Systematic review of clinical safety and efficacy of AAV gene therapies

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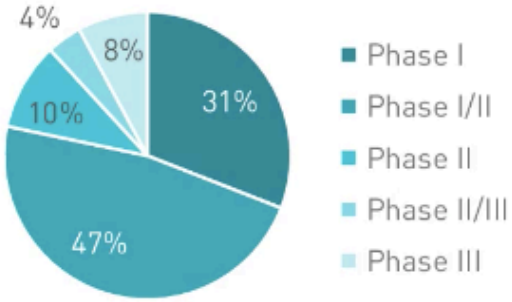
ASGCT 2020

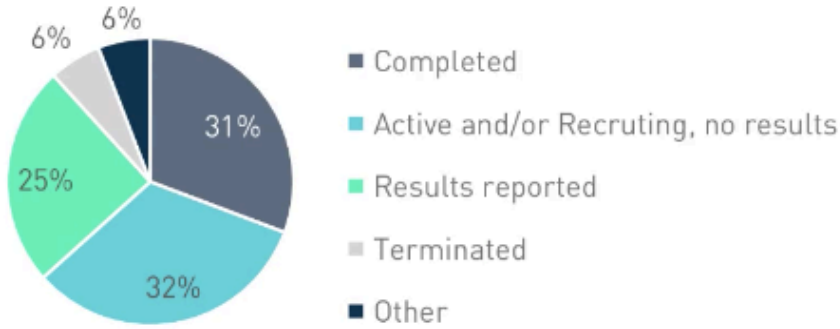
Dataset methodology and validation

- Source data from clinicaltrials.gov
- Cross-validation using peer-reviewed publications, conference presentations, SEC 10-K and S-1 forms, corporate press-releases, as well as commercially available databases including *GlobalData* and *Thomson Reuters*
- Trial inclusion cut-off as of Dec 31st, 2019
- Trial data cut-off as of Mar 31st, 2020
- Trials reported before 2007 are hard to validate and were excluded from most analyses
- **Quality of disclosure on protocol, construct and even route of administration still limited, 13 years after public reporting was mandated**

