HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YUVIWEL safely and effectively. See full prescribing information for YUVIWEL.

YUVIWEL® (navepegritide) for injection, for subcutaneous use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------

YUVIWEL is a C-type natriuretic peptide (CNP) analog indicated to increase linear growth in pediatric patients 2 years of age and older with achondroplasia with open epiphyses. (1)

This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer once-weekly by subcutaneous injection. Dosage is based on body weight. (2.1)
- Periodically monitor growth and adjust dose according to body weight. Discontinue when no further growth potential, as indicated by epiphyseal closure. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 1.3 mg, 2.8 mg, and 5.5 mg as a lyophilized powder in single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

Risk of Low Blood Pressure: Transient decreases in blood pressure have been reported with a once daily CNP analog. Advise patients to contact their healthcare provider if they experience symptoms of decreased blood pressure while being treated with YUVIWEL. (5.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 5%): vomiting, injection-site reaction, pain in extremity, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ascendis Pharma at 1-844-442-7236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Renal Impairment: Not recommended for patients with moderate or severe renal impairment (eGFR < 60 mL/min/1.73 m^2). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

YUVIWEL® is indicated to increase linear growth in pediatric patients 2 years of age and older with achondroplasia with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

The recommended once-weekly dosage of YUVIWEL is based on the patient´s body weight (see Table 1).

YUVIWEL is administered by subcutaneous injection. YUVIWEL must be reconstituted prior to use *[see Dosage and Administration (2.3)]*.

Table 1: Recommended YUVIWEL Weekly Dosage and Injection Volume

Patient Body weight	Weekly Dose	Injection Volume	Vial Strength for Reconstitution*
8 to 9.9 kg	0.88 mg	0.4 mL	1.3 mg
10 to 13.4 kg	1.2 mg	0.55 mL	
13.5 to 17.5 kg	1.6 mg	0.35 mL	2.8 mg
17.6 to 23 kg	2.1 mg	0.45 mL	
23.1 to 30.5 kg	2.8 mg	0.6 mL	
30.6 to 41.2 kg	3.6 mg	0.65 mL	5.5 mg
41.3 to 55.9 kg	5 mg	0.9 mL	
56 to 73.5 kg	6.6 mg	1.2 mL (use 2 Kits) Administer 0.6 mL from each Kit	
73.6 to 90 kg	8.8 mg	1.6 mL (use 2 Kits) Administer 0.8 mL from each Kit	

*The concentration of navepegritide is 2.2 mg/mL in a reconstituted 1.3 mg vial; 4.6 mg/mL in a reconstituted 2.8 mg vial; and 5.5 mg/mL in a reconstituted 5.5 mg vial.

Switching from Daily C-type Natriuretic Peptide (CNP) Analog

Start once-weekly YUVIWEL on the day after completing the last dose of daily CNP therapy.

2.2 Monitor Growth

Periodically monitor the patient's growth and adjust the dosage according to the actual body weight *[see Dosage and Administration (2.1)]*. Discontinue YUVIWEL upon confirmation of no further growth potential, indicated by closure of the epiphyses.

2.3 Preparation of YUVIWEL for Administration

Patients and caregivers who will administer YUVIWEL should receive appropriate training by a healthcare provider prior to use. Refer to the Instructions for Use for complete preparation and administration instructions with illustrations.

Before administration, reconstitute YUVIWEL using the provided prefilled diluent syringe containing Sterile Water for Injection as described below.

