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A Critique View On Skytrofa

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***Abstract*: The aim of this article is to bring awareness about skytrofa a branded drug which is used for children with Growth Hormone Deficiency (GHD). Auto injector is mostly focused on pediatric patients who are at least 1year of age and who are experiencing growth failure caused by an inadequate secretion of endogenous growth hormone. It is based on assessed the safety and efficacy of skytrofa. Skytrofa (lonapegsomatropin-tcgd) is also known as Trans Con hGH or ACP011.Lonapegsomatropin is a long acting, once-weekly prodrug for the treatment of Growth Hormone Deficiency. This review concludes that GHD this is not only important for weight and height but also for endocrine health and development.**

***Keywords*: Growth hormone deficiency, Idiopathic short stature, Lonapegsomatropin-tcgd (Tetrahymena comparative genomics database), Noonan syndrome, prepubertal, skytrofa, somatropin, Turner syndrome.**

1. Introduction

FDA Approved: FDA Approved on August 25th, 2021.

Brand name: Skytrofa

Generic name: Lonapegsomatropin-tcgd Dosage form: for injection Treatment: pediatric Growth Hormone Deficiency.

Sponsor: Ascendis pharma A/S.Company Last updated: last updated by Judith Stewart.

- Skytrofa FDA was first approved on August 25th, 2021, by Ascendis pharma Stewart, B. Pharm.
- The Brand name of drug is Skytrofa and the Generic name is Lonapegsomatropin-tcgd.
- COPENHAGEN, Denmark of Ascendis pharma AS (Nasdaq: ASND). A Biopharmaceutical company that exploit its Innovative Trans Con Technologies to create a new treatment in difference patients lives, and U.S. FDA has Approved skytrofa.
- Skytrofa (Lonapegsomatropin-tcgd) is a human growth hormone and it is used to treat the pediatric patients of 1 year and older whose weight at least 11.5kg (25.4Lb) and have growth failure caused by an Inadequate secretion of endogenous growth hormone. [1], [8]

Fig. 1. Skytrofa TM Auto injector for skytrofa cartridges

- Growth Hormone is a Hormone that promotes growth maintenance of normal body composition and which is secreted by pituitary gland and also promotes overall endocrine health.
- Growth Hormone exerts its mainly effects both direct binding and indirect binding. It's directly binding to specific cell surface receptor and indirectly binding to Insulin like growth factor. Since from 1987, children with Growth Hormone Deficiency have been treated.
- In 2015 the Growth Hormone Research society recognized the requirement for a long acting growth hormone (LAGH). LAGH agreed that by decreasing Injection frequency and contributing various Pharmacokinetic properties.
- Growth Hormone (GH) is a major key role for organ development like ex: Cardiovascular Function, Cognition and metabolism.
- Growth Hormone deficiency is a disease characterized by short stature and metabolic complication.
- Lonapegsomatropin is also known as
  Lonapegsomatropin-tcgd,
  RhGH- PEG,
  TransconpeghGH and
  Transcopeg-hGH
- Formula: C1051H1627N269O317S9[C2H4O]4n
- Lonapegsomatropin was approved for medical use in the United States in August 2021
- Lonapegsomatropin is a growth hormone therapy indicated to treat growth hormone deficiency.
- Somatropin has a various brands of this medication are used for the treatment of the following medical conditions like growth failure, growth hormone deficiency, intestinal disorders, short bowel syndrome or HIV related weight loss.
- Somatropin is also used to increases the height in children with certain disorders, such as Turner syndrome, Idiopathic short stature.
- Somatropin which requires daily dosing.
- This medication is given to new born, (infants), it mix with sterile water for injection that doesn't contain a preservative. (Benzyl alcohol).
- If we given by injection to infants during the first month.

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The risk is greater due to lower birth weight of infants and it is greater with increased amounts of Benzyl alcohol. [2]

2. Adverse Reaction of Skytrofa Includes

- Viral infection,
- Increased risk of viral infection,
- Fever,
- Cough,
- Nausea and vomiting,
- Bleeding,
- Diarrhea,
- Abdominal Pain,
- Joint pain, stiffness, Swelling, & Arthralgia. [3]
- Arthritis,
- Hemorrhage,
- Bruising petechiae,
- Bloody nose. [4]

Table 1

Adverse Reaction	Daily Somatropin (N=56) n(%)	Skytrofa (N=105) n(%)
Infection ,viral	6(11%)	16(15%)
Pyrexia	5(9%)	16(15%)
Cough	4(7%)	11(11%)
Nausea & vomiting	4(7%)	11(11%)
Hemorrhage	1(2%)	7(7%)
Diarrhea	3(5%)	6(6%)
Abdominal pain	2(4%)	6(6%)
Arthralgia & Arthritis	1(2%)	6(6%)

