Introduction

History of Growth Hormone Therapy

In 1921, Evans and Long demonstrated the efficacy of growth hormone (GH) from bovine pituitary gland on growth in rats (1). Until the 1930s, GH was investigated for its effects not only on growth but also on glucose metabolism, proteins, minerals, and lipids. In 1944, Li and Evans isolated GH from bovine and human pituitary glands and identified GH as a protein of 191 amino acids (2). During the 1940s and 1950s, GH was purified from various species and tested in animal and human subjects. In 1979, human GH (hGH) could be expressed by recombinant DNA technology (3). In 1985, the United States Food and Drug Administration (FDA) approved recombinant GH (rhGH) produced in E. coli. Long-term effects of rhGH were monitored in several studies including the National Collaborative Growth Study (NCGS) and Kabi International Growth Study (KIGS). Over a period of more than 25 years, data from nearly two hundred thousand patients treated with rhGH, and studies on long-term efficacy and safety have been presented (4, 5).

Daily Growth Hormone Therapy

The first study on GH dosing used pituitary hGH administered twice weekly. Later, further increase was shown in growth velocity when the three times weekly pit-hGH regimen switched to once daily injections (6,7). Current recommendation for GH therapy involves daily rhGH injections. Daily dose of GH may vary from 25 to 45 mg/kg body weight while the dose can be increased in puberty or syndromic disorders with short stature (8).

Adherence With Growth Hormone Therapy

Adherence with GH therapy is critical to treatment success. Poor adherence is the leading cause of inadequate growth velocity in patients receiving GH therapy (9). In 2022, 12-month treatment adherence rates were found to vary from 73.3 to 95.3% with a mean adherence rate of 79.3% in a systematic review of 41 eligible studies (10). In studies conducted in our country, the adherence rate was 92% in a series of 689 patients treated with rhGH, and studies on long-term efficacy and safety have been presented (4, 5).

Paradigms Improving Adherence with Growth Hormone Therapy

Treatment adherence can be affected by a variety of factors including needle phobia (fear, reasons associated with injections), forgetfulness, treatment duration, low socioeconomic status, injection device used, unmet treatment expectations, poor understanding of consequences of missed doses (11). Treatment adherence was assessed during the first 2-year in a study conducted in 110 patients and negative correlations were found between treatment adherence and age, pretreatment growth velocity and treatment duration while treatment adherence was positively correlated with parents’ educational attainment (9). Treatment adherence is further affected by access to medicines, patients’, and parents’ motivation, having received necessary training. Other significant factors include individual differences in response to GH therapy, diagnostic differences, age at diagnosis, current age, dose of medication (12).

Another factor reducing treatment adherence was defined as injection refusal among adolescents and the importance of family support was underlined (17). Regional differences may affect adherence with treatment. Medication costs, inability to access medicine, concerns about diagnostic differences, age at diagnosis, current age, dose of medication (16).

Reimbursement. Novel long-acting GH formulations (LAGH) with extended half-life can be administered less frequently and target to improve patient convenience and consequently to improve adherence and responses to treatment. LAGH formulations can restore growth velocity and body composition as effectively as daily treatment, without unexpected adverse effects as reported in randomized clinical trials.

Keywords: Recombinant growth hormone, long-acting growth hormone, treatment adherence, review, future aspects.
approved in US and EU, and LAGH analogue Somatrogon (Ngenla®) was approved in EU, Australia, Canada, Japan, United Kingdom, Brazil, India, US and most recently in Turkey and Kingdom of Saudi Arabia. Other LAGH analogues are in various stages of clinical development. This article is focused on somatrogon (Ngenla®), lonapegsomatropin-tcg (Skytrofa®), somapacitan-beco (Sogroya®) considering that these LAGH formulations have been approved by the US FDA and European Medicines Agency (EMA) for use in children and adolescents (Table 1) (19).

