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Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Macimorelin in Children with Suspected Growth Hormone Deficiency: An Open-Label, Group Comparison, Dose-Escalation Trial

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Keywords
Growth hormone deficiency · Macimorelin · Drug safety · Tolerability · Drug tolerance · Paediatrics · Pharmacokinetics · Pharmacodynamics

Abstract
Background/Aims: Diagnosis of growth hormone deficiency (GHD) in children requires the use of provocative growth hormone (GH) stimulation tests, which can have limited reliability and are potentially contraindicated in some patients. This is the first paediatric study to test the safety, tolerability, and pharmacokinetics (PK)/pharmacodynamics (PD) of macimorelin, an oral GH secretagogue, approved for diagnosis of adult GHD. ***Methods:*** In this open-label, group comparison, single-dose escalation trial (EudraCT 2018-001988-23), sequential cohorts of patients (C1–C3) received ascending single doses of macimorelin: 0.25 (C1), 0.5 (C2), and 1.0 (C3) mg/kg. Primary endpoints were safety and tolerability, and secondary endpoints were PK/PD. ***Results:*** Twenty-four patients aged between 2 and <18 with suspected GHD participated in the study. No macimorelin-related adverse events were reported, and macimorelin was well tolerated.

Trial ID: EudraCT 2018-001988-23.
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Plasma macimorelin concentrations increased with dose: mean areas under the curve were 6.69 (C1), 18.02 (C2), and 30.92 (C3) h × ng/mL; mean maximum concentrations were 3.46 (C1), 8.13 (C2), and 12.87 (C3) ng/mL. GH concentration increased following macimorelin administration: mean times of maximum measured concentration were 52.5 (C1), 37.5 (C2), and 37.5 (C3) min. ***Conclusion:*** All 3 doses of macimorelin had excellent safety and tolerability with PK/PD profiles in expected ranges. These results support the use of 1.0 mg/mL macimorelin in a Phase 3 test validation trial in children.

Introduction

Growth hormone deficiency (GHD) is a rare condition in children characterised by impaired growth which, if left untreated, can lead to permanent short stature and impaired quality of life due to psychological problems such as depression, anxiety, and sleep disturbance [1]. GHD is effectively treated with replacement growth hormone (GH) therapy, and accurate diagnosis at an early stage is very important for the timely management of the condition [2].

Failure to correctly diagnose the condition early, or an initial false-negative diagnosis, can result in a poor treatment outcome, while false-positive diagnosis can potentially lead to years of unnecessary and costly injections [2]. Despite the importance of accurate and timely diagnosis, there is currently no true "gold standard" method for the diagnosis of GHD [2]. Diagnosis of GHD usually involves 2 independent provocative GH stimulation tests (GHSTs), which most commonly include the use of agents such as insulin (i.e., the insulin tolerance test [ITT]), glucagon, clonidine, arginine, or L-dopa [2–4]. Preferences for the use of particular GHSTs can vary substantially between countries [5]. Furthermore, provocative GHSTs can be invasive and time-consuming, and some may be contraindicated in children [4, 5]. Several studies have also indicated that the reproducibility of provocative GHSTs is generally poor, hence the necessity to perform 2 provocation tests to confirm diagnosis [2, 5–7]. Furthermore, data regarding diagnostic cut-off concentrations for peak GH using GHSTs are limited, and a universal standard is yet to be established, leading to variation in how GHD is diagnosed between regions [2, 5, 8].

Macimorelin is an orally administered GH secretagogue receptor agonist that has been approved by both the US Food and Drug Administration and European Commission specifically for use in the diagnosis of adult GHD [9, 10]. Macimorelin binds to the ghrelin receptor and stimulates dose-dependent increases in GH levels, which can be used to assess GH production in patients with suspected GHD [11]. Previous studies have reported favourable safety and tolerability in adult populations using single oral doses of macimorelin up to 2.0 mg/kg [7, 11, 12]. A recent study also investigated the compound's pharmacokinetics (PK) and pharmacodynamics (PD) in adult patients [12].

This trial is the first to investigate the safety, tolerability, PK, and PD of single-dose macimorelin in a paediatric population of patients with suspected GHD. The primary endpoint was the safety and tolerability of macimorelin after ascending single oral doses of 0.25, 0.5, and 1.0 mg/kg. Secondary endpoints included the PK and PD of macimorelin as well as the PK/PD relationship, following administration of single doses.

Materials and Methods

This open-label, group comparison, single-dose escalation trial (EudraCT 2018-001988-23) was conducted at 11 trial centres across 6 countries (Belarus, Hungary, Poland, Russia, Serbia, and Ukraine). The trial started on 7 February 2019 with the first signed informed consent form and was completed on 24 January 2020 with the last patient visit.

Study Design

Sequential cohorts of patients received macimorelin at ascending single oral doses, starting at 0.25 mg/kg (Cohort 1, C1), which is 50% of the dose used for adult testing, followed by 0.5 mg/kg (Cohort 2, C2) and 1.0 mg/kg (Cohort 3, C3). Dosing proceeded to the next level if a Data Review Committee confirmed safety and tolerability to be acceptable.

The macimorelin GHST was performed between 2 standard GHSTs (sGHSTs), with a recovery period of 7–28 days between tests. sGHSTs followed the established procedures of the trial test sites. The following pharmacological agents were permitted during the study: insulin (ITT), arginine, arginine/GH-releasing hormone, clonidine, glucagon, and L-dopa. For PK/PD analyses, blood samples were collected pre-dose, then 15, 30, 45, 60, 90, 120, and 360 min following administration of macimorelin.

Patients

Eligible patients were between the ages of 2 and <18 years, had suspected GHD based on auxological and clinical criteria, and were indicated for the performance of provocative GHSTs. Additionally, patients with sex steroid priming prior to sGHSTs must also have had sex steroid priming for the macimorelin GHST. Patients could be considered ineligible due to lack of suitability for the trial, safety concerns, or administrative reasons. A full list of exclusion criteria is summarized in Table 1.

