FINOSE joint assessment report of Libmeldy – Company response

Orchard Therapeutics thanks the FINOSE initiative for their evaluation of Libmeldy (atidarsagene autotemcel). The Company welcomes the acknowledgement in the clinical section of the evaluation report that treatment with Libmeldy is associated with improvement in survival for late infantile patients as well as improved motor and cognitive function for all treated MLD subtypes relative to untreated patients.[*] However, Orchard Therapeutics has concerns with some of the conclusions in the health economic section of the evaluation report, which in our view contradicts the conclusions from the clinical section of the report and is out of step with evaluations from other HTA bodies. Specifically, Orchard Therapeutics believes that scenarios 1 and 2 presented by the assessors are based on clinical assumptions which are not supported by the clinical trial data nor reflect the disease mechanisms of MLD and hence are biologically implausible. Hence the consequences of these scenarios underestimates Libmeldy's cost-effectiveness.

Section 1: Concerns with Scenario 1: reclassification of treatment response

This section outlines the concerns that Orchard Therapeutics has with Scenario 1 presented by the FINOSE health economic (HE) assessors as an alternative estimate of Libmeldy's cost-effectiveness. In Scenario 1, patients treated with Libmeldy are reclassified according to decision rules created by the FINOSE HE assessors. Orchard Therapeutics maintains that there are several methodological issues with these decision rules as well as in their implementation, which makes the FINOSE classification an inaccurate representation of the evidence base provided by Orchard.

Issue 1: The decision rules proposed by the FINOSE team *may not* have been clinically validated by clinical experts.

The evaluation report does not provide evidence that clinical experts have validated the **decision rules** used by FINOSE HE assessors to classify patients into the three response groups (i) full responders, (ii) stable partial responders and (iii) unstable partial responders. The decision rules proposed by the assessors are such that a patient is classified as a full responder only if they have stable GMFC-MLD score for 30 months (for PS-LI) or 3 years (for PS-EJ) from predicted onset of symptoms; otherwise the patient is classified as an 'unstable partial responder' who will have continued disease progression, albeit at a slower rate than the natural history cohort. The rationale provided for this decision rule was based on the single LI patient who progressed after being stable for 30 months after the expected onset of the disease. While Orchard Therapeutics recognises the assessors right to explore alternative decision rules for their classification, it has three concerns with the approach, in addition to the lack of validation by clinical experts:

Firstly, Orchard Therapeutics disagrees with the view by the FINOSE assessor that the LI patient was stable for 30 months after the expected onset of symptoms as although this patient's GMFC -MLD score was stable, the clinical trial data presented by Orchard show that all other clinical parameters of this patients (including GMFM, MRI, DQp and NCV scores) worsened throughout the follow-up period, indicating that this patient was not stable and, hence the classification as an unstable partial responder by the company.

Secondly, Orchard Therapeutics does not agree with classification of treatment response based solely on GMFC-MLD score, which seems to be the approach used by the FINOSE assessors. Feedback obtained by Orchard from international and local clinical experts indicates that as MLD is a multi-systemic disease, any classification of treatment response has to be based on a holistic assessment of all relevant clinical outcomes (GMFC-MLD, GMFM, DQp and MRI score) and not just based on a single outcome measure (GMFC-MLD score).

Finally, Orchard Therapeutics does not agree with the approach of arbitrarily using data from patients who have progressed throughout the follow-up period post-treatment to generalise the prediction of the disease trajectory of patients who have stabilised over a longer follow-up period. The consequence of this is that patients who stabilised across all clinical outcomes (GMFC, GMFM, MRI and DQp) for over 5-years post treatment are reclassified by FINOSE as unstable partial responders (i.e. have continued disease progression with declining motor and cognitive function).

Issue 2: The application of the decision rules does not appear to be done in a systematic manner

The application of the decision rules does not appear to be done in a systematic manner in that having follow-up data less than 30 months/ 3 years after expected onset of symptoms seems to be sufficient for classifying patients as stable partial responders, but not in classifying patients as full responders. As such the clinical benefits are valued greater for

[*] Page 27 and 28 of the FINOSE joint assessment report.

patients who have developed some minor impairments in their motor function (i.e., GMFC-MLD scores (1 or 2)) post treatment, compared to those patients who have not developed any impairments in their motor function (i.e., stabilised at GMFC-MLD 0) post treatment, despite being followed up over the same follow-up period.

