Ascendis Pharma A/S Announces U.S. Food and Drug Administration Approval of SKYTROFA® (lonapegsomatropin-tcgd), the First Once-weekly Treatment for Pediatric Growth Hormone Deficiency

August 25, 2021

- SKYTROFA, the first FDA approved treatment utilizing TransCon™ technology, is a long-acting prodrug of somatropin that releases the same somatropin used in daily therapies –

- Once weekly SKYTROFA demonstrated higher annualized height velocity (AHV) at week 52 compared to a daily growth hormone with similar safety and tolerability –

- Availability in the U.S. expected shortly supported by a full suite of patient support programs –

- Ascendis Pharma to host investor conference call today, Wednesday, August 25 at 4:30 p.m. E.T. -

COPENHAGEN, Denmark, Aug. 25, 2021 (GLOBE NEWSWIRE) -- Ascendis Pharma A/S (Nasdaq: ASND), a biopharmaceutical company that utilizes its innovative TransCon technologies to potentially create new treatments that make a meaningful difference in patients' lives, today announced that the U.S. Food and Drug Administration (FDA) has approved SKYTROFA (lonapegsomatropin-tcgd) for the treatment of pediatric patients one year and older who weigh at least 11.5 kg (25.4 lb) and have growth failure due to inadequate secretion of endogenous growth hormone (GH).

As a once-weekly injection, SKYTROFA is the first FDA approved product that delivers somatropin (growth hormone) by sustained release over one week.

"Today's approval represents an important new choice for children with GHD and their families, who will now have a once-weekly treatment option. In the pivotal head-to-head clinical trial, once-weekly SKYTROFA demonstrated higher annualized height velocity at week 52 compared to somatropin[i]," said Paul Thornton, M.B. B.Ch., MRCPI, a clinical investigator and pediatric endocrinologist in Fort Worth, Texas. "This once-weekly treatment could reduce treatment burden and potentially replace the daily somatropin therapies, which have been the standard of care for over 30 years."

Growth hormone deficiency is a serious orphan disease characterized by short stature and metabolic complications. In GHD, the pituitary gland does not produce sufficient growth hormone, which is important not only for height but also for a child's overall endocrine health and development.

The approval includes the new SKYTROFA® Auto-Injector and cartridges which, after first removed from a refrigerator, allow families to store the medicine at room temperature for up to six months. With a weekly injection, patients switching from injections every day can experience up to 86 percent fewer injection days per year.

"SKYTROFA is the first product using our innovative TransCon technology platform that we have developed from design phase through non-clinical and clinical development, manufacturing and device optimization, and out to the patients. It reflects our commitment and dedication to addressing unmet medical needs by developing a pipeline of highly differentiated proprietary products across multiple therapeutic areas," said Jan Mikkelsen, Ascendis Pharma's President and Chief Executive Officer. "We are grateful to the patients, caregivers, clinicians, clinical investigators, and our employees, who have all contributed to bringing this new treatment option to children in the U.S. with GHD."

In connection with the commercialization of SKYTROFA, the company is committed to offering a full suite of patient support programs, including educating families on proper injection procedures for SKYTROFA as the first once-weekly treatment for children with GHD.

"It is wonderful that patients and their families now have the option of a once-weekly growth hormone therapy," said Mary Andrews, Chief Executive Officer and co-founder of the MAGIC Foundation, a global leader in endocrine health, advocacy, education, and support. "GHD is often overlooked and undertreated in our children and managing it can be challenging for families. We are excited about this news as treating GHD is important, and children have a short time to grow."

The FDA approval of SKYTROFA was based on results from the phase 3 heiGHt Trial, a 52-week, global, randomized, open-label, active-controlled, parallel-group trial that compared once-weekly SKYTROFA to daily somatropin (Genotropin®) in 161 treatment-naïve children with GHD[ii]. The primary endpoint was, AHV at 52 weeks for weekly SKYTROFA and daily hGH treatment groups. Other endpoints included adverse events, injection-site reactions, incidence of anti-hGH antibodies, annualized height velocity, change in height SDS, proportion of subjects with IGF-1 SDS (0.0 to +2.0), PK/PD in subjects < 3 years, and preference for and satisfaction with SKYTROFA.

