Summary of the 1st research period (01 March 2021 – 31 August 2022)

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. Worldwide, 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 event leading to failure of these organs is severe liver inflammation, which leads to senescence of the liver cells, culminating in failed regeneration. It is this senescence of liver cells that spreads to affect other organs. In preclinical studies, the consortium also demonstrated that this blockage can be overcome by combining an inhibitor of a toll-like receptor that drives hepatic inflammation and senescence and a drug that mobilises stem cells (granulocyte colony stimulating factor, G-CSF) and 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).

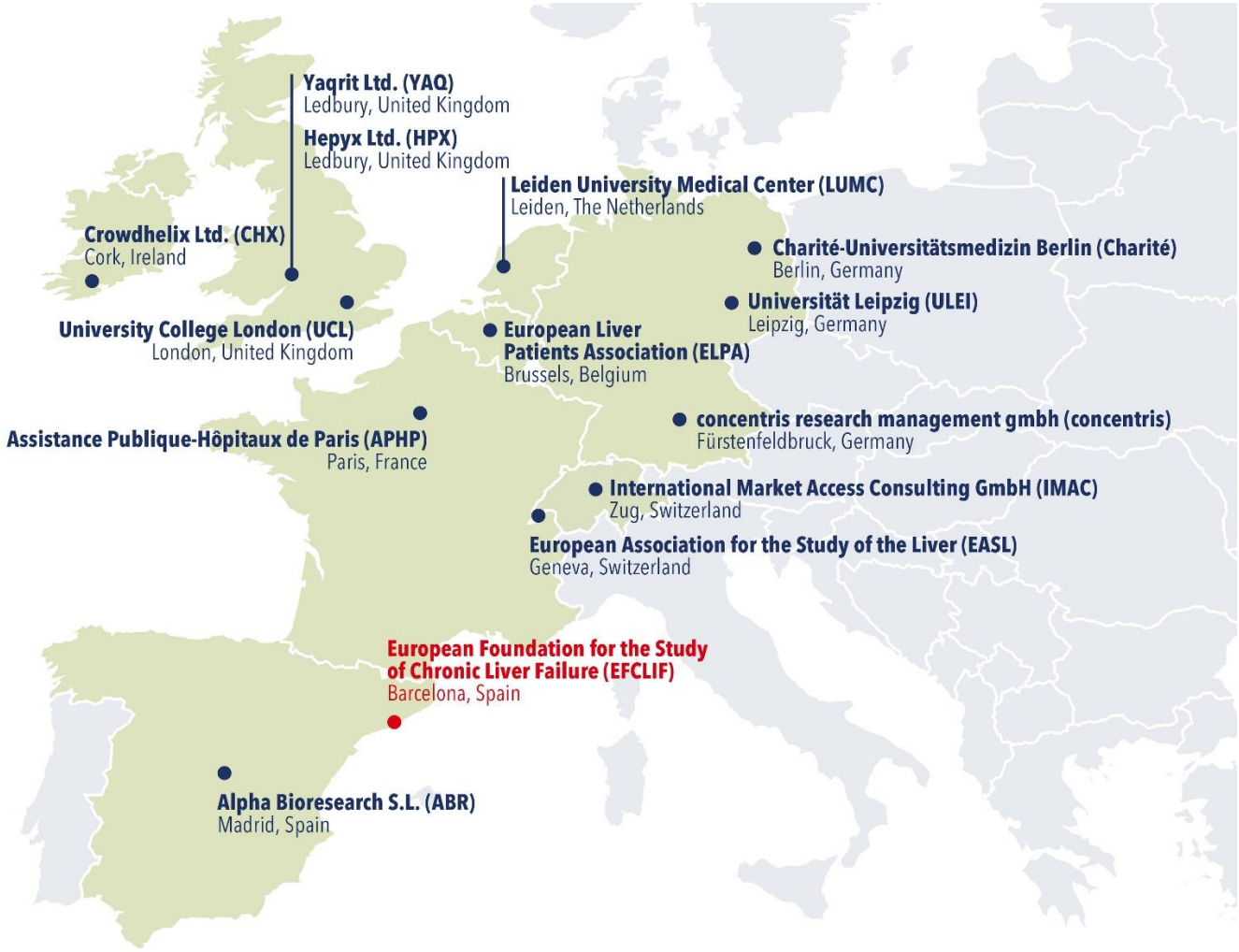

Figure 1. Map of project partners within Europe. A-TANGO is an international research project, spearheaded by EF CLIF, that brings together fourteen institutions from eight countries.

