**Supplementary Materials**

**Supplementary Methods 1: Search Strategy**

Searches were run on October 6, 2020 in Embase 1974 week 1 to 2020 week 40, using the search strategy below, in the Ovid interface (Table S1).

**Table S1** |Embase search strategy.

| **Step** | **Search string** | **Hits** |
| --- | --- | --- |
| 1 | (child\* or p?diatric or infant or juvenile or youth or prepubertal or pre-pubertal or preadolescen\* or pre-adolescen\* or preteen\* or pre-teen\* or preschool\* orpre-school\* or adolescen\* or pubertal or teen\*).mp. | 3,868,709 |
| 2 | (growth hormone or growth-hormone or human growth hormone or somatotro?in\* or somatotro?ic or growth hormone deficiency or growth hormone disorder or growth hormone disease or growth hormone condition or growth hormone insufficiency or achondroplasia or Noonan syndrome or SHOX deficiency or short stature homeobox-containing gene deficiency or small for gestational age or idiopathic short stature or Turner syndrome or Prader?Willisyndrome or chronic renal insufficiency).mp. | 132,549 |
| 3 | (growth hormone or growth-hormone or rGH or rhGH or human growth hormone or recombinant growth hormone or somatropin or Genotropin or Saizen or Zomacton or NutropinAq or Nutropin or Norditropin or Serostim orOmnitrope or Humatrope).mp | 97,396 |
| 4 | 2 and 3 | 96,842 |
| 5 | exp Arthritis, Juvenile/ | 21,442 |
| 6 | ((Juvenile adj2 arthritis) or (still\* adj2 disease) or JIA or JRA or sJIA or soJIA).mp | 37,092 |
| 7 | exp inflammatory bowel disease/ | 153,190 |
| 8 | inflammatory bowel disease.mp | 85,885 |
| 9 | or/5-8 | 209,318 |
| 10 | (etanercept or Enbrel or adalimumab or Humira or Certolizumab pegol or Cimzia or Infliximab or remicade or rituximab or Rituxan or Golimumab or Simponi or canakinumab or abatacept or Orencia or anakinra or Kineret or tocilizumab orActemra).mp | 168,161 |
| 11 | (anti-TNF\* or TNFi\* or (TNF\* adj blocker) or (TNF\* adj inhibit\*)).ti,ab | 33,280 |
| 12 | (DMARD\* or disease modifying).ti,ab. | 39,613 |
| 13 | or/10-12 | 212,597 |
| 14 | 9 and 13 | 36,055 |
| 15 | exp Multiple Sclerosis/ | 130,242 |
| 16 | multiple sclerosis.mp | 142,873 |
| 17 | (interferon or glatiramer acetate or Copaxone or Glatopa or Avonex or Rebif orBetaseron or Extavia or peginterferon or Plegridy).mp. | 402,353 |
| 18 | (DMARD\* or disease modifying).ti,ab | 39,613 |
| 19 | 15 or 16 | 142,873 |
| 20 | 17 or 18 | 438,209 |
| 21 | 19 and 20 | 27,608 |
| 22 | (adheren\* or nonadheren\* or non-adheren\* or non adheren\* or complian\* or noncomplian\* or non-complian\* or non complian\* or persistence or nonpersisten\* or non-persisten\* or non persisten\* or concordan\* or discordan\*or continu\* or discontinu\* or dis-continu\* or cessation).mp. | 2,462,209 |
| 23 | 1 and 4 and 22 | 2911 |
| 24 | 1 and 14 and 22 | 2627 |
| 25 | 1 and 21 and 22 | 305 |
| 26 | 23 or 24 or 25 | 5806 |
| 27 | ((animal$ not human$) or in vitro or nonhuman).sh,hw. | 8,496,500 |
| 28 | (animal\* or in vitro or tissue\* or murine or mouse or mice or swine\* or pig\* or porcine or rat or rats or rodent\* or monkey or simian or ape or dog or canine\* or cats or cat or feline\* or cow or bovine or horse or equine or fish or piscine orrabbit\*).ti | 2,927,994 |
| 29 | (conference abstract or congress or editorial or comment\* or letter or note).pt.or (congress or conference or symposium).ti,sh | 6,582,914 |
| 30 | (cancer\* or chemo\* or radiotherapy\* or radiation or carcinoma\* or sarcoma\*ortumor\* or tumour\*).ti,ab. | 3,965,213 |
| 31 | or/27-30 | 16,976,127 |
| 32 | 26 not 31 | 2852 |
| 33 | limit 32 to yr="2015 -Current" | 780 |
| 34 | Remove duplicates from 33 | 763 |

Searches were run in Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to October 1, 2020, using the search strategy below. Searches were run October 6, 2020.

