ΠΑΝΕΠΙΣΤΗΜΙΟ ΔΥΤΙΚΗΣ ΑΤΤΙΚΗΣ

ΣΧΟΛΗ ΔΗΜΟΣΙΑΣ ΥΓΕΙΑΣ

ΤΜΗΜΑ ΠΟΛΙΤΙΚΩΝ ΔΗΜΟΣΙΑΣ ΥΓΕΙΑΣ

ΠΜΣ ΗΓΕΣΙΑ, ΚΑΙΝΟΤΟΜΙΑ & ΠΟΛΙΤΙΚΕΣ ΑΞΙΑΣ ΣΤΗΝ ΥΓΕΙΑ

ΠΜΣ Ηγεσία, Καινοτομία και Πολιτικές Αξίας στην Υγεία

Μεταπτυχιακή Διπλωματική Εργασία

Ακαδημαϊκό έτος: 2020-21

Οικονομική αξιολόγηση της γονιδιακής θεραπείας Onasemnogene Abeparvovec (Zolgensma) για τη θεραπεία ασθενών με Νωτιαία Μυϊκή Ατροφία στην Ελλάδα

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SCHOOL OF PUBLIC HEALTH

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MSc in LEADERSHIP, INNOVATION AND VALUE BASED HEALTH POLICIES

ΠΜΣ Ηγεσία, Καινοτομία και Πολιτικές Αξίας στην Υγεία

Ειδίκευση 2: Έρευνα & αξιολόγηση καινοτομίας & πολιτικών Υγείας

Διπλωματική Εργασία
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Economic Evaluation of Onasemnogene Abeparvovec (Zolgensma) GENe therapy for the treatment of patients with Spinal Muscular Atrophy (SMA) in the Greek Market

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Athens, December 2022

ΠΑΝΕΠΙΣΤΗΜΙΟ ΔΥΤΙΚΗΣ ΑΤΤΙΚΗΣ

ΣΧΟΛΗ ΔΗΜΟΣΙΑΣ ΥΓΕΙΑΣ

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Τίτλος Εργασίας

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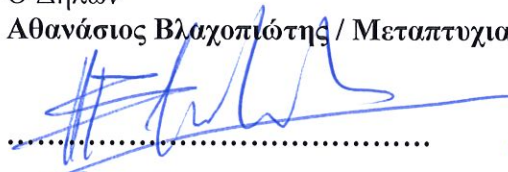**ΔΗΛΩΣΗ ΣΥΓΓΡΑΦΕΑ ΜΕΤΑΠΤΥΧΙΑΚΗΣ ΕΡΓΑΣΙΑΣ**

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«Είμαι συγγραφέας αυτής της μεταπτυχιακής εργασίας και ότι κάθε βοήθεια την οποία είχα για την προετοιμασία της, είναι πλήρως αναγνωρισμένη και αναφέρεται στην εργασία. Επίσης, οι όποιες πηγές από τις οποίες έκανα χρήση δεδομένων, ιδεών ή λέξεων, είτε ακριβώς είτε παραφρασμένες, αναφέρονται στο σύνολό τους, με πλήρη αναφορά στους συγγραφείς, τον εκδοτικό οίκο ή το περιοδικό, συμπεριλαμβανομένων και των πηγών που ενδεχομένως χρησιμοποιήθηκαν από το διαδίκτυο. Επίσης, βεβαιώνω ότι αυτή η εργασία έχει συγγραφεί από μένα αποκλειστικά και αποτελεί προϊόν πνευματικής ιδιοκτησίας τόσο δικής μου, όσο και του Ιδρύματος.
Παράβαση της ανωτέρω ακαδημαϊκής μου ευθύνης αποτελεί ουσιώδη λόγο για την ανάκληση του πτυχίου μου».

*Επιθυμώ την απαγόρευση πρόσβασης στο πλήρες κείμενο της εργασίας μου μέχρι
………………………… και έπειτα από αίτηση μου στη Βιβλιοθήκη και έγκριση του επιβλέποντα καθηγητή.

Ο Δηλών
Αθανάσιος Βλαχοπιώτης / Μεταπτυχιακός Φοιτητής

………………………………… 6/3/2023

*** Εάν κάποιος επιθυμεί απαγόρευση πρόσβασης στην εργασία για χρονικό διάστημα 6-12 μηνών (embargo), θα πρέπει να υπογράψει ψηφιακά ο/η επιβλέπων/ουσα καθηγητής/τρια, για να γνωστοποιεί ότι είναι ενημερωμένος/η και συναινεί.**

Η παρούσα διπλωματική εργασία εκπονήθηκε στο πλαίσιο των απαιτήσεων του Μεταπτυχιακού Προγράμματος Ηγεσία, Καινοτομία και Πολιτικές Αξίας στην Υγεία του Τμήματος Πολιτικών Δημόσιας Υγείας, του Πανεπιστημίου Δυτικής Αττικής. Η έγκρισή της δεν υποδηλώνει απαραιτήτως και την αποδοχή των απόψεων του συγγραφέα εκ μέρους του Τμήματος Πολιτικών Δημόσιας Υγείας.

Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές που αναφέρω έχω χρησιμοποιήσει εισαγωγικά όπου απαιτείται και έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας.

Όνομα: Αθανάσιος Γεωργίου Βλαχοπιώτης

Υπογραφή: ....

6/3/2023

Σκοπός της παρούσας εργασίας είναι η οικονομική αξιολόγηση της γονιδιακής θεραπείας με δραστική ουσία onasemnogene abeparvovec, για ασθενείς με Νωτιαία Μυϊκή Ατροφία έναντι του Standard of Care στη νόσο (SoC), που αποτελεί το φαρμακευτικό ιδιοσκεύασμα nusinersen. Καθώς η καινοτομία στην τεχνολογία υγείας εξελίσσεται, νέες θεραπείες αναδύονται προσφέροντας θεραπευτικές λύσεις σε νοσήματα τα οποία μέχρι πρότινος ήταν ανίατα και καταληκτικά. Οι νέες αυτές γονιδιακές θεραπείες είναι ειδικά εξειδικευμένες με στοχευμένη γενετική δράση η οποία όμως έχει και σαφώς υψηλότερο κόστος, επιβαρύνοντας τα συστήματα υγείας.

Το **αρχικό ερώτημα** που καλούνται να απαντήσουν οι οικονομολόγοι της υγείας είναι η αποτελεσματική κατανομή κατά των πόρων ώστε να μεγιστοποιηθεί η προσφορά υγείας δεδομένων των πεπερασμένων πόρων. Κατά την οικονομική αξιολόγηση μίας τεχνολογίας της υγείας, το ζήτημα είναι πότε η χρήση και αποζημίωση μιας νέας θεραπείας υπό αξιολόγηση θεωρείται βέλτιστη λύση ως προς την αποδοτικότητα (cost-effectiveness) και την κατανομή των πόρων, σε σχέση με εναλλακτικές θεραπείες παρά το ότι δεν προσφέρει πλήρη ίαση και δεν εξασφαλίζει σε όλες τις περιπτώσεις σαφές θεραπευτικό αποτέλεσμα.

Με βάση τα παραπάνω δεδομένα το **κρίσιμο ερώτημα** που προκύπτει σε αυτά τα πλαίσια έχει να κάνει με το αν η υπό αξιολόγηση γονιαδική θεραπεία είναι cost-effective και πόσο θα πρέπει να αποζημιώνεται η από τα συστήματα υγείας βάση της κλινικής της αξίας, δεδομένου μάλιστα ότι το κόστος της περιορίζεται στην έναρξη της θεραπείας καθώς πρόκειται για εφάπαξ χορήγηση. Από την άλλη, όταν το standard of care έχει ένα δεδομένο θεραπευτικό αποτέλεσμα αλλά απαιτεί δια βίου χορήγηση, με όχι ίσο μεν αλλά υψηλό κόστος, τότε η μεταξύ τους σύγκριση, σε σχέση με τις υπόλοιπες συνοδές επιβαρύνσεις είναι απαραίτητη.

Το **υλικό της μελέτης** αποτέλεσε παράθεση δεδομένων συνολικού κόστους και αποτελεσματικότητας των δύο φαρμάκων και η μεταξύ του σύγκριση.

Για την ανάλυση και προκειμένου να οδηγηθούμε σε σαφή και τεκμηριωμένα συμπεράσματα, χρησιμοποιήθηκαν οι μέθοδοι Cost Effectiveness, Cost Utility καθώς και η μέθοδος μοντέλου Markov και υφιστάμενα επιστημονικά άρθρα.

ΛΕΞΕΙΣ – ΚΛΕΙΔΙΑ: Νωτιαία Μυϊκή Ατροφία, SMA, Γονιδιακή θεραπεία, onasemnogene abeparvovec, Onasemnogene Abeparvovec, nusinersen, Nusinersen,

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ABSTRACT

Objective: The aim of the present study is to evaluate the cost-effectiveness of Onasemnogene Abeparvovec compared to the standard of care (SoC; Nusinersen) treatment of patients with Spinal Muscular Atrophy (SMA) in the Greek healthcare setting from a third-party payer perspective.

Methods: A model-based economic evaluation was conducted to estimate the cost-effectiveness of Onasemnogene Abeparvovec versus SoC (Nusinersen) for the treatment of patients SMA1. To conduct the cost-utility analysis, a Markov model was developed based on precedent economic models on SMA1. The analysis was conducted over a lifetime horizon based on the fact that initially SMA1 patients are expected to survive up to 2 years, but following treatment are expected to achieve benefits that increase the life expectancy of the majority of patients to 25 years or even longer. A non-systematic search of the literature was conducted to identify the model inputs. Clinical data that informed transition probabilities between health states were sourced from pivotal studies of Onasemnogene Abeparvovec (START, STRIVE) and Nusinersen (ENDEAR, CHERISH). The health-related quality of life associated with different model health states was described in the form of health utilities. Multiple cost inputs were considered in the model to reflect the drug acquisition and administration, as well as disease management cost. Primary outcomes included patients' life years, quality-adjusted life years, total costs and incremental cost-effectiveness ratios per QALY and LY gained. To determine whether Onasemnogene Abeparvovec is a cost-effective alternative against SoC, a cost-effectiveness threshold of 55,560 EUR per QALY (3x GDP) was used as a decision rule [33].

Results: The analysis showed that over a patient's lifetime, Onasemnogene Abeparvovec is associated with improved survival (6 LYs gained), but also quality of life adjusted survival (4.6 QALYs gained) compared with Nusinersen. Onasemnogene Abeparvovec was the most costly treatment regimen. This difference was mainly attributed to the default higher acquisition cost of Onasemnogene Abeparvovec in first and only administration versus SoC (Table 4). The incremental analysis showed that Onasemnogene Abeparvovec had an ICER of 55.560,00€ per QALY gained relative to SoC - Nusinersen (Tables 14, 16).

Conclusion: Onasemnogene Abeparvovec constitutes a cost-effective treatment for patients with SMA Type I in Greece. However, there is uncertainty around the results of this analysis that the

decision makers need to take into account. Decision makers should further note that the significance of providing both Zolgenmsa and Nusinersen for the national healthcare system is not just a matter of additional costs per QALY gained. Although the demand for health care is low here, given that SMA disease is very rare, managing the symptoms of SMA without drug intervention until Nusinersen became the SoC was generally supportive and often required substantial healthcare resources. The main issue here is that both treatments are expensive, considered that none of them is cure for SMA, and that relapses to previous states are possible even while treated. Apart Moreover, Onasemnogene Abeparvovec's one off administration with a lifelong efficacy expectation, and the demand for 100% reimbursement upfront regardless of treatment outcomes, makes it critical as caregivers might demand the additional treatment with SoC in case of relapse, maximizing the cost of the disease management.

On the other hand, Nusinersen, administered every 4 months is considered easier to manage in terms of cost, as the treatment can be stopped after the patient's annual assessment. It should be noted here that SMA is a leading genetic cause of infant mortality, challenging not only patients but also their families and caregivers, as well as medical personnel and society as a whole. The high, unmet medical need for an effective treatment of the disease lessened with the approval of Nusinersen, which transformed the course of SMA by conferring improvements in both motor function and the survival of patients. However, whether Greek society is willing to pay more for novel treatments of rare disorders than for more prevalent diseases is uncertain. Nevertheless, the results of the present study suggest that the breakthrough targeted SMA therapy of Onasemnogene Abeparvovec offers significant health gains in terms of LY and QALYs compared to Nusinersen, covering the unmet medical needs of Greek patients.

1. OBJECTIVE OF THE STUDY

The aim of the present study is to conduct an economic evaluation of Onasemnogene Abeparvovec for the treatment of SMA, by estimating the cost-effectiveness of Onasemnogene Abeparvovec compared to the standard of care (SoC; Nusinersen) for the treatment of this patient population in the Greek healthcare setting.

