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Letter of support for the VABS-II Adaptive Behavior Composite (VABS-II-ABC) score as measure of adaptive social functioning in people with Autism Spectrum Disorders (ASD) without intellectual disability

On 17 April 2020, the Applicant Roche Registration GmBH, acting on behalf of the AIMS-2-Trials Consortium, requested a follow-up qualification advice on the Vineland Adaptive Behavior Scales II (VABS-II) Adaptive Behavior Composite (VABS-II-ABC) score as a measure of adaptive social functioning in people with Autism Spectrum Disorders (ASD), pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

AIMS-2-TRIALS (Autism Innovative Medicine Studies-2-Trials) is a public-private research project at the forefront of autism research funded under the Innovative Medicines Initiative-2. It began in June 2018 and will run until May 2023. The research programme includes a range of studies carried out by different groups exploring how autism develops, from before birth to adulthood, and how this varies in different people. The Consortium will seek to identify prognostic biomarkers, which indicate whether a person with autism has or may develop particular characteristics, and predictive biomarkers that could also help to identify who may ultimately benefit from particular treatments.

Background and proposed context of use

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by qualitative impairments in two core domains: social interaction and communication; and the presence of repetitive or restricted behaviours, interests, or activities and sensory abnormalities. To date, there are no approved pharmacological treatments that effectively improve the core symptoms of ASD and, given the significant impact on the quality of life of individuals with ASD and their caregivers, the unmet medical need is high.

It is likely that different pathophysiological pathways contribute to the core symptomatic domains and account for the heterogeneity of the autistic population in terms of symptom expression and severity. This heterogeneity presents a challenge to the development of pharmacological interventions aimed to alleviate the core symptoms of ASD. The inclusion of more homogenous groups of patients in treatment trials could accelerate the pace of intervention development in ASD (Loth et al. 2016).

Expertise with faces is central to social interaction and face expertise is often associated with increased speed of processing. A common approach to measuring the speed of particular neural processes is the

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generation of 'event-related potentials' (ERPs) – brain responses that reliably occur time-locked to the onset of a particular stimulus.

The N170 is an ERP that has been shown to be sensitive to expertise effects, particularly social expertise, and has been linked to core regions of the "social brain" such as bilateral temporal cortex and posterior fusiform (Schurz et al. 2014)

A long history of research has shown that there are atypicalities in the N170 in ASD (McPartland et al. 2004). A recent meta-analysis confirmed that across 16 studies, autistic people show a longer latency (slower) N170 to faces stimuli than neurotypical controls (Kang et al. 2018).

The EU-AIMS Longitudinal European Autism Project (LEAP) is a large multicentre observational study that aims to identify factors that contribute to differences in brain development, difficulties in social behaviour and other core symptoms of ASD.

Results of the LEAP study confirmed that the N170 latency to upright faces is on average altered in individuals with ASD relative to the neurotypical population, providing initial evidence of its putative suitability as a diagnostic biomarker for core symptom domains. The LEAP study data also offers:

1. Evidence that the variation in N170 latency within the ASD group is not confounded by the presence of associated psychiatric conditions.
2. Evidence of an association between N170 latency and the face-sensitive response in the right fusiform gyrus as measured by functional magnetic resonance imaging (fMRI).
3. Evidence that N170 latency predicts change in socialisation metrics (specifically, parent report of play and leisure time activities, a subdomain of the VinelandTM-II Adaptive Behavior Scales).

The Consortium wants to qualify the Vineland Adaptive Behavior Scales II (VABS-II) Adaptive Behavior Composite (VABS-II-ABC) score as a valid measure of adaptive functioning in a paediatric (6-17 year old) ASD population with IQ $\geq$ 75. More specifically it is proposed that the three Vineland-II domains (Communication, Socialization, and Daily Living Skills), which directly map to core ASD symptoms and impact on daily functioning, are a suitable measure of adaptive functioning in an autistic paediatric population without intellectual disability.

