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SLIDES FOR PUBLIC OBSERVERS

Risdiplam for treating spinal muscular atrophy [ID1631]

Chair presentation

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Company: Roche

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Key abbreviations

BSC	Best supportive care	NUS	Nusinersen
BSID-III	Bayley Scales of Infant and Toddler Development	NR	Not reported
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders	OS	Overall survival
EAMS	Early Access to Medicines Scheme	PAS	Patient Access Scheme
EMA	European Medicines Agency	PV	Permanent ventilation
HINE-2	Hammersmith Infant Neurological Examination Module 2	QALY	Quality-adjusted life year
HFMSE	Hammersmith Functional Motor Scale Expanded	RIS	Risdiplam
HRQoL	Health-related quality of life	RULM	Revised Upper Limb Module
ICER	Incremental cost-effectiveness ratio	SE	Standard error
ITQOL-SF47	Infant and Toddler Quality of Life Questionnaire (47 item short form)	SMA	Spinal muscular atrophy
LY	Life years	SMAIS	SMA independence scale
MAA	Managed access agreement	SMN	Survival motor neuron
MAIC	Matched adjusted indirect comparison	T1	Type 1 SMA
MFM32	Motor Function Measure - 32 items	T2/3	Type 2/3 SMA

Risdiplam (Evrysdi, Roche)

Covers pre-symptomatic SMA but no ICERs for this group

Marketing authorisation	MA (MHRA): Treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies
Mechanism of action	Risdiplam is a survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency.
Administration	Risdiplam is taken orally once a day using the re-usable oral syringe provided. The recommended once daily dose of risdiplam is determined by age and body weight. • 2 months to < 2 years of age: 0.20 mg/kg • ≥2 years of age (<20 kg): 0.25 mg/kg • ≥2 years of age (≥20 kg): 5 mg
Price	£7,900 per 60 mg/80 ml vial. Simple PAS discount approved (updated post TE). Annual list price: £240,292 (estimated by tech team, assumes 5 mg dosing based on ≥2 years of age [≥20 kg])

Current treatment pathway for SMA

*Risdiplam was available through EAMS (≥2 months, type 1 or 2 SMA for whom authorised treatments are not suitable)

Confirmation of 5q SMA diagnosis

Multidisciplinary assessment

Symptomatic treatment

Infantile onset type 1 SMA

Later onset type 2 SMA

Later onset type 3 SMA

Treatment options

Nusinersen has MAA (also recommended for pre-symptomatic SMA)

Risdiplam*

Risdiplam*

BSC

Onasemnogene (HST15 recommends for type 1 SMA ≤12 months and pre-symptomatic)

Source: Based on figure 1 in company submission

Note: NUS & Onasemnogene not comparators in this appraisal

Summary of main clinical evidence

SUNFISH trial part 2 (type 2/3 SMA)

Children and young adults with Type 2/3 SMA, not previously treated, non-ambulatory, age 2-25 years

Placebo controlled period 12 -months	24-month follow up (placebo switch to RIS)
Risdiplam (n=120)	Risdiplam (n=120)
Placebo (n=60)	Switch to risdiplam (n=60)

FIREFISH study (type 1 SMA)

Infants with Type 1 SMA with 2 copies of SMN2, not previously treated, not receiving chronic ventilation, age 1-7 months.

24-month follow up (single arm)

Risdiplam (n=41)

Company compare to pre-defined criterion based on natural history findings for type 1 SMA

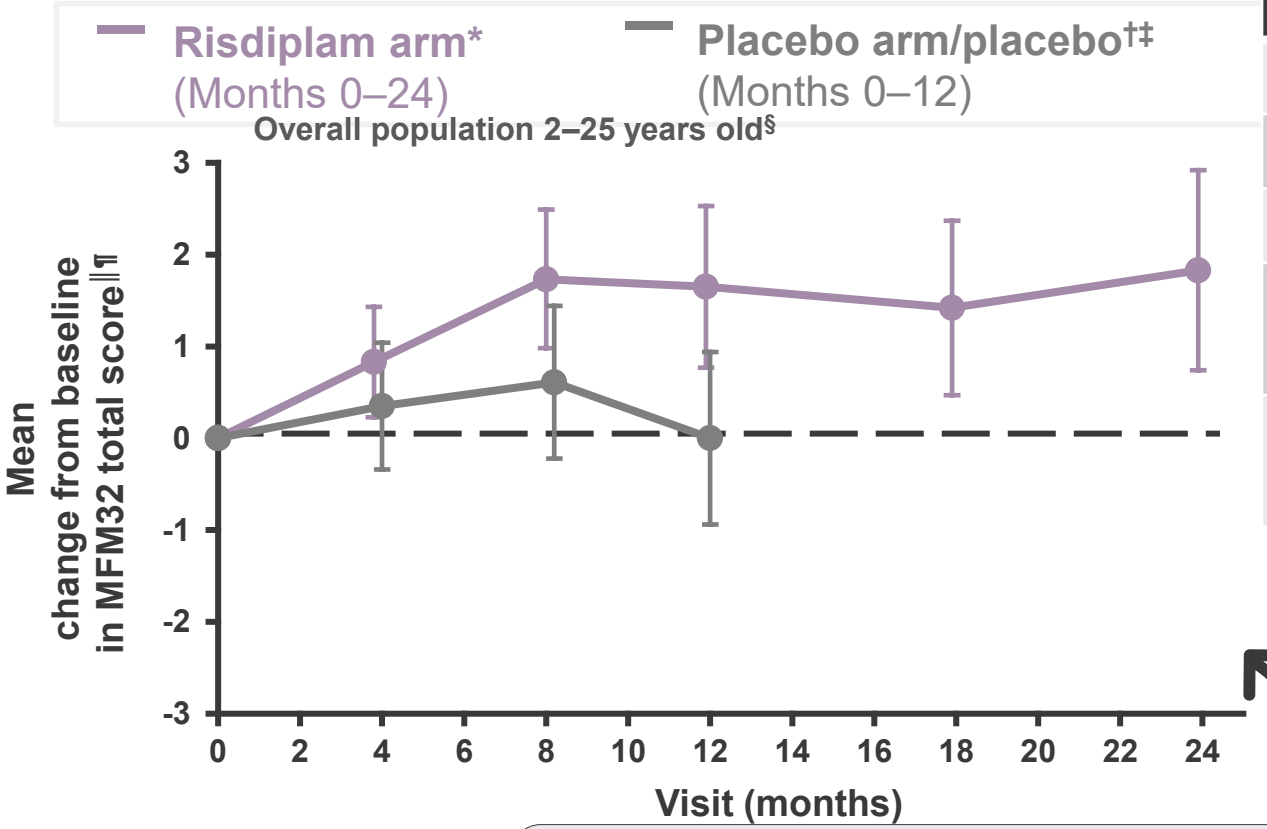
Note: Part 1 was exploratory dose-finding, Part 2 was used to examine the efficacy and safety of the selected dose of risdiplam in each study. Different patients were recruited to Parts 1 and 2 for each study

New evidence

SUNFISH results 24 month – type 2/3 SMA

Higher scores indicate improvement

SUNFISH results → measured least squares mean change from baseline at 24-month follow-up



