2 Summary description of project context and objectives

In BALANCE, two Academic Centers and three SME's joined forces to offer Acute Liver Failure (ALF) patients a bioartificial liver-support system (BAL) for bridging the waiting period for liver transplantation or recovery of the diseased liver.

ALF is a highly lethal disorder and liver transplantation is the only life-saving therapy. However, limited availability of donor livers severely reduces its impact. A bioartificial liver (BAL) may support ALF patients by temporary and extracorporeal treatment of their plasma through a bioreactor with functional human liver cells. The BAL may also support another group of liver patients suffering from Acute on Chronic Liver Disease (AoCLD). This group comprises patients with liver cirrhosis that go through at least one episode of life threatening deterioration.

The central objective of BALANCE was to develop a clinical-size-BAL based on the human progenitor cell line HepaRG (HepaRG-BAL) that executes essential key liver functions for a clinically relevant period in ALF, to reach proof of safety, efficacy and feasibility in a large pre-clinical model of ALF and to prepare for a clinical trial. A laboratory-size HepaRG-BAL had already shown proof of principle by effectively supporting rats with ALF.

A two-staged approach has been adopted. Stage I is designed for in-vitro optimisation of the BAL and the human cell line and stage II comprises of the ex-vivo activities in which the optimized and up scaled BAL is tested and validated in subjects (controlled study). In addition approval of a Phase I/IIa trial in humans has been prepared.
In detail, the work is organized in 7 work packages (WPs) with specified objectives:
The initially included WP7 comprising the clinical trial has been deleted from the final workplan.

WP1: Consortium management
Central objective: To ensure compliance with the Grant Agreement and Consortium agreement
Specific objectives:

Task 1.1:	To secure day-to-day management of BALANCE including: monitoring of scientific progress; communication between partners and with the EC; financial management; reporting; decision making; conflict management
Task 1.2:	To organise meetings
Task 1.3:	To provide a secured web-based tool for supporting daily management and reporting, open communication between all consortium members and for dissemination of project results to the general audience

WP2: Characterization and cell banking of HepaRG cells
Central objective: To prepare the HepaRG cell line for cell-culture production and for certification
Specific objectives:

Task 2.1:	To develop pathogen-free master and working cell banks
Task 2.2:	To assess stability and phenotype of cells
Task 2.3:	To assess genotype and karyotype of monolayer cells
Task 2.4:	To determine tumorigenicity status in vivo

WP3: BAL hardware
Central objective: To validate the safety of upscaled BALs for clinical testing, to develop transport, storage and incubation systems that guarantee optimal clinical performance and to prepare for certification of these hardware items.
Specific objectives:

Task 3.1:	To produce the current bioreactor in laboratory and clinically relevant scale
Task 3.2:	To validate the safety of upscaled BALs
Task 3.3:	To assess optimal transport, storage and incubation conditions for large bioreactor
Task 3.4:	To prepare for certification of the large bioreactor
Task 3.5:	To adapt and purchase of a transport system of the large bioreactor
Task 3.6:	To adapt and purchase of 2 large bioreactor incubators

WP4: Production of HepaRG-bioreactor cultures

Central objective: To select, develop and qualify the manufacturing process of HepaRG-bioreactor cultures

Specific objectives:

Task 4.1: To transfer HepaRG technology and methods to partner 5

Task 4.2: To develop a production process for HepaRG BAL cell cultures

Task 4.3: To investigate serum reduction

Task 4.4: To specify preservation conditions

Task 4.5: To assess stability of bioreactor cultures loaded in BALs before and after ALF treatment

WP5: Safety and efficacy in subjects with ALF

Central objective: To obtain proof of principle for safety and efficacy in a pre-clinical model of ALF

Specific objectives:

Task 5.1: To develop a reproducible invasively-monitored model of paracetamol-induced ALF in a pre-clinical study;

Task 5.2: To assess clinical and biochemical parameters in a paracetamol-induced ALF pre-clinical model under ICU monitoring and therapy conditions;

Task 5.3: To assess efficacy/ safety of HepaRG-BAL in three groups of 7 subjects

WP6: Preparation clinical trial

Central objective: To obtain regulatory approval for the planned phase I/II a study and to make practical preparations for clinical testing

Specific objectives:

Task 6.1: To prepare IMPD and QA/QC documents for approval of future clinical trial.

Task 6.2: To complete the study protocol.

WP8: Dissemination and exploitation

Central objective: To adequately inform the external stakeholders of BALANCE of the results obtained;
To effectively translate the main deliverables of BALANCE into solutions for healthcare and related markets.

Specific objectives:

Task 8.1: To disseminate results obtained to external stakeholders

Task 8.2: To plan exploitation of main deliverables and to attract financing for next (clinical)phases

Task 8.3: To secure intellectual property rights