Safety and Tolerability of Onasemnogene Abeparvovec for Patients with Spinal Muscular Atrophy Weighing ≤17 kg and ≤24 Months Old: Phase 4 OFELIA Study

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Introduction

- The worldwide incidence of SMA is estimated to be one per 6,000 to 10,000 live births,[1–3] but the actual incidence in Latin America is unknown[4,5]
- Latin America is a heterogeneous region comprised of 33 countries. Access to health systems vary across the region, and referral services, especially for neuromuscular diseases such as SMA, are rare[6]
- Data describing clinical and demographic characteristics, compliance to standards-of-care recommendations, and timely access to diagnosis for patients with SMA in Latin America are limited[4,5]
- IV onasemnogene abeparvovec demonstrated efficacy and safety for patients with SMA in previous clinical trials, but these studies only enrolled patients weighing <8.5 kg and ≤9 months old at the time of treatment. The majority of patients included were from North America or Europe.[7–13]
- OFELIA (NCT05073133) was a phase 4, open-label, multicenter study conducted in Latin America that enrolled patients with symptomatic SMA weighing ≤17 kg and ≤24 months of age

Objective

- OFELIA assessed the safety, tolerability, and efficacy of single-dose IV onasemnogene abeparvovec for patients weighing ≤17 kg and ≤24 months old over 18 months post-infusion

Methods

- OFELIA was a phase 4, open-label, single-arm, multicenter study
- Patients received a one-time infusion of onasemnogene abeparvovec (1.1×10^{14} vg/kg). Patients were admitted for inpatient treatment before the infusion and monitored for up to 48 hours after the infusion.
- Patients were followed for up to 18 months post-infusion

Key inclusion criteria

- Symptomatic SMA diagnosis based on gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations) and any number of copies of the *SMN2* gene
- Age ≤24 months at time of treatment
- Weight ≤17 kg at the time of Screening Visit 4
- Naïve to treatment or have discontinued an approved drug/therapy

Key exclusion criteria

- Previous onasemnogene abeparvovec use or previous use of any AAV9 gene therapy
- History of aspiration pneumonia or signs of aspiration (e.g., coughing or sputtering of food) within four weeks prior to screening
- Anti-AAV9 antibody titers >1:50
- Hepatic dysfunction at screening
- Inability to take corticosteroids
- Previous nusinersen treatment within 4 months prior to screening or prior risdiplam treatment within 15 days prior to screening

Primary endpoint: SAFETY
TEAEs, serious TEAEs, AESIs, and hematology/laboratory changes

Secondary endpoint: EFFICACY
WHO MGRS motor milestone achievement at 6, 12, and 18 months post-infusion

Exploratory endpoints
Bulbar function (NdSSS, Rosenbeck's Penetration-Aspiration Scale) and quality of life (ACEND)

- Data were summarized descriptively

Results

Patient disposition

- Ten patients were enrolled from three sites in Brazil, and six were enrolled from two sites in Argentina (**Table 1**)
- At dosing, the median (range) age was 17.88 (3.95–23.75) months and the median (range) weight was 8.35 (6.10–12.10) kg
- Most patients had SMA type 1 (n=10; 62.5%)
- Of the 16 patients enrolled, three (18.8%) were previously treated with nusinersen
- Half of the patients (n=8; 50.0%) had two and half (n=8; 50.0%) had three copies of *SMN2*

Table 1. Demographics and baseline clinical characteristics

Characteristics	Overall population (N=16)
Age at diagnosis, months	
Mean (SD)	10.64 (5.63)
Median (range)	10.82 (2.83–21.25)
Age at dosing, months	
Mean (SD)	15.79 (5.89)
Median (range)	17.88 (3.95–23.75)
Age group at dosing, n (%)	
0–12 months	5 (31.3)
>12–24 months	11 (68.8)
Sex, n (%)	
Female	11 (68.8)
Male	5 (31.3)
Weight at dosing, kg	
Mean (SD)	8.93 (1.82)
Median (range)	8.35 (6.10–12.10)
Weight group at dosing, n (%)	
<8.5 kg	9 (56.3)
≥8.5 kg	7 (43.8)
SMA type, n (%)	
Type 1	10 (62.5)
Type 2	6 (37.5)
Previous DMT for SMA, n (%)	
Risdiplam	0
Nusinersen	3 (18.8)
None	13 (81.3)
***SMN2* copy number, n (%)**	
Two	8 (50.0)
Three	8 (50.0)

DMT, disease-modifying treatment; SD, standard deviation; SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2* gene.

