Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1589 - Prognostic value of the number of copies of the survival of motor neurone 2 (SMN2) gene for the severity of spinal muscular atrophy to determine eligibility for nusinersen in pre-symptomatic patients.

Applicant: **Biogen Australia Pty Ltd**

Date of MSAC consideration: **MSAC 76th Meeting, 1-2 August 2019**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

This codependent technology submission requested consideration of an extension to the current PBS listing for nusinersen to include the treatment of patients who are genetically diagnosed with spinal muscular atrophy (SMA) (survival motor neuron 1 (*SMN1*) gene deletion or mutation) with an *SMN2* copy number of 1, 2 or 3 prior to the onset of symptoms (referred to as 'pre-symptomatic SMA' hereafter).

2. MSAC's advice to the Minister

MSAC advised the Minister and PBAC on the consequences of different prognostic options for further investigation of young patients with pre-symptomatic spinal muscular atrophy. It also advised on the basis for determining the likely proportions of these patients who would be suitable for nusinersen depending on the option selected, and the proportions who would potentially receive nusinersen unnecessarily.

Consumer summary
This application is 'codependent' because it is linked to the Biogen Australia Pty Ltd submission to the Pharmaceutical Benefits Advisory Committee (PBAC) for a medicine called nusinersen. The PBAC sought advice about the clinical performance of copy number testing for *SMN2*, which is a genetic test to help predict the future severity of spinal muscular atrophy (SMA) in infants or young children. Nusinersen would then be given to these children before they develop any symptoms of SMA (called pre-symptomatic treatment). The application argues that if children start on lifelong treatment with nusinersen as early as possible – and before symptoms are observed, their SMA symptoms will be slower to develop and they will have a better quality of life. SMA is a rare disease. Patients with SMA typically develop weak muscles, and may have trouble walking and breathing. SMA can be very different for different patients. The

Consumer summary

diagnosis of SMA is usually made in infants and young children by clinical observations of their development, followed by genetic testing.

The severity of SMA is partially influenced by the number of copies of a gene called *SMN2* the patient has. The test proposed is for determining the number of copies of *SMN2* an infant has before any symptoms develop, as a way to predict how severe their SMA may be in the future. However, it is possible that these tests would produce false positives (i.e. the test indicates that the child has severe SMA when they do not) and false negatives (i.e. the test indicates that the child does not have severe SMA when they do). This means that some children who don't need it will receive lifelong treatment with nusinersen, and some children who do need it won't be treated until their symptoms show the severity of their SMA. Once a patient commences lifelong nusinersen treatment before the onset of symptoms, there is no method to subsequently determine whether the patient really needed treatment or not.

MSAC's recommendation to the Commonwealth Health Minister

MSAC accepted that *SMN2* copy number can predict, to an extent, how severe the SMA may become. Based on the evidence and analyses provided, MSAC considered that infants with one or two copies of *SMN2* were more likely to develop more severe SMA than infants with three or more copies of *SMN2*. However, MSAC accepted that the correlation between *SMN2* copy number and disease severity was not perfect, and that more data would be helpful. MSAC accepted that the false positive and false negative proportions were quite low, but did not know for sure how many there might be without further information. MSAC therefore advised that patients with pre-symptomatic SMA and one or two copies of *SMN2* could be considered suitable for nusinersen, whereas patients with pre-symptomatic SMA and three copies of *SMN2* should be tested further to confirm suitability for nusinersen.

3. Summary of consideration and rationale for MSAC's advice

Nusinersen is currently approved for use in symptomatic patients with spinal muscular atrophy (SMA). This application proposes using nusinersen in pre-symptomatic patients based on the predicted severity of the disease according to the number of *SMN2* gene copies.

MSAC considered the studies presented to inform distribution of *SMN2* copy numbers in each phenotype, and the respective false positive and false negative proportions. It agreed that the most relevant data come from the studies that reported SMA Types IIIa and IIIb separately (Tables 2 and 3). However, including all available studies provided similar results, and varying the basis for estimating the distribution of phenotypes across SMA types also provided similar results. However MSAC advised that using PBS data (i.e. from symptomatic children receiving nusinersen) for estimating the distribution of phenotypes across SMA types in a sensitivity analysis was an unreliable basis for these calculations, as this dataset was subject to survivor bias (overestimating PBS-eligible milder disease given most children starting treatment were older than 5 years of age, and underestimating PBS-eligible severe disease given some patients with Type I might have already died). This dataset also did not include any children with Types IIIb or IV SMA who would not be PBS-eligible (i.e. only Types I–IIIa were included).