3. Undesirable Effects of Skytrofa

- Hypersensitivity reactions,
- Increased risk of malignancy progression,
- Decreased insulin sensitivity,
- Increased risk of scoliosis progression,
- Pancreatitis,
- Intracranial hypertension,
- Fluid retention,
- Hypoadrenalism,
- Hypothyroidism. [3], [4]

4. Preparation and Administration

- Skytrofa (Lonapegsomatropin-tcgd) is for injection and it is a sterile, preservative-free and white lyophilized powder. It is supplied as a single dose. The skytrofa cartridge has been designed for use only with auto injector.
- The cartridge has 2 chambers, 1 filled with powder and another one filled with water. The auto injector automatically mixes the powder and water during preparation, make it ready for injection.
- If refrigerated, then skytrofa cartridge must be kept at Room temperature for 15mins before administer or use.
- Skytrofa was approved by FDA based on results of the phase 3heiGHt trial. When compared to skytrofa once-weekly & Somatropin (Genotropin) daily receive.
- In comparison, skytrofa demonstrated higher annualized height velocity (AHV) at 52 weeks with similar safety & tolerability.
- The Auto-injector needle is inserted into the skin (subcutaneously). Once in a week based upon patient's weight (0.24mg/kg). The device automatically delivers the drug product.
- If the auto-injector is dirty or if solution containing air bubbles. Don't inject if the solution.
- Skytrofa comes in a single-use cartridge.
- The use of Skytrofa cartridges within 4 hrs after reconstitution. Discard after 4hrs reconstitution when stored at room temperature up to 30°c (86°F).
- Skytrofa is available in 9 different doses. Administration. Skytrofa should be done by an experienced physician.
- Selection of appropriate cartridge is based on prescribed dose (mg/kg) and patients body weight (kg).
- The prescribing dose is 0.24mg/kg/week.
- The patient's body weight is 11.5 to 100 kg.
- Total weekly dose(mg)=prescribed weekly dose (mg/kg) × Patient's body weight (kg). [4], [5]

Fig. 2.

Table 2
Recommended dosing

Weight (kg)	Dose(mg)
11.5-13.9 kg	3mg/week
14-16.4 Kg	3.6mg/week
16.5-19.9 Kg	4.3mg/week
20-23.9 Kg	5.2 mg/week
24-28.9 Kg	6.3 mg/week
29-34.9 Kg	7.6mg/week
35-41.9 Kg	9.1mg/week
42-50.9 Kg	11 mg/week
51-60.4 Kg	13.3 mg/week
60.5-69.9 Kg	15.2 mg/week (use2 cartridge of 7.6mg each)
70-84.9 Kg	18.2 mg/week (using 2 cartridges of 9.1 mg each)
85-100 Kg	22(using 2 cartridges of 11 mg each)

5. Mechanism of Action

- Skytrofa (lonapegsomatropin-tcgd) is a long acting pro drug and it is a human growth hormone. By using E.coli Recombinant DNA technology, somatropin was produced.
- This somatropin is conjugated with methoxypolyethylene glycol carrier (4×10DamPEG) via a proprietary Transcon linker. In vitro assay confirms that the minimum potency as released somatropin.
- The half-life of somatropin is released from Lonapegsomatropin.

- It approximately 251U/Mg. As established in clinical phase 1 trial with identical 191Aminoacids.
- Both growth hormone and daily Somatropin therapy is designed to maintain mode of action, distribution& intracellular signalling. Permitting the once-a-week dosing internal. Whereas unmodified somatropin; an inert carrier and a proprietary linker that temporarily binds to the somatropin and carrier.
- The carrier has shielding effects that minimizes renal excretion and receptor renal clearance.
- Linker cleavages are dependent upon physiologic condition. So, Lonapegsomatropin predictably releases somatropin with therapeutic levels over one week. [5], [11]

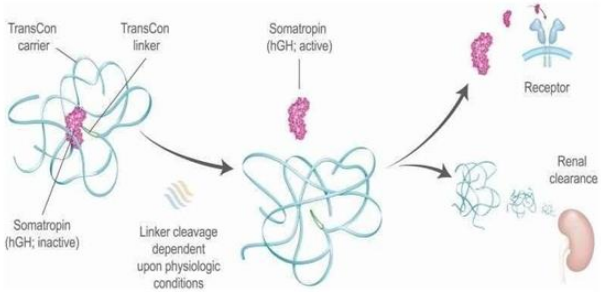

Fig. 3.