Outcome	Mean change (SD) RIS arm	
	12-month	24-month
MFM-32	**1.65 (4.70)**	**1.83 (5.59)**
HFMSE	1.81 (3.68)	2.15 (5.28)
RULM	1.91 (3.87)	2.79 (4.38)
Caregiver SMAIS	1.68 (4.95)	2.73 (5.16)
Patient SMAIS	0.95 (3.78)	0.82 (4.83)

Company suggests 24-month data shows stable disease vs. natural history studies that show decline in MFM-32

MFM-32 is primary outcome. 24-month data suggest improvement or stable disease

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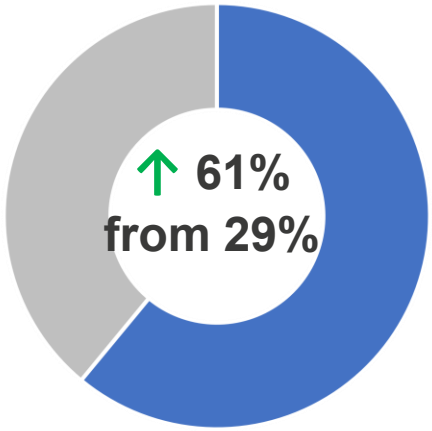
New evidence

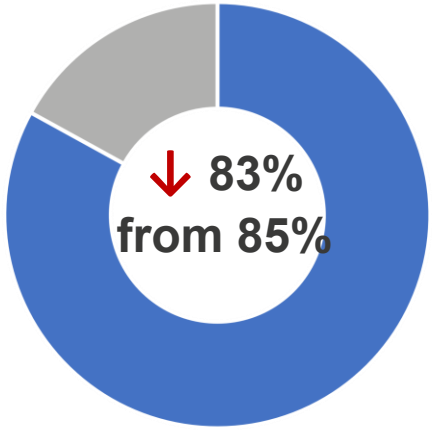
FIREFISH results 24-month – type 1 SMA

FIREFISH results → measured proportions at 24-month follow-up

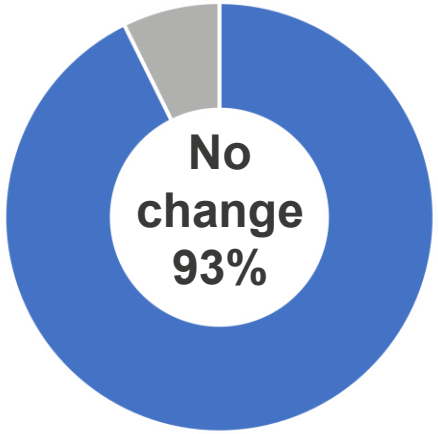
Sitting without support for at least 5 seconds (primary outcome)



Alive without permanent ventilation



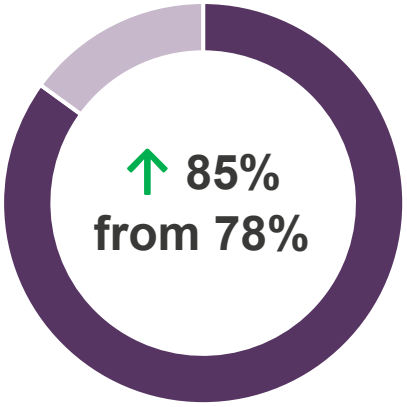
Alive



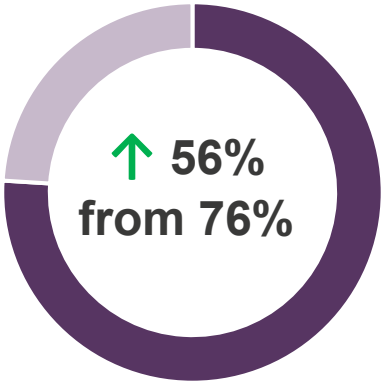
Natural history data not shown

HINE-2 also showed improvements in proportion able to stand with support & bounce. 1 patient progressed to 'cruising' milestone

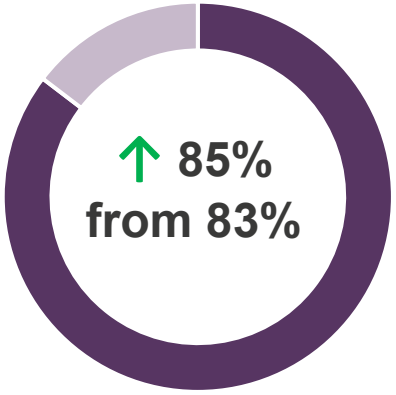
HINE-2 responders



CHOP INTEND score at least 40/64



Ability to feed orally



Company's new interim evidence

- Marketing Authorisation includes pre-symptomatic population but no evidence at ACM 1
- Company would also like committee to consider risdiplam for people who have previously had treatments such as nusinersen but no evidence at ACM 1
- Company present interim evidence from 2 ongoing trials:
  - RAINBOWFISH included patients with pre-symptomatic SMA
  - JEWELFISH included patients previously treated SMA
  - Supplementary evidence from EAMS

New evidence

RAINBOWFISH– pre-symptomatic SMA

RAINBOWFISH results → interim results from 5 patients treated for at least 12 months

Single-arm study. Currently recruiting infants from birth to 6 weeks old (at first dose), regardless of SMN2 copy number

Risdiplam for 24 months → **36-month extension**

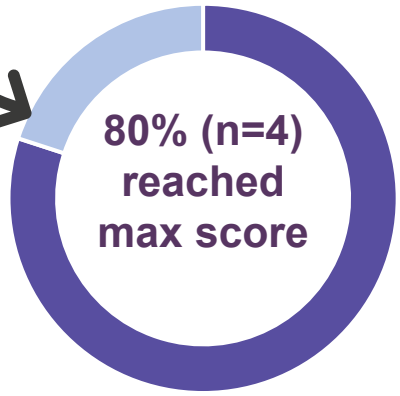
12 mo interim

Of the 5 patients with interim data two have 2 SMN2 copies and three have>2 SMN2 copies

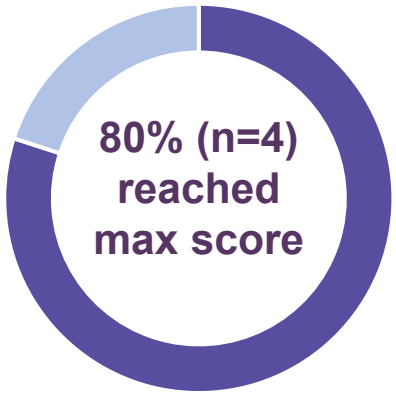
Not started yet

Max CHOP-INTEND score (64) after 12 months

1 patient scored 63/64



Max HINE-2 score (26) after 12 months



Results promising compared with natural history data:

ANCHOVY chart review (n=60, 50% with confirmed SMN2 copy number)

- No patient gained any level of sitting or head control after 9 months of age
- By 12 months, no HINE-2 milestones gained for rolling, voluntary grasp and kicking
- No patients achieved any level of crawling, standing or walking

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ERG: No ICERs for this population

JEWELFISH – previously treated SMA (1/2)

