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Efficacy, safety, quality of life, adherence and cost-effectiveness of long-acting growth hormone replacement therapy compared to daily growth hormone in children with growth hormone deficiency: A systematic review and meta-analysis☆

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ABSTRACT

We evaluated the efficacy, safety, adherence, quality of life (QoL) and cost-effectiveness of long-acting growth hormone (LAGH) vs daily growth hormone (GH) preparations in the treatment of growth hormone deficiency (GHD) in children. Systematic searches were performed in PubMed, Embase and Web of Science up to July 2022 on randomized and non-randomized studies involving children with GHD receiving LAGH as compared to daily GH. Meta-analyses for efficacy and safety were performed comparing different LAGH/daily GH formulations. From the initial 1393 records, we included 16 studies for efficacy and safety, 8 studies for adherence and 2 studies for QoL. No studies reporting cost-effectiveness were found. Pooled mean differences of mean annualized height velocity (cm/year) showed no difference between LAGH and daily GH: Eutropin Plus® vs Eutropin® [− 0.14 (−0.43, 0.15)], Eutropin Plus® vs Genotropin® [− 0.74 (−1.83, 0.34)], Jintrolong® vs Jintropin AQ® [0.05 (−0.54, 0.65)], Somatrogon vs Genotropin® [− 1.40 (−2.91, 0.10)], TransCon vs Genotropin® [0.93 (0.26, 1.61)]. Also, other efficacy and safety outcomes, QoL and adherence were comparable for LAGH and daily GH.

Our results showed that, although most of the included studies had some concerns for risk of bias, regarding efficacy and safety all the LAGH formulations were similar to daily GH. Future high quality studies are needed to confirm these data. Adherence and QoL should be addressed from real-world data studies for both the mid and long term and in a larger population. Cost-effectiveness studies are needed to measure the economic impact of LAGH from the healthcare payer's perspective.

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1. Introduction

Recombinant human growth hormone (rhGH) treatment in patients with GH deficiency (GHD) has been used since the 1980 s. This therapy was found to be safe and effective in promoting adequate height growth in paediatric age and an improvement in clinical and metabolic alterations in patients affected by GHD [1].

The need to administer rhGH daily subcutaneously for many years hinders optimal adherence and, in some cases, was found to limit its effectiveness [2,3].

Over the years research therefore focused on the development of long-acting GH (LAGH) preparations to prolong the half-life of the GH molecule and thus to reduce the frequency of administration [4]. These new products could reduce the treatment burden and help to improve patient adherence and clinical outcomes, particularly in patients with poor adherence to daily GH injections [5,6]. Moreover, quality of life and cost-effectiveness could also be influenced by the introduction in clinical practice of LAGH in pediatric population.

Several formulations of LAGH with different pharmacokinetic and pharmacodynamic profile were developed and are currently being studied in children [4]. Those include unmodified rhGH in a depot formulation (Eutropin Plus®), pegylated rhGH (Jintrolong®), modified rhGH with increased albumin binding (somapacitan, Sogroya®), prodrug formulation (lonapegsomatropin, Skytrofa®) and rhGH fusion proteins (somatrogon, NGENLA®). Many of them were recently approved for the use in paediatric patients affected by GHD in some Countries (Eutropin Plus® in South Korea, Jintrolong® in China, Skytrofa® in USA) and NGENLA® in EU, Australia, Canada, Japan, UK, Brazil and India. However, some important issues regarding the use of LAGH formulation in paediatric population need to be addressed. In fact, it is unclear whether long-acting GH is as effective as daily rhGH in promoting the child growth maintaining a high safety profile in children affected by GHD. Moreover, the impact of LAGH therapy on adherence, quality of life, and cost-effectiveness needs to be better explored. As a result, the aim of this systematic review is to evaluate the efficacy, safety, adherence, quality of life, and cost-effectiveness of long-acting growth hormone vs daily growth hormone in the treatment of growth hormone deficiency (GHD) children. To this end, this systematic review answers the following questions:

- Review question (RQ) 1: What is the comparative efficacy and safety of long-acting growth hormone replacement therapy compared to daily growth hormone in children with growth hormone deficiency?
- RQ 2: Does long-acting growth hormone replacement therapy versus daily growth hormone in children with growth hormone deficiency improve treatment adherence?
- RQ 3: Does long-acting growth hormone replacement therapy versus daily growth hormone improve the quality of life of children with growth hormone deficiency and their parents?
- RQ 4: What is the cost-effectiveness of long-acting growth hormone replacement therapy compared to daily growth hormone in children with growth hormone deficiency?

2. Methods

We performed the review in accordance with the PRISMA 2020 guidelines [7,8].

We selected studies according to the following inclusion and exclusion criteria.

2.1. Inclusion criteria

We included studies according to the PICO framework (Population, Intervention, Comparator, Outcome).

2.1.1. Types of studies

For all the research questions, we included randomized controlled trials (RCTs), except phase 1 trial; observational studies, such as controlled before-and-after studies, comparative cohort studies, case-control studies. As for RQ3 (quality of life), we also included cross-sectional studies and case series. As for RQ4 (cost-effectiveness), we also included economic studies, such as cost-effectiveness, cost-utility and cost-benefit analyses.

2.1.2. Population

For all the research questions, we included children/adolescents (<18 years) with growth hormone deficiency (GHD).

2.1.3. Intervention

Long-acting growth hormone.

2.1.4. Comparator

Daily growth hormone; for the RQ2 (adherence) and RQ3 (quality of life) we also considered studies without a control group.

2.1.5. Outcome

RQ1 (efficacy and safety).

- Efficacy: 1) height velocity (HV); 2) HV standard deviation scores (SDS); 3) height SDS chronological age; 4) height SDS bone age; 5) change in height SDS; 6) insulin-like growth factor 1 (IGF-1) SDS; 7) insulin-like growth factor binding protein-3 (IGFBP-3); 8) IGFBP-3 SDS.
- Safety: 1) incidence of adverse events; 2) fasting glucose; 3) hemoglobin A1c; 4) thyroid function.

2.1.5.1. RQ2 (adherence).

- = treatment adherence, in terms of medication possession ratio (MPR), proportion of days covered (PDC), proportion of doses administered vs prescribed, etc.

2.1.5.2. RQ3 (quality of life).

- = quality of life (QoL)

2.1.5.3. RQ4 (cost-effectiveness).

- = cost-effectiveness, cost-utility, cost-benefit

2.2. Exclusion criteria

- non-human studies;.
- reviews, editorials, commentaries, letters.

2.3. Information sources

Systematic searches were performed in PubMed, Embase and Web of Science from their inception to July 2022. Reference lists of relevant articles were also screened. No date or language limits were imposed on the search.

2.4. Search strategy

Literature search strategies were developed using medical subject headings (MeSH) and text words related to long-acting growth hormone in pediatric population. The full search strategy for the three databases is reported in the Supplementary Table 1.

2.5. Selection process

Bibliographic citations were imported in the software EndNote™ X7.4 and duplicates were removed. Then the references were exported in a Microsoft Excel spreadsheet, which was used for study selection and data extraction. The study selection process was performed by two independent review authors (MO, LG). Any disagreement was solved through discussion and, when no consensus was reached on which articles to select, a third reviewer was contacted (CM) to make the final decision. Study selection was conducted in two phases. Initially, the reviewers assessed the records through the titles and abstracts screening against the inclusion criteria. In the second phase, the review authors assessed the full texts of the potential eligible studies. The final studies included in the review were described in the main text and in the tables, while a list of excluded studies along with the reasons for exclusion has been published as Supplementary Table 2.

2.6. Data collection process

Data extraction was performed by two independent reviewers (MO, LG) using a standardized form. To ensure consistency across reviewers, calibration exercises were conducted before starting the review. Any discrepancies on the data extracted were solved through discussion or involving a third reviewer (CM) who made the final decision.

2.7. Data items

For all the research questions, we collected data on study ID (first author, year), study design, trial name, registration number, number of centres, countries, length of follow-up, type of LAGH and daily GH formulations, dosage, number of patients included in each treatment arm, and mean age. For RQ1, we extracted available clinical outcomes reported in each study. Mean annualized height velocity was reported in all studies, and in almost all of them was the primary outcome. The second most reported outcome was insulin-like growth factor 1 (IGF-1) SDS, followed by height SDS chronological age and change in height SDS, while the other outcomes were reported by fewer studies. Incidence of adverse events was reported in most of the studies included. All available outcomes were collected, but the length of follow-up was considered when interpreting study findings and in deciding which outcomes were similar enough to combine for meta-analysis.

For the RQ2, we collected the treatment adherence in terms of adherence rate, calculated as the number of doses administered/number of doses expected × 100.

For the RQ3, we extracted data about quality of life measured through validated tools, i.e. the Quality of Life in Short Stature Youth (QoLISSY) questionnaire and the Growth Hormone Deficiency - Child Impact Measure observer-report (GHD-CIM ObsRO) tool.

About the RQ4, no cost-effectiveness study was found, thus none of the anticipated economic measure were reported.

2.8. Study risk of bias assessment

The following tools were used for the different study design:

2.8.1. RCTs

To assess the risk of bias in RCTs we used the RoB 2 tool - A revised Cochrane risk of bias tool for randomized trials [9]. For the efficacy outcomes, we assessed the effect of assignment to intervention (the 'intention-to-treat' effect), while for safety outcomes we assessed the effect of adhering to intervention (the 'per-protocol' effect).

2.8.2. Non-randomized studies

To assess the risk of bias in non-randomized studies we used the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) [10].

Case series and economic studies would be assessed by the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies [11] and by the Consensus Health Economic Criteria (CHEC) list [12], respectively. However, we did not include studies with such a design in our review.

The risk of bias assessment was performed by two independent reviewers (MO, LG). Any discrepancies in judgements of risk of bias were resolved by discussion to reach consensus between the two review authors, with a third review author (BP) acting as an arbiter if necessary.

2.9. Statistical analysis

We conducted meta-analyses in case of clinical and methodological homogeneity of data among the included studies, in terms of study population, type of LAGH, type of daily GH, outcomes measures, and study design. We performed meta-analyses only for RQ 1 (efficacy and safety). The other RQs were reported narratively for the following reasons: for RQ2 (adherence) only one study reported the number of administrated doses versus scheduled doses, while the other studies reported the adherence rate as a percentage, not allowing to perform proportion meta-analysis; for RQ3, the two included studies used different tools and outcome measures to measure the QoL; in addition, one study did not report standard deviations, thus it was not possible to pool their results. Finally, we did not find any study for RQ4.