**Pharmacological Characteristics of Long-Acting Growth Hormone Formulations**

Human GH is protein containing 191 amino acids with a molecular weight of 22 kDa and an isoelectric pH of 5.8. Currently available rhGH formulations have similar molecular weight and characteristics to hGH although not identical. rhGH has a half-life of 3 to 4 hours following subcutaneous injection and 0.36 hours following intravenous injection with an effect duration of less than 24 hours. Blood GH levels vary depending on age, sex, physiological state, and environmental conditions. GH secretion surges several peaks occur throughout the day and shows an episodic and pulsatile pattern with increasing frequency during sleep (particularly in the second half of the night) in humans. Therefore, treatment with once daily rhGH injections does not mimic actual pattern of hGH release they provide a unimodal blood level pattern. However, rhGH may provide an adequate growth response in children and adolescents with GH deficiency (20, 21). As with once daily rhGH formulations, the pharmacodynamics of LAGH formulations may not be identical with hGH secretion, but treatment responses are not inferior to those induced by once-daily formulations (19).

Several techniques including depot formulations, PEGylated formulations, pro-drug formulations, non-covalent albumin binding GH formulations, GH fusion proteins have been used in the development process of LAGH analogues to extend the half-life of the formulation. Approved LAGH formulations are presented in Table 2 (19). Long-acting therapies have been previously developed for several medical conditions including hemophilia and type 2 diabetes and such therapies have proved to be safe and are associated with higher treatment adherence, greater patient satisfaction and improved quality of life (10, 22, 23).

The produg formulation ACP-001 (Skytrofa®, lonapegsomatropin-tcg) is an unmodified rhGH transiently conjugated with a methoxy-PEG containing carrier molecule which is hydrolysable depending on pH and temperature. ACP-001, was approved by the US FDA and EMA in 2021 for use in pediatric patients (aged 1 year with a body weight of 11.5 kg) (24).

The non-covalent albumin binding GH formulation NNC0195-0092 (Sogroya®, Somapacitan-beco) was approved by FDA in August 2020 for use in adults with GH deficiency. Non-covalent binding of albumin to GH with single point mutation, was terminal fatty acid linker resulted in a reduced clearance rate and a longer half-life. The Phase III pediatric study REAL-4 has started in 2019 (25, 26). Somatrogon is a chimeric product consisting of the fusion of rhGH with three copies of carboxyl-terminal peptide (CTP) of human chorionic gonadotropin β-subunit (molecular weight: 47.5 kDa). In historical process, as shown in Table 3, the development of LAGH formulations is a long process that will require accumulated experience and allocation of a large budget. Any approved GH formulation is obviously a product of a challenging process and experience. Nonetheless, further efforts are still needed (27, 28).

**Long-acting growth hormones**

In theory, clinical indications for the use of LAGH formulations include needle phobia in children, non-adherence in adolescents, pediatric patients without a consistent caregiver, general children in institutional care, treatment fatigue in patients on long-term therapy when compared with once-daily GH formulations. In addition, the ability to administer LAGH at any time in a given day may be considered as an advantage of weekly formulations over once-daily formulations. LAGH preparations may improve patient adherence, quality of life and clinical outcomes (29).

LAGH formulations approved by the US FDA and EMA for use in children and adolescents include somatrogon (Ngenla®), lonapegsomatropin-tcg (Skytrofa®) and somapacitan-beco (Sogroya®). In standard 52-week phase III clinical trials, once weekly lonapegsomatropin, somatropin and somapacitan have been found to yield non-inferior height velocities. This three LAGH formulations have similar safety profiles to daily GH in children with pediatric GH deficiency (29).

