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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Translarna

ataluren

Procedure no: EMEA/H/C/002720/P46/028

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

In August 2021, the MAH submitted a completed paediatric study for *"treatment of Nonsense Mutation Aniridia"*, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that PTC-124-GD-028-ANI is a stand-alone study to assess the efficacy and safety of ataluren for the treatment of aniridia.

Aniridia, a familial condition with autosomal dominant inheritance, is a bilateral, panocular disorder affecting the cornea, iris, intraocular pressure, lens, fovea, and optic nerve (Valenzuela 2004, Netland 2011, Hingorani 2012, Chang 2014). The vast majority of cases of aniridia are associated with mutations in the PAX6 gene, which is located on chromosome 11p13 and regulates ocular development. The phenotype is variable between and within families; however, affected individuals usually show little variability between the 2 eyes. Individuals with aniridia characteristically show the absence of iris, nystagmus, impaired visual acuity (usually 20/100 to 20/200), and foveal hypoplasia.

Aniridia mainly manifests in the eye, but there are additional characteristics of aniridia, including obesity (Netland 2011) and impaired glucose tolerance and/or diabetes (Wen 2009) as PAX6 regulates not only eye development but also islet cell development (Yasuda 2002). PAX6 continues to be expressed through adulthood, contributing to the maintenance of function in the eye and other tissues. Individuals with isolated aniridia may show reduced olfaction and cognition, behavioural problems, or developmental delay.

Nonsense mutations are the cause of congenital aniridia in ~40% of patients (Tzoulaki 2005). Nonsense mutations in deoxyribonucleic acid (DNA) correspond to premature stop codons in mRNA. Ataluren is a small-molecule drug that promotes ribosomal readthrough of mRNA containing a premature stop codon. Through this mechanism of action, ataluren is thought to overcome the genetic defect in patients with a nonsense mutation that causes aniridia.

2.2. Information on the pharmaceutical formulation used in the study

Ataluren used in the study is the same drug as approved in the EU for nonsense mutation Duchenne muscular dystrophy (nmDMD) ambulatory subjects. Ataluren is available as white to off-white granules for oral suspension packaged in child-resistant sachets (packets) and supplied in dose strengths containing 125, 250, or 1000 mg of the active drug substance. All excipients were tested to pharmaceutical or food grade and are generally recognized as safe.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- PTC-124-GD-028-ANI; randomized, double-masked, placebo-controlled study of ataluren in children ≥2 years old with aniridia whose disease is mediated by a nonsense mutation (nmAniridia).

2.3.2. Clinical study

PTC-124-GD-028-ANI

Description

Study PTC124-GD-028-ANI was a randomized, double-masked, placebo-controlled study of ataluren in children ≥2 years old with aniridia whose disease is mediated by a nonsense mutation (nmAniridia).

Methods

Objective(s)

The therapeutic rationale for the study was to evaluate whether ataluren may offer an effective therapy by restoring critical protein production for aniridia.

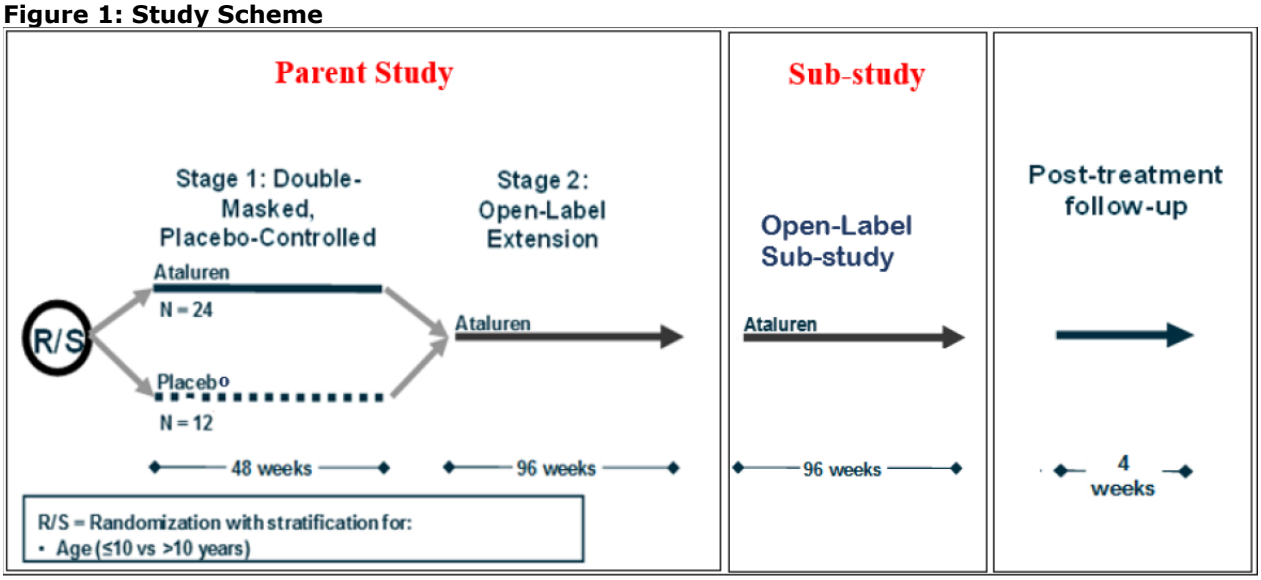
The *primary objective* of this study was to evaluate the effect of ataluren on Maximum Reading Speed as measured using the Minnesota Low Vision Reading Test (MNREAD) Acuity Charts.