Separate meta-analyses were performed for RCTs and non-RCTs. Continuous data were aggregated as mean difference (MD), while dichotomous data as pooled risk ratio (RR). Random effect model with inverse variance method was adopted. 95% confidence intervals were reported. Heterogeneity was assessed through I^2 statistic, and was interpreted as follows: I^2 = 0–40%: not important heterogeneity; I^2 = 40–60%: moderate heterogeneity; I^2 = 60–80%: substantial heterogeneity; I^2 = 80–100%: considerable heterogeneity [13]. Our primary unit of analysis was individual participants from parallel group trials; we considered only the first phase of cross-over trials to avoid the carry-over effect. In the case of studies having multiple arms with different doses and a single control group of daily GH, in order to avoid a unit-of-analysis error we split the control group into subgroups of (nearly) equal size, one for each treatment. All the analyses were performed by the RevMan 5.4 software.

We conducted subgroup analyses to explore possible sources of heterogeneity by different doses of LAGH/daily GH. Sensitivity analyses were not performed. We planned to perform sensitivity analyses excluding the studies having a high risk of bias but, in some meta-

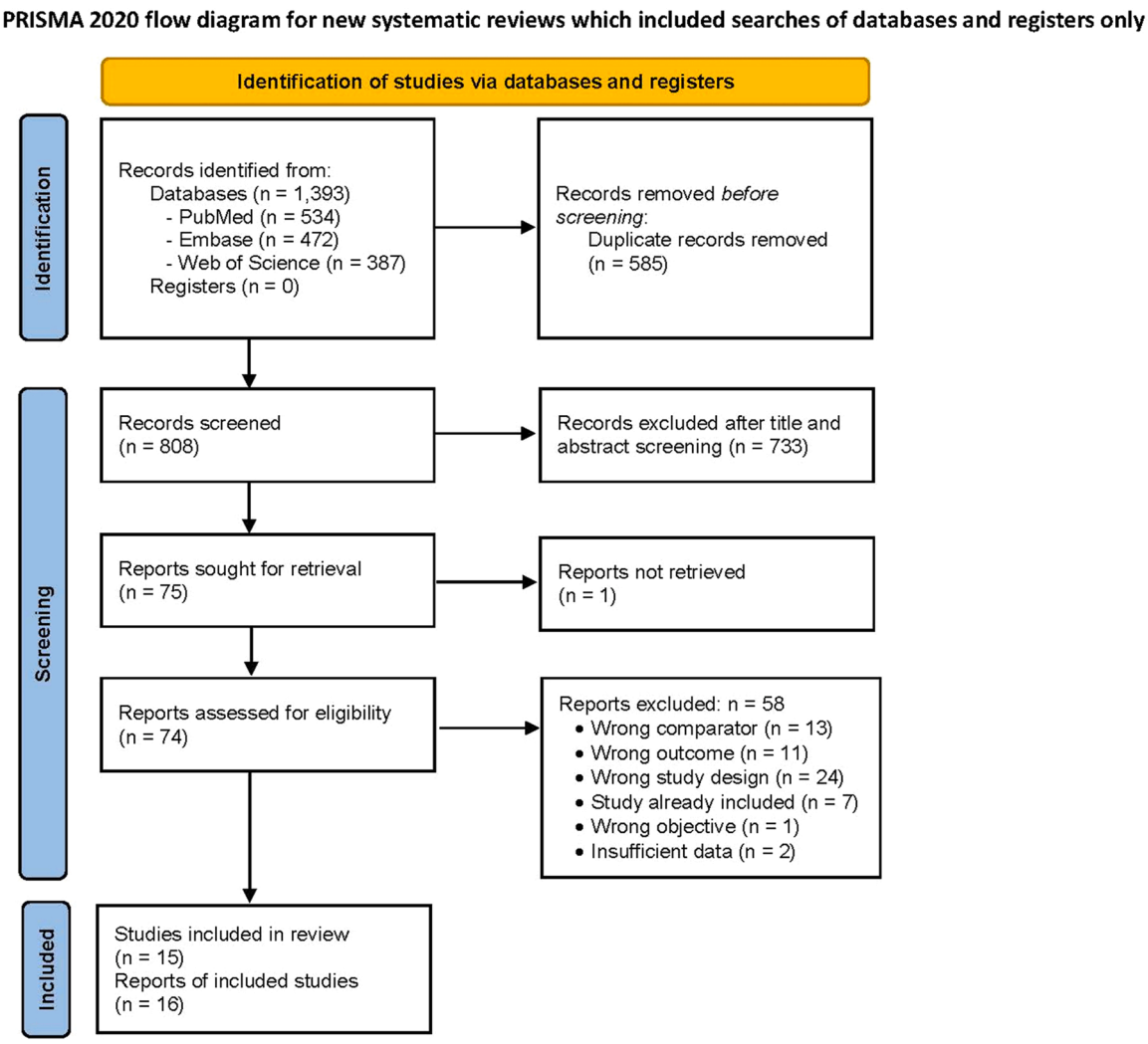

Fig. 1. PRISMA 2020 flow diagram for RQ1.

analysis, no high risk of bias studies were included while, in other meta-analyses, after the exclusion of high risk of bias studies, only a single study would remain.

We did not assess the risk of reporting bias through a statistical test because no meta-analysis included at least 10 studies, as suggested by the Cochrane Handbook [14]; however, through the visual examination of the funnel plots, we did not detect any apparent asymmetry.

2.10. Certainty assessment

We assessed the overall certainty of the body of evidence for the outcomes judged by the clinical experts as critical or important using the GRADE method [15]. The overall quality of evidence was assessed across the domains of risk of bias, consistency, directness, precision and publication bias. We considered that evidence from randomized controlled trials starts with a high-certainty level and we downgraded the certainty of the evidence by one level for serious (or two levels for very serious) limitations in each of the above domains. As for risk of bias, we downgraded by one level if at least one study was judged having some concerns for risk of bias, while we downgraded by two levels if most of studies had a high risk of bias in more than one domain. Regarding consistency, we assessed whether there was unexplained heterogeneity of results, according to the cut-offs reported above. As for directness, we evaluated whether the population, interventions, comparators and outcome measures considered in the included studies correspond to those we were interested in. We downgraded for imprecision if the effect estimates are from studies with a small sample size and had wide confidence intervals; in addition, we assessed whether a non-inferiority margin was specified for the primary outcome and the sample size calculation was based on this non-inferiority margin. As for publication bias, we assessed through visual examination of funnel plots whether there was asymmetry.

Conversely, factors that can increase the certainty level, such as large magnitude of an effect, dose-response gradient, and effect of plausible

Table 1
Characteristics of included studies for RQ1.

Study ID	Design	Trial name / registr. N	Centres (N)	Countries (N)	Countries	Follow-up (weeks)	Intervention group (LAGH)	Dose mg/kg/wk (N. of patients; mean age)	Control group (daily GH)	Dose mg/kg/day (N. of patients; mean age)	Mean annualized height velocity (HV)	Adverse events (% of patients)
Chatelain 2017[17]	RCT phase 2	NCT01947907	38	14	European countries and Egypt	26	TransCon (ACP-001)	• 0.14 [N = 12; 8.2 (SD 2.9)] • 0.21 [N = 14; 8.4 (SD 2.1)] • 0.30 [N = 14; 7.5 (SD 2.8)]	Genotropin®	0.03 [N = 13; 7.7 (SD 2.5)]	• LAGH: 0.14 mg: 11.9 cm; 0.21 mg: 12.9 cm; 0.30 mg: 13.9 cm • DAILY GH: 11.6 cm	• LAGH: range 43–58% • DAILY GH: 61.5%
Chung 2016 [18]	cohort	NCT01604395	NR	1	South Korea	52	Eutropin Plus®	Dose: NR [N = 287; 8.9 (SD 3.2)]	Eutropin®	Dose: NR [N = 797; 7.9 (SD 3.1)]	• LAGH: 8.7 cm • DAILY GH: 8.8 cm	• LAGH: 15.4% • DAILY GH: 17.1%
Deal 2022 [19]	RCT phase 3	NCT02968004	83	21	International	52	Somatrogon (MOD-4023)	0.66 [N = 109; 7.8 (range 3.0–12.0)]	Genotropin®	0.034 [N = 115; 7.6 (range 3.1–11.9)]	• LAGH: 10.1 cm • DAILY GH: 9.8 cm	• LAGH: 87.2% • DAILY GH: 84.3%
Du 2022 [20]	RCT	NR	1	1	China	52	Jintrolong®	• 0.12 [N = 25; 10.4 (SD 5.4)] • 0.20 [N = 23; 8.9 (SD 3.9)]	Jintropin AQ®	0.04 [N = 23; 8.9 (SD 3.0)]	• LAGH: 0.12 mg: 8.13 cm; 0.20 mg: 9.35 cm • DAILY GH: 8.38 cm	NR
Horikawa 2022[21]	RCT phase 3	NCT03874013	32	1	Japan	52	Somatrogon	0.66 [N = 22; 5.3 (SD 1.8)]	Genotropin®	0.025 [N = 22; 6.8 (SD 2.3)]	• LAGH: 9.65 cm • DAILY GH: 7.87 cm	• LAGH: 100% • DAILY GH: 86.4%
Hwang 2013 [22]	RCT	NR	14	1	South Korea	52	Eutropin Plus® (LB03002)	0.5 [N = 30; 9.1 (SD 2.6)]	Eutropin®	0.03 [N = 30; 9.3 (SD 2.5)]	• LAGH: 9.06 cm • DAILY GH: 9.72 cm	• LAGH: 80% • DAILY GH: 83%
Khadilkar 2014[23]	RCT phase 3	NCT00271518	31	NR	International	52	Eutropin Plus® (LB03002)	0.5 [N = 91; 7.8 (SD 2.5)]	Genotropin®	0.03 [N = 87; 7.8 (SD 2.5)]	• LAGH: 11.63 cm • DAILY GH: 11.97 cm	• LAGH: 82.4% • DAILY GH: 72.4%
Luo 2017 [24]	RCT phase 2	NCT01342146	6	1	China	25	Jintrolong®	• 0.1 [N = 32; 10.9 (SD 3.3)] • 0.2 [N = 31; 11.8 (SD 4.0)]	Jintropin AQ®	0.0357 [N = 34; 10.5 (SD 4.1)]	• LAGH: 0.1 mg: 11.63 cm; 0.2 mg: 12.65 cm • DAILY GH: 14.06 cm	• LAGH: 0.1 mg: 53%; 0.2 mg: 51.6% • DAILY GH: 58.8%
	RCT phase 3	NCT01495468	6	1	China	25	Jintrolong®	0.2 [N = 228; 11.3 (SD 3.5)]	Jintropin AQ®	0.0357 [N = 115; 11.8 (SD 3.6)]	• LAGH: 13.41 cm • DAILY GH: 12.55 cm	• LAGH: 37.3% • DAILY GH: 36.5%
Malieyskiy 2018[25]	RCT phase 2	NCT03309891	27	10	Europe, Middle East and Republic of Korea	52	GX-H9	• 0.8 [N = 14; 6.8 (SD 2.3)] • 1.2 [N = 13; 6.7 (SD 2.0)] • 2.4 (bi-wk) [N = 13; 7.0 (SD 2.6)]	Genotropin®	0.03 [N = 14; 6.9 (SD 1.9)]	• LAGH: 0.8 mg: 10.50 cm; 1.2 mg: 11.76 cm; 2.4 mg: 11.03 cm • DAILY GH: 9.14 cm	NR
Peter 2012 [26]	RCT phase 2/3a	NR	11	6	European countries	52	Eutropin Plus® (LB03002)	• 0.2 [N = 13; 7.0 (SD 2.0)] • 0.5 [N = 13; (7.1 (SD 2.1)] • 0.7 [N = 13; 7.8; (SD 2.1)]	Genotropin®	0.03 [N = 12; 7.3 (SD 2.3)]	• LAGH: 0.2 mg: 9.76 cm; 0.5 mg: 11.75 cm; 0.7 mg: 12.44 cm • DAILY GH: 12.17 cm	• LAGH: 0.2 mg: 92.3%; 0.5 mg: 92.3%; 0.7 mg: 69.2% • DAILY GH: 75%