JEWELFISH results → open label study with interim results at 12 months

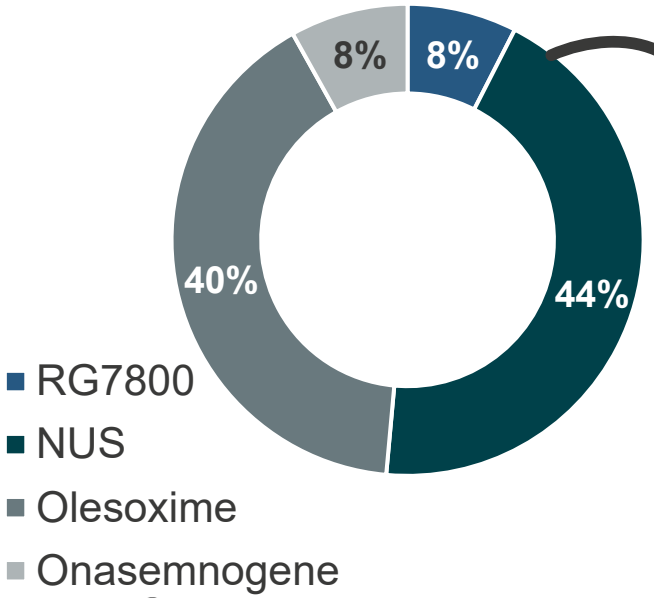
Single-arm study of 174 infants, children & adults (6 months to 60 years) with previously treated SMA

Risdiplam for 24 months → **36-month extension**

Interim 12 mo

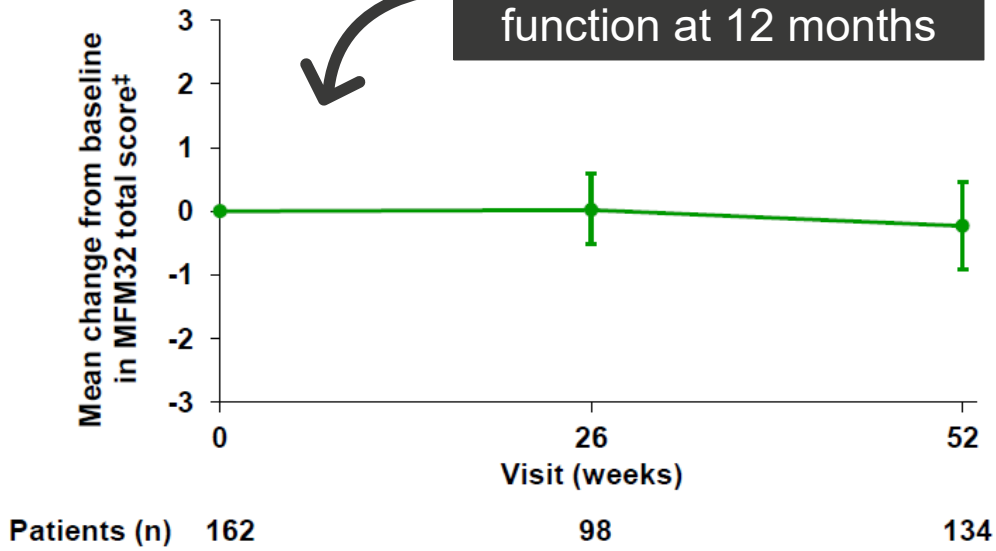
Primary endpoint: Safety & pharmacokinetics
Exploratory endpoint: MFM32

Previous treatments at baseline



Previous NUS (n=76):
- 31% NUS tolerability concerns
- 4 stopped RIS

Stabilisation of motor function at 12 months



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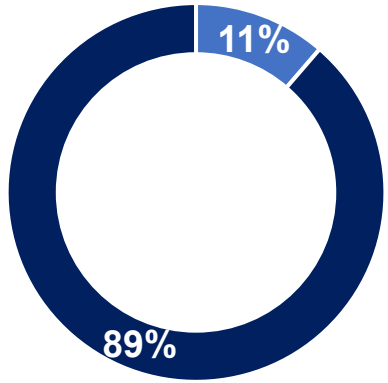
New evidence

EAMS – previously treated SMA (2/2)

EAMS → early access to RIS in 203 patients

Real world evidence of 203 patients with type 1 or type 2 SMA (age range <1 year to 69 years)

SMA type in EAMS



Only 30 (15%) had previous treatment

- Olesoxime (n=3)
- NUS (n=27)

Reasons for switching from NUS:

- scoliosis and spinal surgery impacting the ability to administer
- adverse events
- inability to tolerate NUS or administration

Company

Company consulted clinical experts (6 neurologists & 1 physio)

- Most clinical experience from switching from NUS → still have benefit from RIS
- Intrathecal administration of NUS much more complex than typical intrathecal administration (e.g. oncology)
  - overexposure to x-rays & sedation

ERG: No ICERs for this population

ACD consultation comments

Comments received from company, SMA reach UK, SMAUK & MDUK and 8 web comments. Comments relevant to issues in later slides.

Recs should apply to all patients with SMA: No barriers to access based on type, those excluded from trials should not be excluded from recs → SMA is a continuum with the same endpoint

Innovation & equality: Home delivered treatment will enable access for disabled population & has several advantages over current treatments (costs, travel, invasive procedures). Oral treatment would be life-changing

Treatment switching: If RIS is recommended, all patients having NUS should have opportunity to switch.

Comparator: Most people with SMA now having treatment with disease modifying drugs → concerns over using BSC

EOL: Agree model overestimates OS for BSC → not in line with clinical practice

Timing: time critical decision → some may lose independence before treatment is available

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Key Issues

Model driver

Issue	Company revised base case	Technical team	Questions for committee
New: 24-month data	T1: Updated data for transitions, EFS & OS T2: transitions only	24-month data suggest continued RIS effectiveness	For T1, are new BSC survival predictions clinically plausible?
Caregiver utility (4)	T1: Amended ERG approach → no loss after mean BSC OS + bereavement disutility	Approaches should align for T1 & T2/3	Should caregiver utility be included? If so, how?
Stopping rule (5)	Apply 'proxy' criteria → affects non-sitting health states	Modelled rule not intended to be used in clinical practice	Is company's proposed stopping rule acceptable? Is the proxy applied in the model acceptable?
Utility values: fine motor skills (10) & uncaptured benefit	Include ↑ utility gain for fine motor skills & additional disutility & costs for complications	Uncertainty around net utility values	Are net utility values after accounting for fine motor skills & complications plausible?

