Long-Acting Growth Hormone Preparations – Current Status and Future Considerations

Bradley S. Miller,[1] Eric Velazquez,[1] and Kevin C.J. Yuen[2]

[1]Division of Endocrinology, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, 55454; and [2]Departments of Neuroendocrinology and Neurosurgery, Barrow Pituitary Center, Barrow Neurological Institute, University of Arizona College of Medicine, Phoenix, Arizona, 85013

ORCiD number: 0000-0003-3663-5473 (Bradley S. Miller).

Context: Long-acting GH (LAGH) preparations are currently being developed in an attempt to improve adherence. The profile of GH action following administration of LAGH raises practical questions about clinical monitoring and long-term safety and efficacy of these new therapeutic agents.

Methods: Recent literature and meeting proceedings regarding LAGH preparations are reviewed.

Results: Multiple LAGH preparations are currently at various stages of development, allowing for decreased GH injection frequency from daily to weekly, biweekly, or monthly. Following administration of LAGH, the serum peak and trough GH and IGF-I levels vary depending upon the mechanism used to prolong GH action. Randomized, controlled clinical trials of some LAGH preparations have reported non-inferiority compared with daily recombinant human GH (rhGH) for improved growth velocity and body composition in children and adults with GH deficiency (GHD), respectively. No significant LAGH-related adverse events have been reported during short-term therapy.

Conclusion: Multiple LAGH preparations are proceeding through clinical development with some showing promising evidence of short-term clinical efficacy and safety in children and adults with GHD. The relationship of transient elevations of GH and IGF-I following administration of LAGH to efficacy and safety remain to be elucidated. For LAGH to replace daily rhGH in the treatment of individuals with GHD, a number of practical questions need to be addressed including methods of dose adjustment, timing of monitoring of IGF-I, safety, efficacy, and cost-effectiveness. Long-term surveillance of efficacy and safety of LAGH preparations will be needed to answer these clinically relevant questions. **(*J Clin Endocrinol Metab* 105: e2121–e2133, 2020)**

Key Words: long acting growth hormone, treatment adherence, growth hormone deficiency, adult, children

Introduction

Recombinant human GH (rhGH) therapy administered as daily subcutaneous injections has been shown to be beneficial in the treatment of GH deficiency (GHD) in children (CGHD) and adults (AGHD). Efficacy of rhGH therapy is dependent upon making the correct diagnosis, administering the appropriate dosage of rhGH, and maintaining patient adherence and persistence with treatment (1, 2). Challenges to adherence and persistence with daily rhGH therapy include device limitations, inconvenience of required dose frequency, lack of

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 31 July 2019. Accepted 30 October 2019.
First Published Online 2 November 2019.
Corrected and Typeset 21 April 2020.

Abbreviations: AGHD, GH deficiency in adults; CGHD, GH deficiency in children; GHD, GH deficiency; HV, high velocity; LAGH, long-acting GH; PEG, poly(ethylene glycol); rhGH, recombinant human GH; SDS, standard deviation score

perceived benefit, insurance issues, and costs (3–5). In the United States, a lack of relevant and consistent criteria for approval of rhGH therapy among insurance companies has made persistence with rhGH therapy more difficult (6). As stated by former Surgeon General C. Everett Koop, "Drugs don't work in patients who don't take them" (7). Poor adherence to rhGH reduced efficacy in children and adults, and recent publications suggest that as few as 30% of patients demonstrate good adherence (missing <1 dose per week) to daily rhGH therapy (8–16). Adherence is particularly poor in teenagers, which may explain why near-adult height outcomes in children remain below the mid-parental target height and the population mean (17, 18). It has been hypothesized that long-acting growth hormone (LAGH) preparations with lower frequency of injections might help mitigate the issue with patient adherence leading to longer persistence and potentially better outcomes.

Hence, there have been multiple studies assessing the efficacy and safety of LAGH preparations. Literature already exists denoting the variety of formulations currently under development, and the search for longer acting GH preparations has given rise to many questions and important considerations when discussing these new agents (19, 20). As we consider the development of new LAGH preparations, it is important to recognize the following issues that currently remain unanswered:

i. Are there metabolic consequences of prolonged elevation of LAGH in circulation?
ii. Are side effects prolonged using LAGH preparations?
iii. Because LAGH preparations with large molecule sizes may impair their ability to penetrate all tissues, will their growth and metabolic effects differ from daily rhGH and other LAGH preparations?
iv. The pharmacodynamics and pharmacokinetics of different LAGH preparations result in serum IGF-1 profiles that differ from daily rhGH. In relation to different LAGH preparations, how and when should serum IGF-1 levels be measured to monitor for safety, and will their measurement be useful to guide titration of LAGH dosing?
v. Because new LAGH preparations are being investigated as noninferior to daily rhGH, will they be a cost-effective alternative therapy?
vi. Will LAGH receive regulatory approval if convenience is not accepted as an added value?
vii. Will LAGH (weekly or longer interval) truly improve compliance and efficacy compared with daily rhGH?
viii. Are the effects of LAGH preparations durable over the long term?
ix. Will the safety profile of LAGH preparations be different from daily rhGH?

Current literature was reviewed for gaps in knowledge. Expert opinion was used to suggest studies help address specific formulations safety and efficacy issues. We conducted electronic database searches of PubMed, MEDLINE, Cochrane Library, and EMBASE in July 2019 of studies published between January 2000 and June 2019; we also reviewed ongoing trials and gray literature. We did not restrict articles by publication type, language, or date, and we independently searched and reviewed references, including all bibliographic references from retrieved articles. We used the search terms "growth hormone," "long-acting growth hormone," "growth hormone deficiency," and "LAGH."

GH Preparation History: Physiology vs Efficacy

Since its introduction in the 1980s, subcutaneous rhGH treatment has been shown in studies that daily treatment is more effective and less inconvenient than previous three-times weekly intramuscular pituitary-derived GH dosing strategy; however, it mimics physiological spontaneous pulsatile GH secretion (21). Although animal models have shown pulsatile administration of GH resulted in better growth and greater IGF-I production, human studies have failed to show the importance of GH pulsatility on metabolism (22, 23). Continuous infusion studies of rhGH in AGHD patients failed to demonstrate clinically meaningful changes to metabolic changes compared with daily rhGH injections (24). To date, a perfect physiological GH replacement regimen has not been found and the debate on pharmacokinetic and pharmacodynamics of different GH preparations continues. There is also significant interindividual variability in the absorption and clearance of rhGH (25). It remains to be determined whether the lack of pulsatility of current and future rhGH preparations induces any long-term negative consequences.

Previous Attempts to Create LAGH Preparations

The first attempt at creating a LAGH formulation was a depot rhGH prepared in a gelatin solution (26). This formulation failed to achieve satisfactory systemic GH concentrations (26). Following this attempt, the next major advancement in LAGH preparation was Nutropin Depot, which was approved for treatment of GHD in 1999 (27–30). This preparation of unmodified rhGH adherent to biodegradable microspheres resulted

in a sustained release of rhGH over a 1-month period. Serum IGF-I levels rose over the first 14 to 17 days and the continued slow GH release extended over to almost 60 days (27–29). Biweekly Nutropin Depot dosing was shown to induce catch-up growth and normal skeletal maturation in CGHD. Adverse events relating to injection site, including nodules, erythema, and postinjection pain were notable (30). In children >30 kg, multiple injections were required to provide the desired dose of rhGH (30). Large-scale manufacturing issues limited continued production and eventually led to the discontinuation of its manufacture in 2004 (31, 32).

Mechanisms of Prolongation of GH Action (Table 1)

The methods for creating LAGH preparations can be classified into formulations that create a subcutaneous depot from which native or modified GH slowly diffuses into the vasculature, and formulations that allow rapid absorption from the subcutaneous delivery site but slow removal from the circulation. Development methods have included reversible complexes to stabilize rhGH, fabrication of sustained release preparations that use various matrices to hold rhGH, and structural modifications of rhGH. Half-life extending structural modifications may alter potency and change receptor-binding affinity. In theory, reduced potency combined with longer half-life should increase exposure and compensate, but this balance has been difficult to achieve.

