GALAXY

GUT-AND-LIVER AXIS IN ALCOHOLIC LIVER FIBROSIS
GRANT NUMBER 668031

DELIVERABLE NUMBER: D8.4
DELIVERABLE DUE DATE: 30 June 2020
COMPLETION DATE OF DELIVERABLE: 30 June 2020
DISSEMINATION LEVEL: PUBLIC

DOCUMENT MAIN AUTHOR: Aleksander Krag, University of Southern Denmark
DOCUMENT SIGNED OFF BY: Project manager Louise Skovborg Just (University of Southern Denmark)

1. AIMS

EXPLOITATION PLAN AND UPDATES

STRATEGIES TO PROTECT AND EXPLOIT THE RESULTS FROM GALAXY DESCRIBED: A DETAILED EXPLOITATION STRATEGY WILL BE DEVELOPED AT THE START OF THE PROJECT AND UPDATED EVERY YEAR INCLUDING IP PROTECTION.

2. RESULTS

Table of content

Neo-epitope diagnostic assay 3
Nordic Bioscience 3
Description of the product, regulatory status and the market potential including competitors. 3
Regulatory status and data 3
Intellectual Property Rights 5
Exploitation through Commercial Partnerships 6
Microbiome based treatment 7
Norgine 7
Nordisk Rebalance 7
Description of the product, regulatory status and the market potential including competitors. 7
Intellectual Property Rights 9
Results, dissemination and interpretations from the Profermin study including status 9
Exploitation through Commercial Partnerships 10
Key Milestones and Timeline 10

Neo-epitope diagnostic assay

Nordic Bioscience

Description of the product, regulatory status and the market potential including competitors.

PRODUCT
Nordic Bioscience has developed a range of serological biomarkers reflecting tissue turnover and fibrosis, of which PRO-C3 is one. PRO-C3 has been shown to predict progression of fibrosis in HEP C and NASH as well as in other fibrotic area. In addition, PRO-C3 is diagnostic for disease and responds as pharmacodynamic biomarkers to efficacious anti-fibrotic treatments.

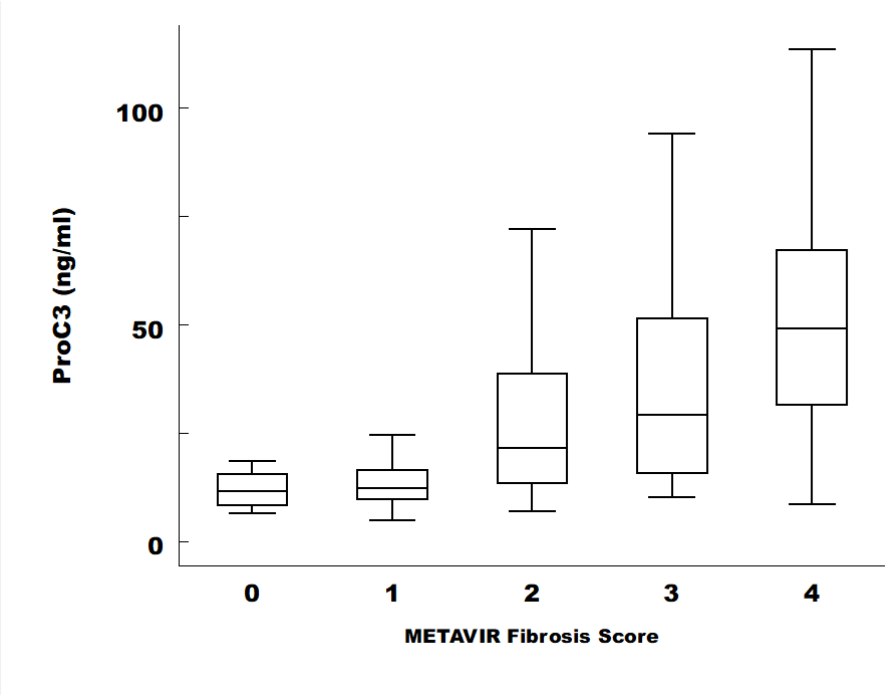
MARKET POTENTIAL
The focus of Galaxy is alcohol induced liver fibrosis/cirrhosis. Cirrhosis of the liver is more common than previously thought, affecting more than 633,000 adults in the US yearly" (Scaglione et al. 2015 J Clin Gastroenterol. 49(8):690-6.) with a great fraction hereof being alcohol induced. The same numbers may be estimated for the EU meaning that the market potential is big. There is a need for continuous monitoring of patients with multiple measurements a year to control and manage patients. We estimate that the marked size of 10.000.000 tests/year 3 years after launch of the product on a worldwide platform.

