Outlook on Rare Neurodegenerative Diseases: ALS and SMA

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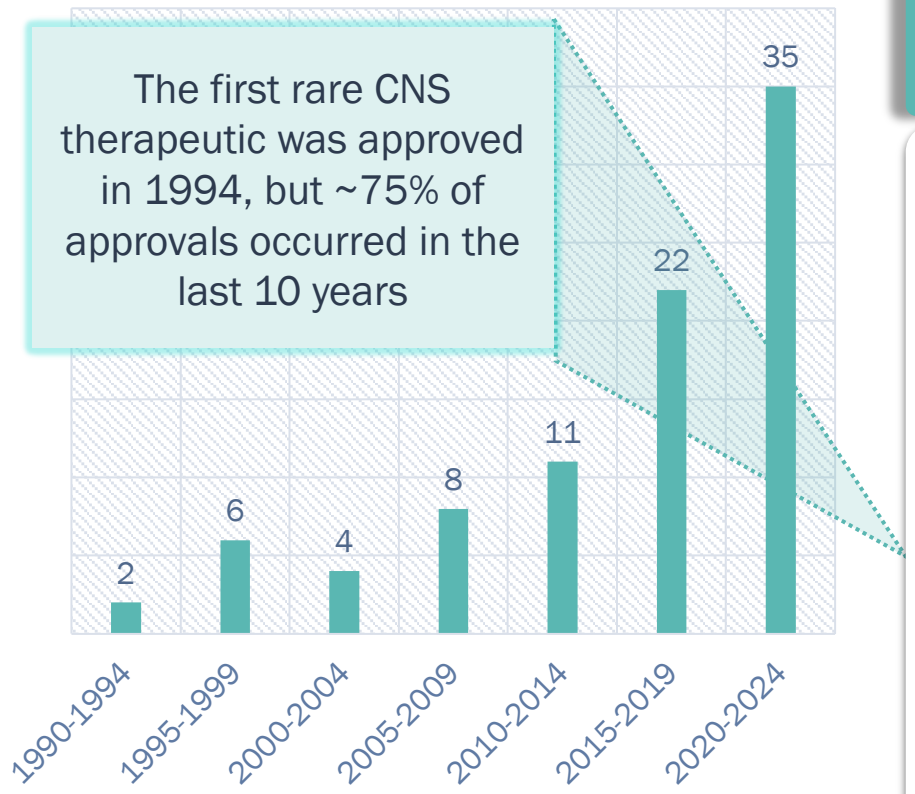
Bluestar BioAdvisors

Strategic Experts in the Business of Life Sciences

Rare CNS diseases are defined by the specialized care they require; recent technological innovations and commercial incentives have spurred investment in this area

Rare Central Nervous System Diseases – Overview

Number of Rare CNS FDA Approvals (1994-2024)[1,2]



Defining rare central nervous system (CNS) diseases

Rare CNS diseases are highly morbid and are associated with high mortality and debilitating symptoms that require chronic treatment by a neurologist or other specialists (e.g., epileptologists, neuromuscular specialists); care is often provided at centers of excellence (CoE) that offer comprehensive multi-disciplinary approach to disease management

Incentives exist for developing rare disease therapies pre and post approval

- **Expedited drug review:** the high disease burden and substantial clinical unmet need often make rare neurodegenerative drugs eligible for fast track or accelerated approval pathways and priority review vouchers
- **Concentrated sales force:** rare diseases are often treated at CoE
- **Orphan drug pricing and exclusivity:** orphan drugs are granted seven year market exclusivity in the U.S and 10 year exclusivity in E.U. Orphan drugs, including those for rare neurodegenerative diseases, command significant pricing power in the U.S., with the average cost reported to be $220K/patient/year compared to $13K/patient/year for non-orphan drugs

Emergence of novel technologies

- 80% of rare CNS diseases are genetic in origin, making them an attractive target for companies developing gene-based approaches (e.g., gene editing, gene replacement)
- Improved, and less invasive delivery technologies to enhance blood brain barrier penetration or biodistribution are also on the rise (e.g., QurAlis' Flex-ASO)

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Source: (1) FDA website (2) Pharmaprojects (3) Kioutchoukova, Ivelina P., et al. " World Journal of Experimental Medicine 13.4 (2023): 59. (4) Althobaiti, Hana, et al. Healthcare. Vol. 11. No. 4. MDPI, 2023