The *secondary objectives* of this study were to evaluate the effect of ataluren on other functional outcome measures (e.g. Best-corrected visual acuity (BCVA), Iris area) and characterize the systemic and ocular safety profile of ataluren in subjects with nonsense mutation aniridia.

Study design

Study PTC124-GD-028-ANI was a Phase 2, multicenter, stratified, randomized, double-masked, placebo-controlled study with a 4-week screening period, a 144-week treatment period, an optional 96-week open-label sub-study, and a 4-week post-treatment follow-up period (either following study completion or early termination [ET]) (Figure 1).

Figure 1: Study Scheme



During the 4-week screening period, subjects were assessed for eligibility, which included a clinical diagnosis of aniridia and the presence of a nonsense mutation in 1 allele of the PAX6 gene. Subjects with other significant ocular or systemic diseases and those undergoing warfarin, phenytoin, or tolbutamide, IV aminoglycoside or IV vancomycin or systemic cyclosporine therapy were excluded.

Eligible subjects were randomized in a masked 2:1 fashion to either ataluren or placebo. Randomization was stratified by age: ≤10 years versus >10 years. Masked study drug was dosed 3 times a day: 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 48 weeks. Subjects (or parent/legal guardian) recorded each dose on a diary card provided by the MAH.

After completing Stage 1 of the parent study (Week 48), subjects were eligible for an additional 96 weeks of open-label ataluren treatment. Subjects who received ataluren during Stage 1 were to continue to receive ataluren; subjects who had been randomized to placebo in Stage 1 were to receive ataluren during Stage 2. During this phase, the posology remained unchanged, i.e. ataluren was dosed 3 times a day.

There was an optional Open-Label (OL) sub-study at the end of the Stage 2 Open-Label Extension (OLE). Subjects were able to consent to receive an additional 96 weeks of ataluren treatment, returning to the clinic every 24 weeks.

Subjects who chose not to participate in the OL sub-study were required to complete the posttreatment follow-up visit at the end of the Stage 2 OLE. The start of the sub-study required prior approval of a protocol amendment from applicable Institutional Review Boards and was planned to continue for 96 weeks.

Analyses of the double-masked phase were conducted after the last subject had completed Week 96. After the subject's last dose of ataluren, there was a 4-week post-treatment follow-up period.

CHMP comment

It should be noted that the study was originally primarily a safety study; however, no explanation was provided why the study was changed into an efficacy study in 2019, i.e. almost 3 years after the first subject was enrolled and 2 months before the last subject enrolled. Furthermore, any explanation for the stratification by age is also lacking.

Study population /Sample size

A minimum of 36 subjects with a confirmed diagnosis of nonsense mutation aniridia who were ≥2 years of age were planned for enrolment into this study at investigator sites in United States (US) and Canada.

Treatments

Ataluren used in the study is the same drug as approved in the EU. Ataluren was provided as granules for oral suspension with a white to off-white powder appearance. For administration, the powder in the sachet could be mixed with water, fruit juice, fruit punch, or milk (skim, 1% fat, 2% fat, whole milk, chocolate milk, soy milk, or lactose -free milk), or semi-solid food (yogurt, pudding, or applesauce).

