Real-world safety and effectiveness of voretigene neparvovec: Year 2 interim results from the PERCEIVE study

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BACKGROUND

- Biallelic *RPE65* mutation–associated IRD is a rare genetic disorder that causes progressive vision loss, and ultimately leads to complete blindness, if left untreated[1]
- Voretigene neparvovec is the first ocular gene therapy available for patients with *RPE65*-associated IRDs who have sufficient viable retinal cells[2,3]
- Post-authorization follow-up of VN-treated patients can provide real-world insights and fill information gaps on the long-term safety and effectiveness of this gene therapy
- PERCEIVE is the first global (ex-US) registry–based post-authorization safety evaluating long-term safety and effectiveness of VN in a real-world setting[4]
- Findings from the study until August 2021 are presented here

IRD, inherited retinal dystrophy; RPE, retinal pigment epithelium; VN, voretigene neparvovec.

1. Russell S et al. *Lancet*. 2017;390:849-60; 2. Gao J et al. *Clin Ophthalmol*. 2020;14:3855-3869; 3. Méjécase C et al. *Am J Med Genet C Semin Med Genet*. 2020;184(3):762-772; 4. EU PASS registration number EUPAS31153. Accessed July 23, 2022. http://www.encepp.eu/encepp/studiesDatabase.jsp

OBJECTIVES AND STUDY DESIGN

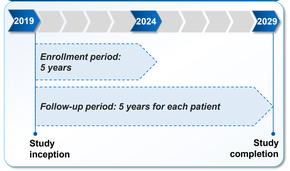
Primary objective

- To characterize the long-term safety profile of VN via systematic collection of AEs of special interest and any other AEs

Secondary objectives

- To follow pregnancy outcomes in patients (and female partners of patients) who received VN
- To assess visual function over time (eg, visual acuity, visual field, FST)

A prospective, longitudinal, multicenter, multinational (ex-US), observational, registry-based study



Key data collection

- Demographics, other relevant information* from medical records, PROs, and CROs
- Information regarding VN surgical administration
- AEs of special interest† and any other AEs
- Information on pregnancy outcomes and lactation
- Ophthalmic examination‡ data for VA, VF, FST, and OCT

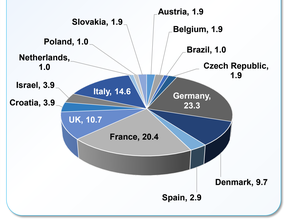
AE, adverse event; CRO, caregiver-reported outcome; FST, full-field light sensitivity threshold testing; IRD, inherited retinal dystrophy; OCT, optical coherence tomography; PRO, patient-reported outcome; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.
*Medical and surgical history, ocular characteristics, diagnosis related to the IRD, and concomitant medications and procedures.
†Ocular AEs. Lack of efficacy and/or decline in efficacy over time, third-party transmission, host immune response, development or exacerbation of oncologic, hematological, neurological, or autoimmune diseases.
‡As there are no mandated visual assessments, the extent of data collection among sites may vary.

RESULTS

Patient disposition, demographics, and baseline characteristics

- A total of 106 patients were enrolled, of whom, 103 patients (183 eyes) received VN
- The mean age* of the patients was 19.5 years with a range of 2-51 years
- About half of the patients were adults (50.5%) and females (50.5%)
- Patients were enrolled from 15 countries. Majority of them were from Germany (23.3%), France (20.4%), and Italy (14.6%)

Proportion of patients (%) from different countries (FAS, N = 103)



- The central OCT showed an outer nuclear layer present in 80.7% of eyes
- The ellipsoid zone line was intact in 32% (41 of 128) eyes, disrupted in 53.9% (69 of 128) and absent in 14.1% (18 of 128)
- Mean BCVA at baseline was 1.14 LogMAR (148 eyes; range: 0.2-2.6 LogMAR)

BCVA, best-corrected visual acuity; FAS, full-analysis set; LogMAR, logarithm of the minimum angle of resolution; N, total number of patients; n, number of patients under the given category; OCT, optical coherence tomography; VN, voretigene neparvovec.
*Age is defined as age at time of study enrollment.
Data cut-off: Aug 31, 2021. Most patients had less than a year follow-up (n = 79; 76.7%). FAS includes all enrolled individuals who received VN in at least 1 eye and provided informed consent, is used to summarize all data.

Surgical details

Treatment and dose information

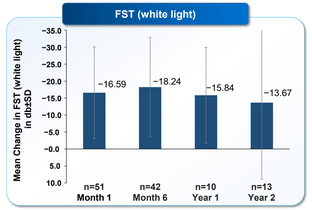
- A total of 183 eyes received VN until the data cut-off
- The recommended dose of 300 µL was administered in 158 (86.3%) eyes; remaining 22 eyes (12%), except for one, received <300 µL dose
- In most cases, single retinotomy sites (132 eyes; 72.1%) and blebs (134 eyes; 73.2%) were created
- Deviations from the standard procedure were mainly the use of an automated injection system and ILM peeling at the injection site
- The median time between first and second eye treatment was 7 (range: 7-476) days

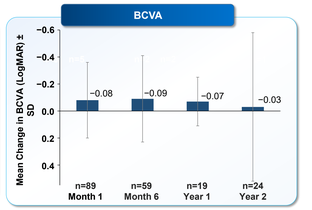
- Mean (SD) duration of follow-up was 0.8 (0.64) years (maximum: 2.3 years)
- Most patients had less than a year follow-up (n = 79; 76.7%)

ILM, internal limiting membrane; N, total number of treated eyes; n, number of patients meeting the criterion for the given categorical variable; VN, voretigene neparvovec.
Full analysis set.
Percentages are based on the total number of eyes treated, ie, N = 183.

