Liver Investigation: Testing Marker Utility in Steatohepatitis

Liver Forum NASH 2020 Updates, Webinar 11 Aug 2020

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Chair Work-Package 7, LITMUS

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IMI consortium activities
LITMUS, Work-package 7 co-lead – NASH biomarker development
EU-PEARL, Work-package 6 co-lead - NASH platform studies

Current position
Director Clinical Development Liver Disease (NASH),
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The overarching objectives of LITMUS are to develop, robustly validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and/or monitor NAFLD/NASH progression and fibrosis stage for use in drug discovery.
LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis)

**FACTS & FIGURES**

- **Start Date**: 01/11/2017
- **End Date**: 31/10/2022
- **Call**: IMI2 - Call 9
- **Grant agreement number**: 777377

**Type of Action**: RIA (Research and Innovation Action)

**Contributions (€)**
- **IMI Funding**: 15 797 881
- **EFPIA in kind**: 24 180 663
- **Other**: 6 483 232
- **Total Cost**: 46 461 776

**PROJECT LINKS**

- **Project website**: [www.litmus-project.eu](http://www.litmus-project.eu)
- **Twitter**: @LITMUS_IMI

Coordinator: Prof Quentin M. Anstee

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The LITMUS Consortium comprises 53 Partners from 14 countries:

- 29 Academic, 23 EFPIA/Industrial, 1 Professional body
Phase 1a

WP3: Patient Cohorts & Biobank

WP4: Central Lab

WP5: Imaging

WP2: Methodological Evaluation & Evidence Synthesis

Candidate Biomarker Selection

Phase 1b

WP6: Reverse Translation & Pre-clinical Models

WP7: ‘QED’ Qualification, Exploitation & Dissemination

WP1: Project Coordination

Validated Diagnostic, Prognostic & Dynamic Biomarkers
Qualification strategy and status (WP7)

Richard Torstenson, for work-package 7

- Nordic Bioscience; Elisabeth Erhardtsen and Morten Karsdal,
- Takeda; Guido Hanauer, Novartis; Cliff Brass, Pfizer; Julia Brosnan
- Newcastle University; Quentin M Anstee, ICAN; Vlad Ratziu
- AMC; Patrick Bossuyt
Qualification strategy

Aim
Early authority feedback on the qualification feasibility and applicability of MetaCohort data (EPoS/FLIP) for exploratory work and the LITMUS trial for confirmation of the biomarker performance

Complexity
Several CoUs and several potential markers for each CoU
To optimize the qualification advice received
  • 2 markers submitted for each CoU
  • Both wet and imaging marker included

FDA
CPIM
Letter of Intent (LOI)
Qualification Package (QP)
Qualification (FQP)
Clinical data package

**METACOHORT**
- Prospective data collection (EPOS/FLIP)
- Biomarkers
  - Retrospective analysis
- Histology based diagnosis
  - N ~ 1000 patients
  - F0-F4 ~20% each (centrally read)
  - Paired histology (appr 600)

**LITMUS study**
- Prospective data collection (Protocol/code book)
- Biomarkers
  - Analysis: FDA standard (CSLI)
- Histology based diagnosis
  - N ~ 2000-2500 samples/patients
  - Paired histology
  - PROs
  - Imaging data (substudy)

**Pharma-Data**
- Prospective data collection (DB clinical data)
- Biomarkers
  - In database
  - Retrospective analysis possible
- Histology based diagnosis
  - N > 2000
  - Paired histology

- Allergan, AstraZeneca, Genfit, Gilead, Intercept, Novartis

**Confirmatory**

**European - NAFLD registry**
EMA

Innovative Task Force (ITF) meeting
• Continue for a Qualification meeting

Qualification Advice
• Briefing package submitted for Diagnostic & Prognostic CoU
• 2 Scientific Advice face to face meetings
• Qualification Advice received

FDA

Critical Path Innovation Meeting (CPIM)
• Meeting not needed, submit LOI

Letter of intent (LOI)
• LOI submitted for Diagnostic & Prognostic CoU
  – Diagnostic LOI approved
    • https://www.fda.gov/media/138542/download
  – Prognostic LOI pending

Qualification Plan (QP)
• pending selection of most promising marker
  – ongoing work in work-package 2
Authority questions/topics of interest

Topics/Questions

- CoU description
- Applicability of data cohorts for each CoU
- Use of industry study data (external validation)
- Biomarker analytical stability
- Reference:
  - Histology assessment, standardised reading
- Statistical analysis
- Specific biomarker feedback
Prioritising of markers for qualification

- **Systematic reviews**
  - summarizing the existing evidence and utility for a range of “wet” and imaging biomarkers

- **Performance analysis ongoing**
  - All LITMUS MetaCohort samples analysed for planned markers
In summary

• Positive authority feedback on LITMUS qualification strategy (FDA/EMA)
• Selection of most optimal marker for each CoU ongoing
• Next stage
  – submission of qualification package
  – analysing LITMUS study for confirmation of biomarker performance
Key Topic Areas for Research:

• **Extended follow-up of European NAFLD Registry**
  – Increased longitudinal follow-up of NAFLD Registry for outcomes data
  – Post-marketing surveillance platform

• **Clinical Trial “Proving Ground”**
  – Response and/or pharmacodynamic biomarkers
  – Proof-of-principle for novel NIT-based trial designs

• **Data Analytics – Artificial Intelligence & Machine Learning**
    (‘Omics’, Registry/Phenotype-Outcomes, Histology)

Interested Industry Partners please contact: quentin.anstee@Newcastle.ac.uk
The LITMUS project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777377. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

www.litmus-project.eu
www.imi.europa.eu