(*continued on next page*)

Table 1 (*continued*)

Study ID	Design	Trial name / registr. N	Centres (N)	Countries (N)	Countries	Follow-up (weeks)	Intervention group (LAGH)	Dose mg/kg/wk (N. of patients; mean age)	Control group (daily GH)	Dose mg/kg/day (N. of patients; mean age)	Mean annualized height velocity (HV)	Adverse events (% of patients)
Qiao 2019 [27]	cohort	NR	1	1	China	52	Jintrolong®	0.2 [N = 49; 5.4 (SD 2.4)]	Jintropin AQ®	0.043 [N = 49; 6.3 (SD 2.4)]	• LAGH: 10.57 cm • DAILY GH: 10.46 cm	NR
Sävendahl 2020[28]	RCT phase 2	REAL 3 NCT02616562	29	11	Europe, USA, Japan	52	Somapacitan	• 0.04 [N = 14; 5.8 (SD 1.8)] • 0.08 [N = 15; 5.9 (SD 1.8)] • 0.16 [N = 14; 6.1 (SD 2.3)]	Norditropin®	0.034 [N = 14; 6.0 (SD 2.0)]	• LAGH: 0.04 mg: 7.5 cm; 0.08 mg: 9.7 cm; 0.16 mg: 11.7 cm • DAILY GH: 9.9 cm	• LAGH: 0.04 mg: 62.5%; 0.08 mg: 73.3%; 0.16 mg: 92.9% • DAILY GH: 100%
Sävendahl 2022[29]	RCT phase 2	REAL 3 NCT02616562	29	11	Europe, USA, Japan	156	Somapacitan	• 0.04/0.16 [N = 14; 5.8 (SD 1.8)] • 0.08/0.16 [N = 15; 5.9 (SD 1.8)] • 0.16 [N = 14; 6.1 (SD 2.3)]	Norditropin®	0.034 [N = 14; 6.0 (SD 2.0)]	• LAGH: 0.04/ 0.16 mg: 8.9 cm; 0.08/0.16 mg: 7.8 cm; 0.16 mg: 8.4 cm • DAILY GH: 7.6 cm	• LAGH (pooled groups): 88.9% • DAILY GH: 100%
Sun 2021 [30]	RCT phase 4	NCT02976675	31	1	China	26	Jintrolong®	• 0.2 (wk) [N = 187; 7.8 (SD 2.8)] • 0.2 (bi-wk) [N = 185; 7.6 (SD 2.7)]	Jintropin AQ®	0.0357 [N = 176; 8.0 (SD 2.9)]	• LAGH: 0.2 mg wk: 10.82 cm; 0.2 mg bi-wk: 8.98 cm • DAILY GH: 10.82 cm	• LAGH: 0.2 mg wk: 39.7%; 0.2 mg bi-wk: 28.0% • DAILY GH: 33.3%
Thornton 2021[31]	RCT phase 3	heiGHt NCT02781727	73	15	Europe, USA, New Zeland	52	Lonapegsomatropin (TransCon)	0.24 [N = 105; 8.5 (SD 2.7)]	Genotropin®	0.034 [N = 56; 8.5 (SD 2.8)]	• LAGH: 11.2 cm • DAILY GH: 10.3 cm	• LAGH: 77.1% • DAILY GH: 69.6%
Zelinska 2017[32]	RCT phase 2	NCT01592500	14	7	Europe, USA, Israel	52	Somatrogon (MOD-4023)	0.25 [N = 13; 6.2 (SD 2.2)] 0.48 [N = 15; 5.8 (SD 2.3)] 0.66 [N = 14; 6.1 (SD 2.2)]	Genotropin®	0.034 [N = 11; 5.7 (SD 1.9)]	• LAGH: 0.25 mg: 10.4 cm; 0.48 mg: 11.0 cm; 0.66 mg: 11.93 cm • DAILY GH: 12.5 cm	• LAGH: 0.25 mg: 69.2%; 0.48 mg: 66.7%; 0.66 mg: 71.4% • DAILY GH: 72.7%

LAGH, long-acting growth hormone; **GH**, growth hormone; **RCT**, randomized controlled trial; **SD**, standard deviation; **NR**, not reported; **bi-wk**, bi-weekly; **wk**, weekly; **HV**, mean annualized height velocity.

residual confounding, were also considered.

For each outcome, the GRADE approach results in an assessment of the quality of a body of evidence in one of four grades: high, moderate, low or very low. Summary of Findings tables were created by GRADEpro GDT software [16].

3. Results

3.1. Study selection

We performed a single literature search for the research questions RQ1-RQ4 that retrieved 1393 records from electronic databases. After duplicates removal, we screened 808 records, from which we reviewed 74 full-text documents, and finally included 16 papers [17–32] for the RQ1, 8 studies [19,24,28,29,31,33–35] for the RQ2, 2 studies [36,37] for the RQ3, while no studies were found for the RQ4 (see PRISMA 2020 flow diagrams in Supplementary Figure 1).

Reference lists of relevant articles were also screened, but no extra articles that fulfilled inclusion criteria were found. The results are described below separately for each research question.

3.2. RQ1 (efficacy and safety)

In the Fig. 1 (PRISMA 2020 flow diagram) the literature selection process is shown. A list of excluded studies along with reasons for exclusion is provided in Supplementary Table 2.

3.2.1. Study characteristics

Among the included studies, 14 [17,19–26,28–32] were RCTs and 2 [18,27] were cohort studies. Two papers by Sävendahl et al. reported on the same study (REAL 3, NCT02616562) but reporting the results at 1 year [28] and at 3 years [29]. In addition, the paper by Luo et al. [24] reported on two studies, a phase 2 RCT and a phase 3 RCT.

The studies were heterogeneous in terms of molecules used and dosage. Three papers (4 RCTs) [20,24,30] and a cohort study [27] investigated Jintrolong® vs Jintropin AQ®; four studies (3 RCTs and 1 cohort study) assessed Eutropin Plus®, but two of them compared it with Eutropin® [18,22] and the other two with Genotropin® [23,26]; three RCTs [19,21,32] compared somatrogon vs Genotropin®; two studies [17,31] investigated TransCon vs Genotropin®; one study [25] compared GX-H9 with Genotropin®; lastly, one study (two papers [28,29]) compared somapacitan with Norditropin®.

The study characteristics are presented in Table 1.

3.2.2. Risk of bias

The risk of bias was assessed for 14 RCTs and one cohort study, while it was not assessed for 2 studies [18,25] reported as conference abstracts, due to insufficient information. A graphical representation of risk of bias for each outcome can be seen in Supplementary Figure 2.

3.3. Risk of bias in randomised controlled trials

As for the outcome mean annualized height velocity, we judged the overall risk of bias to be low for 3 studies [19,28,29], some concerns for 8 studies [17,21–23,26,30–32], and high risk for 3 studies [20,24]. Most of studies (9/14) did not report methods used to generate the random sequence and to conceal the allocation. Two studies were judged as 'some concerns' due to deviations to the intended intervention. Three studies were at high risk for missing outcome data. All the studies were rated as 'low risk' for the measurement of the outcome domain. Three studies showed 'some concerns' for the selection of the reported result, because this outcome was not specified in the study protocol.

Four studies were included for the outcome HV SDS; two of them [28,29] have an overall low risk of bias, while the other two studies [31,32] were rated as 'some concerns', due to lack of reporting of the randomisation process and some concerns about the selection of the reported results.

Seven studies assessed the outcome height SDS chronological age; of these, one study were judged to have an overall low risk of bias [29], three studies were rated as 'some concerns' [22,26,30], and three studies as 'high risk' [23,24].

Only one study [22] was assessed for the outcome height SDS bone age, and its overall risk of bias was rated as 'some concerns'.

The risk of bias for the outcome change in height SDS was assessed in 9 studies. Three of them [19,28,29] were deemed to have an overall low risk of bias, 5 studies 'some concerns' [17,22,26,31,32], and one study [24] high risk.

As for IGF-1 SDS, 13 studies were assessed. Three studies [19,28,29] were judged to have a low risk of bias, 8 studies [17,21–23,26,30–32] as 'some concerns', and two studies [24] as high risk.

Four studies were assessed for the outcome IGFBP-3 SDS; two of them [28,29] had an overall low risk of bias, while the other two studies [22,23] were rated as 'some concerns'.

All studies were assessed for the outcome incidence of adverse events. Two studies were judged to have an overall low risk of bias [28,29], 9 studies 'some concerns' [17,19,21–23,26,30–32], and 3 studies a high risk of bias [20,24].

3.4. Risk of bias in non-randomised studies

We assessed the risk of bias of the only non-randomised study included using the ROBINS-I tool. We present the full judgement in the Supplementary Table 3.

The overall quality of Qiao 2019 [27] was judged moderate, both for outcomes assessed to estimate the "effect of assignment to the intervention" and for outcomes assessed to estimate the "effect of adherence to the intervention". We judged the risk of bias due to confounding to be moderate because confounding was expected but possible confounders were assessed through regression analyses. Also, the bias in selection of participants into the study was deemed moderate; in fact, parents of GHD children chose the type of GH therapy, and they could have been influenced by the different cost of the two drugs. The bias in classification of interventions was rated to be low, because the intervention status is well defined and intervention definition is based solely on information collected at the time of intervention. The bias due to deviations from intended interventions was judged moderate because five patients of the PEGylated rhGH group switched to using daily rhGH in view of the high price of PEGylated rhGH. The last three bias domains (bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result) was rated to be at low risk of bias.