- Needles and syringes supplied with YUVIWEL are for single use only.
- If the product was refrigerated, allow the YUVIWEL vial and the prefilled diluent syringe to reach room temperature (about 30 minutes) before reconstitution.
- Screw a preparation needle onto the prefilled diluent syringe and inject the entire diluent volume into the vial. Shake the vial up and down for 15 seconds. Do not swirl or roll. The reconstituted YUVIWEL vial should stand at room temperature for 5 minutes after shaking. Dispose the diluent syringe with attached preparation needle immediately after injecting the diluent into the vial.
- YUVIWEL should be visually inspected for particles or discoloration prior to administration, whenever solution and container permit. Once reconstituted, YUVIWEL is a clear and colorless solution. Do not use the solution if it is discolored, cloudy or contains visible particles. Air bubbles may be seen, and this is normal.
- Screw a new preparation needle onto the injection syringe and withdraw the prescribed injection volume from the reconstituted vial. Remove air from the withdrawn dose volume before continuing and ensure the withdrawn dose volume is correct after removing any air.
- Remove and dispose the preparation needle from the injection syringe.
- Screw the injection needle onto the injection syringe before administration.
- Two Kits are needed to achieve a complete dose for patients with body weight 56 kg or greater, where the prescribed injection volume is greater than 1 mL.
- Reconstituted YUVIWEL can be stored at room temperature up to 30˚C (86˚F) for up to 4 hours.

2.4 Administration Instructions

Refer to the Instructions for Use for complete administration instructions with illustrations.

- Using the prepared syringe, administer the prescribed injection volume *[see Dosage and Administration (2.1, 2.3)]*.
- Administer YUVIWEL subcutaneously in the abdominal region (2 inches from the belly button) or thighs. If a caregiver is administering YUVIWEL, subcutaneous injection in the buttocks or back of the upper arm is also acceptable.
- Rotate injection sites. Do not give an injection into sites other than described above. Avoid injecting where the skin is red, swollen, or scarred.
- Administer YUVIWEL once weekly on the dosing day, at any time of day.
- All YUVIWEL components are for single use only. Do not draw up more than one injection volume, as specified in Table 1, from a vial. For injection volumes greater than 1 mL, use two Kits to achieve a complete dose. The two injections must be given one after the other, using different injection sites.
- Discard the unused reconstituted solution.

2.5 Missed Dose

- If a dose of YUVIWEL is missed, administer the missed dose as soon as possible but not more than 2 days after the missed dosing day.
- To avoid missed doses, YUVIWEL can be taken up to 2 days before or 2 days after the scheduled dosing day. Resume once-weekly dosing for the next dose at the previously scheduled dosing day.
- If more than 2 days have passed from the dosing day, skip the missed dose and administer the dose on the next regularly scheduled day.
- At least 5 days should elapse between doses.

3 DOSAGE FORMS AND STRENGTHS

For injection: 1.3 mg, 2.8 mg, and 5.5 mg of CNP(89-126) as a white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Low Blood Pressure

Transient decreases in blood pressure have been reported with a once daily CNP analog. Subjects with hemodynamically significant cardiovascular disease were excluded from participation in navepegritide clinical trials. Advise patients to contact their healthcare provider if they experience symptoms of decreased blood pressure (e.g., dizziness, fatigue and/or nausea) while being treated with YUVIWEL.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of YUVIWEL was evaluated in pediatric patients with achondroplasia in two randomized, placebo-controlled trials of navepegritide. Trial 1 included a 52-week, randomized, double-blind, placebo-controlled period, followed by a 52-week, single-arm, open-label extension (OLE) period. In Trial 1, 84 pediatric participants with achondroplasia (mean age 5.7 years; range: 2 to 12 years) were randomized to subcutaneous navepegritide 0.1 mg/kg/week (n = 57) or placebo (n = 27) *[see Clinical Studies (14)]*. Trial 2 included a randomized, double-blind, placebo-controlled dose-finding period. In Trial 2, 57 pediatric participants with achondroplasia (mean age 5.9 years; range: 2 to 10 years) were randomized 3:1 to subcutaneous navepegritide 0.006, 0.02, 0.05, or 0.1 mg/kg or placebo for 52 weeks. At Week 52, all participants transitioned to an OLE period during which they received navepegritide 0.1 mg/kg/week for 104 weeks.

The adverse reaction rates for navepegritide were derived from pediatric participants with achondroplasia who received navepegritide 0.1 mg/kg/week or placebo during the double-blind period of Trials 1 and 2. Of the dosages evaluated in Trials 1 and 2, 0.1 mg/kg/week is most similar to the approved weight-based dosage listed in Table 1.

Adverse reactions reported in the placebo-controlled pooled periods of Trials 1 and 2 in ≥ 5% of navepegritide-treated patients and at an incidence at least 2% greater than with placebo are presented in Table 2.