For placebo, a white to off-white granule placebo formulation was provided for oral suspension. The placebo formulation was manufactured under cGMP conditions. The dry granules and the liquid suspension of the drug matched the active formulation in appearance, odour, and taste. The placebo formulation contained excipients similar to those used in the active product. The placebo was packaged in the same aluminum foil, child-resistant sachets using weights and volumes to match each of the 125-, 250-, and 1000-mg dose strengths of active drug sachets.

CHMP comment

The same ataluren was used in the study as approved for Duchenne muscular dystrophy (DMD) treatment.

Outcomes/endpoints

The *primary endpoint* of the study is percent change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of both eyes (OU) as measured using the Minnesota Low Vision Reading Test (MNREAD) Acuity Charts.

The *secondary endpoint* included the characterization of the systemic and ocular safety profile of ataluren. All safety presentations were based on the Safety Population and were based only on data included in the analysis period of interest.

Secondary efficacy outcomes included the effect of ataluren on Reading Accessibility Index, Best-corrected visual acuity (BCVA), Critical Print Size, Reading Acuity, Severity of corneal keratopathy and Iris area.

Exploratory endpoints were also included to evaluate the effect of ataluren further. These included assessment of Ocular surface epithelial cell differentiation, Central corneal thickness, Retinal thickness, Iris length, Foveal hypoplasia, Ocular symptoms, Intraocular pressure, Levels of paired box 6 (PAX6) protein and downstream ocular proteins regulated by PAX6 (e.g., matrix metallopeptidase 9, in ocular tissue), Insulin/c-peptide level and Ataluren concentrations in aqueous humour.

CHMP comment

Note that subjects were enrolled into the study when the study was still primarily designed as a safety study (in 2016). As indicated previously the study was changed into an efficacy study almost 3 years after the first subject was enrolled and 2 months before the last subject enrolled. An adequate assessment of the outcome of the study is questioned as the chosen primary endpoint cannot be reliably assessed in the population included in the trial. The study includes subjects from 2 years of age and older, while the MNREAD acuity can only be reliably assessed in subjects ≥8 years of age. In addition also for subjects >8 years of age different performance levels are distinguished; children 8-16 years show an increase with age, while persons 16-40 years show no change and middle aged to older adults show a decreases. As, there is no upper age limit in the study, differences in performance based on age etc., should be accounted for.

The MAH did not provide a justification for the chosen primary endpoint. The use of the MNREAD acuity chart is questioned as this may not be the most relevant outcome measure for subjects with aniridia - apart from the questionable suitability for the population included. Subjects with aniridia generally present with symptoms of photosensitivity, which is not included in the study. In addition, in isolated aniridia, cognitive functioning may be impaired, or subjects could suffer from cognitive disfunction or developmental delay. Both impact the performance on the MNREAD.

Statistical Methods

For a statistical hypothesis test for any efficacy endpoint, the study would have 60% power to detect an effect size (i.e., standardized mean difference) of 0.85, or 80% power to detect an effect size of 1.06, at the 0.05 significance level (two-sided).

Eligible subjects were randomized in a masked 2:1 fashion to either ataluren or placebo. Randomization was stratified by age: ≤10 years versus >10 years

Two analysis populations were defined for the statistical analyses:

- Intent-to-Treat (ITT) Population / Safety Population: This population included all randomized subjects who received at least 1 dose of study drug.
- Efficacy Analysis Populations: For each efficacy outcome measure, this population included all subjects who had a baseline value and at least 1 postbaseline value.

The ITT and efficacy populations are identical in the study, so, only data from ITT Population is presented.

CHMP comment

The power calculation based on an effect on any efficacy endpoint follows the change in study design from a safety study to an efficacy study. No rationale is given for the low predefined power in the context of a higher likelihood of not demonstrating an true effect. Furthermore, it is unknown which endpoint is the best to assess clinically relevant differences. An effect size of 0.85 or 1.06 is considered marginal on some of the scales, e.g. BCVA where a clinically relevant difference is 5 letters or retina thickness falls within the natural variability ranges. Furthermore, the choice for stratification at age 10 is not understood but could be related to the original study design where the focus was on safety rather than efficacy. However, these concern are not pursued as the study is not appropriate to conclude on efficacy of the product in treatment of aniridia and the flaws that are also acknowledged by the MAH.