**Somatrogon (Ngenla®):**

Somatrogon is the first LAGH formulation approved in our country. Somatrogon significantly reduces treatment burden compared to daily GH (Genotropin®) therapy and its effectiveness is non inferior (30). Somatrogon is produced by recombinant DNA technology and administered subcutaneously. Since somatrogon is a fusion protein, its half-life is long, its renal clearance is low, and its diffusion into the growth plate is good (31). Somatrogon is indicated for the treatment of children from three years of age with GH deficiency. In a randomized controlled phase 2 study involving 42 subjects, doses of 0.25, 0.48, 0.66 mg/kg/week on daily GH (at a dose of 0.34 mg/kg/gün, Genotropin®) was administered to 53 prepubertal GH deficient children, the growth responses of somatrogon at doses of 0.25, 0.48, 0.66 mg/kg/week were found 7,73±1,89, 7,54±1,28 ve 8,81±1,12 cm/year respectively (32). In the phase 3 study in which somatrogon (0.66 mg/kg/week) or daily GH (0.24 mg/kg/week, Genotropin®) were administered to 228 children with GH deficiency, the annual change in height standard deviation score was found to be similar (33). These studies have shown that long-acting somatrogon is well tolerated, safe, and effective with similar or better effects similar to daily growth hormone therapy (myositis, injection site pain, water retention including edema, arthralgia, carpal tunnel syndrome, benign intracranial hypertension etc). These studies were suggested that mean/average IGF-1 levels should be taken from 4 post somatrogon administration. The authors reported in this study that this sampling time for IGF-1 level was a more useful and representative time for overall systemic exposure to IGF-1 levels. Somatrogon has been found to have similar safety and tolerability to daily growth hormone. The currently recommended/approved dosage of somatrogon in our country is 0.66 mg/kg body weight administered once weekly by subcutaneous injection (33). When switching from daily GH therapy, somatrogon may be administered subcutaneously at a weekly dose of 0.66 mg/kg body weight on the day following the last daily injection. In the phase 3 study in which somatrogon (0.66 mg/kg/week) was given to children with pituitary GH deficiency, the average IGF1 SDS values was 0.66, while the daily GH was found to be 0.69 (29). Serum IGF-1 concentrations should be monitored regularly and blood samples should be collected 4 days after the prior dose. If serum IGF-1 concentrations exceed the mean reference value by >2 SDS, the dose of somatrogon should be reduced by 15%. Higher dose reductions may be required in some patients. Height velocity should be monitored particularly during the first year of treatment and treatment adherence should be supervised. Zadik et al. found treatment compliance to be >90% in the patient group followed for 5 years with somatrogon treatment. (32).

When needed, the day of weekly injection can be changed if time from the last injection is more than 72 hours. If a dose is missed, the missed dose can be administered as soon as possible, if the delay is less than 3 days. If the delay is more than 3 days, the missed dose should be skipped and the next dose should be administered on the scheduled day. Underdose and overdose should be managed based on the experience with daily GH therapy. At recommended doses, significant changes have not been reported in insulin sensitivity and glucose metabolism during treatment with somatrogon. Other effects on glucose metabolism are similar to those of daily GH therapy (32).

Somatrogon is not recommended in pediatric patients with multiple pituitary hormone deficiency (MHPD) below 3 years of age due to the challenges associated with the management of the risk for hypoglycemia. There is not enough research on this issue (32).

24 pediatric endocrinologists from 12 countries with experience in GH therapy were surveyed concerning GH adherence monitoring, device use, injection regimen, and disclosure of missed injections to address concerns of the patient's family or caretaker. In general, 75% of pediatric endocrinologists preferred weekly somatrogon. 79.2% found it more useful, 83.3% stated that they would prefer to prescribe somatrogon in the future, and 50% stated that they thought it was beneficial for patients. It was also observed that somatrogon provided
62.5% satisfaction among physicians in reducing the frequency of injections and reducing the burden on family and caregivers (34). In a survey conducted on the families and caregivers of 87 GH-deficient pediatric patients, somapacitan was reported to be the more preferred treatment method with a lower treatment burden than daily GH therapy (35). Anti-drug antibodies developed against the drug have not been shown to have any effect on growth when using somatostatin (29). In a meta-analysis, it was predicted that somatostatin provided higher near-final height compared to daily GH in pediatric GH deficiency cases, improved the quality of life, and reduced the cost per cm (36).

Zelinka et al. reported that there was no significant change in glucose and HbA1c levels in patients using somatostatin (37).

