Macimorelin as a diagnostic test for AGHD

Macimorelin as a Diagnostic Test for Adult Growth Hormone Deficiency

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ABSTRACT

PURPOSE: Diagnosis of adult growth hormone deficiency (AGHD) is challenging and often requires confirmation with a GH stimulation test (GHST). The insulin tolerance test (ITT) is considered the gold standard GHST but is labor-intensive, may cause severe hypoglycemia, and is contraindicated in certain patients. Macimorelin, an orally-active GH secretagogue, could be used to diagnose AGHD by measuring stimulated GH levels after an oral dose.

METHODS: This multicenter, open-label, randomized, 2-way crossover trial was designed to validate the efficacy and safety of a single-dose oral macimorelin for AGHD diagnosis compared to the ITT. Subjects with high (n=38), intermediate (n=37), and low (n=39) likelihood for AGHD and healthy, matched controls (n=25) were included in the efficacy analysis of the study.

RESULTS: After the first test, 99% of macimorelin and 82% of ITTs were evaluable. Using GH cut-off levels of 2.8 ng/mL for macimorelin and 5.1 ng/mL for the ITT, negative agreement was 95.38% (CI 87%-99%), positive agreement was 74.32% (CI 63%-84%), sensitivity was 87%, and specificity was 96%. Upon retesting, reproducibility was 97% for macimorelin (n=33). In post-hoc analyses, a GH cut-off of 5.1 ng/mL for both tests resulted in 94% (CI 85-98%) negative agreement, 82% (CI 72-90%) positive agreement, 92% sensitivity and 96% specificity. No serious adverse events were reported for macimorelin.

CONCLUSIONS: Oral macimorelin is a simple, well-tolerated, reproducible, and safe diagnostic test for AGHD with comparable accuracy to the ITT. A GH cut-off of 5.1 ng/mL for the macimorelin test provides excellent balance between sensitivity and specificity.

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**PRECIS**

This multicenter, open-label, randomized, 2-way crossover trial of macimorelin vs. the ITT shows that macimorelin is a simple, well-tolerated, reproducible, and safe diagnostic test for AGHD.
INTRODUCTION

Growth hormone (GH) therapy offers clinical benefits in individuals with adult GH deficiency (AGHD) (1-6). However, diagnosing this condition is often challenging and remains a barrier to initiating GH treatment. Random GH levels do not distinguish GH-deficient from GH-sufficient subjects reliably. Accordingly, the diagnosis of AGHD often depends on GH stimulation tests (GHSTs) using agents known to provoke GH release above a certain level in healthy individuals.

The insulin tolerance test (ITT) is considered the gold standard GHST; however, the test is labor-intensive, may be unpleasant for patients, has potential risks including severe hypoglycemia, and is contraindicated in elderly patients and in those with seizure disorders and heart disease (7,8). Other alternative provocative tests such as the arginine+GH releasing hormone (GHRH), arginine alone and glucagon stimulation tests are either not available in the U.S. or have significant limitations including requiring intramuscular administration, long duration, and/or low accuracy. Thus, there remains an unmet medical need for alternative GHSTs that are safe, reliable, and have received approval by a regulatory authority.

Ghrelin is known to potently stimulate GH release (9) mediated by specific ghrelin receptors in the pituitary and hypothalamus (10,11). This effect is shared by synthetic agonists of this receptor known as ghrelin mimetics or GH secretagogues. Macimorelin acetate is an oral ghrelin receptor agonist with GH secretagogue (GHS) activity that is readily absorbed and effectively stimulates endogenous GH secretion in healthy volunteers with good tolerability (12).
This trial was designed to validate the use of a single-dose oral macimorelin test for diagnosis of AGHD using the ITT as the comparator. The secondary objective was to characterize the safety of macimorelin in this setting.