Study Drug

Macimorelin was provided in single-use aluminium sachets, each containing 63.6 mg macimorelin acetate. Sachet contents were dissolved in 120 mL of water to produce 0.5 mg/mL macimo-

Table 1. List of eligibility exclusion criteria

Lack of suitability for trial
Established diagnosis of another disease that explains growth deficiency
Ongoing GH therapy
A medical history and clinical signs of not adequately treated thyroid dysfunction or a change in thyroid therapy within 30 days prior to the proposed macimorelin test day
Untreated hypogonadism or lack of stable substitution treatment within 30 days prior to the proposed macimorelin test day
Treatment with drugs directing affecting pituitary secretion of somatotropin or provoking the release of somatostatin
Concomitant use of a CYP3A4 inducer or inhibitor
A medical history of ongoing clinically symptomatic psychiatric disorders
Cushing's disease or supraphysiological glucocorticoid therapy within 30 days prior to the proposed macimorelin test day
Participation in a trial with any investigational drug within 30 days prior to trial entry
Vigorous physical exercise within 24 h prior to the macimorelin test
Safety concerns
Including hypersensitivity to any of the constituents of the macimorelin preparation
Prolonged ECG QT interval (defined as QTc >500 ms)
Concomitant treatment with any drugs that might prolong QT/QTc
Indication of hepatic or renal dysfunction or damage
Active malignancy other than non-melanoma skin cancer
Females of childbearing age without effective contraception
Administrative reasons
Lack of ability of willingness to give informed consent (by patient or their legal representative)
Anticipated non-availability for trial visits or procedures

GH, growth hormone; ECG, electrocardiogram.

relin oral suspension. Macimorelin oral suspension was prepared by trial personnel, who also supervised its administration. Patients were advised to drink the entire dose over a period of no more than 30 s and were required to fast for 8 h prior to the start of the macimorelin stimulation test and throughout the sampling period.

PK/PD

Assessment of PK was based on concentration-time profiles of macimorelin, including area under the curve (AUC), time of maximum measured concentration (T_{max}), maximum concentration (C_{max}), and elimination half-life ($T_{1/2}$). Analysis of macimorelin plasma concentration was carried out by Prolytic GmbH, Frankfurt am Main, Germany, using a validated liquid chromatography-mass spectrometry method with a detection limit of 0.2 ng/mL. PD was assessed based on concentration-time profiles of GH, including C_{max} and T_{max}. Serum concentrations of GH were measured using a validated immunochemiluminometric assay (IDS-iSYS Human Growth Hormone Assay; Immunodiagnostic Systems Ltd, Boldon Colliery, UK) at the Central Laboratory Synevo, Łódź, Poland.

Safety and Tolerability

Tolerability was assessed by a GHST tolerability questionnaire, which was completed by the patient or by the parent/legal guardian, and included questions based on acceptability of taste, impact on sleep and appetite, and effect on gastrointestinal behaviour. The questionnaire took the form of predefined statements, to which patients were required to record whether they agreed, strongly agreed, disagreed, strongly disagreed, or neither agreed nor disagreed.

Safety was assessed based on occurrence of adverse events (AEs) and treatment-emergent AEs (TEAEs), which could be volunteered by the patient, discovered during questioning by a trial investigator, or detected through physical examination, laboratory testing, or other means. AEs were recorded from the moment of signing the informed consent form until the end of the trial. Any AEs occurring after the administration of a trial drug (macimorelin or sGHST) were considered as TEAEs. Judgement as to whether a TEAE had a causal relationship with a trial drug was based on investigator assessment and was classified as either "not related," "unlikely," "possibly," "probably," or "definitely." The influence of macimorelin on vital parameters (pulse rate, blood pressure, and electrocardiogram) was also investigated.

Diagnostic Testing

Diagnosis of GHD was based on peak GH concentrations. For sGHSTs, the diagnostic outcome was considered to be "confirmed" if both initial and follow-up sGHSTs resulted in a GH peak of ≤7 ng/mL or "not confirmed" if at least one of the peaks was above 7 ng/mL. The diagnostic outcome of "not confirmed" was categorised further to either "excluded," if both sGHST results were available, and the GH peaks were both above the cut-off value or "equivocal," if the outcome did not fit any of those described above (e.g., if only one sGHST peak >7 ng/mL). The investigator's assessment was made based on local diagnostic standard practice. Macimorelin GHSTs were tested against cut-off points calculated from the individual peak GH values: 10.03 ng/mL (C1), 10.43 ng/mL (C2), and 17.13 ng/mL (C3).

Statistical Analysis

All statistical analyses were considered exploratory in nature and performed using SAS Version 9.3 or above.

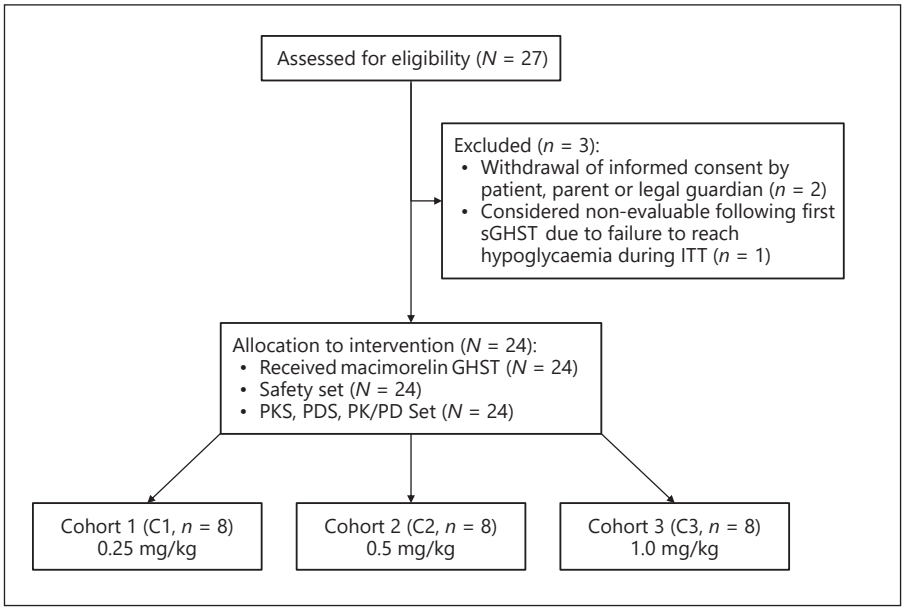

Fig. 1. Trial population overview. (s)GHST, (standard) growth hormone stimulation test; ITT, insulin tolerance test; PD, pharmacodynamic; PDS, pharmacodynamic analysis set; PK, pharmacokinetic; PKS, pharmacokinetic analysis set

