Supplemental data

Table I: Search strings for PubMed, Embase, and trial registries search

Database	**PubMed**	**Embase**	**Trial registries**
Search string	("Amyotrophic Lateral Sclerosis"[Mesh] OR "Motor Neuron Disease"[Mesh] OR "ALS"[TIAB] OR "amyotrophic lateral sclerosis"[TIAB] OR "Gehrig*"[TIAB] OR "Motor Neuron Disease*"[TIAB] OR "Charcot*"[TIAB] OR "MND"[TIAB] AND (1999/1/1:2023/01/01[pdat])) AND ("Clinical Trials as Topic"[Mesh] OR "trial*"[TIAB] OR "randomi*"[TIAB] AND (1999/1/1:2024/01/01[pdat]))	('amyotrophic lateral sclerosis'/exp OR 'motor neuron disease'/exp OR 'als':ti,ab,kw OR 'amytrophic lateral sclerosis':ti,ab,kw OR 'gehrig*':ti,ab,kw OR 'motor neuron disease*':ti,ab,kw OR 'charcot*':ti,ab,kw) AND ('clinical trial'/exp OR 'trial*':ti,ab,kw OR 'randomi*':ti,ab,kw) AND [1999-2023]/py AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	ALS \(Amyotrophic Lateral Sclerosis\) | Completed, Terminated studies | Interventional studies | Study start from 01/01/1999 to 01/01/2024

Table II: Preselected studies used for ASReview

Eligible studies	**Ineligible studies**
1. "Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis" (2020, NEJM) 2. "Trial of celecoxib in amyotrophic lateral sclerosis" (2006, Neurology)	1. "Genetic variation in APOE, GRN, and TP53 are phenotype modifiers in frontotemporal dementia" (2020, Neurobiology of Aging) 2. "MTBVAC vaccine mediates immune response through the

3. "Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial" (2013, The Lancet Neurology) 4. "Efficacy and safety of CNM-Au8 in amyotrophic lateral sclerosis (RESCUE-ALS study): a phase 2, randomised, double-blind, placebo-controlled trial and open label extension" (2023, Elsevier) 5. "Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomized trial" (2007, The Lancet Neurology) **6.** "A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis" (2003, Neurology)	upregulation of T-regulatory cells in an ALS mouse model" (2021, Cell Reports Medicine)

Table III: IPD variables

Individual patient data variables

• Study information
  ○ Study ID
  ○ Country
• Patient data
  ○ Patient ID
  ○ Age (years)
  ○ Sex (male/female)
  ○ Height (cm)
  ○ Weight (kg)
  ○ Site of onset (bulbar/spinal)
  ○ Symptom duration (months)
  ○ Diagnostic delay (months)

- Intervention data
  - Treatment group
  - Mode of administration
  - Follow-up duration (months)
- Longitudinal
  - ALSFRS-R total
  - ALSFRS-R items (1-12)
  - ALSFRS-R date
  - Predicted VC (%)
  - VC (liter)
  - VC date
- Time-to-event data
  - Death or composite survival endpoint (days)
  - Censor if not deceased (days)
  - Dropout (days)

7

Table IV: AD variables

Aggregate-level data variables	**Variable name**
General information • First author • Year • PMID • Title • DOI • Country • Sponsor	**General information** • AUTHOR • YEAR • PMID • TITLE • DOI • COUNTRY • SPONSOR
Baseline data (for each treatment group) • Group size • Age (mean yrs at enrollment) • Standard deviation age • Sex (% male) • Weight (mean kg) • Standard deviation weight • BMI • Standard deviation BMI • Site of onset (% bulbar) • Symptom duration (mean months) • Standard deviation symptom duration • Diagnostic delay (mean months) • Standard deviation diagnostic delay • Diagnostic duration (mean months) • Standard deviation diagnostic duration • Riluzole use at enrollment • ALSFRS-R total score (at baseline) • Standard deviation total score • VC (%predicted) at baseline	**Baseline data** • N • AGE • AGE_SD • SEX • WEIGHT • WEIGHT_SD • BMI • BMI_SD • ONSET • DISDUR • DISDUR_SD • DXDELAY • DXDELAY_SD • DXDUR • DXDUR_SD • RILUSE • TOTAL • TOTAL_SD • VC