Currently there is only one competitor in the markers, which is the SIEMENS ELF test. This test is a composite score of three biomarkers. The ELF test is not focused on ALD, rater NASH. Another differentiation is the Nordic Bioscience collagen panel, which contains 10+ biomarkers. This panel will be used in combination of PRO-C3 to be tested in the GALAXY cohort to development the best possible algorithm for ALD.

Regulatory status and data

Nordic Bioscience joined the Galaxy consortium and research project due to the big market and the possibility a collagen profile may be able to identify patients at risk for progression and death with ALD.

The data generated in GALAXY, have provided data suggesting that PRO-C3 may be used as a diagnostic biomarker in ALD. The preliminary dataset comprised 126 patients in the high-a priori risk group and 70 patients in the low-a priori risk group. The spectrum of fibrosis was well covered among the 196 patients with METAVIR scores of F0/1/2/3/4 in 12/102/35/13/34 patients. Among the 34 with cirrhosis, median Child-Pugh was 6 (IQR 2). Median age was 56 years (IQR 13). The prevalence of significant fibrosis (≥F2) and cirrhosis (F4) in the high risk group were 56% and 25%, versus 17% and 4% in the low risk group. Median proC3 was 15.0 ng/ml (IQR 20.5; range 4.9-235.7). AUROC analyses of ProC3 to diagnose significant fibrosis (≥F2) and cirrhosis (F4) was: 1) all patients ≥F2 = 0.84 (95% CI 0.78-0.90), =F4 = 0.85 (0.77-0.92), 2) ≥F2 in high-risk group = 0.85 (0.78-0.91), =F4 in high risk group= 0.80 (0.71-0.90), 3) ≥F2 in low-risk group= 0.71 (0.50-0.92), =F4 in low-risk group= 0.94 (0.84-1.00). A cut-off of 11.3 ng/ml rule out cirrhosis with a Sensitivity 97% and NPV of 98%. Below 11.3 ng/ml only one patient has cirrhosis. These data have shown that ProC3 shows high diagnostic accuracy to diagnose significant fibrosis and cirrhosis in two independent populations of patients with alcohol overuse and no known liver disease.



To provide a commercial platform the use of such a biomarker, PRO-C3 is currently being technically validated according to FDA standards, to generate a CLSI validated biomarker. A list of 11 specific protocols needs to be undertaken and validated to allow the biomarkers to be used as clinical decision tools. The CLSI validation comprise the following protocols

1. Detection limits
   Purpose: To describe and specify the requirement for a successful validation of the detection limits
2. Linearity
   Purpose: to provide the requirements for the validation of linearity
3. Assay dilutional parallelism
   Purpose: to provide the requirements for the validation of linear dilution with assay buffer
4. Reference range
   Purpose: to describe and specify the requirements for a successful validation of a healthy reference range
5. High dose hook effect
   Purpose: to provide the requirement for the validation of a specified ELISA safety profile by ensuring that no high dose “hook” effect due to antigen excess occurs
6. Reproducibility
   Purpose: to describe and specify the requirements for a successful validation of the precision performance
7. Analytical specificity
   Purpose: to provide the requirements for the validation of analytical specificity
8. Carry-over and cross-contamination
   Purpose: provide the requirements for the validation of the safety profile by evaluating

the risk of producing false positive results due to analyte transportation (carry-over) from a high sample to a low sample within a single run.

9. Sample stability
   Purpose: to describe and specify the requirements for a successful validation of analyte stability
10. Reagent characterization
    Purpose: to provide the requirements for the validation of guard banding parameters
11. Reagent stability
    Purpose: describe and specify the requirements for a successful validation of reagent stability

Following the completion of the 11 protocols the ELISA PRO-C3 assay can be used for clinical decision making. The PRO-C3, and other assays, will be tested in combination with standard clinical parameters such as suggested by the FDA, to generate new and improved diagnostic, prognostic and monitoring biomarkers. This will results in patentable algorithms which will be used for diagnostic, prognostic and monitoring purposes.