Table 2. Demographic and other characteristics at screening

Parameter	Cohort 1 0.25 mg/kg (*n* = 8)	Cohort 2 0.5 mg/kg (*n* = 8)	Cohort 3 1 mg/kg (*n* = 8)	Overall (*N* = 24)
Gender, *n* (%)				
Male	5 (62.5)	5 (62.5)	7 (87.5)	17 (70.8)
Female	3 (37.5)	3 (37.5)	1 (12.5)	7 (29.2)
Race, *n* (%)				
White	8 (100)	8 (100)	8 (100)	24 (100)
Tanner status, *n* (%)				
I	4 (50)	5 (62.5)	4 (50)	13 (54.2)
II	4 (50)	3 (37.5)	4 (50)	11 (45.8)
Age, years				
Mean ± SD	9.8±3.5	9.0±4.2	10.5±3.9	9.8±3.8
Median (min–max)	10.5 (5–15)	8.0 (4–14)	12.5 (4–14)	10.5 (4–15)
Height, cm				
Mean ± SD	111.19±32.79	118.85±20.95	127.71±19.67	119.25±25.02
Median (min–max)	114.80 (46.0–152.5)	117.65 (90.0–145.0)	137.60 (97.5–147.0)	123.35 (46.0–152.5)
Weight, kg				
Mean ± SD	23.1±10.1	27.0±10.9	29.0±10.0	26.4±10.2
Median (min–max)	19.5 (12–40)	27.5 (12–43)	30.5 (17–41)	25.5 (12–43)
BMI, kg/m^2				
Mean ± SD	14.83±2.56	17.33±2.41	17.09±2.29	16.41±2.59
Median (min–max)	14.30 (12.4–19.8)	16.85 (14.1–21.0)	16.50 (14.6–21.4)	16.10 (12.4–21.4)

BMI, body mass index; SD, standard deviation.

Results

Patients

Overall, 24 paediatric patients with suspected GHD were allocated to receive macimorelin (8 per cohort; Fig. 1). Of the 27 patients initially assessed for eligibility, 2 withdrew informed consent, and one had a non-evaluable first sGHST (i.e., hypoglycaemia could not be achieved during the first or repeated ITT; Fig. 1). Five males and 3 females were enrolled in C1 and C2, while 7 males and one female were enrolled in C3. At least 3 patients in each cohort represented Tanner stages I or II (Table 2). Of the 24 patients, 13 were