Depot formulations/microspheres

Multiple LAGH preparations have been investigated using microspheres made with different compounds and zinc concentrations (33). Difficulty maintaining integrity and bioactivity have limited some attempts at microspheres but use of super-critical carbon dioxide or protein crystallization have been some of the more recent techniques studied (19). Attempts at other microsphere formulations have relied on zinc complex technology and often were associated with sustained release of GH over 14 days to 1 month in animal studies. The major issues continued to be limitations in loading the amount of rhGH within a microsphere, necessitating large volumes to provide appropriate dose delivery (28, 34, 35). Creating larger sized microspheres to contain more rhGH or using large-volume injections to deliver ideal concentrations increases adverse event risks. Other important issues include a higher initial burst release of GH, delayed release following an initial burst, risks of protein aggregation, GH denaturation in an acidic environment, and difficulty of standardized delivery with microspheres of larger sizes (36). How these characteristics affect the sustained duration of GH action, tissue localization and release of rhGH, and the utility and timing of measuring serum IGF-I levels as a biomarker of therapy is unknown. An example of LAGH currently in development using microsphere technology is Declage (Eutropin Plus, LB03002), in which native rhGH is incorporated into sodium hyaluronate microspheres suspended in medium chain triglycerides before injection. Release of native rhGH from the microspheres is regulated by tissue hyaluronidase at the injection sites. Pharmacokinetic studies have demonstrated the potential for once-weekly dosing of LB03002 in CGHD (37).

PEGylated formulations

Poly(ethylene glycol) (PEG) is a hydrophilic polymer with low immunogenicity that has been used to modify therapeutic proteins and peptides to increase solubility, lower toxicity, and prolong circulation half-life, but increases the molecular weight (38). Early PEGylated-GH hydrogels, formed by cross-linking PEG monomers, had an undesirable high initial burst of therapeutic effect (36). Modification of the PEG with fluorocarbon end groups resulted in better sustained-release forms (39). In preclinical testing, repeated-dose toxicity studies in cynomolgus monkey receiving PEG moieties >40 kDa for at least 6 weeks showed cellular vacuolation in choroid plexus epithelial cells and other tissues (40, 41) However, numerous commercially available PEGylated medications for treatment of other conditions have not demonstrated long-term neurological issues (42, 43). Multiple early versions of PEGylated-GH were found to cause injection site lipoatrophy thought to be related to the delayed absorption of the high-molecular-weight LAGH at the subcutaneous depot location (44). Repeated injections of daily rhGH in the same location are known to cause lipoatrophy. This adverse event subsequently led to discontinuation of the development of numerous PEGylated-GH products. Jintrolong is a PEGylated rhGH formulation permanently attached via its amino terminus to a 40-kDa branched hydrophilic PEG residue and has not demonstrated lipoatrophy (42, 45). Pharmacokinetic studies demonstrated the potential for once-weekly dosing in CGHD and AGHD (42, 45, 46).

Pro-drug formulations

The generation of LAGH by binding rhGH reversibly to a long-acting carrier to form a prodrug has been investigated as a means to release rhGH over a defined period of time. The only current LAGH product under development using this approach is TransCon-GH® (ACP-001).

Table 1. Summary of LAGH Product Development History

Company	Product	Modification to GH Molecule (Molecular Weight)	Frequency of Administration	Current Status	Research
Depot formulation		**Depot Chemical**			
Altus Pharmaceuticals	ALTU-238	Long extended-release formulation using protein crystallization technology (22 kDa) (19)	7 d	Bankrupt in 2009, stopped phase 2 study in CGHD, Althea acquired assets in 2010.	No recent studies
Critical Pharmaceuticals	CP016	Supercritical carbon dioxide, formed when carbon dioxide exceeds its thermodynamic critical point, used to create the depot (22 kDa) (19)	14 d	Company under liquidation	Evidence of ongoing studies at other corporations
Genentech in partnership with Alkermes	Nutropin Depot	Encapsulated in biocompatible, biodegradable, polylactide-coglycolide polymer microsphere (22 kDa) (27)	14 d	Removed from market (19)	
LG Life Sciences, Ltd	Declage (Eutropin Plus, LB03002)	Microparticles containing GH incorporated into sodium hyaluronate and dispersed in an oil base of medium-chain triglycerides (22 kDa)	7 d	Marketed in Korea for CGHD; approved in Europe but not marketed in the EU	Phase 3 trials in children suggest noninferiority (47)
PEGylated formulations		**PEGylation prolongs *in vivo* mean residence time of GH, through slowing absorption and protection from proteolysis**			
Ambrx	ARX201	30-kDa PEG added to unnatural amino acid incorporated into GH (52 kDa)	7 d	No longer being developed (19); PEGylated-containing vacuoles in the epithelial cells of the choroid plexus in monkeys (40, 41)	
Bolder BioTechnology	BBT-031	Site-specific PEGylated GH analog (not available)	7 d (planned)	Preclinical studies (48)	
GeneScience Pharmaceuticals Co, Ltd	Jintrolong	40-kDa PEG attached to GH (62 kDa)	7 d (42, 45)	Marketed in China for CGHD	Phase 3 studies show good IGF-I profile
Novo Nordisk	NNC126-0083	43-kDa PEG residue attached to glutamine 141 (65 kDa)	7 d	Unsatisfactory IGF-I profile peak and duration (49)	No longer being developed as of 2011
Pfizer	PHA-794428	Branched 40-kDa PEG on N-terminus of GH (62 kDa)	7 d	High rate of lipoatrophy at injection site (44)	No longer being developed as of 2009
Prodrug formulation		**Mechanism of conversion to active drug**			
Ascendis	TransCon GH (ACP-001)	Unmodified rhGH transiently bound to a PEG carrier molecule via a self-cleaving linker that is dependent upon pH and temperature (22 kDa)	7 d (50–52)	Phase 2 studies in CGHD and AGHD showed comparable IGF-I profile to daily GH dosing Phase 3 studies in CGHD showed preliminary positive growth response (53)	Phase 3 study in CGHD ongoing and phase 3 study in AGHD planned
Noncovalent albumin binding GH compound(s)		**Albumin binding**			
Novo Nordisk A/S	Somapacitan (NNC0195-0092)	Single-point mutation in GH, with albumin binding moiety attached (noncovalent albumin-binding properties) (54, 55) (23 kDa)	7 d (56)	Phase 2 studies in CGHD showed comparable IGF-I profile to daily GH dosing (57) Phase 3 studies in AGHD well tolerated (56)	Phase 3 studies in CGHD and extension study in AGHD ongoing

Table 1. Continued

Company	Product	Modification to GH Molecule (Molecular Weight)	Frequency of Administration	Current Status	Research
GH fusion proteins		**Protein fused with GH**			
Ahngook Pharmaceutical Co, Ltd	AG-B1512	Recombinant GH genetically fused to a polypeptide linker and an anti-human serum albumin Fab antibody (~72 kDa)	14 or 28 d (58)	Preclinical studies show IGF-I level elevation sustained for 20 d	Ongoing research
Alteogen	ALT-P1	rhGH fused with NexP, recombinant a1-antitrypsin (~74 kDa) (59)	Unknown	Phase 1 study completed (60)	Phase 2 study in AGHD ongoing
Asterion	ProFuse GH	GH binding protein (~82 kDa) (61)	1 mo (planned)	Preclinical studies to provide intravascular stores of inactive GH	
Genexine and Handok	GX-H9	rhGH fused to hybrid noncytolytic immunoglobulin Fc portions of IgD and IgG4 (100 kDa) (62)	7–14 d (63)	Phase 2 studies in AGHD completed (64) Phase 2 studies in CGHD showed reassuring height changes.	Phase 3 studies in CGHD with twice-monthly dosing ongoing
Hanmi Pharmaceutical Co	LAPS rhGH (HM10560A)	Homodimeric aglycosylated IgG4 Fc fragment (~51 kDa) (65)	7–14 d (65)	Phase 2 in AGHD show good tolerability	Phase 3 studies in AGHD (66)
JCR Pharmaceuticals	JR-142	Engineered rhGH fused at C-terminus with modified human serum albumin at N-terminus (~88 kDa) (67)	7 d	Preclinical trials	Phase 1 study completed (68)
OPKO Health and Pfizer	Somatrogon (MOD-4023)	rhGH fused to 3 copies of carboxyl-terminal peptide of hCG B-subunit (47.5 kDa)	7 d (69, 70)	Phase 2 studies in CGHD (71) Phase 3 studies in AGHD did not meet primary endpoint of truncal fat reduction (72)	Phase 3 study in CGHD (73)
Teva	Albutropin (TV-1106)	Human serum albumin fused to N-terminus of GH (88 kDa)	7 d (74, 75)	Studies in AGHD discontinued for unknown reason; presumed unfavorable benefit:risk profile	
Versartis	Somavaratan (VRS-317)	XTEN sequence: naturally occurring hydrophilic amino acids (119 kDa) (76)	7–30 d (77, 78)	Pediatric phase 3 trial (VELOCITY) missed noninferiority target (79) Adult trials discontinued	Discontinued all studies

Abbreviations: AGHD, GH deficiency in adults; CGHD, GH deficiency in children; PEG, poly(ethylene glycol); rhGH, recombinant human GH.