At week 52, the treatment difference in AHV was 0.9 cm/year (11.2 cm/year for SKYTROFA compared with 10.3 cm/year for daily somatropin) with a 95 percent confidence interval [0.2, 1.5] cm/year. The primary objective of non-inferiority in AHV was met for SKYTROFA in this trial and further demonstrated a higher AHV at week 52 for lonapegsomatropin compared to daily somatropin, with similar safety, in treatment-naïve children with GHD.

No serious adverse events or discontinuations related to SKYTROFA were reported. Most common adverse reactions (≥ 5%) in pediatric patients include: infection, viral (15%), pyrexia (15%), cough (11%), nausea and vomiting (11%), hemorrhage (7%), diarrhea (6%), abdominal pain (6%), and arthralgia and arthritis (6%)[ii]. In addition, both arms of the study reported low incidences of transient, non-neutralizing anti-hGH binding antibodies and no cases of persistent antibodies.

Conference Call and Webcast Information

Date	Wednesday, August 25, 2021
Time	4:30 p.m. ET/1:30 p.m. Pacific Time
Dial In (U.S.)	844-290-3904
Dial In (International)	574-990-1036
Access Code	8553236

A live webcast of the conference call will be available on the Investors and News section of the Ascendis Pharma website at www.ascendispharma.com. A webcast replay will be available on this website shortly after conclusion of the event for 30 days.

The Following Information is Intended for the U.S. Audience Only

INDICATION

SKYTROFA® is a human growth hormone indicated for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH).

IMPORTANT SAFETY INFORMATION

- SKYTROFA is contraindicated in patients with:
  - Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or if you have acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin.
  - Hypersensitivity to somatropin or any of the excipients in SKYTROFA. Systemic hypersensitivity reactions have been reported with post-marketing use of somatropin products.
  - Closed epiphyses for growth promotion.
  - Active malignancy.
  - Active proliferative or severe non-proliferative diabetic retinopathy.
  - Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea or have severe respiratory impairment due to the risk of sudden death.

- Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic doses of somatropin. Safety of continuing SKYTROFA treatment in patients receiving replacement doses for the approved indication who concurrently develop these illnesses has not been established.

- Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Do not use SKYTROFA in patients with known hypersensitivity to somatropin or any of the excipients in SKYTROFA.

- There is an increased risk of malignancy progression with somatropin treatment in patients with active malignancy. Preexisting malignancy should be inactive with treatment completed prior to starting SKYTROFA. Discontinue SKYTROFA if there is evidence of recurrent activity.

- In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent growth hormone deficiency (GHD) and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. Monitor all patients with a history of GHD secondary to an intracranial neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor.

- Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, carefully monitor these patients for development of neoplasms. Monitor patients on somatropin therapy carefully for increased growth, or potential malignant changes of preexisting nevi. Advise patients/caregivers to report marked changes in behavior, onset of headaches, vision disturbances and/or changes in skin pigmentation or changes in the appearance of preexisting nevi.

- Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes mellitus has been reported in patients taking somatropin. Undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked. Monitor glucose levels periodically in all patients receiving SKYTROFA. Adjust the doses of antihyperglycemic drugs as needed when SKYTROFA is initiated in patients.

- Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a

small number of patients treated with somatropin. Symptoms usually occurred within the first 8 weeks after the initiation of somatropin and resolved rapidly after cessation or reduction in dose in all reported cases. Fundoscopic exam should be performed before initiation of therapy and periodically thereafter. If somatropin-induced IH is diagnosed, restart treatment with SKYTROFA at a lower dose after IH-associated signs and symptoms have resolved.

