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ORIGINAL RESEARCH

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Cost-effectiveness of somatrogon in the Spanish pediatric population with growth hormone deficiency

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ABSTRACT

Objective: To analyze the cost-effectiveness of weekly somatrogon compared to daily growth hormones (GH-d) in the pediatric population of Spain with growth hormone deficiency (GHD).

Methods: Markov model with two states (patients with or without GH-d or somatrogon treatment) in prepubertal children (3 to 11 years and 3 to 12 years in girls and boys, respectively) with GHD in isolation or as part of multiple pituitary hormone deficiency and without previous treatment, from the perspective of the National Health System. The simulation of the economic model ends at the age of 18. The costs of hormones and monitoring were obtained from Spanish sources. The utilities were obtained from the literature. Spanish clinical experts validated the assumptions of the model.

Results: In the deterministic analysis, somatrogon would be cost-effective, compared to GH-d, with a cost per QALY (quality-adjusted life year) gained of €19,259 and a clinically relevant QALY gain (0.336). This result was confirmed in deterministic sensitivity analyses. According to the probabilistic analysis, somatrogon would be the dominant treatment, with a 61% probability of a willingness to pay of €25,000 per QALY gained.

Conclusion: Compared to GH-d, somatrogon is cost-effective in the Spanish pediatric population with GHD.

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KEYWORDS
Cost-effectiveness; economic evaluation; GHD; GH-d; somatrogon

1. Introduction

Short stature is defined by a height less than −2 standard deviations (SD) for age, sex and reference population. Only one in five children who meet this definition have underlying pathology, which rises to 50% if height falls below −3 SD [1]. Height follows a normal distribution in the population according to sex and age [2,3] and, approximately 0.6% to 2.3% of healthy children are short [3,4]. The prevalence of GH deficiency (GHD) in childhood ranges between 1/3480, 1/4018 and 1/5600, depending on the series [5–7]. The current annual cost of monitoring and treating a patient with GHD is estimated, based on a study published in 2012 [8] at €10,146.

The main goal of growth hormone (GH, somatropin) treatment during childhood and puberty in patients with GHD is to achieve a normal height in accordance with genetic height [9]. Daily injections of recombinant human growth hormone (somatropin) (GH-d) are the current standard treatment for GHD, which has been shown to be safe and effective [10]. However, GH-d is associated with suboptimal adherence (prevalence of non-adherence from 5% to 82%) [11,12], one of the main reasons is patient exhaustion due to the need for long-term daily injections [12,13]. Suboptimal adherence is associated with decreased efficacy of GH-d therapy, leading to lower annual growth [12,14–16] and decreased long-term response [12].

Somatrogon is a 47.5 kDa recombinant GH molecule formed by joining the 191 amino acid sequence of human growth hormone (hGH) with 3 copies of the C-terminal peptide (CTP) of human chorionic hormone (hCG). Glycosylated CTP determines the prolongation of the half-life of hGH by allowing its once-weekly subcutaneous administration, and has been shown to be clinically non-inferior to GH-d [12,17] and significantly less vital interference compared to daily somatropin [2,18]. Therefore, the weekly Somatrogon injections can increase patients' adherence, decrease treatment burden and improve their quality of life, which would lead, in the long term, to an improvement in adult height versus long-term GH-d [12].

The present study aims to analyze the cost-effectiveness/cost-utility of somatrogon compared to GH-d in Spain, using an economic model in GHD in the pediatric age group.

2. Methods

2.1. Design and structure

This Markov model was originally developed in Excel (Evidera) to simulate the evolution of patients aged 3 to 12 who start treatment with somatrogon or GH-d. The model consists of two health states (Figure 1): (i) alive and on-treatment

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Article highlights

- Clinical studies of somatrogon have shown that it is not inferior to somatropin. However, the effects of long-term growth hormone deficiency treatment in clinical practice need to be investigated, particularly the implications of weekly (somatrogon) versus daily somatropin (GH-d) dosing on treatment adherence and consequent effectiveness.
- According to the Markov model carried out, somatrogon would be cost-effective, compared to GH-d, with a cost per QALY (quality-adjusted life year) gained of €19,259 and a clinically relevant QALY gain (0.336).
- This result was confirmed in the probabilistic analysis; somatrogon would be the dominant treatment, with a 61% probability of a willingness to pay of €25,000 per QALY gained.

patients: patients receiving GH therapy (daily GH or weekly somatrogon). These patients will experience growth recovery due to GH therapy; and (ii) alive, untreated patients: patients who discontinue treatment. It is assumed in the model that these patients return to the standard deviations (SD) of the initial heights. Death status is not considered, as the modeled time horizon ends at 18 years of age, with reduced mortality. It is also considered that GHD is not associated with excess mortality compared to the general population [12].