ALS and SMA are two rare neurodegenerative CNS diseases of differing pathophysiological complexity and available treatment options

Background on ALS and SMA

Amyotrophic Lateral Sclerosis (ALS)

- ALS is a fatal neurodegenerative disease that affects the brain and spinal cord, which causes gradual deterioration and death of motor neurons that control voluntary muscle movements; the average life expectancy from the time of diagnosis is two to five years, but some patients may live for decades
- Most cases are sporadic, i.e. present with no family history, while 15% are familial in origin (e.g., SOD1 or FUS mutations)
- Disease is highly heterogenous clinically including region of onset (bulbar or limb), degree of motor neuron involvement, rate of disease progression, and presence of cognitive/behavioral changes
- Therapies approved for ALS (FDA approval dates) include:
  - **Riluzole (Rilutek, Tiglutik, Exservan, 1995):** believed to reduce motor neuron damage as a glutaminergic blocker
  - **Nuedexta (2010):** indicated specifically for pseudobulbar affect symptoms via sigma-1 agonist/NMDA receptor antagonist activity
  - **Edaravone (Radicava, 2017):** believed to act as a neuroprotective agent that prevents oxidative stress damage
  - **Tofersen (Qalsody, 2023)**: antisense oligonucleotide that blocks SOD1 protein production; established neurofilament (NfL) as a biomarker
  - **Relyvrio (2022)**: believed to prevent nerve cell death; withdrawn in April 2024 after confirmatory trial failure

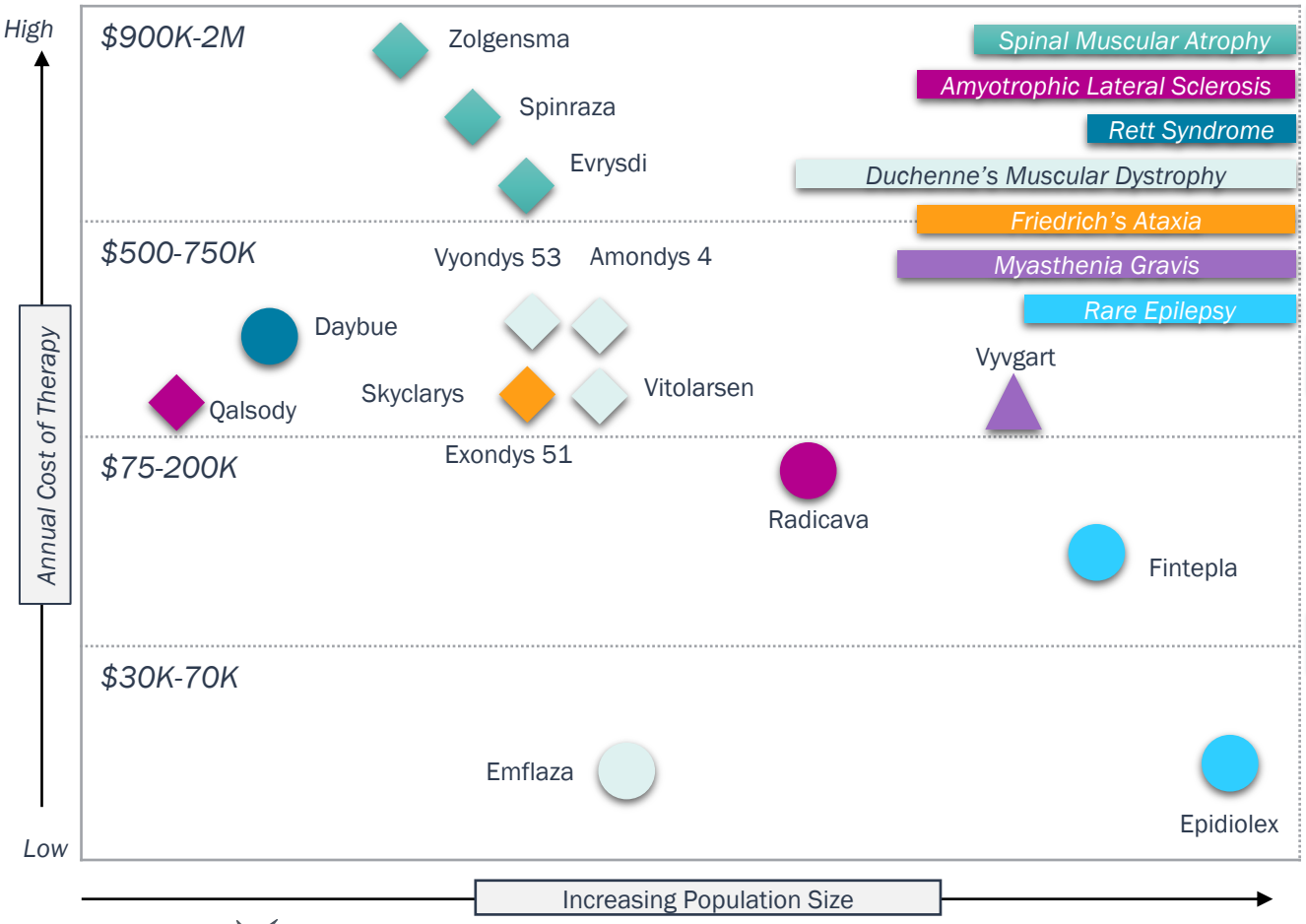
Spinal Muscular Atrophy (SMA)