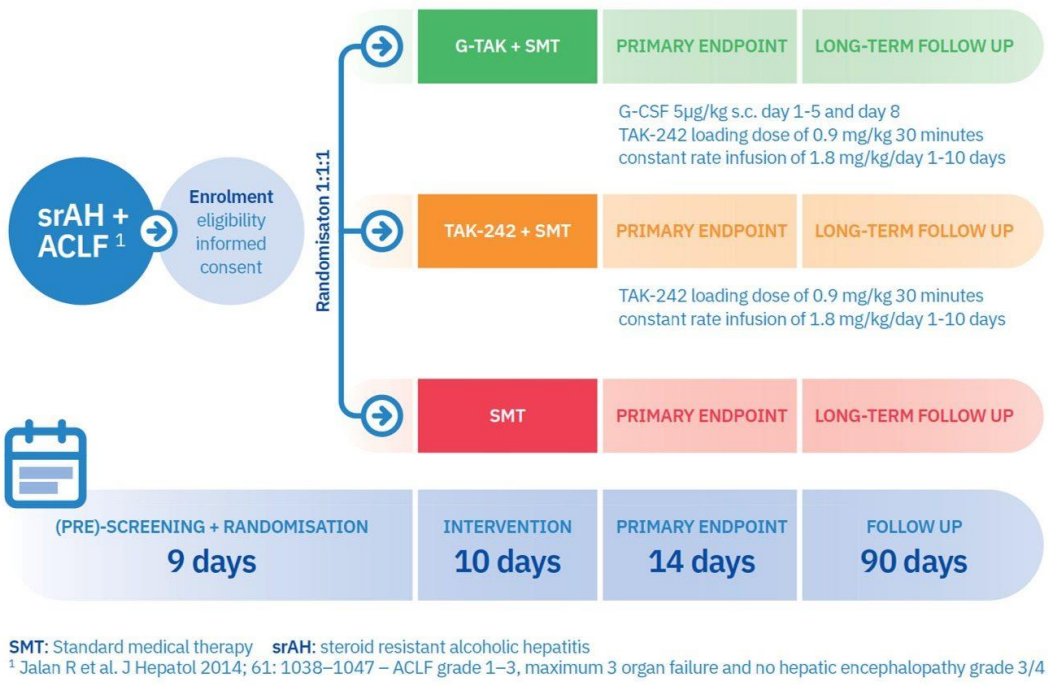

Figure 2. Expected impact of A-TANGO. Currently, up to 40% of patients that come to the hospital with an acute phase of acute-on-chronic liver failure (ACLF) die despite best possible treatment with standard medical treatment (SMT). A-TANGO strives to increase the survival rate of these patients with 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.

SMT: Standard medical therapy **srAH:** steroid resistant alcoholic hepatitis
[1] Jalan R et al. J Hepatol 2014; 61: 1038–1047 – ACLF grade 1–3, maximum 3 organ failure and no hepatic encephalopathy grade 3/4

- ## Why is it important for society

A-TANGO is hugely important for society as it addresses the unmet need of patients with acute-on-chronic liver failure (ACLF). At present, there is no solution besides liver transplantation. In addition to the sad reality that 30% of the patients with ACLF die, there is a huge healthcare burden because of 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 destigmatise 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 also 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 **pathomechanisms** 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 in the 1st research period and main results so far

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

- The A-TANGO consortium is well on its way to initiate the clinical trial, which is due to recruit the first patient in the first quarter of 2023. The protocol and regulatory documentation have been completed and have received ethical and Medicines and Healthcare products Regulatory Agency (MHRA) clearance in the United Kingdom (UK). The EU submission is imminent. Difficulties with drug manufacturing, which led to delays, have been overcome and the investigational medicinal products and placebos will be available soon for the start of the trial. The clinical trial sites have been engaged and education on the protocol will occur within the next 2 months.

- The dissemination activities have been on target with the establishment of the project website, social media channels, patient-initiated activities, and the project has already started to make impact. Three measurable impacts are the engagement of the A-TANGO coordinator with the United States (US) Food and Drug Administration (FDA) 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, namely the Journal of Hepatology.

- The intellectual property is owned by one of the A-TANGO partners, Hepyx. This has now entered the national phase, prompting interest from a medium-sized pharmaceutical company.

- The early career scientists have built a network and will constitute the next generation of clinician-scientists with an interest in ACLF.

- Although the costs of drug manufacturing have exceeded earlier estimates, the reduction in the sample size helped 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 through stage 2 clinical trials (Figure 3). This novel combinatorial therapy has a high potential to improve outcomes for patients with ACLF and will impact on the disease burden of individual patients and healthcare 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 project partner ELPA, A-TANGO will improve information about and awareness of ACLF and develop strategies to improve patient care using G-TAK. Importantly, A-TANGO will strengthen the competitiveness and growth of participating small and medium-sized enterprises (SMEs) and will create new market opportunities for European companies.

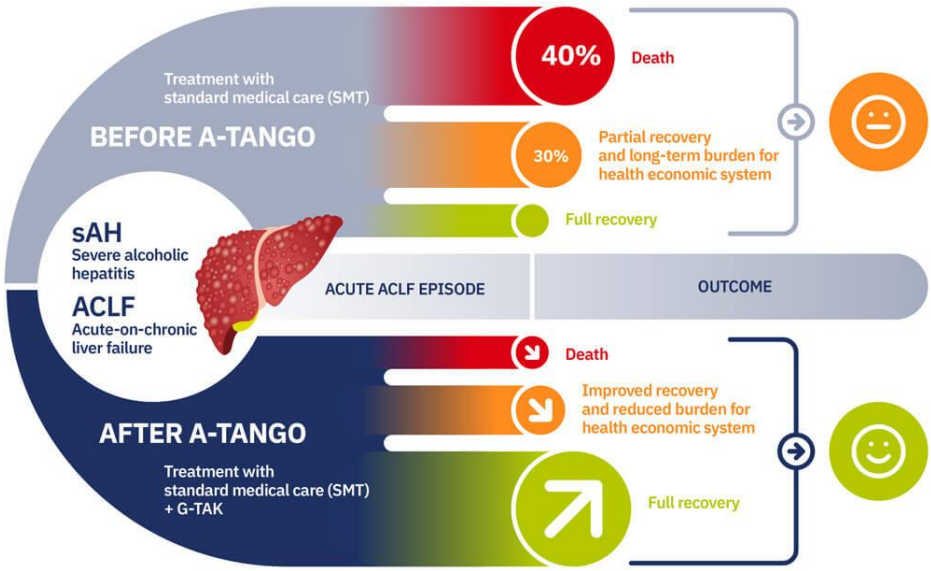

Figure 3. Design of A-TANGO's clinical trial. The purpose of this phase II clinical trial is to investigate the safety of TAK-242, an inhibitor of Toll-like receptor (TLR) 4 signalling, in combination with granulocyte colony stimulating factor (G-CSF) in patients with steroid-resistant alcoholic hepatitis (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/