Pre-symptomatic & previously treated pop: New interim data but no ICERs → Is it reasonable to include these populations in recs? Note: Trials restricted age (type 1: 1-7 months, type 2: 2-25 years) and FIREFISH also excluded those on chronic ventilation

Company's new model changes

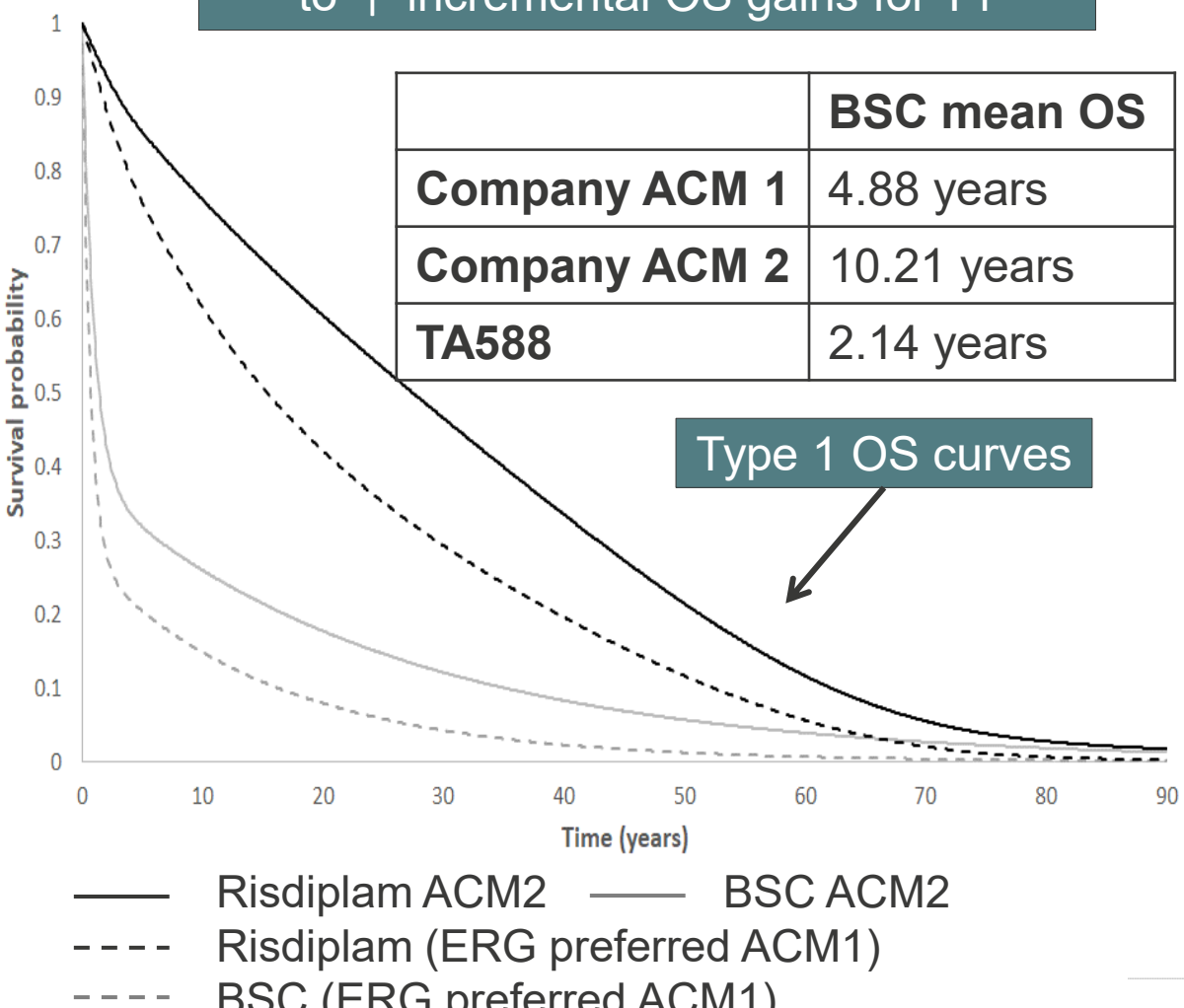
Health state	Caregiver QALYs	Discontinuation rule	Fine motor skills	Complication costs & disutility
Type 1 SMA model (plateau timepoint 66 months)				
Non sitting	3 analyses: (i) Revised base case → disutilities capped at mean BSC OS, (ii) capped in state; (iii) additive approach (ACM1) absolute carer QALYs	Discontinue at plateau (costs stop, no impact on outcomes)	Utility gains added (patients +0.20, carers +0.05)	Disutilities & costs added (100% BSC, 50% risdiplam)
PV			N	
Sitting		N	Utility gains added (patients +0.20, carers +0.05)	N
Standing		N	N	N
Walking		N	N	N
Type 2/3 SMA model (plateau timepoint 26 months)				
Non sitting	Revised base case: ERG carer disutility approach	Discontinue at plateau (costs stop, transitions wane linearly to BSC values over 120 mos, no impact on utility/mortality)	Utility gains added (patients +0.20, carers +0.05)	Disutilities & costs added (100% BSC, 50% risdiplam)
Sitting supported				
Sitting unsupported		N		N
Standing		N	N	N
Walking		N	N	N

T1 SMA only

24-month data – ERG comments

New model with 24-month data predicts ↑ proportion standing or walking & leads to ↑ incremental OS gains for T1

	BSC mean OS
Company ACM 1	4.88 years
Company ACM 2	10.21 years
TA588	2.14 years



ERG

Type 1 SMA

- OS, EFS & transitions updated. Because inverse HR applied to RIS, better RIS data = better BSC data
- Mean OS in BSC arm may not be clinically plausible (ERG scenarios)
- Unclear if patients would progress to independent walking (predicted by model) & length of gains
- Structural assumption for standing to walking differs from old model → no rationale but affects only few patients

Type 2/3 SMA

- Only transitions updated, not OS (external data source used)
- Smaller impact of 24-month data.

? In type 1 model, are new predictions for BSC clinically plausible?

T1 SMA only

Issue 4. Caregiver QALY loss

ACD section 3.13

- Company's additive approach not appropriate
- ERG's approach is consistent with TA588. Accepted logic of ERG's modelling, but did not agree that including carer quality of life would result in fewer QALYs for carers when risdiplam extends survival.
- Welcome alternative approaches

Company

Type 1 SMA

- Revised base case → ERG approach with disutilities capped at mean OS of BSC
  - carer QALY losses for RIS from extending survival have been disregarded from the analysis
- Scenario → QALY losses capped for each individual health state
- Additive approach from ACM1 → absolute carer QALYs

Type 2/3 SMA

- Revised base case → ERG disutility approach (ACM1)

ERG do not consider scenario meaningful & cttee did not consider additive approach appropriate. Only revised base case considered further & this is limited (next slides)

Issue 4. T1 Company base case ERG comments

T1 SMA only

Issue 4. T1 Company base case ERG comments

Extending OS without cure	• Treatments that extend OS for disabled patients with extensive caregiver needs but do not provide full cure will result in additional caregiver burden during additional survival time • Inconsistent to assume disease impacts caregiver to specific timepoint but not beyond
Model	• Cohort-level state transition → no data for pairs of patients with & without RIS so cannot isolate additional extension to life from RIS • Company use mean OS for BSC → would be reasonable estimate of additional extension if all BSC patients had short survival but model predicts 24% still alive after cap. • Company approach should have no impact on QALY losses in BSC arm but this is not the case
Bereavement QALY loss	• Underestimated in both groups → only reflects 1 caregiver (2.2 assumed before cap)
Other TAs	• TA588 uses ERG's disutility approach (no bereavement disutility) • HST 15 onasemnogene → caregiver utility only in scenario
Summary	• Partially including caregiver utility could set precedent for future • Either value caregiver impact fully (including judgement of impact of bereavement) or exclude caregiver effect from model

Should caregiver utility be included? If so, how?

Issue 5. Stopping rule

ACD section 3.11

- Company's rules may not be appropriate
- Would like to see rules based on clinical criteria that have been agreed with clinical and patient experts.

