ILC 2017: New therapy has potential to be a significant advance for the treatment of paediatric cholestatic liver diseases

An ongoing, multiple-dose, open-label, multicentre study demonstrates that the ileal bile acid transport inhibitor, A4250, reduced itching and the level of bile acids in the blood of children with cholestatic diseases

April 22, 2017, Amsterdam, The Netherlands: Results presented today from a study of a novel ileal bile acid transport inhibitor, A4250, demonstrated that it reduced levels of blood (serum) bile acids, which are characteristic of many liver diseases and often associated with severe liver damage, in children with cholestatic liver diseases. The data, presented at The International Liver Congress™ 2017 in Amsterdam, The Netherlands, showed that oral treatment with A4250 also improved pruritus (itching) in 74% of patients and was well tolerated, with mostly mild and transient side effects.

Children can be affected by diseases that either destroy or impair the development of the biliary tree; other diseases alter the ability of liver cells to produce bile. These diseases can lead to progressive liver injury and cirrhosis, even at very early ages and often result in the need for a liver transplant. Among other symptoms or abnormalities, patients may suffer from bile acid retention, which is related to pruritus. Pruritus can be a very debilitating symptom: it is often severe and difficult to treat, while hampering quality of life. Novel therapies for the management of increased bile acid serum levels and pruritus are urgently needed by patients and clinicians. A previous animal study demonstrated that A4250 can reduce elevated levels of serum bile acids without severe side effects,[1] and serum bile acid lowering was also shown in a Phase 1 study of A4250 in healthy individuals.[2,3]

“There is a real need for novel and effective therapies for paediatric cholestatic diseases,” said Dr Ulrich Baumann, Hannover Medical School, Germany, and lead author of the study. “The safety and efficacy data from this study show the potential for A4250 to become a significant and novel advance for the treatment of paediatric cholestatic liver diseases.”

This study evaluated five doses of A4250 (0.01-0.2 mg/kg), with the dataset including four patients who received each dose. Patients with cholestatic disease and intractable itching were initially administered a single dose of A4250. As there were no safety issues, patients were then given the drug in tablet form for four weeks. If needed, therapy with ursodeoxycholic acid (UDCA) or rifampicin could also be given during the study. The dataset included nineteen patients aged 1-17 years and itching was measured by a visual itch score using patient reported diary data.

Pruritus improved in 14 of 19 cases. Mean levels of serum bile acids were reduced at all doses. In particular, there were substantial reductions in serum bile acids in seven out of nine patients with progressive familial intrahepatic cholestasis, ranging from a 43% to 98% reduction. Most

side effects were mild and transient and considered to be unrelated to the drug, and there were no serious side effects.

A4250 is a highly potent inhibitor of the ileal bile acid transporter (IBAT) that acts locally in the gut with minimal systemic exposure.[3] It reduces levels of bile acids in serum by blocking the IBAT in the last part of the small intestine in the gut. This interrupts the re-absorption of intestinal bile acids and their re-circulation for further secretion.[1]

"The study results are crucial as they address pruritus, a significant issue in chronic cholestatic diseases. Currently, there are few therapeutic options with limited efficacy, so new treatment strategies for pruritus are of great importance for clinical practice," said Prof Marco Marzioni, Professor of Gastroenterology, Università Politecnica delle Marche – "Ospedali Riuniti" University Hospital of Ancona, Italy and EASL Governing Board Member.

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The International Liver Congress™
This annual congress is the biggest event in the EASL calendar, attracting scientific and medical experts from around the world to learn about the latest in liver research. Attending specialists present, share, debate and conclude on the latest science and research in hepatology, working to enhance the treatment and management of liver disease in clinical practice. This year, the congress is expected to attract approximately 10,000 delegates from all corners of the globe. The International Liver Congress™ 2017 will take place from April 19 – 23, at the RAI Amsterdam, Amsterdam, The Netherlands.

About The European Association for the Study of the Liver (EASL) (www.easl.eu)
Since its foundation in 1966, this not-for-profit organisation has grown to over 4,000 members from all over the world, including many of the leading hepatologists in Europe and beyond. EASL is the leading liver association in Europe, having evolved into a major European Association with international influence, with an impressive track record in promoting research in liver disease, supporting wider education and promoting changes in European liver policy.

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Onsite location reference
Session title: Late breaker session
Time, date and location of session: 16:00 – 18:00, Saturday 22 April, Hall 5
Presenter: Ulrich Baumann, Germany
Abstract: The Ileal Bile Acid Transport inhibitor A4250 decreases pruritus and serum bile acids in cholestatic liver diseases – an ongoing multiple dose, open-label, multicentre study (LBO-04), 16:45 – 17:00

Author disclosures
Grants, speaker fees, and consultancy work for Astellas, Novartis, Alexion, Alnylum, Nestle.

References

1 Baghdasaryan A, et al. Inhibition of intestinal bile acid absorption improves cholestatic liver and bile duct injury in a mouse model of sclerosing cholangitis. *J Hepatol.* 2016;64(3):674–681.

2 Hanns-Ulrich M, et al. The ileal bile acid transporter inhibitor A4250 modulates bile acid synthesis and decreases serum bile acids. Presented at the Liver Meeting® 2015, San Francisco, CA, USA, November 13–17, 2015. Abstract 810.

3 Graffner H, et al. The ileal bile acid transporter inhibitor A4250 decreases serum bile acids by interrupting the enterohepatic circulation. *Aliment Pharmacol Ther.* 2016;43:303–310.