Patient growth was modeled using age- and sex-specific growth curves for each age range [12]. Once the treatment completion age (18 years) is reached, patients in the 'alive on-treatment' health state remain in the same health state without accruing further costs or benefits from GH treatment.

2.2. Population

Prepubertal children (aged 3–10 years for girls and 3–11 years for boys) with isolated GHD or GHD as part of multiple pituitary hormone deficiency and no previous treatment (in line with the phase III clinical trial population comparing somatrogon and GH-d, reference NCT02968004 on ClinicalTrials.gov) [17]. Patients whose etiology was an intracranial tumor were excluded.

2.3. Comparators

Somatrogon (weekly administration) is compared with GH-d marketed in Spain (Genotonorm®, Norditropin®, Saizen®, Humatrope®, Nutropin AQ®, Zomacton®, Omnitrope®).

2.4. Perspective and time horizon

The perspective of the study is that of the Spanish National Health System (NHS). Therefore, only direct health costs are considered. The simulation of the economic model ends at the age of 18. An annual cost and utility discount of 3% was applied.

2.5. Model assumptions and clinical validation

The main assumptions of the model are presented in Table 1 and the supplementary tables (Tables S1 to S5) [9,15,16,19–25]. All model assumptions were clinically validated by a panel of three Spanish clinical experts with extensive experience managing GHD, co-authors of the present paper (MAAC, LCF, JILA). Among the different assumptions of the model, the following are worth highlighting, corroborated by clinical expert opinion: (i) It was assumed that adherence would be 5% higher with weekly than with daily injections of growth hormone, according to a study published in 2021 [19]; (ii) that this increase in adherence associated with weekly versus daily GH would not decrease over time; and (iii) treatment adherence rates over 10 years, according to studies by Maggio et al. [15] and Rodriguez-Arnao et al.[16]

2.6. Efficacy data

The model uses efficacy data from the Phase 3 clinical trial [17], whose protocol and results are available on the clinicaltrials.gov clinical trials database [26]. The main results are presented in Table 2. Somatrogon, injected once a week, has been shown to be clinically non-inferior to somatropin [12,18].

2.7. Estimating resources and costs

Two costs have been considered in the economic model: the pharmacological cost of GH-d and somatrogon, and the cost of disease monitoring. The acquisition cost of GH-d was calculated, considering that the price per mg of GH-d is €17.50 - per mg, according to the Royal Decree on reference prices of medicines in the Spanish National Health System [21]. This average price was weighted according to the market shares in Spain of the GH-d. The parity price of somatrogon compared to GH-d was calculated, excluding in the base case of the analysis the 4% deduction for orphan drugs, established in articles 8, 9 and 10 of Royal Decree-Law 8/2010, as amended by Royal Decree-Law 9/2011 (Table 1). The monitoring cost included outpatient endocrinology consultations, primary care

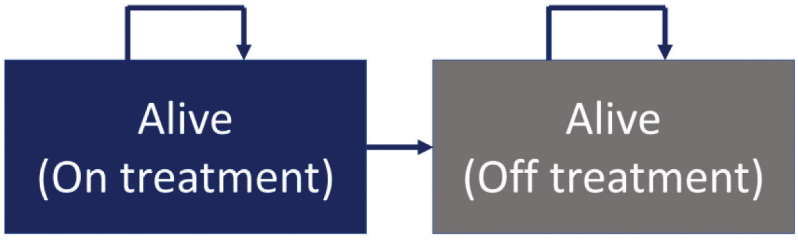

Figure 1. Markov model scheme.

Table 1. Main assumptions of the economic model.