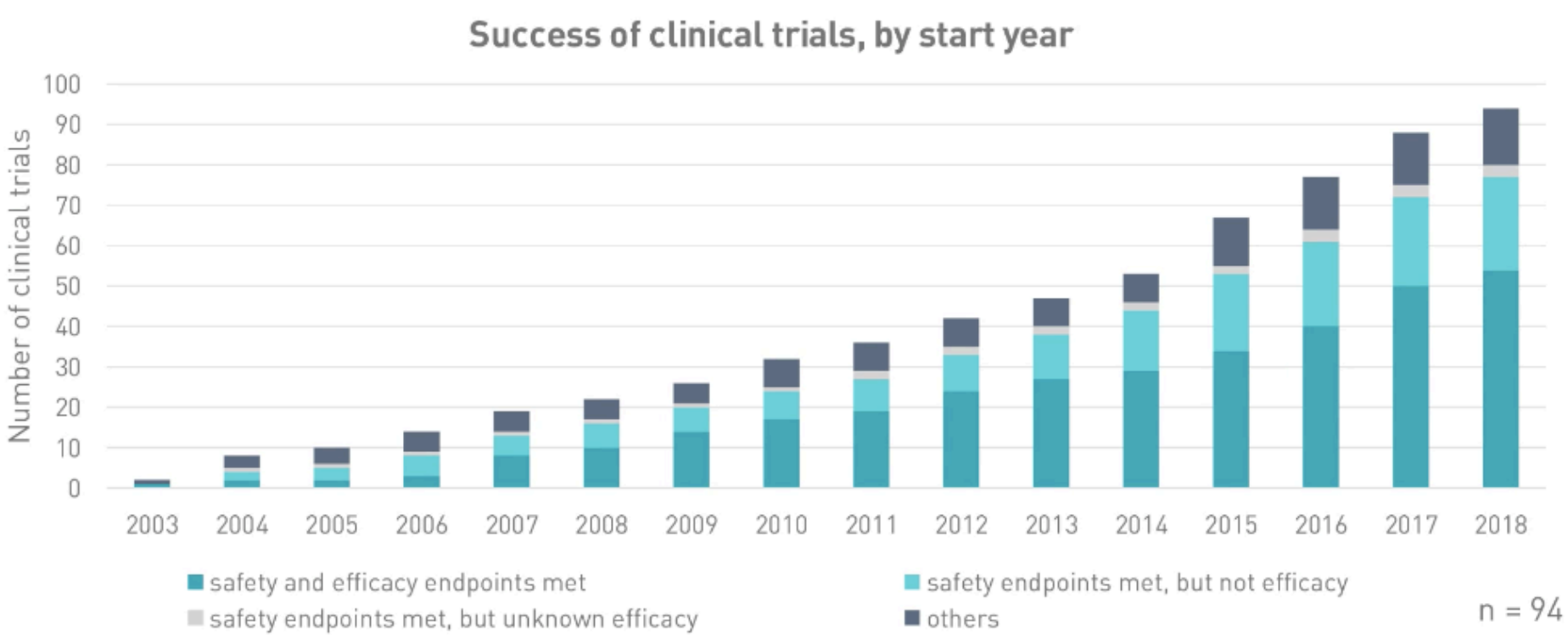
Trials by phase



Trials by results status

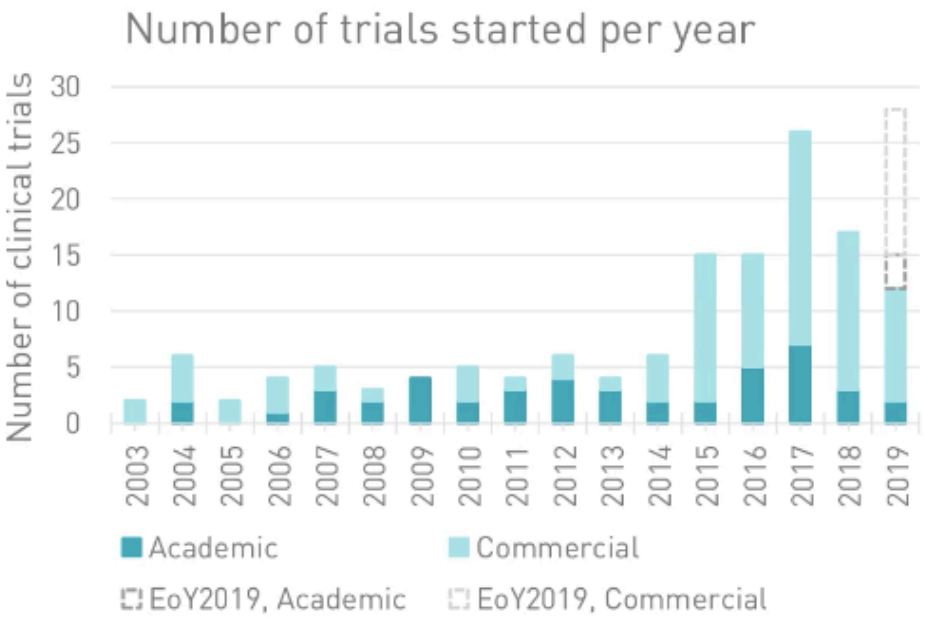


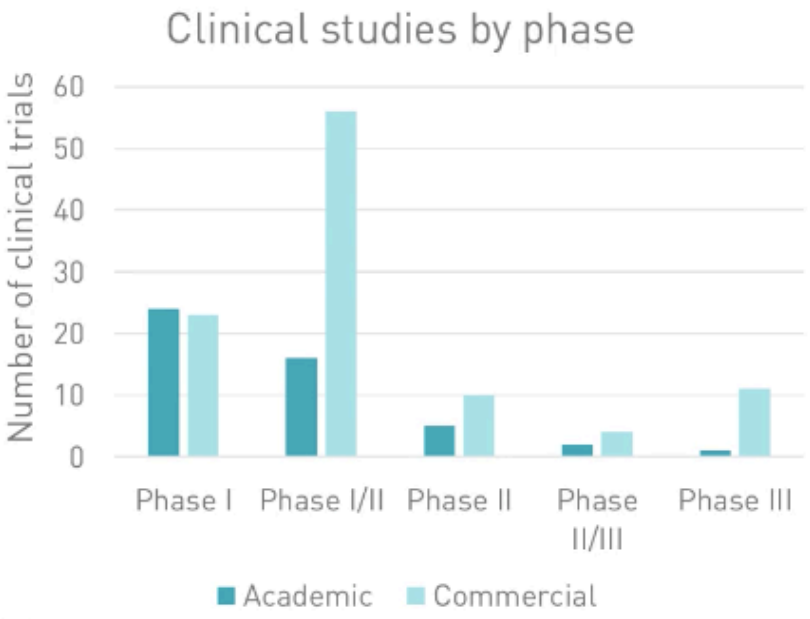
AAV has successful proof of concept across 50+ completed trials



No trials initiated in 2019 and 2020 reported their primary completions as of the cut-off date

Industry has taken the lead since 2014



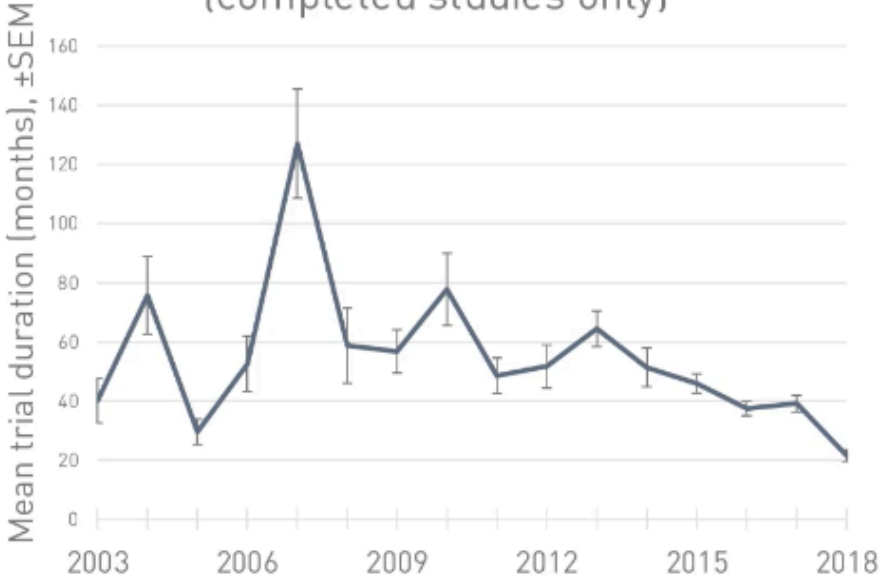


n = 149

We estimate >85% of commercial trials are done by venture-backed companies
Industrial initiations in 2018 appear to be under-reported – to be updated later in 2020

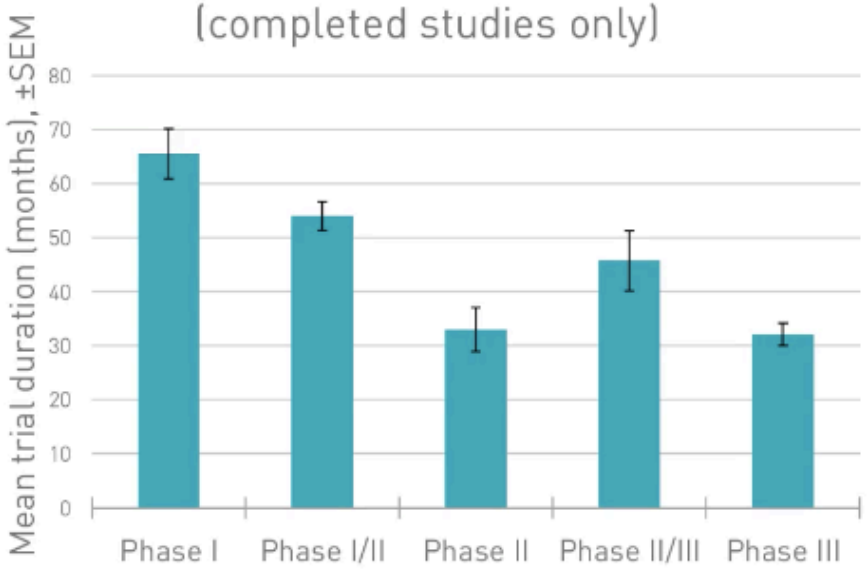
Trial duration trending down with experience

Trial duration by start year
(completed studies only)