To generate more advanced algorithms with better diagnostic and prognostic sensitivity and accuracy, additional fibrosis biomarkers will be analysed. A list of 12 others biomarkers will be tested in the same cohort, to generate data and an algorithm superior for the diagnosis of ALD patients. This list of biomarkers will be measured and analysed. The special feature of the neo-epitope platform is that we are able to separate tissue formation from tissue degradation. This allows for assessment of the tissue balance. This tissue balance is a unique and patents characteristic of the neo-epitopes.

Subject to change pending clinical data - the biomarkers to be evaluated are

PRO-C5 – type V collagen formation
C5M – type V collagen degradation
PRO-C6 – type VI collagen formation
C6M – type VI collagen degradation
PRO-C3x – type III collagen formation
CTX-III – type III collagen degradation
C3M – type III collagen degradation
PRO-C4 – type IV collagen formation
C4M – type IV collagen degradation
PRO-C14 – type XIV collagen formation
PRO-C2 – type III collagen formation
PRO-C10 – type X collagen formation

Intellectual Property Rights

Nordic Bioscience has submitted patent applications and has been granted patents before entering the Galaxy project on all biomarkers. Below is highlighted the PRO-C3 patent.

US009726674B2

(12) **United States Patent**
Leeming et al.

(10) **Patent No.: US 9,726,674 B2**
(45) **Date of Patent: Aug. 8, 2017**

(54) **PIIINP NEO-EPITOPE ASSAY**

(71) Applicant: **Nordic Bioscience A/S**, Herlev (DK)

(72) Inventors: **Diana Julie Leeming**, Klampenborg (DK); **Mette Juul Nielsen**, Kobenhavn S (DK); **Morten Karsdal**, Kobenhavn O (DK)

Friedman SL. Mechanisms of disease: Mechanisms of hepatic fibrosis and therapeutic implications. Nat Clin Pract Gastroenterol Hepatol 2004;1:98-105.
Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol 2002;3:349-363.
Wynn TA. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J Clin Invest 2007;117:524-529.
Bosman,F.T., and Stamenkovic,I. 2003. Functional structure and

Exploitation through Commercial Partnerships

Nordic Bioscience is a SME who is not able to fully exploit the worldwide commercial potential of a biomarker. Such a biomarker needs a platform that enables assessment in labs worldwide. Consequently, we have initiated and completed partnerships.

Data from PRO-C3 originating from the GALAXY study and many other fibrosis studies has been presented to different conferences and in publications. This has validated PRO-C3 as the best collagen biomarker for estimating efficacy, prognosis of liver related events and to predict response to treatment. At the same time, the 11 point CLSI validation for the manual version of the assay had been completed for NASH, documenting the stability and robustness of the assay. This has resulted in a commercial collaboration with Roche Diagnostics, in which the assay will be adopted to the automated COBAS platform. Consequently, the PRO-C3 assay may be measured in more than the 20000 COBAS machine worldwide, from approximately 2022. This will supply the CDx market.

At the same time, is anticipated that the GALAXY project will CLSI validate the PRO-C3 on a smaller scale platform to serve the RUO market. This test will be available in the Nordic Bioscience CAP/CLIA certified laboratories, as a fee for service test, to research groups and pharma companies worldwide. The additionally 10 biomarkers are currently under testing and will support the ROU marked and the Nordic Bioscience CAP/CLIA certified lab.

Microbiome based treatment
(Nordisk Rebalance/Norgine)

Norgine

Within the GALAXY project, results (including any associated arising intellectual property) are owned by the beneficiary that generates them. Under the GALAXY-related agreements, Odense Universitetshospital (OUH) has granted to Norgine an exclusive licence to OUH's Results under Workpackage 1 (WP1) within the Field of Use ("any and all therapeutic uses and/or new indications arising therefrom with respect to the Product, XIFAXAN 550 (rifaximin), including the anti-fibrotic effect of the Product on alcoholic liver disease"). For Results under other Work Packages, Norgine has an Option to purchase or license Results within this Field of Use, on fair and reasonable market conditions.

As and when relevant Results are generated, Norgine will work with its GALAXY partners to identify any arising intellectual property (including any potentially patentable inventions), and to ensure appropriate steps are taken to protect such intellectual property where possible (for example, by the filing of patent applications before any publication of the Results is made).

