HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZANVASTRO™ (zilganersen) injection, for intrathecal use
Initial U.S. Approval: 2026

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

ZANVASTRO is a glial fibrillary acidic protein (GFAP)-directed antisense oligonucleotide indicated for the treatment of Alexander disease in pediatric and adult patients. (1)

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

- ZANVASTRO is administered intrathecally. (2.1)
- The recommended dosage is 50 mg every 3 months. (2.1)

Dilution, Preparation, and Administration

- ZANVASTRO must be diluted with accompanying artificial cerebrospinal fluid (aCSF) diluent prior to administration. (2.2)
- After dilution, administer as an intrathecal bolus injection over 1 to 3 minutes. (2.3)
- See full prescribing information for complete preparation and administration instructions. (2.2, 2.3)

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

Injection: 56 mg/2.8 mL (20 mg/mL) in a single-dose vial (3)

Artificial cerebrospinal fluid Diluent: 21 mL solution in a single-dose vial for dilution of ZANVASTRO (3)

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

None. (4)

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

Most common adverse reactions (incidence >25% patients treated with ZANVASTRO and greater than control) were vomiting, back pain, cough, headache, and post-lumbar puncture syndrome. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ionis Pharmaceuticals, Inc. at 1-833-644-6647 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZANVASTRO is indicated for the treatment of Alexander disease in pediatric and adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Administer ZANVASTRO intrathecally after dilution using a lumbar puncture by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

The recommended dosage of ZANVASTRO is 50 mg intrathecally every 3 months.

The final dose volume of the intrathecal injection is determined by the patient's age *[see Dosage and Administration (2.2)]*.

Missed Dose(s)

If a dose of ZANVASTRO is missed, administer ZANVASTRO as soon as possible. Resume treatment at the recommended dosing frequency from the date of the most recently administered dose.

2.2 Dilution and Preparation Instructions

Read the entire Instructions for Use provided in the carton before diluting and preparing ZANVASTRO for intrathecal administration.

Each carton contains 1 vial of ZANVASTRO and 1 vial of diluent to be used together to prepare a single dose. The diluent vial contains more volume than needed. Discard excess diluent prior to dilution as instructed below.

Prepare ZANVASTRO according to the instructions below and in Table 1.
Use aseptic technique when preparing and administering ZANVASTRO intrathecally.

1. Use a 3 mL and/or 10 mL syringe with an 18G to 22G needle to withdraw excess aCSF diluent from the diluent vial as determined by Table 1 based on the patient's age. Keep the diluent vial containing the remaining diluent for Step 3. Discard the syringe(s) containing the excess diluent.
2. Use a 3 mL syringe with an 18G to 22G needle to withdraw 2.8 mL of ZANVASTRO from the ZANVASTRO vial.
3. Add the withdrawn volume of ZANVASTRO to the diluent vial.
4. Gently invert the diluent vial (which now also contains ZANVASTRO) several times to mix the solution.
5. Attach an 18G or 19G filter needle (5 micron) to a 20 mL syringe. Withdraw the recommended dose volume of diluted ZANVASTRO from the diluent vial as determined by Table 1 based on the patient's age.
6. Remove the filter needle. Attach a syringe tip cap to the prepared dosing syringe.
7. Label the prepared dosing syringe per institution procedures prior to use or transport.
8. Discard any unused portion of the diluted solution and any unused contents of the ZANVASTRO vial.

Table 1. ZANVASTRO Dilution Procedure

Patient Age	Volume of excess aCSF diluent to withdraw from the diluent vial and discard	Volume of ZANVASTRO to add to the diluent vial	Volume of diluted ZANVASTRO to withdraw from the diluent vial for administration (dose volume)
Less than 2 years old	12.6 mL	2.8 mL	10 mL
2 to 7 years old (inclusive)	7.0 mL	2.8 mL	15 mL
8 years old and above	1.4 mL	2.8 mL	20 mL

Storage of Prepared Dosing Syringe

ZANVASTRO contains no preservatives. Once drawn into the dosing syringe, the solution must be administered within:

- 4 hours of preparation if kept at room temperature up to 30°C (86°F).
- 24 hours of preparation if refrigerated at 2°C to 8°C (36°F to 46°F).

Do not freeze. Do not expose to heat. Protect the prepared dosing syringe from light as a precaution.

2.3 Administration Instructions

Procedural Preparation Instructions

- If indicated by the clinical condition of the patient, consider sedation or local anesthesia.
- If indicated by the clinical condition of the patient, consider imaging to guide intrathecal administration of ZANVASTRO.
- Evaluate patients prior to intrathecal injection for factors that increase risks associated with lumbar puncture.

