance

Insulin resistance can result in hyperinsulinism and in rare cases in hyperglycaemia.

Hypothyroidism has been reported in a small number of patients during SAIZEN therapy. It should be noted, however, that hypothyroidism can occur in untreated Turner Syndrome patients.

Fluid retention is expected during growth hormone replacement therapy in adults. Oedema, joint swelling, arthralgias, myalgias and paresthesias may be clinical manifestations of fluid retention. However, these symptoms / signs are usually transient and dose dependent.

Adult patients with growth hormone deficiency following diagnosis of growth hormone deficiency in childhood, reported adverse effects less frequently than those with adult onset growth hormone deficiency.

As with all somatropin-containing products, a small percentage of patients may develop antibodies to SAIZEN. The clinical significance of these antibodies is unknown, though to date the antibodies have been of low binding capacity and have not been associated with growth attenuation except in patients with gene deletions. In very rare instances, where short stature is due to deletion of the growth hormone gene complex, treatment with growth hormone may induce growth attenuating antibodies.

Common adverse effects reported in SAIZEN trials that were not considered to be treatment related included: upper respiratory tract infection, fever, headache, pharyngitis, otitis media, coughing, vomiting, dyspepsia.

Glucose intolerance was not seen during clinical studies, but a number of subjects had relatively high insulin levels during oral glucose tolerance tests.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Moreover, somatropin overdose is likely to cause fluid retention. Long-term overdosage could result in signs and symptoms of acromegaly.

Contact the Poisons Information Centre on (telephone 131 126 in Australia or 0800 764 766 in New Zealand) for advice on the management of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Pituitary and hypothalamic hormones and analogues
Anterior pituitary lobe hormones and analogues

ATC code: somatropin (H01AC01)

Mechanism of action
Human growth hormone (hGH) is normally secreted at night during sleep and promotes skeletal, visceral and general body growth through the action of somatomedins or insulin-like growth factors. Somatropin raises the serum levels of IGF-1. Growth hormone has a role in building and sustaining lean body mass, facilitating the utilisation of fat mass for energy needs, and maintaining bone mineral density. Apart from its effects on growth, hGH has a variety of effects on lipid, protein and carbohydrate metabolism.

Clinical efficacy and safety

Inadequate Endogenous Growth Hormone Secretion

Efficacy and safety of SAIZEN have been studied in five pivotal studies using pretreatment growth measurements compared with treatment growth measured as a method of control.

The effectiveness of growth hormone treatment on growth was assessed primarily by changes in Height Velocity Standard Deviation Score (HV SDS) and Height SDS (H SDS) after at least 24 months of treatment. r-hGH was administered subcutaneously in all of the studies. Patients were randomised in two groups: Group 1 (n=203; 178 naïve, 25 non-naïve) who received r-hGH 0.6 IU/kg body weight/week (0.2 mg/kg/week) via subcutaneous injections three times a week (higher dose, lower frequency); and Group 2 (n=101; 47 naïve, 54 non-naïve) who received r-hGH 0.45 IU/kg body weight/week (0.15 mg/kg/week) seven times a week (lower dose, higher frequency).

Of the 304 prepubertal children included, 225 were previously untreated (treatment-naïve children) and 79 had been switched to r-hGH (SAIZEN) from pituitary-derived hGH after interruption of therapy for at least 6 months. For both naïve and transfer patients in both groups, there was a significant increase in HV, HV SDS and H SDS, at 1 and 2 years, as shown in Table 1.