Concept	Assumption	Validation References
Efficacy	The same efficacy is considered for all GH administered daily.	Experts panel
Mortality	The state of death is not considered, since the modeled time horizon ends at 18 years of age, with reduced mortality, also taking into account that GHD is not associated with excess mortality compared to the general population.	Experts panel
Abandonment of treatment	Abandonment of treatment in the first year is not considered because it is irrelevant.	Experts panel
Treatment adherence	Assumed 5% higher with weekly injection compared to daily injection (**Table S1**).	Experts panel [19]
Treatment adherence	It is estimated that this increase in adherence due to the weekly versus daily GH regimen would not be reduced over time.	Experts panel
Adherence to daily GH	Adherence up to 10 years is assumed based on the studies by Maggio (2018) and Rodríguez-Arnao (2019).	Experts panel [15,16]
Growth rate	With somatrogon (**Table S2**) an GH-d (**Table S3**).	Experts panel
Somatrogon dose	0.66 mg/kg/week	SmPC dose [20]
GH-d dose	Average: 0.21 mg/kg/week Minimum: 0.175 mg/kg/week Maximum: 0.245 mg/kg/week	Experts panel [9]
Cost per mg	GH-d: 17.50 € Somatrogon: 5.59 € (excluding 4% discount in the base case)	[21] *
GH-d market shares	Genotonorm®: 22.24% Norditropin®: 4.69% Saizen®: 24.25% Humatrope®: 12.49% Nutropin AQ®: 6.75% Zomacton®: 1.77% Omnitrope®: 27.81%	IQVIA
Product losses	Not considered.	Experts panel
Monitorization cost	See **Table S4**.	Experts panel [22]
Utilities	Utilities according to height (**Table S5**).	[23]
Utilities	Additional utility of weekly versus daily injection: 0.02 ± 0.01	[24]

*Note: *The calculation of the cost of €/mg of Somatrogon equivalent to €/mg of Somatropin, has been carried out taking into account the average dose of the posology recommended in the Technical Data Sheet of the GH-d indication*. SmPC: Summary of Product Characteristics.

Table 2. Efficacy result of clinical trial with somatrogon [26].

Ítem	Somatrogon	Genotropin
Treatment	Somatrogon weekly subcutaneous injection	GH daily injection
Number of patients analyzed	109	115
Annual growth rate (cm)	10.10	9.78
Mean (95% CI)	(9.58–10.63)	(9.29–10.26)

physician consultations, blood tests, hand X-rays and growth hormone stimulation tests. In this case, it was assumed the pituitary function test would include the following tests: prolactin, LH, FSH, TSH, free T4, ACTH, cortisol, GH and IGF-1, according to clinical expert opinion [MAAC, LCF JILA] (Table S4) [22]. Although the Pharmacy Department is involved in the storage and collection of the treatment, it was not accounted for in the model.

2.8. Utilities

The model considered utilities by height (Table S5) and the additional utilities of weekly versus daily injection [23] (Table 1). These utilities were used to calculate the quality-adjusted life years (QALYs) gained in a patient treated with somatrogon and GH-d.

The utilities for the different heights were calculated according to the estimates made by NICE in the report 'Human growth hormone (somatropin) for the treatment of growth failure in children Technology appraisal guidance [TA188],' published on 26 May 2010 [23]. In a study carried out in England, in a general population of 14,416 adults, the inter-relationship between quality of life and height SDS was estimated using EuroQoL (EQ-5D) using linear regression, controlling for age, body weight, sex, social class and long-standing illness. 'The study identified a positive correlation between an increase in height and a participant's EQ-5D score. An increase in height SDS of 1.0 was associated with an increase in EQ-5D score in the shortest group of 0.061, an increase of 0.010 in the middle group, and an increase of 0.002 in the group with average or above average height' [23] (Table S5).

2.9. Analyses performed

A deterministic base case was performed according to the assumptions shown in Table 1. Univariate deterministic sensitivity analyses were also carried out, modifying the values of 15 variables (with the intervals indicated in Table 4). Three additional sensitivity analyzes were performed. A first analysis including the 4% discount on the price of somatrogon, as it is an orphan drug.