Table 2: Adverse Reactions Reported in ≥ 5% of Participants Treated with Navepegritide 0.1 mg/kg/week and ≥ 2% Higher Than Placebo During the Placebo-Controlled Period of Trials 1 and 2

Adverse Reaction	NAVEPEGRITIDE 0.1 mg /kg/week N = 68 n (%)	Placebo N = 42 n (%)
Vomiting	14 (21)	6 (14)
Injection-site reaction*	13 (19)	6 (14)
Pain in extremity	8 (12)	3 (7)
Nausea	4 (6)	0

*Includes injection-site swelling, injection-site erythema, injection-site bruising, injection-site reaction, injection-site pruritus, injection-site discoloration, injection-site hemorrhage, injection-site pain, injection-site vesicles, and injection-site edema.

Injection-Site Reactions

During the 52-week double-blind period of Trials 1 and 2, 13 of 68 (19%) participants receiving navepegritide 0.1 mg/kg/week experienced a total of 25 events of injection-site reactions, while 6 of 42 (14%) participants receiving placebo experienced a total of 6 events of injection site reactions, corresponding to 0.4 events per person year exposure and 0.2 events per person year exposure, respectively.

Other Adverse Reactions from Trials 1 and 2 (Pooled)

Hypertrichosis

Hypertrichosis was reported in 2 of 68 patients (3%) receiving navepegritide 0.1 mg/kg/week compared to none receiving placebo in the double-blind periods of Trials 1 and 2. Cases presented as localized hair growth at injection sites or generalized increased body hair growth affecting limbs, back, or shoulders. To reduce the risk of local skin changes, rotate the site of injection with each dose.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of YUVIWEL in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, subcutaneous administration of navepegritide during the period of organogenesis in pregnant rats and rabbits resulted in no impact on embryo-fetal survival or congenital malformations at doses up to 10- and 7-fold, respectively, the exposure at the maximum recommended human dose (MRHD) *(see Data)*.

Achondroplasia is an autosomal dominant genetic disorder with 100% penetrance. Therefore, there is a 50% risk for a parent with achondroplasia to have a child with achondroplasia. The estimated background risk of birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal developmental toxicity study in pregnant rats, navepegritide was administered subcutaneously during the period of organogenesis (gestation day 6 to 20) at doses from 0.45 to 1.3 mg/kg/day.

There was no effect on embryo-fetal survival, fetal toxicity, or embryo-fetal development up to the highest dose tested, corresponding to 10-fold the exposure at the MRHD [based on area under the curve (AUC)].

In an embryo-fetal developmental toxicity study in pregnant rabbits, navepegritide was administered subcutaneously during the period of organogenesis (gestation day 7 to 27) at doses from 0.3 to 0.9 mg/kg/every fourth day. There was no effect on embryo-fetal survival, fetal toxicity, or congenital malformations up to the highest dose tested, corresponding to 7-fold the exposure at the MRHD (based on AUC).

8.2 Lactation

Risk Summary

There is no information available regarding the presence of navepegritide in human milk or regarding the potential effects on milk production or on the breastfed newborn/infant. High molecular weight therapeutic compounds, including navepegritide, are expected to have low passage into human milk. Further, no or low anticipated oral absorption of navepegritide will limit any systemic bioavailability in the breastfed newborn/infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YUVIWEL and any potential adverse effects on the breastfed infant from YUVIWEL or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of YUVIWEL to increase linear growth have been established in pediatric patients aged 2 years and older with achondroplasia with open epiphyses.