Issue 3: Errors in the application of FINOSE decision rules

The third concern relates to the misapplication of FINOSE's own decision rules. For the PS EJ patients, the FINOSE assessors have re-classified response such that only 20% are full responders and 80% are unstable partial responders. However, the clinical evidence provided to FINOSE shows that 3/5 (60%) of the PS-EJ patients are full responders with at least 4 years of data from the predicted onset of symptoms – thereby fulfilling FINOSE's criteria of at least 3 years follow-up post predicted onset of symptoms. Therefore, even applying FINOSE's criteria for classification of response, the percentage of PS-EJ full responders is significantly greater than the 20%.

Issue 4: The progression modifier used for unstable partial responders was not updated following reclassification of the additional patients

According to the FINOSE assumptions, any patient with less than 3 years of follow-up has been classified as an unstable partial responder (regardless of whether they were in GMFC-MLD 0 and met normal values of all clinical endpoints throughout the follow-up period) and so will have continued disease progression albeit at a slower rate than natural history. In the modelling, the slower rate of progression is generated from 'the progression modifier parameter', which is calculated as the ratio of the difference in the time to transition from each GMFC-MLD health state to the next from the Libmeldy OTL-200 clinical trials and the OSR TIGET natural history data for only those LI and EJ patients that received treatment but continued to progress. Whilst Orchard Therapeutics accepts there can be differences in opinion in the classification of response, it is surprised that the FINOSE HE assessors did not recalculate the progression modifiers after reclassifying a significant proportion of patients from full responders to unstable partial responders. If FINOSE wished to reclassify patients who clearly have no disease progression to be unstable partial responders that progress, then re-computation of the progression modifier parameters should have been performed based on all the GMFC-MLD data for patients classified by FINOSE to be unstable partial responders rather than crudely applying existing progression modifier values. This has an impact of significantly underestimating Libmeldy's treatment benefit.

As a consequence of the four issues discussed above, the FINOSE reclassification of response results in a significant underestimation of Libmeldy's clinical benefits. To illustrate this, the FINOSE model predicts that only 26.2% of the PS-EJ cohort would retain their ability to walk independently (i.e. remain in GMFC-MLD 0 or 1) five years post treatment and 30% would be completely bedridden (i.e. be in GMFC-MLD 5 or 6); whereas the clinical trial results show that 5 years post-treatment, 75% of treated PS-EJ patients were in GMFC-MLD 0 or 1 and 0% were in GMFC-MLD 5 or 6, hence compromising the internal validity of the FINOSE model. Over time, this difference between the FINOSE modelled scenario and clinical trial data adds up to significant underestimation of treatment benefits. In contrast the Orchard model predicts 77% treated patients would be in GMFC-MLD 0 or 1 at 5 years post treatment and 9% in GMFC-MLD 5 or 6, which better aligns with the observed clinical trial data. The same effect is seen in the PS LI cohort (see Table 1 and 2). Consequently, the resulting ICER calculations from Scenario 1 are not appropriate for decision making.

Section 2: Concerns with Scenario 2: 15 years of durability of effect

In Scenario 2, the FINOSE assessors have assumed treatment response lasts for 15 years and then patients will have disease progression at the same rate as natural history patients. Orchard understands that without extensive long-term data (e.g. 30 years) there are always going to be uncertainties when extrapolating data beyond the study duration to a lifetime horizon in the economic modelling, but to definitively cap treatment benefit at 15 years without providing any clinical justification and consequently assume progression to be equivalent to natural history is not supported by the mechanism of action of Libmeldy, whereby the use of a lentiviral vector means that the inserted gene is a permanent part of the cells genome and will be transferred into progeny cells throughout the patients' lifetime - the inserted gene cannot be removed from the genome of the stem cell. Neither is the FINOSE assumption for durability of treatment response supported by the clinical experience of the use of HSCT based treatments in other lysosomal storage disorders where stable engraftment has been demonstrated for up to 30 years and beyond;[1] nor does it reflect the clinical experiences of ex-vivo HSCT gene therapy (Strimvelis) to date which has demonstrated over 20 years durability of effect.[2]

Table 1: Percentage of PS EJ patients in each GMFC-MLD health state from the clinical trial, the Orchard model and the FINOSE Scenario 1 assumption