Searches were run in Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to October 01, 2020, using the search strategy below (Table S2). Searches were run 6 October 2020.

**Table S2** |Medline search strategy.

| **Step** | **Search string** | **Hits** |
| --- | --- | --- |
| 1 | (child\* or p?diatric or infant or juvenile or youth or prepubertal or pre-pubertal or preadolescen\* or pre-adolescen\* or preteen\* or pre-teen\* or preschool\* orpre-school\* or adolescen\* or pubertal or teen\*).mp. | 4,219,342 |
| 2 | (growth hormone or growth-hormone or human growth hormone or somatotro?in\* or somatotro?ic or growth hormone deficiency or growth hormone disorder or growth hormone disease or growth hormone condition or growth hormone insufficiency or achondroplasia or Noonan syndrome or SHOX deficiency or short stature homeobox-containing gene deficiency or small for gestational age or idiopathic short stature or Turner syndrome or Prader?Willi syndrome or chronic renal insufficiency).mp. | 107,120 |
| 3 | (growth hormone or growth-hormone or rGH or rhGH or human growth hormone or recombinant growth hormone or somatropin or Genotropin or Saizen or Zomacton or NutropinAq or Nutropin or Norditropin or Serostim or Omnitrope or Humatrope).mp | 75,842 |
| 4 | 2 and 3 | 75,537 |
| 5 | exp Arthritis, Juvenile/ | 10,464 |
| 6 | ((Juvenile adj2 arthritis) or (still\* adj2 disease) or JIA or JRA or sJIA or soJIA).mp | 23,431 |
| 7 | exp Inflammatory Bowel Diseases/ | 81,488 |
| 8 | inflammatory bowel disease.mp | 47,762 |
| 9 | or/5-8 | 124,900 |
| 10 | (etanercept or Enbrel or adalimumab or Humira or Certolizumab pegol or Cimzia or Infliximab or remicade or rituximab or Rituxan or Golimumab or Simponi or canakinumab or abatacept or Orencia or anakinra or Kineret or tocilizumab or Actemra).mp | 58,875 |
| 11 | (anti-TNF\* or TNFi\* or (TNF\* adj blocker) or (TNF\* adj inhibit\*)).ti,ab | 15,830 |
| 12 | (DMARD\* or disease modifying).ti,ab. | 20,371 |
| 13 | or/10-12 | 84,922 |
| 14 | 9 and 13 | 10,619 |
| 15 | exp Multiple Sclerosis/ | 59,304 |
| 16 | multiple sclerosis.mp | 88,777 |
| 17 | (interferon or glatiramer acetate or Copaxone or Glatopa or Avonex or Rebif orBetaseron or Extavia or peginterferon or Plegridy).mp. | 202,452 |
| 18 | (DMARD\* or disease modifying).ti,ab | 20,371 |
| 19 | 15 or 16 | 88,777 |
| 20 | 17 or 18 | 221,609 |
| 21 | 19 and 20 | 10,696 |
| 22 | (adheren\* or nonadheren\* or non-adheren\* or non adheren\* or complian\* or noncomplian\* or non-complian\* or non complian\* or persistence or nonpersisten\* or non-persisten\* or non persisten\* or concordan\* or discordan\*or continu\* or discontinu\* or dis-continu\* or cessation).mp. | 1,848,245 |
| 23 | 1 and 4 and 22 | 1910 |
| 24 | 1 and 14 and 22 | 759 |
| 25 | 1 and 21 and 22 | 204 |
| 26 | 23 or 24 or 25 | 2872 |
| 27 | ((animals not (humans and animals)) or in vitro or nonhuman).sh | 4,709,572 |
| 28 | (animal\* or in vitro or tissue\* or murine or mouse or mice or swine\* or pig\* or porcine or rat or rats or rodent\* or monkey or simian or ape or dog or canine\* or cats or cat or feline\* or cow or bovine or horse or equine or fish or piscine or rabbit\*).ti | 2,818,702 |
| 29 | (editorial or comment\* or letter or note).pt. | 1,917,987 |
| 30 | (cancer\* or chemo\* or radiotherapy\* or radiation or carcinoma\* or sarcoma\*or tumor\* or tumour\*).ti,ab. | 3,100,656 |
| 31 | or/27-30 | 10,128,377 |
| 32 | 26 not 31 | 2531 |
| 33 | limit 32 to yr="2015 -Current" | 674 |
| 34 | Remove duplicates from 33 | 619 |

