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Research Paper

Safety of Onasemnogene Abeparvovec for Patients With Spinal Muscular Atrophy 8.5 kg or Heavier in a Global Managed Access Program

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ABSTRACT

Background: Spinal muscular atrophy is a rare, neurodegenerative disorder caused by biallelic deletions in the *survival motor neuron* (*SMN1*) gene. Onasemnogene abeparvovec is a one-time, intravenous gene replacement therapy designed to deliver the *SMN1* transgene. Although available in many geographies, it is not approved globally. The Global Managed Access Program (GMAP) expanded treatment access to patients in countries where treatment was not approved. Previous onasemnogene abeparvovec clinical trials included patients with body weight <8.5 kg. Through GMAP, children weighing ≥8.5 kg received onasemnogene abeparvovec. We describe safety data for heavier patients in GMAP.

Methods: GMAP records were reviewed to identify patients weighing ≥8.5 kg at onasemnogene abeparvovec dosing. To obtain corresponding adverse event (AE) data, the Novartis ARGUS safety database was searched using patient identification numbers and birth dates/dosing dates for any reported AE for GMAP patients.

Results: As of September 2, 2021, 102 patients weighing ≥8.5 kg at time of dosing were identified. Fifty-four (53%) had one or more reported AEs. Three patients were reported to be deceased. All three deaths were assessed to be secondary to acute respiratory events. Most (62%) AEs were non-serious. The most frequently reported AEs included increases in hepatic laboratory values, decreased platelets and thrombocytopenia, pyrexia, vomiting, and decreased appetite.

Conclusions: Safety findings for patients weighing ≥8.5 kg administered onasemnogene abeparvovec through GMAP were consistent with those described in clinical trials and included hepatotoxicity, thrombotic microangiopathy, and thrombocytopenia.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease caused by biallelic deletions in the *survival motor neuron 1* (*SMN1*) gene, leading to survival motor neuron (SMN) protein deficiency. This protein deficiency causes loss of motor neurons, resulting in progressive muscle atrophy and weakness and early death (often by age two years) in the most severe and most common form of the disease.[1,2] Disease onset and severity is roughly correlated to the number of copies of the *survival motor neuron 2* (*SMN2*) gene, which is a backup gene to *SMN1*. For example, patients with two or fewer copies of *SMN2* will typically exhibit the most severe SMA phenotype.[3,4] Furthermore, SMA has been typically classified into three major phenotypes (SMA types 1, 2, and 3), which are differentiated by the child's age at symptom onset and the maximum motor milestone achieved.[5,6]

SMA is rare, with an incidence of approximately 1 in 10,000 live births,[7] without racial, sex, or ethnic predilection. Although disease-modifying treatments are available in some geographic regions, a substantial number of patients with SMA worldwide

Conflicts of Interest: D.C., S.M., R.S., N.L., S.R., and T.S. are employees of Novartis Gene Therapies, Inc., the manufacturer of onasemnogene abeparvovec, and hold Novartis stock/stock options.

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still lack access to these life-saving therapies or may be unable to receive these therapies because of medical contraindications.[8,9]

Onasemnogene abeparvovec is a one-time, single-dose gene replacement therapy designed to deliver a functional human *SMN* transgene to motor neurons through intravenous infusion and is composed of a recombinant, self-complementary adeno-associated virus serotype 9 vector that delivers a copy of the gene encoding the human SMN protein. Onasemnogene abeparvovec is the only treatment for SMA designed to rapidly and continuously deliver a full-length functional SMN protein.[8] Other therapies, including nusinersen and risdiplam, increase *SMN2* gene protein concentrations and SMN protein activity. However, these treatments do not address the underlying etiology of SMA and they require lifelong treatment.

Onasemnogene abeparvovec has been approved in more than 40 countries and regions with variations in indications with respect to age/weight. For example, in the United States, onasemnogene abeparvovec is indicated for use in patients up to 2 years of age. In other regions such as Europe and Canada, dosing is indicated for patients up to 21 kg. The safety of onasemnogene abeparvovec has been described for symptomatic type 1 SMA, as well as presymptomatic patients weighing <8.5 kg in clinical trials (START [NCT02122952],[10] STR1VE-US [NCT03306277],[11] STR1VE-EU [NCT03461289],[12] SPR1NT [NCT03505099][13,14]).