This Qualification procedure refers to the LEAP study during which the semi-structured parent interview of the VABS-II has been used to assess adaptive functioning across three domains in >6- year-olds: communication, socialization, and daily living skills. For each domain, standard scores have a mean of 100 (SD = 15), with lower scores indicating greater functional impairment. Each domain consists of several subscales. The relevant domains for social communication include the Communication Domain (with Receptive, Expressive, and Written subdomains), the Socialization domain (with Interpersonal Relationships, Play and Leisure Time, and Coping Skills subdomains) and the Daily Living skills domain (with Personal, Domestic, Community).

Overall, the context of use of the Vineland-II Adaptive Behaviour Composite Score and the three domains is unclear and only a very high-level overview of a conceptual model of these three domains that map to deficits in ASD subjects and the psychometric properties of the VABS-II-ABC standard score was presented.

The Vineland Adaptive Behavior scales II (VABS-II, Vineland-II)

The Vineland Adaptive Behavior scales II (VABS-II, hereafter also referred to as Vineland-II) is the second revision of the early Vineland Social Maturity Scale (VSMS) (Doll, 1935). The first revision, the

Vineland Adaptive Behavior Scales (VABS) was published in 1984 (survey and expanded forms) and 1985 (classroom edition), (Sparrow and Cicchetti, 1985).

The VABS-II is designed to measure 5 major aspects of adaptive behavior in daily settings for children and adults from birth to 90 years of age (Sparrow et al., 2005). It has been widely used in clinics and across trials. The VABS-II can be completed as a questionnaire by the parent or primary caregiver (Parent/Caregiver Rating Form) or as an interview with the parent (Survey Interview). There is also an expanded interview form and a teacher version that includes questions on adaptive and academic functioning in the school setting.

The Vineland-II items are arranged from 11 simple to more complex behavior subdomains across four main domains: Communication, Daily Living Skills, Socialization, and Motor Skills. It also provides an optional Maladaptive Behavior Index. Two of the domains are not specific for core ASD symptoms (i.e. Motor Skills, maladaptive behaviors). The Communication, Daily Living Skills and Socialization scales make up the Vineland-II Adaptive Behavior Composite, which is a standardized score of the individual's overall level of adaptive functioning. In individuals aged from birth through 6 years, the Motor skills domain is also included in the calculation of the Composite Score. The rationale for not including the Motor skills in subjects >6 years or older in the original scale is that Motor skills should be fully developed by this age.

The VABS-II has a high internal consistency, test-retest reliability, inter-interviewer reliability and interrater reliability. Draw-backs are the length of the instrument which depending on the format (interview or self-report form) can take 20 to 60 minutes to complete, the training required and the sensitivity to detect change (responsiveness 0.27 to 0.34) which requires longer trials (see also Agnostou 2015).

The Consortium presents a high-level overview in the psychometric properties of the Vineland-II Adaptive Behavior Composite standard score. It is acknowledged that the Vineland-II has undergone extensive psychometric evaluation across multiple populations which demonstrates robust reliability, validity and sensitivity to change. However, what constitutes a clinically meaningful effect size in this population is not yet established.

A further revision of the scale is now available. The Vineland-3 is the latest iteration of the Vineland scale (Sparrow et al. 2016). The Vineland-3 has the same domain and subdomain structure of the Vineland-II. It contains a number of revisions in comparison to the Vineland-II including updated item content which reflect changes in the nature of everyday life (e.g. advances in electronic technology) and updated normative reference data.

When the VABS-II was compared to the previous version of the Vineland scale, the correlation ranged between 0.69 to 0.96 across domains/subdomains and across ages. It is unclear how the VABS-II performs in comparison to the Vineland-3 scale and how the link will be established. This needs to be clarified since the clinical community is now transitioning to the Vineland-3, and the Vineland-II will soon become obsolete.