**Somapacitan-beco (Sogroya®):**

Somapacitan is a LAGH with an extended half-life by reversible non-covalent binding to albumin. Somapacitan was approved for the treatment of patients aged 2.5 years and older. Somapacitan is the second LAGH approved in our country after somatostatin. Somapacitan is produced by recombinant DNA technology and is administered by subcutaneous injections. When LAGH formulations were provided annual growth of 7.5, 9.7, and 11.7 cm/year at doses of 0.04, 0.08, and 0.16 mg/kg/week, respectively, daily GH (Norditropin®) provided 9.9 cm/year growth (38). In our country, the dose of suggestion for GH deficient pediatric patient is 0.16 mg/kg/week. In the Phase 3 REAL4 study, in 200 GH deficient children aged 2.5-11 years, somapacitan (0.16 mg/kg/week) provided growth non inferior to the daily GH (0.034 mg/kg/day) (11.2 cm/year vs. 11.7 cm/year, respectively). Side effects (such as nasopharyngitis, fever, headache, injection site pain) were seen in 5% of the cases (39). In the study where somapacitan and daily GH (Norditropin®) treatment was given for 3 years, the growth velocity SDS change was found to be 2.9, 2.3, and 2.4 for somapacitan and 2.1 for daily GH according to years (40). In phase 1, phase 2 (REAL 3), phase 3 (REAL 4) studies, 1473 pharmacokinetic samples (210 treated with somapacitan) were taken from 210 GH deficient children treated with somapacitan and IGF1 SDS values were determined. While the IGF 1 SDS value did not exceed +3 in those receiving somatostatin, it ranged between -2 and +2 in those receiving daily GH (41). In a study, it was also reported that while the adverse effect rate was 71.1% in those receiving somapacitan, it was 71.4% in those receiving daily GH (40). In a 3-year study comparing somapacitan with daily GH (Norditropin®) treatment, no significant changes in glucose and HbA1c were detected (40). In a study with a small sample size, patients using somapacitan daily growth was compared in terms of their quality of life and no significant difference was found between them (42). The approved dose for initiating treatment with Somapacitan or switching from daily GH therapy is 0.16 mg/kg once weekly (40).

**Lonapegsomatropin-tcgd (Skytrofa®):**

Lonapegsomatropin is the first FDA-approved LAGH formulation. Lonapegsomatropin is a preservative-free, reversible Pegylated rhGH preparation. Therefore, the treatment cost of lonapegsomatropin was calculated to be 20-40% higher than the preservative-free Genotropin® treatment (43). FDA approval for use in patients aged one year and older or weight more than 11.5 kg. In the study comparing lonapegsomatropin (0.24 mg/kg/week) and daily GH (0.24 mg/kg/week, Genotropin®) treatments, the annual growth rate was found to be 11.2 and 10.3 cm, respectively (44).

In the 104-week heGHt, fltGH and continued enliGHten study comparing lonapegsomatropin and daily GH, it was shown that the height SDS value improved from -2.89 to -1.37 and from -3 to -1.5, respectively. In this study, adverse effects were reported except fever and local reaction. Average. In this study, IGF-1 value five days after lonapegsomatropin injection was found +1.46 SDS (45). The recommended dose for starting and dose for switching from daily GHs 0.24 mg/kg body weight administered subcutaneously once weekly. In addition to adverse effects associated with other formulations, lonapegsomatropin-tcgd label also included a higher risk for pancreatitis. Follow-up recommendations for lonapegsomatropin-tcgd include routine monitoring of serum phosphate, alkaline phosphatase and parathormone levels in addition to other recommendation for LAGH formulations, because serum levels of phosphate, alkaline phosphatase, and parathyroid hormone may increase after somatostatin treatment. Missed doses should be administered as soon as possible and within less than 2 days. Dosing intervals should be 5 days at least. Neutralizing anti-drug antibodies were not detected against this active substance during the treatment period of 72 weeks. These recommendations were presented in the prospectus but were not reported. (38).

**Fate of IGF-1 and LAGH safety:**

In a recent online article on somatrogon, non-adherence rates have been reported as low as 4% for the first year of treatment (adherence rates 99.7 with daily recombinant GH therapy and between 99.2% and 99.4% with LAGH analogues.

