Disease	Product	Route	Highest Dose	AAV serotype	Related NCT (phase)	Signals of efficacy (phase)
SMA-1	onasemnogene abeparvovec	IV	1.1 × 10^14 vg/kg	scAAV9	NCT02122952 (1) NCT03306277 (3) NCT03461289 (3) NCT03505099 (3) NCT03837184 (3) Approved	**Independent sitting >30 seconds. Improvement CHOP-INTEND score. Alive without permenant ventilation at 18 months (3)** **No control group.**
SMA-2	onasemnogene abeparvovec	IT	2.4 X 10^14 vg/kg	AAV9	NCT03381729 (1)	increase of HFMSE in younger patients No control group.(SUSPENDED)
XMTM	resamirigene bilparvovec	IV	3.5 x 10^14 vg/kg	AAV8	NCT03199469 (1,2)	**Increased hours off ventilation, Improvement in CHOP-INTEND. Compared to delayed treatment controls(1,2)**
DMD	scAAV9.U7.ACCA	IV	3.0 × 10^13 vg/kg	AAV9	NCT04240314 (1)	Protein expression
	SGT-001	IV	2.0 X 10^14 vg/kg	AAV9	NCT03368742 (1)	Improvement in NSAA, 6MWT and lung function compared to natural history data
	rAAVrh74.MHCK7. micro-dystrophin	IV	1.33 × 10^14 vg/kg	AAVrh74	NCT03375164 (1,2) NCT04626674 (1) NCT03769116 (3)	**Improvement in NSAA, microdystrophin expression. Pre- dose self control (1)** Improvement NSAA , RCT (3)
	GNT 0004	IV	?	?	Genethon, no NCT	No data, on hold for safety reason
	PF-06939926	IV	2 × 10^ 14 vg/kg	AAV9	NCT03362502 (1) NCT04281485 (3)	Improvement in/stable NSAA. Self pre-treatment control (1)
LGMD2E	rAAVrh74.MHCK7.SGCB	IV	5×10^ 13 vg/kg	AAVrh74	NCT03652259 (1)	Improvement in NSAD. Self, pre-treatment control

Table 1a. Clinical Trials for Neuromuscular Disorders. **BOLD**= data from peer reviewed journal. SMA-1/2= Spinal Muscular Atrophy type ½. XMTM= X-linked Myotubular Myopathy. DMD= Duchenne Muscular Dystrophy. LGMD2E= Limb Girdle Muscular Dystrophy 2E. CHOP-INTEND= Children's Hospital of Phildelphia Infant Test of Neuromuscular Disorders. HFMSE= Hammersmith Functional Motor Score Expanded. NSAA= North Star Ambulatory Assessment. RCT= Randomised Controlled Trial. NSAD= North Star Assessment for dysferlinopathy. 6MWT=6 minute walk test. IV= intravenous. IT= intrathecal

Disease	Product (route)	Route	Dose	AAV serotype	Related NCT (phase)	Signals of efficacy (phase)
GAN	scAAv9/JeT-GAN	IT	3.5x10^14 vg	AAV9	NCT02362438 (1)	no data
GM1	AAV9-GLB1	IV	4.5x10^13vg/kg	AAV9	NCT03952637 (1,2)	Less functional deterioration (BSID, VBAS, CGI) compared to natural history studies. No clinical evidence of disease progression at 6 months post dosing
	LYS-GM101	IV	8x10^12 vg/Kg	AAVrh10	NCT04273269 (1)	No data
GM2	AAVrh8-HEXA	IT	4.5x10^13 vg/kg	AAVrh8	NCT04669535 (1)	No data
	TSHA-101	IT	?	AAV9	NCT04798235 (1)	No data
CD	AV2-NSE-ASPA -WPRE-bGHpA	IC	1 × 10^12 vg	AAV2	No number (1)	**reversal in brain NAA accumulation, motor improvement compared to baseline (GMFM) (1)**
	rAAV9-CB6-ASPA	IC&IV	?	AAV9	I&D	Improvements in motor development (GMFM),Restoration of vision Improvements in myelination Reduction in brain oedema (MRI), Decrease CSF NAA level. Compared to patient baseline.
	AAV9 BBP-812	IV	?	AAV9	NCT04998396 (1,2)	no data
	rAAV-Olig001-ASPA	IC	3.7 x 10^13 v.g	AAV/Olig001	NCT04833907 (1,2)	no data
	SPK-3006	IV	?	AAV-rh74	NCT04093349 (1)	No data