Safety

- Safety was consistent with previous studies of onasemnogene abeparvovec (**Table 2**)[7–12]

Table 2. Treatment-emergent adverse events

Category, n (%)	Age group		Weight group		Overall (N=16)
	≤12 months old at dosing (n=5)	>12–24 months old at dosing (n=11)	<8.5 kg at dosing (n=9)	≥8.5 kg at dosing (n-7)	
Any TEAE	5 (100)	11 (100)	9 (100)	7 (100)	16 (100)
Any serious TEAE	3 (60.0)	8 (72.7)	5 (55.6)	6 (85.7)	11 (68.8)
Any serious TEAE related to onasemnogene abeparvovec	1 (33.3)	2 (25.0)	1 (20.0)	2 (33.3)	3 (27.3)
AESIs	4 (80.0)	8 (72.7)	7 (77.8)	5 (71.4)	12 (75.0)[a]
Hepatotoxicity	3 (75.0)	8 (100)	6 (85.7)	5 (100)	11 (91.7)
Thrombocytopenia	2 (50.0)	3 (37.5)	4 (57.1)	1 (20.0)	5 (41.7)
TMA	0	2 (25.0)	0	2 (40.0)	2 (16.7)

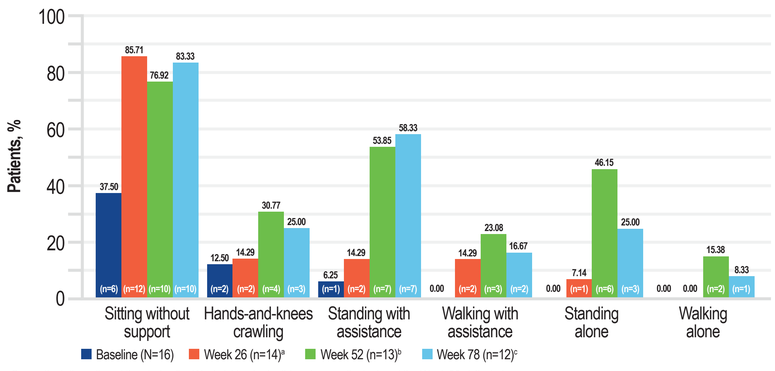
AE, adverse event; AESI, adverse event of special interest; TEAE, treatment-emergent adverse event.
[a]Of these 12, 11 (91.7%) experienced AESIs that were possibly related to onasemnogene abeparvovec.

- Two of six (33.3%) patients had an increase in troponin I after treatment
- Two (12.5%) deaths occurred:
  - One death was due to an AESI of TMA. Per the investigator, the death was determined to be related to treatment.
  - The second death was due to a respiratory tract infection. Per the investigator, the death was determined not to be related to treatment.
- Patients received a median (range) post-infusion corticosteroid dose of 0.90 (0.10–2.00) mg/kg for a median (range) of 183.50 (11.00–600.00) days

Efficacy

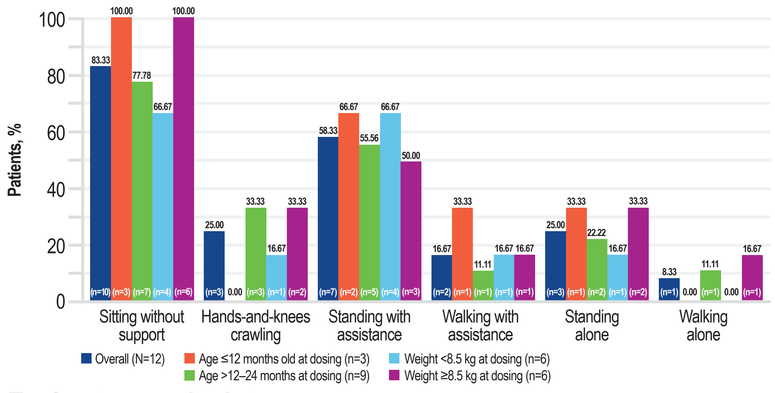
- Most patients maintained or improved motor function during the study (**Figure 1**)
- Most patients (10/12; 83.3%) were able to sit without support by the end of the study, and more than half (7/13; 53.9%) could stand with assistance by Week 52 (**Figure 1**)
- Patients maintained or achieved new motor milestones regardless of age or weight at time of dosing (**Figure 2**)

Figure 1. Achievement of motor milestones during study period



[a]One patient discontinued the study after Week 1 (due to death) and one patient missed the Week 26 visit window.
[b]One patient discontinued the study after Week 26 (due to death) and one patient missed the Week 52 visit window.
[c]Two patients missed the Week 78 visit window.