1.1 SPINAL MUSCULAR ATROPHY (SMA)

Spinal Muscular Atrophy (SMA) is a genetic, autosomal recessive, neuromuscular disease characterized by degeneration of the alpha motor neurons of the spinal cord anterior horn cells, leading to progressive proximal muscle weakness and atrophy and, in the most severe types, paralysis. The most common form of SMA is caused by defects in both copies of the survival motor neuron 1 gene (SMN1) on chromosome 5q. This gene produces the survival motor neuron (SMN) protein which maintains the health and normal function of motor neurons. All patients with spinal muscular atrophy have at least one "backup gene," known as SMN2. The SMN2 gene has a similar structure to SMN1, but only a small amount (10%) of the protein it produces is full-length functional SMN protein. This low level of SMN protein is not effective enough to sustain the survival of motor neurons in the CNS. As a result, lower motor neurons dysfunction and the primary symptom of SMA5q is weakness and later atrophy of the voluntary muscles. The muscles most affected are the proximal ones, such as those of the shoulders, hips, thighs, and upper back. The lower limbs seem to be affected more than the upper limbs, and deep tendon reflexes are decreased. Special complications occur when the respiratory muscles and bulbar functions are affected, resulting in abnormalities in breathing and swallowing. Weakening of trunk muscles lead to spinal complexities such as scoliosis, that in severe cases need surgical intervention.

Furthermore, many SMA patients need support for feeding and breathing with feeding tubes and mechanical ventilation. The number of SMN2 genes may vary, and a higher SMN2 copy number is associated with less-severe symptoms of spinal muscular atrophy. Nevertheless, the disease has a wide range of symptoms, and it is difficult to predict severity based on the number of SMN2 copies alone [6].

Despite being a rare disease, SMA is a leading genetic cause of infant mortality, with a reported birth prevalence ranging from 8.5 to 10.3 per 100,000 live births[2-4]. Infants with the most severe form of SMA (Type 0) do not survive beyond the first weeks or few months after birth if left untreated[5] and have a life span of less than 6 months[1]. Patients with all other forms of SMA are either asymptomatic or slightly symptomatic at birth, which lasts for a variable length of time but is usually correlated with disease severity, with more severe disease associated with earlier symptom onset[1]. The most common symptom in new-borns is hypotonia and tongue fasciculations, that leads the physician to run gene- test.

More specifically, the clinical phenotype of SMA is heterogeneous, ranging from a severe to a mild phenotype. It is generally divided into three main subtypes: patients with type I SMA (Werding-Hoffman) usually have onset before 6 months of age, are never able to sit, and their natural age of death is often before 2 years of age. These patients have impaired head control, with a weak cry and cough. Swallowing, feeding, and handling of oral secretion are affected before 1 year of age[6, 7].

Patients with SMA Type II (Dubowitz) have symptoms onset between 7–18 months of age with delayed motor milestones, are never able to stand, and typically live beyond 2 years of age. Swallowing difficulties due to bulbar weakness may lead to poor weight gain in some children. Scoliosis eventually develops in children, and bracing or spinal surgery is needed[6].

Patients with SMA Type III (Kugelberg-Welander) are usually diagnosed when older, after 18 months of age, are able to stand and walk, and typically survive to adulthood. Some patients lose the ability to walk in childhood, yet others maintain the ability to walk until adolescence or adulthood. Scoliosis and difficulties in swallowing, coughing, and nocturnal hypoventilation may still occur[7]. In addition, two types of SMA type III have been described contingent on age of onset before (3a) or after age 3 years (3b). Type 3a patients presenting under age 18 months have a more severe phenotype as 48% lose the ability to walk within 10 years of onset; whereas about 90% of 3b patients are ambulatory 20 years after diagnosis.[8]

Table 1. Types of Spinal Muscular Atrophy (SMA)

Types of Spinal Muscular Atrophy			
Spinal Muscular Atrophy Type	Alternate Name	Age of Onset	Description
I	Werdnig-Hoffman disease	Birth	• Most severe involvement of spinal muscular atrophy types • Death by 2 years of age
II	Dubowitz disease	6-18 mo.	• Able to sit (some can stand) but not walk • Commonly reach adulthood
III	Kugelberg-Welander disease	After 18 mo.	• Least severe of spinal muscular atrophy types • Normal life expectancy • Can walk, although often become wheelchair-bound later in life

Type I: These patients show symptoms before 6 months of age, never achieve the motor milestone of sitting unsupported, and generally do not survive past two years of age due to respiratory failure. SMA Type I is the most common type of SMA, accounting for about 60% of SMA diagnoses. Almost all SMA type I patients have two or three copies of SMN2, giving rise to a broad range of phenotypes. Additional subtypes of IA, IB, and IC have been proposed based on age of onset, with IA being the earliest and most severe subtype. SMA type 0 is sometimes included in classification systems and presents in neonates as joint contractures, severe weakness and hypotonia, respiratory insufficiency, and a life expectancy of less than six months. Muscle weakness in SMA type I is severe to the point where patients typically cannot perform antigravity limb movements and have no head control, though facial muscles are spared. Fine motor skills are affected, with infants unable to grasp using their whole hand. Weakness in the intercostal muscles in combination with sparing of the diaphragm leads to paradoxical breathing and a bell-shaped chest. Bulbar weakness results in difficulty swallowing and feeding, with risk of failure to thrive and aspiration. Reflux and impaired cough and swallowing contribute to risk of aspiration and recurrent pulmonary infections. A gastrostomy tube for feeding combined with nighttime and possibly daytime non-invasive ventilation with bi-level positive airway pressure (BiPAP) can improve quality of life and life expectancy. Aggressive intervention with a tracheostomy and permanent ventilation is also possible and can prolong life expectancy; however, this is a decision to be made by the family with the support of health care providers.

Type II: Patients with type II SMA achieve the milestone of sitting unsupported, but never walk independently. Symptoms generally appear between 6 to 18 months after birth and most patients will survive past the age of 25 with life expectancy improved by aggressive supportive care. Type II patients represent about 20% to 30% of SMA cases and most SMA type II patients have three copies of SMN2. In addition to the inability to walk independently, common symptoms are fine tremors of the upper extremities, tongue fasciculation, joint contractures, and scoliosis. Scoliosis and weak intercostal muscles can cause restrictive lung disease. There is a range in severity, with weaker patients requiring non-invasive ventilation. Difficulty swallowing is less common than in Type I patients and difficulty with feeding comes from masticatory muscle weakness.

Type III: Type III SMA makes up about 10% to 20% of SMA cases and presents between 18 months of age and adulthood. These patients are able to walk independently at some point in their life and typically have a normal life expectancy. Most type III patients have three or four copies of SMN2. An age of onset prior to 3 years is associated with estimated probabilities of 73%, 44%, and 34% of walking 10, 20, and 40 years after onset. In those with age of onset after 3 years, the estimated probabilities are 97%, 89%, and 67% for walking 10, 20, and 40 years after onset. SMA type III patients have little or no respiratory weakness. Ambulatory patients may exhibit abnormal gait characteristics due to proximal weakness while patients who lose the ability to walk often develop scoliosis.

Type IV: A very small proportion of SMA cases are type IV or adult-onset SMA, the mildest form of the disease. Although muscle weakness is present, these patients retain the ability to walk, have a normal life expectancy, and do not suffer from respiratory or nutritional issues. [29]

However, these, phenotypes are seen more as a continuum rather than as distinct subtypes and sometimes further subtypes at both ends of the spectrum are observed. SMA type 0 is a very severe form with onset in utero, reduced or absent movements, contractures, and requirement for mechanical ventilation support at birth and death before six months of age, while SMA type IV is a mild late (adult) onset form that has a normal life expectancy[5].

Living with SMA is challenging not only for patients but also for their families and caregivers, as well as medical personnel and the society. Managing the symptoms of SMA often requires a large amount of healthcare resources. Depending on the severity of the condition, patients with SMA

may require apart from physiotherapy and multidisciplinary medical care in which many specialties are included for the patients holistic management, mechanical ventilation, surgery, feeding tubes and electric wheelchair[9].

Until 5 years ago there were no approved therapies for SMA and a high unmet medical need for effective treatment management of the disease existed. Management was generally supportive in nature; limited to respiratory support, nutritional status, orthopedic considerations, and several non-interventional treatments which represented the standard of care (SoC) at the time.

In May 2017, the European Medicines Agency (EMA) approved nusinersen (Nusinersen) for the management of 5q SMA. Nusinersen was the first and only, at that specific time, disease-modifying treatment that conferred improvements in both motor function and survival, transforming the course of SMA. The results of nusinersen's pivotal studies on early and later onset patients were significant in efficacy parameters such as survival, Overall Survival (OS) and motor scales improvement, whilst proving a well-tolerated and safe profile. Soon after, nusinersen was reimbursed, with or without restrictions, in many countries, for patients with SMA Types 1-3 and became the standard of care, changing the disease trajectory. Almost 10,000 patients were treated with Nusinersen globally, when a second treatment for SMA patients was approved by the EMA. Onasemnogene Abeparvovec (Zolgensma) is a gene therapy medicine for treating spinal muscular atrophy. It has proven to be a very promising one-off gene replacement treatment tackling the main cause of the disease: the deletion or mutation of the SMN1 gene in SMA patients. It is intended for patients with inherited mutations affecting genes known as SMN1, who have either been diagnosed with SMA type 1 (the most severe type) or have up to 3 copies of another gene known as SMN2. The two treatments are not indicated and reimbursed for the same patient populations. The main type that both treatments are studied and indicated for is SMA type 1, on which this cost effectiveness study will focus on.

In 2007, an International Conference on the Standards of Care for SMA published a consensus statement on SMA standards of care that has been widely used throughout the world. In 2018, a two-part update of these earlier recommendations was published, which includes changes to the management and care of patients with SMA, along with information around new care options, including and featuring Nusinersen as Standard of care for SMA.

For the cost effectiveness comparison of these two treatments only Type 1 patients will be included, as this is the main group both treatments are indicated and reimbursed for. Moreover, there is also clinical data with the population similarities for these two groups.

1.2 GENE THERAPIES

Gene therapy is a medical approach that treats or prevents disease by correcting the underlying genetic problem. Gene therapy techniques allow doctors to treat a disorder by altering a person's genetic makeup instead of using drugs or surgery. The earliest method of gene therapy, often called gene transfer or gene addition, was developed to:

A) Introduce a new gene into cells to help fight a disease.

B) Introduce a non-faulty copy of a gene to stand in for the altered copy causing disease. Later studies led to advances in gene therapy techniques. A newer technique, called genome editing (an example of which is CRISPR-Cas9), uses a different approach to correct genetic differences. Instead of introducing new genetic material into cells, genome editing introduces molecular tools to change the existing DNA in the cell. Genome editing is being studied to either fix a genetic alteration underlying a disorder, so the gene can function properly, turn on a gene to help fight a disease, turn off a gene that is functioning improperly, or remove a piece of DNA that is impairing gene function and causing disease. Gene therapies are being used to treat a small number of diseases, including an eye disorder called Leber congenital amaurosis and a muscle disorder called spinal muscular atrophy. Many more gene therapies are undergoing research to make sure that they will be safe and effective. Genome editing is a promising technique also under study that doctors hope to use soon to treat disorders in people. [27]

1.3 NUSINERSEN (Spinraza)

As mentioned above until 5 years ago there were no approved therapies for SMA and a high unmet medical need for effective treatment management of the disease existed. In May 2017, EMA approved nusinersen (Spinraza) for the management of 5q SMA and became in 2018 the SoC.

Nusinersen was the first and only, at that specific time, disease-modifying treatment that confered improvements in both motor function and survival, transforming the course of SMA. Nusinersen is a SMN2 directed antisense oligonucleotide (ASO) drug designed to increase the production of SMN protein from the SMN2 gene. Nusisnersen is administered by intrathecal injection with patients receiving it with four loading doses the days 0,14,28, 63 followed by maintenance doses every four months. The results of nusinersen's pivotal studies on early and later onset patients were significant in efficacy parameters such as survival, overall survival and motor scales improvement, whilst proving a well-tolerated and safe profile. Soon after, Nusinersen was reimbursed, with or without restrictions, in many countries, for patients with SMA Types 1-3 and became the standard of care as it was included in the standards of care publication in 2017, changing the disease trajectory.

More specifically, the ENDEAR clinical trial[10] was a Phase III randomized, double blind sham procedure controlled trial, which followed-up 122 patients over a 13-month period and demonstrated that those with infantile-onset SMA (most likely to develop Type 1) treated with Nusinersen achieved and sustained clinically meaningful improvement in motor function (the ability to kick, head control, rolling, sitting and crawling) compared to the placebo group. Additionally, a greater percentage of patients survived compared to the untreated patients (23% death in Nusinersen group vs 43% in untreated group). There was a statistically significant reduction in the risk of death or permanent ventilation in Nusinersen-treated individuals compared to untreated individuals at the end of the study analysis. ENDEAR & CHERISH studies were extended in an open label long term one called SHINE.

In CHERISH trial[11], there was a statistically significant and clinically meaningful improvement in motor function in individuals treated with Nusinersen with later-onset SMA (most likely to develop Type 2 or Type 3) compared to untreated individuals at the interim analysis. Improvements were measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). The HFMSE is a reliable and validated tool specifically designed to assess motor function in children with SMA.

Nusinersen enabled many patients to achieve and/or maintain normal developmental motor milestones in presymptomatic, infantile-onset, and later-onset SMA. Furthermore, Nusinersen has been shown to be a safe and well-tolerated treatment in all studied populations and it is delivered

intrathecally by lumbar puncture once every 4 months (following initial loading doses) directly to the cerebrospinal fluid. This allows the patient to achieve the clinical benefit at a lower drug dose with peripheral administration.