- Fluid retention during somatropin therapy may occur and is usually transient and dose dependent.
- Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of SKYTROFA therapy. Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism.
- Undiagnosed or untreated hypothyroidism may prevent response to SKYTROFA. In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during SKYTROFA treatment. Perform thyroid function tests periodically and consider thyroid hormone replacement.
- Slipped capital femoral epiphysis may occur more frequently in patients undergoing rapid growth. Evaluate pediatric patients with the onset of a limp or complaints of persistent hip or knee pain.
- Somatropin increases the growth rate and progression of existing scoliosis can occur in patients who experience rapid growth. Somatropin has not been shown to increase the occurrence of scoliosis. Monitor patients with a history of scoliosis for disease progression.
- Cases of pancreatitis have been reported in pediatric patients receiving somatropin. The risk may be greater in pediatric patients compared with adults. Consider pancreatitis in patients who develop persistent severe abdominal pain.
- When SKYTROFA is administered subcutaneously at the same site over a long period of time, lipoatrophy may result. Rotate injection sites when administering SKYTROFA to reduce this risk.
- There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. SKYTROFA is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.
- Serum levels of inorganic phosphorus, alkaline phosphatase, and parathyroid hormone may increase after somatropin treatment.
- The most common adverse reactions (≥5%) in patients treated with SKYTROFA were: viral infection (15%), pyrexia (15%), cough (11%), nausea and vomiting (11%), hemorrhage (7%), diarrhea (6%), abdominal pain (6%), and arthralgia and arthritis (6%).
- SKYTROFA can interact with the following drugs:
    - Glucocorticoids: SKYTROFA may reduce serum cortisol concentrations which may require an increase in the dose of glucocorticoids.
    - Oral Estrogen: Oral estrogens may reduce the response to SKYTROFA. Higher doses of SKYTROFA may be required.
    - Insulin and/or Other Hypoglycemic Agents: SKYTROFA may decrease insulin sensitivity. Patients with diabetes mellitus may require adjustment of insulin or hypoglycemic agents.
    - Cytochrome P450-Metabolized Drugs: Somatropin may increase cytochrome P450 (CYP450)-mediated antipyrine clearance. Carefully monitor patients using drugs metabolized by CYP450 liver enzymes in combination with SKYTROFA.

You are encouraged to report side effects to FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Ascendis Pharma at 1-844-442-7236.

Please click here for full Prescribing Information for SKYTROFA.

About SKYTROFA® (lonapegsomatropin-tcgd)

SKYTROFA® is a once-weekly prodrug designed to deliver somatropin over a one-week period. The released somatropin has the same 191 amino acid sequence as daily somatropin.

SKYTROFA single-use, prefilled cartridges are available in nine dosage strengths, allowing for convenient dosing flexibility. They are designed for use only with the SKYTROFA® Auto-Injector and may be stored at room temperature for up to six months. The recommended dose of SKYTROFA for treatment-naïve patients and patients switching from daily somatropin is 0.24 mg/kg body weight, administered once weekly. The dose may be adjusted based on the child's weight and insulin-like growth factor-1 (IGF-1) SDS.

SKYTROFA has been studied in over 300 children with GHD across the Phase 3 program which consists of the heiGHt Trial (for treatment-naïve patients), the fliGHt Trial (for treatment-experienced patients), and the enliGHten Trial (an ongoing long-term extension trial). Patients who completed the heiGHt Trial or the fliGHt Trial were able to continue into the enliGHten Trial and some have been on SKYTROFA for over four years.

SKYTROFA is being evaluated for pediatric GHD in Phase 3 trials in Japan and Greater China, including the People's Republic of China, Hong Kong, Macau and Taiwan. Ascendis Pharma is also conducting the global Phase 3 foresiGHt Trial in adults with GHD. SKYTROFA has been granted orphan designation for GHD in both the U.S. and Europe.

About TransCon™ Technologies

TransCon refers to "transient conjugation." The proprietary TransCon platform is an innovative technology to create new therapies that are designed to potentially optimize therapeutic effect, including efficacy, safety and dosing frequency. TransCon molecules have three components: an unmodified parent drug, an inert carrier that protects it, and a linker that temporarily binds the two. When bound, the carrier inactivates and shields the parent drug from clearance. When injected into the body, physiologic conditions (e.g., pH and temperature) initiate the release of the active, unmodified parent drug in a predictable manner. Because the parent drug is unmodified, its original mode of action is expected to be maintained. TransCon technology can be applied broadly to a protein, peptide or small molecule in multiple therapeutic areas, and can be used systemically or locally.