Managed access programs offer an alternative mechanism to provide patients with a serious or life-threatening disease or condition access to needed therapies that are not yet approved in their countries or that are available only as part of a clinical trial. These programs are also known as *Compassionate Use* or *Named Patient* programs and are commonly implemented for rare diseases, such as SMA, for which treatment options are limited. The Global Managed Access Program (GMAP) was launched by Novartis Gene Therapies, Inc., in January 2020 to provide onasemnogene abeparvovec therapy to eligible patients with SMA. The GMAP represents the first time that a one-time, single-dose gene therapy has been made available to patients before regulatory approval via a free program.

The GMAP includes patients up to 24 months of age, regardless of phenotype or genotype. In addition, the protocol for the GMAP was amended, via feedback from the global SMA community, to include only patients who did not have access to or who were not medically eligible for available disease-modifying therapies. Thus, the spectrum of eligible patients and the geographic coverage for the GMAP are considerably broader than the patient populations treated in previous interventional trials. In summary, the GMAP allows for onasemnogene abeparvovec treatment for patients who were treated in a real-world setting within a variety of health care systems.

Key safety risks for onasemnogene abeparvovec described for humans include hepatotoxicity, thrombotic microangiopathy (TMA), thrombocytopenia, and troponin increases.[8] Onasemnogene abeparvovec safety data have been published by Day et al.,[15] but this study consisted of data representing clinical trials and commercial use. A significant limitation in the analysis of post-marketing data is the variable degree of detail provided through spontaneous reporting. Although every attempt is made to obtain complete information from post-marketing data, safety staff are often unable to obtain further information, including age at the time of dosing. The current published literature regarding use of onasemnogene abeparvovec in heavier children is limited. Waldrop and colleagues[16] reported their experience with gene therapy for the treatment of patients with SMA weighing up to 11.7 kg, including eight of 21 patients weighing ≥8.5 kg. Similarly, Weiss et al.[17] described their experience with onasemnogene abeparvovec for patients weighing up to 15 kg. However, their data analyses were stratified by age rather than weight.

This article details the safety experience of 102 patients weighing 8.5 kg or more at the time of dosing who received onasemnogene abeparvovec through the GMAP. Further analyses and details for patients weighing ≥13.5 kg at the time of dosing are also provided. Because onasemnogene abeparvovec is a weight-based therapy, this analysis is based on the patient's weight at the time of dosing rather than age.

Methods

As of September 2, 2021, data from the GMAP records were reviewed to identify patients weighing ≥8.5 kg at the time of onasemnogene abeparvovec dosing, with further stratification of patients ≥13.5 kg at the time of dosing. A search of the Novartis ARGUS safety database (an adverse event [AE] management system used for routine data monitoring) was conducted using patient identification numbers for any reported AEs in 102 GMAP patients. In addition to comparison of patient identification numbers, dates of birth and dosing were matched to help identify these heavier patients in the ARGUS database.

Adverse events reported in these patients were extracted using the methodology described earlier. Physicians received training and acknowledged that they understood the AE definitions and reporting requirements and process during enrollment into the GMAP. All reported AEs were entered into the Novartis ARGUS safety database. Extracted data from the ARGUS database included all AEs coded using conventional Medical Dictionary for Regulatory Activities (MedDRA) terms (Version 24.0). AEs reported by clinicians were coded to MedDRA-preferred terms based on the verbatim terms, which allowed for quantification of terms. Counts were calculated for all AEs. Furthermore, criteria for categorizing an AE as serious were a result of one or more of the following:

- Death;
- A life-threatening condition;
- Hospitalization or prolongation of existing hospitalization;
- Persistent/significant disability or incapacity; or
- An important medical event that may jeopardize the patient or may require medical intervention

Based on experience from nonclinical studies, as well as clinical trials and post-marketing experience, AEs of special interest for onasemnogene abeparvovec included hepatotoxicity, thrombocytopenia, thrombotic microangiopathy (TMA), cardiac AEs, and ganglionopathy. Acute liver failure was defined as any case with a diagnostic term of “acute hepatic failure” or “hepatic failure,” or any hepatic case with international normalized ratio >1.5 plus encephalopathy or international normalized ratio >2.0 without encephalopathy. This definition was selected from the published diagnostic criteria for acute liver failure for pediatric patients.[18]

To systematically search for events within AEs of special interest category, we specified predefined standardized MedDRA queries (SMQs), which are used by pharmaceutical companies for focused signal detection and monitoring. SMQs are validated, standard sets of predefined MedDRA terms that have undergone extensive review, testing, analysis, and expert discussion. Although SMQs are generally used for regulatory purposes, they can provide a framework for safety monitoring and reporting in general.