Also, the Consortium already proposes the use of the Vineland-3 in future studies in support of the qualification of the ERP N170 latency (see Letter of support in the parallel advice on the ERP-N170 latency).

The socialisation domain of the Vineland-3 is proposed as primary endpoint e.g. in the Abaclofen trial in 130 individuals with ASD aged 5-17 years and the pre-school longitudinal study. During the discussion meeting it was clarified that also the Vineland-3 has strong psychometric properties and that there is significant overlap between items across the three core domains of the scale (Socialization, Communication, and Daily living Skills). Although additional items in all nine domains

are included in the Vineland-3, the Consortium highlighted that the concepts assessed remain appropriate to core social communication symptoms. Given the significant overlap in content with the Vineland-II, the Consortium is confident that the Vineland-3 will demonstrate a similar ability to detect change over time. This is acknowledged but remains to be supported by emerging data in the future.

As mentioned above the Consortium wants to qualify the Vineland-II as a suitable measure of daily functioning. In support of this aim a survey of an FDA public meeting and a publication by McDougall et al 2018 is presented highlighting social impairments and communication difficulties as among the most important treatment and measurement targets in ASD. However, the latter study is based on face-to face interviews with very few autism subjects (n=10). More caregivers were recruited than people with autism (n=26) and some concepts included in the model were only reported by the caregivers.

In the AIMS-2 project the ERP N170 latency is anchored to changes in social functioning as measured by the socialization domain of the VABS-II. Of the three subdomains only the Play and Leisure Time (PLT) subdomain score showed a significant relationship to the ERP N170 latency to upright faces after 12- 18 months whereas the subdomains Coping and Interpersonal Relationships showed no relation. Results for the domains communication and daily functioning and their respective subdomains were not presented.

During the discussion meeting it was clarified that the intention is to seek qualification of the Vineland-II and specifically the PLT subdomain as an anchor for ERP N170 latency to describe the social functioning of the population and NOT as a qualified primary or secondary endpoint at this stage. The Vineland-II will be used to characterise the patient population in a trial.

Overall it is accepted that socialisation is an important domain affected in ASD but it is not so obvious that only the Vineland Play and Leisure Time (PLT) should be in the focus in this population.

Previously, the AIMS consortium received a letter of support to encourage the further study of parent/self-reported measures of core ASD symptoms including:

- the Social Responsiveness Scale, 2nd Edition (SRS-2)
- Short Sensory Profile
- Repetitive Behavior Scale-Revised
- Autism Spectrum Quotient
- Children's Social Behavior Questionnaire (CSBQ)

It is unclear how these scales performed in the LEAP study and why anchors e.g. to the SRS-2 were not considered. During the discussion meeting the Consortium clarified that several considerations influenced the decision not to investigate these parent- or self-reported measures of ASD symptoms in relation to the N170 biomarker signature. Data were presented that in relation to the N170 latency marker, this was not associated with a change in the SRS-2 score which is rather surprising.

Explanation was given that the SRS and other scales mentioned above measure symptoms (impairments) and also traits (stable over time) whereas the Vineland-II is designed to measure social skills that may change over time. This is understood.

The Consortium further focusses on a paediatric (6-17 year old) ASD population with IQ $\geq$ 75. It is acknowledged that there is a pronounced discrepancy between level of cognitive ability and adaptive functioning and that this is particularly prominent among higher ability individuals (Tillmann 2019). However, by focussing on higher IQ individuals the usability of the scale in patients with intellectual disability which is quite common in ASD remains unclear. During the discussion meeting it was

proposed that further studies will provide more data on both N170 biomarker and social adaptive function in a wider ability range of younger children with a wider IQ range. This is supported.

In conclusion, while it may be acceptable to use the scale or one of it domains as anchor for a biomarker for research purposes the ability to rely only on a specifically selected subdomain and specifically only the PLT subdomain is seen rather critical and needs further support by upcoming data. The Consortium is invited to come for Qualification opinion as soon as these data are available.

Yours sincerely,

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Executive Director

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