According to the article by Deal et al [17], the estimated levels of mean IGF-I, according to the PK/PD models, remain within normality and only 1.9% of the samples presented

levels above 2 SDS (this corresponded to three patients). Somatrogon PK/PD levels indicate that sample collection 96 hours after somatrogon administration represents the mean IGF-I level over the weekly dosing interval. For this reason, the control is very similar to that done with daily GH and it is recommended to obtain the sample 96 hours after the administration of the somatrogon dose. Obviously, if the IGF-I level is elevated, it should be repeated. In the base case analysis, it was assumed that somatrogon monitoring will be very similar to that of daily GH. However, we performed a second sensitivity analysis, considering that the cost of monitoring was 20% higher with somatrogon than with GH-d. Finally, a sensitivity analysis was performed, considering a 2% increase in adherence with somatrogon vs GH-d.

A probabilistic analysis was also performed using second-order Monte Carlo simulations [27,28] to calculate the probability that somatrogon is cost-effective versus GH-d.

3. Results

3.1. Deterministic base case

In the base case, weekly somatrogon would be cost-effective versus GH-d, as the cost of gaining one QALY would be €19,259, below a willingness to pay of €25,000 to €60,000 per QALY gained [29] (Table 3). For each patient treated with weekly somatrogon, there would be, compared to GH-d, an additional expenditure of €6,471 and a gain of 0.336 QALYs (a clinically relevant difference) [30–33]. Furthermore, according to the model results, there would be a 4.11 cm gain in height compared to GH-d (170.28 cm and 166.17 cm, respectively).

3.2. Univariate sensitivity analysis

In the tornado analysis, including all sensitivity analyses, all net monetary benefit results were positive, meaning that somatrogon was the cost-effective treatment versus GH-d for a willingness to pay of €25,000 per QALY gained (the threshold below which the most effective treatment is also considered cost-effective), with only one exception: when the upper limit of somatrogon acquisition cost was considered (Table 4). When the 4% price discount for somatrogon was included, the cost per QALY gained was reduced to €3,899, compared to GH-d. Considering that the cost of monitoring was 20% higher with somatrogon than with GH-d, the cost of gaining a QALY with somatrogon amounted to €23,042. Finally, a sensitivity analysis was performed, considering a 2% increase in adherence with

Table 3. Result of the deterministic base case.

	Somatrogon	GH-d	Difference
Cost-effectiveness			
Cost			
Administered drugs	66,383 €	59,912 €	6,471 €
Monitorization	6,292 €	6,292 €	0 €
Total	72,675 €	66,204 €	6,471 €
Height (cm) – end of treatment	170.28	166.17	4.11
Cost per cm gained with the most effective treatment			1,574 €
Cost-utility			
Cost			
Administered drugs	66,383 €	59,912 €	6,471 €
Monitorization	6,292 €	6,292 €	0 €
Total	72,675 €	66,204 €	6,471 €
QALY	7.455	7.119	0.336
Cost per QALY gained with the most effective treatment			19,259 €

QALY: quality-adjusted life years; GH-d: growth hormone (somatropin) daily.

Table 4. Univariate sensitivity analysis.

Analysis	Parameter	Minimum value	Maximum value	Lower limit INMB	Uper limit INMB
1	Somatrogon: unit cost (per device/cartridge) – 60 mg	272.89 €	404.25 €	11,376 €	–8,506 €
2	Additional utility of weekly injection versus daily injection	0.00	0.05	–1,990 €	8,654 €
3	Somatrogon: unit cost (per device/cartridge) – 24 mg	109.16 €	161.70 €	4,826 €	–1,291 €
4	Omnitrope®: unit cost (per device/cartridge) – 10 mg	142.39 €	210.93 €	172 €	3,836 €
5	Saizen®: unit cost (per device/cartridge) – 5 mg	71.19 €	105.46 €	575 €	3,391 €
6	Saizen®: unit cost (per device/cartridge) – 8,8 mg	113.91 €	168.74 €	575 €	3,391 €
7	Genotonorm®: unit cost (per device/cartridge) – 12 mg	170.86 €	253.11 €	804 €	3,140 €
8	Annual discount rate for life years and QALYs	0%	5%	3,379 €	1,119 €
9	Nutropin AQ®: unit cost (per device/cartridge) – 10 mg	142.39 €	210.93 €	875 €	3,062 €
10	Annual cost discount rate	0%	5%	624 €	2,612 €
11	Height Utility – HtSDS Score from –1.5 to –1	0.82	0.85	2,921 €	944 €
12	Genotonorm® MiniQuick: unit cost (per device/cartridge) (2 mg, pre-filled syringe)	28.48 €	42.19 €	1,101 €	2,812 €
13	Height Utility – HtSDS Score from –1 to –0.5	0.84	0.86	1,097 €	2,707 €
14	Genotonorm®: unit cost (per device/cartridge) – 5 mg	71.19 €	105.46 €	1,161 €	2,746 €
15	Humatrope®: unit cost (per device/cartridge) – 6 mg	85.43 €	126.56 €	1,274 €	2,622 €