MSAC considered that *SMN2* copy number variation does offer some prognostic value – that is, more copies of *SMN2* generally results in less severe SMA, and vice versa. Based on

several studies, MSAC noted that infants with three copies of *SMN2* resulted in infants developing all types of SMA, from Type I (most severe) to Type IV (least severe), with most developing Type II. However, infants with two copies of *SMN2* usually developed Type I SMA, with much fewer developing Type II or Type III disease. Infants with one copy of *SMN2* almost always developed Type I SMA. Thus, MSAC considered that the prognostic value was more reliable for infants with ≤2 copies of *SMN2* compared with ≤3 copies. However, this correlation between *SMN2* copy number and disease severity appears to be imperfect.

Based on recent data from studies separating Types IIIa and IIIb (Tables 2 and 3), MSAC noted the following proportions of patients eligible for nusinersen based on *SMN2* copy number:

- ≤2 *SMN2* copies: 28.01% of all patients (overall false positive proportion of 0.56%)
- ≤3 *SMN2* copies: 80.99% of all patients (overall false positive proportion of 4.28%).

MSAC advised that patients with pre-symptomatic SMA and one or two copies of *SMN2* could be considered suitable as a prerequisite part of the eligibility criteria for any extended PBS restriction for nusinersen. However, MSAC also advised that patients with pre-symptomatic SMA and three copies of *SMN2* should also undergo clinical assessment and electromyography testing by a neuromuscular specialist to detect any early signs of motor abnormality as a prerequisite part of the eligibility criteria for any extended PBS restriction for nusinersen. The purpose of this would be to reduce some of the negative consequences of the false positive rate estimated above at 4.28% based on *SMN2* copy number alone.

MSAC noted the alternative methods of testing used (multiplex ligation-dependent probe amplification and quantitative polymerase chain reaction) had similar analytic performance. However, neither method detects hybrid *SMN1–SMN2* genes, which may have increased the proportion of false positive patients. Further, although variation in *SMN2* copy number seems to be the dominant source of prognostic value for SMA severity, MSAC advised that there are several other genetic components besides the *SMN2* copy number which also may modify the phenotype to some extent. However, there are limited data available to assess their incremental prognostic value over *SMN2* copy number variation.

MSAC noted that nusinersen appears to be more effective in patients with more *SMN2* copy numbers (i.e. less severe SMA) – for example, in patients with two or three copies of *SMN2*. MSAC considered this to be plausible because nusinersen achieves its pharmacological effect by increasing the function of existing *SMN2* genes. Therefore, MSAC proposed that based on the current evidence, nusinersen could possibly be more effective if a patient with SMA has at least two copies of *SMN2*. Noting that the single-arm study of nusinersen in patients with pre-symptomatic SMA provided as the clinical basis for the submission to the PBAC was limited to patients with two or three copies of *SMN2*.

MSAC noted the trade-off between overtreating false positive patients compared with some delay in starting treatment of patients with false negative results, expecting that pre-symptomatic patients with *SMN2* results not meeting a defined threshold for subsidised nusinersen would be followed up more intensively as a result of the *SMN1*-based genetic diagnosis. MSAC considered the prospect of overtreatment with nusinersen to be a more significant risk to patients. MSAC noted that, in the NURTURE trial, 100% of the patients had adverse events (AEs): 18 were moderate or severe, and 5 were severe. Six of the AEs were related to the lumbar puncture. Nusinersen is administered as an intrathecal bolus injection using a spinal anaesthesia needle. The patient will receive this treatment for life. In addition, once a patient initiates treatment based on *SMN2* copy number alone, overtreatment will never be able to be ascertained.

MSAC noted that newborn screening for SMA is not currently routinely conducted; however, there is at least one state-based pilot study for SMA as part of the Newborn Bloodspot Screening program. A shift from disease-based screening to population-based newborn screening would increase the overall numbers of false-positive results and thus overtreatment to some extent. On the other hand, wider uptake of pre-pregnancy carrier screening, or first trimester screening, may reduce the number of individuals born with SMA. MSAC noted that the general experience with introducing any wider screening program has been that the yield of diagnoses is greater than expected based on estimates generated before the wider screening program. MSAC considered that a review of the results of the ongoing screening trial would be informative, noting that the clinical outcomes for most patients genetically diagnosed with SMA are also likely to be influenced by the treatments they subsequently receive.