• Standard deviation %VC • ΔFRS • Standard deviation ΔFRS	• VC_SD • SLOPE • SLOPE_SD *Add [_CON] for control group* *Add [_TRT] for treatment group* *Add [_TRT2] for second treatment etc* *e.g.: N_CON, N_TRT*
Intervention data • Name intervention (+ dosage) • Type of intervention (pharm, cell, suppl) • Mode of administration • Mechanism of action class • Randomization ratio • Trial study design • Lead-in duration (months) • Treatment duration (mean months) • Total duration (months)	**Intervention data** • NAME_INT • TYPE_INT • ADMIN • CLASS • RATIO • DESIGN • DUR_LEAD • DUR_TRT • DUR_TOT
Outcome data (for each treatment group) • Analysis used for outcome • Mean ALSFRS-R score (at end of FU) • St. error mean ALSFRS-R • Mean difference ALSFRS-R • St. error mean difference ALSFRS-R • 95% CI mean difference • Comparison arm mean difference • Mean ALSFRS-R (monthly) slope • St. error mean ALSFRS-R slope • Mean difference ALSFRS-R slope • Mean difference slope p-value	**Outcome data (end of follow-up)** • ANALYSIS • FRSR_MEAN • FRSR_MEAN_SE • FRSR_MEAN_DIFF • FRSR_MEAN_DIFF_P • FRSR_MEAN_DIFF_CI • FRSR_MEAN_DIFF_COMP • FRSR_SLOPE • FRSR_SLOPE_SE • FRSR_SLOPE_DIFF • FRSR_SLOPE_DIFF_P

• 95% CI mean difference slope	• FRSR_SLOPE_DIFF_CI
• Comparison arm mean difference slope	• FRSR_SLOPE_DIFF_COMP
• ALSFRS-R change from baseline (CFB)	• FRSR_CFB
• ALSFRS-R CFB p-value	• FRSR_CFB_P
• ALSFRS-R CFB 95% CI	• FRSR_CFB_CI
• Comparison arm ALSFRS-R CFB	• FRSR_CFB_COMP
• ALSFRS-R CFB timeframe (months)	• FRSR_CFB_TIME
• Adjusted variables in ALSFRS-R analysis	• ADJUST
• N of ALSFRS-R in analysis	• N_FU
• Mean VC (at end FU)	• VC_MEAN
• St. error mean VC	• VC_MEAN_SE
• Mean difference VC	• VC_MEAN_DIFF
• St. error mean difference VC	• VC_MEAN_DIFF_P
• 95% CI mean difference VC	• VC_MEAN_DIFF_CI
• Comparison arm mean difference VC	• VC_MEAN_DIFF_COMP
• Mean VC (monthly) slope	• VC_SLOPE
• St. error mean VC slope	• VC_SLOPE_SE
• Mean difference VC slope	• VC_SLOPE_DIFF
• Mean difference VC slope p-value	• VC_SLOPE_DIFF_P
• 95% CI mean difference slope	• VC_SLOPE_DIFF_CI
• Comparison arm mean difference slope	• VC_SLOPE_DIFF_COMP
• Adjustment variables in FVC analysis	• VC_ADJUST
• N of VC in analysis	• VC_N_FU
• **Survival:**	• **Survival:**
○ Mean hazard ratio	○ SURV_HR
○ St. error hazard ratio	○ SURV_HR_SE
○ 95% CI hazard ratio	○ SURV_HR_CI
○ Hazard ratio p-value	○ SURV_HR_P
○ Comparison arm hazard ratio	○ SURV_COMP
• **Drop-outs:**	• **Dropout:**
○ Death	○ DROP_DEATH
○ Adverse event	○ DROP_AE

○ Termination of participation ○ Disease progression ○ Other reasons • AEs reported • SAEs reported	○ DROP_TERM ○ DROP_PROG ○ DROP_OTHER • AE • SAE *Add [_CON] for control group* *Add [_TRT] for treatment group* *Add [_TRT2] for second treatment etc* *e.g.: N_CON, N_TRT*
Study descriptives • Primary outcome (ALSFRS-R, VC, survival) • Protocol published/accessible? (y/n) • IPD published/accessible? (y/n) • Kaplan-Meier survival curve present? (y/n) • ALSFRS-R analysis method mentioned? (y/n) • Survival analysis method mentioned? (y/n) • Definition of survival event • Sample size calculation mentioned (y/n) • Placebo arm? (y/n) • **Outcome reported?** ○ ALSFRS-R (y/n) ○ VC (y/n) ○ Survival (y/n) ○ Electrophysiology (y/n) ○ Muscle strength (ISOMETRIC/HHD/MRC) (y/n) ○ Neurofilament Light Chain (y/n)	**Dummies** • OUTCOME • PROT_ACC • IPD_ACC • KAPMEI • FRS-R_METH • SURV_METH • SURV_DEF • SAMP_CALC • PLACEBO • **Reported:** ○ FRS-R_REP ○ VC_REP ○ SURV_REP ○ ELECT_REP ○ MUSC_REP ○ NFL_REP