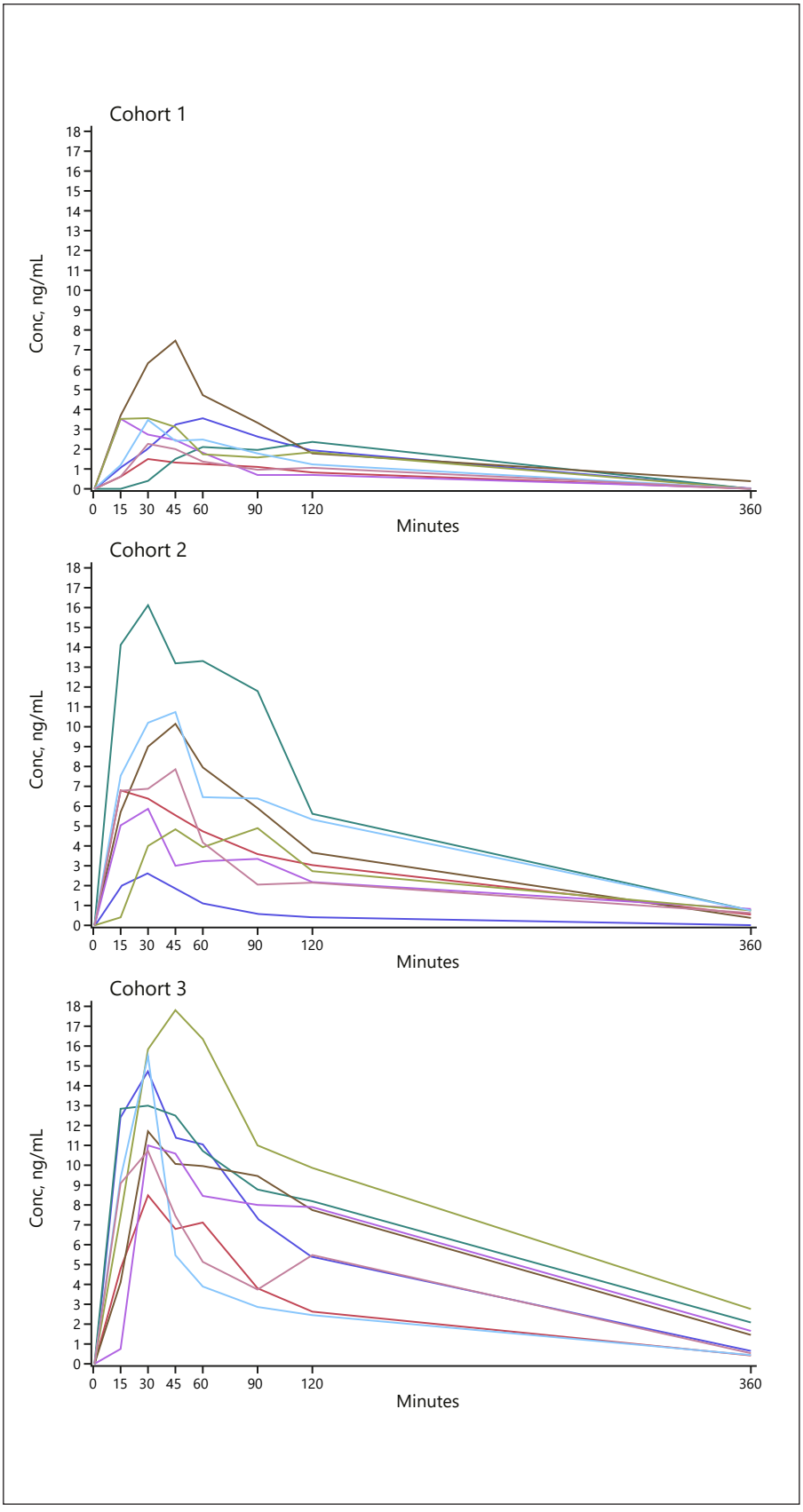

Fig. 2. Individual macimorelin concentration versus time by cohort (linear scale; PK set, $N = 24$). Macimorelin doses for each cohort are 0.25 mg/kg (C1), 0.5 mg/kg (C2) and 1 mg/kg (C3). Graphs show PK profiles of individual patients ($n = 8$ per cohort). PK, pharmacokinetic.

Table 3. Summary of main PK parameters (PK set, *N* = 24)

Cohort	Statistics	AUC_{0-6} (h × ng/mL)	C_{max} (ng/mL)	T_{max} (min)	$T_{1/2}$ (min)
Cohort 1 (0.25 mg/kg)	*n*	8	8	8	4
	Arithmetic mean (SD)	6.685 (3.093)	3.460 (1.783)	45.5 (32.8)	73.183 (29.437)
	Arithmetic CV, %	46.273	51.543	72.1	40.225
	Min–Max	3.35–12.49	1.51–7.44	15–120	39.45–105.96
Cohort 2 (0.5 mg/kg)	*n*	8	8	8	7
	Arithmetic mean (SD)	18.015 (9.800)	8.126 (4.176)	40.6 (22.3)	96.307 (41.031)
	Arithmetic CV, %	54.399	51.393	54.8	42.604
	Min–Max	3.28–35.98	2.62–16.1	15–90	41.39–151.01
Cohort 3 (1 mg/kg)	*n*	8	8	8	8
	Arithmetic mean (SD)	30.920 (11.510)	12.868 (3.011)	31.9 (5.3)	102.851 (19.938)
	Arithmetic CV, %	37.227	23.402	16.6	19.385
	Min–Max	16.31–49.73	8.5–17.79	30–45	77.66–133.36

AUC, area under the curve; C_{max}, maximum concentration; CV, coefficient of variation; SD, standard deviation; T_{max}, time of maximum measured concentration; PK, pharmacokinetic.

prepubertal (Tanner stage I), and 11 were pubertal (Tanner stage II). The median age of patients was 10.5 (C1), 8.0 (C2), and 12.5 (C3) years (with a range of 4–15 years) and with an overall median body mass index of 16.1 kg/m^2 (with a range of 12.4–21.4 kg/m^2). Sex steroid priming was applied in 2 male patients in C3 (13 years [Tanner stage I] and 14 years of age [Tanner stage II]). Both patients were administered a testosterone depot preparation intramuscularly. Demographics and baseline characteristics at screening are summarized in Table 2.

Pharmacokinetics

In general, macimorelin plasma concentrations showed a dose-dependent increase, with high variability between patients (Fig. 2). In all 3 cohorts, plasma concentrations of macimorelin rapidly increased immediately following administration, with maximum levels observed between 15 and 120 min (Fig. 2). Mean AUC_{0-6} and C_{max} values increased in a dose-dependent manner (Table 3). T_{max} was comparable between dosing cohorts, and $T_{1/2}$ showed a slight increase with higher doses of macimorelin (Table 3).

Pharmacodynamics

GH concentration increased following administration of macimorelin, with a tendency to higher values with ascending dose (Fig. 3). Peak GH levels were observed between 15 and 60 min across dosing cohorts (Fig. 3), with mean T_{max} values of 52.5 min (C1), 37.5 min (C2), and 37.5 min (C3) (Table 4). Inter-patient variability was high, though this was to be expected in the observed population.

Table 4. Summary of main PD parameters (PK/PD set, *N* = 24)

Cohort	Statistics	C_{max} (ng/mL)	T_{max} (min)
Cohort 1 (0.25 mg/kg)	*n*	8	8
	Arithmetic mean (SD)	9.791 (6.226)	52.5 (11.3)
	Arithmetic CV, %	63.585	21.6
	Median	9.195	60.0
	Min–Max	0.51–21.73	30–60
Cohort 2 (0.5 mg/kg)	*n*	8	8
	Arithmetic mean (SD)	14.590 (8.046)	37.5 (13.9)
	Arithmetic CV, %	55.149	37.0
	Median	13.040	37.5
	Min–Max	5.06–27.42	15–60
Cohort 3 (1 mg/kg)	*n*	8	8
	Arithmetic mean (SD)	29.533 (18.829)	37.5 (8.0)
	Arithmetic CV, %	63.757	21.4
	Median	21.100	37.5
	Min–Max	11.35–59.73	30–45

C_{max}, maximum concentration; CV, coefficient of variation; SD, standard deviation; T_{max}, time of maximum measured concentration; PK, pharmacokinetic; PD, pharmacodynamic.

Diagnostic Testing

When comparing the diagnostic outcomes of sGHSTs with investigator assessments made according to local standard practice, there was an agreement for 21 of 24 patients (87.5%; 8 confirmed GHD, 13 not confirmed GHD). In the remaining 3 patients (12.5%), the investigator assessment confirmed GHD, but the sGHST result was not confirmed ("excluded" in 1 patient and "equivocal" in 2 patients).