Results

Recruitment/ Number analysed

A total of 44 individuals were screened and 39 were randomized across 3 study sites, all of whom met the definition for the ITT and Safety Populations. Of these 39 subjects, 34 (87%) completed Week 48 (Stage 1), 19 (56%) completed the open-label portion through Week 144 (Stage 2), and 5 (26%) completed the open-label sub-study through Week 240 (Table 1).

Table 1: Overall Subject Disposition

Disposition		Ataluren (n=26) n (%)	Placebo (n=13) n (%)	Total (n=39) n (%)
Screened				44
Screening failures				5
Randomized		26 (100)	13 (100)	39 (100)
Completed Week 48	Yes	22 (84.6)	12 (92.3)	34 (87.2)
	No	4 (15.4)	1 (7.7)	5 (12.8)
	Non-compliance with study drug	0	1 (7.7)	1 (2.6)
	Other	4 (15.4)	0	4 (10.3)
Completed Stage 1 but did not enter open-label portion of study		0	1 (8.3)	1 (2.9)
Completed open-label (144 weeks)[a]	Yes	12 (54.5)	7 (58.3)	19 (55.9)
	No	10 (45.5)	4 (33.3)	14 (41.2)
	Adverse event	2 (9.1)	1 (8.3)	3 (8.8)
	Lost to Follow-Up	0	0	0
	Other	8 (36.4)	3 (25)	11 (32.4)
Completed open-label (144 weeks) but did not enter open-label sub-study		2 (16.7)	0	2 (10.5)
Completed open-label (240 weeks)[a]	Yes	2 (16.7)	3 (42.9)	5 (26.3)
	No	8 (66.7)	4 (57.1)	12 (63.2)
	Adverse event	0	0	0
	Lost to Follow-Up	1 (8.3)	0	1 (5.3)
	Other	7 (58.3)	4 (57.1)	11 (57.9)

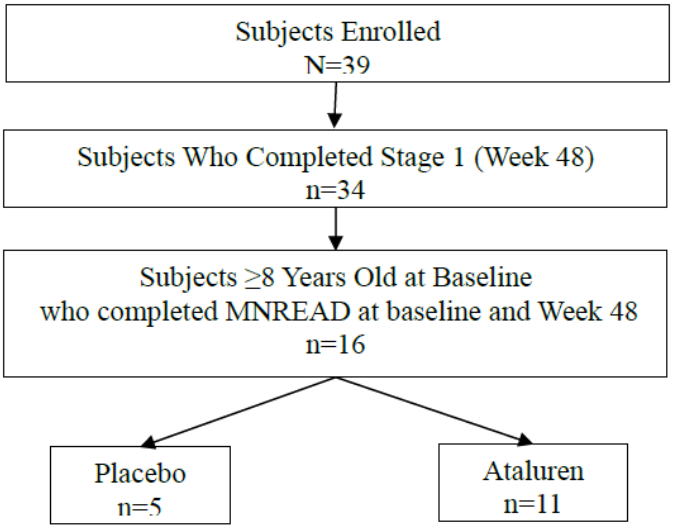
[a] Percentage based on number of subjects entering open-label portion of study.

CHMP comment

A participant flow chart would have been clearer than the provided tabulated overview. Compared with placebo, fewer patients in the ataluren group completed stage 1, i.e. the Week 48 double-blind phase. In the open-label extension, when placebo switched to ataluren, completion was comparable.

The subjects who received a placebo during the double-blind phase switched to ataluren treatment after week 48. Therefore, this should be the delayed start group as they no longer received a placebo. During the open-label phase the drop-out rate was comparable between the delayed start group and the early start group.

Figure 2: participants flow chart for primary endpoint efficacy population



Of the 5 subjects who did not complete treatment through Week 48 (Stage 1), 4 were in the ataluren group (3 subjects withdrew consent at Week 24 and 1 subject was unable to tolerate the treatment); 1 subject in the placebo group was noncompliant with study drug.

Of the 14 (41%) subjects who did not complete Stage 2, 3 terminated the study due to AEs and 11 withdrew due to other reasons, including loss of interest (8 subjects), social and resource stresses (1 subject), start of a new job (1 subject), and difficulty of medication preparation and administration for parents (1 subject).