LOPD	AT845	IV	1×10^14 vg/kg	AAV8	NCT04174105 (1,2)	No data
	AAV2/8-LSPhGAA	IV	2x10^12 vg/kg	AAV2/8	NCT03533673 (1)	No data
MPS I	RGX-111	IC	5x10^10 GC/g brain mass	AAV9	NCT03580083 (1)	Reduction in CSF HS. Better neuro-development (WISC, BSID, VBAS) than natural history
MPS II	RGX-121	IC	2.0x10^11 GC/g brain mass	AAV9	NCT03566043 (1)	Reduction in CSF HS. Ongoing neurodevelopmental skill acquisition.
	AAV9.CB7.hIDS	IC	6.5 × 10^10 GC/g brain mass	AAV9	NCT04571970 (1)	No data
MPS IIIA	AAVrh10-h.SGSH	IC	7.2×10^11 vg	AAVrh10	NCT03612869 (1)	No data
	SAF-301	IC	2·4 × 10^11 vg	AAVrh10	NCT01474343 (1)	**Moderate improvement in sleep, attenetion and behaviour.** **Slowed brain atrophy compared to natural history (1)**
	ABO-102/scAAV9.U1a.hSGSH	IV	3 X 10^13 vg/kg	AAV9	NCT02716246 (1,2) NCT04088734 (1,2)	Neurocognitive development within the normal range of a non-affected child 30-36 months post administration (BSID, MDQ, VBAS, CGI)
MPS IIIB	rAAV2/5-hNAGLU	IC	4x10^12 vg	AAV2	NCT03300453 (1,2)	**Neurocognitive progression (PEP-3, Vineland-II, TBAQ) improved compared to natural history(1,2)**
	rAAV9.CMV.hNAGLU	IV	1 X 10^14 vg/kg	AAV9	NCT03315182 (1,2)	Reduction in CSF HS. Plasma and urine HS decreased. Longer follow up needed to evaluate neurodevelopmental changes
MPS VI	AAV2/8.TBG.hARSB	IV	6 x 10^12 vg/kg	AAV2/8	NCT03173521 (1,2)	No data

CLN2	AV2CUhCLN2	IC	3x10^12 particle units	AAV2	NCT00151216 (3)	**Better neurodevelopment than natural history (LINCL scale)(3)**
	AAVrh.10CUCLN2	IC	9x10^11 molecules	AAVrh10	NCT01414985 (3)	**Better neurodevelopment than natural history (LINCL scale) (3)**
CLN3	AAV9-CLN3	IT	1.2×10^14 vg	AAV9	NCT03770572 (1)	No data
CLN6	scAAV9.CB.CLN6	IT	?	AAV9	NCT02725580 (1)	Slowed disease progression compared to natural history
MLD	AAVrh.10cuARSA	IC	?	AAVrh10	NCT01801709 (1)	No data
KD	AAVrh.10-hGALC	IV	?	AAVrh10	NCT04693598 (1,2)	No data
GD	PRV-GD2-101/PR001	IC	?	AAV9	NCT04411654 (2)	No data
AADC-D	AAV-2 hAADC (IC)	IC	1·81 × 10^{11} vg	AAV2	NCT01395641 (1)	**PDMS-2 scores increased compared to patient's baseline (1)**
FTD	FTD-GRN (IC)	IC	?	AAV9	NCT04408625 (1,2)	No data
	PBFT02 (IC)	IC	2.2 x 10^11 GC/g brain weight	AAV1	NCT04747431 (1,2)	No data
MSA	AAV2-GDNF (IC)	IC	?	AAV2	NCT04680065 (1)	No data
PD	AAV-GAD (IC)	IC	1×1012 vg/mL	AAV2	NCT00195143 (1)	**Improvement in UPDRS score(1)** **No control**
	AAV-hAADC-2 (IC)	IC	3 x 10^11 vg	AAV2	NCT00229736 (1)	**Improvement in UPDRS score (1)** **No control**
	AAV2-NRTN (IC)	IC	2.4 x 10^12 vg	AAV2	NCT00985517 (1)	**Primary efficacy outcome not met(1)**
	PRV-PD101/PR001(IC)	IC	?	AAV9	NCT04127578 (1)	No data
	AAV2-GDNF (IC)	IC	3 x 10^12 vg	AAV2	NCT01621581 (1)	No data

