Summary of the 2nd reporting period (01 September 2022 – 28 February 2024)

Summary of the context and overall objectives of the project

- ### The problem A-TANGO will address

The A-TANGO project has been designed to address unmet needs for patients with alcohol related cirrhosis who go on to develop a condition called acute on chronic liver failure (ACLF). ACLF is characterised by failure of multiple organs that includes the liver, kidneys, coagulation, brain, circulation and lungs. World-wide, this condition accounts for the deaths of over 1M people. About 30% patients with this condition will die within 28-days of hospitalisation. Besides, liver transplantation, the treatment of this condition is an unmet clinical need, which A-TANGO is designed to address.

The A-TANGO Consortium is a group of European experts who have identified the unique mechanisms underlying this syndrome (Figure 1). They have shown through their innovative studies that the key events leading to the failure of these organs is severe liver inflammation which leads to senescence of the liver cells that culminates in a failure of regeneration. It is this senescence of the liver cells that spreads to affect the other organs. They also showed in their preclinical studies that this block could be overcome by using a combination of an inhibitor of a receptor called the toll-like receptor that drives hepatic inflammation and senescence. The addition of a drug that mobilises the stem cells (granulocyte colony stimulating factor) could stimulate liver regeneration. Thus, they identified a novel combinatorial therapy called G-TAK. The primary aim of A-TANGO is to explore in a clinical trial whether this approach impacts on the severity of ACLF (Figure 2).

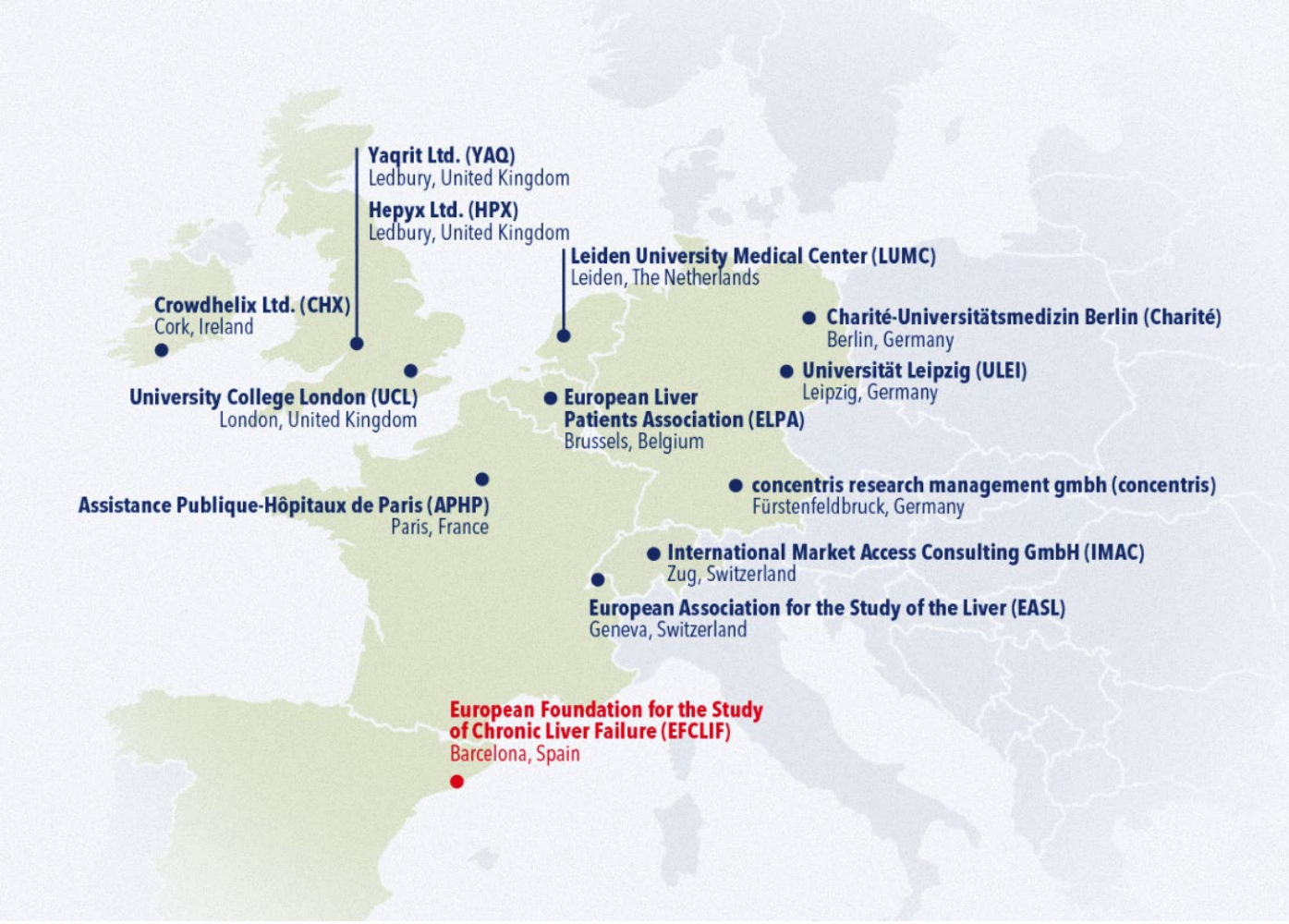

Figure 1. Map of project partners within Europe. A-TANGO is an international research project, spearheaded by EF CLIF, that brings together fourteen institutions from eight countries.