The results related to Rifaximin will occur when the RCT study 3 (GAB-ALD) is completed and the results have been evaluated. This is expected to be earliest on 30 June 2021.

Regarding exploitation of the Results (whether patentable or not), Norgine may undertake the development, manufacturing and marketing of innovative pharmaceutical products that may arise from the GALAXY project. Norgine has a direct presence in nearly all EU member states, which provides a solid foundation to launch new products and a strong infrastructure to bring new products to the market.

In addition, any publications relating to the Results should enhance the scientific understanding of the gut-and-liver axis, plus important diseases or conditions including alcoholic liver fibrosis, as well as diagnoses and therapies. Norgine will participate in the dissemination of this information to benefit patients, doctors and other medical practitioners throughout the EU.

Nordisk Rebalance

Description of the product, regulatory status and the market potential including competitors

Nordic Rebalance A/S (NRB) has developed Profermin®, which is a fermented food product developed for the dietetic treatment of gastrointestinal diseases. Profermin has been shown in a RCT study to be "Efficacious in Patients with Active Ulcerative Colitis" and able to reduce UC symptoms at a statistically and clinically significant level in patients with mild-to-moderate UC with a flare-up. The mode of action of Profermin is largely unknown, but it seems obvious that Profermin positively affects the microbiota in the patients in one way or another. The hypothesis is that the short chain fatty acids (SCFA) in Profermin i) constitute an important supplementation for energy nourishment for colonocytes, ii) together with other substances built during fermentation affect the intestinal microbiota to stop or reduce a so-called dysbiosis and iii) are important for building and maintaining a healthy intestinal barrier, which is imperative for a healthy immune system.

The focus of Galaxy is alcohol induced liver fibrosis/cirrhosis, which is believed to be initiated and continuously aggravated by a dysbiosis in the intestinal microbiota of patients. "Cirrhosis of the liver is more common than previously thought, affecting more than 633,000 adults in the US yearly" (Scaglione et al. 2015 J Clin Gastroenterol. 49(8):690-6.) with a great fraction hereof being alcohol induced. The same numbers may be

estimated for the EU meaning that the market potential is big. There are no accepted antifibrotic medical treatments of alcohol related liver fibrosis and cirrhosis and new treatment strategies target the gut microbiota including locally acting antibiotics aiming to stop the dysbiosis of the intestinal microbiota. Profermin will definitely have an advantage in the latter case because the society will prefer to avoid further use of antibiotics. If Profermin shows to be effective against Liver fibrosis/cirrhosis the Pros include that Profermin is a natural product without side effects, which is ideal for patients who are in a long-term treatment. The Cons include that medical doctors are reluctant to use other products than medicines for the treatment of patients. This means that a great deal of marketing resources should be devoted to reducing this barrier.

Today, Profermin is categorized as food for special medical purposes (FSMP) in Sweden. In Denmark, the authorities have decided that Profermin does not qualify for this category. However, data from the Galaxy clinical study is expected to support why Profermin actually shall be categorized as a FSMP and using these results, NRB will probably reopen the discussions with the Danish authorities.

There are currently no direct competitors in the market since there are no accepted drugs for long-term treatment of liver fibrosis/cirrhosis. Medicinal companies producing locally acting antibiotics such as Rifaximin will be competitors. Likewise, will companies that target the composition and behavior of the intestinal microbiota in other ways be competitors, for instance companies focusing on fecal transplantations or other compositions intended to modify the microbiota.

NRB joined the Galaxy consortium and research project due to the big market and the possibility that Profermin can stop intestinal dysbiosis and thereby stop or reverse the liver disease. However, the opportunity to clarify the first steps in the mode of action of Profermin was the other reason for joining the consortium.

In Fig 1., it is shown that RCT has successfully been performed on UC with Profermin and currently Profermin is used in the RCT in Galaxy on liver fibrosis/cirrhosis. If the clinical results from Galaxy show that Profermin can stop or reduce liver fibrosis/cirrhosis, NRB will have two indications that can be treated with Profermin. As also shown in Fig. 1, NRB is usually met with the question from health care professionals, commercial partner candidates and others: Very good, but how does Profermin work? NRB is aware that it is necessary to be able to answer the question at least with some results that confirm part of the hypothesis of Mode of Action (MoA). In other words, knowledge on MoA is a key business value since no knowledge on MoA can be a barrier for health care professionals to use a product and for partner candidates to enter into commercial agreements. On top of that, knowledge on MoA provides tool for developing new and optimizing existing products and to obtain issued patents without many discussions with examiners.

