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ORIGINAL ARTICLE

Matching-adjusted indirect treatment comparison of onasemnogene abeparvovec and nusinersen for the treatment of symptomatic patients with spinal muscular atrophy type 1

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ABSTRACT

Objective: Onasemnogene abeparvovec, a one-time intravenous gene replacement therapy, and nusinersen, an antisense oligonucleotide that requires ongoing intrathecal administration, have been evaluated as treatments for spinal muscular atrophy (SMA) type 1 in separate Phase III trials, but no head-to-head comparison studies have been conducted. Onasemnogene abeparvovec was compared with nusinersen using a matching-adjusted indirect comparison (MAIC) to estimate the treatment effect of onasemnogene abeparvovec relative to nusinersen for the treatment of symptomatic patients with SMA type 1 for up to 24 months of follow-up.

Methods: In the absence of studies for both onasemnogene abeparvovec and nusinersen with a common comparator, a Bayesian naïve indirect treatment comparison (ITC) and MAIC between onasemnogene abeparvovec and nusinersen were conducted to compare efficacy and safety of onasemnogene abeparvovec with nusinersen. Outcomes of interest were event-free survival (EFS), overall survival (OS), and motor milestone achievements (independent sitting and independent walking). Relative treatment effects were expressed as relative risk (RR) and risk difference.

Results: Pooled and weighted patient-level data illustrated a favorable effect toward onasemnogene abeparvovec, suggesting longer EFS for patients compared with nusinersen (HR of onasemnogene abeparvovec vs. nusinersen: 0.19 [95% CI: 0.07–0.54; 99% CI: 0.05–0.74]). At 24 months of follow-up, patients receiving onasemnogene abeparvovec were statistically significantly more likely to achieve the motor milestone of sitting independently compared with patients treated with nusinersen. Although statistically significant differences were not observed at 6 to 18 months between treatment options, the likelihood of sitting independently at 12 and 18 months numerically favored onasemnogene abeparvovec. A numerically greater likelihood of walking by 18 and 24 months was also observed for patients treated with onasemnogene abeparvovec compared with nusinersen. Onasemnogene abeparvovec therapy was also associated with a favorable (but statistically nonsignificant) outcome for OS and may be associated with prolonged survival compared with nusinersen (HR of onasemnogene abeparvovec vs. nusinersen: 0.35 [95% CI: 0.09–1.32; 99% CI: 0.06–2.01]). Bayesian naïve ITC results were similar to the MAIC analysis for EFS, OS, and motor milestone achievements. Small sample size limited covariate matching to baseline CHOP INTEND and nutritional support requirement, leading to wider CIs and statistically inconclusive outcomes for some of the results.

Conclusions: Despite limitations of the current MAIC analysis (mainly a small sample size for statistical testing, even for the pooled onasemnogene abeparvovec trials, and potential differences in prognostic and predictive factors between studies), the relative treatment effects in EFS, OS, and motor milestone achievement indicate that onasemnogene abeparvovec may offer continued benefit compared with nusinersen through 24 months of follow-up.

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Introduction

Spinal muscular atrophy (SMA) is a debilitating hereditary neuromuscular disease, primarily affecting spinal motor neurons and leading to progressive muscle weakness of skeletal and respiratory muscles, muscle atrophy, and disability [1–4]. The incidence of SMA is one in 11,000 live births [5], with a spectrum of severity ranging from the most severe (SMA type 0 with prenatal onset) to severe cases with onset during the first 6 months of life (SMA type 1) to later onset during childhood or adolescence associated with milder disease (SMA types 2 to 4)

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[3,6–8]. SMA type 1 is the most common phenotype, accounting for 45% to 60% of all SMA cases [5,9,10]. If left untreated, SMA type 1 is associated with a high rate of infant mortality and functional impairments, with patients dying or requiring permanent ventilation by 2 years of age [8,11–13].

SMA is a monogenic disorder caused by biallelic mutations of the survival motor neuron 1 (*SMN1*) gene and insufficient production of functional SMN protein [4]. For humans, there is a second, almost homologous, gene called *SMN2*, which differs from *SMN1* by only five nucleotides [14,15]. The number of *SMN2* copies varies between individuals and is the main predictor for disease severity [2]. The low amount (approximately 10%) of full-length functional SMN protein produced by the *SMN2* gene only partially compensates for the lack of *SMN1* gene [15]. Greater *SMN2* gene copy number is associated with milder phenotypes [16].

The approvals of three disease-modifying treatments during the last 5 years have significantly changed the course of SMA [17–23]. Treatment options designed to either restore a fully functional copy of the human *SMN* gene or to increase the expression of *SMN2* gene to compensate for the lack of SMN protein [24–28] are available. Onasemnogene abeparvovec (Zolgensma[i]), a one-time intravenous infusion gene replacement therapy, received United States Food and Drug Administration (US FDA) approval in May 2019 for the treatment of patients with SMA aged <2 years [19]. In March 2020, the European Medicines Agency (EMA) granted conditional marketing authorization for the treatment of patients with 5q SMA with a biallelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1; or for patients with 5q SMA with a biallelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene [20]. Nusinersen (Spinraza[ii]) was approved by the US FDA in 2016 and the EMA in 2017 for the treatment of patients with SMA [21,22]. Nusinersen attenuates the underlying genetic disorder by increasing production of the SMN protein; treatment is administered as four loading doses on days 0, 14, 27, and 63, with maintenance doses every 4 months via an intrathecal injection [29]. Risdiplam (Evrysdi[iii]) is a daily, orally administered *SMN2*-directed RNA splicing modifier approved by the US FDA in 2020 and the EMA in 2021 for the treatment of patients with SMA aged ≥2 months [23,30,31].