TransCon-GH® links an unmodified 22 kDa rhGH molecule covalently to a PEG carrier via a hydrolysable linker. The characteristics of the hydrolyzable TransCon linker determine the pH, temperature, and timeframe over which the unmodified rhGH is released. Pharmacokinetic studies have demonstrated the potential for weekly dosing of TransCon-GH in CGHD (50–53, 80).

Modified rhGH with increased albumin binding

One method of prolonging the half-life of a medication is to increase its affinity for common serum proteins such as albumin. Somapacitan (NNC0195-0092) is a reversible albumin-binding GH derivative in which a fatty acid with noncovalent albumin-binding properties has been conjugated by alkylation to GH with a single amino acid change resulting in a 23-kDa molecule (54, 55). The protein modification of somapacitan to promote albumin binding, adding a fatty acid linker, has been successfully used in other commercially available products to prolong half-life: insulin detemir (C14 myristic acid linked by native lysine), insulin degludec (C16 palmitic acid linked via glutamic acid to native lysine), liraglutide (C16 palmitic acid linked by added glutamate to native lysine), and semaglutide (C18 stearic acid linked to native lysine with a hydrophilic spacer) (81–85). Pharmacokinetic studies have demonstrated

the potential for weekly dosing of Somapacitan in CGHD and AGHD (56).

Fusion proteins

GH structure and size is tightly conserved across various animal species, with molecular weight ranging from 19.4 kDa to 22 kDa. This conservation of size may represent an evolutionary control to allow GH to transit less well-vascularized tissues (fat, bone and growth plates) and well-vascularized tissues (muscle, heart). Studies with labeled dextrans show a 40-kDa molecular weight cutoff for diffusion into the growth plate of mice, but other studies suggest that protein's cartilage penetration molecular weight limit may actually be between 240 to 440 kDa (86, 87). Fusion proteins prolong half-life and reduce clearance of rhGH but may dramatically increase molecular weight, which may affect tissue penetrance. GH fusion proteins have been developed with albumin (Albutropin [TV-1106] (74, 75), JR-142 (67, 68, 88)), custom immunoglobulin fragments (AG-B1512 (58), GX-H9 (62, 89), LAPSrhGH [HM10560A] (65, 66)), the extracellular GH binding protein segment of the GH receptor (ProFuse GH binding protein (61)), the C-terminal peptide of human chorionic gonadotropin (Somatrogon [MOD-4023] (69–72)), an engineered form of alpha-1 anti-trypsin (ALT-P1 [CJ-40002] (59, 60)), and nonsense amino acid sequences (Somavaratan [VRS317] (76–78)). Fusion proteins consisting of IGF-I attached to an antibody fragment of 58 kDa with high affinity for the cartilage-specific protein matrilin-3 has been shown to promote linear bone growth in mice (90). Theoretically, GH analogs >40 kDa may be capable of generating hepatic IGF-I, but not able to activate lipolysis in adipose tissue or promote the entry of resting chondrocytes into the proliferative zone of the growth plate. Thus, large GH fusion proteins may generate a response that is more characteristic of IGF-I therapy with suboptimal growth and increased fat mass/body mass index (91). However, the ability of LAGH to reach different target tissues may depend upon characteristics other than molecular size, including the charge of the molecule (87).

Potential Safety Issues Unique to LAGH Preparations

The safety of rhGH therapy has been the topic of intense study with extensive postmarketing registries as well as long-term follow-up studies. The safety of rhGH during treatment of children with multiple different conditions has been well-documented, with intracranial hypertension and slipped capitofemoral epiphysis being rare but serious complications of therapy (92–99). In adults, the majority of the side effects of short-term rhGH replacement therapy are related to the sodium and water retention properties or reduction in insulin sensitivity (100–103). Long-term safety after rhGH treatment during childhood and during treatment of AGHD remains an area of continued investigation. Recently, concerns arose regarding an increased risk of cerebrovascular disease years after rhGH therapy, but were only observed in 1 of 8 European countries studied (104–107). Additionally, risks of cerebrovascular disease have been shown to be increased in individuals with short stature, and abrogated when data are adjusted for low birth weight (108).

We expect LAGH to share all of the known and unknown risks of daily rhGH. However, there may be additional safety risks that depend upon the mechanism by which GH action is prolonged. Aspects that may lead to new safety concerns include the formation of neutralizing antidrug antibodies and growth and metabolic effects related to the profile of serum GH and IGF-I levels during therapy.

In those drugs where the GH molecule has been modified, there may be a risk of developing anti-GH antibodies. Anti-GH antibodies formed against rhGH given as a daily injection have not been shown to be clinically relevant, except in the case of individuals with GH gene deletions (109, 110). If neutralizing antibodies develop against a modified GH molecule, it is possible that the individual would no longer be able to respond to unmodified rhGH. Because the methods of measurement of antidrug antibodies vary, it is important to determine clinical impact to determine relevance. In addition, it will be necessary to have antidrug antibody assays for each LAGH available to clinicians. The likelihood of developing antidrug antibodies may be increased if an individual receives more than 1 LAGH product.

The potential negative impact of high levels of GH shortly after an injection of LAGH will depend upon the bioavailability of the GH in each preparation. The lack of the natural pulsatile secretion pattern or the daily nocturnal peak associated with daily rhGH injections at bedtime may have metabolic consequences because GH is involved in regulating fat metabolism and body composition (19, 111, 112). As previously mentioned, large GH fusion proteins may have different metabolic side effects if the size of the molecule prevents access of the modified GH to key target

tissues. Some infants with congenital GHD develop hypoglycemia prevented by daily rhGH therapy. The low trough levels of GH that are expected at the end of the interval for LAGH injections may be insufficient to prevent hypoglycemia and may not be safe to use in this population.

The profile of the IGF-I response to each LAGH may also have unique safety concerns. Because of epidemiological studies showing associations of high normal IGF-I levels with an increased risk of multiple forms of cancer, IGF-I levels achieved during rhGH therapy have been a subject of close scrutiny (113). A specific level of IGF-I has not been identified above which there is documented increase in the risk of any known side effect of rhGH (114). With daily rhGH, stable IGF-I levels are achieved within days to weeks of starting on a new dose (115). Depending upon the bioavailability of the LAGH preparation and the dose given, the peak IGF-I levels with LAGH may need to be relatively higher to achieve clinical efficacy. The negative effects of transient elevations of serum IGF-I levels remain to be determined. The pharmacokinetic and pharmacodynamic profiles of each LAGH preparation will be required to gauge the optimal timing of serum IGF-I measurement for both safety and efficacy. When blood is drawn at any random time point in between injections, mathematical formulae may be used to estimate serum IGF-I peaks, trough, average, and area under the curve following LAGH administration to guide dose adjustments and interpretation of safety data.

Because clinical trials of LAGH preparations will be short term, it will be important to monitor clinically for long-term side effects including subtle signs of iatrogenic acromegaly. Notably, long-term safety and postmarketing surveillance registries will be crucial to assess for efficacy, safety, tolerability, cost-effectiveness, and to improve our understanding of the effects of prolonged exposure to these new classes of molecules. Because each new LAGH preparation will be unique in terms of its formulation, studies will need to be performed for each individual molecule. It would be preferable to have a combined registry of all LAGH molecules in an independent data repository supported by manufacturers of LAGH preparations. This would allow companies to fulfill obligatory safety reporting requirements while increasing the power of studies through combining the populations of patients receiving LAGH. Additionally, a global registry will be essential in capturing the effect of patients being switched from daily rhGH to LAGH preparations and from 1 LAGH preparation to another.

Economic Issues for LAGH Preparations

When new LAGH products become commercially available, their use in clinical practice will be determined by availability through insurance programs. In countries with a single payer, LAGH products will be assessed not only for safety and efficacy, but also for cost-effectiveness. It is unlikely that insurance carriers and government insurance programs will pay a premium for the "convenience" of a LAGH product that uses doses less frequent than daily injections. If a LAGH product is demonstrated to be clinically and statistically superior to daily rhGH, this could have regulatory and marketing advantages and could increase the likelihood of the medication being available. The price of the remaining available daily rhGH products may also affect access to LAGH. If manufacturers of daily rhGH cut their price, it may prevent or decrease the access of LAGH products. Once a LAGH product is approved, it is plausible that individuals could receive this therapy off-label in circumstances of noncompliance or other clinical scenarios.

