Use of interim decisions boundaries in pivotal trials to inform production or portfolio

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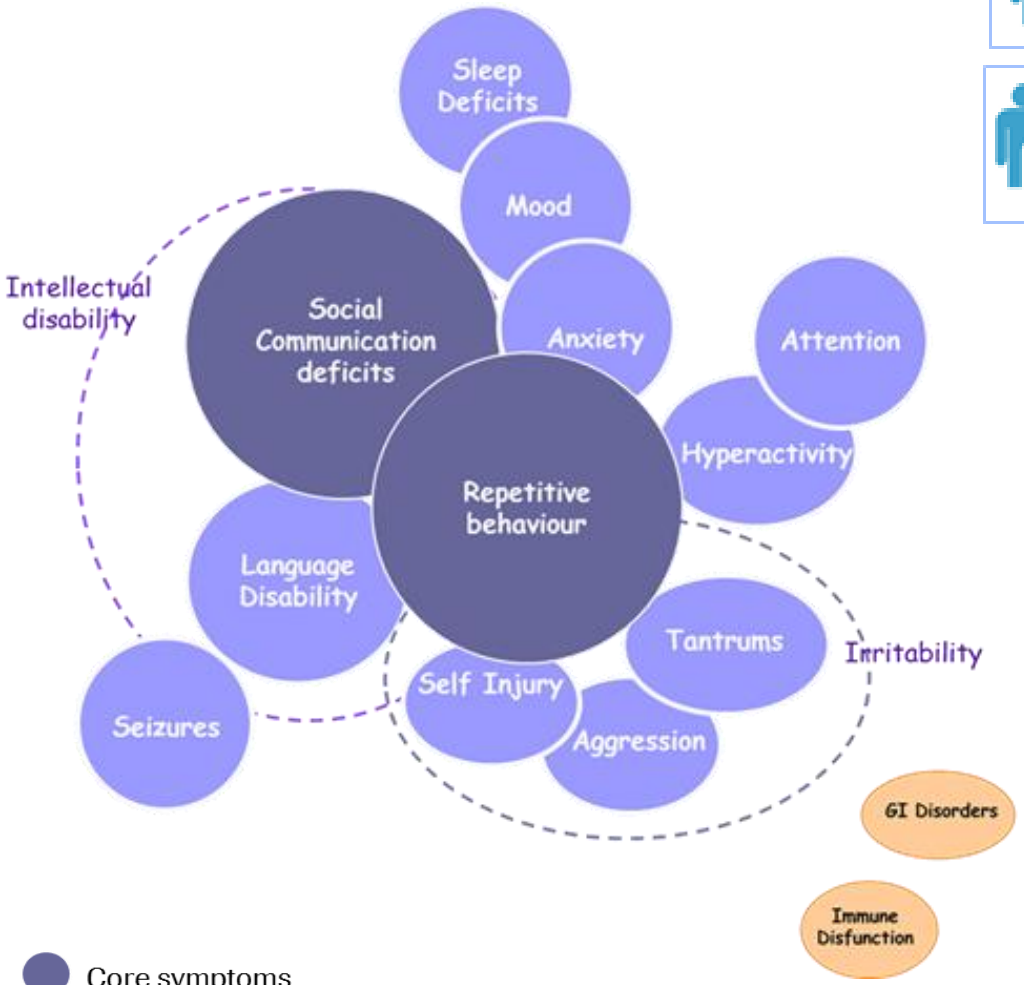
5th EFSPI Regulatory Statistics Workshop
12th October 2020

Study Case

- V1ADUCT: a Phase-III trial in ASD (Autism Spectrum Disorders) with a 2-level thresholds Interim Analysis
- iDMC (independent Data Monitoring Committee) role
- Health Authorities feedback

