D7.2: Detailed plan for submission of biomarkers to the regulatory authorities (EMA and FDA) for qualification

LITMUS

Liver Investigation: Testing Marker Utility in Steatohepatitis

Grant Agreement No. 777377

WP7 – 'QED' Qualification, Exploitation & Dissemination

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V1.0	09 APR 2018	First Draft
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1 Publishable Summary

The overarching aim of LITMUS is to develop, robustly validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and/or monitor NAFLD/NASH progression and fibrosis stage. This will be achieved through a goal-oriented, tri-partite collaboration delivering a definitive and impartial evaluation platform for biomarkers, bringing together: (i) End-users of biomarker technologies (clinicians with expertise in NAFLD and the pharmaceutical industry); (ii) Independent academics with expertise in the evaluation of medical test/biomarker performance; and (iii) Biomarker researchers and developers (academic or commercial). LITMUS has the demonstrable capability to fulfil the IMI call remit. Built upon foundations laid by the EU funded FLIP/EPoS projects and long-established, successful scientific collaborations amongst many of Europe's leading clinical-academic centres, LITMUS is at a unique advantage due to its existing large-scale patient cohorts, bioresources and multi-omics datasets.

Thus, LITMUS is powered to provide clarity on biomarker validity for NAFLD at scale and pace: supporting drug development and the targeting of medical care and limited healthcare resources to those at greatest need.

The current status of LITMUS is that 55 biomarkers have been identified along with defined requirements for technical as well as clinical validation of the biomarkers. The next step is to start communications with regulatory agencies with the end goal of getting some of the biomarkers approved using the qualification route. However, due to the complexity of the LITMUS program a decision has been made to start with a Critical Pathway Innovation Meeting (CPIM) in the US and, for EU, to start with a meeting with the Innovation Task Force (ITF). Feedback from these meetings is expected during third quarter of 2018.

2 Introduction

Strongly associated with the epidemics of obesity and type 2 diabetes that are testing healthcare systems worldwide, Non-Alcoholic Fatty Liver Disease (NAFLD) is an increasingly common cause of advanced liver disease that is characterized by substantial inter-patient variability in severity and rate of progression. It is currently assessed by liver biopsy, an invasive, costly and risky procedure. The lack of non-invasive biomarkers has hampered patient care and impeded drug development by complicating conduct of clinical trials. The overarching aim of LITMUS is to develop, robustly validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and/or monitor NAFLD/NASH progression and fibrosis stage. This will be achieved through a goal-oriented, tri-partite collaboration delivering a definitive and impartial evaluation platform for biomarkers, bringing together: (i) End-users of biomarker technologies (clinicians with expertise in NAFLD and the pharmaceutical industry); (ii) Independent academics with expertise in the evaluation of medical test/biomarker performance; and (iii) Biomarker researchers and developers (academic or commercial). LITMUS has the demonstrable capability to fulfil the IMI call remit. Built upon foundations laid by the EU funded FLIP/EPoS projects and long-established, successful scientific collaborations amongst many of Europe's leading clinical-academic centres, LITMUS is at a unique advantage due to its existing large-scale patient cohorts, bioresources and multi-omics datasets. Consortium members are internationally recognised experts with substantial relevant

expertise supporting the project's clear focus on biomarker identification, validation and accelerating EMA/FDA qualification.

Thus, LITMUS is powered to provide clarity on biomarker validity for NAFLD at scale and pace: supporting drug development and the targeting of medical care and limited healthcare resources to those at greatest need.

This document describes the regulatory pathway for biomarkers in the LITMUS program.

3 Qualification of a biomarker

Regulatory qualification of a biomarker is the process through which a biomarker can be approved for use in designing clinical trials, in order to enrich the trial population and thereby decrease the number of patients needed and/or the time for the clinical study. In NASH patients, the diagnosis is defined by the use of a liver biopsy which is a costly and risky procedure. Therefore, the LITMUS project is also focused on the validation and qualification of biomarkers that can be used either as diagnostics or as an aid in defining the diagnosis.