3.5. Summary of findings

Summary of findings 1. Jintrolong compared to Jintropin AQ for growth hormone deficiency children

Patient or population: growth hormone deficiency children
Intervention: Jintrolong
Comparison: Jintropin AQ

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Jintropin AQ	**Risk with Jintrolong**				
Mean annualized height velocity	The mean mean annualized height velocity was **0**	MD **0.03 lower** (0.81 lower to 0.76 higher)	-	874 (4 RCTs)	⨁⨁⨁◯ Moderate[a]	Jintrolong likely results in little to no difference in mean annualized height velocity.
Height SDS	The mean height SDS was **0**	MD **0.03 higher** (0.12 lower to 0.19 higher)	-	715 (3 RCTs)	⨁⨁⨁◯ Moderate[b]	Jintrolong likely results in little to no difference in height SDS.
IGF-1 SDS	The mean IGF-1 SDS was **0**	MD **0.3 higher** (0.04 higher to 0.55 higher)	-	803 (3 RCTs)	⨁⨁⨁◯ Moderate[b]	Jintrolong likely results in little to no difference in iGF-1 SDS.
N. of participants with adverse events	371 per 1.000	**390 per 1.000** (327 to 468)	**RR 1.05** (0.88 to 1.26)	806 (3 RCTs)	⨁⨁⨁◯ Moderate[b]	Jintrolong likely results in little to no difference in n. of participants with adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level due to serious risk of bias. Three studies (Du 2022; Luo 2017_phase 2; Luo 2017_phase 3) have a high risk of bias due to missing outcome data. One study (Sun 2021) has 'some concerns' due to unclear randomisation process.
b. Downgraded by one level due to serious risk of bias. Two studies (Luo 2017_phase 2; Luo 2017_phase 3) have a high risk of bias due to missing outcome data. One study (Sun 2021) has 'some concerns' due to unclear randomisation process.

Summary of findings 2. Eutropin Plus compared to Eutropin for growth hormone deficiency children

Patient or population: growth hormone deficiency children
Intervention: Eutropin Plus
Comparison: Eutropin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Eutropin	**Risk with Eutropin Plus**				
Mean annualized height velocity	The mean mean annualized height velocity was **0**	MD **0.66 lower** (1.67 lower to 0.35 higher)	-	60 (1 RCT)	⨁⨁◯◯ Low[a,b]	Eutropin Plus may result in little to no difference in mean annualized height velocity.
N. of participants with adverse events	833 per 1.000	**800 per 1.000** (633 to 1.000)	**RR 0.96** (0.76 to 1.22)	60 (1 RCT)	⨁⨁◯◯ Low[a,b]	Eutropin Plus may result in little to no difference in n. of participants with adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level due to serious risk of bias. Some concerns due to randomization process and selection of the reported results.
b. Downgraded by one level due to serious imprecision: risk ratio is from a single RCT (Hwang 2013) with a small sample size (60 patients). In addition, this study did not specify the non-inferiority margin for the primary outcome (mean annualized height velocity), nor calculated the sample size based on the non-inferiority margin.

Summary of findings 3. Eutropin Plus compared to Genotropin for growth hormone deficiency children

Patient or population: growth hormone deficiency children
Intervention: Eutropin Plus
Comparison: Genotropin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Genotropin	**Risk with Eutropin Plus**				
Mean annualized height velocity	The mean mean annualized height velocity was **0**	MD **0.74 lower** (1.83 lower to 0.34 higher)	-	229 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	Eutropin Plus likely results in little to no difference in mean annualized height velocity.
Height SDS	The mean height SDS was **0**	MD **0.01 higher** (0.4 lower to 0.43 higher)	-	218 (2 RCTs)	⨁⨁◯◯ Low[b]	Eutropin Plus may result in little to no difference in height SDS.
N. of participants with adverse events	727 per 1.000	**829 per 1.000** (713 to 960)	**RR 1.14** (0.98 to 1.32)	229 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	Eutropin Plus likely results in little to no difference in n. of participants with adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level due to serious risk of bias. Some concerns due to randomisation process and deviations from the intended interventions (Khadilkar 2014) and randomisation process and selection of the reported results (Peter 2012).
b. Downgraded by two levels due to very serious risk of bias. High risk of bias due to randomisation process, deviations from the intended interventions, missing outcome data, and selection of the reported results (Khadilkar 2014) and randomisation process and selection of the reported results (Peter 2012).
c. Downgraded by one level due to serious risk of bias. High risk of bias due to randomisation process, measurement of the outcome, and selection of the reported results (Khadilkar 2014) and randomisation process and selection of the reported results (Peter 2012).

Summary of findings 4. Somatrogon compared to Genotropin for growth hormone deficiency children

Patient or population: growth hormone deficiency children
Intervention: Somatrogon
Comparison: Genotropin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Genotropin	**Risk with Somatrogon**				
Mean annualized height velocity	The mean mean annualized height velocity was **0**	MD **1.4 lower** (2.91 lower to 0.1 higher)	-	53 (1 RCT)	⨁⨁◯◯ Low[a,b]	Somatrogon may result in little to no difference in mean annualized height velocity.
N. of participants with adverse events	838 per 1.000	**888 per 1.000** (813 to 972)	**RR 1.06** (0.97 to 1.16)	321 (1 RCT)	⨁⨁⨁◯ Moderate[c]	Somatrogon likely results in little to no difference in n. of participants with adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level due to serious risk of bias: some concerns due to randomisation process.
b. Downgraded by one level due to serious imprecision: mean difference is from a single dose-finding RCT (Zelinska 2017) with a small sample size (53 patients). Also, this study did not calculate the sample size.
c. Downgraded by one level due to serious risk of bias: some concerns due to randomisation process and selection of the reported results.

Summary of findings 5. TransCon compared to Genotropin for growth hormone deficiency children

Patient or population: growth hormone deficiency children
Intervention: TransCon
Comparison: Genotropin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Genotropin	**Risk with TransCon**				
Mean annualized height velocity	The mean mean annualized height velocity was **0**	MD **0.93 higher** (0.26 higher to 1.61 higher)	-	214 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	TransCon likely results in little to no difference in mean annualized height velocity.
Change in height SDS	The mean change in height SDS was **0**	MD **0.14 higher** (0.03 higher to 0.25 higher)	-	214 (2 RCTs)	⨁⨁⨁◯ Moderate[b]	TransCon likely results in little to no difference in change in height SDS.
N. of particpants with adverse events	638 per 1.000	**695 per 1.000** (568 to 842)	**RR 1.09** (0.89 to 1.32)	214 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	TransCon likely results in little to no difference in n. of particpants with adverse events.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level due to serious risk of bias: some concerns due to randomisation process.
b. Downgraded by one level due to serious risk of bias: some concerns due to randomisation process and selection of the reported results (Chatelein 2017) and randomisation process (Thornton 2021).
c. Downgraded by one level due to serious risk of bias: some concerns due to randomisation process and measurement of the outcome (Chatelein 2017) and randomisation process (Thornton 2021).

3.6. Mean annualized height velocity

3.6.1. Jintrolong® vs Jintropin AQ®

Four trials and an observational study assessed mean annualized height velocity (HV). Meta-analyses of RCTs showed no difference between intervention and control group (−0.03 [−0.81, 0.76]; p = 0.95; I^2 =60%; GRADE certainty: moderate ⨁⨁⨁◯) (Fig. 2). Similar results were obtained in the subgroup analyses by LAGH dose or including the cohort study in the meta-analysis (Supplementary Figure 3a).

3.6.2. Eutropin Plus® vs Eutropin®

Two studies were included, one RCT and one cohort study. The RCT showed no difference between Eutropin Plus® and Eutropin® (−0.66 [−1.67, 0.35]; p = 0.20; GRADE certainty: low ⨁⨁◯◯). Similarly, the meta-analysis of the two studies showed no difference in mean annualized HV (−0.14 [−0.43, 0.15]; p = 0.33; I^2 =14%) (Fig. 3).

3.6.3. Eutropin Plus® vs Genotropin®

Pooled results of two studies showed no difference between intervention and control group (−0.74 [−1.83, 0.34]; p = 0.18; I^2 =57%; GRADE certainty: moderate ⨁⨁⨁◯). The subgroup with the lower dose (0.20 mg/kg/week) of Eutropin Plus® showed a superiority of daily Genotropin® (−2.50 [−4.05, −0.95]; p = 0.002) (Fig. 4).

3.6.4. Somatrogon vs Genotropin®

Three studies were included, but two of them did not contribute to the meta-analysis due to lack of standard deviation (SD) reporting. Pooled results of the three groups by LAGH dose showed no difference between intervention and control group (−1.40 [−2.91, 0.10]; p = 0.07; I^2 =0%; GRADE certainty: low ⨁⨁◯◯) (Fig. 5).

3.6.5. TransCon vs Genotropin®

A meta-analysis of two RCTs showed a higher mean annualized HV in the TransCon group compared to the Genotropin® group (0.93 [0.26, 1.61]; p = 0.007; I^2 =0%; GRADE certainty: moderate ⨁⨁⨁◯). This superiority was evident only in the subgroup 0.21–0.24 mg/kg/week (p = 0.01) (Fig. 6).

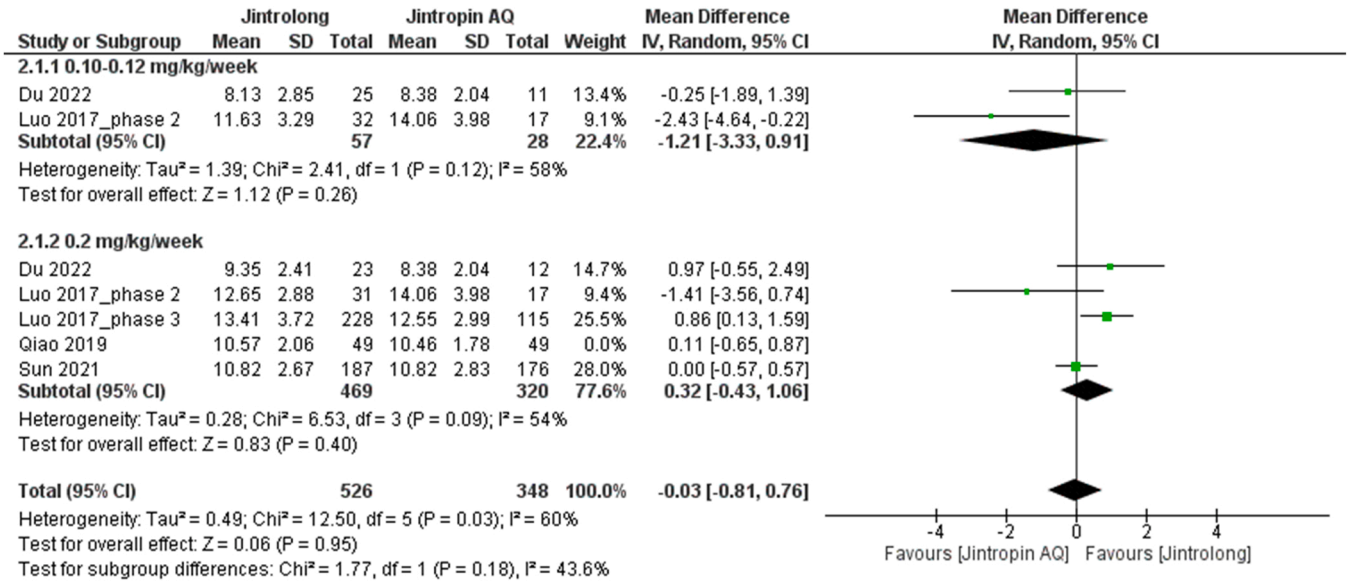

Fig. 2. Meta-analysis of mean annualized HV for the comparison Jintrolong® vs Jintropin AQ®, including only RCTs.