**Treatment adherence and other expectations with LAGH formulations:**

Efficacy and safety, treatment adherence, child’s and parental quality of life, cost-effectiveness analyses were conducted in a recently published meta-analysis on LAGH analogues vs. daily rhGH therapy. Based on these analyses, treatment adherence varied between 87.2 and 99.7 with daily recombinant GH therapy and between 91.3% and 99.2% with LAGH analogues. Although the efficacy and safety of LAGH analogues were comparable to those of daily recombinant GH formulations, well- designed, medium to long-term studies on quality of life of the child and parents and cost-effectiveness studies are still needed (38).

In a recent online article on somatrogon, non-adherence rates have been reported as low as 4% for the first year of treatment (adherence rates reported in daily GH formulations in 95.6% to 95.8%). The analysis showed that 71.4% of patients achieved the target height for sex (28). Analyses of long-term treatment responses, adverse effects, treatment costs, effects on lipid and glucose metabolism, follow-up parameters and safety and efficacy are becoming increasingly important as LAGH formulations are reimbursed, currently.

**Theoretical concerns about LAGH formulations:**

The issues of theoretical concern are the effect of LAGH analogues on fat and glucose metabolism, their effectiveness in correcting hypoglycemia in infants with hypoglycemia associated with severe GH deficiency, and their different therapeutic efficacy profiles in different tissues, especially due to the large size of the fusion proteins. When IGF-I levels above the physiological value are obtained for a very long time, risk states for intragrowth acromegaly, neoplasia and glucose intolerance are unclear. Elevated and high-normal serum IGF-1 levels in early epidemiological studies have raised concerns about the potential of an increased risk of malignancies. A safe serum IGF cut-off level is another area for further investigation (46).

**Future Goals for LAGH Therapy:**

Theoretical concerns associated with the use of LAGH analogues suggest the importance of establishing the safety of various LAGH formulations. Dosages in treatment-naive patients, dosages in patients switching from daily recombinant therapy LAGH therapy, potential differences in starting doses, dose adjustments and methodology to be used in dose adjustments, timing of serum IGF-1 measurements, safety, sustainability, cost-effectiveness, and effects on the quality of life and treatment adherence should be assessed. There are guidelines like PROGRES and GloBE-Reg. National registries will also be useful to collect and analyze data from these patients on a yearly basis and the results should be communicated (47). https://globe-reg.net/.

**Reliability, follow-up parameters and unknown factors in LAGH therapy:**

It is important to establish a Future Research Agenda for LAGH therapy to compare weekly and daily GH therapy in long-term treatment responses, to conduct analyses on adverse effects, treatment costs, effects on lipid and glucose metabolism, follow-up parameters and safety and efficacy, effects on quality of life and treatment adherence and to update follow-up plans based on data collected from these analyses. Studies have shown that day 4 is recommended for optimum IGF1 evaluation but longitudinal studies are needed to determine IGF-I levels after dosing, how to make dose reductions in case of an adverse effect, risk for developing acromegaly, neoplasia or glucose intolerance. The dose, efficacy and reliability of treatment with LAGH therapies in Turner syndrome, born small for gestational age (SGA), Prader-Willi syndrome, Silver-Russell syndrome, intracranial malignancies or other cancer survivors, the use in severe GH deficiency presenting with neonatal hypoglycemia, the use patients younger than three years (not approved for time being under 2-3 years of age), dosing in obese patients, the level of growth response in each individual organ and tissue, neutralizing antibody status, development of neutralizing antibodies against each individual formulation, several parameters including adherence, treatment costs and growth response data over decades.
Disclosure: Dr Furkan Erdoğan from Pfizer Turkey is a coauthor in this paper. He has been involved in the concept and the especially literature review including presentations from recent congresses, there are no conflict of interest other than the authorship between Pfizer and the authors.

Acknowledgements: F. Erdoğan is an employee of Pfizer Inc.

References:
19. Miller BS. What do we do now that the long-acting growth hormone is here? Front Endocrinol (Lausanne). 2022 Aug 1;13:980979.
22. Miller BS. What do we do now that the long-acting growth hormone is here? Front Endocrinol (Lausanne). 2022 Aug 1;13:980979.