MATERIALS AND METHODS

This phase III study was an open-label, randomized, multicenter, 2-way crossover study of the macimorelin test versus the ITT (core study). Additionally, a subset of patients (n=33) underwent the macimorelin test twice to evaluate the reproducibility of this test (reproducibility sub-study). The study was conducted in 5 sites in the U.S. and 25 sites across Europe. The protocol was approved by the Institutional Review Boards at each institution and was conducted in compliance with the Declarations of Helsinki and its amendments and the International Conference on Harmonization Guideline for Good Clinical Practices. Recruitment for the study took place between September, 2015 and November, 2016.

Eligibility criteria

Inclusion criteria were age between 18 and 65 years, suspected GH deficiency (GHD) based on one of the following: structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma as an adult, evidence of other pituitary hormone deficiencies, or idiopathic childhood-onset GHD (1). Exclusion criteria were GH therapy within the previous month, having had a GH stimulation test in the previous 7 days, thyroid disorder or hypogonadism that were untreated or not on stable substitution treatment (postmenopausal status was not considered an exclusion criterion), treatment with drugs affecting GH secretion or somatostatin, anti-muscarinic agents, CYP3A4 inducers, ongoing symptomatic severe
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psychiatric disorders, Parkinson’s disease, active Cushing’s disease or patients on  
supraphysiologic glucocorticoid therapy, type 1 diabetes or poorly controlled type 2 diabetes  
mellitus (HbA1c >8%), body mass index (BMI) $\geq$40 kg/m$^2$, participation in a trial with  
investigational drugs within 30 days, vigorous physical exercise within 24 hours prior to each  
GHST, clinically significant cardiovascular or cerebrovascular disease, prolonged QT interval  
(QTc $>$500 msec), concomitant treatment with drugs that prolong QT/QTc, hepatic or renal  
dysfunction, history of seizure disorders, immunosuppression, active malignancy other than  
non-melanoma skin cancer, breastfeeding or positive urine pregnancy test, or women of  
childbearing age without contraception.  

Subjects with high, intermediate and low likelihood for AGHD were included in the study (at  
least 25% of AGHD subjects in the high and low likelihood groups). “High likelihood”  
(Group A) was defined as: a structural hypothalamic or pituitary lesion and low insulin-like  
growth factor-1 (IGF-1) levels, three or more pituitary hormone deficiencies (PHD) and low  
IGF-1 levels, or childhood onset GHD with structural lesions and low IGF-1 levels. “Low  
likelihood” (Group C) was defined as one risk factor for AGHD, such as history of distant  
traumatic brain injury (TBI), only one pituitary hormone deficiency or childhood-onset  
isolated GHD. Subjects were included in the “Intermediate likelihood” group (Group B) when  
not qualifying for the other groups. A group of healthy subjects (Group D) matching Group A  
subjects by sex, age, BMI, and estrogen status was also included. A subset of subjects from  
Groups A-C underwent a second macimorelin GHST and were included in the reproducibility  
sub-study.  

Study procedures
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Subjects were randomized to a sequence of both tests (macimorelin GHST then ITT or vice-versa) performed 7-30 days apart and while fasting 8 hours prior to the start and throughout the test. A test was classified as “positive” for GHD when the peak GH value was below the cut-point established a priori, suggesting the patient had the disease. A test was classified as “negative” for GHD when the peak GH value was above that cut-point, suggesting the patient does not have the disease.

Macimorelin test: Macimorelin oral solution was prepared by trial personnel at a dose of 0.5 mg/kg of body weight to be administered within 30 minutes. Blood samples for GH serum levels were collected at pre-dose, then at 30, 45, 60, and 90 minutes (±5-minute window) after administration of macimorelin.