Table 1: HV, HV SDS and H SDS Prior to and during the 1st and 2nd Years of Treatment (a) Naïve and (b) Transfer Patients who Completed 2 Years of Therapy

	(a) Naïve Patients (24-month treatment only)					
	Group 1* (n=87)			Group 2* (n=22)		
	Baseline	1st year	2nd year	Baseline	1st year	2nd year
HV (cm/year)	3.5 ± 1.2	8.6 ± 2.0	6.6 ± 1.4	3.4 ± 1.1	11.0 ± 2.7	7.1 ± 1.2
HV SDS	-2.8 ± 1.6	+4.2 ± 2.2	+2.0 ± 1.5	-3.3 ± 1.5	+5.7 ± 2.0	+1.8 ± 1.7
H SDS	-4.2 ± 1.3	-3.4 ± 1.1	-3.0 ± 1.2	-4.4 ± 1.0	-3.1 ± 0.8	-2.7 ± 0.9
	(b) Transfer Patients (24-month treatment only)					
	Group 1* (n=14)			Group 2* (n=32)		
	Baseline	1st year	2nd year	Baseline	1st year	2nd year
HV (cm/year)	3.2 ± 1.1	7.2 ± 2.9	5.0 ± 1.6	2.3 ± 1.3	10.0 ± 1.9	6.8 ± 1.2
HV SDS	-2.2 ± 1.7	+4.2 ± 4.3	+1.6 ± 2.4	-3.3 ± 2.4	+7.8 ± 2.5	+3.9 ± 2.6
H SDS	-3.9 ± 1.5	-3.3 ± 1.6	-3.1 ± 1.5	-4.4 ± 1.5	-3.3 ± 1.4	-2.8 ± 1.4

*Group 1: 3 injections/week; Group 2: 7 injections/week

Standards according to Prader (Prader A, Largu RH, Molinari L, Issler C. Acta Paediatr 1998;52:1-125), extrapolated for prepubertal children (Preece, In Halliday MA, Barrett TM, Vernier RL, eds. Paediatric Nephrology. Baltimore: Williams and Wilkins, 1986:14-30).

Values are ± SD

Children receiving daily injections of r-hGH (both treatment-naïve and previously treated with pituitary-derived hGH) demonstrated a higher growth rate than those receiving three injections per week (Group 1 vs Group 2; $p<0.001$).

An extension study assessed growth response in 69 prepubertal children (19 girls) with idiopathic (n=48) or organic (n=21) growth hormone deficiency receiving r-hGH (SAIZEN) 0.6 IU/kg/week (0.2 mg/kg/week) via three subcutaneous injections. The initial treatment period (2 years), as described above, was followed by an optional extended treatment period during which the total weekly dose of r-hGH was unchanged; however, in most cases, dosing frequency increased to six or seven times per week. The mean duration of treatment was 64.4 months (range 1.2 – 140.9 months). The median H SDS at the start of the study was -3.8, and this improved significantly to -3.3 ($p < 0.001$) during the first year after the start of r-

hGH therapy; this improvement was maintained throughout the study, resulting in a median value of -1.5 H SDS after 7 years of SAIZEN therapy. During the first year of r-hGH treatment, the median HV of patients was 8.5 cm/year (-2.8 SDS). During treatment years 2 – 7, patients' median HVs ranged between 5.5 and 6.7 cm/year (1.0 – 1.8 SDS). Bone age (BA) did not advance rapidly in response to treatment with r-hGH (1.3 ± 1.0 years/year, compared to 1.4 ± 0.3 years/year in change of height age (HA).

All studies conducted in prepubertal or pubertal children with inadequate endogenous growth hormone secretion (five studies) demonstrated the safety of somatropin and confirmed the known safety profile. Two patients developed anti-hGH antibodies. In both cases, the antibodies did not have any growth inhibiting effect. None of the patients developed antibodies to host cell protein. Three transfer patients who had anti-h-GH antibodies prior to treatment became negative within 6 months of treatment with SAIZEN.

Turner Syndrome

An open, randomised multicentre study (Phase III) was conducted to assess the efficacy and safety of SAIZEN (r-hGH) and of the combination with oxandrolone in 91 growth retarded girls with Turner Syndrome (TS).