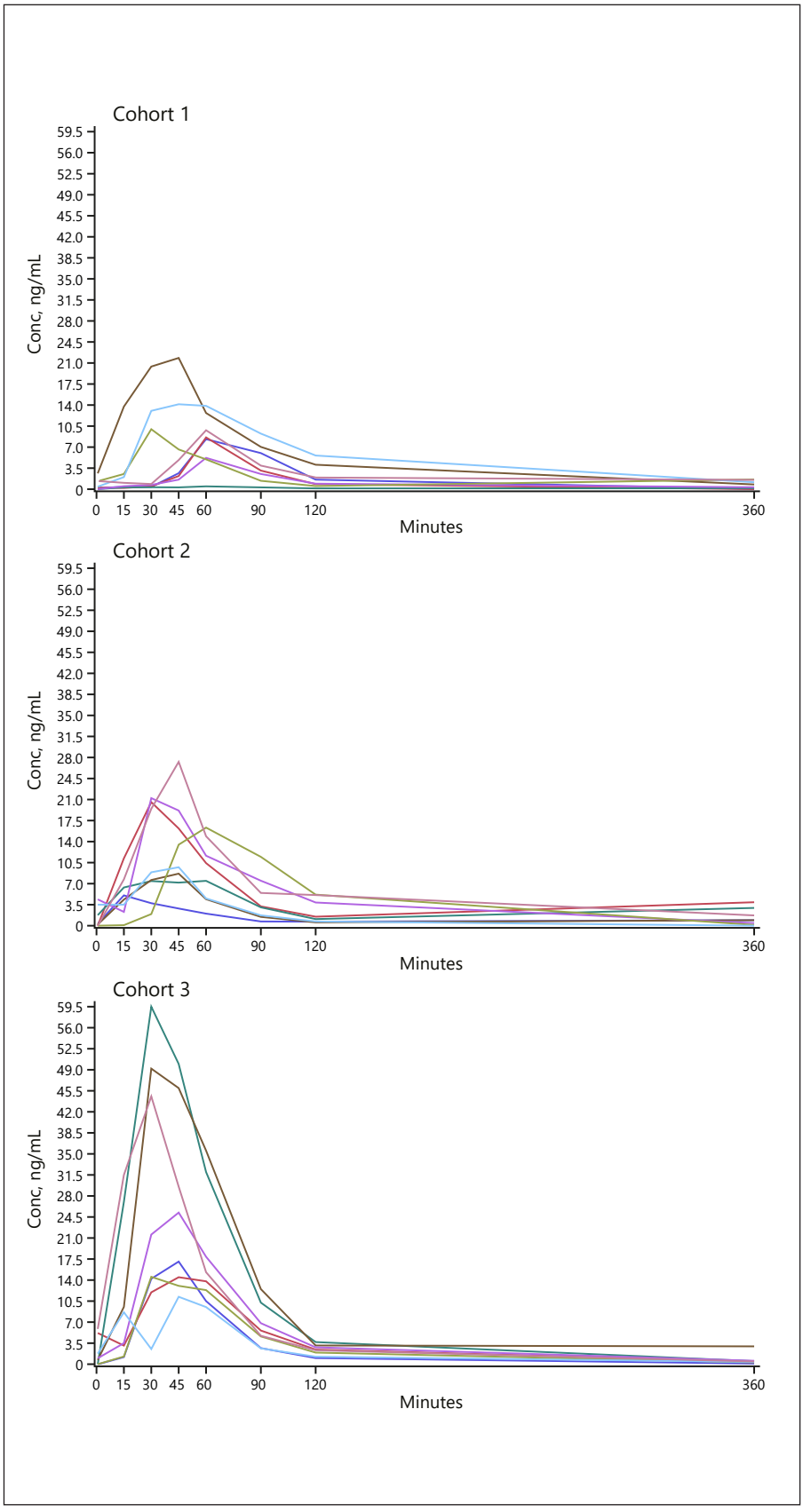

Fig. 3. Individual GH concentration versus time by cohort (linear scale; PD set, N = 24). Macimorelin doses for each cohort are 0.25 mg/kg (C1), 0.5 mg/kg (C2) and 1 mg/kg (C3). Graphs show PD profiles of individual patients (n = 8 per cohort). GH, growth hormone; PD, pharmacodynamic.

Table 5. Summary of diagnostic results of macimorelin GHST versus sGHST and investigator assessment

	Macimorelin GHST	Principal investigator assessment		sGHST	
		GHD (n = 11), n (%)	non-GHD (n = 13), n (%)	confirmed (n = 8), n (%)	not confirmed (n = 16), n (%)
Cohort 1 (0.25 mg/kg)	Confirmed	3 (27.27)	3 (23.08)	1 (12.50)	5 (31.25)
	Not confirmed	0	2 (15.38)	0	2 (12.50)
	Total	3 (27.27)	5 (38.46)	1 (12.50)	7 (43.75)
Cohort 2 (0.5 mg/kg)	Confirmed	4 (36.36)	0	3 (37.50)	1 (6.25)
	Not confirmed	1 (9.09)	3 (23.08)	1 (12.50)	3 (18.75)
	Total	5 (45.45)	3 (23.08)	4 (50.00)	4 (25.00)
Cohort 3 (1 mg/kg)	Confirmed	3 (27.27)	1 (7.69)	3 (37.50)	1 (6.25)
	Not confirmed	0	4 (30.77)	0	4 (25.00)
	Total	3 (27.27)	5 (38.46)	3 (37.50)	5 (31.25)

Diagnosis of GHD using standard GHSTs was based on a cut-off of 7 ng/mL ("confirmed" if initial and follow-up sGHSTs resulted in a GH peak of ≤7 ng/mL, "not confirmed" if at least one of the peaks was above 7 ng/mL). Diagnosis using the macimorelin test was based on cut-off points calculated from individual peak GH values (10.03 ng/mL, C1; 10.43 ng/mL, C2; 17.13 ng/mL, C3). GHD, growth hormone deficiency; GHST, growth hormone stimulation test; GH, growth hormone; sGHST, standard growth hormone stimulation test.

A comparison of diagnostic results of the macimorelin GHST with investigator assessments and sGHST outcomes is shown in Table 5. Of the 11 patients across all 3 cohorts who were assessed to have GHD by the principal investigator, 1 patient from C2 was not confirmed as having GHD according to the macimorelin GHST. Of the 13 patients from all cohorts who were assessed as "non-GHD" by the principal investigator, the macimorelin GHST showed 4 patients (n = 3, C1; n = 1, C3) to have confirmed GHD. The corresponding sGHST results were listed as "equivocal" in each case.