Administration

If the prepared dosing syringe is refrigerated prior to administration, allow the dosing syringe to warm to room temperature for at least 30 minutes prior to use for patient comfort. Do not use external heat sources to warm the dosing syringe *[see Storage and Handling (16.2)]*.

Prior to administration, remove a volume of the patient's CSF approximately equal to the intended dose volume as appropriate for age, based on Table 2, using a lumbar puncture needle.

Table 2. Recommended Injection Dose Volume

Age	Injection Dose Volume After Dilution
Less than 2 years old	10 mL
2 years old to 7 years old (inclusive)	15 mL
8 years old and above	20 mL

Administer ZANVASTRO as an intrathecal bolus injection over 1 to 3 minutes using the lumbar puncture needle. Do not flush the needle or any attached extension catheter, if used, after administration.

Discard the dosing syringe.

3 DOSAGE FORMS AND STRENGTHS

Injection: 56 mg/2.8 mL (20 mg/mL) zilganersen as a clear, colorless to slightly yellow solution in a single-dose vial

Artificial cerebrospinal fluid diluent: 21 mL as a clear and colorless solution in a single-dose vial for dilution of ZANVASTRO

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Aseptic Meningitis

If symptoms consistent with aseptic meningitis develop, diagnostic workup and treatment should be initiated according to the standard of care.

Adverse reactions of aseptic meningitis (also called chemical meningitis or drug-induced aseptic meningitis) were reported in patients treated with ZANVASTRO during the double-blind and open-label periods of Study 1. One patient experienced a serious adverse reaction of aseptic meningitis during the double-blind treatment period of Study 1, which reoccurred in the open-label extension period and required dose interruption and pretreatment with intravenous dexamethasone prior to subsequent administration of ZANVASTRO. Despite corticosteroid premedication, CSF white blood cell (WBC) and protein increased with continued exposure but the patient remained asymptomatic and did not require discontinuation from treatment. In addition, nonserious adverse drug reactions of CSF WBC increased have also been reported with ZANVASTRO *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Aseptic Meningitis *[see Warnings and Precautions (5.1)]*

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 ZANVASTRO was evaluated in 53 pediatric and adult patients with Alexander disease in Study 1 *[see Clinical Studies (14)]*. Thirty-eight patients received ZANVASTRO for 1 year, and 18 patients received ZANVASTRO for 2 years. The median exposure was 60 weeks in all groups.

The most common adverse reactions during the Double-Blind Treatment Period (incidence >25% of patients treated with ZANVASTRO 50 mg and greater than control) were vomiting, back pain, cough, headache, and post-lumbar puncture syndrome. Table 3 includes the common adverse reactions that occurred in ≥10% of patients treated with ZANVASTRO and 10% greater than control.

Table 1. Adverse Reactions in Patients with Alexander Disease that Occurred in ≥10% of Patients Treated with ZANVASTRO and 10% Greater than Control

Adverse Reaction	**ZANVASTRO 50 mg N=24 %**	**Control N=17 %**
Vomiting	50	29
Back pain	50	18
Cough	38	18
Headache	29	12
Post lumbar puncture syndrome	29	6
Arthralgia	25	6
Oropharyngeal pain	21	0
Dysphagia	17	6

Patients Less Than 2 Years of Age

The adverse reactions of patients less than 2 years of age are expected to be similar to that of pediatric patients 2 years of age and older.

Increased White Blood Cell Count in the CSF

Pleocytosis (or increased white blood cell count in CSF) was observed in 7 (29%) patients treated with ZANVASTRO 50 mg following the administration of the first 2 to 4 doses, compared to 3 (18%) patients in the control group in the double-blind treatment period of the Main Study, and in an additional 6 patients treated with ZANVASTRO in the open-label extension period *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on ZANVASTRO use in pregnant women to inform drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

No adverse effects on embryofetal development were observed when zilganersen was administered every 2 weeks prior to mating and every two days during mating and through organogenesis at doses up to 60 mg/kg. The high dose was approximately 6 times the maximum recommended human dose on a per-dose BSA basis.

Zilganersen has not been evaluated for potential effects on embryofetal development in rabbits or in pre- and postnatal development toxicity studies.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data
No adverse effects on embryofetal development were noted in a combined fertility and embryo-fetal development study in CD1 mice, which were subcutaneously administered zilganersen at doses of 10, 30, and 60 mg/kg every two weeks prior to mating and every two days during mating and through organogenesis (the high dose is equivalent to up to 6 times the maximum recommended human dose [MRHD, 50 mg quarterly] on a per-dose body-surface-area [BSA] basis.

