Spinal Muscular Atrophy

May 2019

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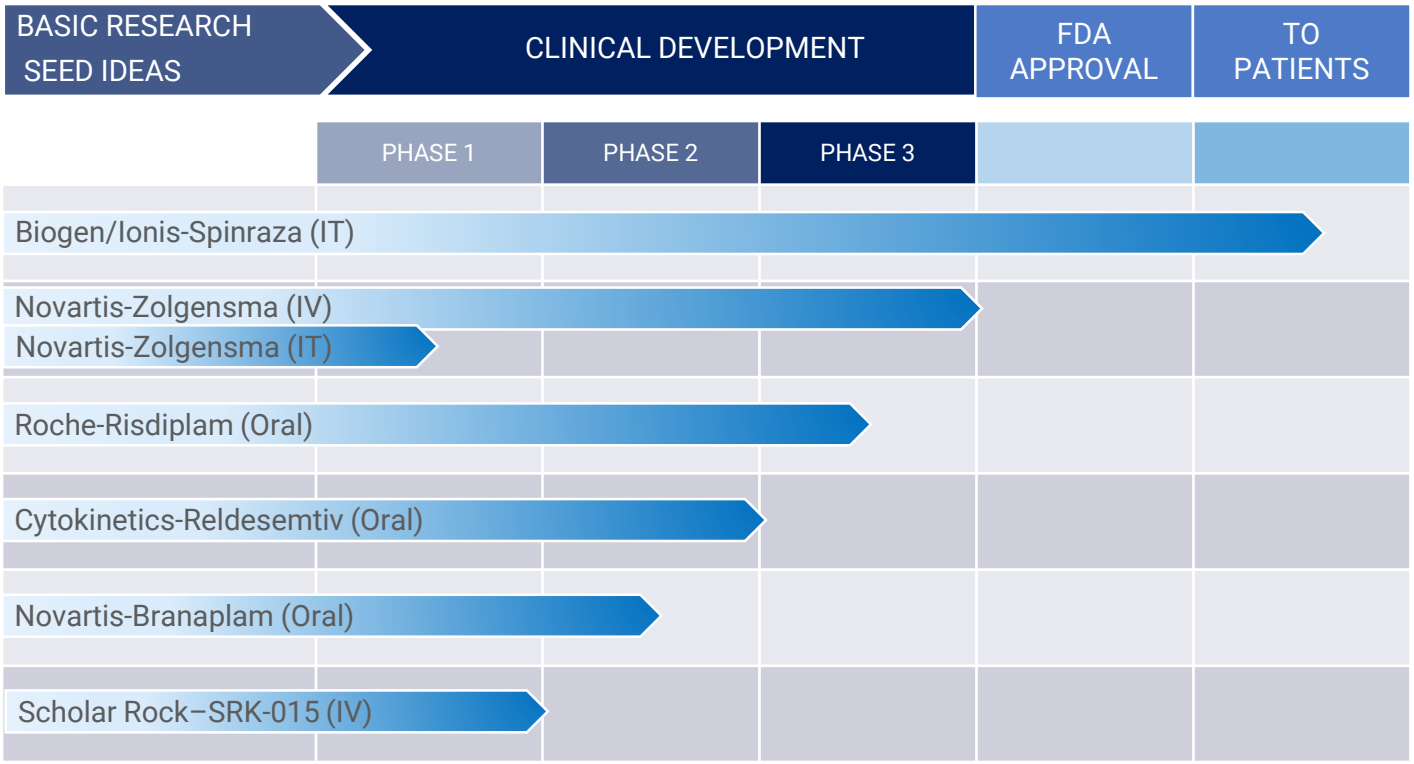
SMA Market

SMA drug pipeline includes programs from both SMN-enhancing and non-SMN approaches



GLOBAL SMA TREATMENT MARKET IS PROJECTED TO GROW AT CAGR OF AROUND 20.3%

WORTH AROUND 4.66 BILLION USD BY 2022

*Estimates achieved from BST data from Spinraza, Zolgensma, and Risdiplam only.

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Novartis' Zolgensma will be approved in May

ZOLGENSMA AS STANDARD OF CARE FOR TYPE 1 PATIENTS

- Expected U.S. approval in **May 2019**, EMA approval in mid 2019, and Japan approval in 1H 2019.
- Initial label in Type 1 to be based on weight rather than age and have **filed for SMA Type 1 patients up to 8.5 kg.**
- SMA type 2 population will be more competitive:
  - a higher proportion of patients expressing antibodies to AAV9.
  - Currently limited Zolgensma data on SMA Type II & III patients.

ROBUST DATA AT AAN

- Interim data reported from **STRONG** in SMA Type 2 showed rapid motor function gains and milestone achievements with IT Zolgensma.
- Interim data from **STR1VE** in SMA Type 1 showed prolonged event-free survival, increases in motor function and significant milestone achievement consistent with Phase 1 START trial.
- Interim data reported for the first time from **SPR1NT** in pre-symptomatic SMA showed age-appropriate motor milestone achievement.

NOVARTIS WILL FILE FOR BROAD INDICATION IN 2020

- Novartis stated it expected to **file for a broad indication for Zolgensma IT in 2020**.
- The filing will be based on the **STRONG trial** data.
- We currently do not know whether the filing will be based mainly on the mid-dose cohort, which would be early 2020 or include the new, high dose cohort, in which case filing would be delayed until 2H 2020.

Zolgensma's challenges once approved

IV DELIVERY

- One-time IV delivery is a major differentiator to Spinraza. However, the **small packaging capacity** of AAV vectors precludes the delivery in patients > **9 months**.
- If Zolgensma wants to expand treatment to older patients, they would have to change **intrathecal** delivery (currently being tested in STRONG and expected to be tested in the REACH trial).