ROC and Sensitivity Analysis

Receiver operator characteristics (ROCs) of macimorelin were also investigated. For all GH cut-off points tested, the ROC curve for C1 showed the lowest sensitivity compared with C2 and C3 (Fig. 4). The strongest test characteristics were observed in C3 (GH cut-off, 17.13 ng/mL; sensitivity, 1.00; specificity, 0.80; ROC AUC, 0.93), compared with C2 (GH cut-off, 10.43 ng/mL; sensitivity, 0.80; specificity, 1.00; ROC AUC, 0.80) and C1 (GH cut-off, 10.03 ng/mL; sensitivity, 1.00; specificity, 0.40; ROC AUC, 0.60) (Fig. 4). A sensitivity analysis was also performed based on diagnostic test outcomes (Table 5). Again, the strongest characteristics were observed in C3 (sensitivity, 1.00; specificity, 0.80; ROC AUC, 0.93), compared with C2 (sensitivity, 0.75; specificity, 0.75; ROC AUC, 0.56) and C1 (sensitivity, 1.00; specificity, 0.71; ROC AUC, 0.71).

Safety and Tolerability

Overall, 88 AEs in 23 patients and 70 TEAEs in 21 patients were reported; however, none of the AEs or TEAEs reported were considered to be in causal relationship with macimorelin administration (Table 6). By contrast, ~88% of patients in each cohort experienced AEs related to sGHSTs (Table 6), the majority of which were purported to be related to the ITT (62 events in 21 patients), followed by clonidine (13 events in 7 patients) and arginine (2 events in 1 patient). No AEs or TEAEs led to patient withdrawal nor were any serious AEs or TEAEs reported.

Results of the tolerability questionnaire indicated that macimorelin was well tolerated in all 3 cohorts, with the majority agreeing or strongly agreeing with predefined statements related to macimorelin. Two patients (n = 1, C1; n = 1, C3) disagreed that the taste was acceptable, 1 patient (C1) reported an unusual bowel movement the following day, and 1 patient (C1) reported that their stomach felt unwell the following day. "Bitter taste" was also reported as handwritten comments by 2 patients or their parents/legal guardians following macimorelin GHST (C3). None of these comments were considered to be AEs by the investigator.

Discussion

Provocative GHSTs are part of the diagnostic process for assessing GHD in paediatric patients, the importance of which has been highlighted in published guidelines

Table 6. Summary of AEs and TEAEs (safety analysis set, *N* = 24)

Category	Cohort 1 0.25 mg/kg (*n* = 8)	Cohort 2 0.5 mg/kg (*n* = 8)	Cohort 3 1.0 mg/kg (*n* = 8)	Overall (*N* = 24)
AEs	8 (27)	8 (28)	7 (33)	23 (88)
TEAEs	8 (22)	6 (24)	7 (24)	21 (70)
Macimorelin-related TEAEs	0 (0)	0 (0)	0 (0)	0 (0)
sGHST-related AEs	7 (25)	7 (27)	7 (25)	21 (77)
Patients receiving an ITT (visit 1/3)*	*n* = 0/8	*n* = 2/5	*n* = 3/4	–
ITT-related AEs	7 (21)	7 (27)	7 (14)	21 (62)
Patients receiving clonidine (visit 1/3)*	*n* = 2/0	*n* = 5/2	*n* = 4/3	–
Clonidine-related AEs	2 (2)	0 (0)	5 (11)	7 (13)
Patients receiving arginine (visit 1/3)*	*n* = 6/0	*n* = 1/0	*n* = 1/0	–
Arginine-related AEs	1 (2)	0 (0)	0 (0)	1 (2)
Patients receiving glucagon (visit 1/3)*	*n* = 0/0	*n* = 0/1	*n* = 0/1	–
Glucagon-related AEs	0 (0)	0 (0)	0 (0)	0 (0)

Reported above are patients (events). AEs were recorded from the moment of informed consent until the end of the trial. TEAEs were all AEs recorded after administration of the trial drug. AE, adverse event; GHST, growth hormone stimulation test; ITT, insulin tolerance test; sGHST, standard growth hormone stimulating test; TEAE, treatment-emergent adverse event. *Number of patients receiving each sGHST at Visit 1 (before macimorelin) and Visit 3 (after macimorelin).

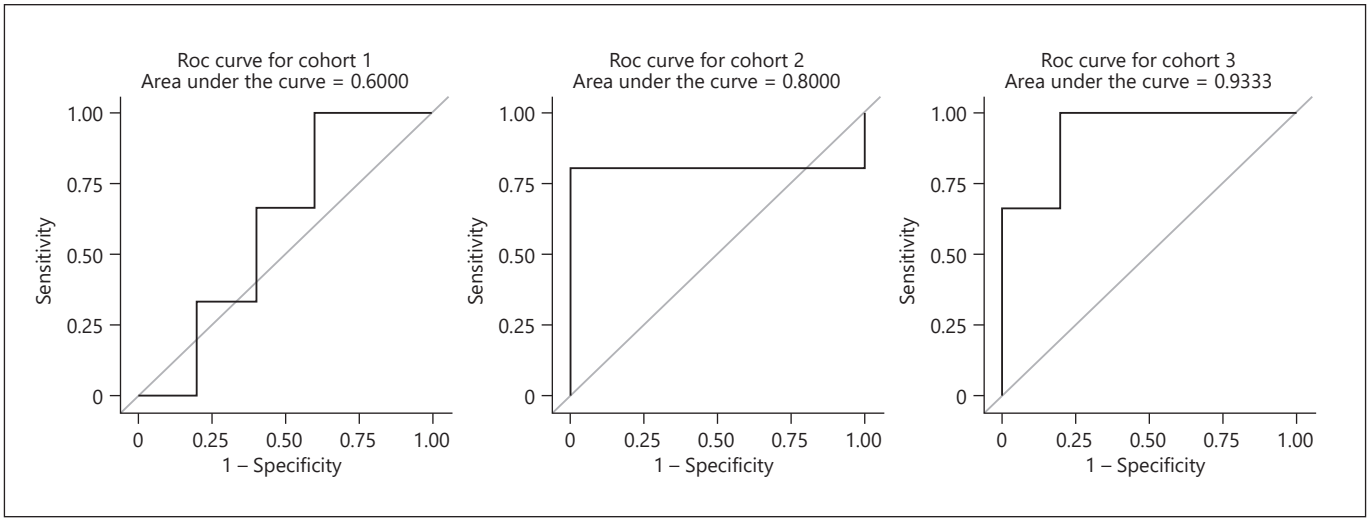

Fig. 4. ROC curves of macimorelin GHST by cohort (PD set, *N* = 24) showing sensitivity versus specificity. Macimorelin doses for each cohort are 0.25 mg/kg (C1), 0.5 mg/kg (C2) and 1 mg/kg (C3). ROC, receiver operating characteristic; GHST, growth hormone stimulation test; PD, pharmacodynamic.