**Supplementary Methods 2: Data-Extraction Elements**

* The following data points were extracted, where available, from eligible studies:
	+ Bibliographic details (authors, title, reference number)
	+ Study name/registry/database
	+ Study design
	+ Aim
	+ Country
	+ Patient eligibility criteria (inclusion/exclusion)
	+ Sample size
	+ Duration of follow-up
	+ Reporting timepoint (timepoint for which data will be extracted)
	+ Patient characteristics at baseline
	+ Age, gender, ethnicity
	+ Clinical indication (GH-related indication, JIA, IBD, MS)
		- For GH-related indications, subgroups may include: GHD, Turner syndrome, SHOX deficiency, small for gestational age (SGA), idiopathic short stature (ISS), Prader–Willi syndrome, neurosecretory dysfunction, intrauterine growth retardation, bioinactive GH, or chronic renal failure
* Intervention/study arm characteristics
	+ Treatment, administration route, and scheduling
	+ Median/mean duration of treatment
	+ Duration of follow-up
* Outcomes:
	+ Method of assessing adherence
	+ Definition of adherence/non-adherence
	+ Adherence prevalence (*n*, %)
	+ Prevalence of adherence/non-adherence (*n*, %)
	+ Stated barriers to adherence
	+ Factors associated with adherence to prescribed treatment
	+ Factors not associated with adherence to prescribed treatment
	+ Recommendations for improving adherence
* For the Chinese publications identified in the targeted search, data were extracted into a brief modified DET to report key information regarding study population and adherence. One researcher (Dejun Li) extracted the data, translated into English. A second researcher (Shuang Li), fluent in Chinese, quality-checked the extracted data against the Chinese-language publications. Any disagreements were resolved by discussion.

*Refer to abbreviation list on last page*

**Table S3** |Characteristics of included studies (*n*=23).

| **Author, year (sponsor)** | **Country, study name, or data source** | **Study design** | **Study period** | **Population and sample size, *n* (%)** | **% Female** | **Mean age (SD), years** |
| --- | --- | --- | --- | --- | --- | --- |
| **Interventional studies (*n* = 2)** |
| Chung, 2018 (1) (Merck) | Korea, SYNERGY | Randomized multicenter, open-label study | Dec 2012– Mar 2015 | ISS: 89 (100)Tx: 59 (66.3)\*Control: 30 (33.7)With 12 mo of data: ISS: 79 (100)Tx: 52 (65.8)\*Control: 27 (34.2) | Tx: 49%\*Control: 43% | Tx: 6.79 (1.54) \*Control: 6.83 (1.61) |
| Sävendahl, 2020 (2) (Novo Nordisk) | Multinational (11 countries), REAL 3 | Phase 2, open-label, multicenter RCT (SOMA dosing was double-blinded; SOMA vs NORD was not blinded) | Mar 2016–Aug 2018 | GHD: 59 (100)57 full analysis set (with baseline data)SOMA (0.04 mg/kg/wk): 14SOMA (0.08 mg/kg/wk):15 SOMA (0.16 mg/kg/wk): 14 NORD Daily (0.034 mg/kg/d): 14 | SOMA (0.04 mg/kg/wk): 50%SOMA (0.08 mg/kg/wk): 33.3%SOMA (0.16 mg/kg/wk): 42.9%NORD daily (0.034 mg/kg/d): 35.7% | SOMA (0.04 mg/kg/wk): 5.8 (1.8) SOMA (0.08 mg/kg/wk): 5.9 (1.8)SOMA (0.16 mg/kg/wk): 6.1 (2.3)NORD Daily (0.034 mg/kg/d): 6.0 (2.0) |