- SMA is a neuromuscular disease that consists of degeneration of a subset of nerve cells in the spinal cord and motor nuclei in the brainstem, resulting in progressive muscle weakness and atrophy
- SMA is genetically driven by biallelic mutations in the survival motor neuron 1 (*SMN1*) gene; loss of *SMN1* may be partially compensated for by a back-up gene *SMN2,* with more *SMN2* copies being associated with less severe phenotypes
- Traditionally SMA consisted of three subtypes, which have now been expanded to five (type 0 to type 4), which are defined by age of onset and the progression of loss of motor function; type 0 and 1 are the most severe and common forms with a life expectancy of less than two years; type 3 appears around 18 months of age and although life expectancy is similar to the general population, type 3 is characterized by difficulties walking; type 4 appears in adulthood and these individuals remain active and enjoy a normal life expectancy
- Therapies approved for SMA (FDA approval dates) include:
  - **Nusinersen (Spinraza, 2016):** antisense oligonucleotide (ASO) that modifies splicing of *SMN2* to upregulate expression of the compensatory splice form of *SMN2*
  - **Onasemnogene abeparvovec-xioi (Zolgensma, 2019):** AAV9 based gene therapy that provides a functional copy of *SMN1*
  - **Risdiplam (Evrysdi, 2020):** small molecule splicing modifier that upregulates the compensatory splice form of *SMN2*

Multiple incentives offset high clinical development risks and costs for drug modalities of all types, as exemplified by marketed drugs for SMA and ALS in the U.S.

Rare CNS Diseases – Clinical and Commercial Incentives

Orphan Drug Pricing of Select Rare CNS Therapies in the U.S. (Annual Costs of Therapy in 2022)



ALS	SMA
Clinical Development Incentives	
Radicava and **Qalsody** were granted priority review and fast track designations; Qalsody was also approved via accelerated pathway	**Zolgensma** was granted breakthrough designation; **Spinraza** and **Everysdi** were granted pediatric priority review vouchers
Specialized Care Means Lower Marketing Spend	
ALS specialists at CoEs are available to patients, e.g. centers certified by ALS Association	SMA patients are identified by newborn screening (NBS) and referred to specialized centers via networks such as CureSMA
Commercial Performance (Select Examples)	
Radicava, approved in 2017, generated $224M in revenues in 2023 (U.S), and ~15K patients in the U.S. have been treated	Evrysidi, approved in 2020, generated $621M in revenues in 2023 (U.S.), and ~8.5K patients have been treated globally

Legend: ◇ Disease Modifying Mechanism of Action (MoA) △ Understood MoA for Symptomatic Treatments ○ Unclear Biological Rationale