Use of YUVIWEL for this indication is supported by evidence from a 52-week, randomized, placebo-controlled trial in 84 pediatric patients with achondroplasia *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

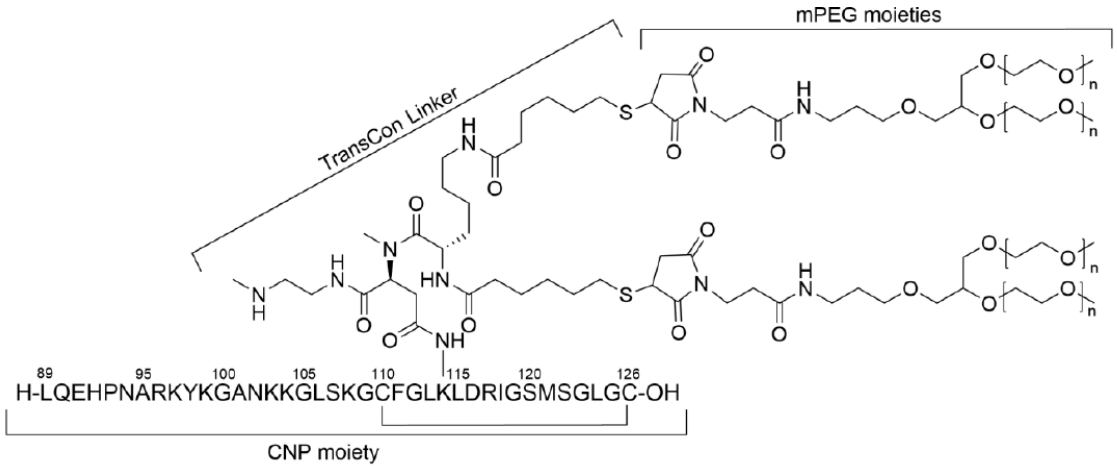
The safety and effectiveness of YUVIWEL in pediatric patients less than 2 years of age have not been established.

8.6 Renal Impairment

YUVIWEL is not recommended for patients with moderate or severe renal impairment (eGFR < 60 mL/min/1.73 m^2). The recommended dosage for patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m^2) is the same as the recommended dosage for patients with normal renal function *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

YUVIWEL for injection contains navepegritide, a C-type natriuretic peptide (CNP) analog. Navepegritide is a prodrug of active CNP consisting of a CNP moiety transiently conjugated to two branched 20 kDa methoxy polyethylene glycol (mPEG) moieties via a proprietary TransCon® Linker. The amino acid sequence of the CNP moiety is identical to the 38 amino acid sequence of residues 89-126 of human CNP. The structural formula of navepegritide is as follows:



Abbreviations: CNP = C-type natriuretic peptide; mPEG = methoxy polyethylene glycol; n≈200-250

The molecular formula is $C_{231}H_{386}N_{64}O_{67}S_5$ + 4 × $(C_2H_4O)n$, where n is between 200 and 250. The average molecular weight is approximately 45 kDa.

YUVIWEL is provided as a sterile, lyophilized white to off-white powder for reconstitution to a colorless solution with Sterile Water for Injection, USP (diluent). The diluent for reconstitution of YUVIWEL is provided in a prefilled syringe.

The compositions of YUVIWEL are shown in Table 3.

Table 3: Content of YUVIWEL

Strength	**Composition of YUVIWEL (gross content per vial)***	**CNP(89-126) Concentration After Reconstitution**
1.3 mg/vial	Navepegritide equivalent to 1.9 mg CNP(89-126), succinic acid (1.0 mg), trehalose dihydrate (72.2 mg), tromethamine and hydrochloric acid (q.s. for adjustment to pH 5.0)	2.2 mg/mL
2.8 mg/vial	Navepegritide equivalent to 4.0 mg CNP(89-126), succinic acid (1.0 mg), trehalose dihydrate (66.7 mg), tromethamine and hydrochloric acid (q.s. for adjustment to pH 5.0)	4.6 mg/mL
5.5 mg/vial	Navepegritide equivalent to 6.9 mg CNP(89-126), succinic acid (1.5 mg), trehalose dihydrate (91.9 mg), tromethamine and hydrochloric acid (q.s. for adjustment to pH 5.0)	5.5 mg/mL

*An overfill is included in the vial to compensate for loss in the vial and during transfer.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CNP released from navepegritide has the same receptor binding affinity and activity as endogenous CNP. CNP binds to natriuretic peptide receptor-B (NPR-B), which inhibits the mitogen activated protein kinase signaling (MAPK) pathway.