INMB: incremental monetary net benefit. A positive BNMI indicates that somatrogon is cost-effective compared to GH-d (Omnitrope, Saizen, Genonorm, Nutropinac, Humatrope). A negative BNMI indicates the opposite.

Table 5. Probabilistic analysis result.

	Mean	95% CI
Cost-effectiveness		
Cost differences	6,592 €	6,235 €; 6,949 €
cm differences	4.10	4.08; 4.12
Cost per cm gained	1,608 €	1,528; 1,686 €
Cost-utility		
Cost differences	6,592 €	6,235 €; 6,949 €
QALY difference	0.333	0.326; 0.340
Cost per QALY gained	19,796 €	19,126; 20438 €

*For a willingness to pay of €25,000 per QALY gained.

somatrogon vs GH-d. The result was also cost-effective: €10,605 per QALY gained.

3.3. Probabilistic analysis

The result of the probabilistic analysis is presented in Table 5 and Figures 2 and 3. The mean cost of gaining one QALY with somatrogon compared to GH-d would be €19,796, with a 95% CI of €19,126 to €20,438 (Table 5). The probability that, compared to GH-d, weekly somatrogon would be the cost-effective treatment would be 61% (for a willingness to pay of €25,000 per QALY gained), with somatrogon being the dominant (most effective, lowest cost) treatment in 12.4% of simulations (Figure 2; Figure 3).

3.4. Price threshold

The threshold price of somatrogon (for a willingness to pay of €25,000/QALY) is €5.75/mg. That is, above that price, the cost of gaining 1 QALY with somatrogon compared to GH-d would exceed €25,000.

4. Discussion

Clinical studies of somatrogon have shown that it is not inferior to somatropin. However, the effects of long-term growth hormone deficiency treatment in clinical practice need to be investigated, particularly the implications of weekly versus daily dosing on treatment adherence and consequent effectiveness.

According to the present analysis, weekly somatrogon is a cost-effective treatment compared to GH-d, with a cost per QALY gained of €19,796 (95%CI €19,126; €20,438) and a clinically relevant QALY gain (0.33) per treated patient. On this last aspect, it should be noted that a difference of 0.33 QALY in favor of somatrogon compared to GH-d is clinically relevant, as it is generally considered that the minimum difference in utility that the patient can detect between two interventions (measured by the EQ-5D, HUI2, HUI3 and SF-6D instruments) would be, depending on the instrument used, 0.074, 0.030, 0.030 and 0.033 QALYs, respectively [30–33].

The economic model simulated, *lato sensu*, the evolution of a cohort of patients with short stature due to GHD treated with