|  |
| --- |
| **Observational studies (*n* = 21; 20 rhGH studies; 1 MS study)** |
| Arrabal Vela, 2018\*\* (3) (NR) | Spain, Pediatric Endocrinology Clinic, Hospital General Universitario de Ciudad Real (medical records) | Retrospective, single center | May 2015– May 2016 | Total: 30GHD: 14 (46.7)SGA: 14 (46.7)Other: 2 (6.6) | 33% | 6.09 (range 4.92–7.25) |
| Bagnasco, 2017 (4) (Novo Nordisk) | Italy, SIEDP/ISPED (46 centers, medical records) | Cross-sectional survey, multicenter | Nov 2015–May 2016 | Total: 1007Parents: 771 (76.6%)Patients: 221 (21.9%)Unknown: 15 (1.5%)Indication: NR (rhGH recipients) | NR | Mode: 14–15 (range 6–15) |
| Blanco-Lopez, 2020\*\* (5) (Merck) | Mexico, ECOS (sub-analysis) | Prospective, multicenter | Nov 2010–Feb 2016 | Total: 147GHD: 118 (80.3)SGA: 24 (16.3)TS: 5 (3.4) | 43.2% | 9.96 (3.41) |
| Cardinale, 2019\*\* (6) (Merck) | Italy (6 centers, medical records) | Retrospective, multicenter | Jan 2015–Sep 2015 | Total: 90GHD: 83 (92)SGA: 5 (6)TS: 2 (2) | 42% | 11.9 (3.04) |
| Centonze, 2019\*\* (7) (Merck) | Italy, ECOS (sub-analysis) | Prospective, multicenter | NR | GHD: 73 (100) | 47.9% | 9.78 (3.20) |
| Charmandari, 2020\*\* (8) (Merck) | Greece, ECOS (sub-analysis) | Prospective, multicenter | NR | Total: 88GHD: 78 (88.6)SGA: 4 (4.6)TS: 3 (3.4)Other/missing: 3 (3.4) | 37.5% | 10.23 (2.79) |
| De Pedro, 2016 (9) (Pfizer) | Spain, EndocrinologyPediatrics, Germans Trias i Pujol University Hospital Badalona (medical records) | Retrospective, single center | 2012 (months NR) | Total: 158GHD: 121 (76.5)SGA 37 (23.5) | 36% | 10.6 (2.7) |
| Dumitrescu, 2020 (10) (Ipsen) | Romania, COMPLIA (13 centers, medical records) | Prospective, multicenter | Jun 2010–Jun 2014 | GHD: 187 (100) | 36.9% | 9.8 (3.6) |
| Farfel, 2019 (11) (Pfizer) | Israel, Clalit Health Maintenance Organization (claims data) | Retrospective, multicenter | Jan 2006–Dec 2015 | Total: 2263 GHD, SGA, or TS (cannot differentiate): 1612 (71.2)ISS: 575 (25.6)CRF: 76 (3.4) | 41% | 8.3 (3.6) |
| Gau, 2017 (12) (none) | Japan, Kawaguchi Municipal Medical Center (medical records) | Retrospective, single center | No PC: 2008–2010PC: 2011–2014 | GHD: 46 (100) | 48% | 7.70 (3.12) |
| Kappelgaard, 2015 (13) (Novo Nordisk) | France, Germany, Italy, USA (surveys) | Cross-sectional survey, multicenter | Apr 2014–Jun 2014 | Storage-flex:Total: 50† GHD/MPHD: 38(76)SGA: 8 (16)TS: 4 (8)Other: 1 (2)Refrigeration-only: Total: 96†GHD/MPHD: 65(68)SGA: 21 (22)TS: 12 (13)ISS: 3 (3)RSS: 4 (4)Other: 3 (3) | Storage-flex:38%Refrigeration-only: 40% | Storage-flex:Mode: 14–17(range <5–25)Refrigeration-only:Mode: 5–7(range <5–25) |
| Koledova, 2018\*\* (14) (Merck) | 24 countries, ECOS | Prospective, multicenter | Nov 2010–Feb 2016 | Total: 1203GHD: 897 (74.6)SGA: 207 (17.2)TS: 82 (6.8)Other: 17 (1.4) | 41.8% | Median: 10 (range: 1–19) |
| Koledova, 2020\*\* (15) (Merck) | Multicounty (NR) | Retrospective, multicenter | Jan 2007–Feb 2019 | Total: 13,553 Indication NR, all patients received rhGH | 42.5% | Boys, by adherence:≥85%: 12.8 (5.3)>56 to <85%: 15.0 (6.6)≤56%: 15.3 (7.6)Girls, by adherence:≥85%: 12.2 (5.2)>56 to <85%: 14.3 (7.9)≤56%: 15.8 (10.6) |
| Lass, 2015\*\* (16) (Merck) | Germany, Vestische Hospital for Children and Adolescents (medical records) | Retrospective, single center | Sep 2014–Feb 2015 | Total: 103GHD: 74 (71.8)SGA: 21 (20.4)TS: 4 (3.9)SHOX deficiency: 3 (2.9)PWS: 1 (1.0) | 35% | At Tx start: 6.6 (2.7)At study start: 10.1 (range: 8.1–12.2)§ |
| Loche, 2016\*\* (17) (Merck) | Italy, 10 clinical sites (medical records) | Prospective, multicenter | Mar 2010–Jan 2013 | GHD: 79 (100) | 34% | Median (IQR): 10 (9–12) |
| Maggio, 2018\*\* (18) (None) | Italy, Paediatric Clinic, G. Di Cristina Children’s Hospital, ARNAS, Palermo (medical records) | Retrospective, single center | 2009–2016(months NR) | Total: 40GHD: 26 (65)SGA: 9 (22.5)TS: 5 (12.5) | 32.5% | At Tx start: 8.65 (2.81)At study start: 11.2 (2.3) |
| Michaelidou, 2019 (19) (Ferring) | UK, University College London Hospitals (pharmacy data) | Retrospective, single center | Jan 2010–Dec 2015 | Total: 52GHD: 34 (65.4)TS: 5 (9.2)Other: 13 (25.0) | 43.3% | 8.50 (3.78) |
| Mohseni, 2018 (20) (Tehran University of Medical Sciences) | Iran, Tehran University of Medical Sciences (pharmacy data and survey) | Cross-sectional survey, single center | NR | Total: 169 Indication NR, all patients received rhGH | 56.8% | 12.29 (3.09) |
| Rodriguez Arnao, 2019\*\* (21) (Merck) | Spain, ECOS | Prospective, multicenter | NR | Total: 238GHD: 144 (60.5)SGA: 86 (36.1)TS: 8 (3.4) | 48.3% | At Tx start: 7.9 (3.2)At study start: 9.0 (3.3) |
| van Dommelen, 2018\*\* (22) (Merck) | 24 countries, ECOS | Prospective and retrospective, multicenter | NR | GHD (Tx-naïve): 95(100) | 24% | At study start: 6.3 (2.1) |
| **Observational studies, agents other than rhGH** |
| Ghezzi, 2017 (23) (Merck) | Italy, FUTURE | Prospective | Jan 2012–Oct 2014 | MS: 40 (100) | 70% | 15 (2.1) |