Results

As of September 2, 2021, a total of 175 patients had received onasemnogene abeparvovec through the GMAP. Review of the GMAP registration forms identified 102 patients who weighed ≥8.5 kg at the time of onasemnogene abeparvovec dosing. Based on

comparison of identification numbers from the GMAP registration forms with the ARGUS database, 52 patients had reported AEs within ARGUS. The supplementary matching of birth and dosing dates identified two more patients who met weight criteria. Thus we determined that 54 of 102 (53%) patients in the GMAP who weighed ≥8.5 kg at the time of onasemnogene abeparvovec dosing experienced at least one AE.

These 54 patients experienced 368 events, the majority of which were non-serious (227 of 368; 62%). The most commonly reported AEs were pyrexia (33 of 368; 9%), aspartate aminotransferase (AST) increased (24 of 368; 7%), vomiting (21 of 368; 6%), transaminases increased (17 of 368; 5%), hepatic enzyme increased (16 of 368; 4%), thrombocytopenia (16 of 368; 4%), alanine aminotransferase (ALT) increased (15 of 368; 4%), platelet count decreased (13/368; 4%), decreased appetite (five of 368; 1%), gamma-glutamyltransferase increased (five of 368; 1%), and hypertransaminasemia (five of 368; 1%). Although pyrexia was the most commonly reported numerically, collectively, the terms associated with transaminitis represent a greater number of events reported. A full list of AEs by MedDRA-preferred term is provided in Supplementary Table 1.

Of the 141 serious adverse events reported, the most commonly reported (five or more) preferred terms included thrombocytopenia (13 of 141; 9%), AST increased (eight of 141; 6%), hepatic enzyme increased (seven of 141; 5%), pyrexia (seven of 141; 5%), transaminases increased (six of 141; 4%), ALT increased (five of 141; 4%), and vomiting (five of 141; 4%). Fatal outcomes were described for the following three patients, and all three were assessed to be secondary to acute respiratory events:

- A 19-month-old female patient (weight at dosing was 8.6 kg) was diagnosed with SMA type 1 (*SMN2* gene: two copies) at age two months. She had a history of apnea, dysphagia from age three to six months, atelectasis (approximately at the age of six to seven months), bronchiolitis, and multiple episodes of respiratory arrests. One month before receiving onasemnogene abeparvovec, the patient was treated with nusinersen (details regarding nusinersen administration were not provided). She was acutely ill with bronchiolitis one week before onasemnogene abeparvovec administration and was treated with unspecified antibiotics that were continued "prophylactically" through onasemnogene abeparvovec treatment. Baseline laboratory tests obtained six days before receiving onasemnogene abeparvovec revealed platelet count 596 × 103/μL (reference range: 150.00 to 450.00 × 103/μL), activated partial thromboplastin time 24.8 seconds (reference range: 26 to 40 seconds), and troponin I less than 3.2 (reference range: <4, unit was not reported). Baseline ALT, AST, and total bilirubin values were within the reference ranges.
  Prednisone (unknown dosage) was initiated one day before until eight days after onasemnogene abeparvovec administration. Concomitant methylprednisolone (unknown dosage and duration) was also initiated. Decreased platelet count (49,000 μmol [reference range: 150,000 to 400,000 μmol]) was observed three days after onasemnogene abeparvovec infusion and was further complicated with bleeding events five days later when the patient's mother attempted to insert a nasogastric tube at home. Emergency services were called the next day, and the patient suffered multiple respiratory arrests en route to and on arrival at the hospital. Laboratory tests demonstrated platelet count 35,000 μmol, serum creatinine 0.71 mg/dL (reference range: 0.2 to 0.41 mg/dL), serum urea 63.2 μg/dL (reference range: 10 to 50 μg/dL), ALT 81 U/L (reference range: 10 to 47 U/L), AST 367 U/L (reference range: 11 to 38 U/L), amylase 184 U/L (reference range: 14 to 97 U/L), albumin 2.8 g/L (reference range: 3.3 to 5.5 g/L), and total protein 5.1 g/L (reference range: 6.4 to 8.1 g/L). Renal function tests continued to worsen, and the patient was reported as "full of ecchymosis." No evidence for hemolysis was present. The patient was diagnosed with disseminated intravascular coagulopathy and multiorgan failure requiring blood and platelet transfusions, induced hypothermia, and peritoneal dialysis. The patient's platelet count increased to 118,000 μmol/L after three days of hospitalization. Renal function improved within four weeks of hospitalization, and dialysis was discontinued. She was extubated and multiorgan failure was reported as resolved. Subsequently, the patient developed a "bacterial suprainfection," and her condition deteriorated. She died 80 days after onasemnogene abeparvovec dosing.
- A 12-month-old male patient (weight at dosing was 9.5 kg) with SMA type 1 (*SMN2* gene: two copies) and a medical history of pulmonary hypoplasia, pneumonopathy, and bilevel positive airway pressure ventilatory support was dosed with onasemnogene abeparvovec at age 12 months. Increases in troponin I (73 ng/L, reference range was not available) and hepatic enzyme (ALT 264 U/L and AST 263 U/L, reference ranges not available) at 22 days and 36 days, respectively, were reported as AEs following administration of onasemnogene abeparvovec. Baseline troponin was 3.9 ng/L (further cardiac details unknown). The patient's concomitant medications included prednisone and prednisolone. The patient developed pyrexia and increased bronchial secretion leading to dyspnea 40 days after onasemnogene abeparvovec infusion and was diagnosed with pneumonia. On the same day, he experienced respiratory failure and became dependent on bilevel positive airway pressure. The patient died because of respiratory failure 106 days after onasemnogene abeparvovec dosing.
- A 28-month-old male patient (weight at dosing was 12.5 kg) with SMA type 2 (*SMN2*: copy number unknown) and a medical history of upper respiratory tract infection died suddenly while sleeping on a hammock. He had a historic condition of upper respiratory tract infection that started three days before his death and a concurrent condition of increased hepatic enzyme (liver function test results not provided). Concomitant medication included prednisone. The patient died 96 days after onasemnogene abeparvovec dosing.

Adverse events of special interest

Hepatotoxicity

Predefined SMQs were used to identify events of hepatotoxicity. This search yielded 98 reported events in 46 patients (Table 1). Of note, no events of acute or chronic liver failure were reported.

Thrombocytopenia

Predefined SMQs were used to identify events of thrombocytopenia. This search yielded 29 reported events (16 events of thrombocytopenia and 13 events of platelet count decreased) in 24 patients. AEs reported for patients experiencing events of thrombocytopenia were also examined for bleeding events, and five patients were identified. The events of thrombocytopenia and AEs identified by the search criteria for bleeding events in these five patients are listed in Table 2. Note that Patient 3 reported seven bleeding events. This patient is described in the earlier discussion under fatal outcomes.

Thrombotic microangiopathy

Predefined SMQs were used to identify events of TMA. This search yielded one reported event.

TABLE 1.
Hepatotoxicity Events

Event MedDRA PT	Count of Event PTs
Aspartate aminotransferase increased	24
Transaminases increased	17
Hepatic enzyme increased	16
Alanine aminotransferase increased	15
Hypertransaminasaemia	5
Gamma-glutamyltransferase increased	5
Blood alkaline phosphatase increased	4
Liver function test increased	3
Blood bilirubin increased	2
Hepatomegaly	2
Blood alkaline phosphatase abnormal	1
Liver function test abnormal	1
Hepatic cytolysis	1
Hepatotoxicity	1
Hepatitis	1
Grand total	98

Abbreviation:
PT = Preferred term

- A 12-month-old female patient (weight at dosing was 12 kg) (*SMN2* gene: three copies), previously treated with nusinersen (dosage and duration unknown), was treated pre-symptomatically. She presented at baseline with no active infections when she received onasemnogene abeparvovec treatment. She developed twice-daily vomiting six days after onasemnogene abeparvovec infusion, although she tolerated oral corticosteroid dosing. The patient presented with reduced oral intake and urine output and was hypertensive eight days post–onasemnogene abeparvovec infusion. Laboratory tests demonstrated hemolysis, thrombocytopenia, transaminitis, and acute kidney injury with microscopic hematuria and significant albuminuria. Renal ultrasound indicated increased echotexture and reduced corticomedullary differentiation. Echocardiography indicated mild pericardial effusion. She began to improve by day 12 postinfusion with supportive care, and complete resolution occurred within four weeks.