CHMP comment

The high proportion of subjects not completing the study is a concern. Particularly as drop-out rate was two times higher in the ataluren group compared to the placebo group in the double blind phase. It is noted that the predefined randomization ratio between subjects available for analysis at 48 weeks remained proportional, i.e. an 2:1 ratio between ataluren and placebo.

The flow chart presented is a bit misleading as the proportion of subjects per arm is only included for the subjects who completed the MNREAD at 48 weeks and not during the full course of the study.

Baseline data

Demographic characteristics of subjects are summarized in Table 2

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Gender distribution was relatively similar in total population with 54% males and 46% females. However, there was a higher proportion of males in the ataluren group (62%), as compared to the placebo group (39%). Race and ethnicity were well-balanced between the 2 groups, with the majority of all subjects white (85%) and not Hispanic or Latino (97%).

Table 2: Demographics and Baseline Characteristics - Safety Population

	Ataluren (N=26)		Placebo (N=13)		Total (N=39)	
Gender						
n	26		13		39	
Male	16	61.5%	5	38.5%	21	53.8%
Female	10	38.5%	8	61.5%	18	46.2%
Age						
n	26		13		39	
Mean (SD)	14.1	(10.12)	19.2	(19.43)	15.8	(13.88)
Median	12.5		12.0		12.0	
Min, Max	2,	41	2,	64	2,	64
Q1, Q3	7,	15	4,	27	6,	22
Age Group 1						
n	26		13		39	
<8 years	7	26.9%	6	46.2%	13	33.3%
≥8 years	19	73.1%	7	53.8%	26	66.7%
Age Group 2						
n	26		13		39	
≤10 years	12	46.2%	6	46.2%	18	46.2%
>10 years	14	53.8%	7	53.8%	21	53.8%

There was an imbalance of age between the 2 groups in the overall population with a mean of 14.1 years in the ataluren group, as compared to 19.2 years in the placebo group. The primary endpoint of

Maximum Reading Speed of OU was measured using the MNREAD Acuity Charts, which could only be assessed in subjects ≥8 years old for which the imbalance was greater than the overall population (mean age of 17.4 versus 32.3 years in the ataluren and placebo groups, respectively). Data for the primary endpoint were available for a total of 11 subjects in the ataluren group and 5 subjects in the placebo group where the imbalance was even more severe (mean age of 16.5 versus 34.0 years, respectively).

CHMP comments

Baseline data are presented with the efficacy results in the section below.
The imbalance in age between the ataluren group and placebo group is a concern as this may impact an unbiased read out of the outcome parameter since performance on the MNREAD is associated with age.

Efficacy results

MNREAD data were available for 11 ataluren-treated subjects and 5 placebo-treated subjects at the Week 48 endpoint, representing fewer than half of the subjects enrolled in the study. The mean (standard deviation) percent change from baseline was 11.14 (30.322) in the ataluren group and -3.68 (29.769) in the placebo group. When the comparison was made by adjusting for baseline values and age, the mean treatment difference was 11% (CI:-22%, 43%) (see Table 3).

Table 3: Maximum Reading Speed (MNREAD) (words per minute) - ITT Population (Age ≥8 years) - Bilateral Vision

		Ataluren (N=19)	Placebo (N=7)
Week 1 (Baseline)	n	12	7
	Mean (SD)	158.72 (56.094)	185.95 (46.129)
	Standard error	16.19	17.44
	Median	156.61	183.83
	Q1, Q3	110.8, 199.0	141.0, 239.1
	Min, Max	84.4, 256.8	121.8, 240.9
Week 48 LOCF value	n	11	5
	Mean (SD)	167.27 (39.845)	154.32 (46.936)
	Standard error	12.01	20.99
	Median	154.88	137.59
	Q1, Q3	130.7, 198.5	124.1, 152.6
	Min, Max	117.6, 239.4	122.0, 235.4
Week 48 LOCF percent change	n	11	5
	Mean (SD)	11.14 (30.322)	-3.68 (29.769)
	Standard error	9.14	13.31
	Median	6.76	-2.44
	Q1, Q3	0.9, 23.7	-17.0, 1.9
	Min, Max	-37.3, 83.6	-41.1, 40.3

Abbreviations: ITT, intend to treat; LOCF, last observation carried forward; MNREAD, Minnesota low vision reading test; SD, standard deviation

Similar results as for the MNREAD were also shown for the Reading Accessibility Index and Critical Print Size. No apparent change in logMAR visual acuity was found.