Table 1: In use long acting growth hormone formulations by Food and Drug Administration and European Medicines Agency of approval

<table>
<thead>
<tr>
<th></th>
<th>Somatrogon</th>
<th>Lonapegsomatropin</th>
<th>Somapacitan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>US, EU, Canada, Japan, Australia, Brazil, Taiwan, UAE, India, KSA, Turkey</td>
<td>US, EU</td>
<td>US, EU, KSA, Canada, Japan</td>
</tr>
</tbody>
</table>

**Abbreviations:** US; United States, EU: European Union, KSA: Saudi Arabia, UAE: United Arab Emirates

Table 2. Characteristics of LAGH formulations by Food and Drug Administration and European Medicines Agency of approval

<table>
<thead>
<tr>
<th></th>
<th>Somatrogon</th>
<th>Lonapegsomatropin</th>
<th>Somapacitan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td>Ngenla®</td>
<td>Skytrofa®</td>
<td>Sogroya®</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Fusion Protein</td>
<td>Prodrug</td>
<td>Increased Albumin-Binding</td>
</tr>
<tr>
<td>Product</td>
<td>Mechanism</td>
<td>Frequency of Administration</td>
<td>Current Status</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>-----------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>ALTU-238</td>
<td>Depot</td>
<td>7 days</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>Nutropin Depot</td>
<td>Depot</td>
<td>14 days</td>
<td>Removed from market</td>
</tr>
<tr>
<td>Eutropin Plus</td>
<td>Depot</td>
<td>7 days</td>
<td>Approved in South Korea, EMA</td>
</tr>
<tr>
<td>ARX201</td>
<td>PEGylation</td>
<td>7 days</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>BBT-031</td>
<td>PEGylation</td>
<td>7 days</td>
<td>Developing stopped at preclinical studies</td>
</tr>
<tr>
<td>PHA-794428</td>
<td>PEGylation</td>
<td>7 days</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>NNC126-0083</td>
<td>PEGylation</td>
<td>7 days</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>Jintrolong</td>
<td>PEGylation</td>
<td>7 days</td>
<td>Approved in China</td>
</tr>
<tr>
<td>Lonapegsomatropin</td>
<td>Prodrug</td>
<td>7 days</td>
<td>Approved in USA, EU</td>
</tr>
<tr>
<td>Somatrogon</td>
<td>Fusion Protein</td>
<td>7 days</td>
<td>Approved in USA, EU, Canada, Australia, Turkey, Japan, Kingdom of Saudi Arabia</td>
</tr>
<tr>
<td>AG-B1512</td>
<td>Fusion Protein</td>
<td>14 or 28 days</td>
<td>Pre-clinical Studies</td>
</tr>
<tr>
<td>ALT-P1</td>
<td>Fusion Protein</td>
<td>Unknown</td>
<td>Developing stopped at phase 2</td>
</tr>
<tr>
<td>Profuse</td>
<td>Fusion Protein</td>
<td>1 month</td>
<td>Developing stopped at preclinical studies</td>
</tr>
<tr>
<td>GX-H9</td>
<td>Fusion Protein</td>
<td>7-14 days</td>
<td>Phase 3 studies</td>
</tr>
<tr>
<td>HM10560A</td>
<td>Fusion Protein</td>
<td>7-14 days</td>
<td>Phase 3 studies</td>
</tr>
<tr>
<td>JR-142</td>
<td>Fusion Protein</td>
<td>7 days</td>
<td>Phase 2 studies</td>
</tr>
<tr>
<td>Albutropin</td>
<td>Fusion Protein</td>
<td>7 days</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>Somavaratan</td>
<td>Fusion Protein</td>
<td>7, 14 or 28 days</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>Somapacitan</td>
<td>Increased Albumin Binding</td>
<td>7 days</td>
<td>Approved in USA, EU, KSA, Canada, Japan</td>
</tr>
</tbody>
</table>

US: United States; EU: European Union; EMA, KSA: Kingdom of Saudi Arabia