8.2 Lactation

Risk Summary

There are no data on the presence or absence of ZANVASTRO or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The presence of ZANVASTRO in breast milk was not studied in animals. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZANVASTRO and any potential adverse effects on the breastfed child from ZANVASTRO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ZANVASTRO for the treatment of Alexander disease have been established in pediatric patients. Use of ZANVASTRO in pediatric patients aged 2 to less than 18 years is supported by evidence from an adequate and well-controlled study *[see Clinical Studies (14)]*. Use of ZANVASTRO in pediatric patients less than 2 years of age is supported by evidence from an adequate and well-controlled study of ZANVASTRO in patients 2 years of age and older with Alexander disease, pharmacokinetic analyses and modeling showing CSF drug exposure levels after a 50 mg dose in patients less than 2 years of age are expected to be similar to those observed after a 50 mg dose in patients 2 years of age and older, and safety data in 4 pediatric patients less than 2 years of age treated with ZANVASTRO *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

Juvenile Animal Toxicity Data

Neurobehavioral deficits including locomotor hypoactivity with a pharmacologically active mouse-specific surrogate ASO at 0.1 mg [9 times the maximum recommended human dose (MRHD), normalized to CSF volume] were noted in an intracerebroventricular toxicity study in juvenile mice administered the surrogate

ASO every six weeks via the intracerebroventricular route for 13 weeks. No adverse effects were observed at doses up to 0.2 mg, at 17 times the MRHD on a per-dose basis, normalized to CSF volume, in the parallel group administered zilganersen (0, 0.05, 0.1, or 0.2 mg) via the same dosing regimen.

Transient patellar reflex losses, occasionally accompanied by foot grip impairment, at 8 mg and 25 mg at 2-5 times the MRHD and neuronal vacuolation in the brain without neuronal degeneration at 25 mg at 5 times the MRHD, on a per-dose basis, normalized to CSF volume, were noted in an intrathecal toxicity study in 9- to 11-month-old monkeys administered zilganersen every four weeks (0, 3, 8, or 25 mg) via the intrathecal route for 9 months. No vacuoles were noted in animals treated with doses up to 8 mg at 2 times the MRHD on a per-dose basis, normalized to CSF volume.

8.5 Geriatric Use

Clinical studies of ZANVASTRO for the treatment of Alexander disease has not been studied in patients aged 65 years and over. No data are available to determine whether they respond differently than younger adult patients.