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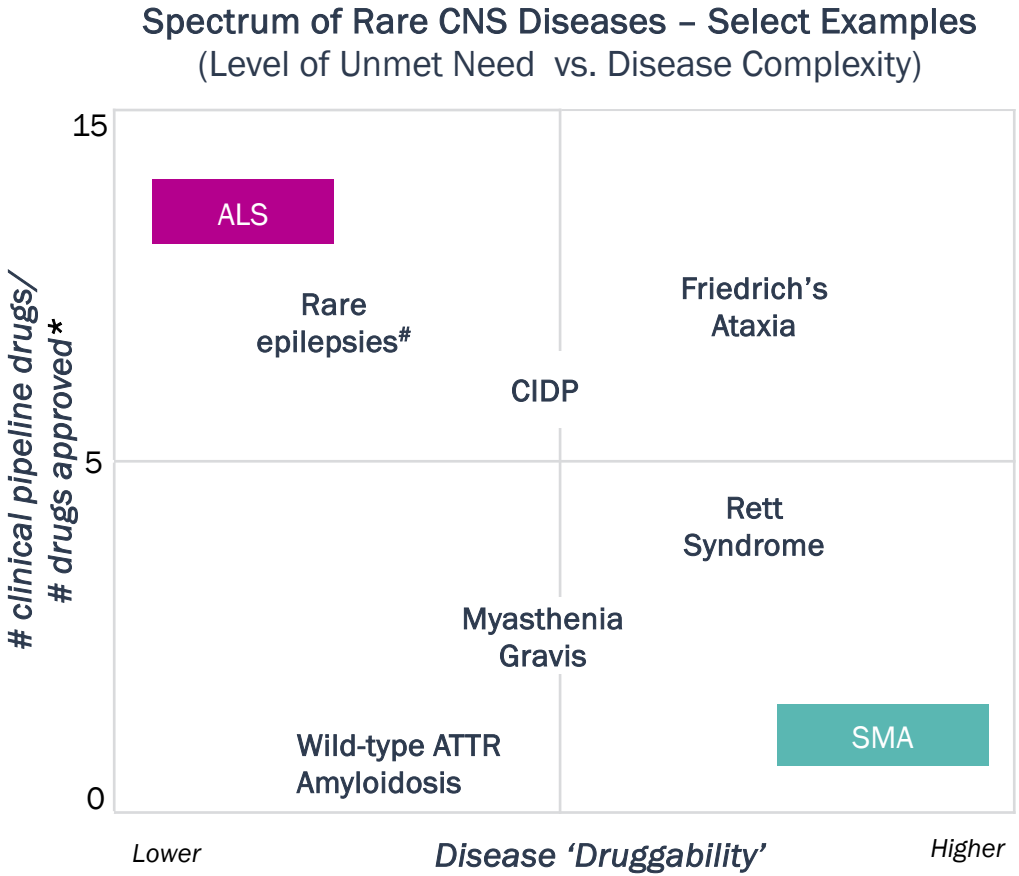
Rare CNS diseases vary in their 'druggability' and unmet need; ALS and SMA are on opposite ends of this spectrum resulting in distinct drug development and clinical trial strategies

Rare CNS Diseases – Druggability and Unmet Need



*counting number of approved therapies in the last 10 years
#includes Lennox Gastaut, Dravet Syndrome, Tuberous Sclerosis
Legend: ATTR: Transthyretin amyloid cardiomyopathy; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy

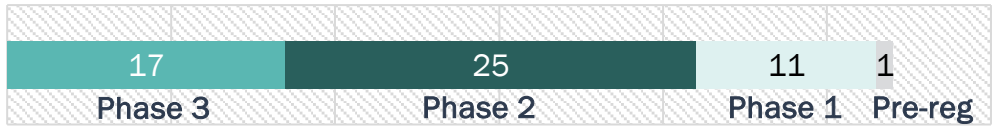
ALS	SMA
Disease 'Druggability': This qualitative metric reflects 1) the degree to which the underlying etiology is known and 2) heterogeneity in clinical presentation and disease progression	
• Multi-factorial and high disease heterogeneity with rare subsets and driver mutations, e.g. SOD1 • Disease is less amenable to targeted therapies and lacks "one-size" fits all approach	• Clearly defined by genetic mutations; however, severity and progression vary across the five SMA subtypes • Disease is more amenable than ALS to specific targeted approaches (e.g., gene therapy)
# of clinical pipeline drugs/#approved drugs*: this ratio is one indicator of the remaining unmet need and level of satisfaction with current therapies. The higher the ratio, the higher the need for better therapies	
Ratio = 45:4	Ratio = 5:3

Source: Pharmaprojects; Bluestar Analysis

Companies investing in ALS are exploring a diverse set of drug modalities and targets to increase the therapeutic potential relative to current therapies and pipeline competitors