[13, 14]. However, due to their poor reproducibility, limited reliability, potential contraindications (e.g., risk of hypoglycaemia), and concomitant discomfort (hypotension, drowsiness, vomiting, and headaches), it is important to develop alternative testing methods [2, 5, 15–17]. Sermorelin (Geref®; EMD Serono, Rockland, MA, USA) was previously available as an injectable GHRH analogue suitable for use as a provocative GHST test (with a higher cut-off value); however, it was removed from the market in the United States due to manufacturing difficulties [18].

Macimorelin is a novel test for GHD that is well tolerated in adults and has accuracy comparable to the ITT and the arginine+GHRH test [7, 11, 12]. Until now, however, macimorelin has been unstudied in paediatric populations. As treatment with GH is highly efficacious,

timely diagnosis of GHD in children using techniques that are both accurate and non-invasive is of great importance [2, 19].

This was the first study to assess safety, tolerability, PK, and PD of macimorelin in a paediatric population of patients with suspected GHD. The objectives of the study were exploratory in nature, with the additional aim of determining the highest safe and well-tolerated dose of macimorelin to be used in a future Phase 3 test validation trial. The sGHSTs performed in this study were not considered to be investigational agents but merely background tests and were therefore not considered as comparators for efficacy evaluation.

Safety and tolerability were found to be favourable using all 3 doses (0.25, 0.5, and 1.0 mg/kg) of macimorelin tested in this paediatric population. No TEAEs with causal relationship to macimorelin were reported nor were any serious AEs or AEs leading to patient withdrawal. Importantly for a paediatric population, no instances of vomiting or nausea were noted following ingestion of macimorelin suspension, and taste was considered acceptable among the majority of patients. Furthermore, no cases of dysgeusia, which had been the most frequently reported AE in a previous adult study with macimorelin 0.5 mg/kg, were reported in this paediatric population [11].

For all 3 doses tested in this paediatric study, PK and PD profiles were found to be within the expected ranges based on the results from adult studies, including a dose-dependent increase in plasma macimorelin C_{max}, $AUC_{0–6}$, and $T_{1/2}$. [11, 12]. A macimorelin dose of 0.25 mg/kg (C1) did not result in maximum stimulation of GH secretion, with higher doses (0.5 and 1.0 mg/kg [C2 and C3, respectively]) showing stronger GH release. In particular, a dose of 1.0 mg/kg (C3) led to a strong and more consistent GH stimulation, most probably due to sufficiently high macimorelin exposure in all patients. Furthermore, the sensitivity analysis supports a macimorelin dose of 1.0 mg/kg (C3) having the strongest test characteristics.

In the adult study by Klaus et al. [12], maximum GH stimulation was achieved with 0.5 mg/kg of macimorelin (the lowest dose used in that trial), with maximum stimulation occurring after 1 h. PK measurements were not dose-proportional, with similar exposure following 0.5 and 1.0 mg/kg doses. However, a considerable increase (approximately 2-fold) from 1.0 to 2.0 mg/kg doses was reported (C_{max} of 13.1 and 21.3 ng/mL and AUC of 37.0 and 84.7 h × ng/mL, respectively) [12]. By contrast, the present study showed a dose-dependent increase in macimorelin C_{max} and AUC across all 3 cohorts. There was however high inter-patient variability, especially at the higher doses. Interestingly, the study by Klaus et al. [12] reported that while serum GH concentration was similar following 0.5 and 1.0 mg/kg doses of macimorelin in adults (C_{max} of 31.9 and 37.8 ng/mL, respectively), GH concentration was actually lower following the higher dose (2.0 mg/kg) of macimorelin (C_{max} of 18.4 ng/mL). In this present study, GH concentration had a tendency to higher values with increasing dose in all 3 doses tested in children, though the highest dose was only 1.0 mg/kg (Fig. 3; Table 4). While there are some disparities in the PK and PD results between this and the Klaus et al. [12] study, such results are not directly comparable due to the difference in population demographic (i.e., children vs. adults), differences in dosing ranges, and the fact that both studies were exploratory in nature. Furthermore, sample sizes in both studies were relatively small (24 participants in this study [n = 8 per dose group] and 28 in the Klaus study [n = 6–9 per dose group]), both studies report high inter-patient variability, and the patients enrolled in the Klaus study were all healthy adults with no indication of GHD [12]. Both studies, however, agreed with respect to the good safety and tolerability profiles in all doses tested, as well as the observation that GH levels increased from baseline following administration of macimorelin (even at the lowest doses tested), highlighting the value of the compound as a diagnostic agent in adult and potentially paediatric patients with suspected GHD.

In conclusion, all 3 doses of macimorelin tested were found to have favourable safety and tolerability, with PK/PD profiles in expected ranges. The results of this study support the choice of a 1.0 mg/kg dose of macimorelin for use in a Phase 3 validity trial in a paediatric population. If, following this planned study, macimorelin is approved for the diagnosis of GHD in children, it will be the first GHD diagnostic test for paediatric patients to be approved based on the results of a randomised controlled trial.