About Ascendis Pharma A/S

Ascendis Pharma is applying its innovative platform technology to build a leading, fully integrated biopharma company focused on making a meaningful difference in patients' lives. Guided by its core values of patients, science and passion, the company utilizes its TransCon technologies to create new and potentially best-in-class therapies.

Ascendis Pharma currently has a pipeline of multiple independent endocrinology rare disease and oncology product candidates in development. The company continues to expand into additional therapeutic areas to address unmet patient needs.

Ascendis is headquartered in Copenhagen, Denmark, with additional facilities in Heidelberg and Berlin, Germany, in Palo Alto and Redwood City, California, and in Princeton, New Jersey.

Please visit www.ascendispharma.com (for global information) or www.ascendispharma.us (for U.S. information).

Forward-Looking Statements

This press release contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, included in this press release regarding Ascendis' future operations, plans and objectives of management are forward-looking statements. Examples of such statements include, but are not limited to, statements relating to (i) Ascendis' expectations regarding the potential benefits of SKYTROFA, (ii) Ascendis' expectations regarding the projected timing of commercial availability in U.S. of SKYTROFA and the SKYTROFA® Auto-Injector, (iii) Ascendis' expectations regarding a full suite of patient support programs, (iv) Ascendis' ability to apply its platform technology to build a leading, fully integrated biopharma company, (v) Ascendis' product pipeline and expansion into additional therapeutic areas and (vi) Ascendis' expectations regarding its ability to utilize its TransCon technologies to create new and potentially best-in-class therapies. Ascendis may not actually achieve the plans, carry out the intentions or meet the expectations or projections disclosed in the forward-looking statements and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions, expectations and projections disclosed in the forward-looking statements. Various important factors could cause actual results or events to differ materially from the forward-looking statements that Ascendis makes, including the following: dependence on third party manufacturers to supply SKYTROFA, the SKYTROFA® Auto-Injector and other study drug for commercial sales and clinical studies; unforeseen safety or efficacy results in its SKYTROFA program or other programs; unforeseen expenses related to commercialization of SKYTROFA and the development of SKYTROFA or other development programs, selling, general and administrative expenses, other research and development expenses and Ascendis' business generally; delays in the development of SKYTROFA or other development programs related to manufacturing, regulatory requirements or other unforeseen delays; Ascendis' ability to obtain additional funding, if needed, to support its business activities and the effects on its business of the worldwide COVID-19 pandemic. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Ascendis' business in general, see Ascendis' Annual Report on Form 20-F filed with the U.S. Securities and Exchange Commission (SEC) on March 10, 2021 and Ascendis' current and future reports filed with, or submitted to, the SEC. Forward-looking statements do not reflect the potential impact of any future in-licensing, collaborations, acquisitions, mergers, dispositions, joint ventures, or investments that Ascendis may enter into or make. Ascendis does not assume any obligation to update any forward-looking statements, except as required by law.

Investor contacts:
Tim Lee
Ascendis Pharma
(650) 374-6343
tle@ascendispharma.com

Media contact:
Melinda Baker
Ascendis Pharma
media@ascendispharma.com

Patti Bank
Westwicke Partners
(415) 513-1284
patti.bank@westwicke.com
ir@ascendispharma.com

[i] Thornton PS, Maniatis AK, Aghajanova E, et al. Weekly Lonapegsomatropin in Treatment-Naïve Children with Growth Hormone Deficiency: The Phase 3 heiGHt Trial. J Clin Endocrinol Metab. 2021 Jul 17;dgab529. doi: 10.1210/clinem/dgab529. Online ahead of print

[ii] SKYTROFA (lonapegsomatropin-tcdg) prescribing information, Ascendis Pharma 2021.

Source: Ascendis Pharma