The diagnosis of TS was made on the basis of clinical characteristics and verified by karyotype analysis. The inclusion criteria were absence of the 2nd X chromosome or chromosome aberrations, chronological age (CA) > 5 years, bone age < 11 years, height at least 2 standard deviations (SD) below the mean for CA and post-stimulatory circulating hGH serum levels of >10 ng/mL.

The girls were randomly allocated to one of two original treatment groups: (1) SAIZEN alone or (2) SAIZEN in combination with the anabolic steroid oxandrolone. Group 1 received 18 IU/m^2/week SAIZEN increasing to 24 IU/m^2/week after the first year. Group 2 received 18 IU/m^2/week SAIZEN and 0.1 mg/kg/day oxandrolone. The oxandrolone dose was reduced to 0.05 mg/kg/day after the first year.

After the second year, the dose of SAIZEN was 24 IU/m^2/week for all groups and two further subgroups were formed: (1a) who received 24 IU/m^2/week SAIZEN and 0.05 mg/kg/day oxandrolone and (2a) who stopped oxandrolone treatment and received 24 IU/m^2/week SAIZEN alone.

<u>Results</u>

This study demonstrated efficacy in Height Velocity (HV), Height SDS - CA, Height, Predicted adult height and Final height, with mean heights in each treatment group ranging from 147.5 to 153.6 cm. The mean (± SD) final height was 150.6 ± 5.5 cm. Fifteen patients developed anti-hGH antibodies on at least 1 occasion. However, as the average height of these patients was 149.3 ± 7.1 cm, the development of antibodies does not appear to have a negative impact on growth.

The use of oxandrolone was not associated with additional final height gain, but was associated with virilising side effects.

Adult Growth Hormone Deficiency (GHD)

A multicenter, randomised, double-blind, placebo-controlled clinical trial was conducted in 115 GHD adults comparing the effects of SAIZEN and placebo on body composition. Patients in the active treatment arm were treated with SAIZEN at an initial dose of 0.005 mg/kg/day for one month which was increased to 0.01 mg/kg/day if tolerated for the remaining five months of the study.

<u>Primary end-points</u>

The primary endpoint was the treatment difference on the change from baseline in lean body mass (LBM) measured by dual energy X-ray absorptiometry (DXA) after 6 months. Treatment with SAIZEN produced highly significant ($p<0.001$) increases from baseline in LBM compared to placebo (Table 1).

Table 1: Lean Body Mass (kg) by DXA

	SAIZEN (n=52)	Placebo (n=51)
LBM Baseline (kg) (mean)	47.7 ± 11.4	54.0 ± 12.0
Change from baseline at 6 months (LBM, kg) (mean)	+ 1.9 ± 2.2	– 0.2 ± 2.3
Treatment difference (LBM, kg) (mean) 95% confidence interval p-value	2.1 (1.3, 2.9) <0.001	

Sixty-seven (58%) of the 115 randomised patients were male. The adjusted mean treatment difference on the increase in LBM from baseline was significantly greater in males (2.9 kg) than females (0.8 kg).

Ninety-seven (84%) of the 115 randomised patients had adult onset (AO) GHD. The adjusted mean treatment differences on the increase in LBM from baseline was significantly different in AO GHD (2.1 kg, $p<0.001$). The difference in childhood onset (CO) GHD (1.0 kg) was not significantly different, however, there were relatively few patients with CO GHD (n=18) on which to base the comparison.

Secondary end-points:

Treadmill exercise test (Weber protocol): there was a slightly greater increase, albeit not statistically significant, in VO_{2max} in the SAIZEN group compared to placebo (SAIZEN: baseline 21.21 ± 7.71 mL/kg/min, N = 36, 6 months 25.50 ± 7.78 mL/kg/min, N = 26; placebo: baseline 23.36 ± 6.98 mL/kg/min, N = 35, 6 months 26.47 ± 8.58 mL/kg/min, N = 31). No statistically significant differences were noted for anaerobic threshold.