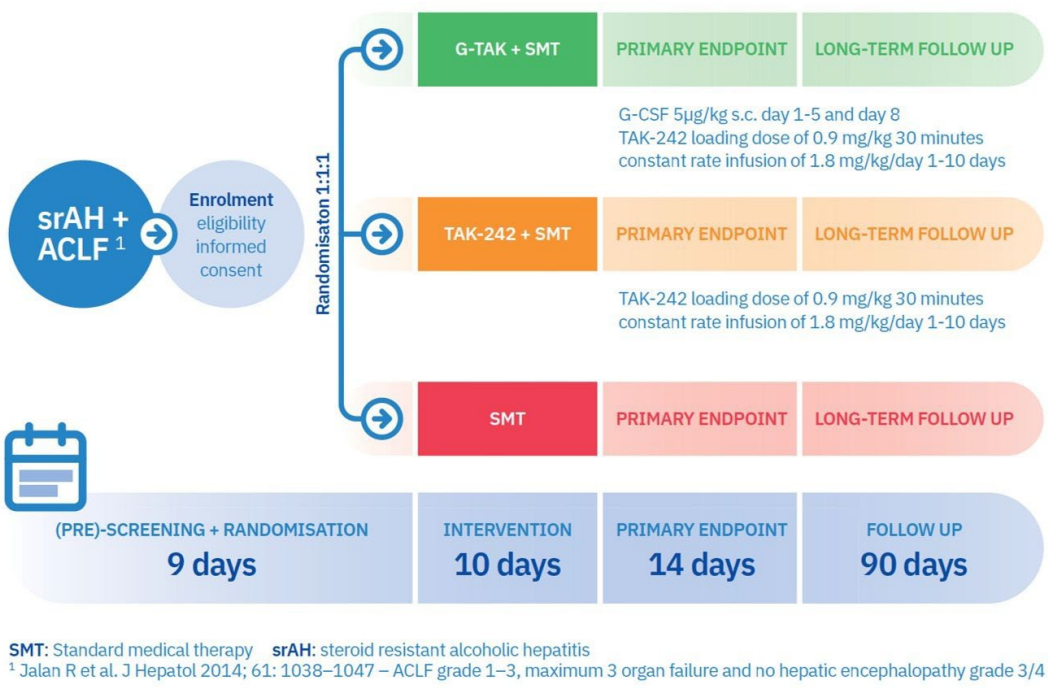

Figure 2. Expected impact of A-TANGO. Currently, up to 40% of patients that come to the hospital with an acute phase of acute-on-chronic liver failure (ACLF) die despite best possible treatment with standard medical treatment (SMT). A-TANGO strives to increase the survival rate of these patients with G-TAK, a novel combinatorial therapy. By improving the percentage of patients recovering fully, A-TANGO also aims to decrease the burden on the healthcare system. Currently, 30% of ACLF patients recover only partially, remaining in need of extensive long-term care.

- ## Why is it important for society

A-TANGO is hugely important for the society as it addresses the unmet need of patients with acute on chronic liver failure (ACLF) that at present have no solution. Besides, 30% of the patients with ACLF that die, there is huge healthcare burden with morbidity and attendant costs. A-TANGO will develop a new therapy that can be readily applied to patients with ACLF to prevent progression and enhance recovery. The dissemination activities will help destigmatize the disease and allow more investment into the problem of ACLF. As the background intellectual property is owned by one of the A-TANGO partners, success of the study would lead to creation of new jobs and economic benefits for the European community.

- ## What are the overall objectives

A-TANGO will pursue the following specific objectives:

- Achieve **ethical and regulatory approvals** of G-TAK for Phase 2 clinical trials in ACLF (WP1).
- Ensure safe and regulated **supply of the drugs**, G-TAK, and respective placebos for clinical trials (WP2).
- Undertake a European multicentre **clinical trial** to establish safety, pharmacokinetics and efficacy in patients with ACLF and produce meaningful advances for this group of patients with non-communicable disease so that G-TAK is ready for late-stage clinical trials (WP3, WP4, WP5).
- To explore **patho-mechanisms** involved in disease progression and evaluate **biomarkers** by using human samples collected during the A-TANGO trial in order to further optimise G-TAK for late phase clinical trials (WP4).
- To evaluate the results in respect to impact of G-TAK on **clinical outcomes and quality of life** (WP5).
- **Exploit the results** of the A-TANGO trial by defining potential health economic benefits, reimbursement strategies and raising commercial interest in the continued development of G-TAK to facilitate smooth entry into general clinical practice (WP6).
- **Disseminate** the therapeutic potential of G-TAK results to a range of stakeholder types and increase awareness of ACLF to patients and a range of practitioners (WP7).