\*Control consisted of 6 months without rhGH treatment, followed by 6 months with rhGH treatment.

\*\*easypod™ study (includes prospective ECOS and retrospective studies).

†Respondents listed any diagnosis for which they received rhGH; sums exceed 100%.

§Mean (range) assumed based on reported values in Lass, 2015 (see Table 1 and text), but not specified in publication.

*Refer to abbreviation list on last page..*

**Table S4** |Quality assessment of RCTs using the Cochrane RoB2.

| **Author, year** **Trial name Study design** | **Was the allocation sequence random?** | **Was the allocation sequence concealed until participants were enrolled****and assigned to interventions?** | **Was knowledge of the allocated interventions adequately concealed from participants and personnel?** | **Was knowledge of the allocated interventions adequately prevented from outcome assessors?** | **Were incomplete outcome data adequately addressed?** | **Are reports of the study free of suggestion of selective outcome reporting?** | **Was the study apparently free of other problems that could put it at a high risk of bias?** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Chung 2018 (1)**SYNERGYOpen-label, randomized, 2-arm, parallel-group, delayed-treatment, group-controlled phase 3 study | **YES**Randomization codes were generated centrally by a contract research organization | **NO**Open label | **NO**Open label | **NO**Open label | **YES**Adherence outcome—appears to be assessed by all with 12-mo data | **YES**No evidence of selective reporting | **PARTIAL YES**Patients/ caregivers may have overestimated adherence (since self-reported); actual adherence may have been higher than in a real-world setting because of being part of a study |
| **Sävendahl 2020 (2)**REALMulticenter, randomized, controlled, double- blind (SOMA doses only; weekly vs daily doses not blinded) phase 2 study | **YES**Random assignment by investigators at trial sites using a trial- specific, web-based, interactive response system | **PARTIAL YES**The three SOMA (wkly GH) doses were double-blinded; wkly vs daily GH could not be blinded | **PARTIAL YES**The three SOMA (wkly GH) doses were double-blinded; wkly vs daily GH could not be blinded | **PARTIAL YES**Adherence was self-reported; the 3 SOMA (weekly GH) doses were double-blinded; wkly vs daily GH could not be blinded | **PARTIAL YES**Except for 1 of 14 patients discontinuing daily GH after 44 days, all appear to have had 52 wks of adherence data. This led to a lower mean adherence for daily GH; median values are more representative | **YES**No evidence of selective reporting | **PARTIAL YES**Patients/ care-givers may have overestimated adherence (since self-reported); actual adherence may have been higher than in a real-world setting because of being part of a study |

Available: <https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials>

*Refer to abbreviation list on last page.*

**Table S5** |Quality assessment of observational studies using NOS.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Selection** | **Comparability** | **Outcome** | **Total** |
| **Author, year** | **Representative-ness of exposed cohort\*** | **Representative -ness of non-exposed cohort/ exposed cohort\*** | **Method to ascertain exposure\*** | **Outcome of interest not present at start\*** | **Comparability of cohorts on basis of design or analysis\*\*** | **Method of assessing outcome\*** | **Follow-up long enough for outcomes to occur\*** | **Adequacy of follow-up of cohorts\*** | **Total score (out of 9)** |
| Arrabal Vela, 2018 (3) | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 5 |
| Blanco-Lopez, 2020 (5) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Cardinale, 2019 (6) | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 4 |
| Centonze, 2019 (7) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 5 |
| Charmandari, 2020 (8) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| De Pedro, 2016 (9) | 0 | 0 | 1 | 1 | 2 | 1 | 1 | 1 | 7 |
| Dumitrescu, 2020 (10) | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 5 |
| Farfel, 2019 (11) | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Gau, 2017 (12) | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 4 |
| Ghezzi, 2017 (23) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 5 |
| Koledova, 2018 (14) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Koledova, 2020 (15) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Lass, 2015 (16) | 0 | 0 | 1 | 1 | 2 | 1 | 1 | 1 | 7 |
| Loche, 2016 (17) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 5 |
| Maggio, 2018 (18) | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 5 |
| Michaelidou, 2019 (19) | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 6 |
| Rodriguez Arnao, 2019 (21) | 1 | 0 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| van Dommelen, 2018 (22) | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |

