Contact: Arthur L. Holden
Chairman,
International Serious Adverse Event Consortium
8770 W. Bryn Mawr Avenue, Suite 1300
Chicago, IL 60631-3515
Phone: 1-773-867-8595

BROAD INSTITUTE AND THE INTERNATIONAL SERIOUS ADVERSE EVENT CONSORTIUM TO PARTNER ON RESEARCH INTO THE GENETICS OF AUGMENTIN INDUCED LIVER INJURY

Broad to lead effort to better understand the role of rare genetic variation in Augmentin-induced Liver Injury (AILI) using whole genome sequencing

Chicago (June 17, 2010) – The International Serious Adverse Events Consortium (SAEC) announced today it will collaborate with Broad Institute (www.broadinstitute.org) to research the genetics of Augmentin-induced Liver Injury (AILI), with the goal to identify potential rare genetic variants predictive of this serious drug induced adverse event. The SAEC is a novel, non-profit international research consortium, formed by the global pharmaceutical industry and the Wellcome Trust, to better understand the role genetics play in drug safety. The Broad Institute brings together world-class researchers from throughout the MIT and Harvard communities and beyond, empowering them to work together to identify and overcome the most critical obstacles to realizing the full promise of genomic medicine.

Augmentin is a widely prescribed oral antibacterial combination consisting of the antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium. Augmentin is an important drug used to treat a wide variety of infections caused by bacteria, such as sinusitis, pneumonia, ear infections, bronchitis, urinary tract infections, and infections of the skin. A very rare, but serious side effect associated with Augmentin and over 200 other medications is drug induced liver injury (DILI). In the US, 13% of acute liver failure cases are associated with DILI. Patients experiencing DILI are at risk of death or may require emergency liver transplantation. DILI is also one of the most frequent causes of safety-related drug marketing withdrawals.

The SAEC, over the past three years has collected almost 500 DNA samples and clinical data from subjects who experienced drug-related liver toxicity via collaborations with three leading drug safety research networks [i.e. the Spanish DILI, Eudragene and the Diligen networks]. Using whole genome genotyping techniques, the Consortium has compared the genetic and clinical data from these “cases” to a healthy control group, to identify genetic mutations associated with the DILI (in general) and Augmentin (in specific). The SAEC has discovered extensive genetic associations in the major-histocompatibility-complex (MHC), located on chromosome six. Through this initial research, a foundation has been created for a next generation of whole genome sequencing studies to further explain the role genetic variations (both rare and common) in the development of DILI. In light of these initial DILI genetic findings, the size of the available case cohort, and the wide spread usage of Augmentin; it is an ideal “pilot case” to apply state of the art whole genome sequencing technology to search for addition genetic associations.

“Our genetic research on drug-induced liver injury points to the strong role of the immune system plays in contributing to these adverse responses.” said Arthur L. Holden, Chairman of the SAEC. “By researching the genetics of Augmentin-induced Liver Injury (AILI), we hope to further our understanding into the genetics of immunologically mediated adverse drug responses. This collaboration with the Broad Institute represents our second pilot to use whole genome sequencing technology to better understand the role of rare genetic variation in such events.” The project will be lead at the Broad by Dr. Mark Daly. Dr. Daly is an Associate Professor at the Massachusetts General Hospital/Harvard Medical School and an Associate Member of the Broad Institute of Harvard and MIT, where he directs computational biology for the Medical and Population Genetics Program.

Founded in the fall of 2007, the SAEC is a private, global partnership of leading pharmaceutical companies, the U.S. Food and Drug Administration and academic institutions from around the world to identify and confirm genetic markers that may help predict which patients are at risk for drug-related

serious adverse events. Through identifying and ultimately validating genetic markers associated with SAEs, the Consortium hopes to reduce the patient and economic costs caused by drug-related SAEs. The SAEC also hopes to improve the flow of safe and effective medical therapies by better addressing idiosyncratic safety risks of new drugs before they reach the market. It provides to qualified researchers, free access to its study data and results.

About the International SAEC
The International Serious Adverse Event Consortium (SAEC, www.saeconsortium.org) is a 501(c) 3 organization dedicated to identifying and validating DNA variants useful in predicting the risk of drug-related serious adverse events. The Consortium brings together the pharmaceutical industry, regulatory authorities, and academic centers to address clinical and scientific issues associated with drug-related serious adverse events.

SAEC members include representatives from the pharmaceutical industries, the scientific community, and the Wellcome Trust.

- Pharmaceutical industry partners are involved in all aspects of the Consortium launch, providing ongoing consultation on the development and structure of the Consortium's scientific model, contributing cohort data, and underwriting costs of the SAEC's studies.

- SAEC members include Abbott, Amgen, Daiichi Sankyo, GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi-Aventis, Takeda, and the Wellcome Trust.

- The FDA provides consultation on the direction of the SAEC, the design and conduct of SAEC studies, and support of research data release.

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