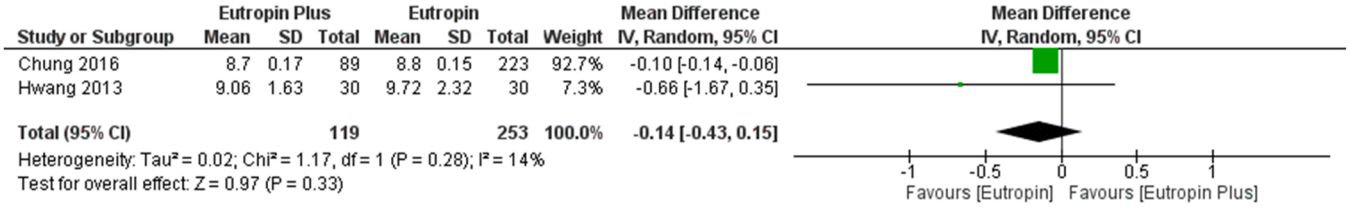

Fig. 3. Meta-analysis of mean annualized HV for the comparison Eutropin Plus® vs Eutropin®, including both RCTs and observational studies.

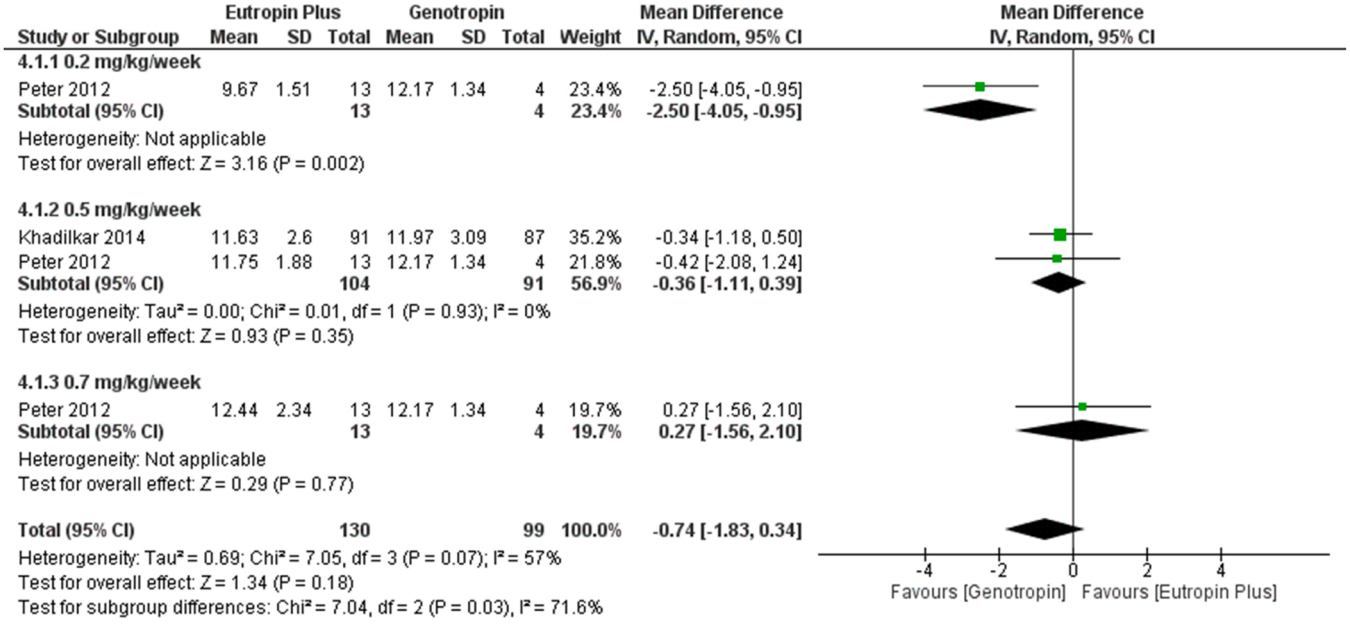

Fig. 4. Meta-analysis of mean annualized HV for the comparison Eutropin Plus® vs Genotropin®.

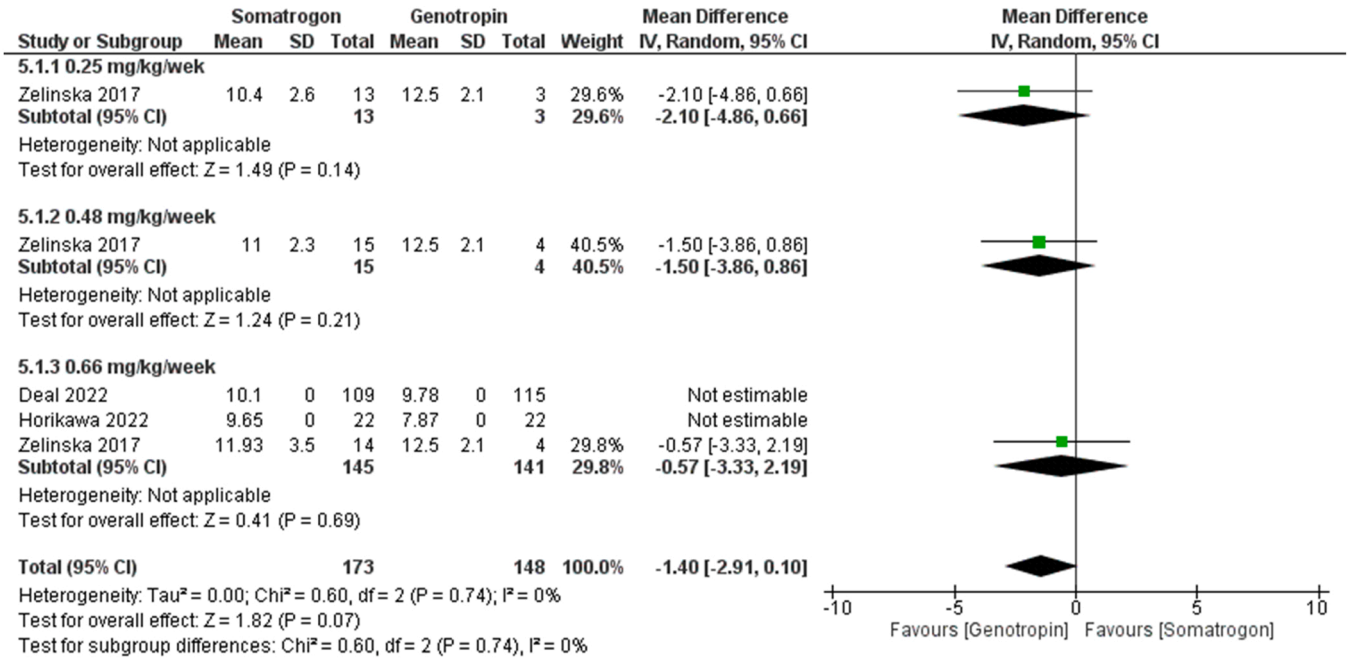

Fig. 5. Meta-analysis of mean annualized HV for the comparison Somatrogon vs Genotropin®.

3.6.6. Somapacitan vs Norditropin®

Only one trial was included for this comparison, reporting the results at 1 year and at 3 years, thus no meta-analysis was performed. At 1 year, estimated mean annualized HV was 7.5, 9.7, and 11.7 cm/year, for somapacitan 0.04, 0.08, and 0.16 mg/kg/week, respectively, and 9.9 cm/year for daily Norditropin®. somapacitan 0.16 mg/kg/week significantly increased mean annualized HV compared to daily GH (1.8 [95% CI 0.5–3.1]).

After the first year, all patients on somapacitan received 0.16 mg/kg/wk. At 3 years, mean annualized HV was 8.9, 7.8, and 8.4 cm/year, for somapacitan 0.04/0.16, 0.08/0.16, and 0.16/0.16 mg/kg/week, respectively, and 7.6 cm/year for daily Norditropin®. The estimated treatment difference for somapacitan 0.16/0.16 mg/kg/week vs daily Norditropin® at year 3 was 0.8 cm/year (95%CI, −0.4 to 2.1).

3.6.7. GX-H9 vs Genotropin®

One RCT compared two doses of weekly GX-H9 and one dose of bi-weekly GX-H9 with daily Genotropin®. At 1 year, mean annualized HV was 10.50, 11.76, and 11.03 cm/year, for GX-H9 0.8, 1.2 mg/kg/week, and 2.4 mg/kg/bi-weekly, respectively, and 9.14 cm/year for daily Genotropin®.