Because of the broad clinical spectrum and rarity of SMA, pivotal trials for these drugs assess patients across a limited spectrum of age and disease severity [25]. Multiple clinical studies with varying numbers of included patients and differing durations evaluating the efficacy and safety of onasemnogene abeparvovec and nusinersen have consistently demonstrated improvement in motor function, event-free survival (EFS), and overall survival (OS) [12,18,32–41]. Four Phase II trials assessing safety and efficacy of risdiplam in different SMA types (1, 2, and 3) also reported positive results, including improvement in motor function [42]. More clinical research is needed to further assess and compare the short- and long-term efficacy and safety of risdiplam, nusinersen, and onasemnogene abeparvovec for SMA patients [43].

No direct evidence for the clinical efficacy of onasemnogene abeparvovec versus active comparators exists, and indirect treatment comparisons (ITCs) are necessary to explore the relative efficacy of treatment options for patients with SMA type 1. Matching-adjusted indirect comparisons (MAICs) use individual-level patient data (IPD) to derive weights such that the weighted covariate distribution of the index trial matches that of a comparator trial for which only summary data are available. The reweighted IPD is then used to derive predicted outcomes in a study population mirroring the comparator trial [44–48]. In the absence of randomized-controlled trials (RCTs) and head-to-head trials with common comparators, MAICs that leverage IPD to reweigh patients in similarly designed trials provide potentially crucial comparative evidence [49]. MAICs have been acknowledged by health technology assessment agencies as a robust analytical method and are becoming commonly used in technology assessments [44,46,50,51]. For the present study, the relative treatment effects of onasemnogene abeparvovec and nusinersen were compared using IPD from onasemnogene abeparvovec clinical trials evaluating safety and efficacy for a target population of patients with SMA type 1 and with two copies of the *SMN2* gene.

Methods

Systematic literature review

Identification and selection of relevant studies for this analysis were based on a systematic literature review (SLR) of RCTs and clinical trials that described clinical efficacy and safety outcomes of treatment for patients with SMA type 1. The SLR followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [52] to identify eligible RCTs and other clinical studies, including searches of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials by using a predefined search strategy. Criteria used to select studies for the ITC and MAIC included population (symptomatic SMA type 1), treatment interventions of interest (onasemnogene abeparvovec and nusinersen), comparators (no restrictions), outcomes (OS, EFS, motor milestones [sitting independently, walking independently]), treatment-related adverse events), and study design (RCTs, single-arm, or non-RCTs). The SLR for the review of clinical efficacy and safety, conducted on 3 March 2020, identified four eligible studies—two of onasemnogene abeparvovec (START [CL-101] [NCT02122952] and STR1VE-US [CL-303] [NCT03306277]) and two of nusinersen (ENDEAR [NCT02193074] and SHINE [NCT02594124]) [18,33,37, 39,40,53]. During the period the SLR was conducted, onasemnogene abeparvovec and nusinersen were the only approved treatments for SMA type 1, and studies completed/published after 3 March 2020 were not included in this analysis. Therefore, our MAIC did not include a comparison with risdiplam.

Matching-adjusted indirect comparison

In the absence of randomized controlled trials with a common comparator, a MAIC can be used to reweight patients in an index trial to match that of a competitor trial. This approach has advantages over other population-adjusted methods, such as simulated treatment comparisons, when

considering time-to-event outcomes and is generally easier to interpret [49]. With MAIC, a propensity score weight is used to adjust for differences between the population in the index trial and the population in the external aggregate data trial. Our MAIC was conducted using methods outlined by NICE [46]. In addition to MAICs, a naïve Bayesian ITC, which simply calculates relative effect measures with no adjustment for potential confounders (see Supplemental Appendix pp. 1–2), was also conducted.

Outcomes

Event-free survival, OS, sitting independently, and walking independently at 6, 12, 18, and 24 months of follow-up were the outcomes included in this analysis. The definition of EFS was similar across the trials. In START [18] and STR1VE-US [33], EFS was defined as the avoidance of the combined endpoint of death or permanent ventilation (defined as tracheostomy or requirement of $\geq$16 h of daily noninvasive ventilatory support for $\geq$14 consecutive days in the absence of acute reversible illness or perioperative ventilation). In the ENDEAR [39] and SHINE trials [37,40,53] of nusinersen, EFS was defined as the time to death or use of permanent ventilation, defined by tracheostomy or ventilatory support for $\geq$16 h per day for $\geq$21 continuous days in the absence of an acute reversible event. Independent sitting was measured in all clinical trials using various assessment tools. The START [18] and STR1VE-US [33] trials used the Bayley Scales Gross Motor Subtest with two different time thresholds to define independent sitting (sits alone for $\geq$5 s in START [18] and $\geq$30 s in STR1VE-US [33]). Therefore, two scenarios were used to define independent sitting from the onasemnogene abeparvovec trials: Scenario A used the $\geq$30 s threshold for both STR1VE-US [33] and START [18]; Scenario B used the $\geq$30 s threshold for STR1VE-US [33] and the $\geq$5 s threshold for START [18]. In ENDEAR [39] and SHINE [37,40,53] trials, independent sitting was defined as stable sitting and pivoting as per the Hammersmith Infant Neurological Examination Section 2 (HINE-2). Independent walking was also assessed in the studies; START [18] and STR1VE-US [33] used walking alone as per the Bayley Scales Gross Motor Subtest, and ENDEAR [39] and SHINE [37,40,53] used walking as stable without assistance per the HINE-2 score scale as assessments.