Status of Current LAGH Products in Development (Tables 1 and 2)

Declage (Eutropin Plus) is the only depot/microsphere LAGH formulation under active clinical development. Phase 3 studies of Declage in CGHD demonstrated noninferiority compared with daily rhGH treatment with no significant differences in height velocity (HV), height SD score (SDS), or serum IGF-I levels. A 26-week phase 2 study in children with idiopathic short stature demonstrated noninferiority of Declage compared with daily rhGH, with an annualized HV of 11.1 cm/y on daily rhGH therapy (0.37 mg/kg/wk) compared with 10.2 cm/y on once-weekly therapy of Declage (0.7 mg/kg/wk) (116). Declage is currently commercially available in South Korea and has been approved by the European Medicines Agency but has yet to be marketed there (41, 47, 117).

Jintrolong is the only irreversibly PEGylated LAGH formulation under active clinical development. In clinical trials in children, administration of Jintrolong led to very high levels of serum GH with low bioavailability and minimal dose response. Phase 3 studies of Jintrolong in children showed good HV and higher serum IGF-I levels compared with daily rhGH therapy (42). Jintrolong is now approved and marketed in China for treatment of CGHD.

TransCon GH, the reversible PEGylation of rhGH that leads to release of unmodified rhGH, recently

Table 2. Summary of Growth Responses in LAGH Clinical Trials in Children with GHD

Drug	Dose (LAGH vs Daily rhGH)	Phase of Study	Annual Height Velocity on LAGH (cm/y)	Annual Height Velocity on daily rhGH (cm/y)
Declage (Eutropin Plus, LB03002)	0.5 mg/kg/wk vs 0.21 mg/kg/wk	Phase 3: 12-mo study + 12-mo uncontrolled extension (117)	Year 1: 11.63 ± 2.60 Year 2: 8.33 ± 1.92	Year 1: 11.97 ± 3.09 Year 2 (switched to LB3002): 7.28 ± 2.34
Jintrolong	0.2 mg/kg/wk vs 0.25 mg/kg/wk	Phase 3: 25-wk study (42)	13.41 ± 3.72	12.55 ± 2.99
TransCon GH (ACP-001)	0.24 mg/kg/wk vs 0.24 mg/kg/wk	Phase 3: 52-wk study (118)	11.2 ± 0.23	10.3 ± 0.30
Somapacitan (NNC0195-0092)	0.04 mg/kg/wk vs 0.08 mg/kg/wk vs 0.16 mg/kg/wk vs 0.24 mg/kg/wk of rhGH	Phase 2: 6-mo study (57)	0.04 mg/kg/wk: 8.0 ± 2.0 0.08 mg/kg/wk: 10.9 ± 1.9 0.16 mg/kg/wk: 12.9 ± 3.5	11.4 ± 3.3
GX-H9	0.8 mg/kg/wk vs 1.2 mg/kg/wk vs 2.4 mg/kg/wk vs 0.21 mg/kg/wk of rhGH	Phase 2: 6-mo results (119)	0.8 mg/kg/wk: 11.50 1.2 mg/kg/wk: 11.54 2.4 mg/kg/wk: 11.86	11.24
Somatrogon (MOD-4023)	0.25 mg/kg/wk vs 0.48 mg/kg/wk vs 0.66 mg/kg/wk vs 0.24 mg/kg/wk of rhGH	Phase 2: 12-mo study (71) Phase 3 study in children using weekly dosing of 0.66 mg/kg/wk (73)	0.25 mg/kg/wk: 10.4 ± 2.6 0.48 mg/kg/wk: 11.0 ± 2.3 0.66 mg/kg/wk: 11.9 ± 3.5	12.5 ± 2.1
Somavaratan (VRS-317)	XTEN sequence: naturally occurring hydrophilic amino acids	Phase 3 trial discontinued (79)	9.44	10.70

Abbreviations: GHD, GH deficiency; LAGH, long-acting GH; rhGH, recombinant human GH.

completed phase 3 testing in CGHD. In a 52-week trial in CGHD, TransCon GH given weekly was shown to have superior HV compared with daily rhGH therapy. No new safety concerns were identified and no neutralizing antidrug antibodies were reported (118).

Somapacitan, a modified GH with increased albumin binding, has been shown to reduce truncal fat percentage and body composition compared with daily rhGH treatment in AGHD with benefits maintained in extension trials (120, 121). These data may soon lead to registration of somapacitan for treatment of AGHD. If approved for AGHD, it is plausible that children could receive this therapy off-label before other products being available. Phase 2 studies in CGHD showed comparable serum IGF-I levels to daily rhGH therapy with annualized HV from the highest dose of somapacitan superior to daily rhGH treatment (57). Phase 3 studies in CGHD and phase 2 studies in children with growth failure resulting from small for gestational age are in progress (122, 123).

In its phase 3 study in CGHD, GX-H9, a fusion of rhGH with a custom immunoglobulin linker, tested 2 doses given twice-monthly with interim HV data showing mild superiority to daily rhGH therapy (63). In phase 2 studies in CGHD, high-dose GX-H9 was associated with larger HV changes compared with daily rhGH; GX-H9 had a smaller decrease in body mass index compared with daily rhGH (119, 124).

Phase 3 trials of somatrogon, a fusion of rhGH with the C-terminal peptide of human chorionic gonadotropin, given weekly in AGHD failed to meet the primary endpoint of reduced truncal fat (72). Slow escalation of somatrogon dose and significant weight loss in a subject in the daily rhGH arm may have contributed to the missed endpoint. Phase 2 studies of somatrogon given weekly in CGHD showed good HV compared with daily rhGH therapy (71). Phase 3 trials of somatrogon in CGHD are under way (73).

Somavaratan, a fusion of GH with nonsense XTEN sequences, given twice-monthly showed good HV compared with historical controls in phases 1b and 2 and extension trials in CGHD. However, somavaratan failed to meet noninferiority compared with daily rhGH in phase 3 testing in CGHD (79). It was speculated that some subjects might have developed neutralizing antibodies that impaired their growth. Another speculation is that somavaratan may have been effective in inducing metabolic changes in AGHD, but these data were never

published. The Investigational New Drug application was withdrawn and final data for the phase 3 trials in CGHD and AGHD were not made available to investigators or regulatory agencies. This is an example in which important information about the efficacy and safety of a new molecule was not published because of commercial interests, and emphasizes the importance for publication of all clinical trial data including negative results.

The theoretical issue related to the size of the various LAGH formulations molecular size and the potential exclusion of larger molecules from the target tissue leading to a robust IGF-I–centric response with poor growth results is often debated (91). Noninferiority HV changes and overall growth responses would argue that a molecule is getting to the growth plate. LAGH molecular structures are important to consider for size of GH, but also binding to various proteins and the effects on binding avidity. TransCon GH delivers native GH, which may account for the growth effects noted in its studies. Somapacitan has a ~1.4-kDa linker that allows reversible binding to albumin. It is unclear if the avidity of this binding allows release to the target tissues, but the clinical responses would suggest that it does. It is notable that only 2 LAGH products have gained approval by the US Food and Drug Administration or European Medicines Agency (ie, Nutropin Depot and LB03002), and both release unmodified rhGH (125). Although arguments have been made that unmodified GH achieves better tissue distribution, the modified rhGH formulations are newer and studies are ongoing.

Although the field of LAGH preparations is in its infancy, a meta-analysis of 7 studies of LAGH in children was recently performed (126), and concluded that there was no significant difference in the efficacy or adverse events with LAGH compared with daily rhGH. However, IGF-I SDS values were significantly elevated in LAGH-treated CGHD compared with daily rhGH. However, this is due to the intentional timing of the blood draws during the studies to obtain peak IGF-I values for pharmacodynamic purposes and does not reflect the average IGF-I SDS during LAGH therapy.

Summary

RhGH is currently approved for daily use and has been shown to restore longitudinal growth and improve body composition and quality of life in CGHD and AGHD, respectively, with relatively few side effects. However, daily injections are inconvenient and can be painful and distressing for some patients, resulting in decreased adherence and efficacy. LAGH preparations represent an advancement over daily rhGH injections because of the need for fewer injections and may offer improved increased acceptance, tolerability, and therapeutic flexibility to children and adult patients.