3.7. HV standard deviation scores (SDS)

Only three studies reported on this outcome for the following comparisons: somatrogon vs Genotropin®; TransCon vs Genotropin®;

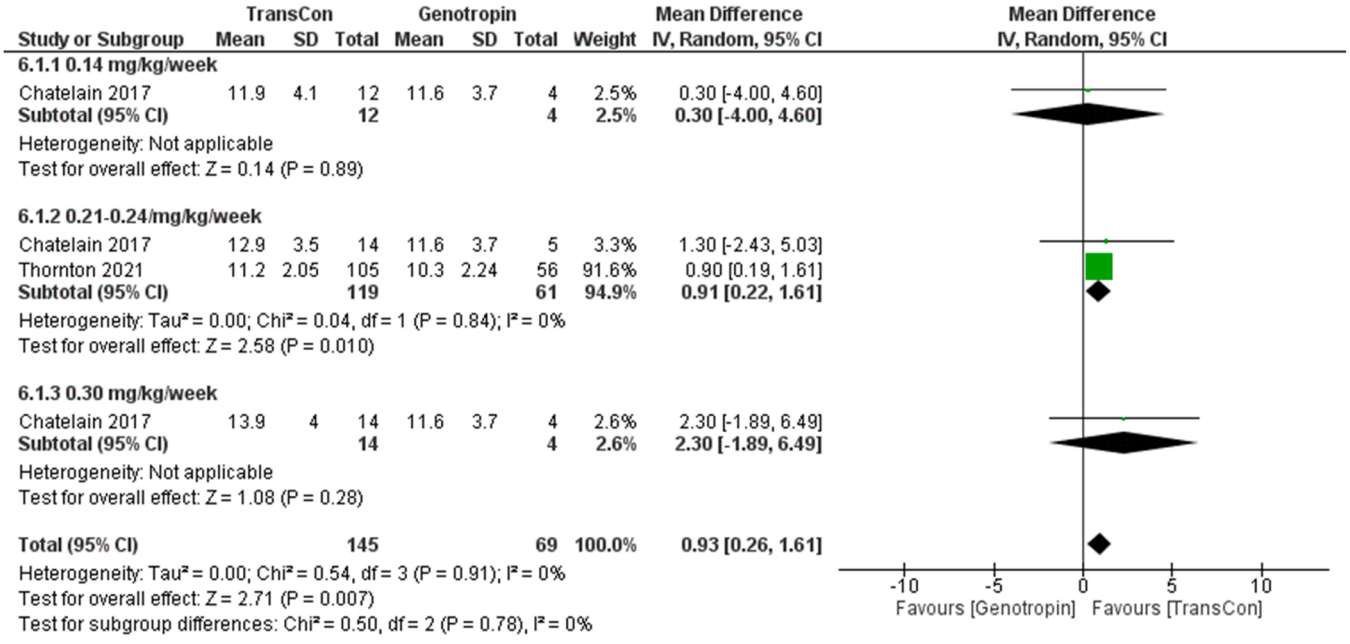

Fig. 6. Meta-analysis of mean annualized HV for the comparison TransCon vs Genotropin®.

somapacitan vs Norditropin®.

3.7.1. Somatrogon vs Genotropin®

Zelinska et al., 2017 reported a mean HV SDS of 5.25, 5.50, and 6.67 for the three somatrogon groups of 0.25, 0.48 and 0.66 mg/kg/week, respectively, vs 7.48 for daily Genotropin®.

3.7.2. TransCon vs Genotropin®

Thornton et al., 2021 reported least squares (LS) mean HV SDS of 5.88 (standard error [SE] 0.31) and 5.06 (SE 0.39) for TransCon and daily Genotropin®, respectively; the estimated treatment difference was 0.82 (95% CI −0.04, 1.67), p = 0.06.

3.7.3. Somapacitan vs Norditropin®

Sävendahl et al., 2020 reported a mean HV SDS at 1 year of 1.9, 4.3, and 5.8 for the somapacitan groups, respectively, vs 4.3 for daily Norditropin®. The mean (SD) change from baseline in HV SDS at 1 year was 4.7 (2.8), 6.1 (3.4), and 8.6 (3.2) for the somapacitan groups, respectively, vs 7.4 (4.1) for daily Norditropin®.

Sävendahl et al., 2022 (3-year results) reported a mean HV SDS at 3 years of 2.9, 2.3, and 2.4 for the three somapacitan groups, respectively, vs 2.1 for daily Norditropin®. The mean (SD) change from baseline in HV SDS at 3 years was 5.4 (2.5), 4.2 (2.8), and 5.3 (3.0) for the somapacitan groups, respectively, vs 5.3 (3.9) for daily Norditropin®.

3.8. Height SDS chronological age

3.8.1. Jintrolong® vs Jintropin AQ®

Three trials and an observational study assessed height SDS chronological age (CA). Meta-analyses of RCTs showed no difference between intervention and control group (0.03 [−0.12, 0.19]; p = 0.68; I^2 =0%; GRADE certainty: moderate ⨁⨁⨁◯) (Supplementary Figure 3b). Similar results were obtained in the subgroup analyses by LAGH dose or including the cohort study in the meta-analysis (Supplementary Figure 3c).

3.8.2. Eutropin Plus® vs Eutropin®

One trial reported height SDS CA, with no difference at 1 year between intervention and control group: median (min, max) was − 0.82 (−2.63, 1.40) in the Eutropin Plus® group vs − 0.75 (−2.84, 1.07) in the Eutropin® group; p = 0.34.

3.8.3. Eutropin Plus® vs Genotropin®

Pooled results of two studies showed no difference between intervention and control group (0.01 [−0.40, 0.43]; p = 0.95; I^2 =0%; GRADE certainty: low ⨁⨁◯◯). Subgroup analysis by dosage confirmed no difference in height SDS CA (Supplementary Figure 3d).

3.8.4. Somatrogon vs Genotropin®, TransCon vs Genotropin® and GX-H9 vs Genotropin®

No studies in these comparisons reported height SDS CA.

3.8.5. Somapacitan vs Norditropin®

Sävendahl et al., 2022 reported a height SDS CA at 3 years of − 1.8, − 1.3, and − 1.2 for the somapacitan groups, respectively, vs − 1.4 for daily Norditropin®.

3.9. Change in height SDS

3.9.1. Jintrolong® vs Jintropin AQ®

Luo et al. reported a mean (SD) change from baseline in height SDS of 0.90 (0.36), 1.01 (0.39), and 1.20 (0.56) for Jintrolong® 0.1 mg/kg/week, Jintrolong® 0.2 mg/kg/week and Jintropin AQ®, respectively (inter-group comparison: p = 0.0063).

3.9.2. Eutropin Plus® vs Eutropin®

Chung et al. reported a mean change from baseline in height SDS of 0.6 in the Eutropin Plus® group, and 0.7 in the Eutropin® group.

3.9.3. Eutropin Plus® vs Genotropin®

Peter et al. reported a mean (SD) change from baseline in height SDS of 1.05 (0.38), 1.37 (0.39), and 1.50 (0.44) in the three Eutropin Plus® groups, vs 1.47 (0.29) in the Genotropin® group.

3.9.4. Somatrogon vs Genotropin®

Zelinska et al. reported a mean (SD) change from baseline in height SDS of 1.14 (0.16), 1.23 (0.12), and 1.45 (0.20) in the three somatrogon groups (0.25, 0.48, 0.66 mg/kg/week), vs 1.54 (0.15) in the Genotropin® group.

Horikawa et al. reported a least-squares mean change in change from baseline in height SDS at 12 months of 0.94 in somatrogon group vs 0.52 in the Genotropin® group (difference, 95% CI: 0.42 [0.23, 0.61]).

Deal et al. reported similar increases in mean change in height SDS from baseline to 6 months in both somatrogon and Genotropin® group: least-squares mean difference 0.05 (95% CI, −0.06, 0.16).

3.9.5. TransCon vs Genotropin®

A meta-analysis of two RCTs showed a higher change in height SDS

Table 2
Characteristics of included studies for RQ2.

Study ID	Design	Trial name / registr. N	Follow-up (weeks)	Type of LAGH	Type of daily GH	Adherence in LAGH group	Adherence in daily GH group
Deal 2022[19]	RCT phase 3	NCT02968004	52	Somatrogon (MOD-4023)	Genotropin®	99.4%	99.7%
Humphriss 2017[33]	Long-term safety study	VISTA study NCT02068521	104	Somavaratan (VRS-317)	no control group	99.6%	-
Luo 2017[24]	RCT phase 3	NCT01495468	25	Jintrolong®	Jintropin AQ®	96.9%	99.1%
Maniatis 2022_a[34]	open-label extension trial	enliGHten trial NCT03344458	104	Lonapegsomatropin (TransCon)	no control group	mean: 98.8%	-
Maniatis 2022_b[35]	single-arm, phase 3	fliGHt Trial NCT03305016	26	Lonapegsomatropin	no control group	mean (SD): 98.4% (4.0)	-
Sävendahl 2020[28]	RCT phase 2	REAL 3 NCT02616562	52	Somapacitan	Norditropin®	mean (SD): 0.04 mg: 97.5% (4.5); 0.08 mg: 98.6% (1.7); 0.16 mg: 96.3% (5.2)	mean (SD): 91.8% (23.0)
Sävendahl 2022[29]	RCT phase 2	REAL 3 NCT02616562	156	Somapacitan	Norditropin®	mean of somapacitan groups: 92.2%	mean: 87.2%
Thornton 2021[31]	RCT phase 3	heiGHt NCT02781727	52	Lonapegsomatropin (TransCon)	Genotropin®	mean: 99.6%	mean: 98.6%

Adherence in LAGH groups was high in all studies, with a range of 92.2–99.6%, and it was comparable with daily GH (range: 87.2–99.7%).

in the TransCon group compared to the Genotropin® group (0.14 [0.03, 0.25]; p = 0.02; I^2 =0%; GRADE certainty: moderate ⨁⨁⨁◯). This superiority was confirmed only in the subgroup 0.21–0.24 mg/kg/week (p = 0.03) (Supplementary Figure 3e).

3.9.6. Somapacitan vs Norditropin®

Sävendahl et al., 2020 reported a greater change from baseline in height SDS at 1 year with somapacitan 0.16 mg/kg/week compared with daily GH (0.35 [0.05–0.65]) but did not differ significantly with somapacitan 0.08 mg/kg/week and daily GH (–0.10 [–0.39–0.20]). The change was significantly greater with daily GH than with somapacitan 0.04 mg/kg/week (–0.58 [–0.88 to –0.28]).

Sävendahl et al., 2022 reported a similar change in height SDS from baseline to year 3 across treatment arms: 2.4 (1.0), 2.4 (1.0), and 2.7 (1.4) in the three somapacitan groups, vs 2.1 (0.9) in the daily Norditropin® group.

3.9.7. GX-H9 vs Genotropin®

Malievskiy et al. reported similar changes in height SDS from baseline to 12 months of treatment across all doses of GX-H9 (1.10 and 1.31) and Genotropin® (0.92).

3.10. Insulin-like growth factor 1 (IGF-1) SDS

3.10.1. Jintrolong® vs Jintropin AQ®

Three trials and an observational study assessed IGF-1 SDS. Meta-analyses of RCTs showed superiority of Jintrolong® vs Jintropin AQ® (0.30 [0.04, 0.55]; p = 0.02; I^2 =57%; GRADE certainty: moderate ⨁⨁⨁◯) (Supplementary Figure 3 f). In the subgroup analyses by LAGH dose, only the group 0.2 mg/kg/week significantly increased IGF-1 SDS. Including the cohort study in the meta-analysis the results were similar (Supplementary Figure 3 g).