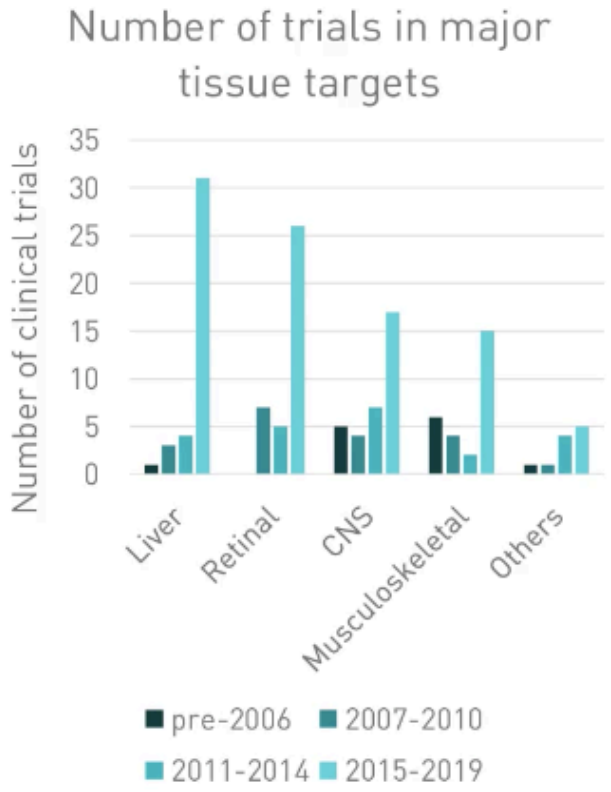
n = 95

Trial duration by phase
(completed studies only)

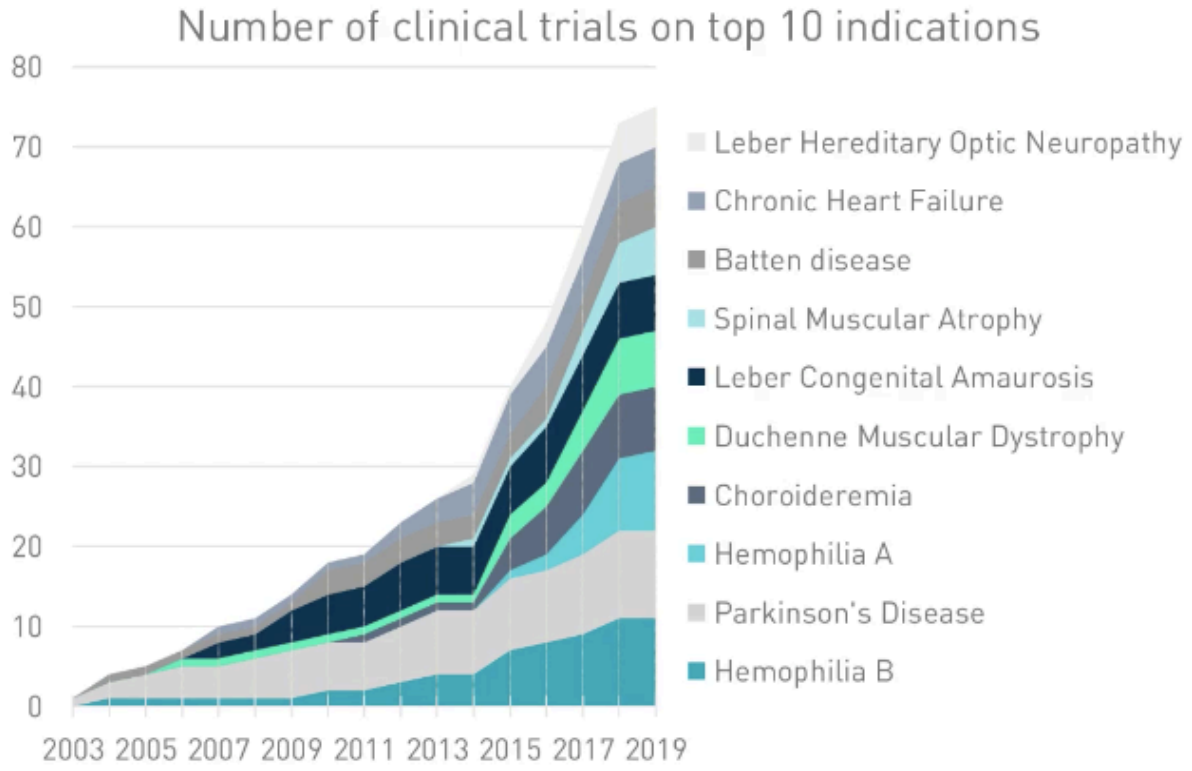


Mean projected duration IND to NDA **86.1±7.2 months** vs. real-life: Luxturna® **115 months**
Zolgensma® **48 months**

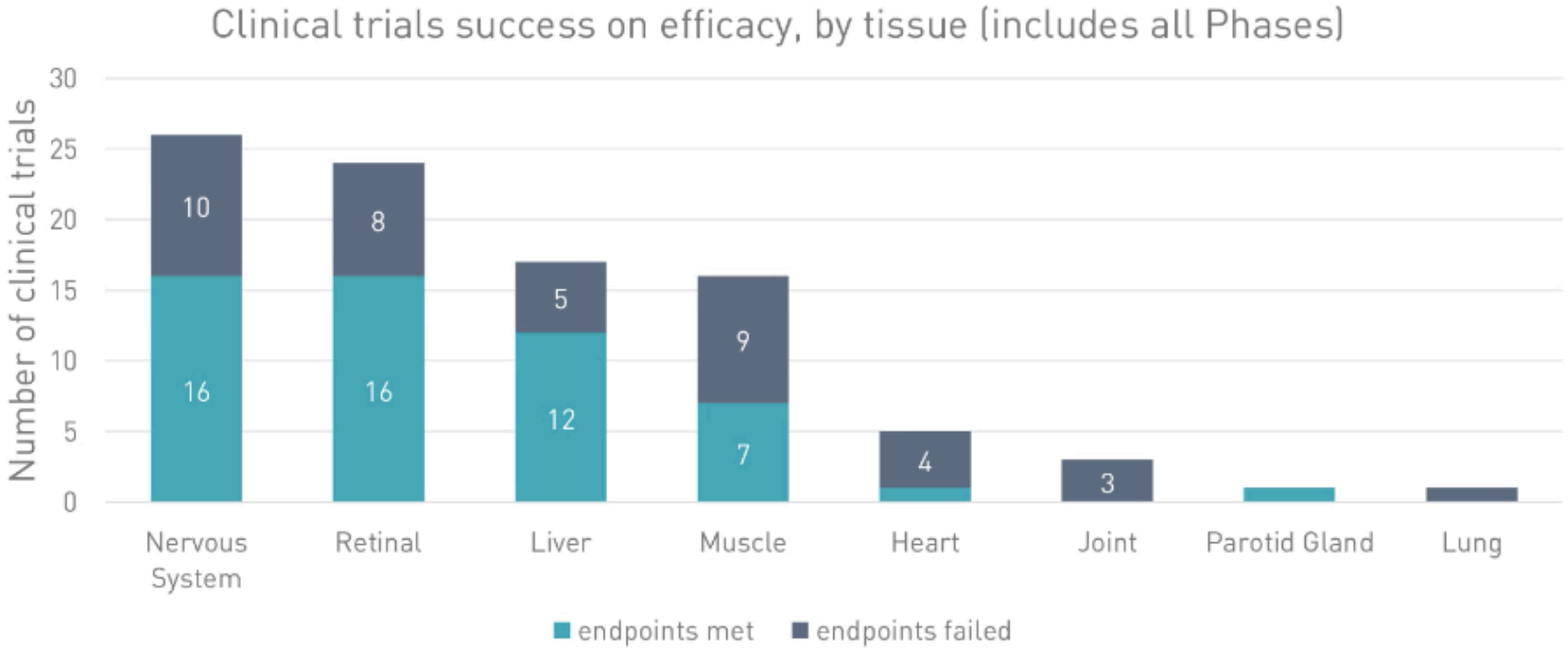
Four compartments dominating the trial landscape