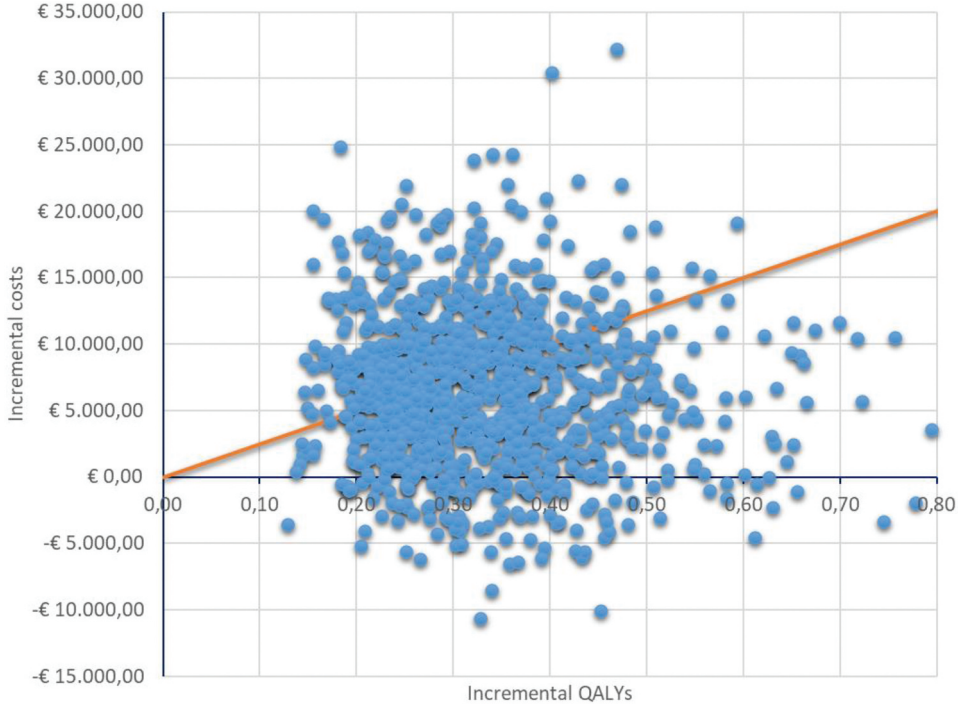

Figure 2. Cost-effectiveness plane of the probabilistic analysis. Weekly somatrogon vs. GH-d.

QALYs: quality-adjusted life years; GH-d: growth hormone (somatropin) daily.

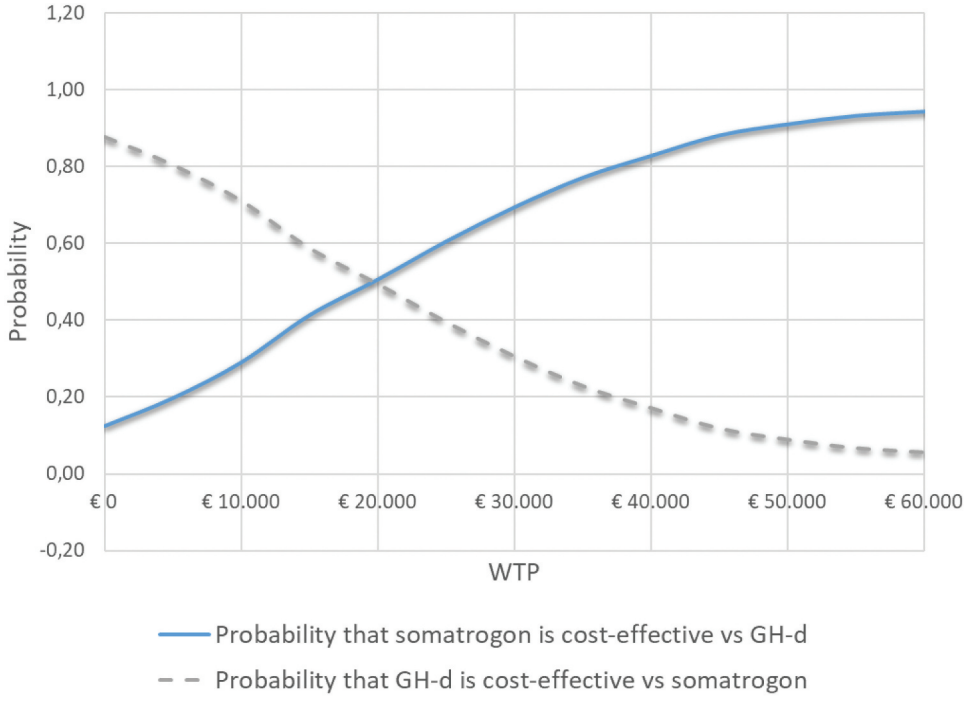

Figure 3. Acceptability curves of the probabilistic analysis. Weekly somatrogon vs. GH-d.
GH-d: growth hormone (somatropin) daily.; WTP: willingness to pay.