Insulin Tolerance Test: The ITT was performed with regular human insulin administered intravenously at 0.1 U/kg (0.15 U/kg if BMI >30 kg/m²). Glucose was monitored in capillary or venous blood every 15 minutes until 60 minutes after insulin administration, thereafter every 30 minutes, and when there was evidence of symptomatic hypoglycemia with diaphoresis or cognitive symptoms. As soon as clinical signs of hypoglycemia were achieved, blood for plasma glucose was taken for confirmation, defined as a glucose value below 2.2 mmol/L (40 mg/dL). An additional insulin bolus of 0.05 U/kg was administered if a glucose value <2.2 mmol/L (40 mg/dL) and symptomatic hypoglycemia had not been achieved within 45 minutes after the initial dose. Blood samples to determine serum GH concentrations were collected at pre-dose, 15, 30, 45, 60, 90 and 120 minutes (±5-minute window) after insulin administration. Intravenous glucose/dextrose was administered if a subject developed severe symptoms of neuroglycopenia, (i.e., seizures). Oral glucose administration was allowed if a
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Patient had a glucose level below 2.2 mmol/L (40 mg/dL) and moderate symptoms of neuroglycopenia (e.g., confusion).

**Determination of Evaluable Tests:** The cut-off values determined *a priori* for stimulated GH levels measured by the IDS-iSYS hGH assay were 2.8 ng/mL for the macimorelin test and 5.1 ng/mL for the ITT based on previously published data (13,14). A Data Review Committee (DRC) that included 4 investigators and representatives from the Sponsor reviewed and qualified each test as “evaluable” or “non-evaluable” prior to the availability of the GH results. Reasons for the DRC to designate a test “non-evaluable” included major deviation in blood sampling, not reaching the target glucose level and symptomatic hypoglycemia (for the ITT), incomplete intake of the dose or vomiting after drinking for macimorelin. Whenever possible, a test declared non-evaluable by the DRC was repeated after at least 7 days. The DRC also reviewed the assignment of study participants to the AGHD likelihood groups A-C.

**GH measurements**

Serum GH concentrations were measured centrally (Synevo Central Lab, Warsaw, Poland) by a validated immunochemiluminometric assay (IDS-iSYS Human GH, Immunodiagnostic Systems Ltd, UK) (15,16). This assay is standardized to the recombinant GH calibration standard WHO 98/574, and complies with recommendations on assay standardization (17).

**Statistical Analysis**

Statistical analyses were performed using SAS® (v9.3, SAS Institute, Inc, Cary, NC). All randomized subjects in whom both GHSTs were evaluable were included in the efficacy analyses. Criteria for an evaluable GHST were: a) the DRC adjudicated the GHST as
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evaluable, b) a peak GH concentration equal or greater than the cut-off rendered the test
evaluable irrespective of the DRC adjudication, and c) for the macimorelin GHST, 45- and 60-
minute post-dose GH concentrations were available or imputable categorically. The safety
population used for the primary safety analyses included all randomized subjects who took at
least one dose of trial medication. It was planned to include at least 110 subjects to achieve 55
with GHD as assessed by ITT and 55 passing the ITT for GH test outcomes. The ITT was
used as comparator, and the primary measures for diagnostic consistency were ‘percent
positive agreement’ and ‘percent negative agreement’. The estimated percent agreements and
the two-sided 95% confidence interval (CI) of the percent agreement based on Clopper-
Pearson (18) were calculated.

The accuracy measures were defined as follows:

<table>
<thead>
<tr>
<th>ITT outcome</th>
<th>positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macimorelin test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>w</td>
<td>U</td>
</tr>
<tr>
<td>negative</td>
<td>y</td>
<td>Z</td>
</tr>
<tr>
<td>Total</td>
<td>w+y</td>
<td>x+z</td>
</tr>
</tbody>
</table>

Positive percent agreement [%] = 100% x \(\frac{w}{w+y}\)

Negative percent agreement [%] = 100% x \(\frac{u}{u+z}\)

Overall percent agreement [%] = 100% x \(\frac{w+z}{w+u+y+z}\)
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The primary efficacy measures (negative and positive agreements) based on the following four methods were analyzed by a hierarchical testing procedure with regard to the sampling time for the macimorelin test: 1) Peak GH concentration among all post baseline samples (30, 45, 60 and 90 minutes); 2) Highest GH concentration among 45- and 60-minute samples; 3) GH concentration at 60 minutes post-dose; and 4) GH concentration at 45 minutes post-dose.