3.10.2. Eutropin Plus® vs Eutropin®

Chung et al., 2016 reported IGF-1 SDS results only in figure, showing similar values at 12 months for the two treatment arms. Hwang et al., 2013 reported at 12 months an IGF-1 SDS of 2.46 (−2.31, 10.9) in the Eutropin Plus® group vs 1.08 (−3.15, 16.82) in the Eutropin® group (p = 0.17).

3.10.3. Eutropin Plus® vs Genotropin®

Khadilkar et al., 2014 reported a mean (SD) IGF-1 SDS at 12 months of − 1.07 (1.86) in the Eutropin Plus® group vs − 1.47 (2.05) in the Genotropin® group.

Peter et al., 2012 reported IGF-1 SDS results only in figure. We estimated the following values: 0.2 mg/kg/week: − 5.3; 0.5 mg/kg/week: − 2.7; 0.7 mg/kg/week: − 3.1; daily: − 1.2.

3.10.4. Somatrogon vs Genotropin®

Deal et al., 2022 reported a IGF-1 SDS at 12 months of 0.65 in the somatrogon group, compared to − 0.69 in the Genotropin® group. Horikawa reported a IGF-1 SDS at 12 months of 1.5 in the somatrogon group, compared to − 0.6 in the Genotropin® group (estimated from figure). Zelinska reported IGF-1 SDS only in graph, with the lowest value for somatrogon 0.25 mg/kg/week (−0.5), the highest value for 0.66 mg/kg/week (0.5), and the medium value for 0.48 mg/kg/week, and for daily Genotropin® that were around zero (estimated from figure).

3.10.5. TransCon vs Genotropin®

Chatelain et al. reported IGF-1 SDS results at 26 weeks only in figure, and only for somatrogon groups, showing a dose-response effect for the three somatrogon doses of 0.14, 0.21, and 0.30 mg/kg/week.

Thornton 2021 et al. reported an average IGF-1 SDS at 1 year of 0.72 (SE 0.09) in the TransCon group vs − 0.02 (SE 0.12) in the Genotropin® group.

3.10.6. Somapacitan vs Norditropin®

Savendhal 2020 et al. reported at week 52, IGF-I SDS mean (SD) values of − 1.41 (1.19), − 0.48 (1.08), and 1.25 (1.72) for somapacitan 0.04, 0.08, and 0.16 mg/kg/week, respectively. vs –0.40 (1.50) for Norditropin®.

Savendhal 2022 et al. reported at 3 years IGF-I SDS mean (SD) values of 0.97 (1.13), 1.03 (1.32), and 1.63 (0.89) for somapacitan 0.04/0.16, 0.08/0.16, and 0.16/0.16 mg/kg/week, respectively. vs 1.30 (0.94) for Norditropin®.

3.10.7. GX-H9 vs Genotropin®

Malievskiy et al. reported IGF-1 SDS of − 2, and − 0.8 for GX-H9 0.8 mg/kg/week and 1.2 mg/kg/week, respectively, vs − 0.5 for daily Genotropin® (estimated from figure).

3.11. Insulin-like growth factor binding protein-3 (IGFBP-3)

No studies reported on this outcome.

3.12. IGFBP-3 SDS

3.12.1. Eutropin Plus® vs Eutropin®

Hwang et al., 2013 reported at 12 months an IGFBP-3 SDS of 0.17 (−2.98, 2.56) in the Eutropin Plus® group vs 0.27 (−4.40, 3.80) in the Eutropin® group (p = 0.69).

3.12.2. Eutropin Plus® vs Genotropin®

Khadilkar et al., 2014 reported a mean (SD) IGFBP-3 SDS at 12 months of − 0.51 (1.35) in the Eutropin Plus® group vs − 1.09 (1.97) in the Genotropin® group.

3.12.3. Somapacitan vs Norditropin®

Savendhal 2020 et al. reported at week 52, IGFBP-3 SDS mean (SD) values of –1.22 (1.21), –0.80 (0.83), and.

0.27 (0.97), for somapacitan 0.04, 0.08, and 0.16 mg/kg/week, respectively. vs –0.74 (1.56) for Norditropin®.

Savendhal 2022 et al. reported at 3 years IGFBP-3 SDS mean (SD) values of − 0.39 (0.96), − 0.08 (0.71), and 0.02 (0.90) for somapacitan 0.04/0.16, 0.08/0.16, and 0.16/0.16 mg/kg/week, respectively. vs 0.29 (0.79) for Norditropin®.

3.12.4. Somatrogon vs Genotropin®, Jintrolong® vs Jintropin AQ®, TransCon vs Genotropin® and GX-H9 vs Genotropin®

No studies in these comparisons reported IGFBP-3 SDS.

3.13. Incidence of adverse events

3.13.1. Jintrolong® vs Jintropin AQ®

Three trials and an observational study assessed safety, in terms of number of participants with adverse events. Meta-analysis of RCTs showed no difference between Jintrolong® and Jintropin AQ® (RR=1.05 [0.88–1.26]; p = 0.55; I^2 =0%; GRADE certainty: moderate ⨁⨁⨁◯) (Supplementary Figure 3 h). Very similar results were obtained in the subgroup analyses by Jintrolong® dose, or including the cohort study in the meta-analysis (Supplementary Figure 3i).

3.13.2. Eutropin Plus® vs Eutropin®

Two studies were included, one RCT and one cohort study. The RCT showed no difference between Eutropin Plus® and Eutropin® (RR=0.96 [0.76, 1.22]; GRADE certainty: low ⨁⨁◯◯). Similarly, the meta-analysis of the two studies showed no difference in the incidence of adverse events (RR=0.94 [0.78, 1.12]; p = 0.47; I^2 =0%) (Supplementary Figure 3j).

3.13.3. Eutropin Plus® vs Genotropin®

Pooled results of two studies showed no difference between

intervention and control group (RR=1.14 [0.98, 1.32]; p = 0.08; I^2 =0%; GRADE certainty: moderate ⨁⨁⨁◯). Subgroup analysis by dosage showed similar results (Supplementary Figure 3k).

3.13.4. Somatrogon vs Genotropin®

Pooled results of three studies showed no difference between intervention and control group (RR=1.06 [0.97, 1.16]; p = 0.23; I^2 =0%; GRADE certainty: moderate ⨁⨁⨁◯) (Supplementary Figure 3 l). Subgroup analysis confirmed this result.

3.13.5. TransCon vs Genotropin®

A meta-analysis of two RCTs showed no difference in the incidence of adverse events in the TransCon group compared to the Genotropin® group (RR=1.09 [0.89, 1.32]; p = 0.41; I^2 =0%; GRADE certainty: moderate ⨁⨁⨁◯). This was confirmed by subgroup analysis (Supplementary Figure 3 m).

3.13.6. Somapacitan vs Norditropin®

Savendhal 2020 et al. reported at week 52, 10/16 (62.5%), 11/15 (73.3%), and 13/14 (92.9%) patients with adverse events in the somapacitan 0.04, 0.08, and 0.16 mg/kg/week groups, respectively, vs 14/14 (100%) of patients in the Norditropin® group.

Savendhal 2020 et al. reported at 3 years in the pooled somapacitan groups 32/45 (71.1%) patients with adverse events, vs 10/14 (71.4%) of patients in the Norditropin® group.

3.13.7. GX-H9 vs Genotropin®

Malievskiy et al. did not provide a description of number of patients with adverse events in the treatment arms.

3.14. Fasting glucose, hemoglobin A1c, thyroid function

3.14.1. Jintrolong® vs Jintropin AQ®

Du et al., 2022 reported a mean (SD) glucose at baseline of 4.87 (0.39) vs 4.98 (0.36) mmol/L in the Jintrolong® group at 12 months (p = 0.207). HbA1c (%) at baseline was 5.12 (SD 0.27) vs 5.26 (SD 0.37) at 12 months (p = 0.009). Thyroid function examinations showed no differences from baseline to 12 months.

Luo et al., 2017 (phase 3 study) reported that fasting blood glucose levels and HbA1c were in the normal range throughout the study and comparable between the treatment arms.

Qiao et al., 2019 reported no significant difference in glucose levels (p = 0.106) and HbA1c (p = 0.310) from baseline to 12 months in the Jintrolong® group.

Sun reported that there were no clinically relevant changes from baseline to week 26 in mean HbA1c and fasting plasma glucose in any of the treatment groups.

3.14.2. Eutropin Plus® vs Eutropin®

Hwang et al., 2013 reported no clinically relevant findings with glucose, HbA1c, and thyroid function test between treatment groups.

3.14.3. Eutropin Plus® vs Genotropin®

Khadilkar et al., 2014 reported in both intervention and control groups an increase from baseline to 12 months in mean fasting glucose (Eutropin Plus®, from 4.01 (1.08) to 4.40 (0.68) mmol/L; Genotropin®, from 4.09 (0.90) to 4.66 (0.55) mmol/L). Persistent glucose intolerance was reported for one patient in both groups. Mean glycated hemoglobin did not differ significantly between the intervention and control group.

Peter et al., 2012 reported that mean fasting glucose concentration increased from 4.05 (0.67) mmol/L at baseline to 4.91 (0.48) mmol/L at 12 months in the 0.7 mg/kg/week Eutropin Plus® group. No other notable changes from baseline in fasting glucose were found. HbA1c concentrations remained within the normal range at all times for each group. There were 14 patients (27%) with laboratory values indicative of hypothyroidism and started T4 replacement during the study.

3.14.4. Somatrogon vs Genotropin®

Deal et al., 2022 reported a slight increase of glucose and HbA1c from baseline and 12 months in both somatrogon vs Genotropin® groups; however, values remained within the normal range. No significant clinically differences in thyroid function were reported.

Horikawa et al., 2022 reported that blood glucose, HbA1c levels and thyroid function remained in the normal range in both groups.

Zelinska et al., 2017 reported no significant findings attributed to somatrogon in glucose and HbA1c levels. There was a single case of impaired fasting glucose in the somatrogon 0.25 mg/kg/week group, that was mild and clinically insignificant.

3.14.5. TransCon vs Genotropin®

Chatelain et al., 2017 reported no safety concerns about laboratory parameters, such as glucose and HbA1c.

Thornton et al., 2021 reported fasting glucose and hemoglobin A1c levels were generally stable over time and within the normal range for both study groups. New onset of secondary hypothyroidism was similar between the groups (6.7% vs 7.1%).

3.14.6. Somapacitan vs Norditropin®

Savendahl et al., 2020 reported no clinically relevant changes from baseline to week 52 in mean HbA1c and fasting glucose for any of the treatment groups.

Savendahl et al., 2022 reported no apparent clinically relevant changes in fasting glucose or mean glycated haemoglobin from baseline to year 3 in any of the treatment groups. In the second year, a child treated with daily GH had 2 events of abnormal glucose metabolism, rated as mild and possibly related to trial product.