Figure 2. Motor milestone achievement at Week 78 according to age and weight at dosing



Exploratory endpoints

- At Week 78, nine of 11 (81.8%) patients had no evidence of penetration or aspiration events (**Table 3**)
- Most patients remained stable or improved throughout the study period according to Rosenbek's Penetration-Aspiration scale (**Figure 3**)

Table 3. Rosenbek's Penetration-Aspiration scale throughout the study period

Patients meeting description, n (%)	Baseline (N=16)	Week 26 (n=14)[a]	Week 52 (n=13)[b]	Week 78 (n=12)[c]
Not assessed	0	0	1 (7.7)	1 (8.3)
No penetration or aspiration	10 (62.5)	11 (78.6)	11 (91.7)	9 (81.8)
Penetration, contrast remains above the vocal folds, subsequently ejected	2 (12.5)	4 (28.6)	1 (8.3)	1 (9.1)
Penetration, contrast remains above the vocal folds, not ejected	0	1 (7.1)	0	1 (9.1)
Penetration, contrast contacts vocal folds, subsequently ejected	1 (6.3)	0	0	0
Penetration, contrast contacts vocal folds, not ejected	2 (12.5)	0	0	0
Aspiration (contrast below vocal folds), subsequently ejected (at least into larynx)	0	0	0	0
Aspiration (contrast below vocal folds), not ejected despite effort	0	0	1 (8.3)	1 (9.1)
Aspiration (contrast below vocal folds), no effort made to eject	2 (12.5)	1 (7.1)	0	0

Patients may have had more than one response.
[a]One patient discontinued the study after Week 1 (due to death) and one patient missed the Week 26 visit window.
[b]One patient discontinued the study after Week 26 (due to death) and one patient missed the Week 52 visit window.
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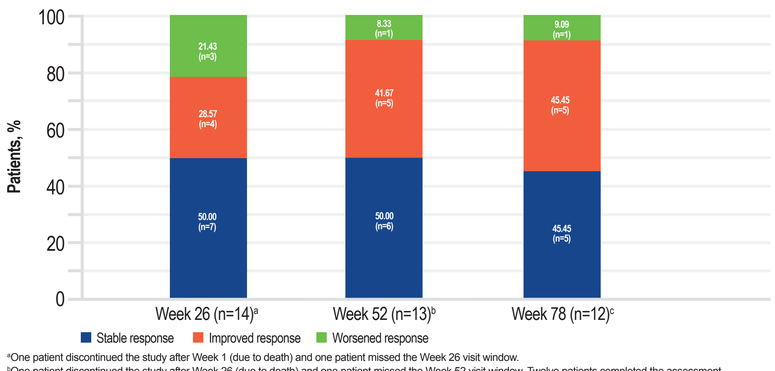
Figure 3. Patients with stable or improved progress on Rosenbek's Penetration-Aspiration scale



[a]One patient discontinued the study after Week 1 (due to death) and one patient missed the Week 26 visit window.
[b]One patient discontinued the study after Week 26 (due to death) and one patient missed the Week 52 visit window. Twelve patients completed the assessment.
[c]Two patients missed the Week 78 visit window. Eleven patients completed the assessment.

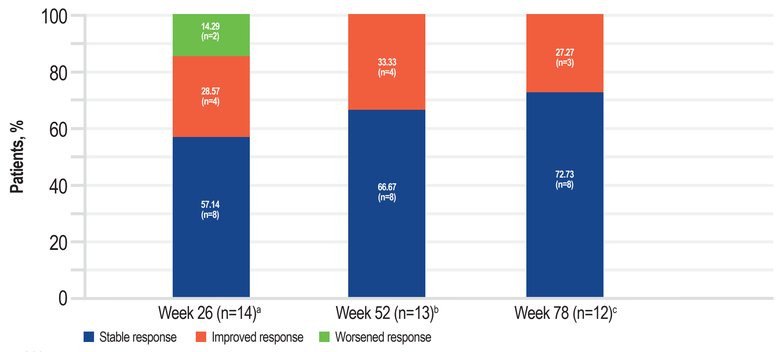
- At Week 78, more than half (6/11; 54.6%) of patients fed orally without restrictions according to the NdSSS (**Table 4**)
- All patients remained stable or improved according to the NdSSS scale by the end of the study period (**Figure 4**)

Table 4. Patients meeting NdSSS criteria throughout the study period[13]

Patients meeting description, n (%)	Baseline (N=16)	Week 26 (n=14)[a]	Week 52 (n=13)[b]	Week 78 (n=12)[c]
Not assessed	1 (6.3)	0	0	1 (8.3)
Level 1: Patient requires tube feeding with saliva suctioning in the oral cavity and can neither discharge nor swallow saliva.	0	0	0	0
Level 2: Patient requires tube feeding without suctioning. Patient cannot feed orally but can discharge and/or swallow saliva.	0	1 (7.1)	0	0
Level 3: Patient is fed via tube feeding with occasional oral intake. Patient can feed orally for fun but not for nourishment.	1 (6.7)	2 (14.3)	2 (15.4)	1 (9.1)
Level 4: Patient only receives supplemental nutrients by mouth, such as with an enteral solution. Patient does not feed orally.	1 (6.7)	0	0	0
Level 5: Patient is fed orally with easy-to-swallow food and supplemental nutrients, such as an enteral solution.	0	0	0	0
Level 6: Patient is fed orally with only easy-to-swallow food. Patient can eat foods that have been processed in a blender and can drink thickened water.	1 (6.7)	0	0	0
Level 7: Patient is fed orally with no difficulties. Patient can eat foods that are not difficult to eat.	7 (46.7)	2 (14.3)	3 (23.1)	4 (36.4)
Level 8: Patient is fed orally with no restrictions. Patient can eat all kinds of food.	5 (33.3)	9 (64.3)	8 (61.5)	6 (54.6)

