A study of risdiplam (RG7916) in babies with pre-symptomatic spinal muscular atrophy

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Study design

• RAINBOWFISH (BN40703) is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, PK, and PD of risdiplam in babies with genetically diagnosed SMA who are not yet presenting with symptoms.

• Babies with two copies of SMN2 and CMAP ≥1.5 mV at baseline as determined by:
  - The proportion of babies sitting without support for 5 seconds after 12 months on treatment as assessed by Gross Motor Scale of the BSID-III.

Background

• Spinal muscular atrophy (SMA) is a severe, progressive, inherited neuromuscular disease leading to loss of motor function and reduced life expectancy.1

• SMA is caused by reduced levels of the survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene.1

• A second SMN gene, SMN2, only produces low levels of functional SMN protein.2

• Risdiplam (RG7916; RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing to increase SMN protein levels.3

• Risdiplam is currently under investigation in three clinical trials in patients with SMA4–6

• Most motor neuron degeneration occurs in the first months of life in babies with Type 1 SMA, thus the timing of therapeutic intervention is crucial.7

• In recent clinical studies babies with pre-symptomatic SMA have shown a higher and more rapid achievement of motor milestones and reduced disease severity when SMN upregulation therapy was administered early.8

Key inclusion criteria

• Genetic documentation of 5q SMN1 homozygous gene deletion or mutation or compound heterozygous mutation (regardless of SMN2 copy number).
• Up to 6 weeks (42 days) of age at the time of first dose.
• Adequately recovered from any acute illness at baseline.
• Absence of clinical signs or symptoms prior to dosing that are strongly suggestive of SMA.

Key exclusion criteria

• Concomitant or previous administration of an SMN2-targeting antisense oligonucleotide, SMN2-splicing modifier, or gene therapy.
• Requiring invasive ventilation, tracheostomy or awake non-invasive ventilation.
• Presence of significant concurrent syndromes or diseases.

Notes

Babies aged up to 42 days with genetically diagnosed and pre-symptomatic SMA regardless of SMN2 gene copy number. Target enrolment ~25 patients*

Primary analysis (n=10)
• Babies with two copies of SMN2 gene and CMAP ≥1.5 mV at baseline.
• Analysis will be conducted when the last enrolled baby reaches 12 months of treatment.

Secondary and exploratory analyses (n~25)
All babies regardless of SMN2 gene copy number.

Key objectives

• To evaluate the efficacy of risdiplam in babies with two SMN2 copies and CMAP ≥1.5 mV at baseline as determined by:
  - The proportion of babies sitting without support for 5 seconds after 12 months on treatment as assessed by Gross Motor Scale of the BSID-III.

Secondary efficacy objectives
To evaluate the efficacy of risdiplam on:

• the development of clinical symptoms of SMA
• survival and permanent ventilation
• the achievement of motor milestones defined in the BSID-III and by the HINE

Additional objectives

• Health status and health-related QoL
• Biomarkers
• PK profile of risdiplam
• Safety of risdiplam
• Other developmental milestones (cognition and speech)

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References


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Abbreviations