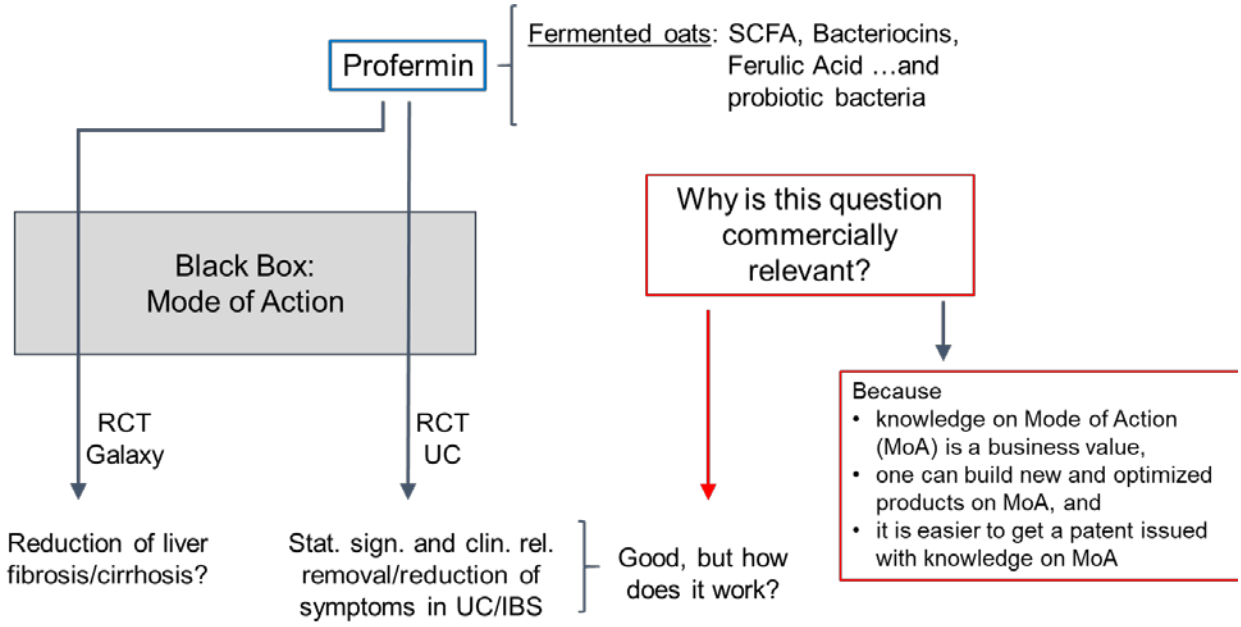


Fig. 1. Commercially facts and questions on Profermin. SCFA: Short Chain Fatty Acids; RCT: Randomized Controlled Trial; UC: Ulcerative colitis

Intellectual Property Rights

Nordic Rebalance (NRB) submitted a patent application on 15 January 2016 before entering the Galaxy project. The title of the application is "Compositions for treatment of a fatty liver of fibrotic liver disease", and it covers the treatment of liver inflammations using the proprietary fermented products of NRB.
The application contains no treatment examples, but such are expected to be added to the application when results emerge from the clinical study in Galaxy with Profermin. Results may be added to a patent application within the first year from submission. The first results from the clinical study with Profermin in Galaxy are at the earliest expected to come forward in 2021, and, therefore, NRB has withdrawn the above-mentioned patent application 360 days following submission and resubmitted the same application the day after the withdrawal. This procedure has been done several times and will be repeated until the first useful results from Galaxy are ready to be included in the application text. This is done both to show the original priority date and to continuously have a registered patent document that can be used as an attachment to a confidential disclosure agreement.

Results, dissemination and interpretations from the Profermin study including status

Currently, 28 patients have been included in SYN-ALD, the Profermin clinical study in Galaxy. 40 patients in total will be included, and the last patient is expected to be included in December 2020 at the latest. Previously, we expected the first results from the study to arise in 2020. However, in AMD-668031-20 the period for inclusion of study subjects in SYN-ALD was extended to last until 31 December 2020. Results from the analyses are expected to arrive in October/November 2021 and interpretations will be completed before end of 2021.