CHMP comment

On a group level, changes are observed. However, as the number of subjects who could reliably perform the MNREAD are limited, mean age was different between groups, and there is a high drop-

out, individual profiles over time would be more informative. Particularly as more subjects are included for the baseline measure than for week 48 (LOCF). As change from baseline is the primary endpoint, BOCF may have given a more accurate account of the effect, as the missing subjects may now drive the effect.
As also indicated by the MAH, the confidence interval has a wide range; therefore, a difference between placebo is not shown/demonstrated.
A more informative representation of the data will not be requested as the aniridia indication is not pursued.
The main requirement of the current procedure is the submission of the study data, which the MAH has complied to.

Safety results

During Stage 1 of the study, the most commonly reported SOCs in the ataluren group were gastrointestinal disorders (19 subjects, 73%), general disorders and administration site conditions (9 subjects, 35%), eye disorders (6 subjects, 23%), and infections and infestations (6 subjects, 23%). For the placebo group, the most commonly reported SOCs were gastrointestinal disorders (8 subjects, 62%), general disorders and administration site conditions (5 subjects, 39%), and eye disorders (5 subjects, 39%). The most commonly occurring individual AEs (>10% subjects) in both groups were upper abdominal pain, malaise, vomiting, dry eye, and nausea. Additionally, flatulence and increased lacrimation occurred in >10% subjects in the ataluren group and eye pruritus, abdominal discomfort, and eye discharge occurred in >10% subjects in the placebo group.

During the open-label extension phase, the most commonly reported SOCs were eye disorders (29 subjects, 78%), gastrointestinal disorders (27 subjects, 73%), infections and infestations (20 subjects, 54%), general disorders and administration site conditions (17 subjects, 46%), and investigations (10 subjects, 27%). The most commonly occurring individual AEs (>10% subjects) were photophobia, eye pruritus, increased lacrimation, upper abdominal pain, dry eye, malaise, vomiting, viral gastroenteritis, influenza, pyrexia, conjunctivitis, eye pain, and nausea

CHMP comment

The adverse events reported are either in line with that known for ataluren treatment or in line with disease progression. No new or unexpected findings were reported.

2.3.3. Discussion on clinical aspects

From an efficacy point of view, no conclusion can be drawn as the study was not properly designed to assess efficacy. The study was modified from a safety study into an efficacy study, which led to an uneven distribution of subjects able to perform the Minnesota Low Vision Reading Test (MNREAD). The choice for this endpoint itself is questioned as this may not be the most relevant for the aniridia population, who generally are presented with photophobia. In addition, the overall number of subjects included was very limited.

The data should have been presented in a different manner to assess the efficacy of ataluren in aniridia, e.g. individual profiles. The confidence interval has a wide range; therefore, a difference from placebo is not shown.

No new or unexpected safety findings were reported, as the adverse events reported are either in line with that known for ataluren treatment or in line with disease progression.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the study PTC124-GD-028-ANI in line with the regulatory requirements and has fulfilled these.

The study was originally a phase II safety study which was modified into an efficacy study 2 months before the last subject enrolled in the study. As a consequence, the chosen primary endpoint could not be reliably assessed in all included subjects. The late choice of the primary endpoint resulted in an uneven distribution in the age of subjects, which is an important effect modifier of MNREAD. Moreover, the choice for the primary endpoint itself is questioned. As cognition may be impaired in these patients or aniridia subjects may show developmental delay, reading speed may be hampered as well. In addition, subjects who suffer from aniridia have photophobia; therefore, an endpoint related to the symptoms would be more logical.

No conclusion can be drawn from the study as the number of subjects was limited, there was an uneven distribution of subjects, the choice of the primary endpoint is questionable the confidence interval has a wide range; therefore, a difference from placebo is not shown. In addition, the data should have been presented in a different manner to allow assessment of efficacy, e.g. presenting individual profiles. However, these major concerns are not pursued as the MAH is not applying for the aniridia indication.

No unexpected safety findings were reported. No additional requirement are needed.

☒ Fulfilled:

No regulatory action required.