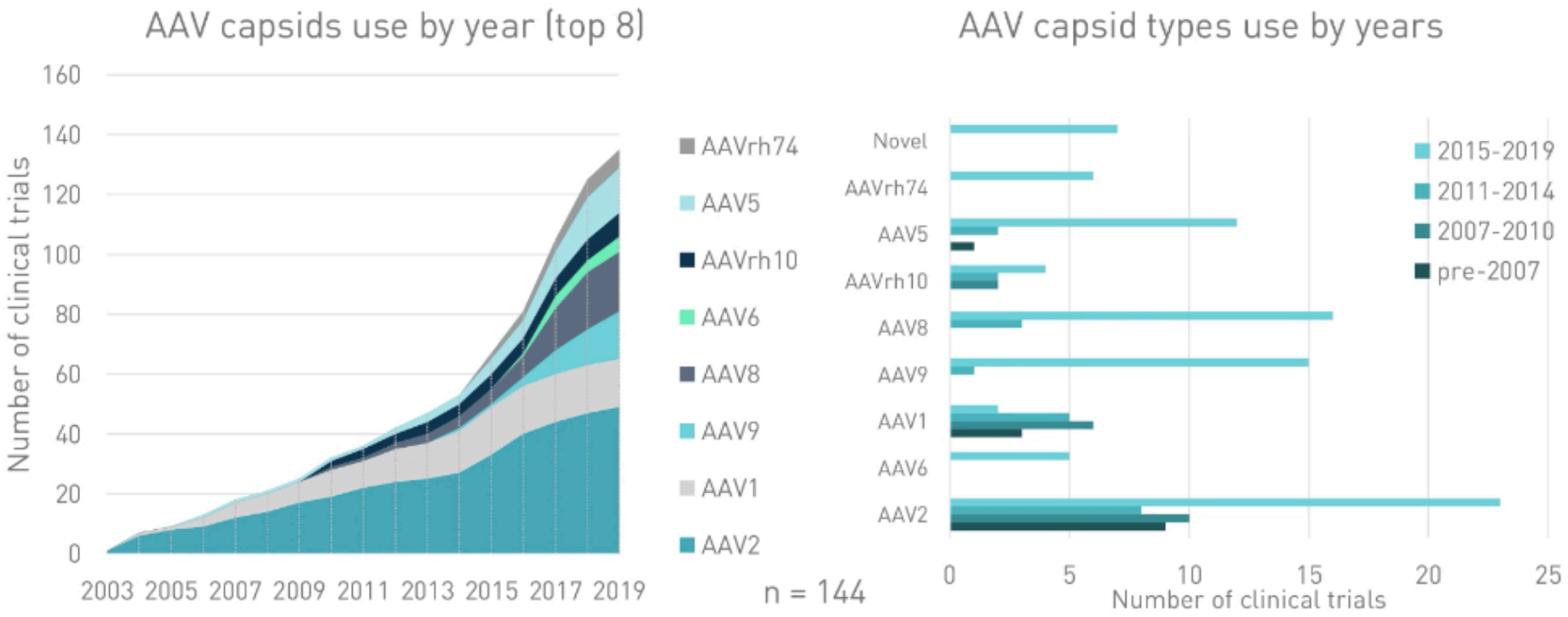
n = 149



Most trial successes are in key compartments

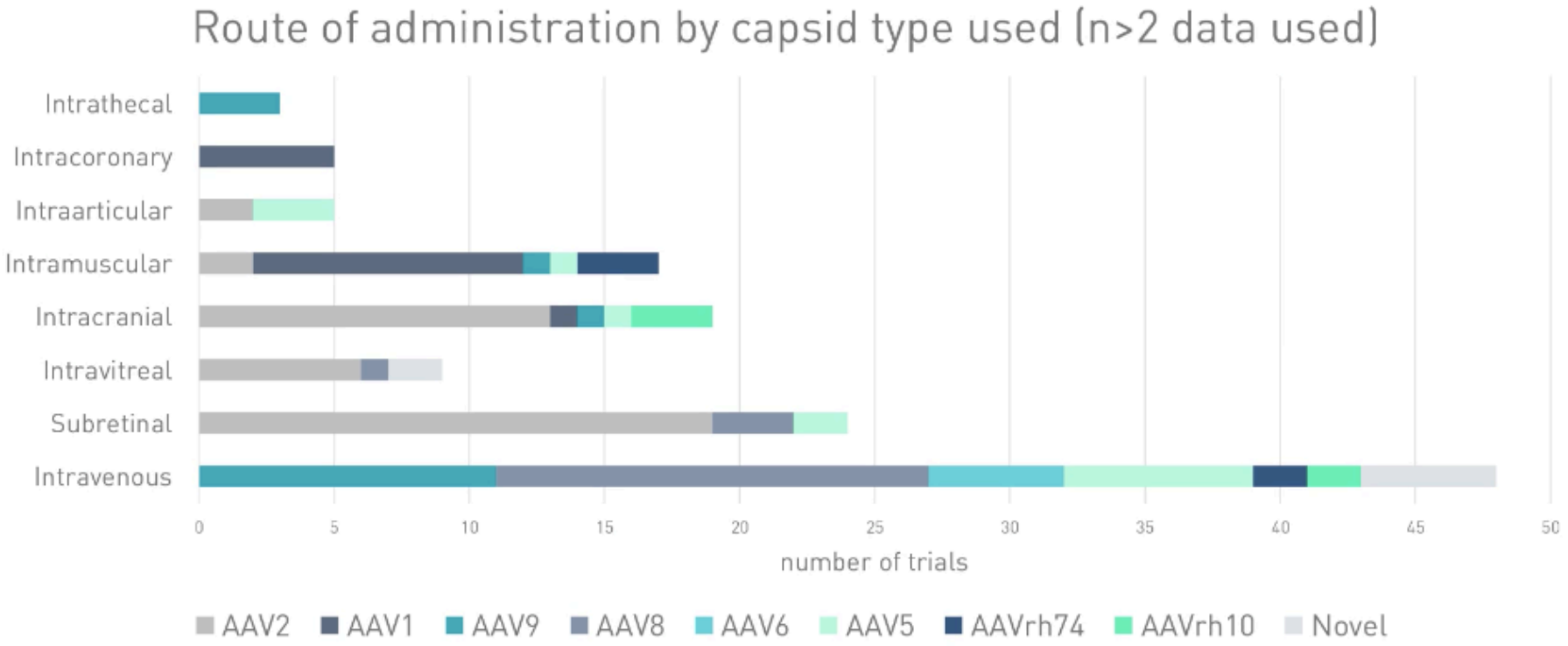


Three generations of vectors now in the clinic



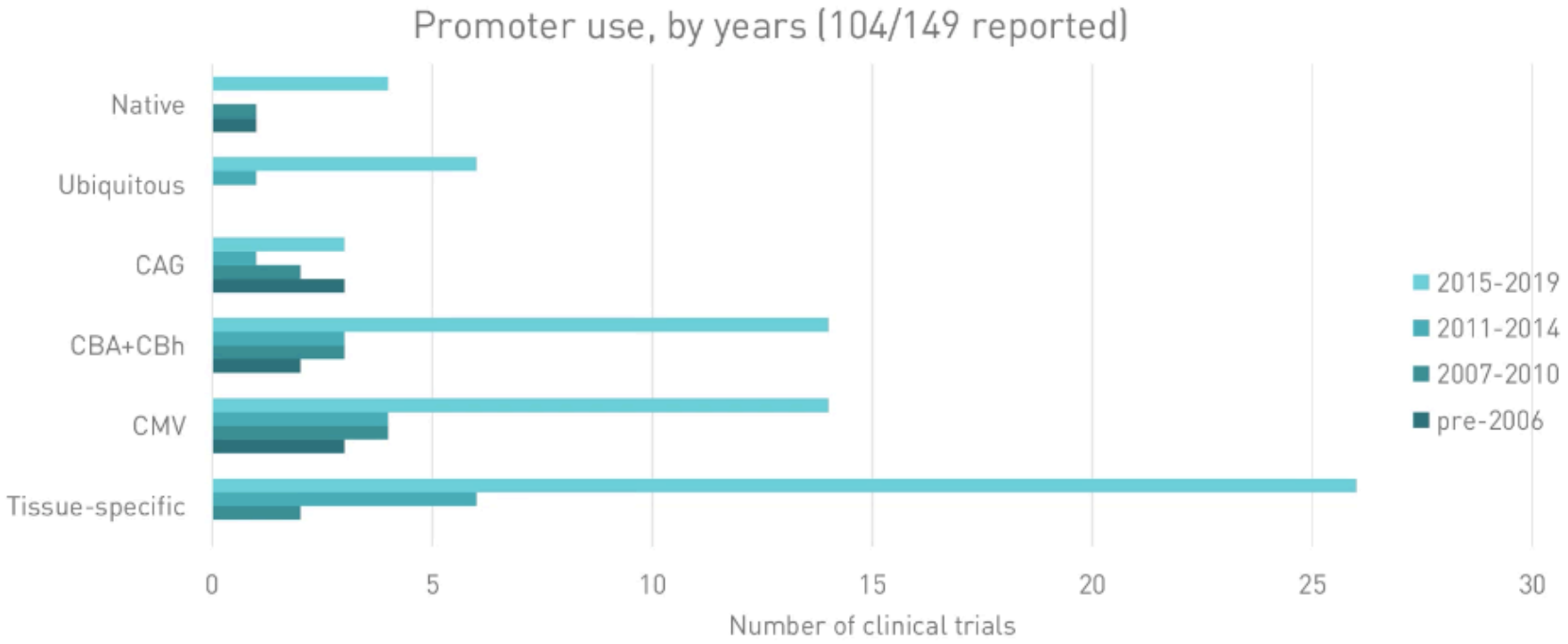