MSAC noted that the epidemiology and treatment for SMA are rapidly evolving. New data may modify the prognostic value of *SMN2* copy number. Data are revealing that, for example, genotypically similar siblings do not necessarily have the same phenotypic features, although this is more likely to be the case .MSAC concluded that some of the prognostic conclusions are therefore still immature.

The pre-MSAC response considered the definition of 'escapees' to be asymptomatic patients with fewer than four copies of *SMN2*. However, MSAC considered escapees to be those who are genotypically abnormal but remain phenotypically normal throughout their life. Such patients are separate and distinct from those with Type IV SMA. MSAC advised that there is insufficient evidence on their prevalence to modify the above estimated proportions of pre-symptomatic patients being eligible for nusinersen based on *SMN2* copy number and associated false positive rates.

4. Background

MSAC has not previously considered the genetic test (*SMN2* copy number variation) used to predict the severity of SMA prior to the onset of symptoms. As the genetic test used to determine the eligibility of SMA patients in the pre-symptomatic setting is currently accessed and funded through the State Public Hospital system or paid for privately, the submission did not seek funding of the test on the MBS. As such, the Department of Health had advised the applicant at a pre-submission meeting that this submission did not need to follow the integrated codependent submission pathway and therefore would not need to navigate the pre-MSAC process (e.g. PASC approval of a PICO document would not be required). However, the applicant understood that MSAC would consider the submission in relation to the performance characteristics (analytical and prognostic performance of *SMN2* copy number variation (CNV) testing) of the test in identifying the severity of disease children with pre-symptomatic SMA at its August 2019 meeting.

In current Australian clinical practice, the test to diagnose SMA in the pre-symptomatic setting is limited to individuals suspected to be at risk of SMA. This would include those patients identified by genetic testing with a known family history of SMA or alerted through carrier testing.

Nusinersen is currently reimbursed on the PBS for the treatment of patients (18 years of age and younger) with SMA Types I, II and IIIa with onset of symptoms prior to 3 years of age. Patients who have a genetic diagnosis of SMA (*SMN1* deletion or mutation) in the absence of any symptoms are not currently eligible for treatment with nusinersen until symptoms develop.

5. Prerequisites to implementation of any funding advice

In Australia, genetic testing for SMA assesses homozygous deletion or mutation of the *SMN1* gene and enables determination of *SMN2* copy number. These tests are conducted by an Australian NATA-accredited laboratory in a sequential manner: the test for homozygous deletion or mutation of the *SMN1* gene is conducted first; if this test is positive (for SMA), a second analysis is conducted to determine the *SMN2* copy number (i.e. *SMN2* CNV detection). Both tests are performed on a single specimen using quantitative real-time polymerase chain reaction (qPCR). Genetic testing may be conducted before the development of SMA symptoms. The state-based pilot study of newborn screening test uses two samples of dried whole blood obtained from a heel prick test.

Confirmation of the test for SMA in the pre-symptomatic setting is conducted by a NATA-accredited laboratory such as the Victorian Clinical Genetics Services (VCGS) using a third blood sample following a positive test for *SMN1* deletion or mutation. NATA accredited laboratory testing requires enrolment in an appropriate external quality control program for SMA such as the European Molecular Genetics Quality Network Assessment Program which assesses both the *SMN1* and *SMN2* tests.

6. Proposal for public funding

This codependent submission did not request funding on the MBS for the test for *SMN1* mutation or deletion nor for *SMN2* copy number variation.

7. Summary of public consultation feedback/consumer issues

There was no public consultation details provided by the applicant.

8. Proposed intervention's place in clinical management

The current and proposed clinical management algorithms for nusinersen for treatment of pre-symptomatic SMA are provided in Figure 1 and Figure 2 respectively. The genetic test used to diagnose SMA in the pre-symptomatic setting (*SMN1* testing) is only routinely offered to individuals suspected to be at risk of SMA (e.g. siblings and other relatives of patients diagnosed with SMA). If the test is positive for SMA, another test would then only be conducted to determine *SMN2* copy number status.