STR1VE-US [33] observed patients to 18 months of age, whereas START [18] followed patients to 24 months post-dose. Therefore, the 18-month age results from STR1VE-US [33] were imputed as an estimate of the number of patients in that trial who achieved motor milestones at 24 months of follow-up.

Selection of baseline variables for matching

In keeping with the goal of the current MAIC methodology approach, differences between the trials were adjusted by matching the baseline characteristics of the study populations using IPD from the trial(s) of one treatment and aggregate data for trial(s) of the other treatment. In this analysis, IPD from START [18] and STR1VE-US [33] were matched with the aggregate data from the SHINE [37,40,53] trial. IPD from the onasemnogene abeparvovec trials were weighted to match the mean and variance of baseline characteristics reported in the nusinersen trials.

Table 1. Treatment effect covariates identified *A Priori*.

1. Mean CHOP INTEND score at baseline
2. Percentage with nutritional support at baseline
3. Percentage with ventilator support at baseline
4. Age at symptom onset
5. Age at study start (first dose)
6. Baseline weight
7. *SMN2* copy number
8. Sex

Expert consensus identified this list of treatment effect covariates for adjustment. All covariates were used and tested in the model.

The MAIC covariates were chosen *a priori* and are listed from highest to lowest importance (Table 1). The covariates were selected and ranked using clinical expert input from two pediatric neurologists (Novartis Gene Therapies, Inc., therapeutic head and an external US clinical investigator involved with the trial program) and reflect their extensive experience working with patients with SMA. The covariates were ordered prior to analysis to avoid selection bias based on the results of the analysis (Table 1). Considered by a team of clinical experts to be most relevant and a critical marker of baseline function, the Children's Hospital of Philadelphia Infant Test of Neurologic Disorders (CHOP INTEND) score is a validated motor outcome measure specifically developed for infants with SMA type 1 and includes 16 items on a 0- to 64-point total score scale; greater scores indicate better motor function [54]. CHOP INTEND has been used to reliably quantify the rapid natural decline of motor function for infants with SMA type 1 who do not receive a disease-modifying therapy [54]. Nutritional support also is a critical indicator of disease progression [55] and was ranked as the second most important covariate in the MAIC. Bulbar dysfunction is universal for patients with severe SMA [56,57]. The development of tongue and swallowing weakness increases feeding and swallowing difficulty over time and leads to weight loss, pulmonary aspiration, and the need for mechanical feeding [57].

The algorithm was run on the full model and covariates were removed until convergence was achieved. The algorithm converged for the two greatest ranked covariates (CHOP INTEND score at baseline and nutritional support at baseline), and these covariates were matched between the onasemnogene abeparvovec IPD and nusinersen aggregate data.

Matching and effective sample size

Pooled IPD from the START [18] and STR1VE-US [33] trials for the onasemnogene abeparvovec treatment arm were compared with aggregate data from the nusinersen arm of the SHINE [37,40,53] trial. Propensity score weighting was used to match the distributions between the pooled STR1VE-US [33] and START [18] data and the population in the external aggregate data from the comparator trial (SHINE [37,40,53]). Joint distribution of covariates was not available in the SHINE [37,40,53] trial. Therefore, the method of moments

approach outlined in Signorovitch and colleagues [45] was used to balance the mean covariate values across populations [46]. Weights were obtained by minimizing $\sum_{i=1}^{N} \exp(\boldsymbol{\alpha}_1^T \boldsymbol{X}_i)$, which estimates weights from a logistic regression model: for each patient *i*, with covariates $\boldsymbol{X}_i$, in the index set.

Because the algorithm used to estimate weights did not converge using the full set of covariates, the included variables were removed in a stepwise fashion until convergence was achieved. For the pooled START and STR1VE-US [18,33] data, convergence was reached using both CHOP INTEND score at baseline and presence of nutritional support at baseline.

Analysis

For time to event data, reconstructed IPD and digitized Kaplan-Meier (KM) curves were used in the estimation of relative treatment effects. A weighted Cox proportional hazards (PH) model was used to estimate a hazard ratio (HR) of onasemnogene abeparvovec versus nusinersen. For binary outcomes (such as achieving a motor milestone), logistic regression models were used to model response as a function of treatment. Relative risks and risk differences between onasemnogene abeparvovec and nusinersen were presented as the measure of treatment effect, along with 95% and 99% confidence intervals (CIs). Because the MAIC is frequentist, the results are CIs; the naïve Bayesian ITC results are credible intervals (CrIs). Both 95% and 99% CIs and CrIs are presented; for relative risks, 95% CIs and CrIs and 99% CIs and CrIs that do not include one can be interpreted as corresponding to *p*-values of less than 0.05 and 0.01, respectively.

Results

Study and patient characteristics

Study characteristics and eligibility criteria of the included studies are presented in Table 2. The eligibility criteria with regard to age of the patient and body weight differed slightly between onasemnogene abeparvovec and the nusinersen trials. The SHINE [37,40,53] trial included 81 patients, while the pooled STR1VE-US [33] and START [18] trials included 34 patients. The MAIC effective sample size after weighting was 24.6 compared with a total patient population of 34. Mean age at study start (first dose) was greater for nusinersen patients compared with pooled onasemnogene abeparvovec patients (164.3 d vs. 108.6 d, respectively); mean age at onset of symptoms was similar (48.7 d vs. 52.5 d, respectively) (Table 3). Onasemnogene abeparvovec-treated patients had a slightly greater mean baseline CHOP INTEND score (30.8) compared with nusinersen patients (26.7). Nutritional support was required by 15% of patients ($n = 5/34$) treated with onasemnogene abeparvovec compared with 9% of patients ($n = 7/80$) treated with nusinersen. Ventilatory support was required by 6% of patients ($n = 2/34$) treated with onasemnogene abeparvovec compared with 26% of the patients ($n = 21/80$) treated with nusinersen. Baseline characteristics used for matching before and after weighting are presented in Table 4.