Adverse events (AEs), clinical laboratory results, and ECGs were evaluated by descriptive statistics. QTcF (Fridericia correction) was centrally re-calculated for all ECGs based on the formula \( \frac{QT \ [msec]}{(RR[sec])^{1/3}} \) (19).

For exploratory analyses, sensitivity and specificity for both GHSTs were estimated, assuming all high probability (Group A) AGHD subjects as “true” AGHD subjects and all healthy matching subjects (Group D) as “true” AGHD negative subjects. ROC analysis results are presented based on these assumptions. Reproducibility of the macimorelin test was analyzed by descriptive statistical analyses. Statistical tests were performed two-sided with a type I error (p-value) of \( \alpha=0.05 \).

RESULTS

One-hundred-sixty-six screened subjects were eligible and enrolled in the study (137 suspected AGHD subjects and 29 healthy subjects). Of these, 157 subjects underwent at least one GHST (safety population), 154 had both GHSTs performed at least once, and in 140 subjects both GHSTs were found evaluable by the DRC. Of these, one subject showed no measurable macimorelin plasma levels at the first macimorelin GHST and detectable macimorelin plasma levels and a GH increase during the macimorelin GHST in the reproducibility sub-study. This was attributed to a non-compliance or dosing error and this
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patient was removed from the efficacy analysis. The study design and patient disposition is shown in Figure 1.

Baseline characteristics are shown in Table 1. In 27 of 157 subjects, the ITT provided a peak GH concentration <5.1 ng/mL, without confirmed hypoglycemia. In only 17 of these 27 subjects the non-evaluable ITT was repeated, and 4 of the subjects were then classified as ITT-negative; 14 of 27 cases with a non-evaluable ITT could not be included in the efficacy analysis. Only 1 of 154 macimorelin GHSTs was non-evaluable and had to be repeated. In this case, the site had not collected blood samples for GH measurements at the initial macimorelin GHST. Among the 139 subjects of the efficacy population, 74 were classified as GHD and 65 as GH sufficient based on the ITT. Thirty-one of the 114 GHD subjects were studied in the US, whereas all subjects in Group D and 83 GHD patients were investigated in Europe.

Negative and positive agreements between the macimorelin GHST and the ITT

Negative agreement was 95.38% (CI 87.10%-99.04%), and positive agreement was 74.32% (CI 62.84%-83.78%) between the macimorelin GHST and the ITT with the pre-specified cut-off points (2.8 ng/mL for the macimorelin GHST and 5.1 ng/mL for the ITT). In a post-hoc analysis using a cut-point of 5.1 ng/mL for both tests, negative agreement was 93.85% (CI 84.99%-98.30%), and positive agreement was 82.43% (CI: 71.83%-90.30%). Supplemental Tables 1 and 2 show the performance of the macimorelin GHST using different cut-off points and the hierarchical step-wise approach, respectively.

Sensitivity and specificity of the macimorelin GHST
Due to the lack of a "standard of truth" to determine the true AGHD status of each participant, sensitivity and specificity for both GHSTs could only be estimated from test outcomes in a subset of the efficacy population: assuming all ‘high likelihood’ AGHD subjects (Group A) as ‘true’ AGHD subjects and all ‘healthy’ matching subjects (Group D) as ‘true’ AGHD negative subjects. When using the pre-defined cut-off points of 2.8 ng/mL for macimorelin, sensitivity was 87%, and specificity was 96%. Figure 2 illustrates the effect of varying GH cut-off points for the macimorelin GHST on the estimated sensitivity and specificity, respectively. The figure shows that increasing the GH cut-off point for the macimorelin GHST between 2.8 ng/mL and approximately 8 ng/mL will increase the sensitivity with a minimal effect on the specificity of the test. When using a cut-off point of 5.1 ng/mL, sensitivity and specificity of the macimorelin GHST were 92% and 96%.