1.4 ONASEMNOGENE ABEPARVOVEC (Zolgensma)

Almost 10,000 patients were treated with Nusinersen globally, when a second treatment for SMA patients was approved by the FDA & EMA. Onasemnogene Abeparvovec (Zolgensma) is a one-off gene replacement therapy for treating Spinal Muscular Atrophy, and a treatment that may provide improvements in clinical outcomes and quality of life compared with the lifelong treatment of Spinraza. It is intended for patients with inherited mutations affecting genes known as SMN1, who have either been diagnosed with SMA type 1 (the most severe type) or have up to 3 copies of another gene known as SMN2. Onasemnogene Abeparvovec uses a self-complementary adeno associated virus serotype 9 (scAAV9) capsid to deliver a functional copy of SMN 1 gene to the patient, which is the main cause of SMA, causing a much higher production of SMN protein, the deficit of which causes the motor neuron death.

Results from a phase 3 study called STR1VE-EU confirmed the safety and efficacy findings of the phase 1 START and phase 3 STR1VE-US studies. The study, funded by Novartis, the manufacturer of Onasemnogene Abeparvovec, showed that patients younger than six months with SMA type 1 experienced therapeutic benefits with a one-time administration of the gene therapy. Due to the size of the adenovirus and the mechanism of action it can cross the blood brain barrier, allowing intravenous administration to be effective in the central nervous system as well.

In a phase 1 dose escalation trial (START), 15 infants with SMA Type 1, with 2 copies of SMN2 gene, received Nusinersen. At 24 months follow up 100% of infants were alive and free of permanent ventilation, and 11/12 patients in the therapeutic dose could sit independently for >5 seconds (92%), 2/12 could stand independently (17%), and 2/12 (17%) could walk independently.

A treatment of Onasemnogene Abeparvovec is priced in Greece at more than 1,945.000€ (ex-f price), and it is often identified as the most expensive drug treatment in history.

In the U.S. phase 3 single arm trial of 22 patients with type 1 SMA, 13 of 22 infants were sitting independently for 30 second or longer at 18 months of age.

The STR1VE-EU is a single-arm phase 3 trial done at nine sites in Italy, the United Kingdom, Belgium, and France. Investigators enrolled patients younger than 6 months with spinal muscular atrophy type 1 with the SMN1 exon 7–8 deletion or point mutations, and one or two copies of SMN2. Thirty-two of 33 patients completed the study.

Investigators reported in Lancet Neurology that 14 of the 32 patients achieved the primary end point of functional independent sitting for at least 10 seconds at any visit up to the 18 months of age, which is a WHO developmental milestone of independent sitting. None of the 23 patients in a matched, untreated natural history cohort achieved this end point.

Additionally, 31 of 32 of the patients who received Onasemnogene Abeparvovec survived free from permanent ventilatory support at 14 months.

Improvements in motor function were evaluated for safety and efficacy using prespecified exploratory motor end points. Twenty-seven of the 33 patients achieved at least one motor milestone during the study. Investigators found that 3 patients achieved head control and 19 patients rolled from theirs back to their sides. In addition, 16 patients sat without support for 30 seconds or longer.

Almost all patients in the EU trial had at least one adverse event and six patients had adverse events that were considered serious and related to the therapy. The most common adverse events were fever (22 patients), upper respiratory infection (11), and increased alanine aminotransferase (nine).

"STR1VE-EU showed the efficacy of onasemnogene abeparvovec, with greater variability in efficacy response than in STR1VE-US because of differences in patient clinical status at baseline. Some of these patients had early onset and more severe disease at enrollment than did patients in STR1VE-US but showed a response to treatment not only in terms of survival but also in functional aspects," the investigators wrote.

In 2018, a two-part update of the Standards of Care for SMA was published, which includes changes to the management and care of patients with SMA, along with information around new care options, including and featuring Nusinersen as Standard of Care for SMA.

For the cost-effectiveness comparison of these two treatments, only Type 1 patients will be included, as this is the main group both treatments are indicated and reimbursed for. Moreover, there is available clinical data with population similarities for these two groups.

Despite the obvious health benefits of both Zolgenmsa and Nusinersen for the treatment of SMA, little research has been carried out into their relative economic value in the Greek healthcare setting. The economic evaluation of new health technologies has become increasingly important in the Greek setting due to the limited resources allocated to healthcare. The last Great Recession of 2008 has had a long-lasting impact on the Greek economy and society as a whole. From the beginning of the crisis, the health and pharmaceutical sectors were the focus of a fiscal consolidation process that required major cuts in public healthcare expenditure, and the application of reduced, closed budgets for public pharmaceutical spending. These developments created a need for the Greek government to allocate limited resources more efficiently, leading to a new environment in which pharmaceutical companies in Greece are expected to highlight the innovative aspects of their medicines and their economic efficiency, basing the cost of the treatment on the 'value added' for the Health Care and Insurance System.

1.5 RISDIPLAM (EVRYSDI)

In 2020 a new oral treatment was approved by the FDA, Risdiplam. As described in Roche's website, Risdiplam is an approved treatment for spinal muscular atrophy (SMA) in adults, children and infants aged 2 months and older. Risdiplam is a survival motor neuron-2 (SMN2) mRNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to survival motor neuron (SMN) protein deficiency.

Risdiplam is expected to be officially reimbursed in the Greek market during February 2023. At this time Risdiplam is conditionally reimbursed and this is the main reason it is excluded from the

model. Moreover, the purpose of this paper is to compare Onasemnogene Abeparvovec with the SoC, which is Nusinersen and not Risdiplam.

Risdiplam is administered daily at home in liquid form by mouth or by feeding tube, making it the first and only medicine for SMA that can be taken at home. It works to increase and sustain the production of the SMN protein in the central nervous system (CNS) and peripheral tissues. SMN protein is found throughout the body and is critical for maintaining healthy motor neurons, responsible for transmitting movement signals from the brain to the muscles. People affected by SMA are dependent on the SMN2 gene to produce SMN protein, as they carry a mutation in chromosome 5q resulting in the SMN1 gene, producing insufficient levels of functional SMN protein. Evidence shows that increasing the levels of SMN protein has significant clinical benefits for people living with a wide range of SMA types.

Risdiplam has demonstrated long term efficacy in a broad population of people living with SMA from birth to 60 years of age, with more than 5,000 patients treated to date.

The development of Risdiplam is part of a collaboration between Roche, PTC Therapeutics and the SMA Foundation. received U.S. Food and Drug Administration (FDA) approval in August 2020 and was approved by the European Commission in March 2021. [28]

Table 2. Clinical Trials Table

Drug	Clinical Trial	Outcome	Active drug	Placebo /Sham
Nusinersen	ENDEAR (n=121) CS3B (Type 1) (Open label long term extension: SHINE STUDY)	Event-free survival: patients who **died** or on permanent ventilation	31(39%)	28(68%)
Nusinersen		Overall survival patients who **died**	13(16%)	16(39%)
Nusinersen		Motor milestones: achieving milestone responder criteria (HINE section 2)	37(51%) P<0.0001	0(0%)

Nusinersen		CHOP INTEND: 4-point improvement	52(71%)	1(3%)
Nusinersen	CHERISH (n=126) CS4 (Type 2-3) (Open label long term extension: SHINE STUDY)	HFMSE: Change from baseline at 15 months	3.9	-1.0
Nusinersen		HFMSE: Proportion of patients with at least 3-point improvement	56.8%	26.3
Nusinersen		RULM: Mean change from baseline to month 15	4.2	0.5
Nusinersen		WHO motor milestones: Proportion of patients at month 15	19.7%	5.9%
Onasemnogene abeparvovec	STR1VE - AVXS-101-CL-303(n=22) Type 1	Survival w/o permanent ventilation	21/22 ≥ 10.5 months 20/22 ≥ 14 months and to 18 months of age	no arm
Onasemnogene abeparvovec		Milestone of sitting for at least 30 sec	14/22	no arm
Onasemnogene abeparvovec		Walking with assistance at 12.9 months	1/22 (4.5%)	no arm
Onasemnogene abeparvovec		Free of ventilation a at 18 months	18/22	no arm
Onasemnogene abeparvovec		CHOP-INTEND score	21/22(95.5%) ≥40 14/22(63.6%) ≥50 9/22(40.9%) ≥58	no arm
Onasemnogene abeparvovec	STRIVE EU - AVXS-101-CL-302(n=33, ITT=32))	Milestone of sitting without support for at least 10 seconds	14/32(43.8%)	no arm
Onasemnogene abeparvovec		Survival without permanent ventilation	31/32(96.6%) ≥14 months of age	no arm
Onasemnogene abeparvovec		CHOP-INTEND score	24/33(72.7%) ≥40 14/33(42.4%) ≥50 3/33(9.1%) ≥58	no arm

Onasemnogene abeparvovec	START - AVXS-101-CL-101(Ph 1) (N=12) Type 1 (Extension: START Long term follow up)	Event free survival	12/12 at 14 months of age	no arm
Onasemnogene abeparvovec		Motor milestone sit w/o support for ≥10 sec	10/12 at 24 months	no arm
Onasemnogene abeparvovec		Motor milestone sit w/o support for ≥30 sec	9/12 at 24 months	no arm
Onasemnogene abeparvovec		Motor milestone stand and walk w/o assistance	2/12 at 24 months	no arm

2. ECONOMIC EVALUATION

Clinical studies measure the general safety and health outcomes associated with healthcare interventions with the aim to determine the safety and efficacy of such interventions. However, choosing the most effective treatment option is by no means an easy task due to the increasing expenditures in healthcare and the constraint of limited resources. Hence, it is of interest to multiple decision makers and stakeholders to understand not only the effectiveness, but also the efficiency (i.e., cost-effectiveness) and affordability of a new healthcare intervention [35].

This problem of paucity of resources and the implied need to make choices that account for the value-for-money of a product is a central topic of health economics. Health economic evaluation provides a framework to not simply measure the costs of an intervention, but go beyond and measure both costs and effects, and combine these two measures in a single measure of efficiency. Economic evaluation has been previously defined as 'the comparative analysis of alternative courses of action in terms of both their costs and consequences [35,36]. For that reason, an economic evaluation can inform which treatment may be considered the best course of action from a perspective of efficiency, in a similar way that a clinical trial would inform a question on which treatment is more safe or effective than another.

The results of an economic evaluation are not always as clear to interpret. For example, a treatment may be cheaper than another, but it may be less effective than the comparator treatment(s). In this case, results are usually interpreted in the form of incremental cost-effectiveness ratios (ICER) and can be interpreted as the incremental cost incurred for an additional unit of the health effect of interest. This measure may also inform how much extra is required in order to achieve a unity of the clinical outcome of interest [35].

In order for a study to be classified as an economic evaluation, it should involve a comparison between costs and outcomes, between a strategy of interest (e.g., a healthcare intervention) and at least one alternative course of action.

2.1 TYPES OF ECONOMIC EVALUATION

There are several types of economic evaluation, and they differ mainly on the basis on which the outcome of interest is defined. The simplest form of an economic evaluation is a cost-minimization analysis. As per the definition, cost-minimization analysis focuses on the costs associated with the intervention, aiming to inform which intervention is less costly. This type of analysis is more relevant when it can be considered that the outcomes associated with alternative course of action are equivalent. Two more types of analyses are discussed in the following sections, the cost-effectiveness analysis and the cost-utility analysis, as they are relevant to the current study. It is acknowledged that other types of economic evaluations exist (e.g., cost-benefit analysis, cost-consequence analysis) but these are not detailed below.

2.1.1 Cost - Effectiveness Analysis

When outcomes of alternative courses of actions cannot be considered equivalent, and the outcomes can be measures in natural units (e.g., deaths averted, change in a disease-related clinical score), a cost-effectiveness analysis is more appropriate. Cost-effectiveness analysis, in contrast with cost-minimization, informs us which course of action is best for achieving a given objective, such as reducing the number of hospital deaths. Effectiveness data that can inform a cost-effectiveness analysis can be usually collected through outcome research. Although there are strengths associated with cost-effectiveness analyses, the drawback of this analysis is that it does not allow for a comparison between interventions in different disease areas. Therefore, it does not fully capture the opportunity cost of reimbursing an intervention for a specific treatment. In other words, it does not allow for the estimation of health benefits that could have been created if the resources would have been allocated in a different area of the healthcare sector.

2.1.2 Incremental Cost-Effectiveness Ratio

In order for the cost-effectiveness analysis to present the incremental costs of a new intervention to the health benefits that this intervention results in, a single measure of comparative efficiency

is necessary. Incremental cost-effectiveness ration (ICER) is the measure of comparative efficiency used by cost-effectiveness analyses and is defined as the incremental cost between the intervention treatment and the comparator treatment ($C_T - C_C$) divided by the incremental efficacy between the intervention treatment and the comparator ($E_T - E_C$):

$$ICER = \frac{C_T - C_C}{E_T - E_C} = \frac{\Delta C}{\Delta E}$$

From the perspective of the decision maker, generally the lower the ICER the more likely an intervention is to be reimbursed. However, economic evaluations aim to inform and not prescribe decisions. Hence even in situations where the ICER is high, there are other considerations that decision makers need to take into account such as unmet need, how threatening the condition is and at which stage of life patients are affected by the condition (e.g., end-of-life), and finally ethical considerations.