Achondroplasia is caused by a gain-of-function variant in the fibroblast growth factor receptor 3 (FGFR3) leading to overactive downstream signaling. The overly active FGFR3 inhibits endochondral ossification leading to short stature and skeletal dysplasia. Like endogenous CNP, CNP released from navepegritide binds to NPR-B, stimulating an increase in cyclic guanosine monophosphate (cGMP) and signaling through protein kinase G, resulting in an inhibition of the MAPK signaling pathway and thereby antagonizing the overactive FGFR3 signaling in achondroplasia. CNP promotes chondrocyte differentiation and proliferation, thereby stimulating skeletal bone growth in patients with achondroplasia.

12.2 Pharmacodynamics

Natriuretic Peptide Receptor B (NPR-B) Activity Marker

There was a dose-dependent (0.006 mg/kg/week to 0.1 mg/kg/week) increase in plasma cGMP levels in pediatric patients with achondroplasia following 52 weeks of once-weekly administration of navepegritide.

Cardiac Electrophysiology

At the approved recommended dose, YUVIWEL does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of navepegritide, a prodrug releasing CNP following subcutaneous administration, have been investigated at single doses of 0.003 to 0.15 mg/kg in healthy adults, and at weekly doses of 0.006 to 0.1 mg/kg in patients with achondroplasia. Plasma concentrations of navepegritide and CNP released from navepegritide increased proportionally with dose within the range of 0.01 to 0.15 mg/kg.

In patients with achondroplasia administered navepegritide 0.1 mg/kg once-weekly, the predicted steady state geometric mean (CV) maximum plasma concentration (C_{max}) of navepegritide was 1,360 ng/mL (8.3%) and the predicted geometric mean (CV) exposure over the weekly dosing interval AUC was 193,000 h*ng/mL (6.1%). For CNP released from navepegritide, the predicted geometric mean (CV) C_{max} was 36.0 pmol/L (23%) and the predicted geometric mean (CV) AUC over the weekly dosing interval was 4,410 h*pmol/L (23%).

In patients with achondroplasia, steady state levels of navepegritide and CNP released from navepegritide were achieved after approximately 3 once-weekly doses. Median accumulation ratios of navepegritide and CNP released from navepegritide following once-weekly dose administration were 1.9 and 1.7, respectively.

Absorption

In patients with achondroplasia administered navepegritide 0.1 mg/kg once-weekly, the geometric mean (CV) time to reach maximum concentration (T_{max}) of navepegritide was 43.4 hours (15%). For CNP released from navepegritide, the geometric mean (CV) T_{max} was 24.4 hours (13%).

The absolute bioavailability of navepegritide following subcutaneous dose administration has not been investigated.

Distribution

The model-derived geometric mean (CV) apparent volume of distribution of navepegritide and CNP released from navepegritide was 1.8 (33%) L and 5.1 (30%) L, respectively.

Elimination

The model-derived geometric mean (CV) steady state apparent clearance of navepegritide and CNP released from navepegritide was 0.052 (33%) and 1,950 (39%) L/day, respectively.

In patients with achondroplasia administered navepegritide 0.1 mg/kg once weekly, the predicted mean apparent elimination half-life of navepegritide was 6.7 days, and the mean apparent elimination half-life of CNP released from navepegritide was 5.3 days.

Metabolism

Following subcutaneous dose administration, navepegritide releases CNP via auto-cleavage of the TransCon Linker that follows first-order kinetics, resulting in continuous systemic exposure of CNP over the weekly dosing interval.

CNP metabolism follows natural degradation pathways for peptides, resulting in small peptide fragments and amino acids.

Specific Populations

Based on a population pharmacokinetic analysis, no clinically meaningful effects on the pharmacokinetics of navepegritide were observed for age (2 to 59.6 years), sex (66% male, 34% female), race (21% Asian, 1.8% Black or African American, 75% White, and 1.8% Other), ethnicity (11% Hispanic or Latino, 87% not Hispanic or Latino, 1% not reported or unknown) and mild (eGFR: 60 to < 89 mL/min/1.73 m^2) renal impairment. The effect of hepatic impairment on the pharmacokinetics of navepegritide was not studied.

Drug Interaction Studies

No in vitro assessments or clinical studies evaluating the drug-drug interaction potential of navepegritide have been conducted.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assays used. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in studies of other products.