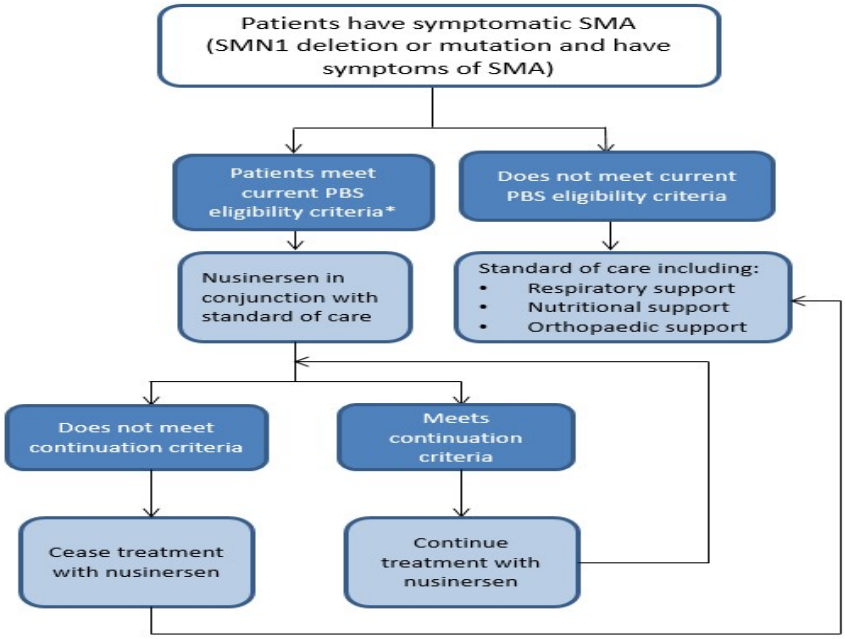

Figure 1: Current clinical management algorithm for patients with symptomatic SMA
Abbreviations: SMA = spinal muscular atrophy; SMN = survival of motor neuron

9. Comparator

The submission nominated standard of care (i.e. no genetic testing and symptomatic treatment with nusinersen upon diagnosis of SMA Types I, II or IIIa and identification of two signs or symptoms of SMA).

The submission stated that the comparator for the genetic test when used in the pre-symptomatic setting is not relevant to this submission as the test is currently accessed and funded through the State Public Hospital System or paid for privately, and the applicant is not seeking funding of the test on the MBS.

10. Comparative safety

N/A (for MSAC assessment).

11. Comparative effectiveness

Prognostic performance of SMN2 *copy number variation testing*
The submission's literature review identified three studies that reported *SMN2* copy number by SMA type: Alias 2011; Arkblad 2009 and Calucho 2018 (systematic review of the correlation between *SMN2* copy number and SMA type in approximately 3,500 SMA patients worldwide). The Critique identified a further 16 publications (n=588) reporting correlations between SMA type and *SMN2* copy number; however including these study results did not affect the results greatly (Critique's amended values provided below).

Based upon these study results, the submission estimated that, in a cohort of 30 incident cases (upper estimate) of SMA identified annually in Australia:

- 22 will be treated earlier (i.e. before the onset of symptoms) than they otherwise would have;
- two would be treated as per the current PBS restriction only once they become symptomatic;
- one would be treated when otherwise they would never have become eligible;
- five would never become eligible either way (Table 1).

Table 1: Proportion of SMA patients eligible for nusinersen with pre-symptomatic initiation of treatment and in current practice based on SMN2 copy number threshold of 3 or less

		Current practice		
		Eligible	Not eligible	All
Pre-symptomatic initiation of treatment	Eligible *Critique's values*	73.80% (True positives) *73.94%*	4.32% (False positives) *4.78%*	78.13% *78.73%*
	Not eligible *Critique's values*	7.64% (False negatives) *7.5%*	14.24% (True negatives) *13.78%*	21.87% *21.27%*
	All	81.44%	18.56%	100.00%

Source: Section 2a of Submission.
Abbreviations: SMA = Spinal Muscular Atrophy, SMN = survival of motor neuron
Critique's amended values italicised

The proportions of overall positives and false positives are dependent on the distribution of SMA sub-types, whether the studies reported results for Type IIIa and IIIb patients separately, and the threshold SMN2 copy number (Table 2 for the requested threshold of 3; Table 3 for the alternative threshold of 2).