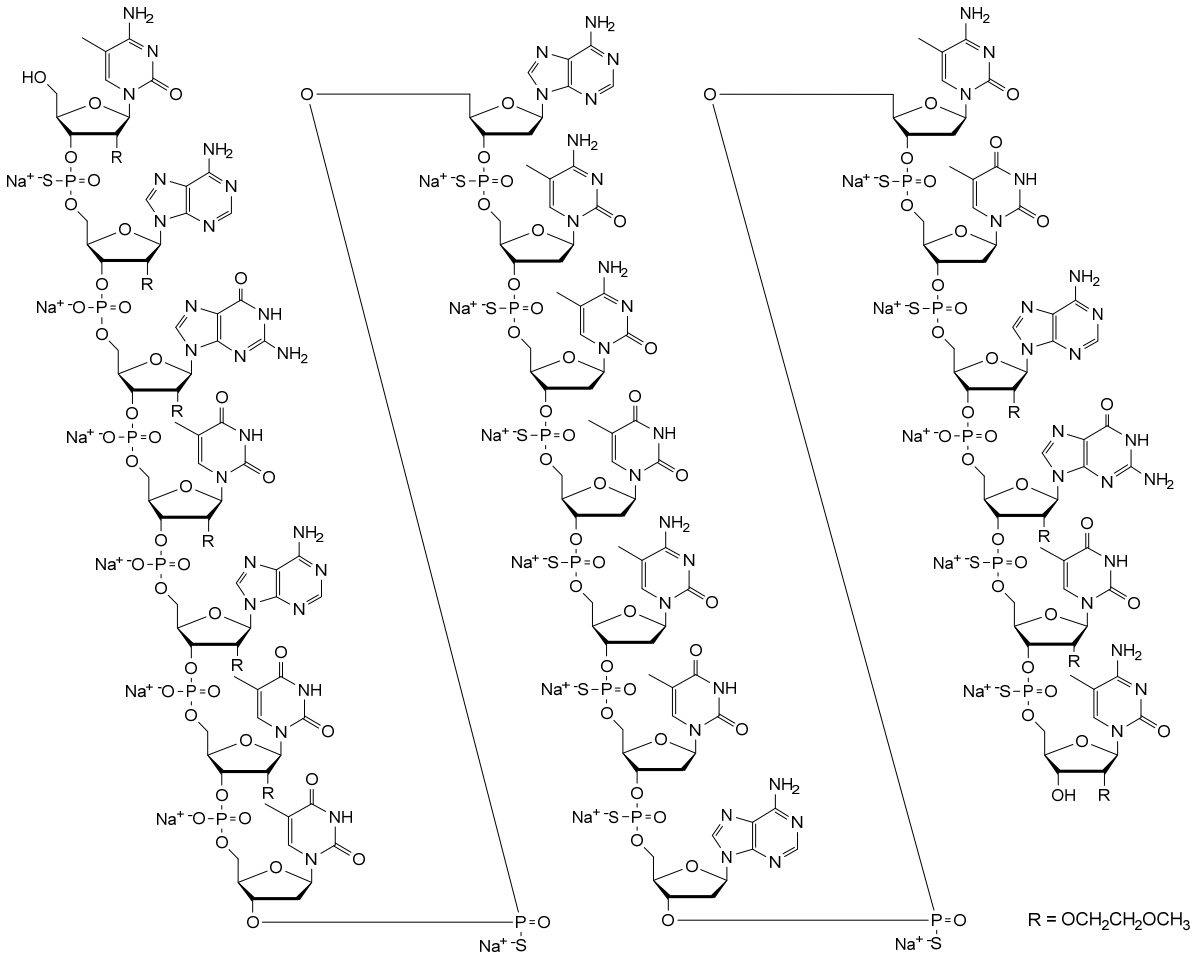
11 DESCRIPTION

Zilganersen sodium is a glial fibrillary acidic protein (GFAP)-directed antisense oligonucleotide.

Zilganersen sodium is a white to yellow solid that is freely soluble in water and in artificial cerebrospinal fluid (aCSF). The molecular formula of zilganersen sodium is $C_{230}H_{301}N_{67}O_{127}P_{19}S_{13}Na_{19}$ and the molecular weight is 7478.4 daltons. The chemical name of zilganersen sodium is DNA, d([2′-O-(2-methoxyethyl)]m5rC-sp-[2′-O-(2-methoxyethyl)]rA-[2′-O-(2-methoxyethyl)]rG-[2′-O-(2-methoxyethyl)]m5rU-[2′-O-(2-methoxyethyl)]rA-[2′-O-(2-methoxyethyl)]m5rU-T-sp-A-sp-m5C-sp-m5C-sp-T-sp-m5C-sp-T-sp-A-sp-m5C- sp-T-sp-[2′-O-(2-methoxyethyl)]rA-[2′-O-(2-methoxyethyl)]rG-sp-[2′-O-(2-methoxyethyl)]m5rU-sp-[2′-O-(2-methoxyethyl)]m5rC), sodium salt (1:19).

The structure of zilganersen sodium is presented in Figure 1.

Figure 1. Zilganersen Sodium Structural Formula



ZANVASTRO is a sterile, preservative-free, parenteral solution for intrathecal (IT) administration. Each vial of ZANVASTRO solution contains 56 mg zilganersen in 2.8 mL at a concentration of 20 mg/mL (equivalent to 21.2 mg of zilganersen sodium) and the following inactive ingredients: calcium chloride (0.58 mg), disodium hydrogen phosphate (0.27 mg), magnesium chloride (0.46 mg), potassium chloride (0.63 mg), sodium chloride (for tonicity), sodium dihydrogen phosphate (0.14 mg), water for injection, and may include sodium hydroxide (q.s.) and/or hydrochloric acid (q.s.) for pH adjustment to a target pH of 7.2. The formulation is intended to be diluted with the provided aCSF Diluent prior to administration by IT injection.