Analysis of the treatment difference on the change from baseline in total fat mass (by DXA) revealed: a statistically significant reduction of total fat mass ($p<0.0001$) in the SAIZEN group compared to placebo (SAIZEN: baseline 27.73 ± 10.72 kg, N = 59, 6 months 23.82 ± 9.65 kg, N = 52; placebo: baseline 28.90 ± 14.83 kg, N= 54, 6 months 29.12 ± 15.33 kg, N = 52). Anthropometry demonstrated no statistically significant differences between the treatment groups for skinfolds, waist/hip ratio or body weight. The sum of circumferences decreased significantly in the SAIZEN group relative to placebo ($p<0.017$).

SAIZEN also produced beneficial effects on several bone turnover markers including: bone specific alkaline phosphatase, C-terminal propeptide, osteocalcin and urine deoxypyridinoline and intact parathyroid. The changes in total bone mineral content and body cell mass were not statistically different between the treatment groups.

Perceived well-being: No significant differences were found in Nottingham Health Profile or the General Well-Being Index.

Handgrip strength: No statistically significant differences were found between the treatment groups in the assessments of dominant or non-dominant hand-grip strength.

Mid-thigh cross-sectional MRI: No statistically significant differences were found between the treatment groups in the assessments of percentages of fat, muscle or bone.

Cardiac function: Two-dimensional echocardiography showed statistically significant differences between the treatment groups for ejection fraction percentage (increase in the SAIZEN group, $p<0.048$; SAIZEN: baseline 54.90 $\pm$ 11.21%, N = 52, 6 months 60.89 $\pm$ 9.47%, N = 48; placebo: baseline 54.41 $\pm$ 12.91%, N = 50, 6 months 57.30 $\pm$ 8.61%, N = 49) and left ventricular end-systolic volume (decrease in the SAIZEN group, $p<0.035$; SAIZEN: baseline 35.83 $\pm$ 17.61 mL, N = 52, 6 months 30.40 $\pm$ 15.35 mL, N = 49; placebo: baseline 39.04 $\pm$ 16.00 mL, N = 48, 6 months 37.69 $\pm$ 16.64 mL, N = 49).

One hundred and eleven patients were treated with SAIZEN for an additional 12 to 36 months in an open label follow up study. During this period, the positive effects on LBM and fat mass achieved during initial treatment were maintained.

Chronic Renal Insufficiency (CRI)

Evidence of the safety and effectiveness of SAIZEN for the treatment of growth disturbance due to CRI is provided by the results of analysis of data from a study (4941) conducted with SAIZEN and published studies of clinical experience with r-hGH identified via a systematic literature review.

Study 4941

An open-label, multicentre study was conducted to evaluate the safety and efficacy of SAIZEN for the treatment of growth failure in children with CRI. Patients with growth failure and CRI were included in the study. CRI was defined as patients with end-stage renal disease on dialysis, or 12 months post kidney transplant, or compensated renal insufficiency with glomerular filtration rate (GFR) ≤ 30 mL/min per 1.73 m^2. Growth failure was defined as height of at least 2 SD and growth velocity of at least 0.5 SD below the mean for CA. Each patient's pre-treatment growth period served as a control for subsequent treatment periods. Patients were treated with SAIZEN 28 IU/m^2/week (0.35 mg/kg/week), administered by daily subcutaneous injections for the first 3 years of treatment, which could be increased to 36 IU/m^2/week (0.45 mg/kg/week) from the fourth year of treatment onwards in patients demonstrating insufficient growth.

A preliminary analysis was performed at one and two year time points. The primary efficacy endpoints for this analysis included increase in HV as well as H SDS and HV SDS for CA, calculated from baseline to the study time points. The secondary endpoint included the change in linear growth relative to the change in skeletal maturation (ΔHA/ΔBA ratio), as a measure of the preservation or loss of potential final height. Sub-group analysis was undertaken in all parameters after stratifying the patients according to their renal status.