The results from the study will be included in an updated version of the current patent application on liver fibrosis. Following, one or more manuscripts to be published in peer reviewed scientific journals will be prepared. Further disseminations will be done according to the plan described in the Galaxy application.

Exploitation through Commercial Partnerships

NRB is a small company who is not able to fully exploit the commercial potential of a product that may show effective against liver fibrosis. Therefore, NRB will seek commercial partnerships with one or more large companies in the market. This may be conventional medicinal companies and/or companies that produce and market nutritional products for dietetic treatment of diseases.

A comprehensive market analysis must of course be carried out. As stated in the Galaxy application, about 20% of the EU population older than 15 years are alcohol over-users who are at risk of developing liver fibrosis and eventually liver cirrhosis. These people make up the primary target market for Profermin. However, in-depth analysis of the clinical results from Galaxy are required to identify the relevant subgroup(s) i.e. the relevant market for Profermin. NRB has decided that resources will be allocated to carry out the in-depth commercial analysis once it is known whether Profermin seems to show the desired effect on liver fibrosis/cirrhosis.

An overview of the Exploitation Plan of NRB is shown in Fig. 2. As indicated, new insight into MoA will both provide value to the commercial activities on liver fibrosis/-cirrhosis and the existing commercial activities on ulcerative colitis and IBS.

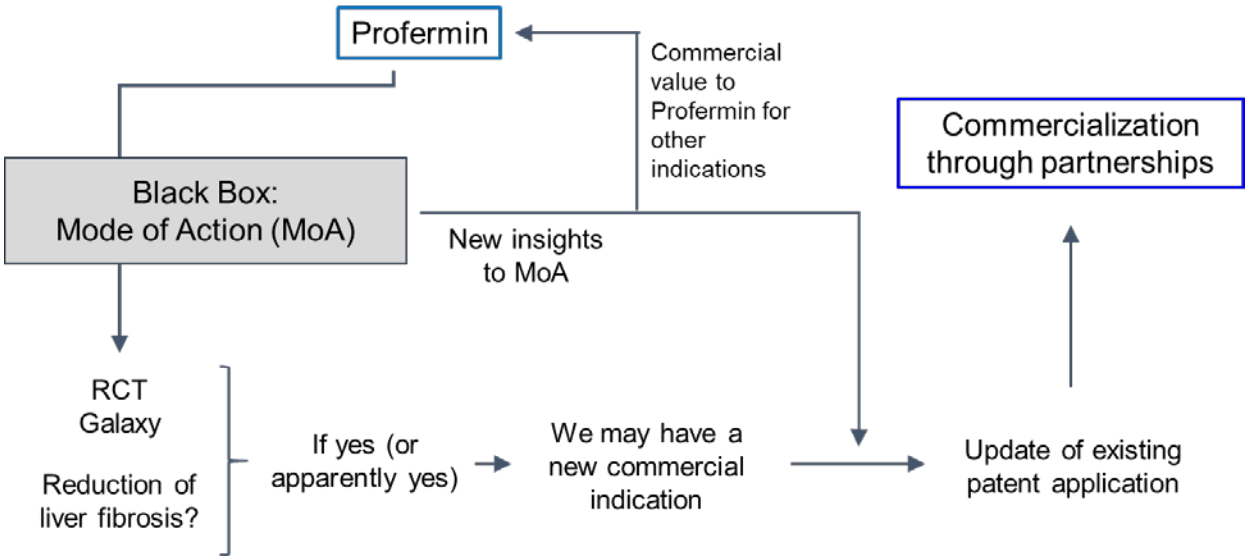


Fig. 2. A schematic representation of the Exploitation Plan of NRB

Key Milestones and Timeline

No.	Milestone	Expected time	Comments
1	Last patient included in the clinical study	December 2020	
2	Last patient has completed the clinical study course	June 2021	
3	Batch of all samples sent to Labs	August 2021	
4	Results received from all Labs	October-November 2021	
5	Interpretation of results completed	December 2021	
6	Comprehensive market analysis completed	March 2022	Milestones from here is relevant only provided positive results from the study

7	In-depth commercial analysis leading to strategy on obtaining commercial partnership(s)	May 2022
8	Identification of and contacting partnership candidates	June-September 2022
9	First meeting with partner candidate(s)	October-December 2022
10	Partnership agreement(s) signed	December 2023