EUnetHTA Joint Action 3 WP5 Strand B:

Post-launch evidence generation (PLEG) and registries

EUnetHTA WP5B PLEG Pilot on Nusinersen (Spinraza®)

Minimum data set report

July 2020

This document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020).

DOCUMENT HISTORY AND CONTRIBUTORS

Version number	Date	Description
V1	08/05/2020	1st draft
V2	27/05/2020	2nd draft
V3	11/06/2020	Minor changes to the text
V4	09/07/2020	Final version integrating comments from pilot team members

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Conflict of interest
All participants involved in the production of this pilot have declared they have no conflicts of interest in relation to the technology assessed, according to the EUnetHTA declaration of interest and confidentiality undertaking form.

Stakeholder involvement
The company in charge of the development of the product has been contacted at the beginning of the pilot and kept informed about different pilot steps and outputs. No other stakeholders have been involved on pilot level at the stage of the production of this report.

How to cite this document
Please cite this document as follows:

EUnetHTA PLEG_FP_01. Pilot Team. PLEG pilot on Nusinersen (Spinraza). Minimum data set report. Diemen (The Netherlands): EUnetHTA; 2020. [Date of citation]. Report No.: PLEG_FP_01. Available from: https://www.eunethta.eu

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SYNOPSIS

This study is conducted in the framework WP5B PLEG product-specific pilot on Spinraza®. For more details on the pilot and its different steps, please see the **Common Evidence Gaps report.**

The present report corresponds to step 5 of the pilot, which consists of agreeing on the common data set for RWD collection for this drug and specifying research methods.

STUDY BACKGROUND

- SMA is an autosomal recessive neuromuscular serious, debilitating, and life-threatening rare disease, with a global incidence of 8.5 to 10.3 per 100,000 live births characterised by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. SMA is the most common genetic disorder linked to infant death worldwide.

- SMA has been categorised into Types 0, I, II, III, and IV which range in severity from babies who are born with severe impairment and die within weeks of birth (Type 0), to disease which manifests in adult life with proximal muscle weakness (Type IV). The most common variants (Types I, II and III) all present with a pre-symptomatic period and can be classified prospectively based on age of symptom onset and SMN2 gene copy number as infantile-onset and later-onset.

- At the time of launch of this pilot, with the exception of Nusinersen (Spinraza®), there were no therapies approved in Europe for the treatment of SMA and medical care was only supportive, focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis via bracing, physical therapy, and surgery[1]. Therefore, a significant unmet clinical need exists for these patients.

- Spinraza® is an antisense oligonucleotide (ASO) which represents the first disease-modifying agent in SMA, increasing the levels of SMN2 protein and therefore improving the motor function.

- Summary of the available literature (evidence) on the health technology as identified by pilot members: **Please see Table 3 of the Common Evidence Gaps report.**

RATIONALE OF THE STUDY

This pilot was proposed by the Italian Medicines Agency (AIFA), considering the uncertainties noticed during the national HTA. The proposal was supported by the following considerations:

- The collection of data such as patients' number and characteristics, treatment duration, and main

[1] In January 2020 the US Food and Drug Administration has authorized Zolgensma®, a gene therapy, for the treatment of pediatric patients aged <2 years with spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (*SMN1*) gene (the first registration in Europe is expected to follow).
On 26 March 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Zolgensma, intended for the treatment of babies and young children who have a rare, serious inherited condition called spinal muscular atrophy (SMA)."

outcome measures will greatly support the decision-making process for pricing and reimbursement, and for subsequent re-assessments.

- In the setting of a rare disease, collaboration among Member States in the definition of a minimum dataset, and in gathering the evidence coming from different registries and databases is crucial for HTA purposes.

The main objectives of this pilot are therefore as follow:

- To build a common and agreed dataset for data collection (which will serve as a basis for common analysis afterwards).
- To gather generated data (when possible), from different sources (databases, registries, health care records); and
- To assess possible levels of cross-border collaboration on the generation and exchange of real world data (RWD).

The present report corresponds to step 5 of the pilot, which consists of agreeing on the common data set for RWD collection for this drug and specifying research methods. This common data set will reflect the basis of RWD collection individually set up on a national level by pilot team members.

RESEARCH QUESTION

As presented in the Common Evidence Gaps report, most team members identified a need for the following further research:

- Full descriptive analysis considering patient characteristics at baseline by different SMA types (e.g., age at diagnosis, motor function at treatment initiation, etc.);
- Collection of data on long-term effects for all SMA types and on robust endpoints, as well as for less-studied subpopulations (e.g., SMA types IV and 0);
- Long-term safety data including reasons for discontinuation;
- Data on quality of life and other patient-reported outcomes;
- Data on treatment duration and sequence and the most appropriate dose to be used for different patient groups;
- Data on the number of patients treated; and
- Validation of new outcome measures for disease progression.