TABLE 2.
Thrombocytopenia and Bleeding Events

Thrombocytopenia Events by MedDRA PT	Events, n	Bleeding Events by MedDRA PTs	Events, n
Patient 1		Patient 1	
Thrombocytopenia	1	Petechiae	1
Patient 2		Patient 2	
Thrombocytopenia	1	Hemoglobin decreased	1
		Hematocrit decreased	1
Patient 3		Patient 3	
Platelet count decreased	1	Cerebral hemorrhage	1
Thrombocytopenia	1	Mouth hemorrhage	1
		Hemorrhage	1
		Disseminated intravascular coagulation	1
		Renal hemorrhage	1
		Epistaxis	1
		Gastrointestinal hemorrhage	1
Patient 4		Patient 4	
Platelet count decreased	1	Hemoglobin decreased	1
Patient 5		Patient 5	
Thrombocytopenia	1	Hematuria	1

Abbreviation:
PT = Preferred term

Cardiac adverse events

Predefined SMQs were used to identify cardiac AEs. This search yielded 22 reported events in 11 patients (Table 3).

Ganglionopathy

No SMQs to identify ganglionopathy exist, and prespecified preferred terms, using a Novartis MedDRA query, were used to identify events of dorsal root ganglia toxicity. This search yielded no reported events.

Patients with weight ≥13.5 kg at time of dosing

Patients weighing ≥13.5 kg were identified to evaluate AEs specific to this subpopulation. Five patients were identified, and demographic information is presented in Table 4. The countries in which these patients were dosed included Brazil, Russia, Taiwan, the United Arab Emirates, and Vietnam.

Three of the five patients weighing ≥13.5 kg at the time of dosing did not experience any reported AEs. The two patients who experienced AEs are summarized below.

- A male patient (weight at dosing was 13.6 kg) with SMA type 1 (*SMN2* gene: three copies) received onasemnogene abeparvovec at age 23 months. Medical history and baseline functional status were not provided. The patient had been treated earlier with nusinersen (dates and duration unknown). The patient had AEs reported of liver function tests elevated, alkaline phosphatase increased, and AST increased, approximately eight days after dosing. Liver function test abnormalities were ALT and AST elevations (>1 to <3 × upper limit of normal) without bilirubin or gamma-glutamyltransferase elevations. The events were reported as resolved with the use of prednisolone. The patient exhibited events of tremor, muscle weakness, and progression of SMA approximately 11 months after onasemnogene abeparvovec dosing. Interval course and specific details were not described.
- A female patient (weight at dosing was 13.5 kg) with SMA type 1 (*SMN2* gene: two copies) received onasemnogene abeparvovec at age 15 months. Medical history and baseline functional status were not provided. The patient exhibited vomiting, thrombocytopenia, and decreased platelet count (55,000/μL, reference range not provided). The dates of onset and resolution and outcomes were not provided.

Discussion

The GMAP was designed to provide onasemnogene abeparvovec therapy to eligible patients with SMA in countries where this treatment had not yet been approved by health authorities. As of September 2, 2021, a total of 175 patients had been dosed through the GMAP, of whom 102 patients weighed ≥8.5 kg at the time of dosing, with five of these patients weighing ≥13.5 kg at the time of dosing. Given that the onasemnogene abeparvovec clinical trials included patients with a body weight <8.5 kg, reported safety data for heavier patients who received onasemnogene abeparvovec for SMA are limited. This report was generated to describe the safety profile for these heavier patients. AEs in the GMAP data analysis were consistent with those already reported after onasemnogene abeparvovec administration.[15] No new safety signals were identified.

