BACKGROUND and AIMS

LPON 1144 is an oral prorud of testosterone developed as a treatment for pre-cirrhotic non-alcoholic steatohepatitis (NASH) and recently completed the 36 weeks, blinded, placebo controlled, paired-biopsy LiFT Phase 2 clinical study in (NCT04134091). Some subjects continued treatment (Open Label Extension, OLE, NCT04665993) for additional 36 weeks. This analysis evaluates the anti-steatotic effect of the treatments using histological (pathologist), Digital Pathology and artificial intelligence (AI) and Imaging methods to optimize the design of a registration study.

METHOD

LIVER TISSUE HISTOLOGY
FFPE sections (4-8 microns) of adequate liver biopsies were stained with Masson Trichrome for Collagen and H&E for assessment of the NAS histological grades (steatosis, ballooning, inflammation).

HISTOLOGICAL GRADING
• Biopsy slides are read by an independent pathologists trained on the NASH-CRN staging system
• Steatosis grades 0 (<5% hepatocytes count with steatosis involvement), 1 (5% to 33%), 2 (33% to 66%) and 3 (> 66%)
• Responders are identified with at least a full categorical stage change

MRI BASED PROTON DENSITY FAT FRACTION (MRI-PDFF)
• Most patients underwent an MRI exam resulting in the calculation of their PDFF
• Responders are identified for a >30% relative reduction of PDFF between baseline and end of treatment

DIGITAL PATHOLOGY AND ARTIFICIAL INTELLIGENCE
• The same slides prepared for and reviewed by Pathologists were digitized at 20X (0.50 micron/pixel) on an Aperio AT WSi system
• The Masson trichrome digital images were read using FibroNest®, a single-fiber, high-content quantitative Digital Pathology image analysis and AI automated, full-tissue method
• The method quantifies large and medium macro-steatosis fat vacuoles as well as the area of scar fibrotic tissue (complex and dense fibrosis) to calculate the non-fibrotic parenchymal tissue fat area ratio (%A)
• Responders are identified for a >30% relative reduction of %A between baseline and end of treatment

RESULTS

Most patients underwent MRI and liver biopsy exams at baseline and end of treatment. Liver exam results are not quantified by the FibroNest method and might explain slight differences in percentage (see p-value relative to histological grade results).

The three perspectives identified comparable level of responses.

CONCLUSION

LPON 1144, both alone and in combination with d-alpha tocopherol, demonstrates a strong antisteatotic effect. Digital Pathology and imaging methods for the continuous assessment of these effects, are highly correlated and provide a robust support of the pathologist-based results.

REFERENCES

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