Clinical trials for new treatments in NASH patients have to be conducted for several years before efficacy on hard clinical endpoints, such as survival and liver transplantation, can be determined. A surrogate marker for efficacy of treatment is the liver biopsy score. Non-invasive biomarkers that can reflect changes to the liver upon treatment with a disease-modifying compound would be a great asset to monitor efficacy of treatment, and may greatly reduce the risk, time and costs associated with clinical trials.

The qualification of a biomarker is a process available in both the EU[1] and US[2]. A qualification of a biomarker results in the definition of a new guideline in which the context of use (COU) is described. It should be noted that "any analytically validated assay, test, or method may be used to measure a qualified biomarker in an IND/NDA/BLA submission, as long as the performance characteristics of the assay, test, or method demonstrate that they can reliably and accurately measure the specific biomarker in a similar manner as the biomarker measurement method used for the biomarker's qualification".[3]

3.1 The qualification procedure in the US

The FDA has established the Biomarker Qualification Program (BQP)[4] to work with external stakeholders to develop and qualify measurable and reliable biomarkers for a specific COU that addresses specified drug development needs. The BQP offers a formal process to guide requestors as they develop a biomarker so that the biomarker is: suited to a particular well defined COU; to ensure that biomarker measurement is feasible and reliable; and that the analytical performance adequately supports the COU. After a biomarker has been qualified, a public consultation is held after the definition of a draft guideline. The guideline will be issued according to the normal process for

1 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf
2 https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm230597.pdf
3 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535882.htm
4 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535882.htm

approving a guideline (Figure 1). The timeline for the FDA qualification procedure is not predefined, but the average time from submitting the Letter of Intent (LOI) until the final guideline becomes available is 2-3 years (Figure 1).