	VY-AADC01	IC	4.7x 10^12 vg	AAV2	NCT01973543 (1)	**Decreased medication requirements** **Improvement in UPDRS score (1)** **No control**
AD	AAV2-NGF (IC)	IC	2.0 X 10^11 vg	AAV2	NCT00876863 (3) NCT00087789 (1)	**Efficacy outcomes not met (1)**
	AAVrh.10hAPOE2 (IC)	IC	5.0 x 10^11 gc/mL CSF	AAVrh10	NCT03634007 (1)	No data
	AAV-hTERT (IT/IV)	IT/IV	?	?	NCT04133454 (1)	No data
HD	rAAV5-miHTT (IC)	IC	6x10^13 gc	AAV5	NCT04120493 (1)	No data
ALS	AAV-miR-SOD1	IT	?	?	I&D	**Inconclusive efficacy**

Table 1b. Clinical Trials for Non- Neuromuscular Disorders. Bold= data from peer reviewed publication. See table one. GAN= Giant Axonal Neuropathy. GM1/2= GM1 /2gangiosidosis. CD= Canavan Disease. LOPD= Late Onset Pompe Disease. MPS= Mucopolysaccharidosis. CNL= Ceroid Neuronal Lipofuscinoses. MLD= Metachromatic Leukodystrophy. KD=Krabbe Disease. GD= Gaucher Disease. AADC-D= AADC Deficiency. FTD= Fronto-temporal Dementia. MSA= Multiple System Atrophy. PD= Parkinson's Disease. Huntington Disease. ALS= Amyotrophic Lateral Sclerosis. TBQA= Toddler Behaviour Assessment Questionnaire, PEP-3= Psychoeducational profile 3. WISC=Wechsler Abbreviated Scale of Intelligence. BSID= Bayley Scales of Infant and Toddler Development. VBAS= vineand behaviour adaptive scales. MDQ= Mullen developmental quotient . CGI= clinical global impression scale. GMFM= Gross Motor Function Measure. MRI= Magnetic Resonance Imaging . KABC= Kaufmann assessment battery for children. PDMS-2: Peabody developmental scale 2. UDRPS score= Unified Parkinson's Disease Rating Scale. LINCL scale= Late Infantile Neuronal Ceroid Lipofuscinosis Scale