ICERs are commonly presented visually within the cost-effectiveness plane [37].Treatments that their ICER fall in the quadrants 2 are 'dominant' as they are considered more effective and less costly, while those falling in quadrant 4 are considered 'dominated' as they are more costly and less effective. For interventions falling in quadrant 1 and 3, ICERs need to be compared as they may be more/less costly and less/more effective. The decision to accept or reject a new healthcare intervention based on the ICER depends on the cost-effectiveness threshold, which reflects the decision maker's maximum willingness to pay for this intervention [38].
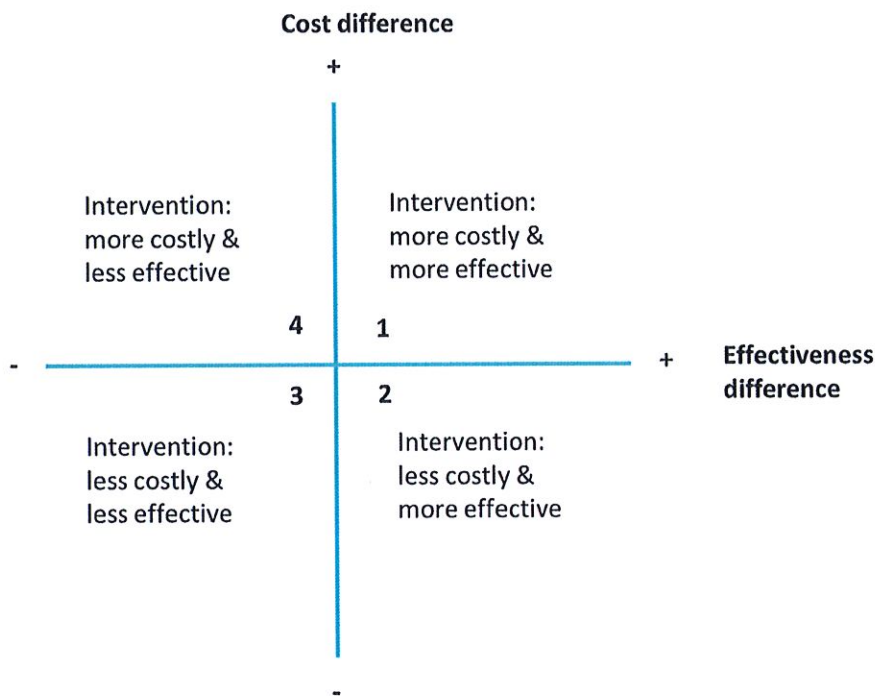
Figure 1. Example of cost-effectiveness plane

2.1.3 Net Monetary Benefit

To overcome some of the limitations associated with the ICER, the Net Monetary Benefit (NMB) can also be used as a measure of cost-effectiveness [35] . However, the estimation of the NMB demands a pre-defined willingness-to-pay threshold per unit of outcome. The (incremental) NMB is defined as:

$$NMB = MaximumWTPx\Delta E - \Delta C$$

There are several advantages of using the NMB in CEA/CUA. One of the key advantages is that the move away from dealing with the estimation of confidence intervals of cost-effectiveness ratios, which may be problematic especially in the context of sensitivity analyses, when confidence intervals of a ratio are more challenging to estimate and interpret, given the ratio cannot indicate in which quadrant the ICER falls (e.g., a negative value of the ICER is possible for both quadrant 2 and 4, in which an intervention is dominant and dominated, respectively) [39].

2.1.4 Cost-Utility Analysis

Another form of economic evaluation for which the term cost-effectiveness analysis is used interchangeably is the cost-utility analysis (CUA) and shares many similarities with cost-effectiveness analysis. The CUA instead of using clinical outcomes as the outcome of interest, puts at a central point the patient's preference for being in a particular health state, and reports outcomes in the form of morbidity combined with quantity of life. The preference outcome that is used to estimate morbidity (or quality of life) is called health utility index and has its basis in the Von Neuman utility [40]. The utility index can take values between 0 and 1 (inclusive), reflecting the state of death and perfect health respectively. In CUA the utility index is used to estimate the total quality-adjusted life years (QALY) gained by an intervention.

The calculation of QALYs requires the measurement of quality of life within a particular health state (i.e., health state utility). The period of time spent by an individual within this specific health state, is weighted by the estimated health state utilities, to result in the total QALYs gained in this period of time [35].

Given that QALY is not a clinical outcome, nor an outcome relevant only for a specific condition, it allows the comparison of different types of interventions within different sections of the healthcare sector and varied range of health care interventions. This trait of the QALY makes CUA a preferred tool by decision makers. Although there are many theoretical, methodological, and ethical concerns with these analyses that are beyond the scope of this article [41]. Well-conducted cost utility analyses comparing interventions within the same area of health care can be a powerful way of assisting decision making, but the use of marginal cost per QALY league tables to compare diverse health care interventions is highly controversial.

2.1.5 Model-Based Economic Evaluations

In most cases, conducting an economic evaluation alongside a clinical trial (i.e., collecting economic outcomes) may not be feasible due to a number of reasons, including the high resource requirements to collect additional economic data, the limited outcomes captures in a clinical study,

the short follow-up of clinical trials that do not provide data over the long-term, and last but not least, the limited number of interventions captured within a clinical trial setting.

Decision modeling provides an evidence synthesis vehicle that can support the conduct of economic evaluations of alternative courses of actions. The use of a decision analytic model (henceforth called economic model) can accommodate the synthesis of evidence from multiple data sources and provides a framework for identifying the most cost-effective treatment option, assisting policy makers and other stakeholders with the decision making process. Hence decision models differ compared to trial-based economic evaluations as data used for this evaluation rely on multiple sources of evidence rather than just a single study.

Similar to all models, decision analytic models used for healthcare economic evaluations require the simplification of complex clinical scenarios. For that reason careful consideration should be given during the development stage of the decision analytic models with regards to multiple critical components of their design. Firstly, the appropriateness and completeness of the list of comparators included in the model-based economic evaluation needs to be considered. Secondly, model-based economic evaluations require multiple types of data inputs including probabilities of events, clinical effect size, baseline clinical data, resource use, costs and utilities. Hence, all relevant clinical and economic data need to be carefully identified and considered carefully in order to ensure the use of the most appropriate clinical data in the model, that will ensure the accuracy and relevance of the results. Thirdly, decision analytic models are often as they can tackle the limited follow-up periods of clinical trials, by providing a framework that can explore multiple scenarios of how clinical outcomes can be extrapolated in the long term. However, it should be considered carefully how intermediate clinical end points can be extrapolated into long-term outcomes and whether extrapolation assumptions and projected values are clinically plausible and meaningful. Finally, it should be considered whether the choice of inputs for the model-based economic evaluations can produce results that are applicable to the decision-making context[35] .

The operationalization of model-based economic evaluation can be done by using decision trees or simulation models that can take the form of state-transition models, or discrete event simulation models.   Decision trees are probably the simplest type of decision analytic models and be considered schematic representations of all possible course of action related to the decision

problem of interest, as well as the relevant consequences that occur by following each course of action. However, decision trees may not be appropriate for use in many decision problems due to a number of inherent limitations. Particularly, decision trees are not able to explicitly for the elapse of time in the analysis. To account for the change of time in the decision trees the model structure should be expanded to the point that can easily become unmanageable. For that reasons simulation models are more commonly used to conduct economic evaluations.

2.1.6 Markov Models

There are different types of simulation models that can be used for decision analysis. State-transition cohort models (i.e., Markov models) are the most used type of models in decision analytical studies, as they can handle more efficiently the complexity that can arise by decision trees due to the increased number of 'branches' that may be needed to account for the lapse of time. Markov models are effective at modelling pathways and problems that are looking into stochastic decisions that evolve over time [42] .This type of models describes the patient journey through the transitions that patients make among pre-defined mutually exclusive and collectively exhaustive (i.e., an individual can be at only one state at a time) health states that describe the condition of interest. At the beginning of each cycle patients, may move to a different state. These health states are associated with costs and health outcomes which are accumulated based on the time patients spend (i.e., number of discrete time-cycles) within each of these states. Transitions between states occur on discrete time periods which are called model cycles. The model cycle length can vary between decision problems, and in cases where a condition develops rapidly, they usually have shorter length to provide sufficient granularity in estimating differences between the modeled treatment arms. The total number of the model cycles multiplied by the cycle length provides the time horizon of the analysis. After transitions in the model have occurred for all model cycles, it is possible to estimate the expected costs and outcomes by aggregating the costs and outcomes that occurred within each cycle of the model.

Despite the strengths and flexibility that Markov models offer compared with decision trees, this type of models also have limitations. Markov models are described in the literature as "memoryless". This trait of Markov models refers to the fact that the probability of transitioning to another health state in the future, depends only on the health state that the patient is currently

occupying without accounting for time spent in previous health states. In some cases, this may be a strong limitation, especially in conditions where the probability of future events depend on the patient's history. Technically there are ways around this limitation. For instance, by assigning 'tunnel' states in the model, in which patients can spend one cycle only before they move to another health state. However, the inclusion of multiple tunnel states may lead to an unwieldy model, similar to complex decision trees. Another alternative is the use of patient-level state transition models, but these are not a focal point of this report [43].

3. METHODS

3.1 DECISION PROBLEM

The analysis covers the Onasemnogene Abeparvovec's marketing authorization for the treatment of SMA1 in patients in Greece. It was deemed that the most appropriate comparator for the analysis is Nusinersen as it is a treatment that is being routinely reimbursed in Greece for the treatment of SMA1 and forms the standard of care within the Onasemnogene Abeparvovec's indication. Further details of the decision problem are shown in the below Table 3.

Table 3. Decision Problem

Decision problem component	Scope of the decision problem
Population	Patients with SMA1
Intervention	Onasemnogene Abeparvovec
Comparator(s)	Nusinersen (SoC)
Outcomes	The outcome measures to be considered include: • Overall survival • Life-years gained. • Health-related quality of life (QALYs) • ICER • INMB

3.2 PATIENT POPULATION

The analysis included patients diagnosed with SMA1. The starting age of patients in the model was assumed to be 3.4 months, of which 58% were female and had an average weight of 5.7kg as per the STRIVE trial [44].

3.3 INTERVENTION & COMPARATORS

- The intervention of interest for the economic evaluation is **Onasemnogene Abeparvovec.** It is approved by the Greek HTA Committee in 2020 and was available to the Greek Market by early 2020 due to Conditional reimbursement. The MAH is **Novartis Gene Therapies. The drug is administered IV, one time only.**

- The comparator of interest for the economic evaluation is **Nusinersen**. It is considered as the SoC for SMA and the only relevant comparator as it has been approved and reimbursed in the Greek Market since 2017, a year before the legislated establishment of the HTA Committee. The MAH is **Biogen** and the drug in Greece is represented by **Genesis Pharma**. According to the EMA smpc, nusinersen is **administered intrathecally, via lumbar puncture and the dosing scheme consists of 4 loading doses (days 0,14,28,63) and a maintenance dose every 4 months thereafter.**

- On the other hand, an alternative treatment for SMA is **Risdiplam**, which is expected to be officially reimbursed in the Greek market during February 2023. It is conditionally reimbursed, and this is the main reason it is **excluded from the model**. In addition, the purpose of this paper is to compare Onasemnogene Abeparvovec with the SoC, which is Nusinersen and not Risdiplam.

3.4 COST – EFFECTIVENESS MODEL SPECIFICATIONS

Table 4 provide a summary of the key model specifications alongside with the rationale. Many of these components are described again in more detail in the following sections.

Table 4. Cost-effectiveness model specifications

Factor	Chosen values	Rationale
Time horizon	Lifetime horizon (up to 100 years of age)	To capture all costs and outcomes associated with BPDCN and relevant treatments
Cycle length	Monthly	To allow for differences between treatments especially in the first model cycles which are described by high mortality rates. Also consistent with precedent economic evaluations in the literature
Half-cycle correction	Yes	To mitigate bias due to cycle length
Perspective	Greek payer perspective	As per the study's scope
Days per year	365.25	NA
Discount rate for utilities and costs	3.5%	The average discount rate found in OECD [45]
Source of utilities	Targeted literature search / desk research	Due to the pragmatic scope of the current study no systematic review was conducted
Source of costs	Government sources / targeted literature search / desk research	Due to the pragmatic scope of the current study no systematic review was conducted

3.5 TYPE OF ECONOMIC EVALUATION & PERSPECTIVE

The current economic evaluation is a CUA. As described in the background section, the principal outcome of the CUA is the cost per QALY gained, expressed as an ICER. The cost per QALY generated by the model is then compared against willingness-to-pay (WTP) thresholds to determine whether the intervention is cost-effective based on the WTP of the decision maker. The analysis follows a third-party payer perspective in Greece, as per the scope of the defined decision problem.

3.6 MODEL STUCTURE

A global model was adjusted to a local one for the purposes of this economic evaluation.