Table 2: Proportion of SMA patients eligible for nusinersen with pre-symptomatic initiation of treatment and in current practice based on SMN2 copy number threshold of 3 or less, using studies which only reported different SMA types including IIIa and IIIb

		Current practice		
		Eligible	Not eligible	All
Pre-symptomatic initiation of treatment	Eligible	76.72% (True positives)	4.28% (False positives)	80.99%
	Not eligible	7.76% (False negatives)	11.25% (True negatives)	19.01%
	All	84.48%	15.52%	100.00%

Source: modified from the Critique.
Abbreviations: SMA = Spinal Muscular Atrophy, SMN = survival of motor neuron

Table 3: Proportion of SMA patients eligible for nusinersen with pre-symptomatic initiation of treatment and in current practice based on SMN2 copy number threshold of 2 or less, using studies which only reported different SMA types including IIIa and IIIb

		Current practice		
		Eligible	Not eligible	All
Pre-symptomatic initiation of treatment	Eligible	27.45% (True positives)	0.56% (False positives)	28.01%
	Not eligible	57.03% (False negatives)	14.96% (True negatives)	71.99%
	All	84.48%	15.52%	100.00%

Source: modified from the Critique.
Abbreviations: SMA = Spinal Muscular Atrophy, SMN = survival of motor neuron

The submission considered an *SMN2* copy number ≤3 to be the most appropriate threshold in order to capture the greatest proportion of current PBS patients early whilst minimising the proportion of false positive patients (i.e. 1-PPV) accessing treatment.

Analytical performance of SMN2 *copy number variation testing*
The submission's literature review identified ten studies: three compared quantitative real-time polymerase chain reaction (qPCR) to other existing technologies, three compared multiplex ligation-dependent probe amplification (MLPA) to other technologies, and four compared qPCR and MLPA to each other. qPCR was considered the reference standard as it was the primary method to determine *SMN2* copy number in the NURTURE trial.

The submission stated that both qPCR and MLPA are well established methods for CNV detection and quantitation and have been widely applied to SMA genes including both *SMN1* and *SMN2*. Both qPCR and MLPA methods appear to have a high degree of accuracy with concordant results to other technologies and to each other, with the majority of identified studies (8/10) reporting a concordance rate of 100%. However, the Critique highlighted that none of the studies were conducted prospectively among a group of patients diagnosed with *SMN1* deletion/mutation where copy numbers were to be determined - the proposed use of the test.

12. Economic evaluation

N/A (for MSAC assessment).

13. Financial/budgetary impacts

N/A (for MSAC assessment).

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Prognostic value	Some studies were omitted in the submission. The definition of SMA varied among the studies. The studies likely show a selection bias, in that the full spectrum of disease is not shown in any of them. The potential of genetic modifiers has had limited assessment. The number of *SMN2* gene copies and clinical manifestation varies and there is an imperfect correlation between the number of *SMN2* gene copies and clinical manifestation of the disease.
False positive rate	Rate of false positives depends on the distribution of the SMA subtypes. The differences between the estimates and PBS usage appear to be reasonable. The reported calculations are inconsistent (range from 5% to 10%) and are not agreed to.
Test providers and test accuracy	Two providers in Australia currently use two tests (qPCR and MLPA). The qPCR and MLPA tests used are highly concordant. However, hybrid *SMN1–SMN2* genes may not be detected.
DNA source is inconsistent	Application is not clear as to how the sample for the test is to be sourced. The number of required test samples is also unclear.
Potential modifier genes	To note that other genetic components besides *SMN2* copy number may modify the phenotype, with limited data available.
MBS item not requested; bypassed PASC	States and territories currently fund this test. ESC was asked to provide clinical advice about the performance of copy number testing for *SMN2*.
Screening pilot for newborn	To note that a pilot screening program is underway in some jurisdictions.
Codependency claim	To note that the evidence base for nusinersen is an interim analysis of a trial in progress, and the question for MSAC is not a classic codependent scenario, but an assessment of the extent to which PBAC can rely on *SMN2* copy number as a predictor of the level of SMA severity already defined by PBAC for eligibility to PBS-subsided nusinersen.
Economic model for test	To note the lack of a specific economic evaluation of the test. Repeat testing for confirmation of patients who receive a positive test was not included in the economic or financial estimates. The proposed listing of nusinersen could increase the number of patients being screened for *SMN1* deletions based on the availability of new treatment. Both issues would be relevant for any future economic evaluation of the test. Testing is a small proportion of overall costs of SMA management.