ACD comments

SMA UK & MDUK: TA588 has reviewed stopping rules and new measures have been agreed by clinicians and patient groups. These reflect stabilisation of disease & greater flexibility in use of scales & measurements.

Company

- Agree stopping rule is appropriate but limited by model structure so need to use proxy.
- Apply stopping criteria to certain health states after 26 months (T2/3) or 66 months (T1)
  - in line with assumed treatment plateau as no further improvement expected
  - 16% type 2/3 and 3% type 1 stop treatment in model
- Request that if committee recommends risdiplam with a stopping rule that this aligns with the updated rules for nusinersen.

Issue 5. Stopping rule

ERG

- Company's stopping criteria does not reflect how stopping rule will be applied in clinical practice.
- Strong assumptions in company's approach may not be appropriate:
  - Lower drug costs but no loss of benefit (indefinite ↓ mortality risk, ↓ complications & upper limb function maintained)
  - Affects few T1 but larger impact on ICERs for T2/3

Issue 5. Nusinersen vs. risdiplam

TA588 FAD 3.13 → "…the final versions of the models were structurally unable to accurately reflect the company's proposed stopping rules within their proposed data collection plans"

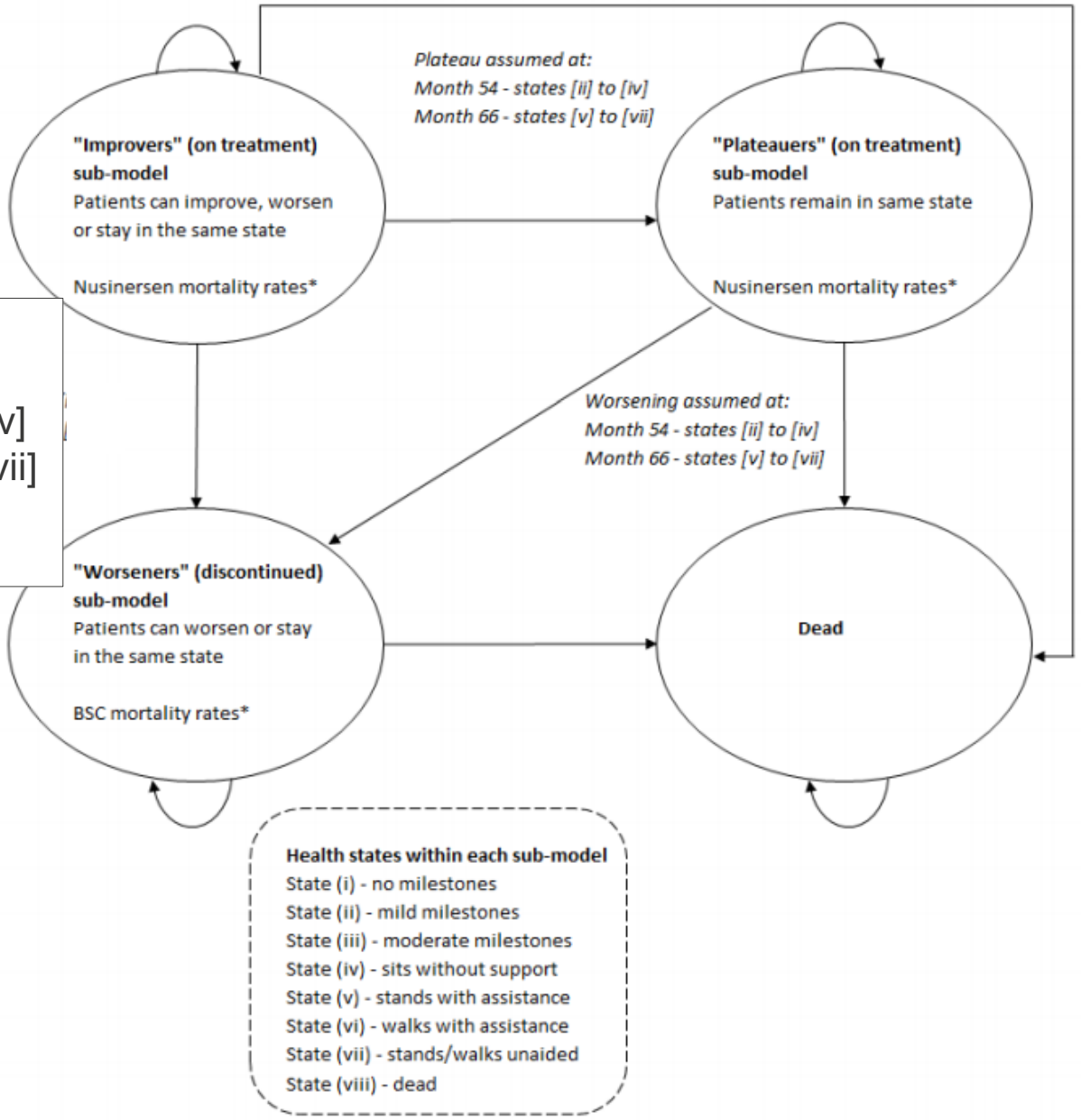
TA588 (from FAD)*	Risdiplam
• permanent ventilation or insertion of permanent tracheostomy • total worsening in motor function scale scores corroborated by 2 consecutive measures (decline of greater than 2 on horizontal kick or 1 on other HINE scores excluding voluntary grasp, decline of greater than 4 points on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale or decline of greater than 3 points on the Revised Hammersmith Scale) • inability to administer nusinersen by intrathecal administration because of spinal fusion surgery • inability to regain ambulation within 12 months of nusinersen initiation in paediatric patients who have lost ambulation in the previous 12 months and who have been initiated on nusinersen • failure, non-compliance (does not have a maintenance dose without rescheduling) or unforeseen worsening of disease.	• Not based on worsening of motor function • Stop treatment: – T1: non-sitting & PV health states after treatment plateau (66 months) – T2/3: non-sitting and supported sitting health states after treatment plateau (26 months)

*** TA588 MAA stopping rules were updated recently to remove bullet 4**

TA588 –Stopping rule in T1 model

TA588 stopping rules couldn't reflect consecutive worsening of motor function in the model

Patients discontinue due to:
No milestone at 13 months – state [i]
Assumed worsening at 54 months – states [ii] to [iv]
Assumed worsening at 66 months – states [v] to [vii]
Scoliosis surgery (non-ambulant) after 12 yrs
Scoliosis surgery (ambulant) after 15 yrs