NEONATAL SCREENING

- Newborn screening would be essential to treat young SMA patients with Zolgensma.
- **SMA has been added to the RUSP for newborns** as the 35th screened disease, but it is up to each state to decide which diseases to include in their screening.

DURABILITY

- **Long-term effects will take time to emerge.**
- Zolgensma uncertainties relates to the **unknown duration of expression of the gene therapy**. If expression wanes over time, subsequent treatment pathway is unclear.
- If **antibodies to AAV form**, patient would be unable to receive another dose of Zolgensma. Newborns can also acquired these antibodies from their mother in utero.

PATIENT POPULATION

- Due to limitations of AAV9 delivery, Zolgensma is seeking approval for **≤6 months of age**. Even still, limited sample size raises **concerns about generalizability** of results to the wider population of infants **with Type I SMA**.

ACCESS

- Patients will still need to travel to **either hospitals or centers of excellence** to receive treatment with Zolgesma.
- Unlikely that payers will reimburse Spinraza patients for Zolgensma treatment.

PRICING AND REIMBURSEMENT

- Spinraza more cost-effective in presymptomatic SMA, and Zolgensma more cost-effective in symptomatic Type I SMA.
- There is a risk that **Zolgensma may require maintenance**, and there are questions of what patients' would have to do, and **how payers would react.**
- **How will U.S. payers handle a multi-million dollar price tag?**

Roche’s Risdiplam will change the market

SYSTEMIC DELIVERY

- **SMA is a disease of ubiquitous depletion of SMN protein.**
- Is paralysis derived solely from dysfunction of motor neurons? If so, then restoring SMN to CNS will be enough to treat SMA. But if it stems from a broader defect of the motor unit, there is reason to **argue for a systemic repletion of the protein.**

PRICING

- **COGS will be lower** allowing for **pricing flexibility.**
- Permitting Risdiplam to be **priced differently in different parts of the world.**

PATIENT POPULATION

- A very **broad** patient population (ALL SMA TYPES).
- **Ranging in functional status** from weak non ambulant to strong ambulant, and with varying degrees of **scoliosis** from none to severe.

ACCESS

- **Oral delivery** means patients will not need to go to hospitals or centers of excellence to benefit from Risdiplam.
- **Accessible globally** to the broad population the clinical trial is covering.

Route of administration, pricing, and reimbursement

SPINRAZA

INTRATHECAL:
- Approved for all types and ages (treatment of 6,000 patients).
- 6 injections (12mg) in first year.
- Maintenance injection every 4 months (12mg).
- Dosing regimen is the same regardless of age, but changing it may complicate pricing.

PRICING:
- $125k per injection.
- $4.1M over 10 years.
- Reimbursement for only Type I and II.

ZOLGESMA

IV and INTRATHECAL:
- Seeking approval for ≤6 months of age (trial of 15 patients).
- One-time injection, no maintenance necessary (but some patients in trial are also receiving Spinraza - may require maintenance).

PRICING:
- Potentially $2.5M for the one-time injection (won't know until launch).
- Insurance companies will offer reimbursement with the risk that patients may need maintenance.

RISDIPLAM

ORAL:
- Seeking approval for all types and ages.
- Small molecule, which given orally, can cross BBB.

PRICING:
- Pricing will rely on optimal dosing chosen in Part 1 of the clinical trial.
- Flexibility to price it at a 10-15% discount to take the market share, especially outside of the U.S.

ROUTE OF ADMINISTRATION:

- **Route of administration will have a great impact on patients/caregivers and could alleviate SMA patients' healthcare burden.**
- **It will also allow payers to look favorable on Risdiplam, since the oral administration will save on hospital cost.**
- **Neurologists administering Spinraza face difficulties especially in patients with compromised spinal cords.**
- **When possible, physicians will most likely want to treat with gene therapy, and supplement with Spinraza/Risdiplam when needed, but it is unlikely payers will approve of this treatment pathway.**

PRICING SOLUTIONS:

- **FAIR VALUE RECOGNITION: Based on lifetime cost-time effectiveness timeframe, based on patient QOL and life extension.**
- **SHARED RISK: Payment only if drug works, up to 80% of price is at risk.**
- **AFFORDABILITY: Spread payment over up to 5 yrs., no increase over CPI.**
- **CHANGE IN PAYER/PORTABILITY: Contract negotiation, mutual recognition.**
- **MEDICAID BEST PRACTICES RULES: Innovative federal/state pilot programs or waivers.**
- **TRACKING OUTCOMES: Through claims and registry data.**

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Our analysts leverage scientific and medical knowledge as well as business acumen to address strategic problems in healthcare.

Our senior principals have Wall Street analyst experience.

We answer questions quickly, always considering the impact to various stakeholders by putting the clinical data, medical opinion, and company business maneuvers into an actionable business context.

Our proprietary inVision platform

allows clients to have all of their critical intelligence in one place, customized for their particular key questions and topics, and accessible on demand.

Our Spinal Muscular Atrophy engagements have included:

- ✓ Competitive Intelligence Monitoring Reports
- ✓ State of the Art Landscape Reports
- ✓ Trial Design Analyses
- ✓ Deep Dive assessments of companies, drugs, and MOAs
- ✓ Licensing opportunity identification and due diligence
- ✓ Conference Coverage
- ✓ KOL interviews
- ✓ Revenue Forecast Modeling
- ✓ Probability of Approval Modeling
- ✓ Target Product Profiles

For More Information

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