9

Table V: variable code list

Name	Definition	Levels
AUTHOR	Name of first author	Nominal
YEAR	Year of publication	Continuous
PMID	PubMed ID of main publication	Nominal
TITLE	Title of article	Nominal
DOI	DOI number	Nominal
COUNTRY	Country	Nominal
SPONSOR	Source of funding	0 = academic, 1 = industry, 2 = mixed
PUB_DATE	Publication date	Date
N (for all treatment groups)	Number of participants in treatment group at enrollment	Continuous
AGE (for all treatment groups)	Mean age at enrollment	Continuous (years)
AGE_SD	Standard deviation age	Continuous
SEX (for all treatment groups)	% of participants that are male	% Male
WEIGHT (for all treatment groups)	Mean weight of participants	Continuous (kg)
WEIGHT_SD	Standard deviation weight	Continuous
BMI (for all treatment groups)	Mean BMI of participants	Continuous (kg/m^2)
BMI_SD	Standard deviation BMI	Continuous
ONSET (for all treatment groups)	% of participants that have bulbar onset	% Bulbar onset

DISDUR (for all treatment groups)	Mean duration of symptoms at enrollment	Continuous (months)
DISDUR_SD	Standard deviation disease duration	Continuous
DXDELAY (for all treatment groups)	Mean time from onset to diagnosis	Continuous (months)
DXDELAY_SD	Standard deviation diagnostic delay	Continuous
DXDUR	Mean time from diagnosis to enrollment	Continuous (months)
DXDUR_SD	Standard deviation diagnostic duration	Continuous
RILUSE (for all treatment groups)	% of participants that use riluzole at enrollment	Percentage users
TOTAL (for all treatment groups)	ALSFRS-R total score at baseline	Continuous
TOTAL_SD	Standard deviation total score	Continuous
VC (for all treatment groups)	VC (%predicted) at baseline	% Of predicted capacity
VC_SD	Standard deviation VC	Continuous
SLOPE	Monthly decline of ALSFRS-R at baseline	Continuous
SLOPE_SD	Standard deviation monthly decline	Continuous
NAME_INT (for all treatment groups)	Name of the treatment	Nominal

TYPE_INT (for all treatment groups)	Treatment type	0 = pharmaceutical, 1 = cell therapy, 2 = supplement
GROUP_INT (for all treatment groups)	Subgrouping	<<undefined>>
ADMIN (for all treatment groups)	Mode of administration	0 = oral, 1 = IV, 2 = intrathecal, 3 = subcutaneous, 4 = intramuscular, 5 = transdermal
CLASS (for all treatment groups)	Mechanism of action class	0 = miscellaneous, 1 = antioxidants, 2 = cell therapy, 3 = genetic therapy, 4 = mitochondrial dysfunction, 5 = neuroinflammation, 6 = proteostasis
RATIO	Randomization ratio of intervention:control	Continuous (ratio)
DESIGN	Type of study design in trial	Nominal
DUR_LEAD	Lead-in duration, time when enrolled but not yet treated	Continuous (months)
DUR_TRT	Treatment duration	Continuous (months)
DUR_TOT	Total duration of study	Continuous (months)
ANALYSIS	Type of analysis used to determine primary outcome	Nominal
FRSR_MEAN (for all treatment groups)	ALSFRS-R total score at end of follow-up	Continuous

FRSR_MEAN_SE (for all treatment groups)	Standard error mean ALSFRS-R total score	Continuous
FRSR_MEAN_DIFF (for all treatment groups)	Mean difference ALSFRS-R total score	Continuous
FRSR_MEAN_DIFF_P (for all treatment groups)	Mean difference ALSFRS-R total score p-value	Continuous
FRSR_MEAN_DIFF_CI (for all treatment groups)	Mean difference ALSFRS-R total score 95% CI	[lower bound, upper bound]
FRSR_MEAN_DIFF_COMP (for all treatment groups)	Mean difference ALSFRS-R total score comparison arm	Nominal
FRSR_SLOPE (for all treatment groups)	Mean ALSFRS-R monthly decline	Continuous
FRSR_SLOPE_SE (for all treatment groups)	Standard error mean ALSFRS-R monthly decline	Continuous
FRSR_SLOPE_DIFF (for all treatment groups)	Mean difference ALSFRS-R monthly decline	Continuous
FRSR_SLOPE_DIFF_P (for all treatment groups)	Mean difference ALSFRS-R monthly decline p-value	Continuous
FRSR_SLOPE_DIFF_CI (for all treatment groups)	Mean difference ALSFRS-R monthly decline 95% CI	[lower bound, upper bound]
FRSR_SLOPE_DIFF_COMP (for all treatment groups)	Mean difference ALSFRS-R monthly decline comparison arm	Nominal
FRSR_CFB (for all treatment groups)	Mean ALSFRS-R change from baseline	Continuous
FRSR_CFB_P (for all treatment groups)	Mean ALSFRS-R change from baseline p-value	Continuous