Event-free survival and overall survival

For EFS, the pooled and weighted patient-level data from START [18] and STR1VE-US [33] demonstrated a longer EFS for patients who received onasemnogene abeparvovec compared with nusinersen (HR of onasemnogene abeparvovec vs. nusinersen: 0.19 [95% CI: 0.07–0.54; 99% CI: 0.05–0.74]) (Table 5). Although not statistically significant, onasemnogene abeparvovec therapy indicated a favorable numerical outcome for OS and may be associated with prolonged survival compared with nusinersen (HR of onasemnogene abeparvovec vs. nusinersen: 0.35 [95% CI: 0.09–1.32; 99% CI: 0.06–2.01]) (*see* Table 5). Figure 1 illustrates the reweighted KM curve for onasemnogene abeparvovec and the reconstructed published KM curve from SHINE [37,40,53] for EFS (Figure 1(A)) and OS (Figure 1(B)).

Motor milestones

Sitting independently

For the analysis using the definition of sitting unassisted for ≥30 s (Scenario A), at 24 months of follow-up, patients receiving onasemnogene abeparvovec were statistically more likely to achieve the motor milestone of sitting independently compared with patients treated with nusinersen at the 95% level (not statistically meaningful at the 99% level) (RR: 2.60; 95% CI: 1.05−6.49; 99% CI: 0.78–8.64]) (Table 6). A statistically significant difference was not observed for the likelihood of sitting independently at 6 to 18 months between treatment options.

For the MAIC regarding achievement of unassisted sitting for ≥30 s in STR1VE-US [33] and ≥5 s in START [18] (Scenario B), the relative treatment effects (expressed as relative risk and risk difference) were similar to Scenario A in which unassisted sitting ≥30 s defined milestone achievement (*see* Table 6). At the 24-month assessment, patients receiving onasemnogene abeparvovec were statistically more likely to sit independently at the 95% level (not statistically meaningful at the 99% level) (RR: 2.79; 95% CI: 1.13–6.89; 99% CI: 0.85–9.15). Although there was no statistically significant difference between onasemnogene abeparvovec and nusinersen in the likelihood of sitting at 6 to 18 months, the results at 12 and 18 months numerically favored onasemnogene abeparvovec.

Walking independently

Although not statistically meaningful, patients receiving onasemnogene abeparvovec had a numerically greater likelihood of walking by 18 and 24 months compared with patients receiving nusinersen (18-month RR: 1.40; 95% CI: 0.04–54.50; 99% CI: 0.01–172.35; 24-month RR: 2.08; 95% CI: 0.06–76.33; 99% CI 0.02–236.73) (Table 7). These results should be regarded as inconclusive as the true denominator of patients on treatment for SHINE [37,40,53] was overestimated

Table 2. Summary of study characteristics and patient eligibility of the included trials.

Trial	Publication	SMA type	Treatment group	Dose	Frequency	Eligibility				
						Age	*SMN* gene	Gestational age	Age at symptom onset	Body weight
SHINE[a] [37,40,53]	NICE 2018	Infantile- and later-onset (type 1, 2, and 3)	Nusinersen	12 mg (scaled[b])	D1, D15, D29, D64, D183[c], D302[c]	≤210 d	Two copies of *SMN2*	37–42 weeks	NR	≥3rd percentile for age
START [18]	Mendell 2017	Type 1; two copies of *SMN2* gene	Onasemnogene abeparvovec (low dose)	6.7×10^{13} vg per kg body weight	D1	≤6 months	Proven mutations of the *SMN1* gene with exactly two copies of *SMN2*	NR	0–6 months	>5th percentile for age
			Onasemnogene abeparvovec (therapeutic dose)	2.0×10^{14} vg per kg body weight[d]	D1					
STR1VE-US [33]	Novartis Gene Therapies, Inc., data on file	Type 1; two copies of *SMN2* gene[e]	Onasemnogene abeparvovec	1.1×10^{14} vg per kg body weight	D1	≤6 months	Proven mutations of the *SMN1* gene with one or two copies of *SMN2*	≥35 weeks	0–6 months	≥3rd percentile for age

Abbreviations. D. day; NICE. National Institute for Health and Care Excellence; NR. not reported; SMN: survival motor neuron.

[a]SHINE (CS11) [37,40,53] is the extension trial for multiple nusinersen trials (CS3A [38], ENDEAR [CS3B] [39], EMBRACE [58], CHERISH [CS4] [32], or CS12 [59]); only data from patients who were enrolled in ENDEAR [39] (active treatment arm) and enrolled in SHINE [37,40,53] were used in the MAIC analysis presented.

[b]Dosage adjusted based on age; 12-mg scaled equivalent dose was given based on projected cerebrospinal fluid (CSF) volume. Each infant received the estimated dose that is proportional to the estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for a 2-year-old child to adult.

[c]Maintenance dosages.

[d]Direct testing of the actual lot of investigational products used in START [18] by an improved and more fully qualified analytical method (droplet digital PCR) has determined the actual dose received by Cohort 2 (therapeutic dose) to be 1.1×10^{14} vg/kg (the same method has been used to establish an equivalent dose for the investigational medicinal product in all Phase III trials).

[e]STR1VE-US [33] allowed patients with one or two copies of *SMN2*. However, only patients with two copies were ultimately enrolled.