Some authors have demonstrated their experience with onasemnogene abeparvovec at single and multiple centers, with subanalyses that included heavier patients. Waldrop et al.[16] described their regional experience with gene therapy for patients with SMA. Although the overall conclusions indicated that onasemnogene abeparvovec was well tolerated, the authors demonstrated that

TABLE 3.
Cardiac Adverse Events

Event MedDRA PT	Count of Event PTs
Dyspnea	4
Troponin I increased	4
Hepatomegaly	2
Tachycardia	2
Troponin T increased	2
Blood creatine phosphokinase MB increased	1
Cardiac failure	1
Cardio-respiratory arrest	1
Disseminated intravascular coagulation	1
Edema	1
Sudden death	1
Thrombotic microangiopathy	1
Troponin increased	1
Grand total	22

Abbreviation:
PT = Preferred term

older and heavier patients had greater elevations in liver transaminases. Based on the raw data provided in the article, the crude percentages of patients with >2× (ratios of patient numbers) were greater for patients weighing ≥8.5 kg than for those weighing <8.5 kg. However, interpreting the data for the <8.5 and ≥8.5 kg weight differences is difficult. Differences in percentages are very uncertain because of the small patient numbers (n = 21; n with weight ≥8.5 kg = 12). Furthermore, in the assessment of the continuous-fold increase over normal, a relationship to body weight is minimal. All patients (100%) who remained on prednisone more than 10 weeks developed more than 2 times normal elevations. All patients who remained on prednisone less than 10 weeks had elevations 2, 3, or 4 times the normal. These differences in elevation have less to do with weight because patients with ≥10 weeks prednisolone have a wide range of body weights. Similarly, Weiss et al.[17] presented data for 76 patients who had received onasemnogene abeparvovec for the treatment of SMA. Although the mean weight of these patients was 9.1 kg at the time of dosing, the number of patients weighing ≥8.5 kg was not provided. The authors stated that maximum elevations were associated with greater weight, but granular data were not provided.

To assess the safety events in the GMAP, only AE reporting could be used because laboratory data were not collected systematically and prospectively. AEs were reported by physicians using terms at their discretion based on what they considered clinically meaningful. For all reported AEs, a coding process occurred upon entering the events into the Novartis ARGUS safety database. This process allowed for completeness during data extraction. AEs reported by physicians were coded to MedDRA preferred terms based on the verbatim terms, which allowed for quantification of terms. A clinician could have used multiple terms (e.g., ALT increased/AST increased/transaminase increase), depending on reporting style. We have clarified, whenever possible, the number of events compared with the number of patients, while recognizing that a patient may have had more than one event. From a clinician perspective, this provides context on multiple events reported for individual patients.

TABLE 4.
Demographics of Five Patients Weighing ≥13.5 kg at the Time of Onasemnogene Abeparvovec Dosing

Age at Treatment	Weight at Dosing, kg	Sex	*SMN2* Copies	SMA Type
23 months	13.60	M	3	1
15 months	13.50	F	2	1
20 months	14.50	F	3	1
23 months	17.00	M	Unknown	2
22 months	13.60	F	2	1

Abbreviations:
F = Female
M = Male
SMA = Spinal muscular atrophy
SMN2 = *Survival motor neuron 2* gene

Three deaths were reported in the GMAP, and all were assessed to be secondary to acute respiratory events considered to be related to SMA. In onasemnogene abeparvovec clinical trials, three deaths were reported: one during the screening period (no onasemnogene abeparvovec received) and two after treatment. All deaths were assessed as attributable to underlying SMA disease. The comorbidities associated with SMA, which can include malnutrition and risk for recurrent respiratory infections because of respiratory muscle weakness, can be serious or even life-threatening. In addition, children affected by SMA are known to have nutritional challenges, making them prone to malnutrition and dehydration. Rigorous management of the overall health status of children with SMA is imperative before and after treatment with onasemnogene abeparvovec.

In our program, which included 175 total GMAP patients, 102 patients weighing ≥8.5 kg were dosed, and hepatotoxicity events were reported for 46 (45%) patients. One patient weighed ≥13.5 kg at the time of dosing. Compared with data from clinical trials covering patients who weighed <8.5 kg at the time of dosing, hepatotoxicity events, based on reported AEs (36%), and transaminase elevations, which were not reported as AEs (53%), were reported for 89% of patients.[15] Acute liver failure has been described for patients following administration of onasemnogene abeparvovec in both weight categories.[19] No patients in the GMAP had reported acute liver failure. Therefore, the hepatotoxicity reported for heavier children in GMAP was similar to that reported for patients weighing <8.5 kg from onasemnogene abeparvovec clinical trials.