3.14.7. GX-H9 vs Genotropin®

Malievskiy et al., 2018 did not report fasting glucose level, hemoglobin A1c, and thyroid function.

3.15. Certainty of evidence

The GRADE assessment was performed within each comparison at outcome level, considering only RCTs due to their higher level of evidence compared with observational studies. The GRADE Summary of Findings tables are reported at the beginning of the results paragraph.

3.16. RQ2 (ADHERENCE)

We included 8 studies to address this research question, five of which were also included in RQ1 [19,24,28,29,31]. The other 3 studies were non-comparative studies investigating adherence of patients taking LAGH [33–35]. The main characteristics of included studies are reported in Table 2.

3.16.1. Risk of bias

3.16.1.1. Risk of bias in randomised controlled trials. Five RCTs were assessed for adherence. Four studies [19,28,29,31] were judged to have an overall risk of bias as 'some concerns', while one study [24] a high risk of bias. None of the studies specified in the study protocol that adherence would be a study outcome (Supplementary Figure 2).

3.16.1.2. Risk of bias in non-randomised studies. Two non-randomised trials [34,35] were assessed by ROBINS-I tool. Both studies were judged to have an overall moderate risk of bias. Maniatis 2022_a et al. [34] did not define the method used to assess the adherence. Both studies did not anticipate in the study protocol that adherence was an outcome of interest (Supplementary Table 3).

3.17. RQ3 (QUALITY OF LIFE)

We included two conference abstract reporting quality of life (QoL) in GHD children treated with LAGH or daily GH [36,37]. Loftus et al. reported QoL results from the RCT by Deal et al. described above [19]. QoL was measured through the validated Quality of Life in Short Stature Youth (QoLISSY) questionnaire. The QoLISSY core module, which includes three subscales (physical, social, emotional) and a total score, was administered to girls aged 3–11 years and boys aged 3–12 years, and to their parents in eight countries. After 12 months of treatment, the total score for QoLISSY-Child was 74.69 in the somatrogon group (n = 35) vs 69.03 in the Genotropin® group (n = 35), with a mean change from baseline of 13.00 (95% CI, 5.81–20.19) and 7.84 (95% CI, 2.71–12.97), respectively. The total score for QoLISSY-Parent was 69.49 in the somatrogon group (n = 19) vs 63.80 in the Genotropin® group (n = 28), with a mean change from baseline of 13.00 (95% CI, 5.81–20.19) and 7.84 (95% CI, 2.71–12.97), respectively.

Brod et al. [36] reported the patient-reported outcomes (PROs) collected from the REAL3 study [28]. PROs were evaluated using the Growth Hormone Deficiency - Child Impact Measure observer-report (GHD-CIM ObsRO) tool, aiming to assess the impact of GHD on physical functioning, and social and emotional wellbeing in children. Among the three somapacitan groups (0.04, 0.08, 0.16 mg/kg/week), only the results of the 0.16 mg/kg/week group were reported. The change from baseline in GHD-CIM ObsRO score was assessed through the estimated treatment differences (ETDs) between somapacitan 0.16 mg/kg/week and daily GH, compared to minimal important differences (MID). At 52 weeks, the ETDs between somapacitan 0.16 mg/kg/week and daily GH exceeded the MID in favor of somapacitan for the emotional wellbeing (ETD −9.34; MID 7) and social wellbeing domains (ETD −10.12; MID 5), as well as total score (ETD −7.43; MID 5). None of these differences were statistically significant.

3.17.1. Risk of bias

The risk of bias was not assessed because the two included conference abstracts provided insufficient information.

3.18. RQ4 (cost-effectiveness)

Our literature search did not find any studies on cost-effectiveness. We found only a technology evaluation study [38] reporting the market costs in North America of lonapegsomatropin (TransCon) and Genotropin®.

This study reported that the average monthly cost of treatment with lonapegsomatropin was 20–40% higher than that of Genotropin® without preservatives. Depending on the weight of children, lonapegsomatropin can be either cost-saving or most expensive when compared to Genotropin® with preservatives (from −18% to +44%). In the case of a child weighing 30 kg, considering a standard dose of 0.24 mg/kg/week, the monthly cost of lonapegsomatropin amounts to $ 6944, compared to $ 5208 of Genotropin® without preservatives (+25.0%), and $ 6814 of Genotropin® with preservatives (+1.9%) (prices in US dollars, 2021).

3.18.1. Risk of bias

No studies included.

4. Discussion

This systematic review focused on efficacy and safety of LAGH vs daily GH in GHD children, treatment adherence, quality of life and costs. Meta-analyses were performed separately for different LAGH and daily GH formulations. Our results showed that all LAGH formulations were comparable to daily GH regarding all efficacy outcomes, with a similar incidence of adverse events. As expected, in trials comparing different LAGH doses with daily GH, higher LAGH doses achieved better results.

Height velocity was the primary endpoint in most of studies. In all of these trials, non-inferiority of LAGH vs daily GH was demonstrated; in a post-hoc analysis, Thornton et al. [31], in addition to non-inferiority, showed also a superiority of lonapegsomatropin vs daily Genotropin®. In the study by Sun et al. [30], the once-weekly Jintrolong® was non-inferior to daily Jintropin AQ® in terms of difference in HtSDSCA at week 26, while bi-weekly Jintrolong® failed the non-inferiority test compared to once-weekly Jintrolong® and daily Jintropin AQ® (the upper limit of 97.5% CI was 0.23 vs a non-inferiority threshold of $\Delta = 0.11$). Khadilkar et al. [23] did not specify the non-inferiority margin for HV.

The included studies showed a similar incidence of adverse events between the LAGH and daily GH arms. Pooled risk ratios for participants with any adverse events ranged from 0.94 to 1.14, with no statistically significant differences between groups. Treatment-emergent adverse events were mostly mild to moderate in intensity and transient in both the LAGH and daily groups. The most common adverse events reported include injection site reactions. Similarly, fasting glucose, hemoglobin A1c, and thyroid function changes from baseline to the end of follow-up were similar between the LAGH and daily GH groups.

As for the expected/potential benefits of LAGH, i.e. an improved treatment adherence and a better quality of life compared to daily GH, we found comparable results for LAGH and daily GH in the included studies. Adherence rates of LAGH were high (>92%) and, in comparative studies, similar to those of daily GH. However, high levels of adherence are expected in clinical trials and may not be generalizable in a real-world setting. Further observational, long-term studies are necessary to confirm these results.

Two studies [36,37] showed that QoL of children taking LAGH was similar to that of children using daily GH. However, these studies had small sample sizes, therefore larger studies are needed to investigate QoL in children treated with LAGH. While QoL would be expected to be similar between LAGH and daily GH because it is primarily related to height gain, the treatment burden associated with the frequency of injections has been shown to be lower in the LAGH than in the daily GH [39].

We did not find cost-effectiveness studies comparing LAGH and daily GH. Economic studies are needed to demonstrate the cost-effectiveness of LAGH preparations.

4.1. Limitations of the evidence included in the review

In our review, although there are few studies for each LAGH formulation, we decided to perform separate meta-analyses rather than a single meta-analysis including all studies as already done by recent systematic reviews [40,41], because LAGH molecules are different in terms of formulations, pharmacokinetics and pharmacodynamics, with potential implications of these differences on clinical and safety parameters.

The quality assessment showed that most of the studies identified here have some concerns for the risk of bias, with only few studies considered having a low risk of bias. The certainty in the effect estimates rated through the GRADE method was moderate to low. In addition to the risk of bias, the certainty was downgraded due to small sample sizes in some comparisons. Therefore, the limitations of the retrieved evidence point to the need for higher quality studies in this research area. In addition, since most of the included studies were conducted in experimental settings, no real world studies were available, especially for adherence and QoL outcomes. At the time of our research, no economic studies have been published on this topic, so we could not provide any cost-effectiveness analysis.

4.1.1. Implications of the results for practice, policy, and future research

This systematic review and meta-analysis showed that, although most of the included studies had some concerns for risk of bias, regarding efficacy and safety all the available LAGH formulations were

similar to daily GH. The advent of LAGH was one of the main discoveries in the field of endocrinology in the last decade and its use is likely to change the clinical practice in the field of treatment of GHD. In fact, reducing the number of injections without affecting efficacy and safety when compared to GH daily formulation will offer benefits to children affected by GHD. Children may benefit from a lower treatment burden and potentially reduced pain due to repeated injections which is one of the main causes of non-adherence in paediatric age [42]. As reported in the literature, the presence of poor adherence to the daily GH treatment regimen is a key factor having an impact on growth response [2,43]. It is known that patients may become non-adherent after months or years of treatment and a wide range of adherence to GH therapy is reported [44,45]. Overall, up to 50%, 60%, or even 70% of patients do not taking GH treatment regularly and an evident relationship between non-adherence and not achieving linear growth targets has been demonstrated [43]. In this well-known scenario, LAGH could help to reduce non adherent patients and to optimize the benefit of GH therapy. Second, simplifying the therapeutic regimen could reduce the treatment burden to both children and their caregivers, as reported for other new drugs and diseases [46].

Considering the above mentioned limitations on available literature, we suggest the following research priorities to fill the gap in the existing knowledge: 1) higher methodological quality studies; 2) considering that there is a correlation between adherence and clinical efficacy, future research would be enriched by real world studies conducted in mid and long term on larger population samples, particularly on adherence and quality of life; 3) cost-effectiveness studies will be needed to measure the economic impact and potential benefit of LAGH use from the health care payer perspective.

4.2. Other information

4.2.1. Registration and protocol

The protocol of this systematic review is registered in PROSPERO (CRD42022350450).

4.2.2. Support

This study was sponsored by Pfizer. Editorial/medical writing support was provided by Barbara Polistena, Daniela d'Angela, Federico Spandonaro, Massimiliano Orso and Liliana Guadagni at C.R.E.A. Sanità and was funded by Pfizer.

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Declaration of Competing Interest

MGW is a consultant for Pfizer, Merck, Sandoz and Novonordisk. CM has spoken for Pfizer. TA has consulted for Pfizer, and Sandoz.

Barbara Polistena has received payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from the following commercial sources: Allergan, Amgen, Astellas, Baxter, BMS, Boehringer-Ingelheim, Celgene, Eli Lilly, Janssen Cilag, Jazzpharma, Mylan, Nestlé HS, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Servier, Shire, Takeda, Teva; in addition, she received consulting fees from UCB.

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Simona Granato and Pietro Bruschini are employees of Pfizer.

CM, GZ, VC, TA, MGW were paid consultants to Pfizer in connection with the development of this manuscript.

Data Availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.106805.

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