Table 3. Patient baseline characteristics of the included trials.

Trial name	Publication	Treatment	N	Mean age at study start (first dose), days (range)	Mean age at onset of symptoms, days (range)	Mean age at genetic diagnosis, days (range)	Female, *n* (%)	Mean weight, kg (range)	Mean CHOP INTEND score (range)	Mean HINE-2 score (range)	Nutritional support, *n* (%)	Ventilator support, *n* (%)
SHINE [37,40,53]	NICE 2018	Nusinersen	81[a]	164.3 (60.8–456.3)	48.7 (0–121.7)	NR	44 (54%)	NR	26.7 (8.1)[b]	1.3 (1.1) [b]	NR	NR
START [18]	Mendell 2017	Onasemnogene abeparvovec (therapeutic dose)	12	103.4 (27.4–240.3)	42.6 (0–91.3)	60 (0–136)	7 (58%)	5.7 (3.6–8.4)	28 (12–50)	NR	5 (42)	2 (17)
STR1VE-US [33]	Novartis Gene Therapies, Inc., data on file	Onasemnogene abeparvovec	22	112.5 (15.2–179.5)	57.8 (0–121.7)	63.9 (15.2–121.7)	12 (55%)	5.8 (3.9–7.5)	32 (18–52)	NR	0	0
STR1VE-US [33] and START [18] pooled	Novartis Gene Therapies, Inc., data on file	Onasemnogene abeparvovec	34	108.6 (15.2–240.3)	52.5 (0–120)	62.5 (0–136)	19 (56%)	5.8 (3.6–8.4)	30.8 (12–52)	NR	5 (15)	2 (6)

Abbreviations. CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Section-2; NR: not reported.
[a]One infant randomized to receive nusinersen in ENDEAR [39] was not dosed but was dosed in SHINE [37,40,53].
[b]Standard deviation.

because of a lack of reported information. Calculations were not performed for time points in which neither study reported an event. A continuity correction was applied for the 18-month analyses as zero events were reported in SHINE [37,40,53]. Because SHINE [37,40,53] was subject to loss of patients to follow-up, the number of observed patients diminished with increasing time on study. By 18 months, only 31 of 81 patients had follow-up data.

Discussion

Clinical trials assessing the efficacy of onasemnogene abeparvovec and nusinersen in SMA type 1 patients have independently shown significant improvement in OS, EFS, and motor function (ability to sit unassisted for ≥5, ≥10, and ≥30 s; head control; roll over; crawl; pull to stand; stand independently; walk independently) compared with historic cohorts or control patients with SMA type 1 [18,33,35,37,38,45]. In the absence of RCTs and head-to-head studies, we employed robust MAIC methodology to compare the relative treatment effects of onasemnogene abeparvovec and nusinersen for the treatment of SMA type 1. Treatment with onasemnogene abeparvovec provided statistically significantly greater EFS compared with nusinersen. Patients treated with onasemnogene abeparvovec had numerically longer OS compared with nusinersen, although this result was not statistically significant. Analysis of motor milestones (independent sitting and independent walking) generally indicated favorable effects for onasemnogene abeparvovec when compared with nusinersen. The likelihood of sitting independently or walking independently at 6 to 18 months for patients treated with onasemnogene abeparvovec was not significantly different compared with patients treated with nusinersen. However, patients treated with onasemnogene abeparvovec were statistically significantly more likely to have been able to sit independently at 24 months of follow-up than patients treated with nusinersen.

Although not statistically meaningful, patients receiving onasemnogene abeparvovec had a numerically greater likelihood of walking by 18 and 24 months compared with patients receiving nusinersen. However, the results were noted as inconclusive because of the lack of reported information. The motor milestone of independent walking was assessed in the studies using scales that are not comparable, with START [18] and STR1VE-US [33] using walking alone as per the Bayley Scales Gross Motor Subtest and ENDEAR [39] and SHINE [37,40,53] using walking as stable without assistance per the HINE-2 scale.

STR1VE-US [33] followed patients up to 18 months of age, while START [18] observed patients up to 24 months post-dose. Therefore, the age of 18 months results from STR1VE-US [33] were imputed as an estimate of the number of patients in that trial who achieved motor milestones at 24 months of follow-up. This approach is considered conservative, because evidence supports that using an 18-month age time point as the basis for estimating maximum motor milestone attainment would result in an underestimation of the potential benefit from onasemnogene abeparvovec.

Table 4. Summary of covariates matching nusinersen pooled average before and after weighting, individual and pooled onasemnogene abeparvovec trials.

Trial	Scenario	Treatment	CHOP INTEND score at baseline	Nutritional support at baseline	Effective sample size
1 (START [18] and STR1VE-US [33] data pooled)	SHINE [37,40,53]	Nusinersen	26.7	9%	24.6
	STR1VE-US and START pooled – after matching	Onasemnogene abeparvovec	26.7	9%	
	STR1VE-US and START pooled – before matching		30.6	15%	
2 (START only) [18]	SHINE [37,40,53]	Nusinersen	26.7	Did not converge	11.8
	STR1VE-US and START pooled – after matching	Onasemnogene abeparvovec	26.7		
	STR1VE-US and START pooled – before matching		28.2		
3 (STR1VE-US only) [33]	SHINE [37, 40, 53]	Nusinersen	26.7	Did not converge	16.4
	STR1VE-US and START pooled – after matching	Onasemnogene abeparvovec	26.7		
	STR1VE-US and START pooled – before matching		32.0		

Table 5. Matching-adjusted indirect comparison of event-free survival and overall survival for onasemnogene abeparvovec (START [18] and STR1VE-US [33]) compared with nusinersen.