A Markov model was built to assess the cost-effectivness of Onasemnogene Abeparvovec compared with Nusinersen in the treatment of patients with SMA1. The CUA model was developed in Microsoft Excel (available for use). The cost-effectiveness model follows a state transition cohort model approach (i.e., Markov model). This type of model has been effectively utilized in previously published economic models for SMA interventions [46 - 50]. SMA is a rare neuromuscular progressive disorder with impact on patients' life expectancy and quality of life over their lifetime, making the Markov model an effective choice for modeling outcomes over the longer-term in patients with SMA. Markov models are suitable for modeling chronic diseases such as SMA and handling longer term outcomes because time is captured explicitly as discrete time periods called cycles [51]. This model structure also allows for non-linear transitions over time that can be taken into consideration, if necessary. In other words, Markov models can accommodate transition probabilities that are conditional with time. These Markov models are usually described as semi-Markov models.

Given that SMA is a rare condition, to ensure that there is sufficient data to populate the model, the complexity of the model structure was carefully considered to ensure a balance between structural simplicity and adequacy of answering the decision problem in place. The model is built on the strengths of a recently published economic models that was developed to answer the same decision problem in a different setting [46].

Error! Reference source not found. provides a visual representation of the CE model structure, as well as possible transitions between health states.
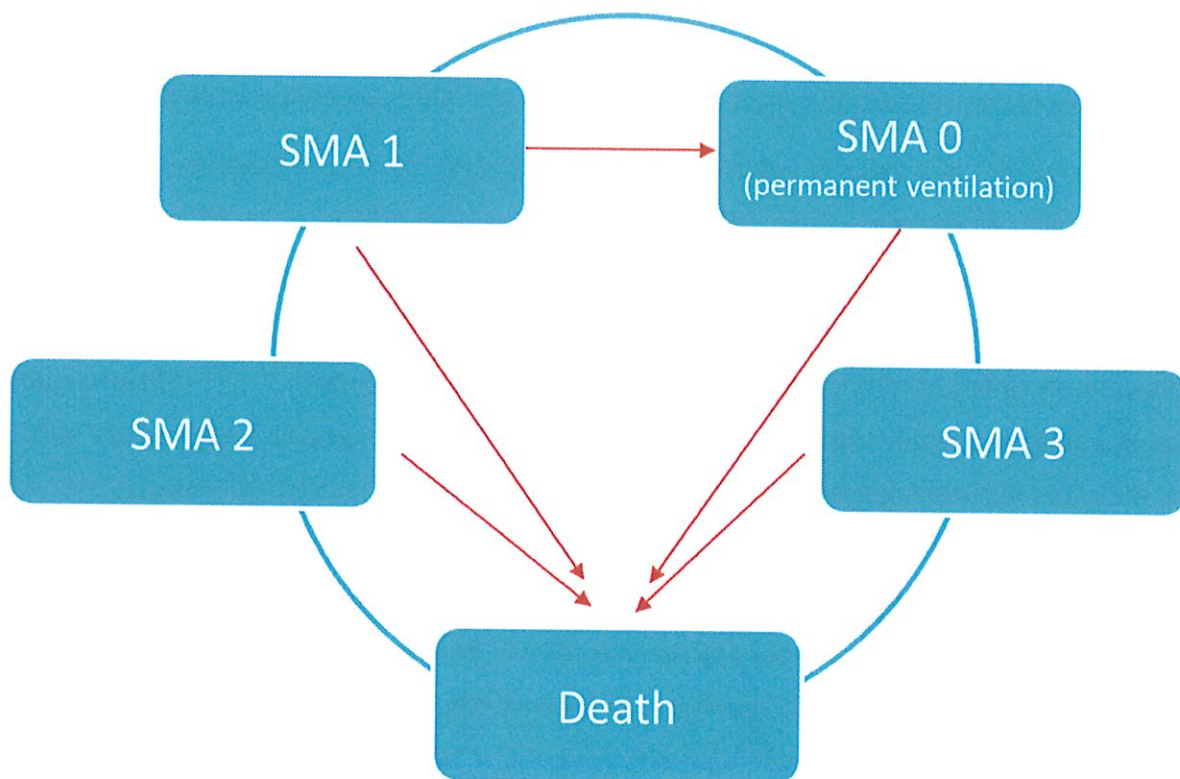
Figure 2. Spinal muscular atrophy type I model structure

The model consists of five health states. The death state is considered the absorbing state of the model, hence patients that enter this state cannot transition to another state. Health states SMA1, SMA2 and SMA3 reflect the severity of the patients' condition as described in the Background section. And additional health state for patients who are in SMA1 but require permanent ventilation (i.e., SMA0) was used as per the previous publications [46 - 49]. Patients entering this health state required ventilatory assistance for at least 16 hours for two weeks or more.

Patients entering the model are assumed to be SMA1 patients. However, the initial distribution of patients (described below) between health states was defined by the distribution of patients in these health states at the end of the follow-up of the relevant pivotal studies for each treatment.

The modeled base case does not allow patients to regress to a more severe health state. Hence, modeled patients transition from their initially attributed health state to the state of death. It is worth noting that a scenario was explored in the model where the worsening of patients with SMA1 was modeled (i.e., patients can regress to SMA0 from SMA1).

The parametric functions that were estimated based on the published survival model parameters were translated into transition probabilities per month to estimate time-dependent transitions between health states.

Health state transitions in the model can occur on a monthly basis and were needed transitions sourced from the literature were adjusted to reflect transitions of a monthly model cycle assuming a constant rate of events. For that purpose, where needed to transform transitions to different model cycles, it was assumed that transition probabilities followed an exponential distribution, and the following formula was applied:

$$P(t1) = 1 - \left(1 - Pt(0)\right)^{t0/t1}$$

Where t1 is the timeframe of interest, t0 is the timeframe reflected by the sourced probability.

The rationale for choosing a monthly model cycle was based on the fact that especially in the early years, the mortality rate for SMA patients in stages SMA1 and SMA0 is very high, hence the shorter model cycle provided sufficient granularity in the estimations to capture differences between the modeled treatments.

3.7 TIME HORIZON & DISCOUNTING

For this analysis a long-enough time horizon was considered to capture differences between Onasemnogene Abeparvovec and Nusinersen over the longer term. Hence a lifetime horizon was applied to the analysis, with the limit that no patient survives beyond 100 years of age. This length for the time horizon was considered necessary as patients who benefit from therapy and move to less severe health states such as SMA3, they were assumed to have a lifespan similar to this of the general population. The impact of the lifetime horizon was further explored in scenario analyses.

In economic evaluations, future costs and benefits are commonly discounted to reflect the impact of time preference. This concept refers to the preference of accruing costs in the future instead of today, as 'a dollar today is worth more than a dollar in the future' reflecting the consistent belief of positive economic growth over time. Similar for health benefits. People tend to value health benefits in the present more than those that may occur in the future. Hence, in economic evaluations, future costs and benefits are discounted to accurately reflect the lower value of outcomes in the future compared to outcomes incurred today. For the purpose of this analysis a

discount rate of 3.5% was assumed for the Greek setting. This was sourced from online available data by the Center for Global Development and it corresponded to the population-weighted average implied social discount rate for upper-middle-income countries [45].

3.8 CLINICAL INPUTS

Transitions in the model were based on published parameter estimates (i.e., rate and scale) of parametric survival model obtained previously from the digitization of Kaplan-Meier curves and fitting standard parametric survival models [46]. To estimate the parameters of the survival models, the authors used the published method from Hoyle & Henley[52] to digitize published Kaplan-Meier curves from published data [53 - 55] and simulate pseudo-individual patient level data. The authors used the Akaike information criterion, Bayesian information criteria, and visual inspection to make judgments on the best statistical fit between the Weibull, log-normal and log-logistic curves. For the scenario in which the transition from SMA1 to SMA0 was allowed, transitions from SMA1 to SMA0 were estimated by subtracting the event free survival curve from the overall survival curve. A noteworthy point of following this approach is that because published Kaplan-Meier curves used different time increments (e.g., weekly, annual), weekly and yearly transition probabilities derived from Kaplan-Meier curves had to be converted to monthly probabilities. This was done in the model by adjusting the time factor of the modeled cumulative survival function for each of these survival curves. The survival model parameters used in the model are presented in Table 5.

Table 5. Clinical inputs used in the input to inform transition probabilities.

Outcome	Default	Min	Max	Model	Time frame	Source
SMA1 to Death (Treatment)				Weibull	Month	[54]
Intercept	4.167	3.527	4.784			
Scale	1.379	0.940	2.004			
SMA1 to EFS (BSC)				Exponential	Week	[53]

Intercept	2.923	2.545	3.296			
SMA1 OS (BSC)						
Intercept	4.248	3.161	5.297	Weibull	Week	[53]
Scale	0.529	0.336	0.815			
SMA II to death				Weibull	Year	[55]
Intercept	3.833	3.646	4.015			
Scale	0.503	0.404	0.620			

Finally, for patients in the SMA3 health state, it was assumed that they had the same risk of mortality as the Greek general population [9]. Risk of mortality for the Greek general population was sourced from WHO [56] and risks applied in the model were weighted to reflect the gender distribution of modeled patients. The weight was the proportion of female patients in the STRIVE study. [44]

Table 6. Life tables for Greek population (Source: https://apps.who.int/gho/data/view.searo.60640?lang=en)

Age Group	Male	Female	Weighted average
<1 year	0.003526	0.002973	**0.003205**
1-4 years	0.00012	0.000105	**0.000111**
5-9 years	8.97E-05	7.82E-05	**0.000083**
10-14 years	0.000103	7.86E-05	**0.000089**
15-19 years	0.000337	0.000134	**0.000219**
20-24 years	0.00054	0.000214	**0.000351**
25-29 years	0.000542	0.000208	**0.000348**
30-34 years	0.000644	0.000321	**0.000456**
35-39 years	0.001031	0.000481	**0.000712**

40-44 years	0.001377	0.000809	**0.001047**
45-49 years	0.002509	0.00133	**0.001825**
50-54 years	0.004709	0.002171	**0.003237**
55-59 years	0.007844	0.003449	**0.005294**
60-64 years	0.012765	0.005212	**0.008384**
65-69 years	0.017661	0.007464	**0.011747**
70-74 years	0.027732	0.013988	**0.019760**
75-79 years	0.040325	0.022913	**0.030226**
80-84 years	0.066854	0.046314	**0.054941**
85+ years	0.142055	0.153225	**0.148533**

The use of parametric models fitted to published Kaplan-Meier curves is a common approach recommended also by NICE DSU (REF) in the absence of access to patient level data [57].

3.9 TREATMENT EFFECT

The treatment effect of Onasemnogene Abeparvovec in the model was captured in the similar manner as in previous models that used the same model structure [47-48]. Particularly, the treatment effect was captured in the form of the patient distribution among different health states (SMA0-SMA3) at the end of the follow-up of each of the pivotal studies for Onasemnogene Abeparvovec and for Nusinersen. The treatment effect, and hence the distribution of patients between health states was assumed to be maintained over time unless patients moved to the state of death. An alternative scenario was explored as part of the sensitivity analysis where this assumption was relaxed, and patients were allowed to move from SMA1 to SMA0.

In the STRIVE clinical trial [44] that studied the effect of Onasemnogene Abeparvovec, twelve SMA1 patients that were enrolled in the study. At the end of the trial follow-up (2 years), 1 patient was considered to be in SMA1, 7 in SMA2, and 4 in SMA3. None of the patients required permanent ventilation at the end of the follow-up hence it was assumed that 0 patients remained or entered in SMA0 state.

In the ENDEAR clinical study that studied the effect of Nusinersen on SMA1 patients 122 patients were followed for a median of 394 days. All patients were diagnosed as SMA1 at the beginning of the study, and at the end of the clinical study 69 patients remained in SMA1, 23 patients moved to SMA2, 30 moved to SMA0, while none of the patients moved to SMA3 state [53]

Although this distribution reflects the state of patients at the end of the trial follow-up, for the purpose of unnecessary complexity in the model development, it was assumed that despite all patients entering the model were initially SMA1 patients, they experience an instant treatment effect. In other words, despite the modelled population includes SMA1 patients, the distribution presented in Table 7 below, reflected the initial patient distribution in the model.

Table 7. Initial distribution of patients among health states of the model

State occupancy at the end of the trial follow-up	Percentage of patients	Number of patients
Onasemnogene Abeparvovec		N=12
SMA1	9.09%	1
SMA0	0.00%	0
SMA2	63.64%	7
SMA3	27.27%	3
Nusinersen		N=122
SMA1	56.56%	69
SMA0	24.59%	30
SMA2	18.85%	23
SMA3	0.00%	0

3.10   HEALTH STATE UTILITIES

As mentioned in Section of treatment effect, patients with SMA I, who entered the model were being assigned to one of the health states SMA0-SMA4, proportional to the outcomes of the STRIVE and the ENDEAR after treatment with Onasemnogene Abeparvovec and Nusinersen, respectively.

Health state utilities were assigned to each of the health states, to reflect the impact of different severities of SMA on patients' quality of life, and the improvement of patients' quality of life over time as a result of effective treatment. To inform the health state utilities, a set of values was sourced from a systematic literature review of health state utilities in SMA. This set of values was chosen for the following three reasons. First, these published utility values correspond to the health states that were included in the current model. Second, the same set of values has been previously used by an economic evaluation in SMA patients, increasing the external validity of the model's results.