Of 73 patients who received navepegritide 0.1 mg/kg once-weekly for up to 3 years, 30% (22/73) developed antibodies against navepegritide or CNP. These antibodies were transiently detected at a low level with no identified clinically significant effect on the pharmacokinetics, efficacy, or safety of navepegritide. The neutralizing ability of anti-drug antibodies is unknown due to the limitations of the neutralizing antibody assay.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Long-term animal studies to address the carcinogenic potential of navepegritide have not been conducted.

Navepegritide was not genotoxic in an in vitro bacterial reverse-mutation assay (Ames test), an in vitro human lymphocyte chromosomal aberration assay or an in vivo rat bone marrow micronucleus assay.

Impairment of Fertility

In fertility studies, navepegritide was administered by subcutaneous injection at 0.5, 1.0, and 2.0 mg/kg/week to male and female rats. Navepegritide had no effect on mating performance, fertility, litter characteristics or early embryo-fetal development up to the highest dose tested corresponding to 3-fold the MRHD in male rats (based on body surface area) and 4-fold exposure in female rats (based on AUC).

14 CLINICAL STUDIES

The effectiveness of YUVIWEL has been established in a clinical trial of navepegritide consisting of a randomized, double-blind, placebo-controlled 52-week period, followed by a single-arm 52-week OLE period (Trial 1; NCT05598320).

Trial 1 enrolled 84 treatment-naïve pediatric patients with genetically confirmed achondroplasia: 57 patients received navepegritide 0.1 mg/kg administered subcutaneously once weekly, and 27 received placebo.

The mean age at enrollment was 5.7 years (range: 2 to 12). Forty-five patients (54%) were male, and 39 patients (46%) were female. Overall, 74 patients (88%) were White, 8 patients (10%) were Asian, and 2 patients (2%) were mixed race. The patients had a mean baseline CDC-based height Z-score of -5.0 and mean baseline height of 89 cm (range: 64 to 120).

The primary efficacy endpoint was annualized growth velocity (AGV) at Week 52. Height Z-scores calculated using reference data from untreated children with achondroplasia (achondroplasia-specific height Z-score) and using reference data from the general population (CDC-based height Z-score) were also evaluated.

Treatment with once-weekly navepegritide for 52 weeks resulted in a least-squares mean treatment difference in AGV of 1.5 cm/year and a least-squares mean increase from baseline in achondroplasia-specific height Z-score of 0.3 (see Table 4).

Table 4: Growth Parameters in Pediatric Patients with Achondroplasia Treated with Navepegritide and Placebo at Week 52 in Trial 1

	NAVEPEGRITIDE (N = 57)	**Placebo (N = 27)**	**Treatment Difference [95% CI][a]**	**p-value**
Annualized growth velocity (cm/year)	5.9	4.4	1.5 [1.0, 1.9]	< 0.0001
Change from baseline				
Achondroplasia-specific height Z-score[b]	0.3	0.0	0.3 [0.2, 0.4]	< 0.0001
CDC height Z-score[c]	0.1	-0.2	0.3 [0.1, 0.5]	NA[d]

Note: Data presented are least-square (LS) means unless otherwise noted.
Abbreviations: AGV, annualized growth velocity; CI, confidence interval; NA, not applicable.
[a]Treatment differences between YUVIWEL and placebo were estimated from an analysis of covariance (ANCOVA) model that included treatment, strata (defined by sex and age), baseline age, and baseline achondroplasia-specific height Z-score as covariates.
[b]Calculated using the reference data from untreated patients with achondroplasia (CLARITY Natural History Study).
[c]Calculated using the Centers for Disease Control and Prevention (CDC) reference data from the general population.
[d]The endpoint was analyzed outside of the pre-specified multiple testing strategy.

Improvements in AGV and height Z-scores were observed in navepegritide-treated patients across all predefined subgroups analyzed, including age group, sex, and region. In patients < 5 years of age, the least-squares mean treatment difference for AGV at Week 52 was 1.0 cm/year. In patients ≥ 5 years of age, the least-squares mean treatment difference was 1.8 cm/year.