somatrogon or GH-d. To properly evaluate the results of the study, both the possible limitations of the study and its consistencies must be taken into account. The study's main strength lies in the stability of the economic model (the direction of the base case result was maintained in the sensitivity analyses), which was confirmed in most deterministic analyses and the probabilistic analysis. According to the latter, compared to GH-d, somatrogon treatment of GHD patients would be cost-effective in 61% of patients for a willingness to pay of €25,000 per QALY gained, with a 95% confidence interval of €19,126 to €20,438. However, a limitation of the study is that it is a theoretical model and therefore a simplified simulation of reality. Therefore, several assumptions about using medical resources in the GHD had to be made. On the contrary, it should be considered a strength of the study that all assumptions made in the economic model were clinically validated by a panel composed of three Spanish clinical experts with extensive experience in the management of GHD, co-authors of the present paper (MAAC, LCF, JILA). In this regard, it is important to point out that most of the assumptions of the economic model were made by the panel of experts. The justification of the assumptions is explained in Table 1, according to the opinion of the panel of experts.

In this study, only direct healthcare costs were considered, since it was carried out exclusively from the perspective of the Spanish National Health System.

The results of several cost-effectiveness analyses of somatrogon compared to GH-d have been published. According to a Markov model with three health states and a 7-year time horizon, the cost of gaining one QALY with somatrogon compared to GH-d would be €190,430 in Germany and £51,957 in the UK [34]. These results are not comparable to those obtained in our study, given that it is a different model in terms of structure and assumptions, and refers to health systems other than the Spanish NHS. Preliminary results of the present model were recently published in five countries (Canada, Spain, United States, Ireland and Sweden) [12]. This concluded that somatrogon treatment led to 1.71 to 4.11 cm height gain and 0.19 to 0.43 QALYs compared with d-HGs. Somatrogon was generally cost-effective versus GH-d, with GH-d dosing, loss of utilities associated with injection frequency, unit costs of GH-d, and adherence to somatrogon being the key cost-effectiveness factors [12]. The full results for Ireland have recently been published [35]. This study concluded that somatrogon weekly injections were estimated to result in higher near adult height, higher QALYs, lower overall cost and lower cost per cm gained than GH-d, in pediatric growth hormone deficiency.

5. Conclusions

In summary, and according to the analyses performed, it can be concluded that somatrogon weekly is a cost-effective treatment compared to GH-d, with a mean cost per QALY gained of €19,796 (95%CI €19,126; €20,438), below a willingness to pay of €25,000 per QALY gained, and with a clinically relevant QALY gain (0.33) per treated patient.

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Author's contribution

C. Rubio-Terres and D. Rubio-Rodríguez have developed the adaptation to the Spanish National Health System of this economic model. M.A. Andreu Crespo, L. Castro-Feijóo, J.I. Labarta-Aizpún, C. Peral and J.A. Barrueta

contributed to study conceptualization, design and revision of model. All authors had accessed to data, contributed to study conceptualization, methodology development and manuscript preparation. All authors listed made substantial contributions to the study in conceptualization and/or design of study, analysis and/or interpretation of data and manuscript preparation and/or review. All authors read, edited and approved the final manuscript. C. Rubio-Terres is the guarantor of the overall content of this manuscript.

Declaration of interest

C. Peral and J.A. Barrueta are employees of Pfizer SLU, Madrid, Spain. M.A. Andreu Crespo, L. Castro-Feijóo and J.I. Labarta-Aizpún has received speaker honoraria from Pfizer (Spain) and have participated in Pfizer advisory boards. D. Rubio-Rodríguez and C. Rubio-Terrés are employees of Health Value who received an honorarium from Pfizer (Spain) in connection with the development of this manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed that they are an investigator in clinical trials of somatrogon for OPKO Health, a consultant for Pfizer and receive research funding from Pfizer. They are also a consultant for Ascendis which also makes a once weekly growth hormone approved in the US and elsewhere. They are a consultant for GenSci which also makes a once weekly growth hormone available in China. They are a consultant for and receive research funding from Novo Nordisk which also makes a once weekly growth hormone available in the US and elsewhere. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

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