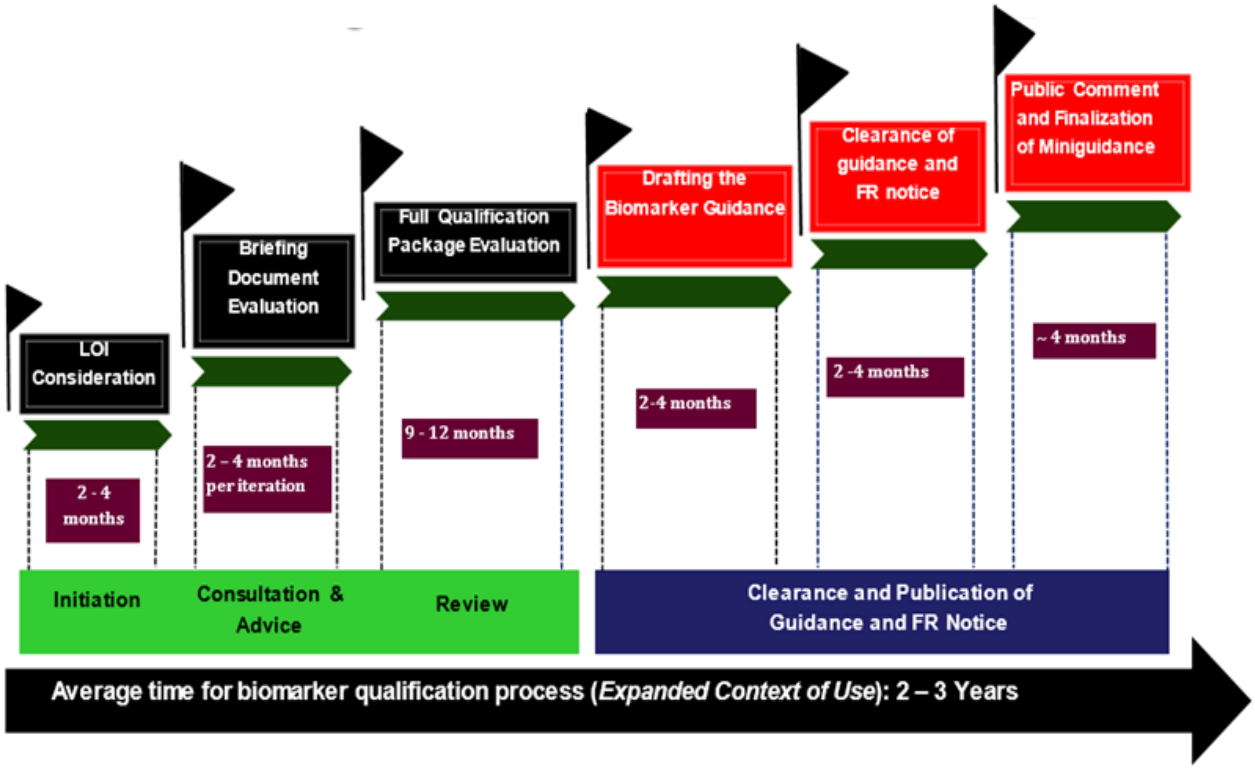

Figure 1: The biomarker qualification procedure of the FDA. Abbreviations: FR, federal register.

3.2 The qualification procedure in EU

A specialised qualification team, appointed by the Committee for Medicinal Products for Human Use (CHMP) and led by a coordinator who is a CHMP and/or Scientific Advice Working Party (SAWP) member, is in charge of the preparatory assessment of data and protocols. The team ensures that efficient use is made of the resources available in the EMA experts' network. The procedure provides qualification advice based on the existing scientific advice procedure adapted to host the activity of the qualification team and to facilitate international collaboration. In addition, a public consultation will be pursued prior to a final qualification opinion to take the views of the scientific community into consideration. The public consultation of the scientific community will ensure that CHMP/SAWP shares information and is open to scientific scrutiny and discussion. The public consultation facilitates the sharing of information across various fields, and thus ensures that the guideline is as comprehensive as possible.

The timeline for the EMA qualification procedure is defined in Figure 2. The procedure starts with a Letter of Intent, and after the first meeting with the applicant (at day 120), a draft report will be issued by the qualification team. If this report states that more data needs to be presented, the applicant can gather that data (e.g. clinical studies), and go back for more discussions. Once acceptable data is presented, the SAWP can accept the data for opinion. When a biomarker has received a positive opinion, a guideline will be issued according to the normal process for approving a guideline.