Disease	Product	N*	Serious Adverse Event (Treatment Related)	Suspected cause	Management
SMA-1/2	onasemnogene abeparvovec	c.1400	9 cases of thrombotic microangiopathy, one lead to death	complement- low c3,c4, high soluble C5b-9 complex	supportive- eculizimab trialled in one IV glucocorticoids, exchange transfusion, dialysis
			1 case hydrocephalus	unknown	VP shunt
			6 severe Liver injury	Likely T-Cell mediated	MethylPrednisolone
			Transaminitis	T-Cell mediated	Extended course prednisolone
XMTM	resamirigene bilparvovec	17 (high dose)	3 deaths, associated liver dysfunction	Associated with higher dose	Unknown
			1 death unknown cause	Unknown- in lower dose group	Unknown
DMD	rAAVrh74.MHCK7.micro-dystrophin	4	Transaminitis	Unknown- T cell response not associated	Supportive
			2 cases rhabdomyolysis	Unknown	Supportive
	PF-06939925	19	2 cases atypical HUS/ thrombotic microangiopathy	complement	Supportive- inc platelet transfusion and dialysis and eculizumab
			2 cases myocarditis (out of 3 of myositis)	related to CRIM negativity, direct anti transgene mediated	Exclude patients with predisposing mutations
			1 case myocarditis- leading to death	unknown, likely transgene unrelated	trial pause
			1 case severe vomiting	unknown	supportive- IV fluids
	SGT-001	7	1 case hyperbilirubinemia	unknown	prednislone
			1 case transaminitis	unknown	prednislone
			2 cases atypical HUS/ thrombotic microangiopathy (immune haemolysis, thrombocytopenia, renal failure, cardiopulmonary insuffiency)	activation of the terminal complement pathway, C5b	Supportive plus eculizumab complement panel now added to monitoring. Empty capsids removed from product. 1 patient dosed since (7th)
	All 3 microdystrophin products	30	5 cases myositis (including noted in pfizer above)	related to CRIM negativity, direct anti transgene mediated	Exclude patients with predisposing mutations (mutation exon 9-13; mutation exon 29 and 30)
			3 cases myocarditis (out of 5 myositis)		
PD	AAV-2 hAADC		12 cases dyskinesia	transgene	Risperidone
			2 cases asymptomatic intracranial haemorrhage	Neurosurgery	Supportive
			1 venous ICH (frontal dysfunction 3/52)	Neurosurgery	Supportive

		16	1 arterial ICH (transient hemiplegia, aphasia)	Neurosurgery	Supportive
CD	AV2-NSE-ASPA-WPRE-bGHpA	13	Post operative fever	Neurosurgery	IV abx
			Brain abscess	Neurosurgery	IV abx
AD	AAV2-NGF	26	2 cases post operative seizures	Neurosurgery	Supportive
			Post surgical hygroma	Neurosurgery	Drainage
CNL2	AV2CUhCLN2	10	1 death status epilepticus	Likely Neurosurgery, unclear	Supportive- EEG monitoring added to protocol
	AAVrh.10CUCLN2	8	2 Increased Seizures	Unclear	Antiepileptics prophylactically
			1 Abnormal movements	Unclear	Nil
			10 Emesis	Likely product	Supportive
CNL6	scAAV9.CB.CLN6	12	1 Vomiting	Unclear	Supportive
			2 Fever	Unclear	Supportive
			1 Abdominal Pain	Unclear	Supportive
LGMD2E	rAAVrh74.MHCK7.SGCB	6	1 transaminitis+ hyperbilirubinemia	unclear	Supportive
			1 vomiting	unclear	Supportive
MPS IIIB	ABO-101	11	1 vomiting and fever	Product related	Supportive
ALS	AAV-miR-SOD1	2	Meningioradiculitis	Product related	MethylPrednisolone

Table 2. Serious Adverse Events. See table one. EEG= Electroencephalogram.