Drug Modality and Target Strategies – ALS

Pipeline Assets (US)



Modalities

Small molecule | Antibody | Nucleic Acid | Cell Therapy | Peptide/ Protein

More frequent → *Less frequent*

Target Strategies

1. Repurposed drugs with established safety profile, known to target biological mechanisms implicated in ALS
2. Broadly acting therapies with a multi-modal approach
3. Precise molecular targeting with validated biomarkers
4. Gene editing for driver mutations in ALS
5. Regenerative cell therapies to restore or reverse ALS disease progression
6. Other, non-active ingredient approaches

Most therapies are being studied on top of standard of care – combination regimen are expected as a multimodal approach

Representative Pipeline Assets

- **PrimeC** (ciprofloxacin+celecoxib) **Neurosense**
- **Masitinib** (tyrosine kinase inhibitor) **ab science**
- Pridopidine (D2 receptor antagonist) **Prilenia**
- **ANX005** (IgG4 MAb) **Annexon**
- **Ulefnersen** (ASO for FUS mutations) **Ionis**
- **NurOwn** (debamestrocel cell therapy) **BrainStorm**
- *Other* **CNM-AU8** (Gold nanocrystals) **Clene**

Legend: ASO = Antisense Nucleotide

Clinical development in ALS is aiming to achieve stronger efficacy signals with more validated endpoints; time- and cost-efficient strategies are also being adopted

ALS Clinical Trial Strategies

Clinical Development Strategies			Select Pipeline Agents with Phase 2 or Phase 3 Clinical Data				
			CNM-AU8 (Clene)	Prime-C (Neurosense)	Masitinib (ab-science)	Pridopidine (Prilenia)	Nurown (Brainstorm)
			Data below reflects data from more recent studies reported				
Raising the Standards for Clinically Meaningful Data	Increased use of **biomarkers (e.g., NfL)** to validate MoA and demonstrate target engagement		✓	✓	-	✓	✓
	Demonstrating **functional benefit and survival** before submitting to FDA	ALSFRS-R	+	+	+	✗	✗
		Survival (overall, complication free)	+	+	+	✗	✗
	Conducting **confirmatory trials** to validate efficacy signal		✓	◇	✓	✓	✓
More Efficient Trial Design	**NfL biomarker** to predict clinical outcomes as a potential pathway to accelerated approval		+	+	-	✓	✓
	Use of cost-efficient **platform trials** to increase trial size and accelerate trial timelines (e.g., Healey Trial)		✓	◇	◇	✓	◇
			Regulatory Status				
			Global Ph3 planned – FDA rejected use of NfL data to support approval	*May not need confirmatory Ph3 pending end of Ph2 meeting*	*Confirmatory Ph3 ongoing focusing on patients in early disease stages*	*Global Ph3 planned – positive data seen in patients early in disease*	*Adcomm initially advised against approval; Ph3b ongoing under SPA*

+	✓	-	◇	✗
Statistically significant positive data	*Strategy is being applied*	*Endpoint is not measured*	*Strategy is not being pursued*	*Failed endpoint, but positive signals seen in secondary endpoints or subgroups to warrant further study*

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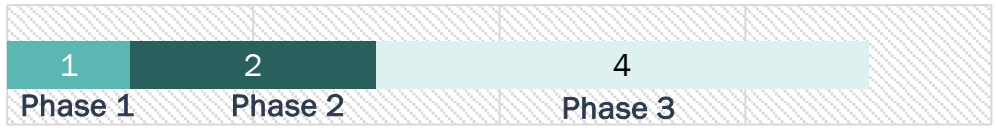
Legend: ALSFRS-R Revised Amyotrophic Lateral Sclerosis Functional Rating Score; Adcomm = Advisory Committee; SPA = Special Protocol Assessment