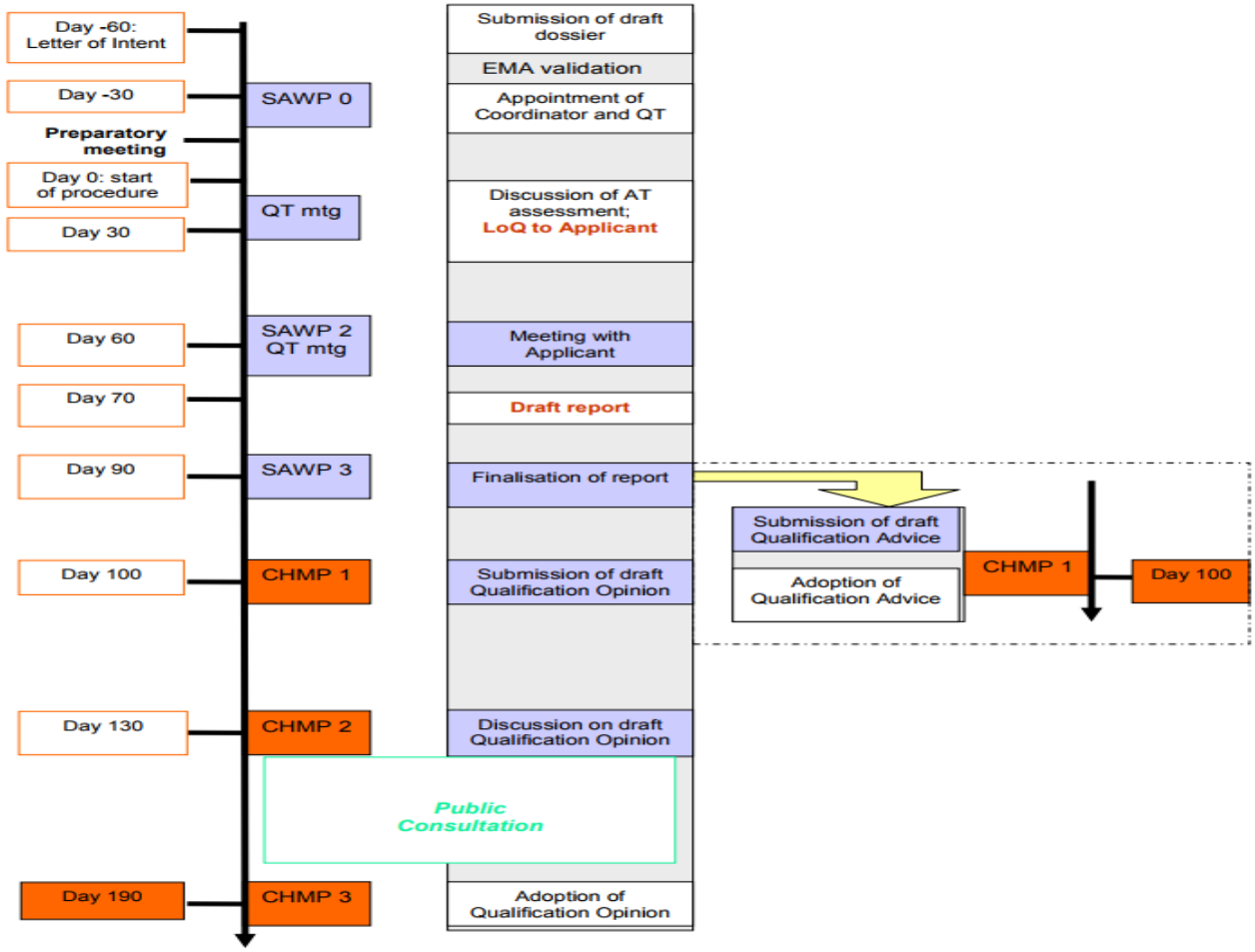

Figure 2. The biomarker qualification procedure of EMA. Abbreviations: SAWP, scientific advice working party; QT, qualification team; mtg, meeting; LoQ, Letter of qualification; CHMP, Committee for Medicinal Products for Human Use

3.3 The LITMUS project

The qualification procedures mentioned above, are meant for qualification of one specific biomarker. As LITMUS includes several biomarkers of different types, WP7 has decided that we should ask the regulatory authorities how to present the LITMUS project for the qualification procedures in the EU[5] and US[6].

This issue has been discussed with relevant regulatory people from FDA and EMA, with the following recommendations: Before requesting a meeting with the relevant offices for the qualification procedures, a meeting should be held in the EU through the ITF[7], while for US a CPIM[8] is recommended.

The objective of these first regulatory meetings is to seek advice on timing and content of the briefing package to start the qualification process in the respective jurisdictions.

5 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf
6 https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm230597.pdf
7 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp
8 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

3.4 Critical Path Innovation Meetings (CPIM) - US

The meeting is requested using an electronical form[9]. Within two weeks, we will be contacted:

- The request should include the following information:
  - Description of organization
  - A document (max 5-6 pages) containing the background and purpose of the meeting, steps taken to advance the project, and specific questions for FDA (if needed)
  - Desired outcome of the meeting
- The information should:
  - Be grounds for a discussion of conceptual drug development issues
  - Not be focused on a particular regulatory submission
- A final preparation package should be submitted two weeks before the meeting including:
  - Objective of the meeting
  - Proposed agenda
  - Presentation slides (if any)
  - Proposed attendees and respective affiliations

The briefing document will include the same information as in Appendix A – but with a different table of contents (TOC) (according to the above).