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Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and/or all relevant federal regulations, in compliance with Good Clinical Practice guidelines, and as per all applicable local regulatory guidelines and the Directive of the European Parliament, including those set out in the publication "The rule governing medicinal products in the EU" and those set by the European Medicines Agency. The clinical trial protocol, patient information sheets, informed consent form, investigator's brochure, and trial conduct were reviewed and approved by relevant Institutional Review Boards/Independent Ethics Committees. All patients, parents, or guardians were required to give written informed consent prior to patient participation. Consent forms were signed by the parent or guardian, by the child (assent was signed in cases in which the patient could read), and by the investigator and/or designated trial team member prior to any protocol related activities.

Conflict of Interest Statement

Violetta Csákváry, Olena V. Bolshova, Dragan Katanic, Evgenia Mikhailova, Agota Muzsnai, Dmitri Raduk, Ganna Senatorova, Mieczysław Szalecki, Zsolt Vajda, Nataliya Zelinska, and Tetyana Chaychenko served as investigators as well as members of the data review committee in this study. Ekaterine Bakhtadze Bagci is an employee of Novo Nordisk and holder of Novo Nordisk stocks. Birgitte Bentz Damholt was an employee of Novo Nordisk at the time this trial was conducted and during the preparation of the manuscript. She is also a holder of Novo Nordisk stocks. Nicola Ammer and Michael Teifel are employees of Aeterna Zentaris GmbH. Nataliya Zelinska has received speaker honoraria, travel, and accommodation support from Medtronic, Berlin-Chemie, ACINO, Novo Nordisk, Pfizer, Sanofi, and Ferring. Mieczyslaw Szalecki has received travel and accommodation support from Sandoz. Zsolt Vajda declares no conflicts of interest.

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Author Contributions

Conceptualization was conceived by N.A. and M.T.; methodology was conceived by N.A. and M.T.; project administration was handled by N.A.; supervision was performed by N.A.; investigation was performed by V.C., N.A., E.B.B., O.V.B., B.B.D., D.K., E.M., A.M., D.R., G.S., M.S., M.T., Z.V., N.Z., and T.C.; resources were contributed by V.C., N.A., O.V.B., D.K., E.M., A.M., D.R., G.S., M.S., M.T., Z.V., N.Z., and T.C.; validation was performed by V.C., N.A., A.M., D.R., M.T., and T.C.; formal analysis was performed by N.A. and M.T.; visualization was performed by N.A., M.T., and T.C.; and writing – review and editing was performed by V.C., N.A., E.B.B., O.V.B., B.B.D., D.K., E.M., A.M., D.R., G.S., M.S., M.T., Z.V., N.Z., and T.C. All the authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The subject-level analysis data sets for the research presented in the publication are available from the corresponding author upon reasonable request.

References

1 Abe S, Okumura A, Mukae T, Nakazawa T, Niijima S, Yamashiro Y, et al. Depressive tendency in children with growth hormone deficiency. J Paediatr Child Health. 2009 Nov; 45(11):636–40.
2 Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. Arch Dis Child. 2016;101(1):96–100.
3 Stanley T. Diagnosis of growth hormone deficiency in childhood. Curr Opin Endocrinol Diabetes Obes. 2012;19(1):47–52.
4 Collett-Solberg PF, Ambler G, Backeljauw PF, Bidlingmaier M, Biller BMK, Boguszewski MCS, et al. Diagnosis, genetics, and therapy of short stature in children: a growth hormone research society international perspective. Horm Res Paediatr. 2019;92(1):1–14.
5 Binder G, Reinehr T, Ibáñez L, Thiele S, Linglart A, Woelfle J, et al. GHD diagnostics in Europe and the US: an audit of national guidelines and practice. Horm Res Paediatr. 2019 Nov 8;92:150–6.
6 Okita K, Iwahashi H, Kozawa J, Okauchi Y, Funahashi T, Imagawa A, et al. Usefulness of the insulin tolerance test in patients with type 2 diabetes receiving insulin therapy. J Diabetes Investig. 2014 May 1;5(3): 305–12.
7 Garcia JM, Biller BMK, Korbonits M, Popovic V, Luger A, Strasburger CJ, et al. Macimorelin as a diagnostic test for adult GH deficiency. J Clin Endocrinol Metab. 2018 Aug 1;103(8): 3083–93.
8 Wagner IV, Paetzold C, Gausche R, Vogel M, Koerner A, Thiery J, et al. Clinical evidence-based cutoff limits for GH stimulation tests in children with a backup of results with reference to mass spectrometry. Eur J Endocrinol. 2014 Sep 1;171(3):389–97.
9 FDA. MACRILEN (macimorelin): prescribing information; 2017.
10 EMA. Macimorelin: EPAR product information; 2019.
11 Garcia JM, Swerdloff R, Wang C, Kyle M, Kipnes M, Biller BM, et al. Macimorelin (AEZS-130)-stimulated growth hormone (GH) test: validation of a novel oral stimulation test for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab. 2013 Jun; 98(6):2422–9.
12 Klaus B, Sachse R, Ammer N, Kelepouris N, Ostrow V. Safety, tolerability, pharmacokinetics, and pharmacodynamics of macimorelin in healthy adults: results of a single-dose, randomized controlled study. Growth Horm IGF Res. 2020 Jun 1;52: 101321.

13 Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of Growth Hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab. 2000;85(11):3990–3. https://doi.org/10.1210/jcem.85.11.6984.
14 Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr. 2016;86(6):361–97.
15 Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab. 2008 Nov;93(11):4210–7.
16 Vyas V, Kumar A, Jain V. Growth hormone deficiency in children: from suspecting to diagnosing. Indian Pediatr. 2017 Nov 15;54(11):955–60.
17 Gabreanu GR. An update on the diagnosis of growth hormone deficiency. Discoveries. 2018;6(1):e82.
18 Ishida J, Saitoh M, Ebner N, Springer J, Anker SD, Haehling S. Growth hormone secretagogues: history, mechanism of action, and clinical development. JCSM Rapid Communications. 2020 Jan 1;3(1):25–37.
19 Brod M, Alolga SL, Beck JF, Wilkinson L, Højbjerre L, Rasmussen MH. Understanding burden of illness for child growth hormone deficiency. Qual Life Res. 2017;26(7):1673–86.