Work performed from the beginning of the project to the end of the 2nd reporting period and main results achieved so far

During the second reporting period of this project, significant hurdles have been overcome and huge progress has been made. Detailed progress is summarised below:

- A modified version of the CLIF-C organ failure (CLIF-C trial score) has been developed for use in the clinical trial. This is more robust to evaluate end points, allows diagnosis of larger numbers of patients and allows drug testing with less number of patients.
- The A-TANGO Consortium is well on its way and will initiate the clinical trial, which is due to recruit the first patient in the last quarter of 2024. The protocol and regulatory documentation have been completed and has received ethical and MHRA clearance in the UK. The EU submission will follow after addressing the comments of the European Medicines Agency. Following difficulties with drug manufacture, which led to delays, this has been overcome and the investigational medicinal products and placebos will be available for the start of the trial. The clinical trial sites are being recruited and education on the protocol is due to start within the next 2 months.
- The dissemination activities have been on target with the establishment of the website, social media interactions, patient facing activities and the project has already started to make impact. Three measurable impacts are the engagement of the A-TANGO Coordinator with the US Food and Drug Administration for trial designs, the initiation of a clinical practice guideline on ACLF commissioned by A-TANGO partner, EASL and publication of the preclinical data in the highest impact liver disease journal, Journal of Hepatology.
- The intellectual property is owned by one of the A-TANGO partners, Hepyx. This has now entered the National Phase. Engagement with future investors and pharmaceuticals are ongoing.
- The early career scientists have built a network and will provide the next generation of clinician scientists with interest in ACLF.
- Although the costs of drug manufacture have exceeded earlier estimates, the reduction in the sample size helps balance the budget to deliver the aims of A-TANGO.

Progress beyond the state of the art, expected results until the end of the project, and potential impacts (including socio-economic impact and wider societal implications)

G-TAK will generate meaningful advances in clinical practice and care for patients with ACLF for late-stage clinical trials (Figure 3). It has a high potential to improve outcomes for patients with ACLF and will impact on the disease burden of individual patients and health care systems following validation in late-stage clinical trials. It will reduce costs associated with treating liver disease and simultaneously strengthen Europe as the global leader in novel therapies for ACLF. Together with ELPA, A-TANGO will improve information and awareness of ACLF and develop strategies to improve their care using the G-TAK. A-TANGO will strengthen the competitiveness and growth of the applicant SMEs and it will create new market opportunities for European companies.

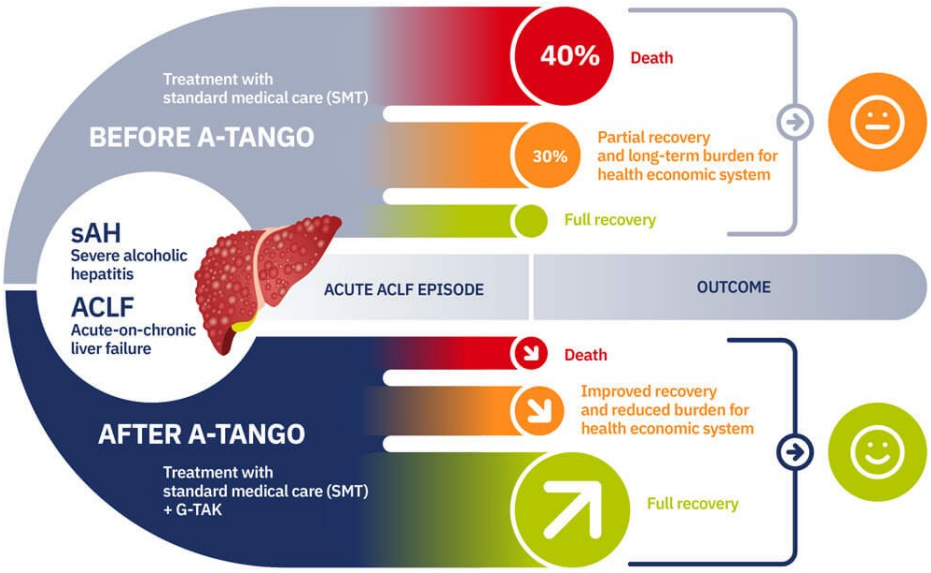

Figure 3. Design of A-TANGO's clinical trial. The purpose of this phase II clinical trial is to investigate the safety of TAK-242, an inhibitor of Toll-like receptor (TLR) 4 signalling, in combination with granulocyte colony stimulating factor (G-CSF) in patients with steroid-resistant alcoholic hepatitis (srAH) and ACLF (name of combinatorial therapy: G-TAK) and assess the effect of G-TAK on the disease severity of ACLF. To do so, patients will be randomised into three treatment arms, namely the green group that receives G-TAK in addition to standard medical treatment (SMT), the orange group that receives TAK-242 in addition to SMT, and the red control group that receives placebo treatments in addition to SMT.

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Address (URL) of the action's public website

https://a-tango.eu/