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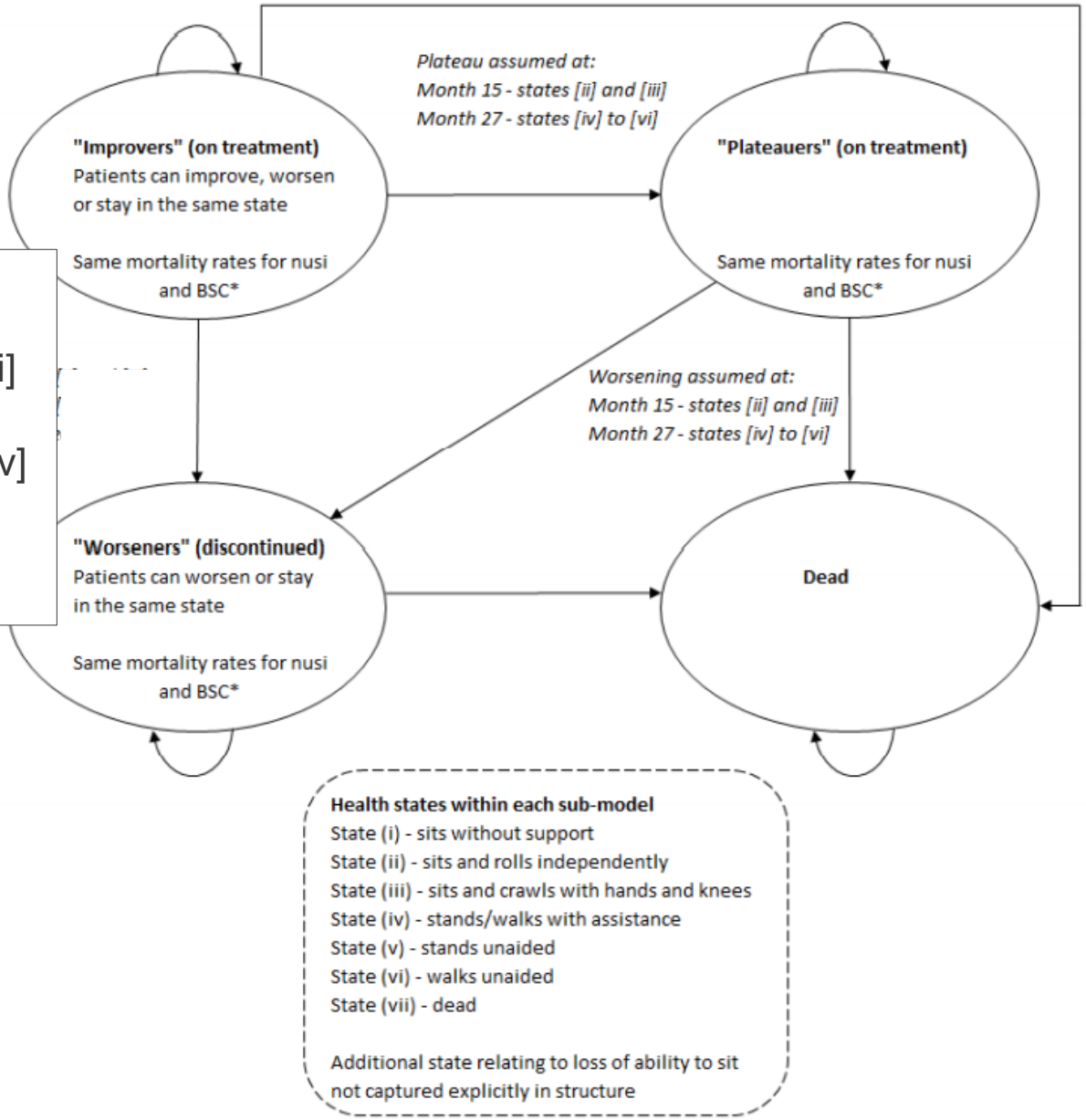
TA588 –Stopping rule in T2/3 model

Patients discontinue due to:
No milestone at 15 months – state [i]
Assumed worsening at 15 months – states [ii] & [iii]
Assumed worsening at 27 months – states [iv] to [vi]
Scoliosis surgery (non-ambulant) after 6 yrs
Scoliosis surgery (ambulant) after 12 yrs



? Can the proxy criteria applied in the model be used for decision-making?

Issue 10. Utility values (fine motor skills & complications)

ACD section 3.12 & 3.17

- Company's utility gain for fine motor skills is acceptable but there is uncertainty around the exact value and the benefit could be larger.
- There could be some benefits not captured in the model.

Company

- Utility gains increased for RIS group for fine motor skills
  - Clinical & patient experts confirmed previous values too low → can improve QoL by 50%
  - Patient utility ↑ by 0.2 in sitting and non-sitting health states and caregiver utility ↑ by 0.05
  - "the effect that upper limb function can have on the QoL is stark according to clinical experts, patients and carers, this estimate is likely to be…conservative"

- Apply additional disutility & costs to account for scoliosis and decline in respiratory and bulbar function (including swallowing, vocalising and communication)

Function	Disutility	Source	Cost
Bulbar function	-0.17	Lloyd 2019	NHS ref 2018/19 (average elective & non-elective)
Scoliosis	-0.085	SUNFISH (part 2)	
Respiratory	-0.07		

Additional utility gains & losses - ERG comments

Uncertainty about utility gain	• Uncertainty around how many patients achieve gain, duration of gains & impact on patients & caregivers.
Double-counting	• Double-counting if apply additional disutility → estimates from clinical experts in TA588 likely to already include impacts relating to bulbar dysfunction, scoliosis and respiratory support for BSC patients • Double-counting costs → already included as part of cost estimates from TA588
Disutility in model	• For T1, not appropriate to apply further disutility for respiratory support to PV state • Not clinically realistic to apply to all BSC patients in every model cycle
Link to stopping rule	• ↑ utility gains & ↓ costs maintained indefinitely even after RIS stopped (issue 5)
Net utility values	• Are resulting net utilities plausible after including fine motor skills & complications (see next slide)?
Summary	• May be appropriate to address concerns in ACD by modelling additional benefits for RIS but not appropriate to make changes for BSC → no reason why these should differ to TA588

Summary of new utility values - Type 1

Health state	ERG-preferred model (both treatment groups)	Company's post-ACD model		
		Risdiplam	BSC	Treatment-specific utility gain in state (risdiplam vs BSC)
Patient utility values				
(i) Not sitting	0.10	0.14	-0.23	0.36
(ii) PV	-0.02	-0.18	-0.35	0.16
(iii) Sitting	0.20	0.40	0.20	0.20
(iv) Standing	0.70	0.70	0.70	-
(v) Walking	0.85	0.85	0.85	-
Caregiver utility values				
(i) Not sitting	0.48	0.53	0.48	0.05
(ii) PV	0.48	0.48	0.48	0.00
(iii) Sitting	0.63	0.68	0.63	0.05
(iv) Standing	0.77	0.77	0.77	-
(v) Walking	0.92	0.92	0.92	-

Note: ERG preferred patient utility values are those used in TA588 (elicited from clinical experts)

Summary of new utility values - Type 2/3

Health state	ERG-preferred model (both treatment groups)	Company's post-ACD model		
		Risdiplam	BSC	Treatment-specific utility gain in state (RIS vs BSC)
Patient utility values				
(i) Not sitting	0.20	0.24	-0.13	0.36
(ii) Sitting (supported)	0.40	0.44	0.07	0.36
(iii) Sitting (unsupported)	0.50	0.70	0.50	0.20
(iv) Standing	0.70	0.70	0.70	-
(v) Walking	0.85	0.85	0.85	-
Caregiver utility values				
(i) Not sitting	0.70	-0.17	-0.22	0.05
(ii) Sitting (supported)	0.77	-0.09	-0.14	0.05
(iii) Sitting (unsupported)	0.84	-0.02	-0.07	0.05
(iv) Standing	0.92	0.00	0.00	-
(v) Walking	0.92	0.00	0.00	-

Are net utility values plausible after accounting for additional utility gains & losses from fine motor skills & complications?