Trials	Comparison	Event-free survival HR (95% CI) (*99% CI*)	Overall survival HR (95% CI) (*99% CI*)
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	Onasemnogene abeparvovec vs. nusinersen	0.19 (0.07–0.54)[a] (*0.05–0.74*)[a]	0.35 (0.09–1.32) (*0.06–2.01*)
	Nusinersen vs. onasemnogene abeparvovec	5.13 (1.87–14.10)[a] (*1.36–19.42*)[a]	2.87 (0.76–10.83) (*0.50–16.50*)

Abbreviations. CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison.
[a]Treatment effect estimate is statistically significant.

A previous ITC conducted to estimate the treatment effects of onasemnogene abeparvovec versus nusinersen for the treatment of symptomatic infants with SMA type 1 suggested a possible efficacy advantage for onasemnogene abeparvovec compared with nusinersen for OS, independence from permanent assisted ventilation, motor function, and motor milestones [60]. The ITC assessed treatment results for 12 patients from START [18] and 80 patients from ENDEAR [39]. A total of 149 infants were screened, and 122 underwent randomization (81 were assigned to the nusinersen group, and 41 were assigned to the control group) [18,33,37,39,53]. One infant randomized to receive nusinersen in ENDEAR [39] was withdrawn from the trial before treatment; and 121 infants underwent the assigned procedure [18,33,37,39]. The current MAIC provides robust evidence on the relative efficacy of onasemnogene abeparvovec versus nusinersen because of the methodologic advantages of a large, robust evidence base, with a larger sample size using pooled data from two clinical trials of onasemnogene abeparvovec. In addition, the current MAIC analysis adjusted for the two highest ranked covariates as defined by clinical experts, including CHOP INTEND score at baseline and nutritional support, which have been clinically validated to be important prognostic factors in the natural history of the disease, and potential effect modifiers.

The treatment arms for the onasemnogene abeparvovec and nusinersen clinical trials differed in baseline characteristics such as age, sex, weight, CHOP INTEND score, and the percentages of patients requiring nutritional and ventilatory support. The present MAIC addressed differences in CHOP INTEND score and nutritional support at baseline. Although this approach has methodologic advantages to other ITCs, some limitations remain. Because of the small sample size in the combined START/STR1VE-US [18,33] populations, matching was only possible on baseline CHOP INTEND scores and requirement of nutritional support. The matching algorithm did not converge when considering additional prognostic factors; this must be regarded as a limitation of the MAIC. In addition, the patients treated with gene therapy in the studies improved from a neuromotor perspective, which may have been an important predictive factor. The reduced effective sample size (24.6 vs. a total population of 34 patients for START [18] and STR1VE-US [33]) led to wider CIs and statistically inconclusive outcomes for some of the results. In addition, START [18] was a Phase I clinical trial with IPD that included two patients identified by screening, who were the only ambulant patients. While the current MAIC study confers favorable results toward onasemnogene abeparvovec, interpretation should follow the context of differences in the characteristics of the individual studies that may offer favorable prognosis for patients who received onasemnogene abeparvovec.

Although a robust method has been utilized to select and rank covariates for matching, the choice of effect modifiers and prognostic factors can be difficult. Reaching the assumption that there are no unmeasured effect modifiers and prognostic factors that are not balanced between treatment groups is almost impossible. Differences in choice of effect modifiers and prognostic factors, therefore, may affect the results of analyses. A key limitation of any MAIC is that the

