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Effects of Balovaptan on Health-Related Quality of Life of Adult Males With Autism Spectrum Disorder: Results From a Phase 2 Randomized Double-blind Placebo-Controlled Study (VANILLA)

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Financial Disclosures

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FB: Employee of F. Hoffmann-La Roche Ltd. at the time of analyses and abstract submission

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Objective

- The phase 2 VANILLA study investigated efficacy and safety of balovaptan, a selective V1a antagonist, in adult men with autism spectrum disorder (ASD) for the treatment of social and communication deficits. An exploratory objective was to evaluate the effect of balovaptan on health-related quality of life (HRQoL)

Methods

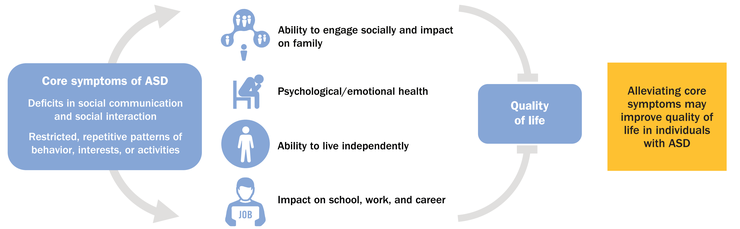
- Participant HRQoL was assessed at baseline, week 6, and week 12 using the PedsQL Generic Core Scales v4.0, which has Young Adult (age 18–25 years) and Adult (age ≥ 26 years) versions. The scale assesses functioning in 4 domains: physical, emotional, social, and school/work, from which Total, Physical Health Summary (Physical Functioning), and Psychosocial Health Summary (Emotional, Social, and School Functioning) scores are derived
- The PedsQL Family Impact Module and Cognitive functioning scale were used to assess impact of acute and chronic health conditions on parents and family, and cognitive functioning, respectively
- A mixed model of repeated measurements was fitted, including main effects for baseline, treatment, visit, and stage (where a dose was administered in different stages), and baseline*visit, treatment*stage, treatment*visit, stage*visit, and stage*visit*treatment interactions. Visit was fitted as a repeated effect with an unstructured correlation structure. Estimates for the differences between balovaptan doses and placebo with associated 90% CIs and *P* values are provided for descriptive purposes only and without any confirmatory meaning

Conclusions

- **The VANILLA trial showed positive trends of improvement in HRQoL with balovaptan 10 mg compared with placebo in adult men with ASD**
- **Trends for improvement in the PedsQL Generic Core Scale and Cognitive Functioning Scale were observed with balovaptan 10 mg compared with placebo, suggesting meaningful improvements in HRQoL**
- **To fully determine the effect of balovaptan on HRQoL, ongoing and future studies will be critical to validate this signal and to extend these findings across the age and gender spectrum of individuals with ASD**

Background

Impaired social communication and social interaction are core symptoms of autism, causing multiple challenges and affecting quality of life[1]



VANILLA (NCT01793441) is the first phase 2 clinical study of balovaptan in adult men with ASD[2]

Primary Outcome Measures	Assessment
Social communication	Social Responsiveness Scale 2nd Edition (SRS-2)
Safety and tolerability	Adverse events and clinical and laboratory assessments
Secondary Outcome Measures	
Adaptive functioning and skills	Vineland™-II Adaptive Behavior Scale 2nd Edition (Vineland™-II)
Behavior/symptoms	Aberrant Behavior Checklist (ABC); Repetitive Behavior Scale-Revised (RBS-R); State-Trait Anxiety Inventory (STAI); Anxiety, Depression and Mood Scale (ADAMS)
Clinical global impressions	Clinical Global Impressions – Improvement (CGI-I)
Pharmacokinetics assessments	Concentration per timepoint, and AUC_{tau}, C_{max}, and C_{min} of balovaptan

Transitions from one stage to the next were decided by an internal monitoring committee and an external scientific oversight committee and the decisions were based on safety data review. AUC_{tau}, steady-state area under the curve; CGI-S, Clinical Global Impressions – Severity; C_{max}, maximum concentration; C_{min}, minimum concentration; IQ, intelligence quotient.