Notable paradigm shift AAV1 & AAV2 -> AAV2/x -> novel capsids

Preferred routes of administration by capsid type



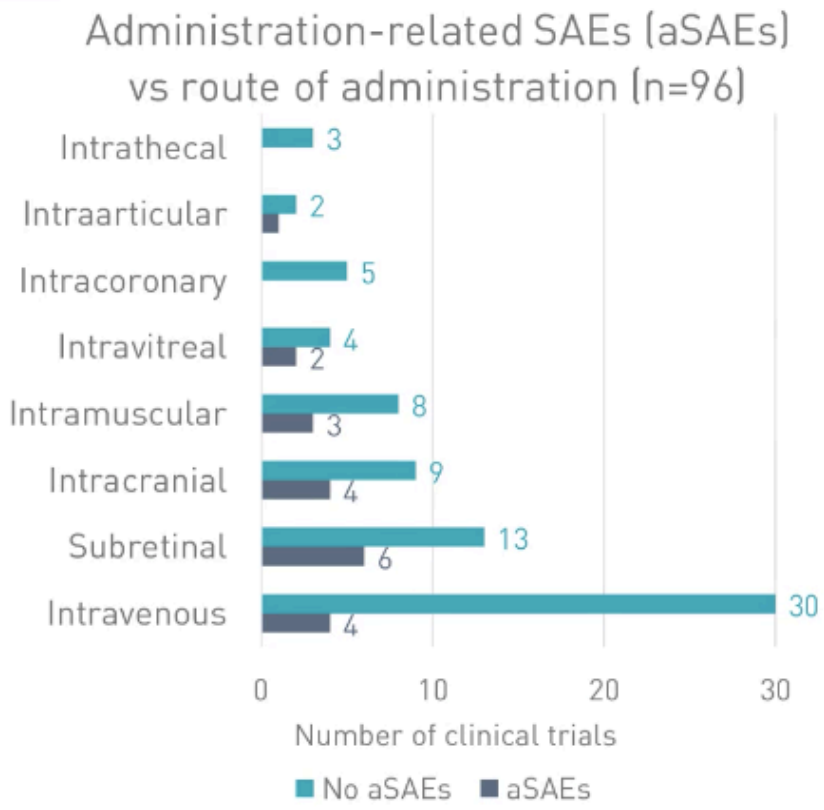
Strong preference for AAV2 in the eye in line with the approved drug; IV least selective