6. Absorption

- AUC:500h.ng/mL
- After administration of Lonapegsomatropintcgd at subcutaneously. The drug undergoes auto cleavage and releases the active somatropin from methoxypolyethylene glycol carrier.
- The prescribing dose is 0.24mg/kg/week.dosing in pediatric patients leads to a somatropin Cmax of 15.2ng/ml with a median Tmax of 12 hrs, and a mean AUC of 500ng/ml.methoxypolyethylene glycol reaches a C_{max} of 13/ug/ml with a median T_{max} of 36hr.
- HGH (somatropin) concentration reaches a mean steady C_{max} of 1230ng/ml with a T_{max} of 25hrs. [7]

A. Peak Plasma Concentration

- Lonapegsomatropin: 1230 nghGH/mL
- Somatropin: 15.2ng/mL
- Methoxypolyethylene glycol carrier: 13.1mcg/L

B. Peak Plasma Time

- Lonapegsomatropin: 25hr
- Somatropin: 12hr Methoxypolyethylene glycol carrier: 36hr.

7. Distribution

- Lonapegsomatropin-tcgd dosing of 0.24 mg/kg/week leads to mean steady state apparent volume of distribution of 0.13L/Kg
- V_d:0.13L/Kg [7]

8. Metabolism

- The metabolism of somatropin contains a catabolism of protein in both liver and kidney.
- Methoxypolyethylene glycol transporter is cleared by the kidneys. [8]

9. Elimination

- With growth hormone deficiency GHD in pediatric patients, Lonapegsomatropin-tcgd apparent clearance at steady was 3.2mL/h/Kg. The subcutaneous administration is 0.24mg/Kg/week. Skytrofa with a mean observation half-life is 30.7. [8]
- The half-life of somatropin released from Lonapegsomatropin was 25 hrs. Lonapegsomatropin:30.7hr
- Somatropin:25hr. [8]

10. Treatments

Table 3
Annualized height velocity at week 52 in pediatric treatment. NaA-ve subjects with GHD

	Once weekly skytrofa (N=105)	**Daily Somatropin (N=56)**	**Estimate of Treatment difference (95%Cl) (Skytrofa minus daily Somatropin)**
Annualized Height Velocity Cm/Year	11.2	10.3	0.9 (0.2-1.5)

- Skytrofa is treated once-weekly for 52 weeks resulted in an annualized height velocity is 11.2cm/Year.
- If skytrofa was treated daily then resulted in an Annualized height velocity is 10.3cm/yr.
- After 52 weeks of treatment 0.9cm/yr. is final Annualized height. [10]

Table 4
Height SDS (standard Deviation Score) over 52 weeks in pediatric treatment. NaA-ve subjects with GHD

	Once-weekly Skytrofa N=105	**Daily Somatropin (N=56)**
Height SDS, baseline	-2.9	-3.0
Height SDS, change from baseline	1.1	0.96

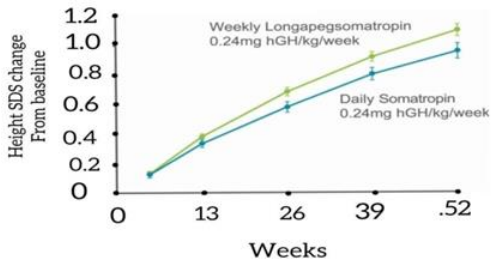

Fig. 4.

11. Important Safety Information

Skytrofa is indicated in patients with:

- Increased mortality in patients with acute critical

illness after open heart surgery, abdominal surgery or multiple accidental traumas.

- And Also Acute Respiratory failure has been reported after the treatment of somatropin with pharmacological doses.
- By the use of somatropin products Systemic hypersensitive reactions have been reported with post-marketing.
- Active fatality
- Active proliferative
- Severe non proliferative diabetic retinopathy.
- The safety of skytrofa continuing treatment in patient by replacement of doses.
- Children with certain rare genetic causes of little stature have an increased risk of developing malignancy.
- Treatment with somatropin may decreases insulin sensitivity, at particular dose.
- Monitoring of glucose-levels in all patients especially it mainly risk factor for type-2 Diabetes mellitus. Such as obesity or family history of type-2 diabetes mellitus.
- Adjust the doses of Anti hyperglycemia drugs are needed when skytrofa is initiated in patients.
- Central hypothyroidism may first become evidence during Skytrofa treatment in GHD patients.
- Periodically performs thyroid function tests &replacement of thyroid hormones.
- The risk may be greater in pediatric patients than adults by receiving somatropin in pediatric patients.
- Patients receiving somatropin therapy who having risk of pituitary hormone deficiency, may be reduced serum cortisol level/or unmasking of central hypoadrenalism. [8], [9]

12. Conclusion

- This review concludes that Growth Hormone Deficiency (GHD) this is not only important for weight and height, but also important for endocrine health and development.
- Numerous brands of skytrofa are used for the treatment of following medical conditions are:
    - Growth hormone deficiency, Intestinal disorder or HIV-related weight loss.
- Somatropin is also used to increase height in children with certain disorders like Noonan syndrome, Turner Syndrome, Idiopathic short stature.

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