Long-term Treatment Effect

All 57 patients in a 52-week randomized, double-blind, placebo-controlled Phase 2 dose-finding trial (Trial 2; NCT04085523) entered the single-arm OLE and continued treatment with navepegritide. AGV was maintained among those who had received 2 years of treatment with navepegritide 0.1 mg/kg once weekly.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

YUVIWEL (navepegritide) for injection is supplied as a lyophilized white to off-white powder in a vial, in three strengths: 1.3 mg, 2.8 mg, and 5.5 mg (see Table 5). Each YUVIWEL carton contains 4 Kits with 1 Prescribing Information, and 1 Instructions for Use.

Table 5: YUVIWEL Strengths and Contents of Each Kit

Strength	Contents of Each Kit (4 Kits in each carton)	Carton NDC
1.3 mg vial	• One 1.3 mg single-dose vial of YUVIWEL for injection with yellow cap • One 0.8 mL Sterile Water for Injection, USP (clear, colorless prefilled diluent syringe) • 2 single use preparation needles (21 gauge) • 1 single use injection syringe • 1 single use injection needle (30 gauge)	73362-201-01
2.8 mg vial	• One 2.8 mg single-dose vial of YUVIWEL for injection with blue cap • One 0.8 mL Sterile Water for Injection, USP (clear, colorless prefilled diluent syringe) • 2 single use preparation needles (21 gauge) • 1 single use injection syringe • 1 single use injection needle (30 gauge)	73362-202-01
5.5 mg vial	• One 5.5 mg single-dose vial of YUVIWEL for injection with violet cap • One 1.1 mL Sterile Water for Injection, USP (clear, colorless prefilled diluent syringe) • 2 single use preparation needles (21 gauge) • 1 single use injection syringe • 1 single use injection needle (30 gauge)	73362-203-01

Only use the vial, needles, and syringes that are in the Kits for handling of YUVIWEL *[see Dosage and Administration (2.3)]* and do not use the components for other medicinal products.

Storage and Handling

- Store YUVIWEL refrigerated between 2°C to 8°C (36°F to 46°F). Store in the original packaging until time of use to protect from light. Do not freeze.
- YUVIWEL can also be stored at room temperature up to 30°C (86°F) for up to 6 months and can be returned to refrigeration within the 6 months. Do not use YUVIWEL beyond the expiration date or 6 months after the date it was first removed from refrigeration (whichever is earlier).
- Reconstituted YUVIWEL can be stored at room temperature up to 30°C (86°F) for up to 4 hours.
- Discard unused reconstituted solution.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Administration Instructions

Provide appropriate instructions for injection to the patient/caregiver based on the YUVIWEL Instructions for Use (available at www.Yuviwel.com). Patients/caregivers and healthcare providers may also call the Ascendis Pharma Customer Support toll-free number at 1-844-442-7236 (1-844-44ASCENDIS) for assistance or additional training, if needed.

- Advise patients/caregivers to refer to the Instructions for Use that accompanies YUVIWEL for complete reconstitution and administration instructions with illustrations *[see Dosage and Administration (2.3, 2.4)]*.
- Advise patients/caregivers to administer YUVIWEL once weekly on the dosing day, at any time of day.
- Advise patients and caregivers to rotate the site of injection to reduce the risk of injection site reactions *[see Dosage and Administration (2.4)]*.

Missed Dose *[see Dosage and Administration (2.5)]*

- Advise patients/caregivers that to avoid missed doses, YUVIWEL can be taken up to 2 days before or 2 days after the scheduled dosing day.
- If a dose is missed and more than 2 days have passed from the scheduled day, advise patients/caregivers to skip the missed dose and administer the next dose on the regularly scheduled day.
- To change the regular dosing day to a different day of the week, advise patients/caregivers to ensure that at least 5 days will elapse between the last dose and the newly established regular dosing day.

Risk of Low Blood Pressure

Advise patients and/or caregivers to contact their healthcare provider if they experience symptoms of decreased blood pressure (e.g., dizziness, fatigue, and/or nausea) while being treated with YUVIWEL *[see Warnings and Precautions (5.1)]*.

Manufactured for:
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