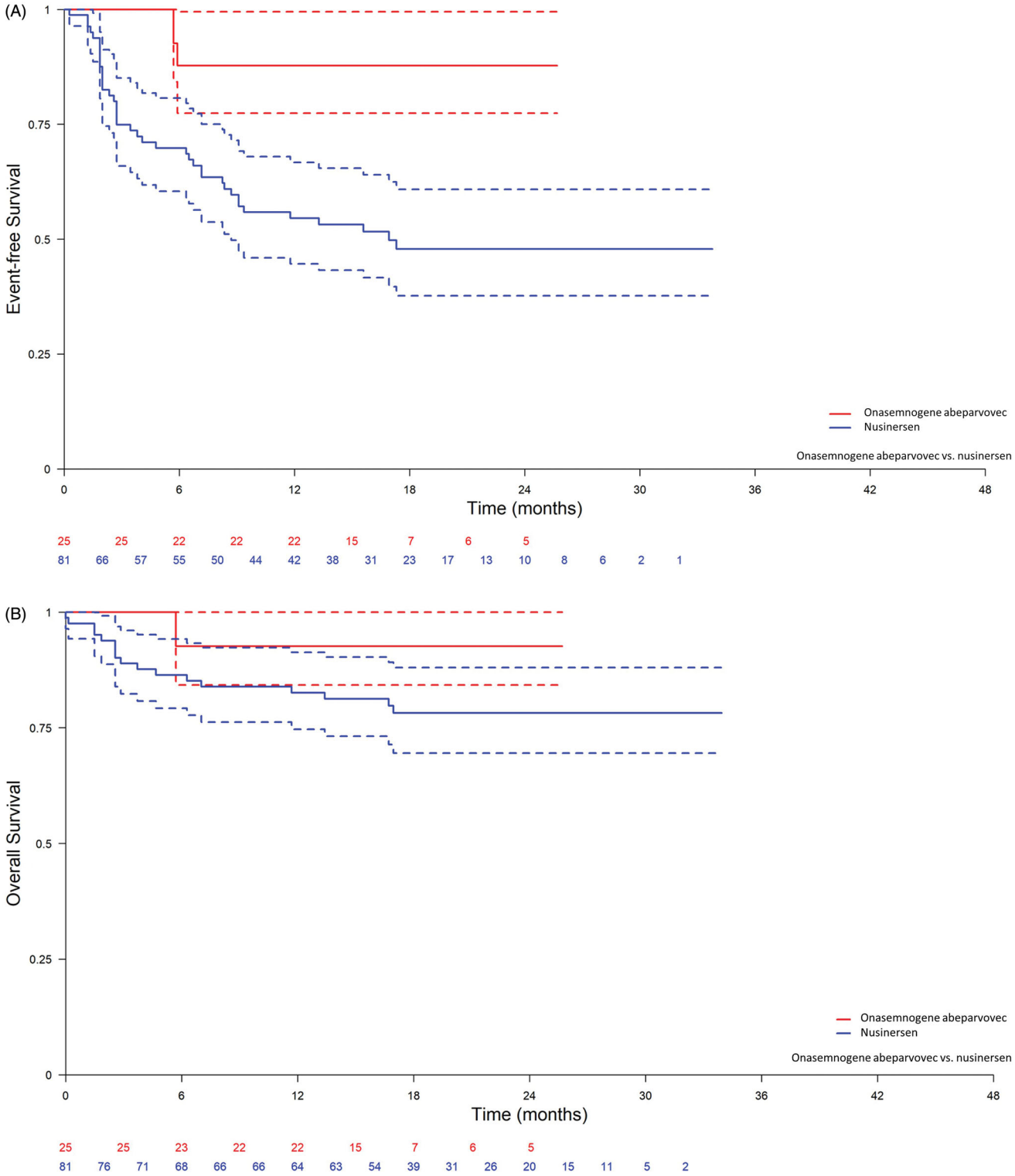

Figure 1. Matching-adjusted indirect comparison of event-free survival and overall survival for onasemnogene abeparvovec (START [18] and STR1VE-US [33]. Because STR1VE-US [33] only followed patients until 18 months of age, patients from this trial are censored at their last date of follow-up.) compared with nusinersen. (A) Event-free survival (B) Overall survival. Dashed lines represent 95% confidence intervals. The Kaplan Meier curves for ENDEAR [39]/SHINE [37, 40, 53] were digitized and reconstructed using the Guyot algorithm [64], which uses the published number at risk at each time point to account for censoring over the course of the study. The Kaplan Meier curves from STR1VE-US [33] and START [18] were constructed directly from patient-level data.

analysis only offers a matching of mean characteristics and standard deviations. Moreover, distribution of baseline characteristics may sometimes vary in different ways not captured by this calculation [61]. Because of the presence of effect modification, treatment effects may vary between patient populations and different conclusions could possibly be reached when different effect modifiers are considered [61]. Results of MAICs must be considered in the context of the specific population to which they apply [61]. Furthermore, for MAICs, if the analysis were run with IPD

Table 6. Onasemnogene abeparvovec (START [18] and STR1VE-US [33]) compared with nusinersen: independent sitting–time on study.[a]

Comparison[b]	Time point	Onasemnogene abeparvovec *n/N* (%)	Nusinersen *n/N* (%)	Relative risk[c] (95% CI) *(99% CI)*	Risk difference[c] (95% CI) *(99% CI)*
Scenario A (≥30 s definition for STR1VE-US [33] and START[18])					
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	6 months	0.8/24.6 (3.3%)	3/65 (4.6%)	0.72 (0.07–7.95) *(0.03–16.89)*	−0.01 (−0.10–0.07) *(−0.13–0.10)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	12 months	6.4/24.6 (26.2%)	7/48 (14.6%)	1.79 (0.69–4.66) *(0.51–6.28)*	0.12 (−0.08–0.32) *(−0.15–0.38)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	18 months	13.3/24.6 (54.1%)	9/31 (29%)	1.86 (0.96–3.60) *(0.78–4.43)*	0.25 (−0.00–0.50) *(−0.08–0.58)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	24 months[d]	15.1/24.6 (61.3%)	4/17 (23.5%)	2.60 **(1.05–6.49)**[c] *(0.78–8.64)*	0.38 **(0.10–0.66)**[c] ***(0.01–0.74)***[c]
Scenario B (≥30 s definition for STR1VE-US [33], ≥5 s for START [18])					
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	6 months	0.8/24.6 (3.3%)	3/65 (4.6%)	0.72 (0.07–7.95) *(0.03–16.89)*	−0.01 (−0.10–0.07) *(−0.13–0.10)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	12 months	6.4/24.6 (26.2%)	7/48 (14.6%)	1.79 (0.69–4.66) *(0.51–6.28)*	0.12 (−0.08–0.32) *(−0.15–0.38)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	18 months	13.5/24.6 (55%)	9/31 (29%)	1.90 (0.98–3.65) *(0.80–4.49)*	0.26 (0.01–0.51) *(−0.07–0.59)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	24 months[d]	16.1/24.6 (65.7%)	4/17 (23.5%)	2.79 **(1.13–6.89)**[c] *(0.85–9.15)*	0.42 **(0.15–0.70)**[c] ***(0.06–0.78)***[c]

Abbreviations. CI, confidence interval; *n*, number.
[a]START [18] and STR1VE-US [33] used the Bayley Scales Gross Motor Subtest to define independent sitting (sits alone for ≥5 s in START [18] and ≥30 s in STR1VE-US [33]). Two scenarios were used to define independent sitting from the onasemnogene abeparvovec trials: Scenario A used the ≥30 s threshold for both STR1VE-US [33] and START [18]; Scenario B used the ≥30 s threshold for STR1VE-US [33] and the ≥5 s threshold for START [18]. In ENDEAR [39] and SHINE [37,40,53], independent sitting was defined as stable sitting and pivoting as per the Hammersmith Infant Neurological Examination Section 2.
[b]Odds ratios are not presented because of unstable estimates.
[c]Relative treatment effect estimate is statistically significant. Relative treatment effect estimates presented in bold are statistically significant.
[d]18-month results for STR1VE-US [33] were carried forward to the 24-month time point.