3.5 The Innovation Task Force (ITF) meeting - EU

The meeting is requested using an electronical form, followed by a brief telephone call[10]. Subsequent to the discussions over the telephone, a briefing document is submitted. The requestor might be asked to provide more information than what is in the briefing document as well as a definition on when and where to meet. The briefing document should include the following topics, which defines the TOCs:

- General background information
- Description of the technology or development method
- Composition of the product and description of the manufacturing process
- Description of the non-clinical and clinical development
- Presentation of the topics for discussion

A TOC and questions for the ITF meeting can be found in Appendix A.

4 Conclusions

Getting biomarkers approved for use in future trial programs requires that the biomarkers are accepted through the qualification process in EU[11] and US[12]. However, due to the complexity of the LITMUS project, it has been decided to start the Regulatory process by requesting a CPIM in the US, and in the EU by requesting a meeting with the ITF. When minutes from these meeting are received, this document will be updated.

9 https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm417627.pdf
10 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp
11 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf
12 https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm230597.pdf

Appendix A – Outline of briefing document for the Innovative Task Force meeting

Objective of meeting:

To seek advice on timing and content of the briefing package to start the qualification process in the EU and US.

The TOC of the briefing document includes the following:

1. General background information

- Define LITMUS. (It is suggested that WP1 defines this text).
- The purpose of this meeting is to seek advice on timing and content of the briefing package to start the Qualification process.

2. Description of the technology or development method

- Describe the different technologies in the LITMUS program and the number of biomarkers in each category (do not mention each individual marker). (It is suggested that WP7 in collaboration with WP4 and WP5 perform this task).

3. Composition of the product and description of the manufacturing process

- Describe the level of GMP in the evaluation and manufacturing of the biomarkers when being analyzed in the Phase 1A (retrospective) and Phase 1B (prospective) studies.
- Describe up to what level the IVD/device have been evaluated (CLSI or Bioanalytical Method Validation 2011 before evaluation in Phase 1A and 1B. (It is suggested that WP7 in collaboration with WP4 perform this task).

4. Description of the non-clinical and clinical development

- Describe the GCP level of the studies including a synopsis of Phase 1A and 1B. It is suggested that WP7 in collaboration with WP3 perform this task).
- Describe that the goal and CoU/Indication of the Prediction, Diagnostic, Diagnostic aid and Monitoring.
- Describe the statistical evaluation for each of the above categories, when evaluating data from Phase 1A and 1B studies.
- Describe the statistical outcome anticipated to be required for a Biomarker to be Qualified? (It is suggested that WP7 in collaboration WP2 perform this task).

5. Presentation of the topics for discussion

A. Do you suggest a different TOC than the one described in this briefing document (the briefing document for the qualification meeting will be more detailed than the current document) when presenting for the Qualification procedure?

B. Should we have the first Qualification meeting before or after the Phase 1A study?

Position: Suggest presenting before Phase 1A, in order to get input for the statistics we are planning to do.

C. For the Qualification briefing package, should we describe all biomarkers or one biomarker from each category?

D. The qualification of the biomarker will be based on two studies. Phase 1A, in which the biomarker will be defined, and Phase 1B, in which the biomarker will be validated. Is the suggested statistical method sufficient for a CoU/indication in relation to Monitoring, Diagnostic, Diagnostic aid and Prediction?

E. Is it sufficient to have the biomarkers evaluated at a non-GMP level for Phase 1A – taking into consideration that we suggest to have biomarkers approved based on the Phase 1A and 1B studies?

F. The biomarkers to be validated for Phase 1B will be evaluated up to CLSI requirements and GMP, manufacturing will also be in compliance with GMP – Are these data sufficient for a biomarker qualification?