NOS, Newcastle–Ottawa Scale.

\*Maximum of 1 point.

\*\*Maximum of 2 points.

Score: ≥7, good; 4–6, fair; 0–3, poor.

**Table S6** |Quality assessment of survey studies using the modified NOS.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Selection** | **Comparability** | **Outcome** | **Total** |
|  | **Representativeness of sample cohort** | **Sufficiency of sample size** | **Adequacy of response rate or data on non-responders** | **Method to ascertain exposure** | **Comparability of cohorts on basis of design or analysis** | **Method to assess outcome** | **Appropriate statistical test used** | **Total score (out of 9)** |
| **Author, year** | **\*** | **\*** | **\*** | **\*** | **\*\*** | **\*\*** | **\*** |  |
| Bagnasco, 2017 (4) | 1 | 1 | 0 | 1 | 2 | 0 | 1 | 6 |
| Kappelgaard, 2015 (13) | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Mohseni, 2018 (20) | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 3 |

NOS, Newcastle–Ottawa Scale.

\*Maximum of 1 point.

\*\*Maximum of 2 points

Score: ≥7, good; 4-6, fair; 0-3, poor.

Source: Herzog R, et al. (24).

**Table S7** |Methods for measuring adherence and reported adherence in included studies (*n* = 23).

| **Author, year (country)** | **Population and sample size, *n* (%)** | **Adherence measurement method** | **Categorical measures of adherence** | **Reported adherence** |
| --- | --- | --- | --- | --- |
| **Interventional studies (*n* = 2)** |  |
| Chung, 2018 (1) (Korea) | With 12 mo of data ISS: 79 (100)Tx: 52 (65.8)**\***Control: 27(34.2) | Self-report: the proportion of prescribed doses administered according to drug diaries | Non-adherent: receipt of <75% of expected injections | Mean over 12 mo: Treated: 93.27%**\***Control: 95.69% (over 6 m) |
| Sävendahl, 2020 (2) (11 countries) | GHD: 59 (100) | Self-report: the proportion of prescribed doses administered according to drug diaries | None reported | Mean (SD); median over 12 mo: SOMA (0.04 mg/kg/wk): 97.5% (4.50); median 99.1%SOMA (0.08 mg/kg/wk): 98.6% (1.66);median 100%SOMA (0.16 mg/kg/wk): 96.3% (5.19);median 99.1%NORD GH (0.034 mg/kg/d):91.8% (23.03); median 99.2% |