Long term analysis was performed following 8 years of treatment. The primary endpoint for the long term analysis was the change in H SDS for CA, calculated from baseline, at onset of puberty and at study endpoint, and stratified according to final height status and overall. The secondary end point included the change in HV SDS during SAIZEN treatment. Other efficacy endpoints included parental adjusted H SDS and mean actual height.

Results

Preliminary analysis (1 and 2 years of treatment)

A total of 81 children were included in the study. The mean (±SD) CA was 8.6 ± 3.9 years with a BA of 5.7 ± 3.0 years.

Changes in Height Velocity (HV)
After 12 months: Of the 63 children available for analysis, 59 (94%) experienced an increase over baseline in HV. Mean HV (±SD) increased by 4.4 ± 4.0 cm/year ($p<0.001$).

After 24 months: Of the 44 children available for analysis, 39 (89%) experienced a sustained increase over baseline in HV. The mean HV for this cohort was 7.5 ± 2.9 cm/year, an increase of 3.0 ± 3.6 cm/year over baseline (p<0.001).

Changes in Height Standard Deviation Score (H SDS)
After 12 months: Of the 63 children available for analysis, 55 (87%) experienced an increase over baseline in H SDS. Mean H SDS increased by 0.7 ± 0.7 (p<0.001).
After 24 months: In the 44 children available for analysis, 39 (89%) experienced a sustained increase over baseline in H SDS. The percentage of children achieving a normal H SDS increased by 43% (19 of 44). For the group as a whole, the mean H SDS increased by 1.2 ± 1.2 (p>0.001).

Changes in Height Velocity Standard Deviation Score (HV SDS)
After 12 months: Of the 54 children available for analysis, 52 (96%) experienced an increase over baseline in HV SDS. Mean HV SDS increased by 6.2 ± 5.0 (p<0.001).
After 24 months: Of the 36 children available for analysis, 34 (94%) experienced a sustained increase over baseline. Mean HV SDS increased by 3.4 ± 3.5 (p<0.001).

The ΔHA/ΔBA was 1.6 ± 2.2 after the first year and 1.1 ± 0.6 after the second year of treatment, suggesting an improvement in predicted final height.

Analysis of Efficacy based on Renal Status
In the sub-group analysis, data were available from 44 children after the second year of treatment. Of these 44 children, 24 were in the compensated group and 8 were in the dialysis group. Data from the first year of treatment showed a significant increase in HV by +5.7 ± 5.1 cm/year over baseline (n=24, p<0.001) in the compensated group, and +4.6 ± 7.5 cm/year over baseline (n=8, p<0.001) in the dialysis group. After two years of treatment, HV increased from 5.0 ± 4.3 at baseline to 8.0 ± 3.8 (n=24, p<0.001) in the compensated group, and from 4.6 ± 6.4 at baseline to 5.9 ± 5.6 (n=8, p=0.211) in the dialysis group.

H SDS increased significantly in the compensated group, from -3.9 ± 2.0 at baseline to -.2.8 ± 1.9 after 12 months of treatment (n=24, p<0.001), to -2.1 ± 2.0 after 24 months of treatment (n=24, p<0.001). In the dialysis group, less pronounced increase was seen in H SDS, although it was still greater than the baseline (from -3.9 ± 3.0 to -3.2 ± 2.8 after 12 months treatment (n=8, p<0.004), to -3.0 ± 3.0 after 24 months treatment (n=8; p=0.014)).

In HV SDS, both compensated and dialysis groups experienced a significant increase after 12 months of treatment, from -2.1 ± 2.5 at baseline to 5.3 ± 4.8 (compensated, n=20, p<0.001), and from -2.0 ± 4.1 to 3.4 ± 7.9 (dialysis, n=7, p<0.001). After two years of treatment, a significant increase in HV SDS was still seen in the compensated group (from -2.1 ± 2.5 to 2.7 ± 4.3 (n=20, p<0.001)). However, the increase was less pronounced in the dialysis group (from -2.0 ± 4.1 to -0.5 ± 7.0 (n=7, p=0.176)).