FRSR_CFB_CI (for all treatment groups)	Mean ALSFRS-R change from baseline 95% CI	[lower bound, upper bound]
FRSR_CFB_COMP (for all treatment groups)	Mean ALSFRS-R change from baseline comparison arm	Nominal
FRSR_CFB_TIME (for all treatment groups)	Mean ALSFRS-R change from baseline timepoint	Continuous (months)
ADJUST (for all treatment groups)	Variables that were used for stratifying or adjusting ALSFRS-R	Nominal
N_FU (for all treatment groups)	Number of patients with ALSFRS-R scores used in analysis	Continuous
VC_MEAN (for all treatment groups)	VC % of predicted capacity at end of follow-up	% Of predicted capacity
VC_MEAN_SE (for all treatment groups)	Standard error mean VC	Continuous
VC_MEAN_DIFF (for all treatment groups)	Mean difference VC	Continuous
VC_MEAN_DIFF_P (for all treatment groups)	Mean difference VC p-value	Continuous
VC_MEAN_DIFF_CI (for all treatment groups)	Mean difference VC 95% CI	[lower bound, upper bound]
VC_MEAN_DIFF_COMP (for all treatment groups)	Mean difference VC comparison arm	Nominal
VC_SLOPE (for all treatment groups)	Mean VC monthly decline	% Of predicted capacity

VC_SLOPE_SE (for all treatment groups)	Standard error mean VC monthly decline	Continuous
VC_SLOPE_DIFF (for all treatment groups)	Mean difference VC monthly decline	% Of predicted capacity
VC_SLOPE_DIFF_P (for all treatment groups)	Mean difference VC monthly decline p-value	Continuous
VC_SLOPE_DIFF_CI (for all treatment groups)	Mean difference VC monthly decline 95% CI	[lower bound, upper bound]
VC_SLOPE_DIFF_COMP (for all treatment groups)	Mean difference VC monthly decline comparison arm	Nominal
ADJUST_VC (for all treatment groups)	Variables that were used for stratifying or adjusting VC	Nominal
N_FU_VC (for all treatment groups)	Number of patients with VC scores used in analysis	Continuous
SURV_HR	Hazard ratio mean	Continuous
SURV_HR_SE	Hazard ratio standard error	Continuous
SURV_HR_CI	Hazard ratio 95% confidence interval	[lower bound, upper bound]
SURV_HR_P	Hazard ratio p-value	Continuous
SURV_COMP	Hazard ratio comparison arm	Nominal
DROP_DEATH (for all treatment groups)	Number of drop-outs due to death	Continuous
DROP_AE (for all treatment groups)	Number of drop-outs due to adverse events	Continuous
DROP_TERM (for all treatment groups)	Number of drop-outs due to terminating participation	Continuous

DROP_PROG (for all treatment groups)	Number of drop-outs due to disease progression	Continuous
DROP_OTHER (for all treatment groups)	Number of drop-outs due to other reasons	Continuous
AE (for all treatment groups)	Number of adverse events in group at end of follow-up	Continuous
SAE (for all treatment groups)	Number of serious adverse events in group at end of follow-up	Continuous
OUTCOME	Primary outcome (e.g., ALSFRS-R, survival, safety)	Nominal
PLACEBO	Is a placebo arm present?	0 = no, 1 = yes
PROT_ACC	Is the study protocol accessible?	0 = no, 1 = yes
IPD_ACC	Is IPD accessible?	0 = no, 1 = yes
KAPMEI	Are Kaplan-Meier survival curves used?	0 = no, 1 = yes
FRSR_METH	Method of ALSFRS-R analysis mentioned?	0 = no, 1 = yes
SURV_METH	Method of survival analysis mentioned?	0 = no, 1 = yes
SURV_DEF	Definition of an event in survival analysis (death/tracheostomy/etc.)	Nominal
SAMP_CALC	Method of sample size calculation mentioned?	0 = no, 1 = yes

FRSR_REP	Is ALSFRS-R reported as outcome?	0 = no, 1 = yes
VC_REP	Is VC reported as outcome?	0 = no, 1 = yes
SURV_REP	Is survival reported as outcome?	0 = no, 1 = yes
ELECT_REP	Is electrophysiology reported as outcome?	0 = no, 1 = yes
MUSC_REP	Is muscle strength reported as outcome? (ISOMETRIC/HHD/MRC)	0 = no, 1 = yes
NFL_REP	Is neurofilament light chain reported as outcome?	0 = no, 1 = yes