Finally, the face validity of these health state utilities has been previously discussed and considered appropriate in the health technology assessment of Nusinersen for the treatment of SMA patients in the UK, by NICE [58-59] Table 8 presents the utility values included in the model. It was assumed that patients requiring permanent ventilation (SMA0), had the same quality of life as patients in the SMA1 health state.

Table 8. Health state utilities included in the model.

Utilities	Point estimate
SMA1	0.733
SMA0 (permanent ventilation)	0.733
SMA2	0.752
SMA3	0.878
Dead	0

It is worth noting that there are challenges in obtaining utility values which can be considered truly reflective of the quality of life of young patients with SMA. That is because there are widely recognized challenges in measuring quality of life in paediatric populations, especially due to the uncertain ability of children to make judgements on their quality of life, and the necessary use of

proxy responders (e.g., parents, physicians) whose response is often different from this of the children [60-63]

The utility values included in the model were derived by the use of Paediatric Quality of Life Inventory (PedsQL) [64] PedsQL is a self- and parent-reported approach for the measurement of health-related quality of life in people between 2-18 years of age providing scores between 0-100 (higher scores indicate better quality of life). This instrument assesses four dimensions of quality life, including physical functioning, emotional functioning, social functioning, and academic functioning. The instrument was designed to also measure HRQOL dimensions in children and adolescents with neuromascular disorders. PedsQL has been frequently used to measure the quality of life in patients with SMA and has been previously validated by the American Spinal Muscular Atrophy Randomized Trials group of children and adolescents with SMA [65]

The aforementioned challenges raise questions on whether these utility values are representative of the quality of life of patients with SMA. Hence, a scenario analysis was conducted in which utility values were sourced from a health technology assessment report by the CER institute in the US for Nusinersen and Onasemnogene Abeparvovec in the treatment of SMA patients [48]

As utility values sourced from the literature were not dependent on age, that meant that the health state utilities applied in the model would remain constant over time. Since this is not a realistic assumption, as patients' quality of life decreases with ageing, an age adjustment was applied to utilities based on the general population utilities categorized in different age groups. Particularly, self-reported EQ VAS mean scores by different age groups in the Greek population was sourced from the literature [66-67] (Table 9). Adjustment factors were then estimated for men and women separately, by calculating the fraction between the age of patients in the model, and the index age group. Since no EQ VAS scores for the 0-18 age group was available, it was assumed that people in the 0-18 age group have the same quality of life as those in the 18-29 age group. The calculated adjustment factors for men and women were weighted by the proportion of females included in the model (58%). For demonstration, a patient in SMA3 health state who reaches the 50th year of age in the model, is applied a utility value related to SMA3 (0.878) weight of 0.83, resulting in a utility of 0.728.

Table 9.. Self-reported EQ VAS scores, and estimated utility age-adjustment factors

| Age Groups | Reported EQ-VAS (Mean) | | HRQoL age-adjustment factor | | |
	Men	Women	Men	Women	Weighted average
18-29 (assumed 0-29)	86.20	84.60	1.00	1.00	**1.00**
30-39	84.20	81.50	0.98	0.96	**0.97**
40-49	82.30	84.10	0.95	0.99	**0.98**
50-59	79.20	64.60	0.92	0.76	**0.83**
60-69	69.70	69.20	0.81	0.82	**0.81**
70-79	60.80	64.20	0.71	0.76	**0.74**
80+	49.50	40.00	0.57	0.47	**0.52**

3.11 COST INPUTS

Two types of costs were included in the model. Costs related to the delivery of the treatment that included drug acquisition and administration cost, and costs related to the disease management (henceforth referred as health state costs).

Drug acquisition and Administration cost

Drug acquisition and administration costs are presented in Table 10. The drug acquisition costs were sourced from the ministry of health page. In 2022 according to the Greek Price Bulletin, Onasemnogene Abeparvovec is officially reimbursed in Greece with ex-f price of 1.945.000 euro and Nusinersen ex-f price is 69.198,26 euro. In the model, the Invoice Price for each of the two treatments was used (table 10).

Administration frequency was sourced from the EMA summary of product information for Onasemnogene Abeparvovec and for Nusinersen [68] These are described in Section 3.3. In summary Zolgesnsma was assumed to be administered with a one-off loading in the first cycle only. As per the EMA SmPC, Nusinersen is administered with 4 loading doses administered on days 0, 14, 28 and 63. Due to the monthly cycles in the model, two doses of Nusinersen were applied to the model for each of the first two cycles. Following the first four dosage, Nusinersen was administered every 4 cycles thereafter as per the SmPC. Similar to a previous economic evaluation in SMA, the base case assumed that patients who remained in SMA0 health state, would discontinue treatment with Nusinersen after the 6th dose [46] · This is a conservative assumption

from the perspective of Onasemnogene Abeparvovec. However, this assumption was relaxed in a scenario analysis where patients receiving Nusinersen were assumed to not discontinue treatment until death. it was assumed that patients on Nusinersen received the 4-monthly follow-dosages for their remaining lifespan.

Moreover, administration cost was considered, on top of drug cost. More specifically, for patients with SMA, it was assumed that treatment administration required to be hospitalized. Hence the administration cost (€177) for hospitalized patients was sourced from government sources [69] . This administration cost was assumed to be applied in all cycles that patients were receiving treatment.

Table 10.. Drug acquisition and administration cost considered in the models.

Drug acquisition cost	Unit Cost	Source
Onasemnogene Abeparvovec	1,945,000€ ex-f price 1,775,007.00€ Hospital price 1,686,256.65 Invoice Price	https://www.moh.gov.gr/
Nusinersen	69,198.26€ ex-f Price 63,150.33€ Hospital Price 59,992.82€ Invoice Price	https://www.moh.gov.gr/
Administration cost	**Unit Cost**	**Source**
Patients with SMA Type 1	€177	Governmental Gazette (Law 2150/27.9.2011)

Disease management cost

In the absence of local data related to the resource utilization of patients with SMA, the cost of disease management for each type of SMA was extracted from literature. In particular, a cost of illness study conducted in Germany analyzed the economic burden of patients with SMA of different severity levels [70] . The study costs were reported in 2013 German prices. To ensure the costs are relevant to the Greek market, the originally extracted data were converted to 2013 Greek prices based on the economic database of Organization for Economic Co-operation and Development (OECD) an adjustment for the different price level of a similar basket of goods in the two countries in 2013 (US $ purchasing-power parity ratio per national currency unit; 0.631

for Greece and 0.775 for Germany[71] . The costs were then adjusted to reflect 2021 prices by using the ratio between the consumer price index for 2021 (101.9) and 2013 (103.9), which led to a deflation ratio of 0.98, as reported by online sources using data from the world data bank IMF [71]. Important to note is that different cost categories were examined in Klug et al. study [23] including respiratory, gastrointestinal, nutritional orthopedic care. Since these costs were reported as annual costs, they were adjusted to the monthly cycles of the model by dividing them by 12 to derive the average health state costs (monthly). Following the aforementioned adjustments of the sourced cost values, the costs presented in Table were used in the model.

Table 11.. Original and adjusted disease management cost considered in the models per SMA subtype.

Sourced health state costs (annual)	SMA1	SMA2	SMA3
Outpatient medical costs	463	392	274
Inpatient medical costs	39,972	4,454	2,488
Rehabilitation costs (in-/outpatient)	594	971	745
Drug treatment costs	389	245	126
Costs for use of rehabilitation services	3,488	2,149	1,814
Costs for artificial nutrition	1,940	247	90
Costs for medical aids	1,648	4,385	3,003
Costs for respiratory management	5,698	2,548	594
Adjusted Health state costs (monthly)	SMA1 & SMA0	SMA2	SMA3
Outpatient medical costs	34	29	20
Inpatient medical costs	2,953	329	184
Rehabilitation costs (in-/outpatient)	44	72	55
Drug treatment costs	29	18	9
Costs for use of rehabilitation services	258	159	134
Costs for artificial nutrition	143	18	7
Costs for medical aids	122	324	222
Costs for respiratory management	421	188	44
Total per cycle	4,003	1,137	675

3.11.1 Data Analysis

The aforementioned approach and data were used to calculate mean estimates of lifetime costs, LYs and QALYs for each comparator. The cost-effectiveness of Zogensma versus Nusinersen was evaluated by calculating the ICER over a patient's lifetime, associated with the use of Onasemnogene Abeparvovec.

To make judgements on whether Onasemnogene Abeparvovec is a cost-effective option compared with Nusinersen a willingness to pay threshold was applied as a decision rule. As there is no widely accepted willingness to pay threshold in Greece, similar to previous studies the current analysis assumed a threshold equal to 1-3 times the Greek GDP. Specifically, given that SMA is a rare condition affecting children, hence there is potential for a great health benefit from Onasemnogene Abeparvovec, the upper range of that threshold was considered (EUR 55,716).

3.11.2 Uncertainty

The most common approach to handle uncertainty around the results of the analysis, is to conduct sensitivity analysis in which the key parameters of the model are changed, and the results of the analysis are recorded for both costs and effects, in order to assess the impact of these changes in the model inputs or structural assumptions. A set of sensitivity analyses is pivotal in order to quantify and describe the uncertainty around the decision [35]. The following types of sensitivity analysis were conducted as part of this economic evaluation.

Univariate sensitivity analysis

The simplest form of a sensitivity analysis is the univariate or deterministic sensitivity analysis (DSA). This type of analysis facilitates the establishment of the set of parameters with the greatest impacts on the model's results (i.e., the decision drivers). To determine the parameters to which the model was most sensitive to, each parameter was assigned a lower and upper value while other parameters remained constant. In this model, upper and lower values of model parameters was determined by varying the mean value of the parameter by 25%. The parameters included in the DSA and the associated values are presented in Table 13.

Scenario analysis

The impact of both structural assumptions and choice of parameter values were further explored through a number of scenario analyses. Scenario analysis is commonly performed by exploring a number of scenarios that test structural assumptions of the model (e.g., time horizon, possible transitions). The scenarios described in were explored in the model to test how certain assumptions affect the results.

Table 22. Model Parameters

Scenario	Justification
Discount rate: 0% and 6%	Given that the benefits but also costs of both treatments occur over the longer-term, different discount rates of future costs and effects were explored
Time horizon: 50 and 25 years	Different time horizons were explored to understand the impact of restricting the analysis to a shorter time period
Varied set of utility values	A different set of utility values used by the CER instituted was applied in a scenario analysis to account for uncertainty around utility values in patients with SMA. The values included in the model were 0.29 0.19, 0.65, and 0.736 for SMA1, SMA0, SMA2, and SM3, respectively.
Patients can regress from SMA1 to SMA0	In this scenario, the assumption of not allowing patients to regress from any health state was relaxed by allowing patients who had stayed in SMA1 following treatment to regress from SMA1 to SMA0.
Utility age-adjustment factor not applied	This scenario explored the impact of not applying the utility age-adjustment factor, similar to other economic evaluations in SMA.
Nusinersen was assumed to not discontinue in patients remaining in SMA0	This scenario tested the assumption that patients with SMA0 (i.e., patients that require permanent ventilation) would cease treatment with Nusinersen after their 6th dose. To explore the impact of this base case assumption a scenario was designed

were the analysis assumed that SMA0 patients receiving Nusinersen do not discontinue treatment until death.

Probabilistic sensitivity analysis

The final type of sensitivity analysis conducted in the model was a stochastic analysis, in the form of a probabilistic sensitivity analysis (PSA). This analysis provides an understanding on how uncertainty characterizing the input parameters is translated into uncertainty around the estimated outputs of the model (i.e., ICER, and NMB). PSA is considered as one of the most comprehensive methods of handling uncertainty economic evaluations. During the PSA, probability distributions are applied to each of the model parameters that are captured in the PSA, and after drawing values from these distributions in an iterative process, a sample of outcomes is produced, leading to an empirical distribution of cost-effectiveness results.

To conduct the PSA therefore, suitable probability distributions were assigned to model parameters to characterize uncertainty around their mean values. The parameters which were assigned a distribution, the of assigned distributions, as well as the parameters of each assigned distribution are described in Table 13.

When available, the mean value and the standard deviation of each parameter were used to parameterise the relevant probability distribution. When the standard deviation or a 95% confidence interval was not reported, probability parameters were parameterised based on a 25% variation in the point estimate of the parameter. The method of moments was used to derive the parameters of each distribution [43]

Values were sampled from the corresponding parameter distributions presented in Table 13 and were assigned to each parameter in an iterative process. This process was repeated for 1,000 times. The results of each of these iterations formed the empirical distribution of the ICER and NMB.

It is worth noting that uncertainty around the parameters that informed the transition probabilities between modelled health states (i.e., the parameters of the parametric survival models) were not included in the PSA. Although this may be a significant assumption that may underestimate the

overall uncertainty of the results, the reason for not including these values in the PSA was because the authors had reported only the confidence intervals of the parameters of the Weibull and exponential survival models. Hence, for the Weibull model that is specified by two parameters (i.e., rate and scale), the authors from the published economic evaluation where these parameters were source, did not publish the covariance matrix between these parameters. As a result, if these parameters were sampled independently instead of using a Cholesky decomposition to sample the parameters jointly, it would result in overestimating the uncertainty around the results [43].