Peak GH response in the macimorelin GHST and ITT by AGHD likelihood Group

Higher peak GH was seen in all groups in the macimorelin GHST compared to the ITT (Figure 3A). Moreover, peak GH levels were inversely related to the likelihood of having AGHD. There was a high correlation between peak GH in the ITT and the macimorelin GHST (Figure 3B).

Reproducibility of the macimorelin GHST

The reproducibility of the macimorelin GHST was 94%. No significant differences were found between the peak GH concentrations measured in the core study and in the reproducibility sub-study (n=33). The lack of a difference was shown not only for the entire population of the repeatability study, but also for both subsets of positive and negative GHST outcome in the core study, i.e. stratified for subjects with a peak GH below or above 2.8
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ng/mL (Supplemental Table 3), and also for those subjects in groups A, B and C (Supplemental Figure 1). The reproducibility of the macimorelin GHST was also maintained using different cut-off points and the hierarchical step-wise approach (Supplemental Tables 1-2).

Safety and tolerability

No serious adverse events (SAE) were reported following an ITT, one case of a broken arm was reported one day after a macimorelin GHST as unrelated to the test. Other non-SAE were more common and of greater severity during ITT than during the macimorelin GHST (see Supplemental material and Supplemental Table 4).

DISCUSSION

Evaluation of AGHD should be based upon medical history, clinical findings, and using the appropriate GHST for biochemical confirmation, except in patients with panhypopituitarism and low IGF-1 levels (1). The ITT remains the gold standard for evaluation of AGHD but it is only reluctantly performed by some endocrinologists because of the potential risk of hypoglycemia and because it requires resources that may not be available in some settings (20). GHRH+arginine was an alternative to ITT until 2008 when Geref®, the only approved GHRH analog in the U.S., was taken off the market, although it remains available in other countries (14). Recognizing the need for an alternative GHST to the ITT, we sought to validate the use of oral macimorelin as a diagnostic test for AGHD.

Acylated ghrelin (21) and agonists of its receptor (22,23) have been evaluated as diagnostic tests for AGHD but none of them are commercially available in the U.S. The ghrelin mimetic
macimorelin is a pseudotripeptide with increased oral bioavailability compared to other GH secretagogues (24). Previous studies have shown that a single oral dose induced a strong dose-dependent increase in GH levels lasting 120 minutes, with peak plasma drug concentrations between 50 and 75 min (12,24).

A previous open-label, crossover, multicenter trial tested the diagnostic accuracy of a single oral dose of macimorelin (0.5 mg/kg) compared to arginine+GHRH in AGHD patients and healthy matched controls (13). Peak GH levels were 2.36±5.69 and 17.71±19.11 ng/mL in AGHD subjects and healthy controls, respectively (p<0.0001), with an optimal GH cut-off ranging between 2.7 ng/mL and 5.2 ng/mL measured by a different immunochemiluminometric assay (Esoterix, LabCorp, Cranford, NJ) than the one used in this study. Unfortunately, after 43 AGHD patients and 10 controls were tested, the GHRH analog Geref Diagnostic® was taken off the market in the U.S. and 10 additional AGHD patients and 38 controls were only dosed with macimorelin limiting the validity of the study (13).

Here, we have validated the use of single-dose oral macimorelin for AGHD diagnosis, using the ITT as the comparator test. Macimorelin induced a robust increase in GH levels in healthy individuals and showed good agreement with the ITT in AGHD patients with a range of pre-test probabilities of having AGHD. The macimorelin test was easy to perform and well-tolerated as it does not depend on the presence of hypoglycemia and only requires collection of four venous blood samples after administration. The high repeatability (94%) and estimated sensitivity (92%) and specificity (96%) when using a GH cut-off of 5.1 ng/mL were remarkable considering that the repeatability of the ITT has been shown to be 90% in one report (25) and to have a coefficient of variation of 58% in another (26). The inverse
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relationship between peak GH and the likelihood of having AGHD we found is consistent with published data showing that peak GH levels were inversely related to the number of pituitary deficiencies (27,28).