An **exploratory objective** of the VANILLA trial was to evaluate the effect of 12-week treatment with balovaptan on HRQoL using the Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scale. Other exploratory assessments included the PedsQL Cognitive Functioning Scale and PedsQL Family Impact Module

Age, IQ, and ASD Severity Measures at Baseline Were Generally Similar and Well Balanced Across Treatment Groups

Mean ± SD	Placebo	Balovaptan 1.5 mg	Balovaptan 4 mg	Balovaptan 10 mg
n[a]	72	30	73	38
Age, y	24.7 ± 6.3	28.2 ± 7.7	24.4 ± 6.4	24.0 ± 5.0
WASI-IQ	96.6 ± 15.1	100.1 ± 17.5	99.5 ± 17.2	97.3 ± 17.8
CGI-S	4.4 ± 0.6	4.4 ± 0.6	4.4 ± 0.5	4.4 ± 0.6
ADOS-2	13.3 ± 3.9	13.0 ± 3.7	13.1 ± 4.3	13.7 ± 4.0
SRS-2 total *t* score (caregiver)	77.7 ± 7.4	78.0 ± 8.0	77.9 ± 7.3	75.4 ± 6.5
Vineland™-II (composite)	60.5 ± 13.4	56.4 ± 14.2	62.7 ± 12.7	60.6 ± 11.4
PedsQL Generic Core Scale total score	69.9 ± 14.7	71.1 ± 20.2	69.9 ± 15.4	69.4 ± 16.9
Psychosocial health summary score	67.8 ± 14.9	68.1 ± 22.3	66.9 ± 17.3	66.6 ± 19.7
Physical health summary score	73.9 ± 19.4	76.6 ± 19.2	75.2 ± 17.9	74.4 ± 17.7
PedsQL Cognitive Functioning Scale	54.2 ± 22.5	58.1 ± 25.8	55.8 ± 23.3	58.3 ± 21.2
PedsQL Family Impact Module total score	64.0 ± 19.8	61.0 ± 17.6	63.4 ± 16.0	58.3 ± 19.4
Use of psychotropic agents, % (n)[b]				
Antipsychotics	14.7 (11)	28.1 (9)	16.9 (13)	25.6 (10)
SSRIs	32.0 (24)	34.4 (11)	35.1 (27)	28.2 (11)
ADHD medications	18.7 (14)	12.5 (4)	23.4 (18)	25.6 (10)

- Study participants lived with (or had substantial periods of contact with) a caregiver who was willing and able to attend on-site visits when required, oversee the participant's compliance with protocol-specified procedures and study medication dosing, and report on the participant's status via completion of study assessments
- Caregivers responsible for completing key assessments were in relationship to the study participants: 75% mothers, 12% fathers, 5% other custodial adults, 4% teachers, and 4% other

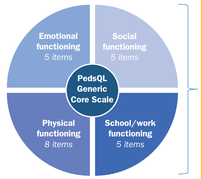
Values are mean ± SD unless otherwise noted.
[a] Modified intention-to-treat (ITT) population.
[b] Safety population: placebo, n = 75; balovaptan 1.5 mg, n = 32; balovaptan 4 mg, n = 77; balovaptan 10 mg, n = 39.
ADHD, attention deficit hyperactivity disorder; ADOS-2, Autism Diagnostic Observation Schedule-2; SSRI, selective serotonin reuptake inhibitor; WASI-IQ, Wechsler Abbreviated Scale of Intelligence.