Artificial cerebrospinal fluid Diluent is a sterile, preservative-free, parenteral solution for dilution of ZANVASTRO. The formulation does not contain any active ingredients. Each vial of the artificial cerebrospinal fluid Diluent contains 21 mL solution with the following inactive ingredients: calcium chloride (4.33 mg), disodium hydrogen phosphate (2.04 mg), magnesium chloride (3.42 mg), potassium chloride (4.70 mg), sodium chloride (for tonicity), sodium dihydrogen phosphate (1.05 mg), water for injection, and may include sodium hydroxide (q.s.) and/or hydrochloric acid (q.s.) for pH adjustment to a target pH of 7.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

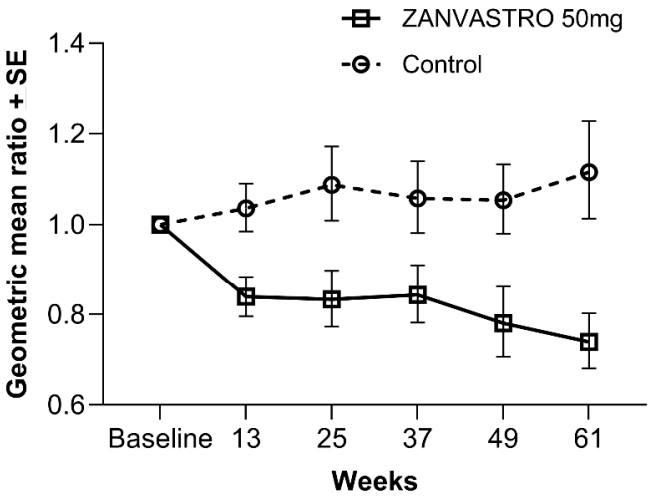
ZANVASTRO is an antisense oligonucleotide that causes degradation of glial fibrillary acidic protein (GFAP) pre-mRNA through binding to GFAP pre-mRNA, which results in a reduction of GFAP protein synthesis.

12.2 Pharmacodynamics

Effect of Zilganersen on Plasma GFAP

Plasma GFAP, an indirect measure of target engagement, was evaluated longitudinally in patients with Alexander disease *[see Clinical Studies (14)]*. At week 61 (after 5 doses), the geometric mean ratio to baseline in plasma GFAP was 33.6% lower in patients on ZANVASTRO compared to controls (see Figure 2).

Figure 2. Mean Change from Baseline in Plasma GFAP (Geometric Mean Ratio ± SE) in Patients Treated with ZANVASTRO 50 mg or Control (Study 1; Main Study)



ZANVASTRO 50 mg:	n =	23	22	22	21	18	18
Control:	n =	17	17	16	16	12	14

Cardiac Electrophysiology

Based on the chemical properties of zilganersen and the absence of cardiac electrophysiology findings in nonclinical studies, zilganersen is not expected to affect the QTc interval.

12.3 Pharmacokinetics

Absorption

The pharmacokinetic properties of zilganersen were evaluated following intrathecal administration of multiple doses given as a 50mg bolus every 12 weeks in pediatric (≥2 years old) and adult patients with Alexander disease. Following 50 mg dosing in patients ≥2 years old, zilganersen was quantifiable in CSF 84 days after injection (trough). The steady state pharmacokinetics are presented as geometric mean (%CV). The steady-state

CSF trough ($C_{trough, CSF, ss}$) concentration was 1.21 ng/mL (40.8%). The steady-state maximum plasma concentration ($C_{max,ss}$) was 908 ng/mL (74.3%), with a median time to maximum plasma concentration ($T_{max,ss}$) of 4.03 hours (range: 1.00–23.7 hours). The steady-state trough plasma concentration ($C_{trough, plasma, ss}$) was 0.252 ng/mL (147%), and the area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0–24h}$) was 7,716 ng·h/mL (97.4%).

No evidence of time-dependent plasma pharmacokinetics was observed between the first and sixth administration of ZANVASTRO in patients >2 years of age.

Distribution

In vitro, greater than 98% of zilganersen binds to human plasma proteins. Following intrathecal administration of ZANVASTRO into the CSF, zilganersen distributes into the systemic circulation and tissues with the central compartment volume of 7.95 L and the peripheral compartment volume of 315 L.

Elimination

The terminal elimination half-life in plasma is approximately 1 month.

Metabolism

Zilganersen undergoes endonuclease and exonuclease-mediated cleavage to shorter oligonucleotide metabolites; it is not a CYP substrate, and CYP450-mediated metabolism is not expected.

Excretion

The primary route of elimination is likely by urinary excretion for zilganersen and its chain-shortened metabolites. The urinary excretion of unchanged zilganersen has not been characterized.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of zilganersen were observed based on age, body weight, sex, race, ethnicity, mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2), or mild hepatic impairment (defined using NCI-ODWG Criteria: total bilirubin ≤1 × ULN and AST >1 × ULN, or total bilirubin >1 to 1.5 × ULN and any AST).