Updated base case assumptions at ACM2

	Company ACM2		ERG comments
	T1	**T2/3**	
24-month data	Updated OS, EFS & transitions	Updated transitions only	Treatment effect for T1 relies inverse HR; results in implausible BSC OS
Caregiver utility 	Limit disutility to BSC life expectancy and add bereavement disutility	ERG disutility approach (no bereavement disutility)	New scenarios to show impact on ICER when using BSC OS from TA588 & ACM 1
Stopping rule 	Discontinue at treatment plateau		Stopping rule does not reflect what would be used in clinical practice
	Non-sitting & PV state ↓ costs & no impact on outcomes	Non-sitting & supported sitting ↓ costs & treatment wane, no impact on utility/mortality	
Utility values 	**Fine motor skills**: ↑ utility gain 0.2 for patients & 0.05 carers **Complications**: Add disutility & costs (100% BSC, 50% RIS)		Uncertain if net utility values after accounting for fine motor skills & complications are plausible

Note: See slide 14 for breakdown by health state. No model changes for pre-symptomatic & previously treated population & no ICERs but to consider as part of recommendations

Company cost effectiveness results – Type 1

24-month data	Stopping rule	Fine motor skills gain	Complications
☑	☑	☑	☑

Option	LYGs	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company revised base case ACM2 – amended ERG caregiver disutility with bereavement disutility						
Risdiplam	30.50	8.55	-3.90	********	-	-
BSC	10.21	-1.86	-3.91	********	-	-
Incremental	20.29	10.41	0.01	********	********	********

Company ICERs for T1 driven by changes to BSC OS as well as other factors (stopping rule & other utility benefits)

ERG exploratory analyses:
******** with BSC OS 4.88 (ACM1)
******** with BSC OS 2.14 (TA588)

Company also presents ICER with original additive caregiver QALY approach: ********

ACD: Company's additive approach not appropriate

ACD: Committee agreed EOL met for type 1 SMA population

ERG cost effectiveness results – type 1 (1/2)

Start point	24-month data	Stopping rule	Fine motor skills gain	Complications
	☒	☒	☒	☒

Option	LYGs	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
1. ERG-preferred at ACM 1 (ERG carer disutility, no stopping rule or additional utility gains)						
RIS	21.68	4.77	-6.68	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	16.8	4.75	-3.54	[redacted]	[redacted]	[redacted]
2. 1) and 24-month data						
Risdiplam	30.47	7.14	-7.32	[redacted]	-	-
BSC	10.21	0.01	-5.49	[redacted]	-	-
Incremental	20.26	7.13	-1.83	[redacted]	[redacted]	[redacted]
3. 2) and BSC OS 4.88 years (ERG preferred ACM1)						
Risdiplam	30.47	7.14	-7.32	[redacted]	-	-
BSC	4.88	0.06	-2.83	[redacted]	-	-
Incremental	25.59	7.08	-4.49	[redacted]	[redacted]	[redacted]
4. 2) and BSC OS 2.14 years (TA588)						
Risdiplam	30.47	7.14	-7.32	[redacted]	-	-
BSC	2.14	0.09	-1.46	[redacted]	-	-
Incremental	28.33	7.05	-5.86	[redacted]	[redacted]	[redacted]

Company cost effectiveness results – Type 2/3

24-month data	Stopping rule	Fine motor skills gain	Complications
☑	☑	☑	☑

Option	LYGs	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company revised base case ACM2 - ERG disutility for carer, 3 carers for non-sitters						
Risdiplam	50.60	14.11	-2.25	[redacted]	-	-
BSC	43.77	1.19	-10.06	[redacted]	-	-
Incremental	6.83	12.91	7.81	[redacted]	[redacted]	[redacted]
Scenario: Company's new caregiver disutility, bereavement disutility, 3 carers						
Risdiplam	50.60	14.11	-2.21	[redacted]	-	-
BSC	43.77	1.19	-9.35	[redacted]	-	-
Incremental	6.83	12.91	7.13	[redacted]	[redacted]	[redacted]

Company ICERs for T2/3 driven by stopping rule & other utility benefits

ERG exploratory analyses: [redacted] if exclude stopping rule

ACD: Committee agreed EOL not met for type 2/3 SMA population

ERG cost effectiveness results – type 2/3

Start point	24-month data	Stopping rule	Fine motor skills gain	Complications
	☒	☒	☒	☒

Option	LYGs	QALYs patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
1. ERG-preferred at ACM 1 (ERG carer disutility, 12-month data, no stopping rule or additional utility gains)						
Risdiplam	50.30	11.42	-3.60	[redacted]	-	-
BSC	43.77	5.98	-10.06	[redacted]	-	-
Incremental	6.53	5.44	6.45	[redacted]	[redacted]	[redacted]
2. 1) and 24-month data						
Risdiplam	50.60	11.39	-3.80	[redacted]	-	-
BSC	43.77	5.98	-10.06	[redacted]	-	-
Incremental	6.83	5.41	6.26	[redacted]	[redacted]	[redacted]
3. 2) and fine motor utility gain 0.2						
Risdiplam	50.60	15.01	-1.75	[redacted]	-	-
BSC	43.77	5.98	-10.06	[redacted]	-	-
Incremental	6.83	9.03	8.30	[redacted]	[redacted]	[redacted]
4. 2) and fine motor utility gain of 0.3						
Risdiplam	50.60	16.83	-1.75	[redacted]	-	-
BSC	43.77	5.98	-10.06	[redacted]	-	-
Incremental	6.83	10.85	8.30	[redacted]	[redacted]	[redacted]

Outstanding modelling issues

1) Impact of inclusion of longer-term data on the effectiveness of risdiplam
2) Discontinuation criteria
3) Inclusion of HRQoL gains associated with upper limb function
4) Inclusion of impacts of SMA complications avoided
5) Caregiver QALYs

ERG comments (1/2)

Issue	ERG suggestions

(2) Discontinuation criteria	• Reconsider discontinuation criteria applied in the model which:
	  ○ Are clinically acceptable to patients and clinicians;
	  ○ Are operationally feasible for the NHS;
	  ○ Reflect how risdiplam is expected to be used in clinical practice (e.g. discontinuing treatment in patients with repeated worsening and/or in those requiring PV);
	• Reconsider the plausibility of assumptions of sustained benefits after discontinuing treatment.

(3) Inclusion of HRQoL gains associated with upper limb function	• In the absence of any evidence to inform the magnitude of utility gains for patients achieving/maintaining upper limb function, the ERG is unsure what might be considered a reasonable assumption • Ensure that the net impact of any assumed additional health benefit on overall utility for model health states is plausible • Consider how many patients will accrue these benefits, their duration and the impact of discontinuation • An expert elicitation exercise to obtain estimates of overall health state utility values for risdiplam-treated patients may be helpful

How should these issues be addressed? Are the ERG suggestions appropriate? Any alternative suggestions?