Disease	Product	Setting/ NCT	AAVab inclusion cut off	Evidence of AAVab post infusion	Evidence of Complement Activation	Evidence of T-Cell Activation	Immune Prophylaxis	Treatment SAE
SMA-1	onasemnogene abeparvovec	NCT02122952	Excluded if anti-AAV9 > 1:1600 ELISA binding immuno-assay	Serum AAVab levels rise	Not measured	IFN-γ Elispot to AAV9 seen, not to SMN. Associated with raised transaminases	Prednisolone (added after 1st patient)	Prednisolone for transaminitis.
		NCT03461289(EU) NCT03306277(US)	Excluded if anti-AAV9 > 1:50 ELISA binding immuno-assay	Serum AAVab levels rise	Not measured	IFN-γ Elispot to AAV9 seen. Not seen to SMN. Associated with raised transaminases. Used to taper prednisolone.	Prednisolone	Prednisolone for transaminitis.
		NCT03505099 (3 copies SMN) NCT03505100 (2 copies SMN)	Excluded if anti-AAV9 > 1:50 ELISA binding immuno-assay	Serum AAVab levels rise	Not measured, but no post infusion thromocytopenia <75,000	Unknown	Prednisolone	Prednisolone for transaminitis.
		Commercial	Excluded if anti-AAV9 >1:50 ELISA binding immuno-assay	Serum AAVab levels rise	Complementopathy associated with thrombocytopenia. C3, C4, Bb fragments, soluble C5b-9 complex, CH50, FH autoantibody, Factor B, factor H and factor I measured.	IFN-γ Elispot response to AAV9. Used to taper prednisolone	Prednisolone	Prednisolone, IV methyl- prednisolone, eculizumab
XMTM	resamirigene bilparvovec	NCT03199469	Excluded if postivie AAV8 abs over a threshold, threshold not stated.	Mention of 'vector antibody complexes'	Unknown	Unknown	Prednisolone	Unknown
DMD	scAAV9. U7.ACCA	NCT04240314	Excluded if AAV9 binding abs >1:1:400 by ELISA.	AAVabs rise	Unknown	Elispot positive AAV, used to taper prednisolone.	Prednisolone	Prednisolone tapered according to transaminases.
	rAAVrh74. MHCK7. micro-' dystrophin	NCT03375164	Excluded if rAAVrh74 binding ab detected > 1:400	AAV ab rise	CH50 measured, no abnormalities. No thrombocytopenia.	rAAVrh74, micro-dystrophin IFN-γ ELISpot. Liver enzymes not associated with T cell response	Prednoslone	Prednisolone tapered according to GGT
	PF-06939925	NCT03362502	Excluded if pre-existing neutralizing AAV9 ab.	Unknown	aHUS complement activation, renal failure, thrombocytopenia.	Unknown	Prednisolone	Eculizumab given for complement activation
	SGT-001	NCT03368742	Excluded if postivie AAV9 abs over a threshold, threshold not stated.	Unknown	Complement activity against capsid detected, resulted in immue haemolysis, thrombocytopenia, renal failure, cardiopulmonary insuffiency. (aHUS). Activation of the terminal limb of the classical complement pathway (C5b) in all subjects.	Unknown	Prednoslone, eculizumab, C1 esterase inhibitor.	Eculizumab given for complement activation- now screened for.
CD	rAAV9-CB6-ASPA	I&D	negative for AAV9	No evidence of response	No evidence of activation.	No evidence of response	Ritixumab and sirolimus	None reported
LGMD2E	rAAVrh74.MHCK 7 .hSGCB	NCT03652259	Negative for AAVrh74	Unknown	No signs of complement activation were observed. No thrombocytopenia.	Unknown	Prednisolone	None reported
MPS IIIA	scAAV9. U1a.hSGSH	NCT02716246	AAV9 total Ab titer >1:100 is exclusion criterion.	Unknown	Mild and transient thrombocytopenia ?cause	Transiently positive Elispot to AAV9 capsid	Prednisolone	None reported
MPS IIIB	rAAV9.CMV. hNAGLU	NCT03315182	total anti-AAV9 antibody titers ≥ 1:100 is exclusion criterion ELISA	Unknown	Unknown	1/4 patients transiently positive Elispot to AAV9 capsid	Prednisolone	None reported
GM1	AAV9-GLB1	NCT03952637	AAV9 total antibody titre must be <1:50	Unknown	Unknown	Unknown	Rituximab, sirolimus, IV methylyprednisolone, prednisolone	None reported

Table 3a. Immune Responses to Systemically Administered Gene Therapies. See tables 1a&1b figure legends. AAV ab= anti- AAV antibody. INF-y= interferon gamma.