ZANVASTRO has not been studied in patients aged ≥65 years, patients with moderate or severe renal impairment, end-stage renal disease, or moderate or severe hepatic impairment.

Drug Interaction Studies

No clinical drug–drug interaction studies have been performed with ZANVASTRO. *In vitro*, studies show that zilganersen is not a substrate or inhibitor of major drug transporters, does not interact with highly plasma protein bound medicines, and is not an inhibitor or inducer of cytochrome P450 (CYP) enzymes.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies

in the study described below with the incidence of anti-drug antibodies in other studies, including those of zilganersen or of other zilganersen products.

The immunogenic response to ZANVASTRO was evaluated in 53 patients for anti-drug antibodies (ADA). Overall, 9/32 (28.1%) ZANVASTRO-treated patients developed treatment-emergent ADA, of which 2 were transient and 7 were persistent. The presence of ADA had no apparent effect on the safety or efficacy profile of ZANVASTRO. The incidence and type of adverse drug reactions were similar between patients who tested ADA-positive and those who were ADA-negative. Two patients developed markedly elevated plasma ADA titers. One of these patients presented with elevations of CSF white blood cell count and protein, in the presence of signs and symptoms of potential aseptic meningitis. No similar findings were observed in other ADA-positive patients.

Zilganersen plasma C_{max} and $AUC_{0\text{-}24h}$ values were similar between ADA-positive and ADA-negative patients. Although ADA development was not found to affect the PK, safety or efficacy of ZANVASTRO in these patients, the available data are limited to make definitive conclusions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies to assess the carcinogenic potential of zilganersen have not been conducted.

Mutagenesis

Zilganersen was negative in *in vitro* (bacterial reverse mutation and mammalian cell chromosomal aberration) and i*n vivo* (mouse micronucleus) assays.

Impairment of Fertility

No adverse effects on male or female fertility were observed when zilganersen (0, 10, 30, or 60 mg/kg) was administered by subcutaneous injection to mice every 2 weeks prior to and during mating and continuing in females every other day throughout organogenesis. The NOAEL (60 mg/kg) provides a safety margin of 6 compared to the maximum recommended human dose (MRHD of 50 mg) when normalized to a per-dose BSA basis.

14 CLINICAL STUDIES

The efficacy of ZANVASTRO was evaluated in a multicenter study in pediatric and adult patients with Alexander disease (Study 1; NCT04849741). Study 1 comprised two parts: a double-blind, randomized, controlled Main Study that enrolled 49 patients aged 2 to 65 years, and an open-label substudy that enrolled 4 patients less than 2 years of age. All patients had Alexander disease confirmed by clinical phenotype, brain MRI, and a pathogenic variant in the GFAP gene.

The Main Study duration was up to 274 weeks, including a 6-week screening period; a 60-week double-blind period (i.e., ended at Week 61) followed by a 60-week open-label period; a 120-week long-term extension; and a 28-week post-treatment follow-up. During the double-blind period, patients 2 years and older were enrolled

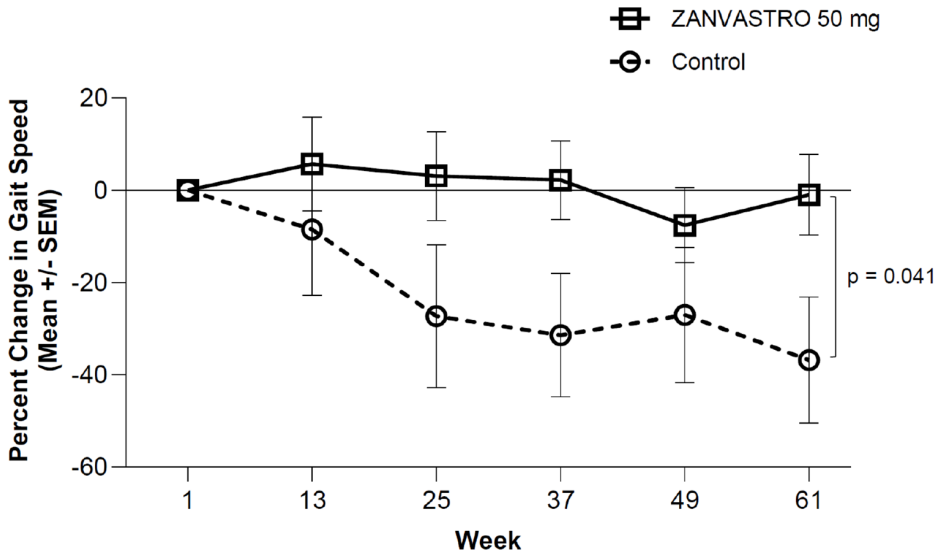
into two ascending-dose cohorts (25 mg; n=8 or 50 mg; n=24) and randomized in each cohort 2:1 to ZANVASTRO every 12 weeks, or control (n=17).