ERG comments (2/2)

Issue	ERG suggestions
(4) Inclusion of impacts of SMA complications avoided	• Apply any expected benefit and/or cost-saving in the risdiplam group only • Ensure that the net impact of any assumed additional health benefit on overall utility for model health states is plausible • Consider how many patients will accrue these benefits, their duration and the impact of discontinuation • An expert elicitation exercise to obtain estimates of overall health state utility values for risdiplam-treated patients may be helpful
(5) Caregiver QALYs	• Either fully quantify positive and negative impacts on caregiver HRQoL, or do not consider them at all • Adopt a consistent position on caregiver QALYs for both model populations

How should these issues be addressed? Are the ERG suggestions appropriate? Any alternative suggestions?

Key Issues

Model driver

Issue	Company revised base case	Technical team	Questions for committee
New: 24-month data	T1: Updated data for transitions, EFS & OS T2: transitions only	24-month data suggest continued RIS effectiveness	For T1, are new BSC survival predictions clinically plausible?
Caregiver utility (4)	T1: Amended ERG approach → no loss after mean BSC OS + bereavement disutility	Approaches should align for T1 & T2/3	Should caregiver utility be included? If so, how?
Stopping rule (5)	Apply 'proxy' criteria → affects non-sitting health states	Modelled rule not intended to be used in clinical practice	Is company's proposed stopping rule acceptable? Is the proxy applied in the model acceptable?
Utility values: fine motor skills (10) & uncaptured benefit	Include ↑ utility gain for fine motor skills & additional disutility & costs for complications	Uncertainty around net utility values	Are net utility values after accounting for fine motor skills & complications plausible?

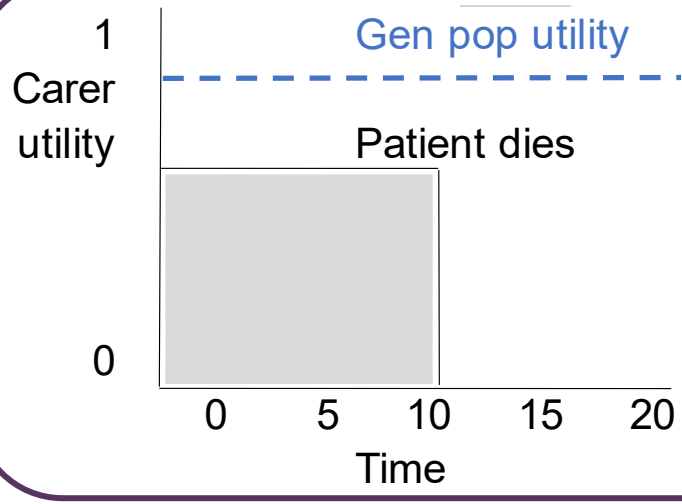
Pre-symptomatic & previously treated pop: New interim data but no ICERs → Is it reasonable to include these populations in recs? Note: Trials restricted age (type 1: 1-7 months, type 2: 2-25 years) and FIREFISH also excluded those on chronic ventilation

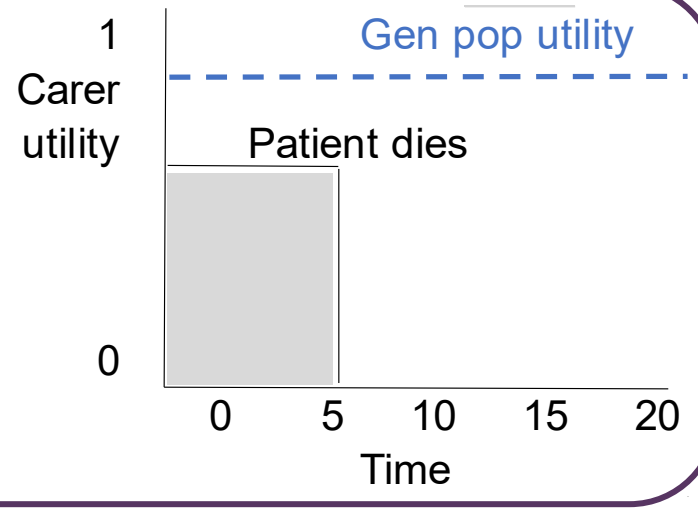
Back up slides

Issue 4. Caregiver QALY gains – conceptual illustration

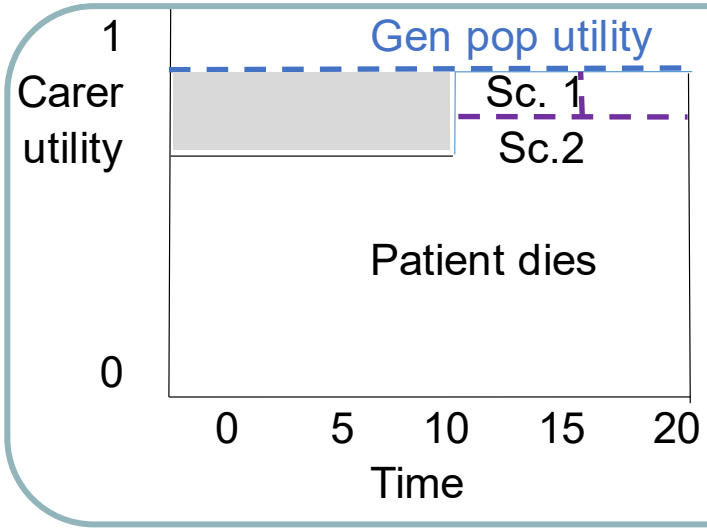
- Patient A is treated with RIS & survives 10 yrs, patient B treated with BSC & survives 5 yrs
- Each patient has 1 carer and general population utility is 0.80. Both patients spent entire survival time in a health state associated with caregiver disutility of 0.20 (caregiver utility 0.60)

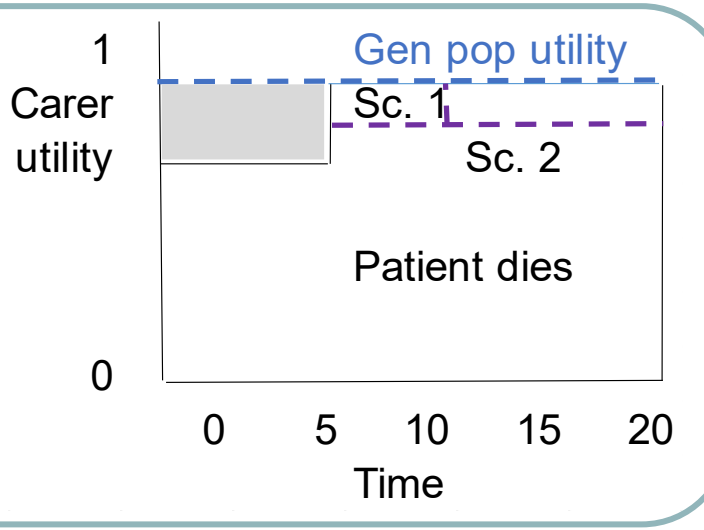
Patient A (RIS) **Patient B (BSC)**





Company additive approach
Carer QALY
Patient A: 0.60 x 10 = 6;
Patient B: 0.60 x 5 = 3;
incremental QALY gained = 6-3 = 3





ERG disutility approach
Carer QALY
Patient A: -0.20 x 10 = -2;
Patient B: -0.20 x 5 = -1;
incremental QALY gained = -1

Sc=scenarios → additional bereavement QALY loss