These research recommendations reported according to the PICO scheme are reported in detail in the Table 4 of the **Common Evidence Gaps report**.

The pilot members reported all research recommendations as raised in their national assessment regardless the setting of the collection of data (real world setting or clinical studies).
The following chapter, dealing with the definition of research methods and study outcomes (common dataset), specifies the parameters to be analysed in the real world setting.

RESEARCH METHODS

Study design

This a prospective and retrospective[2], longitudinal, descriptive study based on data from Nusinersen registries monitoring treatment of the SMA 1, 2, and 3 populations.

Study population

Patients from six European countries, with a genetic documentation of 5q SMA (homozygous deletion, mutation, or compound heterozygosis in SMN1) of type 1,2 or 3 with a maximum of 4 SMN2 gene copies. No age limit is in place.

Intervention and comparator

Intervention: Nusinersen (Spinraza)
The recommended dosage is 12 mg (5 ml) per administration. 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter.
Duration of treatment:
The need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to the therapy.
Comparator: 1. basal characteristics*[3]

Study outcomes and variables to be collected (minimum data set)

Motor Function:

- Total CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) Score (Mean, Median, IQR)
- Total HINE-2 (Hammersmith Infant Neurological Examination) Score (Mean, Median, IQR)
- Total HFMSE (Hammersmith Functional Motor Scale – Expanded) Score (Mean, Median, IQR)
- Total RULM (Revised Upper Limb Module) Score
- 6 MWT (METERS)

Need for respiratory support
Type of ventilation
Length of ventilation
Need for feeding support
Disease Characteristics

- Ability to sit
- Ability to stand
- Ability to walk

Lumbar puncture administration failure
Frequency of dosing
Serious Adverse Events
Reasons for stopping

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[2] Depending on the date of the implementation of national data collections in each country (see also Setting, duration and follow-up). Of note, national HTAs were performed at different time points after centralised marketing authorisation approval (See Common Evidence Gaps report for more details). These different timings also had an impact on the implementation of national data collections among pilot members.

[3] There are different issues regarding the comparison with Zolgensma for the timing of this study. The first issue is related to the time gap between the two medicines which could lead to compare and multivariate analysis may not be able to correct it.
Considering only patients treated from the moment in which both medicines are available, there would be a problem of patients numbers which would affect the follow-up period to be guaranteed for the study (which should be much longer for the subgroup analysis).
Furthermore, at the moment of the production of this report, it is not obvious that a new register will be foreseen on the new medicine and that the dataset of the register of the new medicine will be comparable to that of Spinraza. .
Any comparison with Zolgensma should be therefore considered in a separate new study.

- Severe Adverse Event
- Mortality
- Disease progression
- Other

Hospitalisation

- Patients requiring hospitalisation (%)
- Length of hospitalisation
- Reason for hospitalisation

Quality of life

Outcomes will be measured at baseline and at 6 and 18 months.

These outcomes will be collected in data sets as presented in the following table.