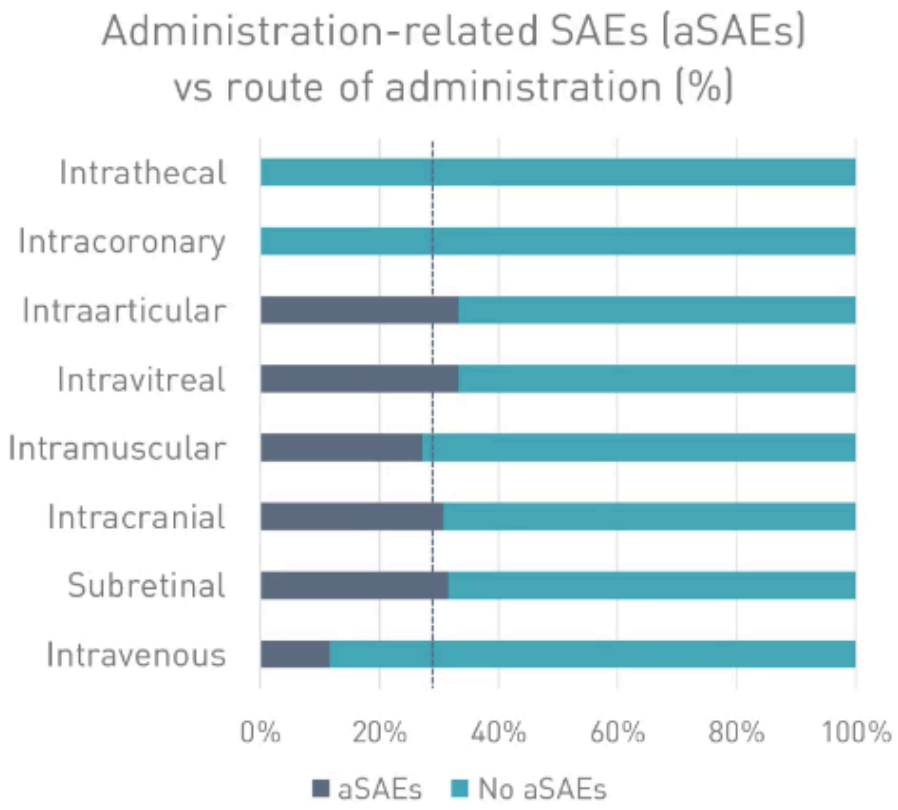
Decrease in use of non-specific promoters



Clear shift from ubiquitous and viral to tissue-specific promoters in recent years