Multiple LAGH preparations are currently at various stages of development, allowing for decreased rhGH injection frequency from daily to weekly or monthly. Attributes of the LAGH preparations, including molecular weight and ionic charge, may affect the access of LAGH to the target tissues resulting in differences in efficacy and safety. Following administration of LAGH, the serum peak and trough GH and IGF-I levels may vary depending upon the mechanism used to prolong GH action. The relationship of transient elevations of GH and IGF-I to efficacy and safety remain to be elucidated. Randomized, controlled trials of some LAGH preparations have reported noninferiority compared with daily rhGH for improved growth velocity and body composition in CGHD and AGHD, respectively, with no new LAGH-related adverse events being reported during short-term therapy.

For LAGH preparations to replace daily rhGH in the treatment of patients with GHD, a number of practical questions need to be addressed, including methods of dose adjustment, timing of monitoring of IGF-I, safety, efficacy, and cost-effectiveness. Long-term surveillance of efficacy and safety of LAGH preparations will be needed to answer these important clinical questions.

Acknowledgments

Financial Support: Dr. Velazquez is a pediatric endocrinology fellow supported by a National Institutes of Health T32 Pre-faculty Research Training in Pediatric Endocrinology T32 DK065519-15

Additional Information

***Correspondence and Reprint Requests*:** Bradley S. Miller, MD, PhD, 8952D, MB671 East Bldg, Division of Endocrinology, Department of Pediatrics, University of Minnesota, 2450 Riverside Avenue, Minneapolis, MN 55454. E-mail: mille685@umn.edu.

Disclosure Summary: Dr. Miller is a consultant for Abbvie, Ferring, Genentech, Novo Nordisk, Pfizer, Sandoz, and Versartis and has received research support from Alexion, Ascendis, Endo Pharmaceuticals, Genentech, Novo Nordisk, Sandoz, Shire, Tolmar, Ultragenyx, and Versartis. Dr. Yuen has received research grant support from Pfizer, Novo Nordisk, Eli Lilly, OPKO Biologics, Teva, Versartis, and Aeterna Zentaris, and has served on the advisory boards for Pfizer, Novo Nordisk, Sandoz, Versartis, Aeterna Zentaris, and Strongbridge. Dr. Velazquez has nothing to disclose.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References and Notes

1. Savage MO, Bang P. The variability of responses to growth hormone therapy in children with short stature. *Indian J Endocrinol Metab*. 2012;**16**(Suppl 2):S178–S184.
2. Acerini CL, Wac K, Bang P, Lehwalder D. Optimizing patient management and adherence for children receiving growth hormone. *Front Endocrinol (Lausanne)*. 2017;**8**:313.
3. Miller BS, Rotenstein D, Deeb LC, Germak J, Wisniewski T. Persistence with growth hormone therapy in pediatric patients. *Am J Pharm Benefits*. 2014;**6**(1):e9–e17.
4. Kremidas D, Wisniewski T, Divino VM, et al. Administration burden associated with recombinant human growth hormone treatment: perspectives of patients and caregivers. *J Pediatr Nurs*. 2013;**28**(1):55–63.
5. Holdaway IM, Hunt P, Manning P, et al. Three-year experience with access to nationally funded growth hormone (GH) replacement for GH-deficient adults. *Clin Endocrinol (Oxf)*. 2015;**83**(1):85–90.
6. Rose SR, Cook DM, Fine MJ. Growth hormone therapy guidelines: clinical and managed care perspectives. *Am J Pharm Benefits*. 2014;**6**(5):e134–e146.
7. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;**353**(5):487–497.
8. Cutfield WS, Derraik JG, Gunn AJ, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. *Plos One*. 2011;**6**(1):e16223.
9. Haverkamp F, Johansson L, Dumas H, et al. Observations of nonadherence to recombinant human growth hormone therapy in clinical practice. *Clin Ther*. 2008;**30**(2):307–316.
10. van Dommelen P, Koledova E, Wit JM. Effect of adherence to growth hormone treatment on 0-2 year catch-up growth in children with growth hormone deficiency. *Plos One*. 2018;**13**(10):e0206009.
11. Farfel A, Shalitin S, Morag N, Meyerovitch J. Long-term adherence to growth hormone therapy in a large health maintenance organization cohort. *Growth Horm IGF Res*. 2019;**44**:1–5.
12. Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract*. 2008;**14**(2):143–154.
13. Auer MK, Stieg MR, Hoffmann J, Stalla GK. Is insulin-like growth factor-I a good marker for treatment adherence in growth hormone deficiency in adulthood? *Clin Endocrinol (Oxf)*. 2016;**84**(6):862–869.
14. Mancini A, Vergani E, Bruno C, Palladino A, Brunetti A. Relevance of adherence monitoring in adult patients with growth hormone deficiency under replacement therapy: preliminary monocentric data with EasypodTM connect. *Front Endocrinol (Lausanne)*. 2019;**10**:416.
15. Graham S, Weinman J, Auyeung V. Identifying potentially modifiable factors associated with treatment non-adherence in paediatric growth hormone deficiency: a systematic review. *Horm Res Paediatr*. 2018;**90**(4):221–227.
16. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML; Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;**96**(6):1587–1609.
17. Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. *J Clin Endocrinol Metab*. 2006;**91**(6):2047–2054.
18. Ross JL, Lee PA, Gut R, Germak J. Attaining genetic height potential: analysis of height outcomes from the ANSWER Program in children treated with growth hormone over 5 years. *Growth Horm IGF Res*. 2015;**25**(6):286–293.
19. Christiansen JS, Backeljauw PF, Bidlingmaier M, et al. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. *Eur J Endocrinol*. 2016;**174**(6):C1–C8.
20. Høybye C, Cohen P, Hoffman AR, Ross R, Biller BM, Christiansen JS. Growth Hormone Research Society. Status of long-acting-growth hormone preparations–2015. *Growth Horm IGF Res*. 2015;**25**(5):201–206.
21. Kastrup KW, Christiansen JS, Andersen JK, Orskov H. Increased growth rate following transfer to daily sc administration from three weekly im injections of hGH in growth hormone deficient children. *Acta Endocrinol (Copenh)*. 1983;**104**(2):148–152. http://www.ncbi.nlm.nih.gov/pubmed/6637329. Accessed December 18, 2018.
22. Jaffe CA, Turgeon DK, Lown K, Demott-Friberg R, Watkins PB. Growth hormone secretion pattern is an independent regulator of growth hormone actions in humans. *Am J Physiol Endocrinol Metab*. 2002;**283**(5):E1008–E1015.
23. Ribeiro-Oliveira A, Barkan AL. Growth hormone pulsatility and its impact on growth and metabolism in humans. In: Ho K, ed. *Growth Hormone Related Diseases and Therapy*. Humana Press; 2011:33–56. doi:10.1007/978-1-60761-317-6_3
24. Laursen T, Gravholt CH, Heickendorff L, et al. Long-term effects of continuous subcutaneous infusion versus daily subcutaneous injections of growth hormone (GH) on the insulin-like growth factor system, insulin sensitivity, body composition, and bone and lipoprotein metabolism in GH-deficient adults. *J Clin Endocrinol Metab*. 2001;**86**(3):1222–1228.
25. Lundberg E, Andersson B, Kriström B, Rosberg S, Albertsson-Wikland K. Broad variability in pharmacokinetics of GH following rhGH injections in children. *Growth Horm IGF Res*. 2018;**40**:61–68.
26. Lippe B, Frasier SD, Kaplan SA. Use of growth hormone-gel. *Arch Dis Child*. 1979;**54**(8):609–613. http://www.ncbi.nlm.nih.gov/pubmed/507915. Accessed April 8, 2019.
27. Johnson OL, Cleland JL, Lee HJ, et al. A month-long effect from a single injection of microencapsulated human growth hormone. *Nat Med*. 1996;**2**(7):795–799. http://www.ncbi.nlm.nih.gov/pubmed/8673926. Accessed April 8, 2019.
28. Johnson OL, Jaworowicz W, Cleland JL, et al. The stabilization and encapsulation of human growth hormone into biodegradable microspheres. *Pharm Res*. 1997;**14**(6):730–735. http://www.ncbi.nlm.nih.gov/pubmed/9210189. Accessed April 8, 2019.
29. Kemp SF, Fielder PJ, Attie KM, et al. Pharmacokinetic and pharmacodynamic characteristics of a long-acting growth hormone (GH) preparation (nutropin depot) in GH-deficient children. *J Clin Endocrinol Metab*. 2004;**89**(7):3234–3240.
30. Silverman BL, Blethen SL, Reiter EO, Attie KM, Neuwirth RB, Ford KM. A long-acting human growth hormone (Nutropin Depot): efficacy and safety following two years of treatment in children with growth hormone deficiency. *J Pediatr Endocrinol Metab*. 2002;**15** Suppl 2:715–722.
31. Herbert P, Murphy K, Johnson O, et al. A large-scale process to produce microencapsulated proteins. *Pharm Res*. 1998;**15**(2):357–361.
32. Tracy MA. Development and scale-up of a microsphere protein delivery system. *Biotechnol Prog*. 1998;**14**(1):108–115.
33. Wei Y, Wang Y, Kang A, et al. A novel sustained-release formulation of recombinant human growth hormone and its pharmacokinetic, pharmacodynamic and safety profiles. *Mol Pharm*. 2012;**9**(7):2039–2048.
34. Kim HK, Chung HJ, Park TG. Biodegradable polymeric microspheres with "open/closed" pores for sustained release of human growth hormone. *J Control Release*. 2006;**112**(2):167–174.