ESC discussion

ESC noted that this codependent submission is unusual in that the applicant is not seeking an MBS item – the test is currently funded by the states and territories. ESC was asked to provide clinical advice about the performance of *SMN2* copy number testing.

ESC noted that this submission is based on interim results from NURTURE, an open-label trial of nusinersen. The applicant has proposed that patients with spinal muscular atrophy (SMA) are candidates for initiation of treatment with nusinersen whilst pre-symptomatic, based on genetic testing showing they have a *SMN2* copy number of 1, 2 or 3. ESC noted the NURTURE trial does not include patients with 1 copy of *SMN2*, although such patients are more likely to be symptomatic at birth or shortly thereafter, and thus already have access to nusinersen once they become eligible under the current PBS restriction.

The applicant proposed a straightforward correlation between the *SMN2* copy number and disease severity: the more copies of *SMN2*, the less severe the disease. However, ESC noted that there is poor correlation between the number of *SMN2* gene copies and clinical manifestation of the disease, as other factors within the *SMN2* gene may modify the phenotype.

ESC noted that some studies had been omitted in the submission, but accepted that adding these studies did not appear to significantly change the distribution of the proportions of patients with SMA type by *SMN2* copy number.

The submission used studies that reported correlations with *SMN2* copy number only among those diagnosed with SMA (i.e. with symptoms). The applicant contended that this is unlikely to change the results. ESC noted that patients with SMA (i.e. the homozygous loss of function of *SMN1*) who are not symptomatic may develop symptoms, and then they will fall into either category captured in the studies. However, such patients may never develop symptoms (i.e. are SMA Type IV patients), so it is important for the studies to include pre-symptomatic patients. ESC considered that including such patients could alter the results.

ESC discussed the importance of the threshold of 3 copies of *SMN2* to receive access to nusinersen. A threshold of 3 copy numbers maximises patient access to nusinersen. Lowering the threshold to 2 copy numbers would decrease the number of patients who can access the drug. However, the NURTURE trial recruited patients with 2–3 copies of *SMN2*, and early data suggest that patients with 3 copy numbers are the ones who may be benefitting from early access to treatment. ESC again noted that the current results are interim and the evidence of clinical benefit of early access to treatment is not confirmed.

ESC noted that other genetic components besides *SMN2* copy number may modify the phenotype. The applicant contended that *SMN2* gene copy number is currently the most biologically understood and accepted disease modifier of SMA. ESC acknowledged that these other genetic components are unproven, but again noted the imperfect correlation between copy number and disease severity.

The Critique stated that the proportion of false positives in the genetic testing is dependent on the distribution of SMA subtypes. ESC noted that there is little information on the distribution of subtypes in Australia, but there are inconsistencies between assumptions in the submission and current treatment data from the PBS. The applicant noted that the PBS restriction limits eligibility for treatment with nusinersen to patients with Type I, II or III SMA who are <3 years old. The applicant estimated a false positive rate of 5.5%. The evaluation assumed that 48% of Type III patients treated on the PBS will be Type IIIa, which leads to a false positive rate of 10%, and which the applicant claims to be inappropriate. ESC

noted that the false positive rate depends on which method is used to calculate it, and there is no indication as to which method is more accurate. ESC also noted the statement that 'the [Victorian Clinical Genetics Services] has conducted approximately 385 confirmatory *SMN1* tests and 119 confirmatory *SMN2* copy number tests. For all the *SMN1* and *SMN2* tests conducted … no false positive or false negative results have been reported'.

ESC noted that there is not enough evidence to accurately determine the false negative rate, but would assume it to be between 5% and 10%. However, other issues with the application include the threshold copy number and the true benefit of early access to treatment.

ESC noted the two tests used to detect *SMN2* copy number are quantitative polymerase chain reaction (qPCR) and multiplex ligation-dependent probe amplification (MLPA), which are highly concordant. ESC accepted the reliability of the testing results, although noted that neither test would be able to detect hybrid *SMN1–SMN2* genes, which could result in an increase of false positive results.

ESC noted the ambiguity around the number of samples required; it is unclear whether two or three are needed. The source of the sample is also not confirmed in the submission.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

Biogen welcomes the MSAC assessment of the application and looks forward to further discussion with the PBAC on the appropriate path forward.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website