In order to minimize the potential for over-diagnosing AGHD, a priori we selected a cut-off point of 2.8 ng/mL, the low end of the range suggested by the previously available data and despite using different GH assays (13). Data from the current study indicate that the optimal cut-off point for macimorelin ranges between 4.6 and 8.1 ng/mL. Using 5.1 ng/mL as the cut-off point resulted in good negative and positive agreement (94% and 82% respectively), with 92% sensitivity and 96% specificity. As measured GH concentrations will depend on the GH assay used, it is important to keep in mind that these data are based on a recommended GH cut-off point of 5.1 ng/mL using the IDS-iSYS Human Growth Hormone assay (Immunodiagnostic Systems Ltd., UK). This cut-off point is identical to the cut-off point recommended for the ITT, allowing endocrinologists using a different GH assay to apply a cut-off point relating to the one used for evaluating ITTs in their local laboratory. Applying a higher GH cut-off point than used for the ITT will increase the sensitivity of macimorelin and lead to higher positive agreement with the ITT, based on the higher stimulated GH concentrations in the macimorelin GHST than in the ITT, but this may be associated with a higher risk of over-diagnosing AGHD.

The macimorelin GHST was safe, not associated with frequent or SAEs that would require specific precautions or close monitoring by medical personnel. The most frequently reported side effect was mild and transient dysgeusia. In a previous study, only one drug-related SAE, an asymptomatic QT interval prolongation on the electrocardiogram resolved spontaneously
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within 24 hours in an individual taking citalopram, a drug now known to be associated with
QT prolongation (29). In this study, no drug related SAEs were observed and no AE was
documented with regards to the QT interval. In general, effects on the QT interval seem to be
more pronounced during the ITT as compared to macimorelin. This is in line with a recent
report showing QT prolongation in more than 20% of individuals undergoing an ITT (30).

The safety profile is particularly favorable when compared to the ITT which has potential for
inducing severe side effects such as hypoglycemia-related seizure and exacerbation of
cardiovascular and cerebrovascular disease. From a clinician’s perspective, this test is also
more convenient, less time-consuming and less resource-intensive than the ITT. This may
increase the likelihood that at risk patients are offered evaluation for AGHD. Another
advantage of the macimorelin GHST is that in some individuals, the ITT had to be repeated
for inadequate hypoglycemia, likely due to insulin resistance, whereas 99% of the
macimorelin tests were evaluable after the first attempt. The macimorelin GHST is also more
convenient than other alternative tests such as the glucagon stimulation test that requires 3-4
hours of testing, intramuscular administration, is associated with more side effects (i.e.;
nausea, vomiting), and has questionable diagnostic accuracy in overweight/obese patients
(31).

There are limitations to the study. This study is relatively small and it may not yet be an
appropriate substitute test for ITT or other provocative tests in all cases until more data is
accumulated. For instance, patients with uncontrolled diabetes, elderly and pediatric patients
were not evaluated in this trial and further studies are needed in such groups. Hence, the
results presented here apply to the specific populations tested here: adults with a history
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compatible with AGHD. Also, only a small number of individuals with hypothalamic disease
or with a BMI >35 kg/m² were included in the study, limiting the generalizability of these
findings to those groups. Due to the lack of a "standard of truth" to determine the true AGHD
status of each participant, it was not possible to measure the true sensitivity and specificity of
the test. Strengths of the study include the use of the ITT as a comparator, enrollment of
matched healthy controls, evaluating patients with a wide range of likelihood to have AGHD,
and a state-of-the-art GH assay measured centrally. Future studies should assess patients
suspected to have AGHD and amenable to GH replacement that are over the age of 65 and
with a BMI over 40. Also, possible interactions between macimorelin and drugs that prolong
QT should be further evaluated.

In summary, GH stimulation with oral macimorelin is a simple, well-tolerated, reproducible
and safe diagnostic test for AGHD, with comparable accuracy to that of the ITT. Evaluating
the test at the same GH cut-off of 5.1 ng/mL as used for the ITT limits the risk of a false-
positive diagnosis while maintaining a high detection rate of affected patients based on the
more potent GH stimulatory effect of macimorelin compared to the ITT.