35. Kwak HH, Shim WS, Choi MK, et al. Development of a sustained-release recombinant human growth hormone formulation. *J Control Release*. 2009;**137**(2):160–165.
36. Cai Y, Xu M, Yuan W, Liu Z, Yuan M. Developments in human growth hormone preparations: sustained-release, prolonged half-life, novel injection devices, and alternative delivery routes. *Int J Nanomedicine*. 2014;**9**:3527.
37. Peter F, Savoy C, Ji HJ, Juhasz M, Bidlingmaier M, Saenger P. Pharmacokinetic and pharmacodynamic profile of a new sustained-release GH formulation, LB03002, in children with GH deficiency. *Eur J Endocrinol*. 2009;**160**(3):349–355.
38. Davis FF. The origin of pegnology. *Adv Drug Deliv Rev*. 2002;**54**(4):457–458.
39. Tae G, Kornfield JA, Hubbell JA. Sustained release of human growth hormone from in situ forming hydrogels using self-assembly of fluoroalkyl-ended poly(ethylene glycol). *Biomaterials*. 2005;**26**(25):5259–5266.
40. Sprogøe K, Mortensen E, Karpf DB, Leff JA. The rationale and design of TransCon growth hormone for the treatment of growth hormone deficiency. *Endocr Connect*. 2017;**6**(8):R171–R181.
41. Eurpoean Medicines Agency. *CHMP Safety Working Party's Response to the PDCO Regarding the Use of PEGylated Drug Products in the Paediatric Population*.; 2012. www.ema.europa.eu. Accessed April 8, 2019.
42. Luo X, Hou L, Liang L, et al. Long-acting PEGylated recombinant human growth hormone (Jintrolong) for children with growth hormone deficiency: phase II and phase III multicenter, randomized studies. *Eur J Endocrinol*. 2017;**177**(2):195–205.
43. Pasut G, Veronese FM. State of the art in PEGylation: the great versatility achieved after forty years of research. *J Controlled Release*. 2012;**161**(2):461–472.
44. Touraine P, D'Souza GA, Kourides I, et al. GH Lipoatrophy Study Group. Lipoatrophy in GH deficient patients treated with a long-acting pegylated GH. *Eur J Endocrinol*. 2009;**161**(4):533–540.
45. Hou L, Chen ZH, Liu D, Cheng YG, Luo XP. Comparative pharmacokinetics and pharmacodynamics of a PEGylated recombinant human growth hormone and daily recombinant human growth hormone in growth hormone-deficient children. *Drug Des Devel Ther*. 2015;**10**:13.
46. Guan Y, He F, Wu J, et al. A long-acting pegylated recombinant human growth hormone (Jintrolong®) in healthy adult subjects: Two single-dose trials evaluating safety, tolerability and pharmacokinetics. *J Clin Pharm Ther*. 2018;**43**(5):640–646.
47. Péter F, Bidlingmaier M, Savoy C, Ji HJ, Saenger PH. Three-year efficacy and safety of LB03002, a once-weekly sustained-release growth hormone (GH) preparation, in prepubertal children with GH deficiency (GHD). *J Clin Endocrinol Metab*. 2012;**97**(2):400–407.
48. Cox G. Long-acting Growth Hormone for Treating HIV-Associated Adipose Redistribution Syn | SBIR.gov. Department of Health and Human Services. https://www.sbir.gov/sbirsearch/detail/112649. Published 2008. Accessed April 8, 2019.
49. de Schepper J, Rasmussen MH, Gucev Z, Eliakim A, Battelino T. Long-acting pegylated human GH in children with GH deficiency: a single-dose, dose-escalation trial investigating safety, tolerability, pharmacokinetics and pharmacodynamics. *Eur J Endocrinol*. 2011;**165**(3):401–409.
50. Chatelain P, Malievskiy O, Radziuk K, et al. TransCon GH Working Group. A randomized phase 2 study of long-acting TransCon GH vs daily GH in childhood GH deficiency. *J Clin Endocrinol Metab*. 2017;**102**(5):1673–1682.
51. Beckert M, Gilfoyle D, Pihl S, Chatelain P. Pediatric phase 2 data demonstrate that TransCon hGH has an anti-hGH immunogenic profile that is comparable to daily hGH. *Growth Horm IGF Res*. 2016;30-31:S41. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01416912/full. Accessed April 8, 2019.
52. Sprogoe K, Beckert M, Christofferson ED, Gilfoyle D, Wegge T. Pharmacokinetic model guided design of transcon growth hormone, to ensure unmodified growth hormone levels comparable to daily growth hormone. In: *Endocrine Society's 98th Annual Meeting and Expo*. Boston, MA; 2016. https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=27656. Accessed April 8, 2019.
53. Beckert M, Brian Karpf D, Mortensen E, Mardell J, Christoffersen ED, Leff JA. Design and rationale for the height trial, a phase 3 transcon GH study in children with growth hormone deficiency. In: *Endocrine Reviews. Conference: 99th Annual Meeting of the Endocrine Society, ENDO 2017. United States*. Vol 38. Orlando, FL; 2017. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01399931/full. Accessed April 8, 2019.
54. Thygesen P, Konradsen G, Schjødt CB, Nielsen PF. Somapacitan (NNC0195-0092) a novel long acting human GH derivative binds tightly, but reversibly to albumin in plasma. In: *Endocrine Society's 98th Annual Meeting and Expo*. Boston, MA; 2016:Poster SAT-034. https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=27415&ID=27415. Accessed April 8, 2019.
55. Thygesen P, Andersen HS, Behrens C, et al. Nonclinical pharmacokinetic and pharmacodynamic characterisation of somapacitan: A reversible non-covalent albumin-binding growth hormone. *Growth Horm IGF Res*. 2017;**35**:8–16.
56. Juul RV, Rasmussen MH, Agersø H, Overgaard RV. Pharmacokinetics and pharmacodynamics of once-weekly somapacitan in children and adults: supporting dosing rationales with a model-based analysis of three phase I trials. *Clin Pharmacokinet*. 2019;**58**(1):63–75.
57. Savendal L, Rasmussen M, Horikawa R, Khadilkar V, Battelino T, Saenger P. Efficacy and safety of once-weekly somapacitan in childhood growth hormone deficiency: results of a randomised open-label, controlled phase 2 trial. *Horm Res Paediatr*. 2018;**82**(Supplement 1). http://abstracts.eurospe.org/hrp/0089/hrp0089fc10.2.htm. Accessed July 8, 2019.
58. Kim Y, Jang JS, Hur B, et al. Preclinical Pharmacokinetic and Pharmacodynamic Studies of a Novel, Long Acting Growth Hormone (AG-B1512). In: *Endocrine Society's 99th Annual Meeting and Expo*. Orlando, FL; 2017:LB MON 56. https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=32939. Accessed April 8, 2019.
59. Lee SM, Cho J-S, Chung H-S, Park MS, Park SJ. Human phase 1 clinical data of ALT-P1 (hGH-NexP) by healthy Korean males. *Horm Res Paediatr*. 2016;**82**(Supplement 1). http://abstracts.eurospe.org/hrp/0086/hrp0086P1-P598. Accessed July 8, 2019.
60. Alteogen Inc - ALT-P1. http://alteogen.cafe24.com/en/alt-p1/. Accessed April 8, 2019.
61. Wilkinson IR, Ferrandis E, Artymiuk PJ, et al. A ligand-receptor fusion of growth hormone forms a dimer and is a potent long-acting agonist. *Nat Med*. 2007;**13**(9):1108–1113.
62. Kim ES, Jang DS, Yang SY, et al. Controlled release of human growth hormone fused with a human hybrid Fc fragment through a nanoporous polymer membrane. *Nanoscale*. 2013;**5**(10):4262–4269.
63. Lee, H, Kim T, Lee J, et al. A pharmacokinetic-pharmacodynamic analysis of GX-H9, a long-acting hybrid Fc-fused recombinant human growth hormone (rhGH). In Children With GH Deficiency. In: *Endocrine Society's 100th Annual Meeting and Expo*. Chicago, IL; 2018:SUN-218. https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=46936. Accessed April 8, 2019.
64. Ku CR, Brue T, Schilbach K, et al. Long-acting FC-fusion rhGH (GX-H9) shows potential for up to twice-monthly administration in GH-deficient adults. *Eur J Endocrinol*. 2018;**179**(3):169–179.
65. Kang J, Kim P, Kwak EH, et al. A novel long acting growth hormone (HM10560A) demonstrated good tolerability and weekly potential in healthy male subjects after single administration. In: *Endocrine Society's 97th Annual Meeting and Expo*. San Diego, CA; 2015:FRI-444. https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=20113. Accessed April 8, 2019.