The results of the PSA were presented within the cost-effectiveness plane in the form of a joint distribution of costs and QALYs, along with a mean value of the ICER and a 95% confidence interval ellipse. The probability that each treatment was cost-effective and results in the highest net monetary benefit was presented over different values of a cost-effectiveness threshold in the form of a cost-effectiveness acceptability curve (CEAC).

Table 13.. Model inputs, and assigned parameters and values for DSA and PSA analyses

Parameter	Mean	PSA	Distribution	Varied in DSA	Lower DSA value (-25%)	Upper DSA value (+25%)
General inputs						
Mean age (months)	3.4	No		Yes	2.55	4.25
Mean weight (kg)	5.7	No		Yes	4.275	7.125
Female (%)	0.58	No		Yes	0.435	0.725
Time horizon (years)	100	No		Yes	75	125
Discount rate: outcomes	0.035	No		Yes	0.02625	0.04375
Discount rate: costs	0.035	No		Yes	0.02625	0.04375
Utilities						
SMA1	0.733	Yes	Beta (1449.31, 527.92)	Yes	0.5495	0.91625
SMA0 (permanent ventilation)	0.733	Yes	Beta (1449.31, 527.92)	Yes	0.54975	0.91625
SMA2	0.752	Yes	Beta (560.63, 184.89)	Yes	0.564	0.94
SMA3	0.878	Yes	Beta (48.85, 6.79)	Yes	0.6585	1.0975
Dead	0	No		Yes	0	0
Health state costs						
Health state costs: SMA1	4,003	Yes	Gamma (6.25, 640.51)	Yes	3,002.412	5,004.02
Health state costs: SMA0	4,003	Yes	Gamma (6.25, 640.51)	Yes	3,002.412	5,004.02
Health state costs: SMA2	1,137	Yes	Gamma (6.25, 181.91)	Yes	852.7111	14,21.185
Health state costs: SMA3	675	Yes	Gamma (6.25, 107.96)	Yes	506.0531	843.4218
Health state costs: dead	0	No		Yes	0	0
Onasemnogene Abeparvovec acquisition cost	1,686,257	No		Yes	1,264,692	2,107,821

Parameter	Mean	PSA	Distribution	Varied in DSA	Lower DSA value (-25%)	Upper DSA value (+25%)
Onasemnogene Abeparvovec administration cost	177	No		Yes	60	100
Onasemnogene Abeparvovec IRF impact	0%	No		Yes	0	0
Nusinersen acquisition cost	59,993	No		Yes	44,994.61	74,991.02
Nusinersen administration cost	177	No		Yes	60	100
Onasemnogene Abeparvovec IRF impact	2%	No		Yes	0.015	0.025
Health state initial distribution						
Onasemnogene Abeparvovec				No		
SMA1	0.091	Yes	Dirichlet (1, 0, 7, 3)	No		
SMA0	0.000	Yes	Dirichlet (1, 0, 7, 3)	No		
SMA2	0.636	Yes	Dirichlet (1, 0, 7, 3)	No		
SMA3	0.273	Yes	Dirichlet (1, 0, 7, 3)	No		
Nusinersen				No		
SMA1	56.6%	Yes	Dirichlet (69, 30, 23, 0)	No		
SMA0	24.6%	Yes	Dirichlet (69, 30, 23, 0)	No		
SMA2	18.9%	Yes	Dirichlet (69, 30, 23, 0)	No		
SMA3	0.0%	Yes	Dirichlet (69, 30, 23, 0)	No		

4. Results

4.1 BASE CASE RESULTS

Results of the base case deterministic analysis are presented in Table. Over a lifetime horizon for modelled patients diagnosed with SMA1 and treated with either Onasemnogene Abeparvovec or Nusinersen, the base case deterministic analysis showed that Onasemnogene Abeparvovec was associated with a greater survival by 8.75 LYs, as well as improved quality adjusted survival by 3.67 QALYs when compared with Nusinersen (Table 14). This shows that despite patients remaining alive for a longer period of time, there is a noticeable impact on their quality of life. Figure 3 presents the health state occupancy of modelled patients in both arms over time.
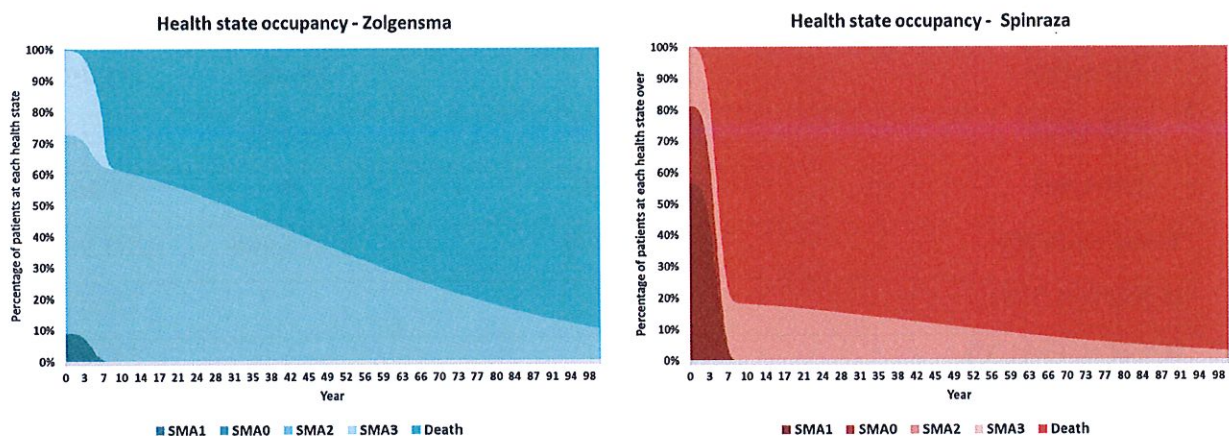

Figure 3 Health state occupancy over time

In terms of treatment-related costs, Onasemnogene Abeparvovec was the most-costly treatment regimen as it was associated with higher total lifetime costs (€1,919,474) compared with Nusinersen (€1,715,488) by €203,986. This difference was almost entirely attributed to the increased drug-acquisition cost difference (€205,846), as there was almost no difference in medical management costs between the two treatments over the patients' lifetime (- €1,860). This can be explained by the fact that although patients with Nusinersen incurred more costs due to their more severe condition, patients with Onasemnogene Abeparvovec incurred a lower amount of costs but for a longer period, summing up to almost equal costs with Nusinersen.

The incremental analysis showed that Onasemnogene Abeparvovec had an ICER of €55,560 per QALY gained relative to SoC- Nusinersen. Assuming a willingness-to-pay threshold of €55,716, this makes Onasemnogene Abeparvovec by margin, a cost-effective treatment compared with Nusinersen.

Table 14.. Results of the base case analysis

Outcome	Onasemnogene Abeparvovec	Nusinersen	Difference
Life years	16.78	8.02	8.75
QALYs	8.10	4.43	3.67
Drug costs (€)	1,685,691	1,479,845	205,846
Health state costs (€)	233,783	235,644	-1,860
SMA1(€)	*19,743*	*122,830*	*-103,086*
SMA0(€)	*0*	*53,404*	*-53,404*
SMA2(€)	*200,537*	*59,410*	*141,127*
SMA3(€)	*13,503*	*0*	*13,503*
Total costs (€)	1,919,474	1,715,488	203,986
ICER (€/LYG)			23,302
ICER (€/QALY)			55,560
INMB (€)			574

4.2 PROBABILISTIC SENSITIVITY ANALYSIS RESULTS

Table 15 presents the results of the PSA. Results were overall similar to the base case deterministic analysis, with a difference in overall costs of €196,233 over lifetime, and an improvement in QALYs by 3.55. These resulting in an ICER of 55,241 €/QALY which remains below the willingness to pay threshold.

Table 3. Results of probabilistic sensitivity analysis

Outcome	Onasemnogene Abeparvovec	Nusinersen	Difference
Costs (€)	1,915,078	1,718,845	196,233
QALYs	8.00	4.45	3.55
ICER (€/QALYs)	-	-	55,241
NMB (€)			1,689

The cost-effectiveness plane below presents visually the uncertainty around the costs and effectiveness estimates of each iteration of the PSA. It can be seen visually that the distribution of the difference in QALYs is much more widely spread compared with the distribution of costs. This is an expected outcome as Onasemnogene Abeparvovec costs occur over the first model cycle and there is not uncertainty around the drug costs for the Onasemnogene Abeparvovec arm, which can be considered a key driver of the model results. Uncertainty around the total QALYs gained is amplified due to the small number of patients included in the pivotal trial of Onasemnogene Abeparvovec. The number of patients in this trial informed the distribution of patients between health states. Due to the low number of patients, there was a lot of uncertainty captured by the Dirichlet distribution which was used to sample the spread of patients between health states. This may have contributed significantly to the wide spread of QALYs gained associated with the use of Onasemnogene Abeparvovec.

Finally, it can be observed that the spread of the results through the 1,000 iterations that the model ran stochastically are spread between the two sides of the willingness to pay threshold in a balanced manner.
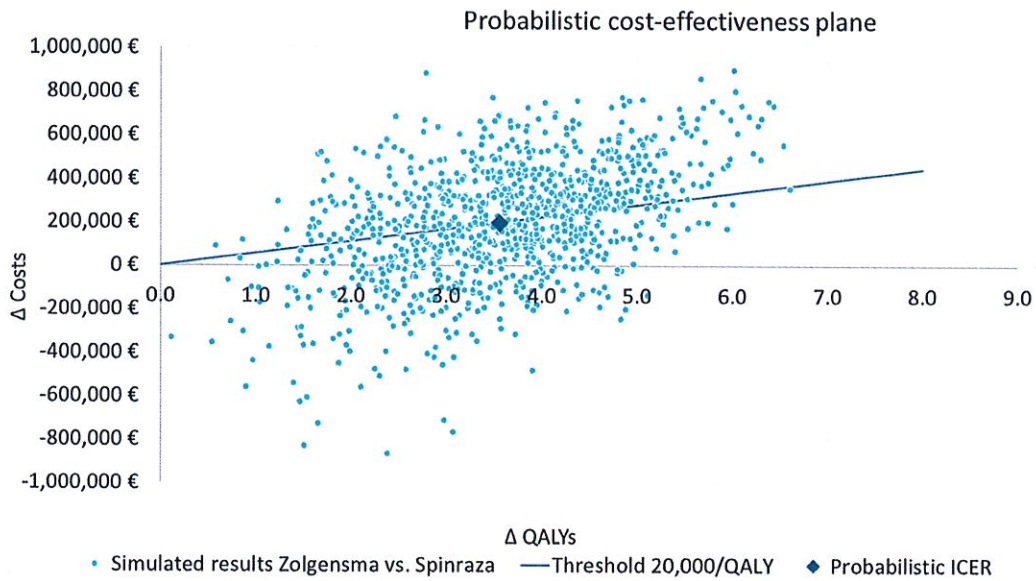
Figure 4. Cost-effectiveness plane of probabilistic analysis

The cost-effectiveness acceptability curve (Figure 5) shows the likelihood that each treatment is cost-effective over different values of the willingness-to-pay threshold. The probability of Onasemnogene Abeparvovec being cost-effective at willingness-to-pay threshold of €55,716 per QALY, was 47.5% for Onasemnogene Abeparvovec versus 52.5% for Nusinersen, indicating the high uncertainty characterizing the results of this analysis.
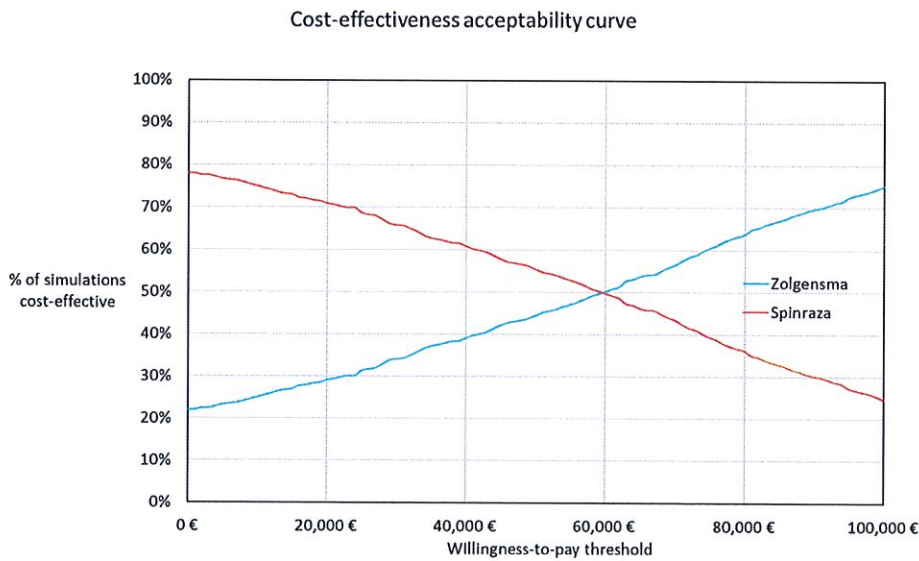