Autism Spectrum Disorders



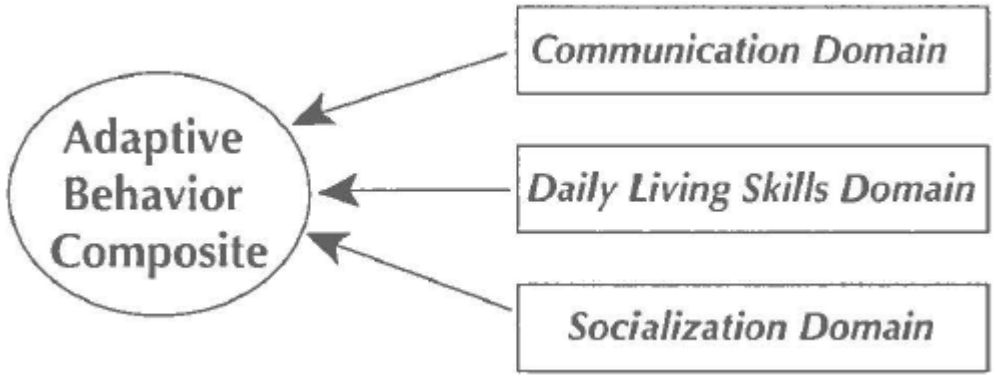
1 in 42 boys[1]
1 in 189 girls
3x more prevalent in boys than girls

1in 68 births
Prevalence in US

1% world's population have ASD
Estimated Global Prevalence of ASD

Antipsychotics indicated for irritability in ASD
Aripiprazole + Risperidone, US only

Vineland-2 Adaptive Behavior Scales



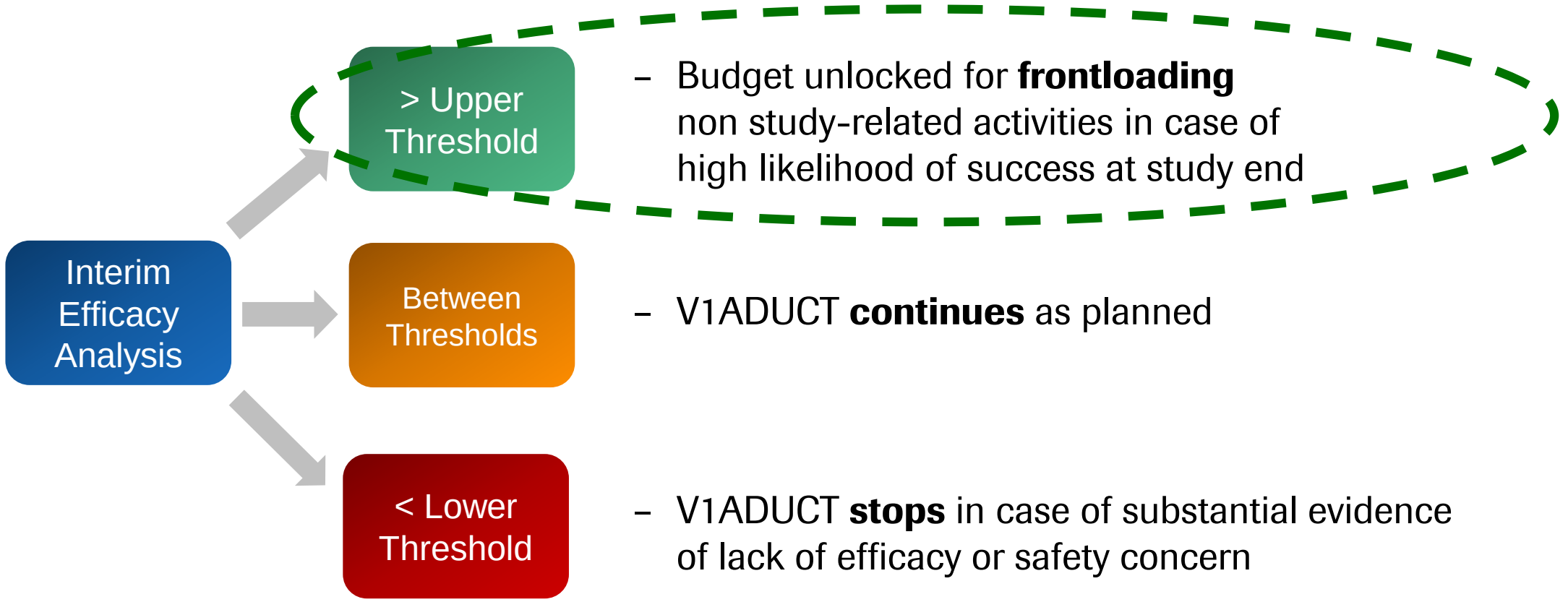
V1ADUCT – original plan

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Balovaptan in Adults with Autism Spectrum Disorder

