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.

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-
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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.

Macimorelin 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 ($T_{\text{max}}$), maximum concentration ($C_{\text{max}}$), 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 $C_{\text{max}}$ and $T_{\text{max}}$. Serum concentrations of GH were measured using a validated immunoassay method (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.
Assessed for eligibility (N = 27)

Excluded (n = 3):
- Withdrawal of informed consent by patient, parent or legal guardian (n = 2)
- Considered non-evaluable following first sGHST due to failure to reach hypoglycaemia during ITT (n = 1)

Allocation to intervention (N = 24):
- Received macimorelin GHST (N = 24)
- Safety set (N = 24)
- PKS, PDS, PK/PD Set (N = 24)

Cohort 1 (C1, n = 8)
0.25 mg/kg

Cohort 2 (C2, n = 8)
0.5 mg/kg

Cohort 3 (C3, n = 8)
1.0 mg/kg

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

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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 (64.0–152.5)         | 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/m²              |                             |                             |                          |                  |
| 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.
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 \(C_{\text{max}}\) values increased in a dose-dependent manner (Table 3). \(T_{\text{max}}\) 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 \(T_{\text{max}}\) 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.

### 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).

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

| Cohort | Statistics | AUC\(_{0–6}\) (h × ng/mL) | \(C_{\text{max}}\) (ng/mL) | \(T_{\text{max}}\) (min) | \(T_{1/2}\) (min) |
|--------|------------|---------------------------|-----------------------------|-------------------------|-----------------|
| Cohort 1 | \(n = 8\) | 8 | 6.685 (3.093) | 3.460 (1.783) | 45.5 (32.8) | 73.183 (29.437) |
| Cohort 1 | Arithmetic mean (SD) | 8 | 51.543 | 72.1 | 40.225 |
| Cohort 1 | Min–Max | 3.35–12.49 | 1.51–7.44 | 15–120 | 39.45–105.96 |

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

| Cohort | Statistics | \(C_{\text{max}}\) (ng/mL) | \(T_{\text{max}}\) (min) |
|--------|------------|-----------------------------|-------------------------|
| Cohort 1 | \(n = 8\) | 8 | 9.791 (6.226) | 52.5 (11.3) |
| Cohort 1 | Arithmetic mean (SD) | 8 | 63.585 | 21.6 |
| Cohort 1 | Arithmetic CV, % | 8 | 9.195 | 60.0 |
| Cohort 1 | Median | 8 | 0.51–21.73 | 30–60 |

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

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

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

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.
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 $C_{\text{max}}$, $\text{AUC}_{0-6}$, 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 ($C_{\text{max}}$ of 13.1 and 21.3 ng/mL and $\text{AUC}$ of 37.0 and 84.7 h $\times$ ng/mL, respectively) [12]. By contrast, the present study showed a dose-dependent increase in macimorelin $C_{\text{max}}$ and $\text{AUC}$ 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 ($C_{\text{max}}$ of 31.9 and 37.8 ng/mL, respectively), GH concentration was actually lower following the higher dose (2.0 mg/kg) of macimorelin ($C_{\text{max}}$ 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, Mieczyslaw 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.

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