Table 7. Onasemnogene abeparvovec (START [18] and STR1VE-US [33]) compared with nusinersen: independent walking–time on study.[a]

Comparison[b]	Time point	Onasemnogene abeparvovec *n/N* (%)	Nusinersen *n/N* (%)	Relative risk (95% CI) *(99% CI)*	Risk difference (95% CI) *(99% CI)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	6 months	0/24.6 (0%)	0/65 (0%)		
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	12 months	0/24.6 (0%)	0/48 (0%)		
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	18 months	0.2/24.6 (0.7%)	0/31[c] (0%)	1.40 (0.04–54.50) *(0.01–172.35)*	1.39 (0.04–50.16) *(0.01–154.90)*
START [18] + STR1VE-US [33] vs. SHINE [37,40,53]	24 months[d]	0.6/24.6 (2.5%)	0/17[c] (0%)	2.08 (0.06–76.33) *(0.02–236.73)*	2.03 (0.06–67.02) *(0.02–201.04)*

Abbreviation. CI, confidence interval.
[a]To assess independent walking, START [18] and STR1VE-US [33] used walking alone as per the Bayley Scales Gross Motor Subtest and ENDEAR [39] and SHINE [37,40,53] used walking as stable without assistance per the HINE-2 score scale.
[b]Odds ratios are not presented because of unstable estimates.
[c]Continuity correction was used.
[d]18-month results for STR1VE-US [33] were carried forward to the 24-month time point.
Italics denote the 99% CI.

from the comparator study matched to aggregate data from the study for the treatment of interest, findings from the analysis may be different [61].

The current MAIC was conducted in March 2020, and studies completed/published after that date were not included in the analysis. Therefore, this MAIC did not include a comparison with risdiplam. Recently published preliminary results of an ITC of risdiplam versus nusinersen or onasemnogene abeparvovec based on the Part 1 results of the FIREFISH study suggested that treatment of infantile onset SMA with risdiplam may yield better results than treatment with nusinersen in patients with SMA type 1 [62]. In this ITC, matching against onasemnogene abeparvovec was not possible because of large baseline factor differences [62]. As with the current MAIC, by matching covariates to those of the comparator trial, we assumed that the comparator trial was the target population, and the results of the analyses may be biased if not all prognostic and predictive factors were included [63]. In the absence of head-to-head trials, results from ITCs are used by regulatory agencies, payers,

and physicians to assess the benefits of different therapies to support clinical decision making. Therefore, because of the limitations associated with ITCs, a critical need exists for valid approaches to address such limitations [63].

Conclusions

In the absence of RCTs and head-to-head comparison trials, MAIC analyses provide important insights into comparative treatment efficacy. With due consideration for its inherent limitations (e.g. a relatively small sample size even for the pooled onasemnogene abeparvovec clinical trials; potential for differences in prognostic and predictive factors between studies) our MAIC analysis indicates that onasemnogene abeparvovec may offer sustained benefits in terms of event-free survival, overall survival, and motor milestone achievement (sitting or walking independently) compared with nusinersen through 24 months of follow-up. Future direct comparisons as well as real-world studies may provide further evidence for the comparative efficacy of onasemnogene abeparvovec and nusinersen for patients with SMA type 1.

Notes

i. Zolgensma is a registered trademark of AveXis, Inc., Bannockburn, IL, USA.
ii. Spinraza is a registered trademark of Biogen, Inc., Cambridge, MA, USA.
iii. Evrysdi is a registered trademark of Genentech, Inc., South San Francisco, CA, USA.

Transparency

Declaration of funding

This research was supported by Novartis Gene Therapies, Inc.

Declaration of financial/other relationships

MB and OD have disclosed that they are salaried employees of Novartis Gene Therapies, Inc., which is the manufacturer of onasemnogene abeparvovec.

ML was a paid employee of Precision HEOR, which was contracted by Novartis Gene Therapies, Inc., to work on this project.

JL is a paid employee of Decision Resources Group, which was contracted by Novartis Gene Therapies, Inc., to work on this project.

ED and CB are employed by Pharmalytics Group, which was contracted by Novartis Gene Therapies, Inc., to work on this project.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors' contributions

All authors and the funder of this study participated in the matching-adjusted indirect comparison design. All authors had access to and analyzed and interpreted the data, participated in the development and critical review of the manuscript, approved the final version of the manuscript submission for publication, and are accountable for the accuracy and integrity of the work.

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Data-sharing statement

Novartis is committed to sharing clinical trial data with external researchers and has been doing so voluntarily since 2014. Novartis was the third member to join ClinicalStudyDataRequest.com (CSDR), which is the first data sharing consortium of clinical study sponsors and funders. CSDR is a leader in the data sharing community inspired to drive scientific innovation and improve medical care by facilitating access to patient-level data from clinical studies (https://www.novartisclinicaltrials.com/TrialConnectWeb/voluntarydataviewmore.nov).

Novartis is committed to sharing, upon requests from qualified external researchers and subsequent approval by an independent review panel based on scientific merit, anonymized patient-level and study-level clinical-trial data, and redacted clinical study reports, for medicines and indications approved in the United States and Europe after the respective study is accepted for publication. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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