66. Kang J, Kim P, Kwak EH, et al. 6 month results of a phase II, randomized, active controlled, open label study of safety and efficacy of HM10560A a long acting r-Hgh-HMC001 conjugate in adult patients with growth hormone deficiency (AGHD). *Endocr Rev.* 2015;**36**(2). https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=19640. Accessed April 8, 2019.
67. JCR Pharmaceuticals Co. JCR Pharmaceuticals Development Pipeline PDF. http://www.jcrpharm.co.jp/en/site/en/biopharmaceutical/pdf/pipeline_190621.pdf. Published 2019. Accessed July 8, 2019.
68. JCR Announces Completion of Phase 1 Clinical Trial Notification of JR-142, A long-acting growth hormone. http://www.jcrpharm.co.jp/en/site/en/ir/en_news/jcr-announces-completion-of-phase-1-clinical-trial-notification-of-jr-142-a-long-acting-growth-hormone. Accessed April 8, 2019.
69. Fisher DM, Rosenfeld RG, Jaron-Mendelson M, Amitzi L, Koren R, Hart G. Pharmacokinetic and pharmacodynamic modeling of MOD-4023, a long-acting human growth hormone, in growth hormone deficiency children. *Horm Res Paediatr.* 2017;**87**(5):324–332.
70. Kramer WG, Jaron-Mendelson M, Koren R, Hershkovitz O, Hart G. Pharmacokinetics, pharmacodynamics, and safety of a long-acting human growth hormone (MOD-4023) in healthy Japanese and Caucasian adults. *Clin Pharmacol Drug Dev.* 2018;**7**(5):554–563.
71. Zelinska N, Iotova V, Skorodok J, et al. Long-acting C-terminal peptide-modified hGH (MOD-4023): results of a safety and dose-finding study in GHD children. *J Clin Endocrinol Metab.* 2017;**102**(5):1578–1587.
72. Strasburger CJ, Vanuga P, Payer J, et al. MOD-4023, a long-acting carboxy-terminal peptide-modified human growth hormone: results of a Phase 2 study in growth hormone-deficient adults. *Eur J Endocrinol.* 2017;**176**(3):283–294.
73. ClinicalTrials.gov. *Safety and Efficacy Study of MOD-4023 to Treat Children With Growth Hormone Deficiency - Full Text View - ClinicalTrials.gov*. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT03874013?term=mod-4023&rank=1. Accessed July 18, 2019.
74. Cohen-Barak O, Sakov A, Rasamoelisolo M, et al. Safety, pharmacokinetic and pharmacodynamic properties of TV-1106, a long-acting GH treatment for GH deficiency. *Eur J Endocrinol.* 2015;**173**(5):541–551.
75. Cohen-Barak O, Barkay H, Rasamoelisolo M, et al. Assessment of the pharmacokinetics, pharmacodynamics, and safety of single doses of TV-1106, a long-acting growth hormone, in healthy Japanese and Caucasian subjects. *Clin Pharmacol Drug Dev.* 2017;**6**(4):331–342.
76. Cleland JL, Geething NC, Moore JA, et al. A novel long-acting human growth hormone fusion protein (VRS-317): enhanced in vivo potency and half-life. *J Pharm Sci.* 2012;**101**(8):2744–2754.
77. Moore WV, Nguyen HJ, Kletter GB, et al. A randomized safety and efficacy study of Somavaratan (VRS-317), a long-acting rhGH, in pediatric growth hormone deficiency. *J Clin Endocrinol Metab.* 2016;**101**(3):1091–1097.
78. Yuen KC, Conway GS, Popovic V, et al. A long-acting human growth hormone with delayed clearance (VRS-317): results of a double-blind, placebo-controlled, single ascending dose study in growth hormone-deficient adults. *J Clin Endocrinol Metab.* 2013;**98**(6):2595–2603.
79. GlobeNewswire. Versartis Announces Phase 3 VELOCITY Trial of Somavaratan in Pediatric Growth Hormone Deficiency Did Not Meet Primary Endpoint | Seeking Alpha. https://seekingalpha.com/pr/16948217-versartis-announces-phase-3-velocity-trial-somavaratan-pediatric-growth-hormone-deficiency. Published 2017. Accessed July 18, 2019.
80. Jensen S, Egesborg H, Fabricius PE, Sørensen B, Vestergård Jacobsen S. User driven development of a new device for weekly growth hormone administration in pediatric patients. In: *Endocrine Society's 99th Annual Meeting and Expo Annual Meeting and Expo*. Orlando, FL; 2017. https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=30291. Accessed April 8, 2019.
81. Battelino T, Rasmussen MH, De Schepper, et al; NN8640-4042 Study Group. Somapacitan, a once-weekly reversible albumin-binding GH derivative, in children with GH deficiency: A randomized dose-escalation trial. *Clin Endocrinol (Oxf).* 2017;**87**(4):350–358.
82. Kurtzhals P, Havelund S, Jonassen I, et al. Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo. *Biochem J.* 1995;**312**(Pt 3):725–731. http://www.ncbi.nlm.nih.gov/pubmed/8554512. Accessed April 8, 2019.
83. Knudsen LB, Nielsen PF, Huusfeldt PO, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem.* 2000;**43**(9):1664–1669. http://www.ncbi.nlm.nih.gov/pubmed/10794683. Accessed April 8, 2019.
84. Wang F, Surh J, Kaur M. Insulin degludec as an ultralong-acting basal insulin once a day: a systematic review. *Diabetes Metab Syndr Obes.* 2012;**5**:191–204.
85. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem.* 2015;**58**(18):7370–7380.
86. Farnum CE, Lenox M, Zipfel W, Horton W, Williams R. In vivo delivery of fluoresceinated dextrans to the murine growth plate: imaging of three vascular routes by multiphoton microscopy. *Anat Rec A Discov Mol Cell Evol Biol.* 2006;**288**(1):91–103.
87. van Lent PL, van den Berg WB, Schalkwijk J, van de Putte LB, van den Bersselaar L. The impact of protein size and charge on its retention in articular cartilage. *J Rheumatol.* 1987;**14**(4):798–805.
88. JCR Pharmaceuticals Co. *JCR Initiates Phase 1 Clinical Trial of JR-142, A Long-Acting Growth Hormone.*; 2019. https://ssl4.eir-parts.net/doc/4552/tdnet/1710585/00.pdf. Accessed July 8, 2019.
89. Mykola A, Malievskiy O, Nataliya Z, et al. A hybrid Fc-fused human growth hormone, GX-H9, shows a potential for weekly and twice-monthly administration in children with growth hormone deficiency. In: *10th International Meeting of Pediatric Endocrinology*. Washington D.C.; 2017. https://www.karger.com/Article/Pdf/481424. Accessed April 8, 2019.
90. Lui JC, Colbert M, Cheung CSF, et al. Cartilage-targeted IGF-1 treatment to promote longitudinal bone growth. *Mol Ther.* 2019;**27**(3):673–680.
91. Saenger P, Karpf DB, Mortensen E, Beckert M, Sprogoe K, Leff JA. Development of a long-acting (LA) growth hormone (GH): size matters. In: *10th International Meeting of Pediatric Endocrinology: Free Communication and Poster Sessions*. Washington D.C.; 2017:P1-837. https://www.karger.com/Article/Pdf/481424. Accessed April 8, 2019.
92. Raman S, Grimberg A, Waguespack SG, et al. Risk of Neoplasia in pediatric patients receiving growth hormone therapy–A report from the Pediatric Endocrine Society Drug and Therapeutics Committee. *J Clin Endocrinol Metab.* 2015;**100**(6):2192–2203.
93. Sävendahl L, Polak M, Backeljauw P, et al. Treatment of children with GH in the United States and Europe: long-term follow-up from NordiNet® IOS and ANSWER program. *J Clin Endocrinol Metab.* 2019;**104**(10):4730–4742.
94. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab.* 2010;**95**(1):167–177.
95. Bell JJ, Lippe B, Romano AA, Cernich JT, Swinford RD, Moawad D. National cooperative growth study: 25 years of growth hormone data, insights, and lessons for future registries. *Pediatr Endocrinol Rev.* 2018;**16**(2):240–255.