Figure 5. Cost-effectiveness acceptability curve

4.3 DETERMINISTIC SENSITIVITY ANALYSIS RESULTS

Results of the DSA showed that the drivers of the cost-effectiveness analysis results were the treatment related costs, followed by the discount rates of costs. Additionally, the utility value of SMA2 health state, and the discount rate applied to outcomes had a less profound impact on the results, but significant enough to allow for a change in the decision on whether Onasemnogene Abeparvovec is cost-effective (i.e., 25% variation in the value of these inputs results in an ICER higher that the willingness to pay threshold).
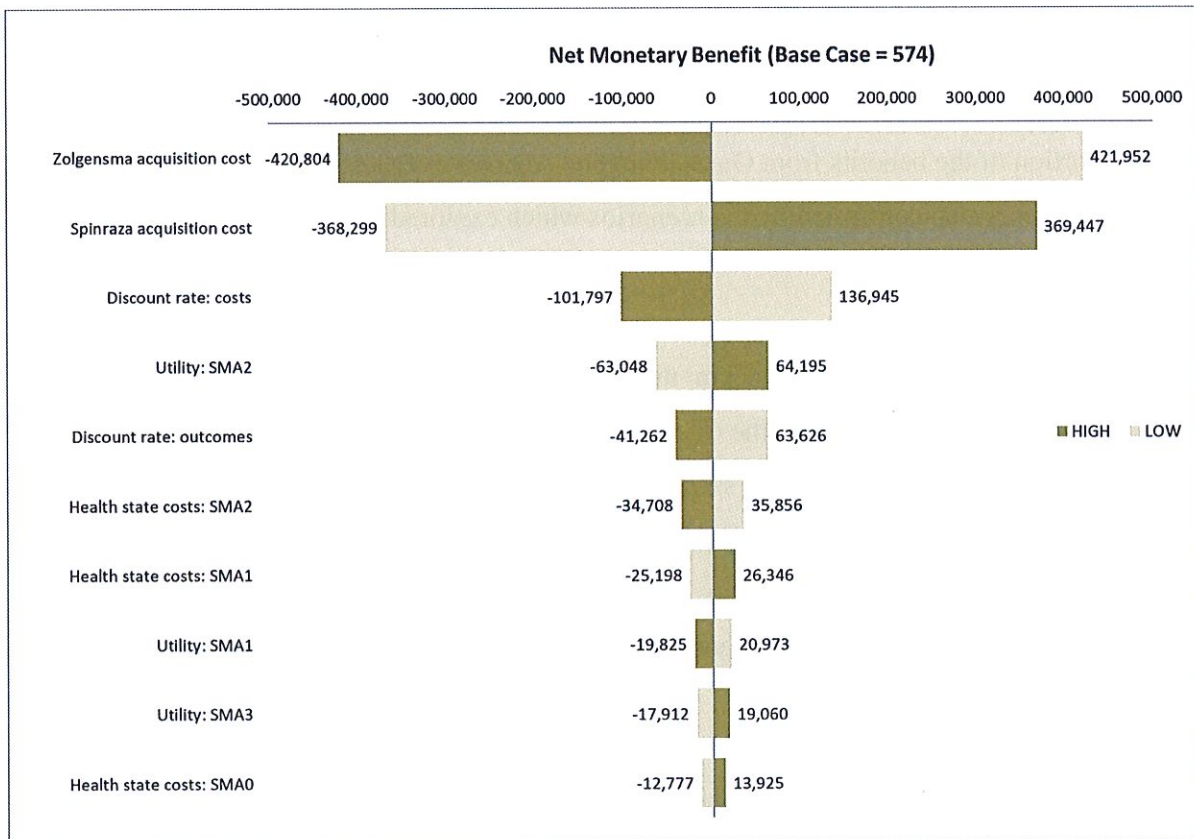

Figure 6. Tornado diagram for the deterministic sensitivity analysis

4.4 SCENARIO ANALYSIS RESULTS

Table 4 presents the results of the scenario analyses conducted to explore the impact of assumption of the model and the subsequent uncertainty around the cost-effectiveness of Onasemnogene Abeparvovec.

Overall, the scenarios exploring the impact of age-adjustment factor for utilities, as well as the choice of utility inputs did not lead to a significant change in the ICER. However, the form did change the direction of the decision in terms of the cost-effective treatment.

The change in the discount rate had a significant impact on the ICER, varying between -48,004 to 215,991 €/QALY when a discount of 0% and 6% was applied, respectively. This indicates that a big proportion of the benefits from Onasemnogene Abeparvovec occur over the longer term. This conclusion is also confirmed by the scenarios which explored the impact of using a shorter time horizon.

One assumption that had a large impact on the results was the assumption that patients in SMA0 would discontinue Nusinersen after the 6th dose. When this assumption was relaxed and it was assumed that patients in SMA0 would still continue treatment with Nusinersen, the ICER was reduced significantly down to 13,107 €/QALY. Although this scenario has a large impact on the results, it is not an unreasonable scenario, as in real world, patients may still continue treatment with Nusinersen for a period of time regardless of whether improvement has been observed within the first year of treatment.

When the assumption that patients could move from SMA1 to the SMA0 health state was tested, the ICER increased up to 155,275 €/QALY, making Onasemnogene Abeparvovec not a cost-effective option. This assumption has such a large impact on the results because more patients with Nusinersen would move to SMA0 and discontinue treatment, hence reducing significantly the costs of treatment in the Spiranza arm, while not resulting in a significantly different life-expectancy and quality of life (as per the model assumptions).

Table 4. Scenario analyses results

Scenario	ICER (€/QALY)	Cost-effective option
Base case	55,560	Onasemnogene Abeparvovec
Discount rate: 0%	-48,004	Onasemnogene Abeparvovec
Discount rate: 6%	215,991	Nusinersen
Time horizon: 50 years	70,309	Nusinersen
Time horizon: 25 years	130,170	Nusinersen
Utilities sourced from CER report	48,145	Onasemnogene Abeparvovec
Patients can regress from SMA1 to SMA0	155,257	Nusinersen
Utility age-adjustment factor is not applied	55,826	Nusinersen
Nusinersen is assumed to continue in patients with SMA0 until death	13,107	Onasemnogene Abeparvovec

Figure 7. Results of the scenario analyses

5. DISCUSSION

Onasemnogene Abeparvovec (Zolgensma) is the only approved gene therapy for the treatment of spinal muscular atrophy (SMA) and the only SMA treatment designed to directly address the genetic root cause of the disease by replacing the function of the missing or non-working *SMN1* gene to halt disease progression through sustained SMN protein expression with a single, one-time IV infusion. Onasemnogene Abeparvovec is now approved in more than 40 countries and more than 1,800 patients have been treated with Onasemnogene Abeparvovec globally across clinical trials, managed access programs, and in the commercial setting.

Nusinersen is the first and only disease-modifying treatment that confers improvements in both motor function and survival, transforming the course of SMA. Nusinersen has been shown to be a safe and well-tolerated treatment in all studied populations and it is delivered intrathecally by lumbar puncture once every 4 months (following initial loading doses) directly to the cerebrospinal fluid. This allows for obtaining clinical benefit at a lower drug dose with peripheral administration. With its clinical launch, treatment with Nusinersen has become an integral part of the SoC for SMA.

In the present study, a cost-utility study was conducted from a payer perspective to examine the long-term cost-effectiveness of Onasemnogene Abeparvovec versus the Standard of care (Nusinersen) in patients with SMA type l, in Greece. This specific type of SMA patients is the one that is in danger of permanent ventilation and death. Permanent ventilation once implemented is almost always irreversible leading to a lower quality of life for those patients and in all cases leading to inevitably death. The cost per QALY was estimated to be € 55.560 for SMA type l patients.

In the probabilistic analysis, uncertainty was not captured in mortality estimates, which can be considered the drivers of the results.

Although economic evaluation methods are becoming more established internationally, doubts have been raised about their use in drugs for rare diseases. Most of the orphan drugs appraised to date have cost-effectiveness thresholds well in excess of the 'accepted' level and would not be reimbursed according to conventional criteria. McCabe et al.[24] reported that this is not an

argument for treating orphan drugs any differently from pharmaceuticals in general and question whether there should be any premium for rarity. On the other hand, Drummond et al.[25] argue that there may be more to assessing the social value of health technologies than the estimation of the incremental cost-effectiveness ratio. However, it's clear that most orphan drugs are for serious disease, for which other treatments may not be available. Orphan drugs also tend to be expensive on a per patient basis, but have limited impact on the health care budget as a whole, as there are so few patients with these health conditions[26].

Despite the results showing Zolgensma is cost-effective, the highest range of the willingness to pay threshold was used which equals 3x the GDP. This may overestimate the willingness to pay threshold in Greece. However, the WTP threshold for an orphan drug indicated for a very young patient population may be even higher. Currently, there is none willingness-to-pay threshold for orphan drugs to be used in Greece. Wider considerations of disease and treatment experiences from a multi-stakeholder standpoint are strongly needed, balanced with the societal desire for fairness and equity in the healthcare system. Orphan drugs have unique circumstances specific to each disease such as small study population, quantification of quality of life benefit, rarely measured spillover effects in families and burden of illness. Hence, assessing the incremental value of orphan drugs under any conventionally used cost-effectiveness threshold is challenging. Probably, the ICERs should not attempt to set national thresholds for the assessment of orphan drugs, instead focus on serving as an advisor that facilitates robust dialogues around the evidence to inform decision-makers.

Due to the nature of economic models, the present one inevitably has some limitations. First, it was assumed that the clinical and utility data for SMA sourced from the literature were applicable to the Greek health care setting. The use of these data may be questionable, however given the lack of local related data, this choice was the only source of relevant data. Furthermore, due to paucity of local data related to the resource utilization of patients with SMA type 1, the cost of disease management for each type of SMA was retrieved from literature. [70] This may raise concerns about the subjectivity of model inputs and leave space for challenging the study results. Last but not least, the current analysis was conducted from the third-party payer perspective of payer and, as such, only direct medical costs were considered. However, an analysis from a broader (societal) perspective may be worthwhile, since direct non-medical cost such as informal care, travel expenses, cost for legal advice, constructional modifications, and indirect costs such as lost

productivity of patients/parents are shown to be significant and essential to reflect thoroughly the economic burden of SMA for society [23]. In particular, Klug et al. [23]study results indicated that both these cost categories summed up to an annual cost of €54,100 (50.18% of total cost) per patient with SMA type l.

5.1 Model Assumptions & Limitations

A few assumptions had to be made to conduct the analysis that can be considered limitations:

- It was assumed that when patients' severity improved after treatment, they have the same survival as patients born with the corresponding SMA-type. This assumption was made to avoid modelling the first few months of patients' life as transitions between health states in this period are not known, but only the distribution of patients' severity at the end of the trial follow-up is known.

- One of the strongest assumptions was that patients remain in the same health state that they were at the end of the trial follow-up, for the rest of their lifetime. This extrapolation assumption was made as there are currently no long-term evidence showing how the disease severity of patients treated with Onasemnogene Abeparvovec and Nusinersen progress over time.

- It was assumed that after treatment, patients' condition cannot worsen, hence needing permanent ventilation. Although this is a strong assumption, in the clinical trials, no treated patients that responded to treatment required ventilation.

The results of this paper show that there is some uncertainty about whether Zolgesma is cost effective. This is because, we have to take into account that there are other parameters. The main one is the high unmet medical need of SMA. We also need to consider the ethical issues of not providing an effective treatment. Lastly, SMA is a rare disease and afflicts the pediatric population.

- Despite the results showing Onasemnogene Abeparvovec is cost-effective, the highest range of the willingness to pay threshold was used which equals 3x the GDP. This may overestimate the willingness to pay threshold in Greece. If a smaller willingness to pay threshold was used, then Onasemnogene Abeparvovec would **not** be a cost-effective option.
- The treatment effect is captured in a static manner by assuming that patients do not transition between health states overtime.
- The model was informed based on a targeted search of evidence. However, a more systematic approach to identifying and collecting evidence should be followed.

6. CONSLUSION

One should further note that the significance of both Zolgenmsa and Nusinersen provision for the national healthcare system is not just a matter of additional costs per QALY gained. Although the demand for health care is low here given that SMA disease is rare, managing the symptoms of SMA without drug intervention until Nusinersen became the SoC, was generally supportive and often required a large and costly amount of healthcare resources. The main issue here, is that both treatments are expensive considered that none of them is cure for SMA, and that relapses to previous states are possible even while treated. Apart from that, Onasemnogene Abeparvovec's one off administration with a lifelong efficacy expectation, and the demand of 100% reimbursement upfront, makes it critical, as caregivers might demand the additional treatment with SoC in case of relapse, maximizing the cost of the disease management. On the other hand, Nusinersen, administered every 4 months is considered easier to manage on terms of cost as it can be stopped, after annual patients' assessment. Further to that, SMA is a leading genetic cause of infant mortality challenging not only patients but also their families and caregivers, as well as medical personnel and the society. The high unmet medical need for effective treatment management of disease was tapered off with the approval of Nusinersen which transformed the course of SMA conferring improvements in both motor function and survival of patients. Whether Greek society is willing to pay more for novel treatments of rare disorders than for more prevalent diseases is uncertain. Nevertheless, the present study results suggest that the breakthrough targeted SMA therapy of Onasemnogene Abeparvovec offers significant health gains in terms of LY and QALYs compared to Nusinersen covering unmet medical need of Greek patients.

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