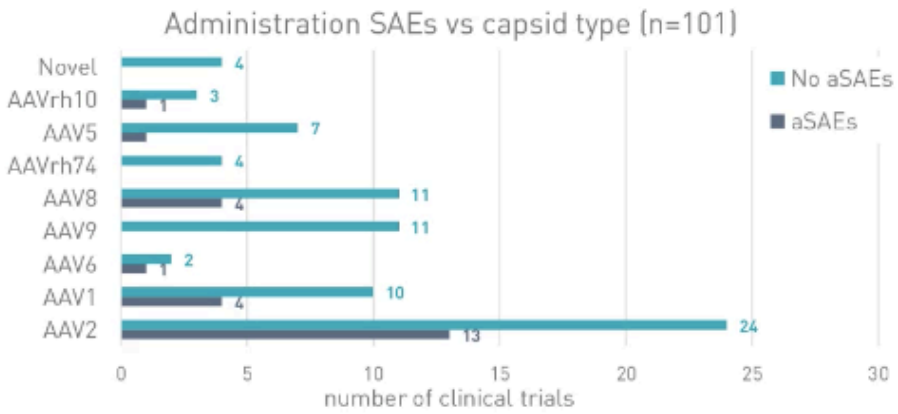
Safety: administration-related SAEs I

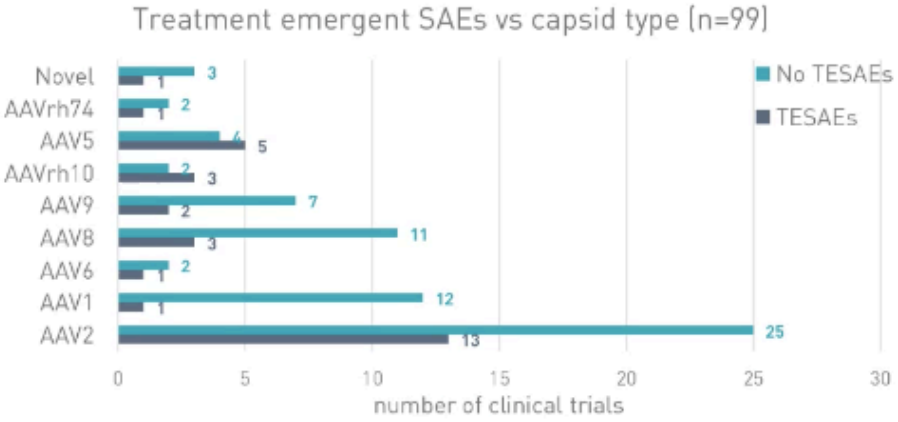


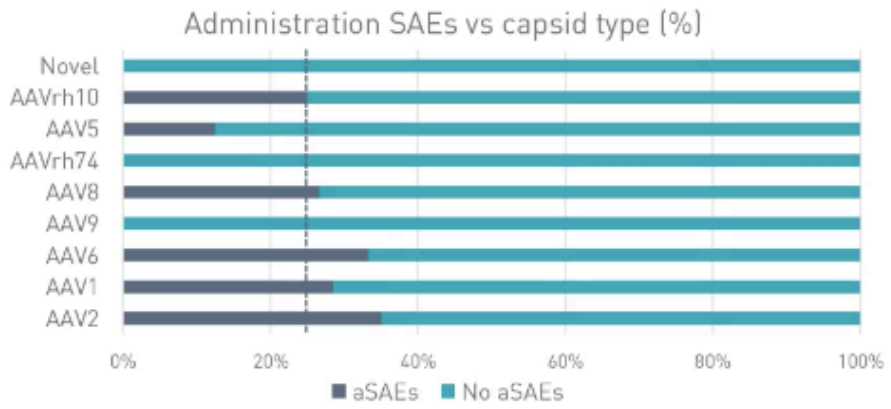


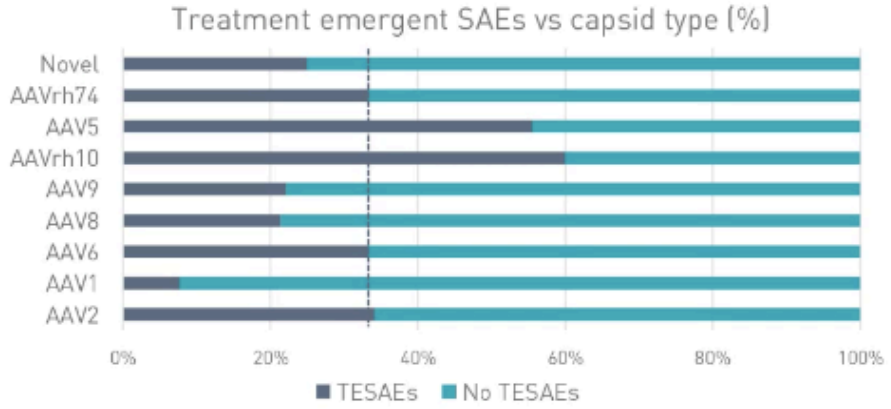
* Here and further trials with >1 reported SAE are counted as having SAEs