96. Darendeliler F, Karagiannis G, Wilton P. Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from the KIGS database. *Horm Res*. 2007;**68**(Suppl 5):41–47.
97. Wilton P, Mattsson AF, Darendeliler F. Growth hormone treatment in children is not associated with an increase in the incidence of cancer: experience from KIGS (Pfizer International Growth Database). *J Pediatr*. 2010;**157**(2):265–270.
98. Pfäffle R, Land C, Schönau E, et al. Growth hormone treatment for short stature in the USA, Germany and France: 15 years of surveillance in the genetics and neuroendocrinology of short-stature international study (GeNeSIS). *Horm Res Paediatr*. 2018;**90**(3):169–180.
99. Miller BS. rhGH safety and efficacy update. *Adv Pediatr*. 2011;**58**:207–211.
100. Attanasio AF, Jung H, Mo D, et al; HypoCCS International Advisory Board. Prevalence and incidence of diabetes mellitus in adult patients on growth hormone replacement for growth hormone deficiency: a surveillance database analysis. *J Clin Endocrinol Metab*. 2011;**96**(7):2255–2261.
101. Mo D, Hardin DS, Erfurth EM, Melmed S. Adult mortality or morbidity is not increased in childhood-onset growth hormone deficient patients who received pediatric GH treatment: an analysis of the Hypopituitary Control and Complications Study (HypoCCS). *Pituitary*. 2014;**17**(5):477–485.
102. Child CJ, Conroy D, Zimmermann AG, Woodmansee WW, Erfurth EM, Robison LL. Incidence of primary cancers and intracranial tumour recurrences in GH-treated and untreated adult hypopituitary patients: analyses from the Hypopituitary Control and Complications Study. *Eur J Endocrinol*. 2015;**172**(6):779–790.
103. Luger A, Feldt-Rasmussen U, Abs R, et al. Lessons learned from 15 years of KIMS and 5 years of ACROSTUDY. *Horm Res Paediatr*. 2011;**76 Suppl 1**:33–38.
104. Swerdlow AJ, Cooke R, Albertsson-Wikland K, et al. Description of the SAGhE Cohort: a large European study of mortality and cancer incidence risks after childhood treatment with recombinant growth hormone. *Horm Res Paediatr*. 2015;**84**(3):172–183.
105. Carel JC, Ecosse E, Landier F, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *J Clin Endocrinol Metab*. 2012;**97**(2):416–425.
106. Sävendahl L, Maes M, Albertsson-Wikland K, et al. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *J Clin Endocrinol Metab*. 2012;**97**(2):E213–E217.
107. Poidvin A, Touzé E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology*. 2014;**83**(9):780–786.
108. Albertsson-Wikland K, Mårtensson A, Sävendahl L, et al. Mortality is not increased in recombinant human growth hormone-treated patients when adjusting for birth characteristics. *J Clin Endocrinol Metab*. 2016;**101**(5):2149–2159.
109. Ahangari G, Ostadali MR, Rabani A, Rashidian J, Sanati MH, Zarindast MR. Growth hormone antibodies formation in patients treated with recombinant human growth hormone. *Int J Immunopathol Pharmacol*. 2004;**17**(1):33–38.
110. Binder G, Heidenreich L, Schnabel D, et al. Biological significance of anti-GH antibodies in children treated with rhGH. *Horm Res Paediatr*. 2019;**91**(1):17–24.
111. Johannsson G. Long-acting growth hormone for replacement therapy. *J Clin Endocrinol Metab*. 2011;**96**(6):1668–1670.
112. Höybye C, Christiansen JS. Long-acting growth hormone. *Paediatr Drugs*. 2013;**15**(6):427–429.
113. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer*. 2008;**8**(12):915–928.
114. Allen DB, Backeljauw P, Bidlingmaier M, et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. *Eur J Endocrinol*. 2016;**174**(2):P1–P9.
115. Yuen KC, Cook DM, Rumbaugh EE, Cook MB, Dunger DB. Individual igf-I responsiveness to a fixed regimen of low-dose growth hormone replacement is increased with less variability in obese compared to non-obese adults with severe growth hormone deficiency. *Horm Res*. 2006;**65**(1):6–13.
116. Hwang JS, Lee HS, Lee KH, et al. Once-weekly administration of sustained-release growth hormone in Korean prepubertal children with idiopathic short stature: a randomized, controlled phase II study. *Horm Res Paediatr*. 2018;**90**(1):54–63.
117. Khadilkar V, Radjuk KA, Bolshova E, et al. 24-month use of once-weekly GH, LB03002, in prepubertal children with GH deficiency. *J Clin Endocrinol Metab*. 2014;**99**(1):126–132.
118. Thornton P, Hofman P, Maniatis AK, et al. *TransConTM Growth Hormone in the Treatment of Pediatric Growth Hormone Deficiency RESULTS OF THE PHASE 3 HeiGHt TRIAL*. https://ascendispharma.com/wp-content/uploads/ENDO-2019-heiGHt-Trial-Presentation.pdf. Accessed July 8, 2019.
119. Malievskiy O, Mykola A, Nataliya Z, et al. Efficacy and safety of long-acting Fc-fusion rhGH (GX-H9) shows a potential for both weekly and twice-monthly administration: results of a phase 1b/2 randomized study in growth hormone-deficient children. In: *Endocrine Society's 100th Annual Meeting and Expo*. Chicago, IL; 2018:SUN-217. https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=46408. Accessed April 8, 2019.
120. Johannsson G, Feldt-Rasmussen U, Håkonsson IH, et al. REAL 2 Study Group. Safety and convenience of once-weekly somapacitan in adult GH deficiency: a 26-week randomized, controlled trial. *Eur J Endocrinol*. 2018;**178**(5):491–499.
121. Johannsson G, Gordon MB, Højby Rasmussen M, et al. Efficacy and safety of once-weekly somapacitan in adult growth hormone deficiency (AGHD) confirmed in a 53-week real 1 trial extension. In: *Endocrine Society's 100th Annual Meeting and Expo*. New Orleans, LA; 2019:SAT-LB074. https://www.abstractsonline.com/pp8/#!/5752/presentation/18788. Accessed April 8, 2019.
122. ClinicalTrials.gov. *A research study in children with a low level of hormone to grow. tretatment is Somapacitan once a week compared to Norditropin once a day (REAL4)*. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT03811535?term=Somapacitan&rank=5. Accessed August 26, 2019.
123. ClinicalTrials.gov. *A research study in children born small and who stayed small. Treatment is Somapacitan once a week compared to Norditropin ONCE A DAY*. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT03878446?term=Somapacitan&recrs=a&rank=2. Accessed August 26, 2019.
124. ClinicalTrials.gov. *A clinical study in AGHD to assess safety, tolerability and efficacy of GX-H9 - full text view - ClinicalTrials.gov*. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/study/NCT02946606. Published 2017. Accessed August 26, 2019.
125. Sprogoe K, Beckert M, Mortensen E, Karpf DB, Leff JA. The rationale and design of TransCon GH. *Horm Res Paediatr*. 2018;**82**(Supplement 1). http://abstracts.eurospe.org/hrp/0089/ESPE2018AbstractBook.pdf. Accessed April 8, 2019.
126. Yang Y, Bai X, Yuan X, et al. Efficacy and safety of long-acting growth hormone in children with short stature: a systematic review and meta-analysis. *Endocrine*. 2019;**65**(1):25–34.