In terms of secondary end-point, the ΔHA/ΔBA ratio in all groups was close to unity at baseline and was greater than 1.0 in all groups after 1 year of treatment reaching statistical significance in the compensated group.

Follow up analysis (2-8 years of treatment)

Longer term data were available from 31 patients who continued after 2 years of treatment and received between 2.2 and 7.8 years of treatment with SAIZEN (mean duration of study was 63.31 ± 18.26 months). Baseline was defined as the last recorded value before or on the day of inclusion.

Of the 31 patients, four patients reached final height (defined as HV < 2 cm/year and Tanner puberty score ≥ 4), 6 patients reached near-final height (defined as HV > 2cm/year, age >16 years (boys) or >14 years (girls) and 21 patients were in non-final height group. In the overall

group, mean H SDS during SAIZEN treatment increased from -3.12 ± 1.22 at baseline to -1.83 ± 1.88 at onset of puberty and there was a further increase to -1.21 ± 1.73 at study end point.

According to final height status, the gain in H SDS from baseline to study end was the greatest in the non-final height group (2.16 ± 1.25, $p<0.0001$) compared to the final height (1.26 ± 0.40, $p=0.1250$) and the near final height (1.44 ±1.66, $p=0.0625$) groups.

5.2 Pharmacokinetic Properties

After intramuscular injection of 4 IU somatropin (rmc)/m^2 body surface, C_{max} (36.9 ± 12.1 ng/mL) was measured at 3 hours (T_{max}). hGH levels returned to pre-injection levels after 12 hours. The AUC_{24} was 183 ng.h/mL. These pharmacokinetic parameters are similar to those reported in the literature for pituitary derived hGH. After subcutaneous injection C_{max} was delayed until 4 - 6 hours post injection. The AUC_{24} for the two routes of administration were similar.

SAIZEN solution for injection (5.83 mg/mL and 8 mg/mL) administered subcutaneously were shown to be bioequivalent to the 8 mg freeze-dried formulation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SAIZEN solution for injection also contains sucrose, poloxamer, phenol and water for injections. Sodium hydroxide and citric acid-anhydrous are used for pH adjustment.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Stored at 2°C to 8°C (Refrigerate. Do not freeze) in the original package. Protect from light.

After the first injection, the contents of the cartridge should be used within 28 days. After the first injection, should refrigeration be temporarily unavailable, the SAIZEN cartridge in the dedicated autoinjector device can be stored for up to 7 days at or below 25 °C (outside a refrigerator). Following this, the SAIZEN Cartridge must be returned to the refrigerator and stored at 2 °C to 8 °C (Refrigerate. Do not freeze) and still used within 28 days after the first injection.

6.5 Nature and contents of container and special equipment for administration

SAIZEN solution for injection is presented as a sterile liquid in glass cartridge for multidose use. It should be used with the dedicated autoinjector devices (electronic and/or manual) provided separately.

SAIZEN solution for injection is supplied in packs of 1 or 5[§] glass cartridges for multidose use in one patient only. Each cartridge contains somatropin (rmc) 6 mg/1.03 mL (5.83 mg/mL), 12 mg/1.5 mL (8 mg/mL) or 20 mg/2.5 mL (8 mg/mL).
[§] Not currently marketed.

6.6 Special precautions for disposal

Do not use if the solution contains particles or if the solution is not clear.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

SAIZEN is supplied in New Zealand by:
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland

SAIZEN is supplied in Australia by:
Merck Healthcare Pty Ltd
11 Talavera Road
Macquarie Park NSW 2113

9. DATE OF FIRST APPROVAL

14 March 2013

10. DATE OF REVISION OF THE TEXT

11 October 2019

SUMMARY TABLE OF CHANGES

Date	Sections	Description
11 Oct 2019	8	Update of Australian sponsor company name and address