One case of TMA was described in the GMAP for patients weighing ≥8.5 kg, and this event resolved. On review of the data presented during the recent US Food and Drug Administration's Cellular, Tissue, and Gene Therapies Advisory Committee Meeting, nine cases of TMA in more than 1400 patients dosed with onasemnogene abeparvovec as of July 31, 2021, were reported.[20] A majority of these patients had potentially contributing factors such as infection, and, in consideration of the small number of cases, drawing formal comparisons between the GMAP data and the safety profile of onasemnogene abeparvovec with granularities is not possible. Rather, the GMAP data for TMA remain consistent with that already described for TMA,[21] which is a treatable condition if diagnosed early. The mechanism for TMA post–onasemnogene abeparvovec administration has not been elucidated, and TMA has been associated with other adeno-associated virus-based gene therapies.[22,23]

Thrombocytopenia was reported as an identified risk after onasemnogene abeparvovec administration. Although events were identified using SMQ, the reported AEs do not necessarily reflect low platelet values. A cross reference to bleeding events was made. One event with a fatal outcome was associated with trauma in the setting of low platelet values as reported. This stresses the need for clear guidance and for parents and caregivers to remain vigilant and seek prompt medical attention in case AEs occur in this fragile population.

Cardiac AEs were reported and mainly secondary with respiratory etiologies or infection as primary in origin. No clinically relevant events that were primarily cardiac in nature were reported. Troponin concentrations continue to be monitored. However, the clinical relevance of elevated troponin remains unclear in this population.[24] Note that troponin increase was not associated with relevant signs or symptoms, and AEs pertaining to impaired cardiac

function were secondary to alternative etiology other than drug-induced or cardiac etiology.

Dorsal root ganglia toxicity was reported in nonhuman primates. However, no clinical events have been reported in humans. The GMAP data search did not reveal any reported ganglionopathies.

Limitations of the GMAP include limited data collection and lack of trial methodology with respect to ongoing data provision. Data presented here are representative of AEs reported from treating physicians in a real-world setting. Although every attempt was made to ensure all relevant AEs were reported and captured, including training and follow-up with physicians, AE reporting based on clinical meaningfulness was at the discretion of the physicians. Each reporting physician provided attestation that all AEs were to be reported. However, full compliance cannot be ensured.

Although AE collection is a requirement of the program, provision of laboratory data is not. As such, objective diagnostic (laboratory and imaging) data cannot be evaluated. For instance, the most commonly reported hepatic AEs were abnormal laboratory test results without complete laboratory values provided. Therefore, the clinical significance of these abnormal test results cannot be fully characterized, but these events accounted for AE incidence. Efficacy information was not collected because of the nature of the program. Furthermore, in consideration of the *Compassionate Use* nature of the program, no standardized guidance for standard of care, which may vary globally, exists, and the baseline functional status of these patients, which was always provided, may be impacted. Patient suitability for dosing was determined by the treating physician, using the GMAP treatment guidelines, and based on individualized medical decision-making.

Conclusions

In summary, the safety findings for patients dosed at a heavier weight, ≥8.5 kg, are consistent with those described for patients who weighed <8.5 kg from onasemnogene abeparvovec clinical trials. Furthermore, two of five (40%) patients with body weights of ≥13.5 kg experienced AEs, such as vomiting, hepatotoxicity (without acute liver failure), and thrombocytopenia, which were consistent with the reported safety profile of onasemnogene abeparvovec, without identification of any new safety signals.[15] Therefore, risk of increased toxicity in the heavier population was not identified from this analysis. Although one patient demonstrated disease progression, the baseline functional status and interval medical history, including nutritional status, therapy services, and other possible management, were not known, and this scenario was not assessable. Children with SMA are fragile because of recurrent respiratory infections and malnutrition, and care should be optimized before, during, and after any therapy provided. Known important risks with onasemnogene abeparvovec administration include hepatotoxicity, thrombocytopenia, and thrombotic microangiopathy. Clinicians must still exercise a greater degree of awareness to identify AEs early, if they occur, and intervene accordingly.

