9 December 2015
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Executive Director

Letter of support to explore MRI methodology to be used to stratify populations of people with Autism Spectrum Disorder (ASD)

On 14 September 2015 the Applicant EU-AIMS Consortium (IMI) requested follow-up qualification advice for MRI methodologies to be used to stratify populations of people with Autism Spectrum Disorder (ASD) pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 03 - 06 November 2015, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 16 – 19 November 2015, the CHMP adopted the advice to be given to the Applicant.

The European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS) is a project funded and run under the Innovative Medicines Initiative (IMI). Among the aims of this project is to develop and validate new methodologies for the advancement of novel therapies to treat Autism spectrum disorders (ASD). The project is managed by an international consortium of research academic institutes and industry.

On the basis of the qualification advice, the Agency is issuing this Letter of Support to the EU-AIMS Consortium (IMI) to encourage the further study and use of the following neuroimaging biomarkers to assess structural and functional abnormalities in paediatric patients with ASD and their potential to stratify patient groups in an exploratory context.

Structural MRI
To examine differences in brain morphometry, we will acquire a high-resolution anatomical three-dimensional T1-weighted accelerated sequence based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (5.5 min), and T2-weighted fast spin-echo and flair scans for visual assessments. The ADNI-based anatomical sequence was selected due to its short acquisition time and compatibility across scanners of different manufacturers.

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Diffusion Tensor Imaging
To examine differences in white matter tracts, a Diffusion Tensor Imaging (DTI) sequence (including cardiac gating) is included (Catani et al 2008; Pugliese et al 2009). During acquisition of these structural sequences, participants will be shown age-appropriate and relaxing video clips. Our previous experience suggests that this aids participants to keep still in the scanner and makes the experience more enjoyable.

MRI Multi-echo Sequence at Resting State
To examine differences in resting connectivity, we will acquire an approximately 7-8 minute resting state sequence using a multi-echo sequence developed by Kundu et al 2012. Participants will be presented with a fixation cross and will be instructed to keep their eyes open.

Animated Shapes Theory of Mind Task – fMRI
This block-designed experiment is based on a spontaneous ToM task previously used with adults with ASD (Castelli et al 2000; White et al 2011). Participants are presented with 12 short videos in which two triangles either move randomly (Random), in a goal-directed manner (GD), or in a goal-directed manner that involves the manipulation of thoughts and feelings of the other triangle (mental interaction [multiple choice questions, MCQ] or ToM). Each set contains four animations. After each video, participants are asked to categorise it as one of these three categories. The definitions of the three categories will be provided beforehand in an out-of scanner practice session. In ToM trials (and irrespective of participants' responses), they are also asked to rate the current state of feeling of each triangle (MCQ-SAM). Pilot data with young children with ASD (N=7, aged 6-10 years) revealed that MCQ-cat ratings did not strongly correlate with spontaneous ToM inferences as transcribed from verbatim narratives (Castelli et al 2000). Nevertheless, in-scanner MCQ-ratings will be maintained primarily with the aim to ensure that volunteers' attention to the video clips. The original narratives procedure will also be administered to separately analyse trials in which participants did ordid not make appropriate ToM inferences.

Social and Non-Social Reward Anticipation Task – fMRI
The task is based on Delmonte et al 2012 and uses an event-related design. It consists of two runs, one with social (happy face) and one with non-social (monetary) rewards. First, an arrow cue indicates whether or not any given trial provides a "win" opportunity (arrows pointing upwards indicate that participants can receive a reward; arrows pointing horizontally indicate trials without the possibility to receive rewards). Participants are instructed to make a fast button press in response to a target (short flashing of the screen). Feedback stimuli indicate the trial outcome with acquired rewards (2€ [or £2] or happy face) or no rewards (circle, ellipse), respectively. An adaptive algorithm ensures that approximately 60% of the trials result in a reinforcing feedback. Analysis of the fMRI pilot data revealed robust activation in the ventral striatum during the reward anticipation phase of both the monetary and social reward anticipation (vs. no win) conditions, albeit with somewhat higher activation in the monetary incentive delay relative to the social incentive delay conditions.

EMA encourage the primary study objective of the EU-AIMS Longitudinal European Autism Project (EU-AIMS LEAP) to identify biomarkers for stratification of patients with distinct subtypes of ASD and to examine how the clinical ASD phenotype and biomarker profile develop over time through re-assessment after 12-24 months and by using an accelerated longitudinal design. Inclusion of psychiatric comorbidities is agreed upon considering the high prevalence of comorbid conditions in the ASD population. Although heterogeneity should be minimized in confirmatory studies, the present

study should allow for more information to be gathered regarding the influence of these conditions on the changes secondary to intervention.

Sincerely,

Guido Rasi
Executive Director
European Medicines Agency