Summary of VANILLA Study Results

- Balovaptan treatment was not associated with a significant change from baseline compared with placebo at 12 weeks in the primary efficacy endpoint **(SRS-2)**
- Dose-dependent, significant, and clinically meaningful improvements on the **Vineland™-II composite score**, driven mainly by improvements in the **Vineland™-II Socialization and Communication domains**, were observed for participants treated with balovaptan 4 mg or 10 mg compared with placebo
- Balovaptan was well tolerated across all doses and no drug-related safety concerns were identified

Results

PedsQL Generic Core Scale Assesses Functioning in 4 Domains: Physical, Emotional, Social, and School/Work[3]



- The 23-item PedsQL Generic Core Scales were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school/work) functioning
- Patient or caregiver-completed (depending on age of patient)[a]
- Validated in young adults (18–25 years) and adults (aged ≥ 26 years)
- Completion time: 5–10 minutes

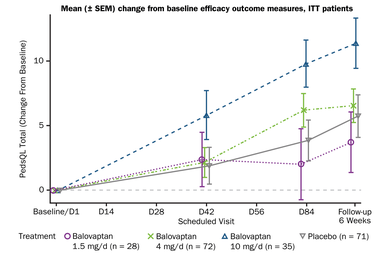
[a] Patient completed in the VANILLA study

Summary of Changes From Baseline at Week 12 in the PedsQL Generic Core Scales, Total Score

PedsQL 4.0 Generic Core Scales, Total Score	Estimated Treatment Difference (90% CI)	Effect Size	*P* Value[a]
Balovaptan dose, mg			
1.5	−3.79 (−11.01, 3.43)	−0.25	0.38
4	2.33 (−1.17, 5.83)	0.22	0.27
10	7.15 (2.09, 12.20)	0.63	0.02

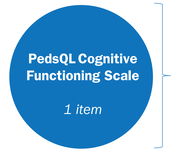
[a] Because HRQoL was an exploratory endpoint, nominal *P* values are provided for descriptive purposes only. ITT population.
Items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQoL.

Improvements in PedsQL Generic Core Scales Total Score Over Time



- Clinically relevant differences[4,5] were observed for balovaptan 10 mg versus placebo on the PedsQL Generic Core Scale total score
- Improvement in PedsQL total score was observed with 10 mg dose of balovaptan at week 12
- Improvements continued with balovaptan 10 mg even at 6 weeks after end of treatment period

PedsQL Cognitive Functioning Scale Measures Cognitive Functioning in Patients With Acute and Chronic Health Conditions as Well as Healthy School and Community Populations[6]



- The PedsQL Cognitive Functioning Scale is composed of 6 items comprising 1 dimension
- Patient or caregiver completed (depending on age of patient)a
- Validated in young adults (18–25 years) and adults (≥ 26 years)
- Completion time: ~5 minutes

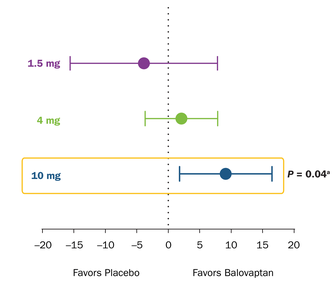
[a] Patient completed in the VANILLA study

Summary of Changes From Baseline at Week 12 in the PedsQL Cognitive Functioning Scale

PedsQL Cognitive Functioning Scale Score	Estimated Treatment Difference (90% CI)	Effect Size	*P* Value[a]
Balovaptan dose, mg			
1.5	−3.87 (−15.59, −7.85)	−0.16	0.58
4	2.10 (−3.68, 7.87)	0.12	0.55
10	9.15 (1.81, 16.49)	0.56	0.04

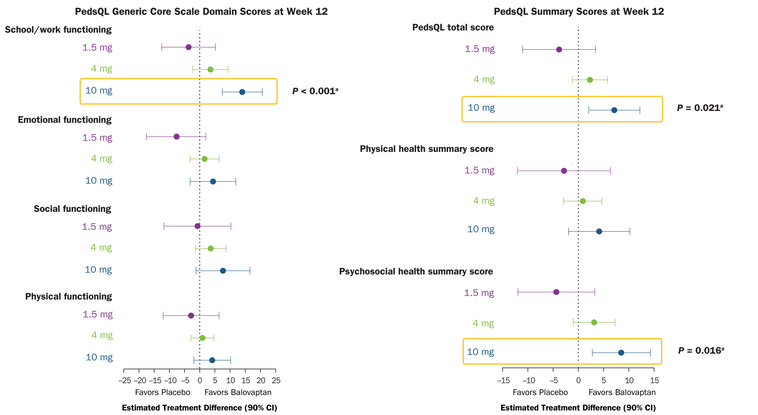
[a] Because HRQoL was an exploratory endpoint, *P* values are nominal. ITT population.
Items are reversed scored and linearly transformed to a 0–100 scale, so that higher scores indicate better HRQoL.