Disease	Product	Setting/NCT	AAVab Inclusion Cut Off	Evidence of AAVab post infusion	Evidence of Complement Activation	Evidence of T-Cell Activation	Cytokine measurement/ WBC measurment	Immune Prophylaxis	Immune Treatment of Adverse Events
GAN	scAAv9/JeT-GAN	NCT02362438	30% patients AAV9abs in serum. no Nabs in CSF	Serum and CSF AAV9 NAb levels rise	Not measured	ELISpot shows T cell response to AAV9. Not to gigaxonin.	Peripheral cytokine analysis/ asymptomatic CSF pleocytosis	IV Methylprednisolone, reducing course oral Prednisolone	None reported
SMA-2	Onasemnogene abeparvovec	NCT03381729	Anti-AAV9 Ab titers<1:50	Unknown	Unknown	Unknown	Unknown	Nil	None reported
CD	AV2-NSE-ASPA-WPRE-bGHpA	I&D	No cut off	No AAV2 nabs in serum. No Nabs in CSF.	No evidence of activation	No evidence of activation	Cytokines: IL2, IL4, IL5, IL8, IL10, IL12, IL13, IFNγ, TNFα measured. No sig. differences pre and post	Rituximab + Sirolimus	None reported
MPS IIIA	AAVrh10-h.SGSH	NCT01474343	No cut off	Anti-AAVrh.10 or antiSGSH abs not detected in serum	Not measured	No evidence of activation	Unknown	Mycophenolate Mofetil, Tacrolimus, Prednisolone	None reported
CNL2	AV2CUhCLN2	NCT00151216	No anti-AAV2abs	Developed, anti-AAV2 abs, gone after 18 months.	Not detected	Not detected	Unknown	Nil	None reported
	AAVrh.10CUCLN2	NCT01414985	One subject Abs prior to transfer	AAV abs detected in serum	Not measured	Activation to capsid and transgene	Unknown/no abnormal inflammatory cells in CSF	Nil	None reported
CNL6	scAAV9.CB.CLN6	NCT02725580	No cut off	Not detected	Not detected	Not detected	Unknown/Unknown	Nil	None reported
PD	AAV-GAD	NCT00195143	No cut off. Some +ve at baseline	No AAV2 ab increased. No anti transgene abs	Not measured	Not Measured	Unknown/Unknown	Nil	None reported
	AAV-hAADC-2	NCT00229736	Nab to AAV-2 1:1,200. is an exclusion critetion	mildly increased AAV2 Nabs for 6/12	Not measured	Not Measured	Unknown/Unknown	Nil	None reported
	AAV2-NRTN	NCT00985517	no cut off	No increase AAV2 abs	Not measured	unknown	Unknown/Unknown	Nil	None reported
AD	AAV2-NGF	NCT00876863	no cut off	No increase AAV2 abs	Not measured	unknown	Unknown/Unknown	Nil	None reported
AADC-D	AAV-2 hAADC	NCT01395641	anti-AAV2 < 1·0 optical density.	No increase AAV2 abs	Not measured	unknown	Unknown/Unknown	Nil	None reported
GD	PRV-GD2-101/PR001	NCT04411654		unknown	unknown	unknown	Unknown/Unknown	Methylprednisolone, prednisolone, sirolimus	None reported
ALS	AAV-miR-SOD1	I&D	unknown	Evidence of B cell activity against capsid patient 1	Unknown	Evidence of T cell activation against capsid patient 1	CSF Pleocytosis	First patient pred only second pred, sirolimus, rituximab	Prednisolone

Table 3b. Immune Responses to Direct CNS Administered Gene Therapies. See tables 1a&1b figure legends