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Macimorelin as a diagnostic test for AGHD

REFERENCES


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FIGURE LEGENDS

Figure 1. CONSORT diagram of study design and patient disposition.

Insulin tolerance test (ITT), macimorelin stimulation test (MAC).
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Figure 2. Specificity and sensitivity of the macimorelin GHST for varying GH cut-off points based on Group A and D subjects.

Error bars represent 95% confidence intervals.
Figure 3A. Peak GH concentrations in MAC and ITT by AGHD likelihood category (n=139)

The bottom and top of the boxes represent the first and third quartiles. The band inside the box is the median. The cross represents the mean and circles are the individual values. The whiskers are the lowest and the highest data points within 1.5 interquartile range of the lower and upper quartiles.
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Figure 3B. Scatter plot showing individual subjects peak GH concentrations, both in MAC and ITT (n=139). The majority of the dots above the bisecting line (y=x) demonstrate the higher stimulation potential of MAC as compared to ITT.

Insulin tolerance test (ITT), macimorelin stimulation test (MAC), growth hormone (GH). Solid line represents bisecting line. Regression equation y=1.0694x + 2.5216, r²=0.6.
### Table 1. Baseline Characteristics

<table>
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<tr>
<th>Parameters</th>
<th>AGHD likelihood Group</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>A (N)</td>
<td>B (N)</td>
</tr>
<tr>
<td>(Safety Population, N = 157)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (59.5)</td>
<td>18 (42.9)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (40.5)</td>
<td>24 (57.1)</td>
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<td>Total</td>
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<td>42 (100)</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Asian</td>
<td>2 (4.8)</td>
<td>1 (2.4)</td>
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<tr>
<td>Caucasian</td>
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<td>Black or African American</td>
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<tr>
<td>Other</td>
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<td>4 (9.5)</td>
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<td>Total</td>
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<td>42 (100)</td>
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<tr>
<td>Ethnicity</td>
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<tr>
<td>Hispanic or Latino</td>
<td>4 (9.5)</td>
<td>9 (21.4)</td>
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<tr>
<td>Not Hispanic or Latino</td>
<td>34 (81)</td>
<td>29 (69.1)</td>
</tr>
<tr>
<td>Not reported</td>
<td>3 (7.1)</td>
<td>4 (9.5)</td>
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<td>Macimorelin as a diagnostic test for AGHD</td>
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<td>------------------------------------------</td>
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<td><strong>Total</strong></td>
<td>42 (100)</td>
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<td><strong>Pituitary</strong></td>
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<td><strong>Adenoma</strong></td>
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<tr>
<td>None</td>
<td>21 (13.4)</td>
<td>12 (7.6)</td>
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<tr>
<td>Macroprolactinoma</td>
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<td>Microprolactinoma</td>
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<td><strong>CNS tumors</strong></td>
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<td>Meningioma</td>
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<tr>
<td>Other</td>
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<tr>
<td><strong>Other abnormalities</strong></td>
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<tr>
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<td>26 (16.6)</td>
<td>35 (22.3)</td>
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<tr>
<td>Childhood onset GHD (idiopathic)</td>
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<tr>
<td>Cyst (Rathke’s Arachnoid, etc.)</td>
<td>4 (2.6)</td>
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<th>Subgroups</th>
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<td></td>
<td>A</td>
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<tr>
<td></td>
<td>N (%)</td>
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<tr>
<td><strong>BMI class</strong></td>
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<td>&lt; 30 kg/m²</td>
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<td>30 - &lt; 35 kg/m²</td>
<td>7 (26.9)</td>
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<td>35 - &lt; 40 kg/m²</td>
<td>4 (26.7)</td>
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<tr>
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<td>18 - ≤ 25 years</td>
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<tr>
<td>&gt; 25 years</td>
<td>31 (27.0)</td>
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<tr>
<td>Total</td>
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