Safety: SAEs by capsid type

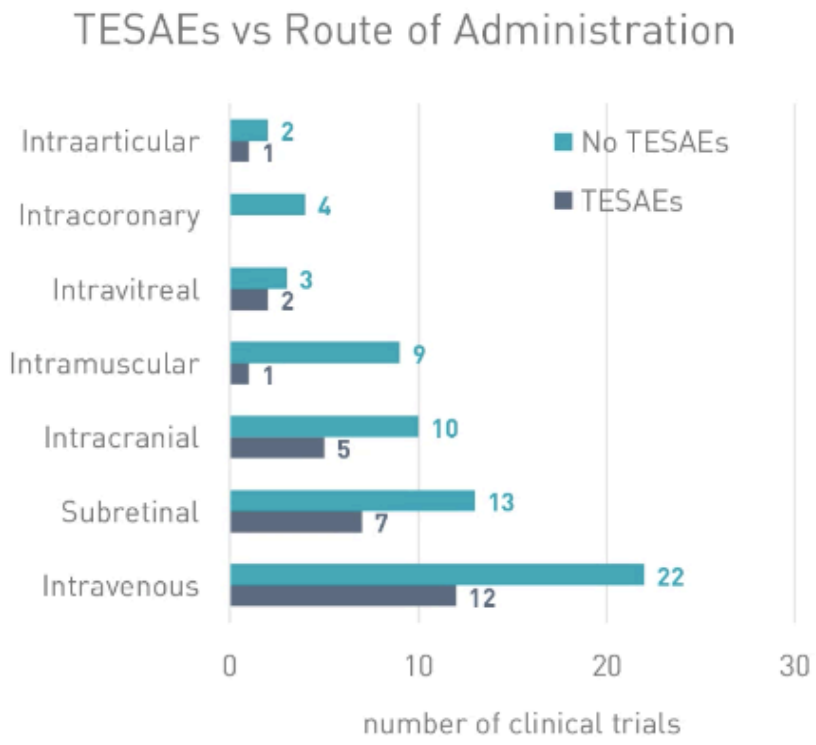


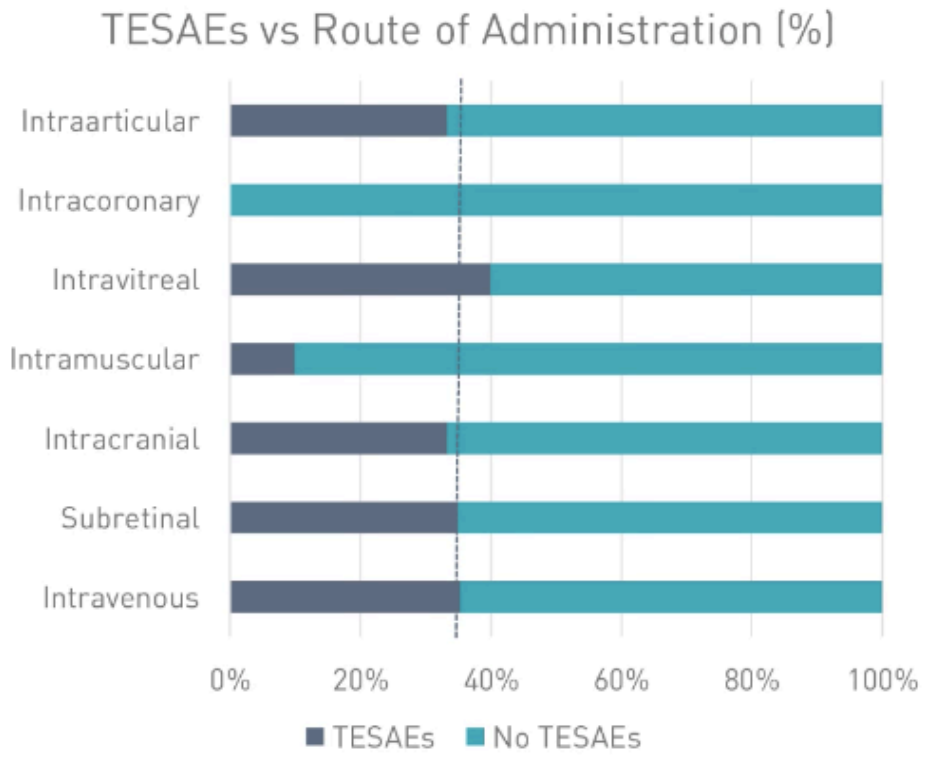






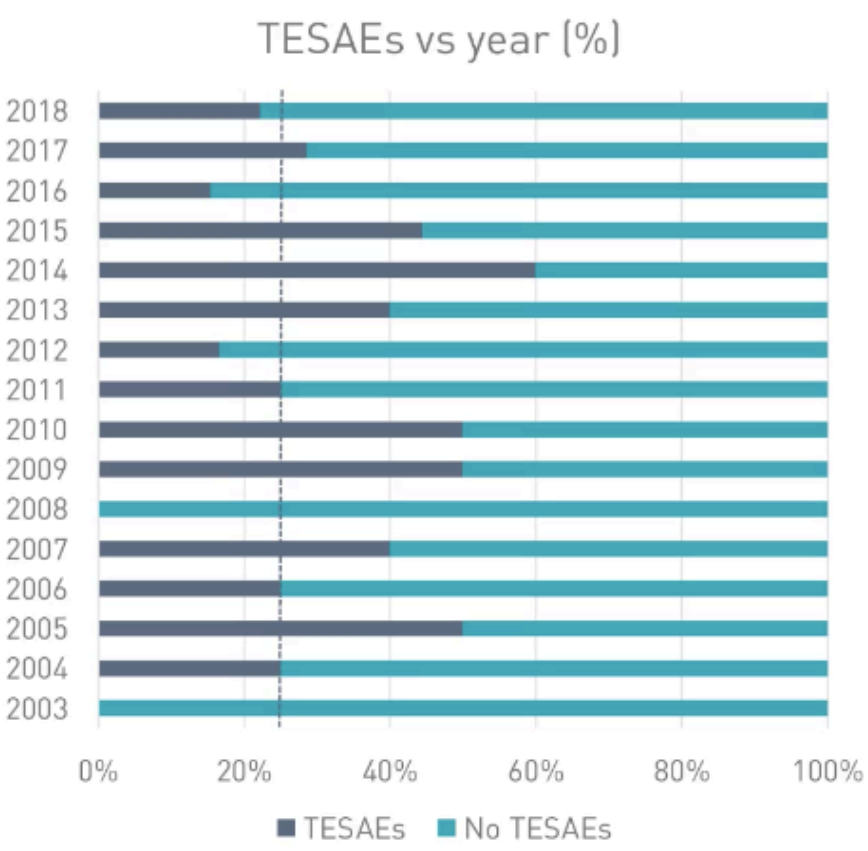
Safety: treatment-emergent SAEs I (Route of Administration)

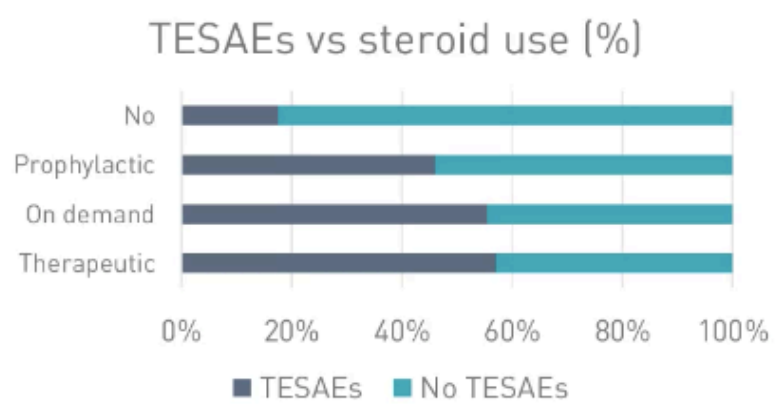


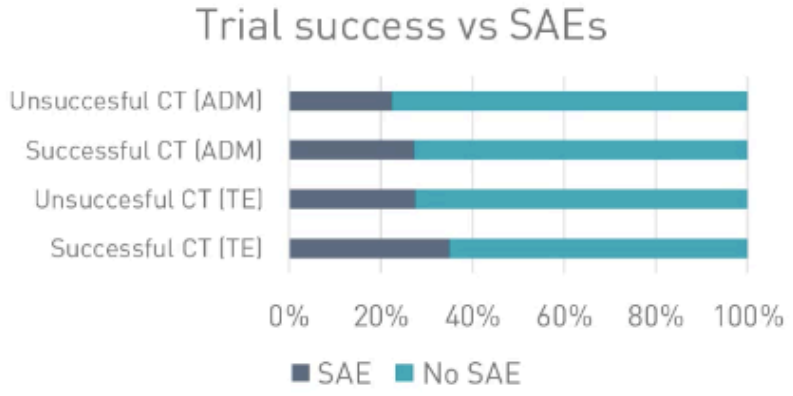


n = 93

Safety overview: treatment-emergent SAEs II (progress)







Efficacy overview – Route of administration

Route of Administration	Phase I	Phase II+I/II	Phase III+II/III
Intravenous	2/3 66.67%	11/15 73.33%	3/4 75.00%
Subretinal	2/3 66.67%	8/12 66.67%	3/3 100.00%
Intracranial	5/7 71.43%	5/9 55.56%	N/A
Intramuscular	3/9 33.33%	1/4 25.00%	2/2 100.00%
Intravitreal	1/1 100.00%	0/1 0.00%	0/2 0.00%
Intracoronary	N/A	1/5 20.00%	N/A
Intraarticular	0/2 0.00%	0/1 0.00%	N/A
Intrathecal	1/1 100.00%	N/A	N/A
Intranasal	0/1 0.00%	N/A	N/A

Efficacy overview – therapeutic areas

Therapeutic area	Phase I	Phase II+I/II	Phase III+II/III	IND to NDA	IND to NDA all Tx**
Ophthalmology	(5/6) 83.3%	(8/13) 61.5%	(3/5) 60.0%	30.7%	23.6%
Neurology	(8/11) 72.7%	(5/9) 55.6%	(2/3) 66.7%	30.0%	19.2%
Metabolic	N / A	(3/7) 42.9%	(2/2) 100.0%	42.9%*	16.3%
Hematology	(3/4) 75.0%	(6/8) 75.0%	(1/1) 100.0%	56.2%	47.1%
Musculoskeletal	(3/8) 37.5%	(3/5) 60.0%	N / A	22.5%*	28.8%

* No drug completed IND to NDA path successfully as of the cut-off date
** Source: *GlobalData*

Conclusions

- AAV gene therapy obtained significant clinical validation since 2003, with 94 completed trials and 51 trials which reached its efficacy endpoints
- Total of 3328 patients treated in clinical trials with only 9 Grade 4/5 SAEs deemed treatment emergent
- Trials are dominated by four key organs: retina, liver, muscle and the brain
- Median duration from IND to NDA is 86.1±7.2 months
- Mean probability of reaching from IND to NDA is 36.46%, significantly better than historical rates for other therapeutics in rare diseases
- On average, 21% of trials have administration-related SAEs (aSAEs), with IV being the safest (12%) and intracranial as well as subretinal the most problematic (~32%)
- No significant correlation between tissue and treatment-emergent SAEs (TESAEs) other than intramuscular and intracoronary being very benign