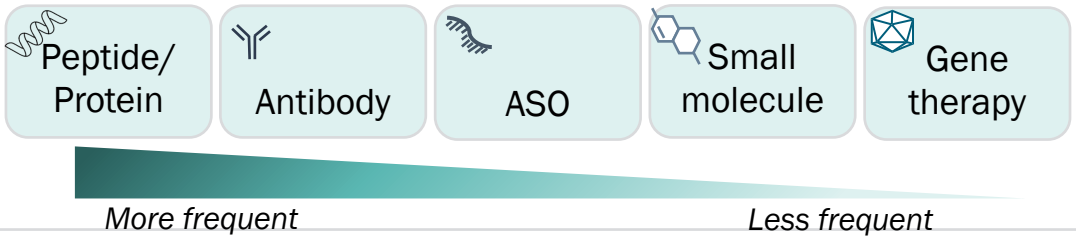
In contrast to ALS, assets in clinical development for SMA aim to augment the effectiveness of marketed products to expand patient eligibility and enhance clinical benefit

Drug Modality and Target Strategies – SMA

Pipeline Assets (US & EU)



Modalities



Target Strategies

1. Improves both the stability and dosing interval of a currently approved ASO splicing modifier strategy
2. Expands the currently approved gene therapy approach (Zolgensma) to older patients (>2 yrs of age) with a different route of administration
3. Targets a synergistic mechanism for use in combination with genetic therapies to improve SMA symptoms

Potential for use in other neuromuscular diseases

Representative Pipeline Assets

- **BIIB-115** (ASO targeting SMN2) **Biogen + Ionis**
- **OAV-101** (AAV9 *SMN1* gene replacement) **Novartis**
- **SRK-015** (latent myostatin inhibitor) **Scholar Rock**
- **BHV-2000** (dual myostatin inhibitor, ActRIIB inhibitor) **Biohaven**
- **RG-6237** (latent myostatin inhibitor) **Roche + PTC**
- **NMD-670** (CIC-1 inhibitor) **NMD Pharma**
- **ALG-801** (ActRIIB ligand trap) **AliveGen USA**

Legend: ASO = Antisense Nucleotide

With regulatory path defined, clinical development in SMA is currently focused on further enhancing the therapeutic benefit in broader patient segments (disease severity and age)

		Approved Therapies	Assets with Ongoing Phase 2/3 Trials			
		FDA labels	*SMN1* ↑	Muscle Function		
		Spinraza, Zolgensma, Evrysdi	OAV101 (Novartis)	taldefgrobep alfa (Biohaven)	RG-6237 (Roche)	SRK-015 (Scholar Rock)
Clinical Development Strategies						
Increasing access to broad, representative patient populations	Ambulatory Status	N/A				
	Age range	<2 yrs / Peds & adults	2-18	4-21	2-25	2-12 *13-21 exploratory*
	Any SMN2 copy number allowed	N/A	✓	✓	✓	✓
	SMA type	N/A	Type 2	Any	Any	Type 2 & 3
Demonstrating utility as a combination	Background Therapies Allowed for Use in Future Combinations	N/A	✗	zolgensma, SPINRAZA, Evrysdi	zolgensma, Evrysdi	zolgensma, SPINRAZA, Evrysdi
	Expected primary completion date		*Q4 2024*	*Q1 2025*	*Q4 2026*	*Q4 2024*

Rare CNS diseases have benefited from an influx of novel therapies, but the remaining unmet needs and clinical development strategies vary by disease and continue to pose a challenge

Outlook on Rare CNS Disease Therapeutics

- There has been an uptick in FDA approvals in the last 10 years for rare CNS disease, which reflects industry's increasing investment in these therapies. This trend can be attributed to the following:
  - Multiple clinical development and commercial incentives associated with rare CNS diseases
  - Advent of novel technologies (e.g., gene-targeting therapies or therapies that enhance biodistribution)
- Rare CNS diseases vary in their "druggability" and their relative unmet need, which consequently impacts drug development strategy, as evidenced by ALS and SMA
  - Several treatments are in development for ALS, reflecting the high unmet need that persists. A variety of approaches and strategic clinical trial designs are being adopted to differentiate from suboptimal standard of care and pipeline competitors
  - Marketed SMA therapies have seen a significant uptake due to NBS, and as a result, fewer therapies are in development than for ALS; drug pipeline in SMA is focusing on maximizing clinical benefit of existing therapies
- There are two future counter-acting initiatives that could alter the drug development landscape for rare CNS:
  - Inflation Reduction Act (IRA): How will it impact commercial incentives that have been critical for drug innovation, including rare diseases?
  - Operation Warp Speed in rare diseases: How will companies alter their drug development strategies in terms of indication selection or investment in cell/gene therapy technologies?