|  |  |
| --- | --- |
| **Observational studies (*n* = 21; 20 rhGH studies; 1 MS study)** |  |
| Arrabal Vela, 2018\*\* (3) (Spain) | Total: 30GHD: 14 (46.7)SGA: 14 (46.7)Other: 2 (6.6) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | Excellent adherence: >95%Good adherence: >85–95%Fair adherence: 75–85%Poor adherence: <75% | Over 12 mo:Mean (95% CI): 92.3% (87.7–96.9%)Excellent adherence (>95%): 60%Good adherence (>85–95%): 30%Fair adherence (75–85%): 3.3%Poor adherence (<75%): 6.7% |
| Bagnasco, 2017 (4) (Italy) | Total: 1007Parents: 771(76.6%)Patients: 221 (21.9%)Unknown: 15 (1.5%)Indication: NR (all were rhGHrecipients) | Self-report (recall): the number of injections missed in a typical week over the past 12 months | Adherent: 0 missed doses in a typical weekNon-adherent: ≥1 misseddose in a typical week | Over 12 mo:94.5% missed ≤1 dose/wk72.1% missed 0 doses/wk22.4% missed 1ose/wk 2.0% missed ≥2 doses/wk 3.5% did not respond |
| Blanco-Lopez, 2020\*\* (5) (Mexico) | Total: 147GHD: 118 (80.3)SGA: 24 (16.3)TS: 5 (3.4) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | NR | Over 12 mo:Mean 85.7%; median 92.9% |
| Cardinale, 2019\*\* (6) (Italy) | Total: 90GHD: 83 (92)SGA: 5 (6)TS: 2 (2) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | NR | Over 977 days:mean (SD) 70% (13%) |
| Centonze, 2019\*\* (7) (Italy) | GHD: 73 (100) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | NR directly, but >85% adherence mentioned as benchmark | Over 12 mo:mean 88.55%; median 92.3% |
| Charmandari, 2020\*\* (8) (Greece) | Total: 88GHD: 78 (88.6)SGA: 4 (4.6)TS: 3 (3.4)Other/missing: 3(3.4) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | Adherent: mean adherencerate ≥85%(≥1 missed dose/wk onaverage) | Over 12 mo:Mean 92.5%; median (IQR) 95.5% (90.05%; 98.25%) |
| De Pedro, 2016 (9) (Spain) | Total: 158GHD: 121 (76.5)SGA 37 (23.5) | Annual dose prescribed compared with the doses patients picked up at the hospital pharmacy | Good: ≥92% of prescribed doses (≤2 doses missed/m) Moderate: 85 to <92%Poor: <85% (≥1 dosemissed/wk) | Good: 66.5% of patients picked up ≥92% of their prescribed medication Moderate–good: 79% picked up ≥85% of their prescribed medication |
| Dumitrescu, 2020 (10) (Romania) | GHD: 187 (100) | Self-report (recall)“During the last 3 mo of therapy, how often was a dose (i.e., injection) missed/skipped?” | Qualitative, 5-item Likert scale:No missed injections1–3 missed injections4–6 missed injections7–10 missed injections>10 missed injections | In past 3 mo, % of patients who missed:0 injections: 85.1% (95% CI: 79.4–90.7%)1–3 injections: 8.4% (95% CI: 4.1–12.8%)4–6 injections: 1.9% (95% CI: 0–4.1%)7–10 injections: 0>10 injections: 4.5% (95% CI: 1.3–7.8%) |
| Farfel, 2019 (11) (Israel) | Total: 2263 GHD, SGA, or TS (cannot differentiate): 1612 (71.2)ISS: 575 (25.6)CRF: 76 (3.4) | The number of months per year of pharmacy purchase of rhGH, assessed over ≥2 yr | Good: 11–12 m purchase/year Moderate: 7–10 m purchase/yearPoor: <7 m purchase/year | Over 12 mo (Year 2): mean (SD) 8.8 (2.6) mo(calculated mean 73.3%) |
| Gau, 2017 (12) (Japan) | GHD: 46 (100) | Self-report (recall): number of missed injections in a week | Good: ≤1 missed dose/wkPoor: >1 missed dose/wk | Over 12 mo, % who missed ≤1 dose/weekNo choice of device: 95% Choice of device: 100% |
| Kappelgaard, 2015 (13) (France, Germany, Italy, USA) | Storage flexible: Total: 50† GHD/MPHD: 38 (76)SGA: 8 (16)TS: 4 (8)Other: 1 (2) Refrigeration-only:Total: 96†GHD/MPHD: 65(68)SGA: 21 (22)TS: 12 (13)ISS: 3 (3)RSS: 4 (4)Other: 3 (3) | Self-report (recall): number of missing/skipped injections in a typical month | Missed no injections/moMissed ≥1 injection/mo | Over 12 mo:% who missed 0 injections/month Total: 64%Storage flexible: 76%Refrigeration-only: 57%% who missed ≥1 injection/monthTotal: 36%Storage flexible: 24%Refrigeration-only: 43% |
| Koledova, 2018\*\* (14) (24 countries) | Total: 1203GHD: 897 (74.6)SGA: 207 (17.2)TS: 82 (6.8)Other: 17 (1.4) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | NR directly, but >80% adherence mentioned as benchmark | Over 12 mo:Total: mean 84.1%; median 93.7%GHD: median 93.4%SGA: median 95.0%TS: median 93.2% |
| Koledova, 2020\*\* (15) (multi-country) | Total: 13,553 Indication NR, all patients received rhGH | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | High: ≥85% (missed ≤1 dose in a typical week) Intermediate: >56–84% Low: ≤56% | Over 12 mo:% patients in each adherence group:High (≥85%): 77%Intermediate (>56–84%): 15%Low (≤56%): 7% |
| Lass, 2015 (16) (Germany) | Total: 103GHD: 74 (71.8)SGA: 21 (20.4)TS: 4 (3.9)SHOX deficiency: 3 (2.9)PWS: 1 (1.0) | (Doses filled at pharmacy/doses prescribed) × 100 | Good: >85.7% (<1 missed dose/wk)Medium: 57.1–85.7% (1–3 missed doses/wk)Poor: <57.1% (>3 missed doses/wk) | Over 12 mo: median (IQR): 91% (55–103%)§% who missed <1 dose/wk (>85.7% adherence)Total (*n*=103): 51%GHD (*n*=74): 53%SGA (*n*=21): 38%TS (*n*=4): 75%SHOX deficiency (*n*=3): 67%PWS (*n*=1): 100% |
| Loche, 2016\*\* (17) (Italy) | GHD: 79 (100) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | Fully adherent: ≥92% | Over 12 mo:52.83% were fully (≥92%) adherent |
| Maggio, 2018\*\* (18) (Italy) | Total: 40GHD: 26 (65)SGA: 9 (22.5)TS: 5 (12.5) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | Good: ≥85% | Time period NR. mean 92.2% |
| Michaelidou, 2019 (19) (UK) | Total: 52GHD: 34 (65.4)TS: 5 (9.2)Other: 13 (25.0) | Proportion of days covered: quantity of device-heads delivered × length of time each head should last [1 wk]/number of days prescribed GH treatment during treatment period | Good: >80% proportion of days covered | Over 12 mo: % with >80% proportion of days coveredTotal: 57.5%GHD: 55.9%TS: 40%Other: 69.2% |
| Mohseni, 2018 (20) (Iran) | Total: 169 Indication NR, all patients received rhGH | Self-reported (2 methods): (1) 8-item MMAS; (2) “auto-compliance method”: number of injections given/number of prescribed injections during the past month | MMAS: adherent = high or moderate adherence (MMAS ≥6)High: MMAS = 8Moderate: MMAS = 6–7.9 Low: MMAS <6Auto-compliance:adherent: adherence >80% | Time period NRMMAS adherence group:Adherent (high + moderate): 57.4% High adherence: 16.6%Moderate adherence: 40.8%Low adherence: 42.6%Auto-compliance (>80% adherent): 95.3% |
| Rodriguez Arnao, 2019\*\* (21) (Spain) | Total: 238GHD: 144 (60.5)SGA: 86 (36.1)TS: 8 (3.4) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | Good: ≥85% (≤1 misseddose/wk)Non-adherent: <85% (>1 missed dose/wk) | Over 12 mo:mean 95.3% (95% CI 93.3–97.2); median: 99.1 |
| van Dommelen, 2018\*\* (22) (24 countries) | GHD (Tx-naïve): 95 (100) | (Days administered at the prescribed dose/days prescribed) × 100 as measured by easypod™ injector device | “Recursive partitioning used to find the cut-off point (the first split) for high and low adherence that maximizes the correlation between adherence and height gain”Year 1: High: ≥98%Year 2: ≥91%Years 1–2: ≥78% | Over 12 mo:Mean (SD); median (min, max)Year 0–1: 80.8% (31.1%); 95.1% (0, 100)Year 1–2: 81.5% (23.0%); 92.9% (0, 100) |
| **Observational studies, agents other than rhGH (*n* = 1)** |
| Ghezzi, 2017 (Italy) | MS: 40 (100) | (Number of administered injections/expected number of injections) × 100 as measuredby the RebiSmart™ device | NR | 67.5% adherence at 12 mo |

