LETTER OF INTENT
DETERMINATION LETTER

DDTBMQ0000104

September 9, 2020

Rosanna Squitti, PhD
IGEA Research Corporation
2600 SW 3rd Avenue, Suite 350
Miami, FL 33129

Dear Dr. Squitti,

We are issuing this letter to IGEA Research Corporation to notify you of our determination on the project submitted to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) Biomarker Qualification Program (BQP). We have completed our review of the Letter of Intent (LOI) for "Free copper in serum assessed by inductively coupled plasma mass spectrometry (ICPMS)" deemed reviewable on June 19, 2020 and have determined that we are unable to accept your LOI into the BQP[1]. Please see the following comments.

Drug Development Need/Biomarker Description Considerations

> ***Requestor's drug development need statement: "****…, we propose the same rationale for the stratification of patients with mild cognitive impairment due to AD (MCI), a prodromal stage of AD, with the aim at predicting the conversion to AD. The stratification of MCI individuals in two groups on the basis of a cut-off revealed that subjects with values higher than a designed Free Copper cut-off had a hazard conversion rate (50% of conversion in 4 years) that was ~3x higher than those with values lower than the cut-off (<20% in 4 years). On this basis, Free Copper can be employed, in association with the standard criteria, as a minimally invasive and cost-effective prognostic biomarker for AD, meeting all the requirements of the "precision medicine" manifesto. It can serve as a prognostic biomarker aimed at identifying MCI individuals who are more likely to develop symptomatic AD and can be used as an inclusion criterion for eligibility assessment in clinical trials testing anti-copper based therapy to delay or prevent AD."*

The drug development need for qualification is insufficient based on the following:

1. The biological role of free Cu in the pathogenesis of AD, if any, is uncertain based on the medical literature.

[1] In December, 2016, the 21st Century Cures Act added section 507 to the Food, Drug, Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.

2. The scientific basis for considering CuAD as a subtype of Alzheimer's disease is questionable, and there is no broad acceptance of this concept in the scientific community.
3. There is currently no scientific basis to support the hypothesis that "anti-copper based treatments," i.e., treatments directed at lowering copper in the brain, might possibly delay or prevent AD.

Context of Use (COU) Considerations

Requestor's COU statement: *"Serum Free Copper is intended to serve as a prognostic biomarker for conversion from mild cognitive impairment (MCI) to symptomatic Alzheimer's disease (AD) typified by copper imbalance. In association with the standard amnestic MCI criteria, it can serve as a minimally invasive and cost-effective prognostic biomarker for MCI that may be used as an inclusion criterion for eligibility assessment in clinical trials testing anti-copper based therapy to delay or prevent AD."*

4. There is currently no scientific basis to support the prognostic value of serum free copper in Alzheimer's disease.

Please Contact **CDER's Biomarker Qualification Program (BQP)** (**CDER-BiomarkerQualificationProgram@fda.hhs.gov)** should you have any questions (refer to **DDTBMQ0000104**).

Sincerely,

Christopher L. Leptak -S

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Christopher Leptak, MD, PhD
Director, CDER Biomarker Qualification Program
Office of New Drugs, Center for Drug Evaluation and Research

Eric P. Bastings -S

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Eric Bastings, MD
Deputy Director (acting)
Office of Neuroscience
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