Change From Baseline to Week 12 in the PedsQL Cognitive Functioning Scale Total Score



Trends for improvements from baseline at week 12 were observed in the balovaptan 10 mg group compared with placebo on the Cognitive Functioning Scale

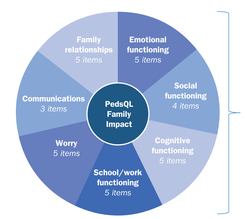
Change From Baseline at Week 12 in the PedsQL Generic Core Scale Domain Scores and Summary Scores



- Improvements in PedsQL total score with balovaptan 10 mg was driven by improvement in school/work functioning domain score and positive trends on other domains
- Clinically relevant differences[4,5] were observed for balovaptan 10 mg versus placebo on the Psychosocial Health Summary Score at week 12: treatment difference, 8.53 (90% CI, 2.79–14.27; *P* = 0.016; effect size vs placebo, 0.67)
- No difference was observed on the Physical Health Summary Score at week 12 with any of the doses

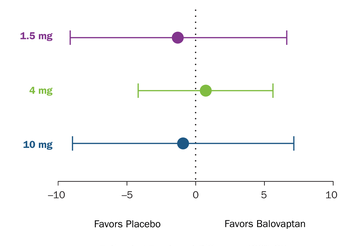
[a] Because HRQoL was an exploratory endpoint, *P* values are nominal. ITT population.
Items are reversed scored and linearly transformed to a 0–100 scale, so that higher scores indicate better HRQoL.

PedsQL Family Impact Module Scale Measures Impact of Acute and Chronic Pediatric Health Conditions on Caregivers and the Family[7]



- The 36-item PedsQL Family Impact Module measures caregiver self-reported physical, emotional, social, and cognitive functioning, communication, and worry
- The module also measures caregiver-reported family daily activities and family relationships
- Caregiver completed
- Completion time: 5–10 minutes

Change From Baseline to Week 12 in the PedsQL Family Impact Module Total Score



Summary of Changes From Baseline at Week 12 in the PedsQL Family Impact Module, Total Score

PedsQL Family Impact, Total Score	Estimated Treatment Difference (90% CI)	Effect Size	*P* Value[a]
Balovaptan dose, mg			
1.5	−1.28 (−9.14, 6.59)	−0.08	0.79
4	0.75 (−4.12, 5.62)	0.05	0.80
10	−0.88 (−8.91, 7.14)	−0.05	0.85

[a] Because HRQoL was an exploratory endpoint, nominal *P* values are provided for descriptive purposes only. ITT population.
Items are reversed scored and linearly transformed to a 0–100 scale, so that higher scores indicate better HRQoL.

No differences were observed between any dose of balovaptan and placebo at week 12 on the PedsQL Family Impact module total score

Reference

1. Center for Drug Evaluation and Research (CDER); U.S. Food and Drug Administration (FDA). The Voice of the Patient: Autism. https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM594722.pdf. Accessed September 20, 2018. 2. Bolognani F, et al. Results of a phase 2 randomized double-blind placebo controlled study (VANILLA) investigating the efficacy and safety of a V1a antagonist (RG7314) in adult men with ASD. Presented at: International Meeting for Autism Research; May 10–13, 2017; San Francisco, CA. 3. Varni JW, et al. *Med Care*. 1999;37(2):126-139. 4. Varni JW, et al. *Clinical Ther*. 2012;134(4):980-992. 5. Varni JW, et al. *Ambul Ped*. 2003;3(6):329-341. 6. Varni, JW, et al; Studies of Pediatric Liver Transplantation Functional Outcomes Group. *Qual Life Res*. 2011;20:913-921. 7. Varni JW, et al. *Health Qual Life Outcomes*. 2004;27;2:55.

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