Basal Characteristics (all types)	Basal Characteristics (by type)	Follow up 6M-18M (by type)
Patients	**Patients**	**Patients**
Age (Median; IQR)	Age (Median; IQR)	Age (Median; IQR)
Age Class	**Age Class**	**Age Class**
0-6 months	0-6 months	0-6 months
7-12 months	7-12 months	7-12 months
13-18 months	13-18 months	13-18 months
19-24 months	19-24 months	19-24 months
>2 years-5 years	>2 years-5 years	>2 years-5 years
6-12 years	6-12 years	6-12 years
>12-30 years	>12-30 years	>12-30 years
30-65 years	31-≥65 years	30-65 years
Gender	**Gender**	**Gender**
Male	Male	Male
Female	Female	Female
SMA Type	**Genetic test**	**Total CHOP INTEND Score (Mean, Median, IQR)**
0	5q (SMN 1 MUTATION)	(Mean, Median, IQR)
I	SMN2 copies	**Total HINE-2 Score (Mean, Median, IQR)**
II	0	(Mean, Median, IQR)
III	1	**Total HFMSE Score (Mean, Median, IQR)**
IV	2	(Mean, Median, IQR)
Genetic test	3	**Total RULM Score**
5q (SMN 1 MUTATION)	4	(Mean, Median, IQR)
SMN2 copies	>4	**6 MWT (METERS)**
0	**Age at first dose (months)**	(Mean, Median, IQR)
1	Median; IQR	**Need for respiratory support**
2	**Age at diagnosis**	**Type of ventilation**
3	Median; IQR	**Lenght of ventilation**
4	**Age at symptom onset**	**Need for feeding support**
>4	Median; IQR	**Lumbar puncture administration failure**
Age at first dose (MONTHS)	**Disease duration**	**If different from authorised, please add the dosage**
Median; IQR	Median; IQR	**Frequency of dosing**
Age at diagnosis	**Total CHOP INTEND Score**	(Mean, Median, IQR)
Median; IQR	(Mean, Median, IQR)	**SAE**
Age at symptom onset	**Total HINE-2 Score**	**Disease Characterisitcs**
Median; IQR	(Mean, Median, IQR)	Ability to sit
Disease duration	**Total HFMSE Score**	Ability to stand
Median; IQR	(Mean, Median, IQR)	Ability to walk
Total CHOP INTEND Score	**Total RULM Score**	**Reason for stopping**
(Mean, Median, IQR)	(Mean, Median, IQR)	Severe Adverse Event
Total HINE-2 Score	**6 MWT (METERS)**	Mortality
(Mean, Median, IQR)	(Mean, Median, IQR)	Disease progression
Total RULM Score	**Disease Characterisitcs**	Other
(Mean, Median, IQR)	Ability to sit	**Hospitalisation (%)**
6 MWT (METERS)	Ability to stand	**Duration of hospitalisation**
(Mean, Median, IQR)	Ability to walk	(Mean, Median, IQR)
Total HFMSE Score	**Need for respiratory support**	**Reason for hospitalisation**
(Mean, Median, IQR)	**Type of ventilation**	**Quality of life**
Disease Characterisitcs	**Lenght of ventilation**	SF-36
Ability to sit	**Need for feeding support**	eq-5d-5l
Ability to stand	**Quality of life**	PedsQL
Ability to walk	SF-36	
Need for respiratory support	eq-5d-5l	
Type of ventilation	PedsQL	
Lenght of ventilation		
Need for feeding support		
Scoliosis/spinal fusion surgery		
Quality of life		
SF-36		
eq-5d-5l		
PedsQL		

STATISTICAL ASPECTS

Sample size calculation

All patients from National registries with 5q SMA type 1,2 or 3 who were prescribed nusinersen.

Statistical analysis

All eligible subjects will be included in the analysis. Changes in the mean score will be calculated to assess motor function outcomes.
Subgroups will be defined considering:

1. Type of disease (1,2 or 3)
2. Number of SMN2 gene copies (0-4)
3. Disease characteristics at baseline as binomial variables (YES/NO):

    a) Ability to sit without support
    b) Ability to walk
    c) Presence of respiratory complications

Outcome based subgroup analyses will be performed using multiple linear regression for numerical outcomes or logistic regression for categorical outcomes, stratifying for demographic characteristics and adjusting to account for the above clinical subgroups. Categorical outcomes might include the number of responders. Responders will be defined according to the criteria reported in N Engl J Med. 2017 Nov 2;377(18):1723-1732 and N Engl J Med. 2018 Feb 15;378(7):625-635

Time to end of treatment for any cause (death, disease progression, unacceptable toxicities, loss to follow up or other) will be investigated by Kaplan-Meier survival analysis. Ongoing patients will be censored at the date of their last recorded prescription or visit (which is the latest).

Treatments for which no data will be available for 120 days since their last prescription or visit will be considered at all means as interrupted and accounted as events in the time to end of treatment analysis.
A p-value of 0.05 will be considered as statistically significant.

SETTING, DURATION AND FOLLOW-UP

All Patients from six European countries, with no age limits and a genetic documentation of 5q SMA (a homozygous deletion, mutation, or compound heterozygote in SMN1) of type 1,2 or 3 who were prescribed Nusinersen through national registries, since the implementation of the registry will be included.

For those registries that will be implemented prospectively, it is recommended to plan the set up of the data collection according to the standards presented in the EUnetHTA REQueST tool[4].

Outcomes will be measured at baseline and at 6 and 18 months.

Since the first enrolled patients, a minimum observation period of at least 36 months is targeted (16 months for enrolling and at least 20 months to record follow up data). At each follow up motor function will be measured using at least one of the following scores: CHOP INTEND, HINE-2, HFMSE, RULM or 6MWT.

[4] https://eunethta.eu/request-tool/

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