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Executive Director

Letter of support to explore EEG utility to measure deficits in social recognition in people with Autism spectrum disorders (ASD) and its potential to stratify patient groups

On 14 September 2015 the Applicant EU-AIMS Consortium (IMI) requested follow-up qualification advice for methodology EEG 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 explore EEG utility to measure deficits in social recognition in paediatric patients with ASD and its potential to stratify patient groups.

Gamma Activity (EEG) Induced by Upright/Inverted Faces
High frequency oscillations in the gamma band (>30Hz) are associated with the entrainment of local networks in the brain, such as during the integration of individually coded features. The task is based Grice et al (2001) which showed abnormalities in individuals with ASD.

Participants will be presented with a sequence of face stimuli, taken from four different actors (based on Tye et al 2013). Faces will be either upright or inverted and presented repeatedly in succession for

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

500ms per trial. They are preceded by a fixation period (200 ms baseline, 800-1200 ms interstimulus interval, with a blank screen). Occasionally, flags will be presented. Participants will be asked press a button when they see a flag to ensure attention throughout the task. Time-frequency analyses of the 500ms stimulus period will be carried out to investigate gamma activity induced by upright and inverted face stimuli.

In addition, the P1 and the N170 event related potential (ERP) components are neural correlates of face processing, which have longer latencies and larger amplitudes to inverted than to upright faces. Hence, we will test whether people with ASD (or ASD subgroups) show the previously demonstrated reduced (and more bilateral) face inversion effect (suggestive of abnormal cortical specialization). Single trial analyses on the C1, P1 and N170 will also be performed to measure intra-individual variability in latency, with the prediction that the ASD group will show increased variability.

It is well known that gamma-band (defined as electric or magnetic activity comprised between 30 and 80 Hz, even if there is increasing evidence of a higher gamma band activity) dysfunctions are characteristic of ASD, probably related to GABA and glutamate neurotransmission disturbances. Both MEG and EEG with spectral analysis can be used for the evaluation of gamma band activity. The Consortium proposes to study gamma activity, both at resting state (spontaneous) and task-stimulation associated with a sequence of face stimuli. Spontaneous gamma is usually studied in conditions of eyes open, closed or both. The gamma activity associated with task stimulation can be divided in evoked and induced, depending on its phase consistency to the stimulus. Evoked gamma-band oscillations are often seen at earlier latencies post-stimulus and some researchers consider them to reflect early sensory or attention processes, while induced gamma is often seen at longer latencies and is commonly inferred to be of import to perceptual closure or feature binding. Gamma band activity, combined with other biomarkers, can be potentially used as a reliable biomarker for diagnostic purposes and also to evaluate the efficacy of the drugs.

The agency agrees that the proposal to study gamma band activity is considered acceptable. As differences in gamma band activities are present in different ages, stratification for age is suggested.

The Consortium clarified that the EEG will be used to classify ASD subjects and characterized in terms of EEG features as follows:

1. The presence of specific interictal or ictal EEG abnormalities can allow to obtain a diagnosis of epilepsy type. This can be considered acceptable.
2. Collect information on epilepsy medication, however, EEG methodology may not be useful for this purpose.
3. The presence of interictal EEG abnormalities in absence of active epilepsy can be useful for a better characterization of the subjects. This can be considered acceptable

The Consortium assumes that EEG methodology is one of the potential biomarkers that may allow a better characterization of the subjects with ASD and if statistical power were sufficient, potential subgroup analysis could be undertaken. The CHMP agrees with the overall assumption.

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