- Primary endpoint: Change from Baseline in 2-DC of Vineland-II at Week 24
- N=350 pts, 85% powered to detect a mean treatment difference of at least 4.0
- Efficacy IA was planned to stop for Futility when ~50% of subjects complete Week 24 visit
- The remit of the iDMC was to evaluate the Efficacy IA and to inform the Sponsor whether the pre-specified futility criteria, based on Conditional Probability of Success as specified in the interim-SAP, have been met
- The iDMC was expected to meet regularly to oversee Safety throughout the trial as described in the iDMC charter

… and then, after some internal discussions

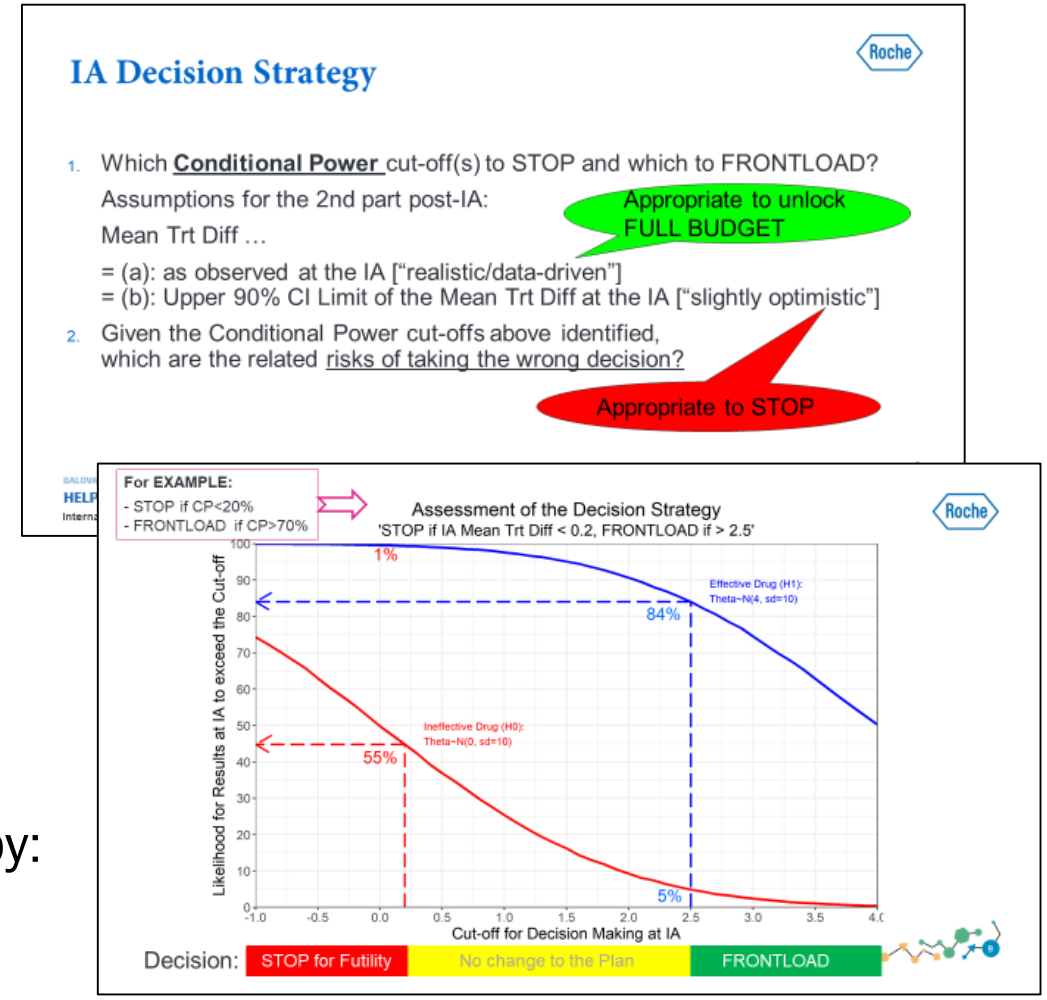
Proposed to set-up 2 thresholds at the IA, such that:



The 2-level IA thresholds

- Selection:
  - The “low bar” (futility) and “high bar” (frontloading) were chosen to correspond to conditional power of 20% and eg. 70%
  - The actual values were documented ONLY in a protected version of the IDMC Charter, which was not widely distributed internally
  - The IDMC reviewed and approved the Charter before the IA

- Confidentiality:
  the actual “high bar” conditional power was known only by:
  - Sponsor Project and Study Statisticians
  - IDMC
  - very few Sponsor Senior Managers in the ASD Therapeutic Area



Appendix 6 iDMC Communication Interim Efficacy Analysis

TO: **Xin Li, Ph.D., Data Review Board Chair**
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FROM: **Sven Bölte, Ph.D., iDMC Chair**

DATE: **"{Date of communication}"**

MOLECULE: **Balovaptan**

PROTOCOL NUMBER: **WN39434**

SUBJECT: **Recommendation following iDMC review of "{e.g., first, etc.}" interim analysis of efficacy data**

The iDMC met by "{Teleconference/Face to Face}" on "{Date of meeting}" for protocol WN39434 (A Phase III, randomized, double-blind, placebo-controlled, efficacy, and safety study of balovaptan in adults with autism spectrum disorder with a 2 year open-lable extension.)

Based on the interim analysis of the primary endpoint data collected from approximately 50% of patients completing the Week 24 visit the following condition is met:

☐ The optimistic version of the conditional probability of success is below the futility threshold of 20%.

☐ The conditional probability of success is above the futility threshold of 20% but below the upper threshold of %.

☐ The central version of the conditional probability of success is above the upper threshold of %.

Signed: _____ Date: _____

Sven Bölte, iDMC Chair

Discussed with HAs: FDA Type B Meeting
→ *"proposal is reasonable"*

- **Question**

For the interim futility analysis of Study WN39434 the Sponsor is considering a two-level thresholds decision rule: one to stop the study for futility and the second to frontload balovaptan development activities outside of Study WN39434. Does the Agency agree with this approach?

- ***FDA Response:*** *Based on the information you presented, we do not object to your plans for a futility analysis. However, we need further information about your plans to "frontload" development activities before we can comment.*

- **Sponsor's Pre-Meeting Comments:** The Sponsor intends to start a second Phase 3 study […] In addition, other study start-up activities might be included such as site and vendor selection. This frontloading could bring the NDA in adults forward by 9 months without exposing patients unnecessarily to a drug that is not efficacious.

- ***Discussion:*** *The proposal to frontload activities is reasonable*

Discussed with HAs: Scientific Advice WP
→ *proposal "may be acceptable"*

- **Question**

For the interim futility analysis of Study WN39434 the Sponsor is considering a two-level thresholds decision rule: one to stop the study for futility and the second to frontload balovaptan development activities outside of Study WN39434. Does CHMP agree with this approach?

- ***CHMP Response:*** *The Applicants plans a 2nd decision rule using a conditional power cut-off of >60%. This may be considered acceptable provided that any action taken will affect exclusively to external activities to study WN39434, and that will not have any impact on this trial. Otherwise, it would be considered as a transformation of study WN39434 into an 'adaptive' design. It is noted that if this was the case, then the design would require supplementary and detailed information […]*
  Finally, it is noted that maintaining the blinding or managing partial unblinding endanger study integrity. The Applicant should carefully consider whether this risk is superseded by the potential benefit of terminating the project or extending further the development program. In this sense the Applicant is reminded the responsibility to put in place all measures to guarantee the study integrity in order to avoid any operational bias.

A Study of Balovaptan in Adults With Autism Spectrum Disorder With a 2-Year Open-Label Extension

ClinicalTrials.gov Identifier: NCT03504917

Recruitment Status : Terminated (A futility analysis assessed that the study is highly unlikely to meet the pre-defined primary objective of the study. No new safety concerns were identified.)
First Posted : April 20, 2018
Last Update Posted : July 23, 2020

Sponsor:
Hoffmann-La Roche

Information provided by (Responsible Party):
Hoffmann-La Roche

Study Description

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