	GMFC-MLD 0			GMFC-MLD 1			GMFC-MLD 2			GMFC-MLD 3			GMFC-MLD 4			GMFC-MLD 5			GMFC-MLD 6		
	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1
At 1 year post-treatment	100.0% (5)	82.0%	42.3%	0.00% (0)	12.7%	40.6%	0.00% (0)	4.17%	13.4%	0.00% (0)	0.99%	3.17%	0.00% (0)	0.16%	0.50%	0.00% (0)	0.02%	0.06%	0.00% (0)	0.00%	0.00%
At 2 years post-treatment	100.0% (4)%	76.9%	26.2%	0.00% (0)%	10.1%	32.4%	0.00% (0)%	7.18%	23.0%	0.00% (0)	3.81%	12.2%	0.00% (0)	1.43%	4.57%	0.00% (0)	0.49%	1.57%	0.00% (0)	0.02%	0.07%
At 3 years post-treatment	100.0% (3)	75.5%	21.7%	(25.0% (1)	6.24%	20.0%	(0.00% (0)	6.84%	21.9%	0.00% (0)	5.68%	18.2%	0.00% (0)	3.37%	10.8%	0.00% (0)	2.15%	6.89%	0.00% (0)	0.16%	0.52%
At 4 years post-treatment	75.00% (3)	75.1%	20.5%	0.00% (0)	3.51%	11.2%	25.00% (1)	5.19%	16.6%	0.00% (0)	5.87%	18.8%	0.00% (0)	4.77%	15.3%	0.00% (0)	4.91%	15.7%	0.00% (0)	0.57%	1.83%
At 5 years post-treatment	(75..00% (3)	75.0%	20.1%	(0.00% (0)	1.90%	6.1%	(0.00% (0)	3.49%	11.2%	25.00% (1)	4.99%	16.0%	0.00% (0)	5.15%	16.5%	0.00% (0)	8.02%	25.7%	0.00% (0)	1.33%	4.25%

Table 2: Percentage of PS LI patients in each GMFC-MLD health state from the clinical trial, the Orchard model and the FINOSE Scenario 1 assumption

	GMFC-MLD 0			GMFC-MLD 1			GMFC-MLD 2			GMFC-MLD 3			GMFC-MLD 4			GMFC-MLD 5			GMFC-MLD 6		
	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1	Trial Result (n)	Model Result	FINOSE scenario 1
At 1 year post-treatment	46.67% (7)	41.6%	22.1%	13.33% (2)	28.8%	38.4%	33.33% (5)	27.7%	26.5%	6.67% (1)	1.4%	9.8%	0.00% (0)	0.4%	2.7%	0.00% (0)	0.1%	0.5%	0.00% (0)	0.0%	0.0%
At 2 years post-treatment	54.55% (6)	40.0%	20.1%	27.27% (3)	21.2%	28.3%	18.18% (2)	34.0%	18.6%	0.00% (0)	2.1%	14.8%	0.00% (0)	1.5%	10.5%	0.00% (0)	1.0%	6.7%	0.00% (0)	0.14%	1.0%
At 3 years post-treatment	50.00% (4)	40.0%	20.0%	12.50% (1)	20.1%	26.9%	25.00% (2)	33.8%	11.1%	12.50% (1)	1.4%	9.7%	0.00% (0)	1.7%	11.6%	0.00% (0)	2,2%	15.7%	0.00% (0)	0.7%	4.9%
At 4 years post-treatment	50.00% (4)	40.0%	20.0%	12.50% (1)	20.0%	26.7%	25.00% (2)	33.5%	8.1%	0.00% (0)	0.7%	4.7%	12.50% (1)	1.2%	8.3%	0.00% (0)	2.9%	20.5%	0.00% (0)	1.6%	11.1%
At 5 years post-treatment	50.00% (4)	40.0%	20.0%	12.50% (1)	20.0%	26.7%	25.00% (1)	33.4%	7.1%	0.00% (0)	0.3%	2.0%	12.50% (1)	0.7%	4.7%	0.00% (0)	2.9%	20.2%	0.00% (0)	2.5%	17.7%

References

[1] Lum S, Miller W, Jones S, Poulton K, Lee H, Wynn R. Changes in the incidence, patterns and outcomes of graft failure following HSCT for Hurler syndrome. Bone Marrow Transplant 2017; 52(6):846-853.

[2] Periodic benefit risk evaluation report (PBRER) for Strimvelis submitted to EMA on 26 January 2021.