\*Control consisted of 6 months without rhGH treatment, followed by 6 months with rhGH treatment. Treated received 12 months of rhGH.

\*\*easypod™ study (includes prospective ECOS and retrospective studies).

†Respondents listed any diagnosis for which they received rhGH; sums exceed 100%.

§Adherence exceeded 100% if patients had filled more doses than prescribed.

**TABLE ABBREVIATIONS**

**CI,** confidence interval; **CRF**, chronic renal failure; **DET**, data-extraction table; **ECOS**, easypod™ Connect Observational Study; **FUTURE**, Quality of liFe in adolescent sUbjecTs affected by mUltiple sclerosis treated with immunomodulatoRy agEnt using self-injecting device; **GHD**, growth hormone disorder; **GH**, growth hormone; **IBS**, irritable bowel disease; **IQR**, interquartile range; **ISS**, idiopathic short stature; kg, kilogram; **MPHD**, multiple pituitary hormone deficiency; **MS**, multiple sclerosis; **NORD**, Norditropin; **NR**, not reported; **PC**, patient choice (of device); **PWS**, Prader–Willi syndrome; **RCT**, randomized controlled trial; **rhGH**, recombinant human growth hormone; **RoB2**, Risk of Bias tool version 2; **RSS**, Russell–Silver syndrome; **SD**, standard deviation; **SGA**, small for gestational age; **SHOX**, short stature homeobox-containing gene; **SIEDP/ISPED**, Italian Society for Pediatric Endocrinology and Diabetes; **SOMA**, somapacitan; **TS**, Turner syndrome; **Tx**, treated/treatment.

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