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Supplementary data

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References

1. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol. 2017;82:883–891.
2. Burghes AH, Beattie CE. Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick? Nat Rev Neurosci. 2009;10:597–609.
3. Calucho M, Bernal S, Alías L, et al. Correlation between SMA type and *SMN2* copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018;28:208–215.
4. Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of *SMN1* and *SMN2* based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002;70:358–368.
5. Dubowitz V. Chaos in the classification of SMA: a possible resolution. Neuromuscul Disord. 1995;5:3–5.
6. Munsat TL, Davies KE. International SMA consortium meeting (26–28 June 1992, Bonn, Germany). Neuromuscul Disord. 1992;2:423–428.
7. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20:27–32.
8. Zolgensma (Onasemnogene Abeparvovec-Xioi). Bannockburn, IL: Novartis Gene Therapies, Inc.; 2021 (package insert).
9. SPINRAZA (Nusinersen). Cambridge, MA: Biogen, Inc.; 2020 (package insert).
10. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377:1713–1771.
11. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy with two copies of SMN2 (STR1VE): an open-label, single-arm, phase 3 study. Lancet Neurol. 2021;20:284–293.
12. Mercuri E, Muntoni F, Baranello G, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20:832–841.
13. Strauss K, Muntoni F, Farrar M, et al. Onasemnogene abeparvovec gene therapy in presymptomatic spinal muscular atrophy (SMA): SPR1NT study update in children with 2 copies of SMN2 (4190). Neurology. 2021;96:AB4190.
14. Strauss KA, Muntoni F, Farrar MA, et al. Onasemnogene abeparvovec gene therapy in presymptomatic spinal muscular atrophy (SMA): SPR1NT study update in children with 3 copies of SMN2 (4163). Neurology. 2021;96:AB4163.
15. Day JW, Mendell JR, Mercuri E, et al. Clinical trial and postmarketing safety of onasemnogene abeparvovec therapy. Drug Saf. 2021;44:1109–1119.
16. Waldrop MA, Karingada C, Storey MA, et al. Gene therapy for spinal muscular atrophy: safety and early outcomes. Pediatrics. 2020;146, e20200729.
17. Weiss C, Ziegler A, Becker LL, et al. Gene replacement therapy with onasemnogene abeparvovec in children with spinal muscular atrophy aged 24 months or younger and bodyweight up to 15 kg: an observational cohort study. Lancet Child Adolesc Health. 2022;6:17–27.
18. Alonso EM, Horslen SP, Behrens E, Doo E. Pediatric acute liver failure of undetermined cause: a research workshop. Hepatology. 2017;65:1026–1037.
19. Feldman AG, Parsons JA, Dutmer CM, et al. Subacute liver failure following gene replacement therapy for spinal muscular atrophy type 1. J Pediatr. 2020;225:252–258.
20. Chand DH. Clinical findings of thrombotic microangiopathy (TMA). Presented at Cellular, Tissue, and Gene Therapies Advisory Committee September 2–3, 2021 Meeting. Available at: https://www.fda.gov/media/151999/download. Accessed November 30, 2021.
21. Chand DH, Zaidman C, Arya K, et al. Thrombotic microangiopathy following onasemnogene abeparvovec for spinal muscular atrophy: a case series. J Pediatr. 2021;231:265–268.
22. Levy D. Complement activation in the setting of gene therapy. Experience with fordadistrogene movaparvovec in Ph1b study of boys with DMD. Presented at Cellular, Tissue, and Gene Therapies Advisory Committee September 2–3, 2021 Meeting. Available at: https://www.fda.gov/media/154121/download. Accessed December 15, 2021.
23. Byrne B, Salabarria S, Berthy J, et al. IGNITE-DMD: phase I/II ascending dose study of single IV infusion of SGT-001 microdystrophin gene therapy for DMD. One year efficacy and safety results. Presented at the MDA Clinical and Scientific Conference 2021; March 15-18, 2021.
24. Yoldas T, Arman Orun U. What is the significance of elevated troponin I in children and adolescents? A diagnostic approach. Pediatr Cardiol. 2019;40:1638–1644.