Randomization in the Main Study was stratified as follows: Stratum 1: (i) patients ≥5 years, (ii) if ≥18 years, had onset of Alexander disease motor symptoms/signs within 5 years, and (iii) demonstrated an abnormality in gross motor skills; Stratum 2: all other enrolled patients. The primary endpoint was evaluated in Stratum 1 and secondary endpoints were assessed in all randomized patients in the Main Study population (both Stratum 1 and Stratum 2). In patients 2-4 years of age enrolled in Stratum 2, efficacy was evaluated using an alternate endpoint, as described below.

Baseline characteristics for the Main Study randomized population (n=49) were similar between the ZANVASTRO and control groups with a median age of 11 years and mean gait speed, as measured by the 10-meter walk test, of 1.2 m/sec. Sixty-five percent were female, 86% White, 8% other/multiple races, 6% Asian, and 10% Hispanic or Latino ethnicity. Twelve (12) patients (Stratum 1 = 9 [75%]) enrolled in the 25 mg dose cohort (half the recommended dosage) and 37 patients (Stratum 1 = 27 [73%]) enrolled in the 50 mg dose cohort.

The primary efficacy analysis for Stratum 1 of the Main Study was the difference in the mean percent change in gait speed from baseline to Week 61, as assessed by the 10-meter walk test (10MWT), comparing ZANVASTRO 50 mg with control. Treatment with ZANVASTRO 50 mg demonstrated a statistically significant difference in gait speed compared to control (-2.1% with ZANVASTRO 50 mg vs. -35.4% with control; adjusted least squares mean difference: 33.3% [95% CI: 1.44, 65.25], p = 0.041) (see Figure 3).

Figure 3. Mean Percent Change in Gait Speed from Baseline in Stratum 1 Patients Treated with ZANVASTRO 50 mg or Control



ZANVASTRO 50mg	n = 17	16	16	16	15	16
Control	n = 13	11	10	10	9	8

n = number of patients with observed data at each timepoint.
The p-value was estimated from an ANCOVA model with treatment group and Baseline value as covariates. The ANCOVA model used prespecified imputation methods that utilized all patients in the primary analysis (n =17 ZANVASTRO 50 mg, n =13 Control).

In the subgroup of patients 2-4 years of age, motor function was assessed as the difference in the mean change from baseline to Week 61 in the Gross Motor Function Measure-88 (GMFM-88) subscales for standing (Dimension D) and for walking, running, and jumping (Dimension E). Patients in this subgroup treated with ZANVASTRO (n=4) had an observed improvement on the GMFM-88 Dimension D and Dimension E combined score while patients in the control arm (n=3) had an observed decline (least squares mean difference: 22.9, standard error: 5.2).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZANVASTRO is supplied as a carton (NDC 71860-304-01) that contains the following:

- One single-dose vial of ZANVASTRO: 56 mg/2.8 mL (20 mg/mL) of a sterile, preservative free, clear, colorless to slightly yellow solution.

- One single-dose vial of artificial cerebrospinal fluid (aCSF) diluent: 21 mL of sterile, preservative free, clear and colorless solution for dilution of ZANVASTRO.

Not made with natural rubber latex.

16.2 Storage and Handling

Store the ZANVASTRO vial and diluent vial in the refrigerator between 2°C and 8°C (36°F and 46°F) in the original carton to protect from light.

Once taken out of the refrigerator, the ZANVASTRO vial and diluent vial can be stored at room temperature up to 30°C (86°F) in the original carton for up to 14 days. If not used within the 14 days stored at room temperature, discard ZANVASTRO.

Do not freeze. Do not expose to heat. Protect from light as a precaution.

See Dosage and Administration (2.2) for instructions on how to store ZANVASTRO diluted solution.

17 PATIENT COUNSELING INFORMATION

Aseptic Meningitis

Inform patients and caregivers that ZANVASTRO could cause aseptic meningitis. Instruct patients and caregivers to contact their healthcare provider if symptoms consistent with meningitis develop *[see Warnings and Precautions (5.1)]*.