Visual function: FST (white light) and BCVA

- Mean FST at baseline was −4.56 db. An increase in mean white light sensitivity from baseline was observed as early as month 1; highest gain was at month 6
- Sustained FST improvement at years 1 and 2 (limited data available)
- Mean BCVA at baseline was 1.14 LogMAR. No clinically meaningful change was observed in mean BCVA from baseline over time





BCVA, best-corrected visual acuity; db, decibel; FST, full-field light sensitivity threshold; LogMAR, logarithm of the minimum angle of resolution; n, number of eyes.
Full analysis set; error bars indicate SD.

Ocular AEs and AEs of special interest

- Ocular AEs were reported in 35 (34.0%) patients, affecting a total of 50 treated eyes (75 events)
- Events of chorioretinal atrophy* were the most common ocular AEs
- Ocular AEs of special interest occurred in 17 (16.5%) patients: foveal degeneration (number of patients [n] = 4), vitritis (n = 4), eye inflammation (n = 3), retinal tear (n = 2), and increased IOP (n = 5)

Ocular AEs

Preferred term	Patients, N = 103 n (%)	Eyes, N = 183 n (%)	No. of events
Number with ≥1 event	**35 (34.0)**	50 (27.3)	**75**
Metamorphopsia	5 (4.9)	5 (2.7)	5
Retinal degeneration	5 (4.9)	8 (4.4)	8
Foveal degeneration	4 (3.9)	5 (2.7)	5
Vitritis	4 (3.9)	6 (3.3)	6
Eye inflammation	3 (2.9)	4 (2.2)	4
Injection-site atrophy	12 (11.7)	18 (9.8)	18
IOP increased	5 (4.9)	7 (3.8)	7

Ocular AEs of special interest

Preferred term	Patients, N = 103 n (%)	Eyes, N = 183 n (%)	No. of events
Number with ≥1 event	**17 (16.5)**	23 (12.6)	**28**
Foveal thinning†	4 (3.9)	5 (2.7)	6
IOP increased	5 (4.9)	7 (3.8)	7
Intraocular inflammation and/or infection related to procedure‡	7 (6.8)	10 (5.5)	10
Macular hole	1 (1.0)	1 (0.5)	1
Maculopathy§	2 (1.9)	2 (1.1)	2
Retinal tear	2 (1.9)	2 (1.1)	2

AE, adverse event; IOP, intraocular pressure; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patient/eyes; n, number of patients/eyes; PT, preferred term; SOC, system organ class.
Full-analysis set. Number of events mentioned for metamorphopsia are for "treated eyes"; 1 patient had 1 event before treatment with VN. are given in the tables. A patient/treated eye with multiple occurrences of an AE for a SOC or PT is counted only once for each SOC or PT. All events including recurrences are counted in column for number of events; PTs are sorted within SOC by descending frequency in the "Patients" column; Ocular AEs with ≥2% frequency are listed under "Ocular AEs" here. MedDRA Version 24.0 was used for the reporting of AEs.
*Chorioretinal atrophy is a group term including the PTs: retinal degeneration, retinal depigmentation, injection site atrophy, and chorioretinal atrophy.
†Includes events of foveal degeneration (4 patients; 5 events) and macular scar (1 event);
‡Includes reports of vitritis (4 patients; 6 events) and eye inflammation (3 patients; 4 events);
§Includes events of macular fibrosis (1 event) and retinoschisis (1 event).

Chorioretinal atrophy, non-ocular, and serious AEs

Chorioretinal atrophy

- Chorioretinal atrophy* was reported in 13 (12.6%) patients and 19 (10.4%) eyes
- Males: 7 (53.8%); mean age: 20.5 (range: 9-33) years
- "Retinal atrophy" were reported in both eyes in 6 of 9 bilaterally treated patients:
  - Atrophy at injection site: 12 patients (18 eyes)
  - "Progressive" atophic changes: 5 patients (8 eyes)
- All events reported were of mild severity
- There was no central vision impairment and/or functional impact to the patients observed

Non-ocular AEs

- Non-ocular AEs occurred in 8 patients: headache (n = 4; 6 events); nervous system disorders (n = 4; 6 events)

Serious AEs

- Three events of ocular serious AEs were reported in 2 patients (3 eyes): eye inflammation (n = 1; 2 eyes; 2 events); increased IOP (n = 1; 1 eye; 1 events)
- Three non-ocular serious AEs of aggression, agitation, delirium (1 event of each) occurred in 1 patient with no history of psychiatric disorder

AE, adverse event; IOP, intraocular inflammation; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients; PT, preferred term; SOC, system organ class.
Full analysis set.
A patient/treated eye with multiple occurrences of an AE for a SOC or PT is counted only once for each SOC or PT; MedDRA Version 24.0 has been used for the reporting of AEs.
*Chorioretinal atrophy is a group term including the PTs: retinal degeneration, retinal depigmentation, injection site atrophy, and chorioretinal atrophy.

CONCLUSIONS

- **Overall, the year 2 interim analysis of the PERCEIVE demonstrates the safety and effectiveness of VN, which is consistent with those observed in the pivotal VN trials**
- **Chorioretinal atrophy has been identified as a new adverse drug reaction from post-marketing experience***
- **As the study progresses, such AEs and the long-term safety profile of VN will be better characterized**
- **Furthermore, PERCEIVE will provide real-world evidence on the long-term durability of vision improvements observed with VN therapy**

AE, adverse event; VN, voretigene neparvovec.
* Luxturna SmPC: *Chorioretinal atrophy was reported as progressive in some patients. Events were temporally related to treatment and occurred in the estimated treated area of the bleb site and outside of the bleb area. Isolated cases of retinal atrophy extending to the fovea with visual impairment were reported.*

Disclosures:
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Rainer Maier is employee of Novartis Pharma AG, Basel, Switzerland
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