NdSSS, Neuromuscular disease swallowing status scale.
[a]One patient discontinued the study after Week 1 (due to death) and one patient missed the Week 26 visit window.
[b]One patient discontinued the study after Week 26 (due to death) and one patient missed the Week 52 visit window.
[c]Two patients missed the Week 78 visit window.

Figure 4. Patients with stable or improved progress on NdSSS scale



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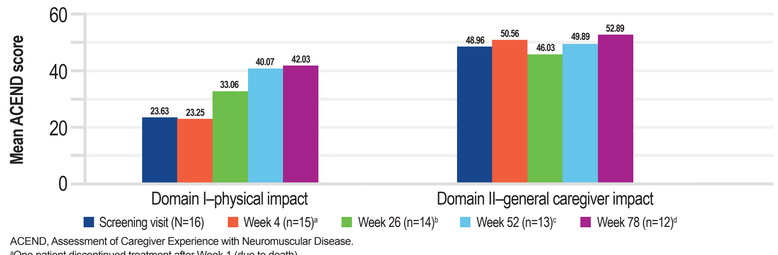
- Scores on both Domain I and Domain II of ACEND increased during the study period, indicating improved HRQOL and caregiver experience (**Figure 5**)

Figure 5. Mean ACEND scores throughout study period



ACEND, Assessment of Caregiver Experience with Neuromuscular Disease.
[a]One patient discontinued treatment after Week 1 (due to death).
[b]One patient missed the Week 26 visit window.
[c]One patient discontinued the study after Week 26 (due to death) and one patient missed the Week 52 visit window.
[d]Two patients missed the Week 78 visit window.

Limitations

- This was a single-arm, open-label study that included no comparator
- The small number of patients included in this study limits the generalizability of the results. Specifically, only seven patients weighed more than the 8.5-kg threshold included in previous studies, and the maximum weight of patients in OFELIA was 12.1 kg, which was below the prespecified threshold of 17 kg.

Conclusions

- OFELIA confirms that onasemnogene abeparvovec is safe and efficacious for patients weighing up to 17 kg and up to 24 months of age and for patients from different geographic locations than previously studied
- Most patients demonstrated maintenance or improvement of motor milestones up to 18 months post-treatment. These findings contrast the natural history of progressive motor function decline for patients with SMA.
- Patients also demonstrated improvement in swallowing ability and feeding orally. HRQOL improved in terms of physical limitations and impact on caregivers.
- Early diagnosis and treatment initiation are essential for timely restoration and preservation of SMN expression and achievement of maximal motor function improvement, which aligns with the current understanding of SMA management

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Abbreviations

AAV9, adeno-associated virus serotype 9; ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AESI, adverse event of special interest; DMT, disease-modifying treatment; HRQOL, health-related quality of life; IV, intravenous; NdSSS, Neuromuscular disease swallowing status scale; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron protein; *SMN1*, *survival motor neuron 1* gene; *SMN2*, *survival motor neuron 2* gene; TEAE, treatment-emergent adverse event; TMA, thrombotic microangiopathy; WHO MGRS, World Health Organization–Multicenter Growth Reference Study.

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Disclosures: PA, **IA**, **SR**, **JMdL**, and **NM** are employees of Novartis and own stock/other equities. **JAS** has been a consultant advisory and principal investigator for Biogen, Novartis, and Roche. **EZ** has been an advisory consultant and speaker for Biogen, Novartis, and Roche. **JM** has been a speaker at events for Biogen, Novartis, Roche, PTC Therapeutics, and Sarepta Laboratories. **JG-G** has served on advisory boards for AveXis/Novartis, Biogen, BioMarin, PTC, Roche, and Sarepta; as Principal Investigator for ongoing clinical PTC and Sarepta trials; and received research funding from CAPES, CNPq, and FAPEMIG (Brazil). **SM** has participated in scientific advisory boards for Biogen, Novartis, Astellas, and GZ; and has been a speaker at events for GZ, Biogen, Sarepta, PTC, and PTC-Teleton Chile.

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