Distributed by: Ionis Pharmaceuticals, Inc., Carlsbad, CA 92010

INSTRUCTIONS FOR USE
ZANVASTRO™ [zan-VASS-troh]
(zilganersen) injection
for intrathecal use

This Instructions for Use is intended for healthcare professionals and contains instructions for preparing ZANVASTRO™ for intrathecal administration. Read this entire Instructions for Use before diluting and preparing ZANVASTRO.

Important information:

- Each carton contains 1 vial of ZANVASTRO and 1 vial of diluent to be used together to prepare a single dose. The final dose volume of the intrathecal injection is determined by the patient's age.
- The diluent vial contains more volume than needed. Discard excess diluent prior to dilution as instructed in the preparation steps below.
- Always use aseptic technique when preparing and administering ZANVASTRO.
- Do not use if expiration date has passed.
- Do not use vials if solution is cloudy, discolored, or contains particles.
- Do not use if vials or carton are damaged.

Storing ZANVASTRO:

- Store the ZANVASTRO vial and diluent vial in the refrigerator between 2°C and 8°C (36°F and 46°F) in the original carton to protect from light. The ZANVASTRO vial and diluent vial can be stored at room temperature up to 30°C (86°F) in the original carton for up to 14 days.
- Do not freeze. Do not expose to heat.
- See Step 7 below for storage of the prepared diluted dosing syringe.

Carton contents:

- One vial of Zanvastro, 56 mg/2.8 mL (20 mg/mL)
- One vial of artificial cerebrospinal fluid (aCSF) diluent, 21 mL

Other recommended supplies for dose preparation (not included in carton):

- 3 mL and/or 10 mL syringe(s) to withdraw excess diluent
- One 3 mL syringe to draw up ZANVASTRO
- Two to three 18G to 22G needles (three needles will be required for patients under 2 years of age)
- One 18G or 19G filter needle (5 micron)
- One 20 mL syringe
- One 20 mL syringe tip cap

Step 1 Withdraw and discard excess aCSF diluent based on patient's age

a) Determine the volume of excess aCSF diluent to withdraw from the diluent vial using the patient's age and Table 1 below.
b) Prepare syringe(s) with an 18G to 22G needle based on the volume of diluent to be removed (3 mL and/or 10 mL syringe recommended).
c) Withdraw the excess diluent from the diluent vial.
d) Keep the diluent vial containing the remaining diluent. You will need it for Step 3.
e) Discard the syringe(s) containing the excess diluent in a sharps container.

Step 2 Withdraw ZANVASTRO

a) Prepare a new 3 mL syringe with a new 18G to 22G needle.
b) Withdraw 2.8 mL of ZANVASTRO from the ZANVASTRO vial.

Step 3 Add ZANVASTRO to the remaining diluent in the diluent vial

a) Add the withdrawn ZANVASTRO to the diluent vial.
b) Dispose of the syringe and ZANVASTRO vial in a sharps container. Some residual medicine may remain in the ZANVASTRO vial.

Step 4 Mix

Gently invert the diluent vial (which now also contains ZANVASTRO) several times to mix the solution.

Step 5 Withdraw dose volume based on patient's age

a) Attach an 18G or 19G filter needle to a 20 mL syringe.
b) Withdraw the recommended dose volume of diluted ZANVASTRO from the diluent vial as determined by Table 1 below based on the patient's age.

Step 6 Prepare the dosing syringe

a) Remove the filter needle and attach a syringe tip cap to the prepared dosing syringe.
b) Dispose of diluent vial and filter needle in a sharps container.
Some residual solution might be in the vial after dose volume is withdrawn.

Step 7 Label the prepared dosing syringe

a) Label the prepared dosing syringe per institution procedures prior to use or transport.
b) ZANVASTRO contains no preservatives. The dose must be administered within:
- 4 hours of preparation if kept at room temperature up to 30°C (86°F).
- 24 hours of preparation if refrigerated at 2°C to 8°C (36°F to 46°F).
- Do not freeze. Do not expose to heat.
- Protect the prepared dosing syringe from light as a precaution.

Table 1: ZANVASTRO Dilution Procedures

Patient age	Volume of excess aCSF diluent to withdraw from the diluent vial and discard	Volume of ZANVASTRO to add to the diluent vial	Volume of diluted Zanvastro to withdraw from the diluent vial for administration (Dose volume)
Less than 2 years old	12.6 mL	2.8 mL	10 mL
2 years old to 7 years old (inclusive)	7 mL	2.8 mL	15 mL
8 years old and above	1.4 mL	2.8 mL	20 mL

Refer to the Prescribing Information for administration instructions.

For more information, go to https://www.ZANVASTRO.com or call 1-833-644-6647.

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