4.1 Final publishable summary report

1 Executive summary

The central objective of BALANCE (see http://fp7balance.eu) 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 acute liver failure (ALF), to reach proof of safety, efficacy and feasibility in a large pre-clinicalmodel of ALF and to prepare for a clinical trial. A two-staged approach has been adopted.

Stage I.

In vitro optimisation of the HepaRG-BAL has been obtained first by up-scaling the bioreactor (without cells) from 9 mL to 550 mL content. Both bioreactor and tubings/ filters meet the criteria for biological and chemical safety, physical integrity and functionality as has been documented by subcontractor RanD (Italy). Second by generation of a Research Cell Bank (RCB) and Master Cell Bank (MCB). Both cell banks were tested for sterility, mycoplasma, endotoxin, viability after thawing and recovery and appeared to be safe. Unfortunately both cell banks showed early transformation and could not be used for pre-clinical experiments.
Yet, the HepaRG cells not deriving from these cell banks showed phenotypic stability (based on detoxification activity and protein, lipid and carbohydrate metabolism) until passage 20 and showed not to be tumorigenic by growth on soft agar and in an in vivo assay in immunodeficient mice. In addition it was established that HepaRG cells carry stable abnormal karyotype up to at least passage 22.
Other results were improvement of the culture conditions of the HepaRG-BAL. In addition, it was found that BAL culturing decreased sensitivity of HepaRG cells to toxicity of plasma, and a 24h culture period further ameliorated the plasma cytotoxicity This implies that repetitive BAL treatments with single BALs with e.g. 24h culture session-intervals may be a possibility, which will significantly expand the therapeutic efficacy of a single BAL and reduce the costs of the treatment.
Due to an internal evaluation of the project results, the Consortium was of the opinion that there was a need to redefine the scope of the work and to concentrate the efforts on the attainment of the planned pre-clinical experiments, the clinical trial being abandoned. This implied that the participation of Pharmacell in the Project was terminated on the date of September 11 2014 and that the Annex 1 had to be revised. Such termination and modification of the Description of Work has been approved by the EU Commission in the amendment number 2 to the Grant Agreement. The remaining partners established the production of sufficient numbers of non-GMP HepaRG-BALs for pre-clinical experiments. Consequently the originally planned Phase I/IIa trial in 10 ALF patients had to be abandoned.

Stage 2

A novel standalone transport system has been developed to transport the HepaRG-BAL from Amsterdam to Edinburgh in which the cell-BAL was perfused with culture medium and gas under temperature control and guidance of a continuous monitoring system.
A clinically relevant model of ALF based on an overdose of paracetamol was successfully established in subjects. Protocols were made and implemented for connection of the subjects to plasmapheresis systems and BAL perfusion by a bio-incubator system: Performer O.Liver. We have established a multifactorial monitoring system including manual and machine-assisted recording of physiological readings and the 1-4-hourly sampling of biofluids and their biochemical analysis, intracranial pressure and haemodynamic parameters.
The completed main study of 23 subjects (9 Controls, 8 Empty BALs and 6 Filled BALs) showed non-inferiority of filled BAL treatment. Furthermore, it appears that pronounced kidney, muscle and liver damage were slowed down or even reversed in the filled BAL treated subjects. Further studies on the biobank samples are in progress.
Although the clinical trial had to be abandoned extensive QA/QC documentation for regulatory approval (MHRA in the UK) has been established: Investigational Medicinal Product Dossier (IMPD) , Clinical Protocol, Case Report Forms to be stored in an electronic database accessible via the website. In addition an extensive risk assessment of the BAL preparation, BAL transport and patient treatment has been made and a list of specifications of the clinical HepaRG-BAL as well. A future clinical Phase I/IIa trial will have directly profit from all these preparations.To plan exploitation of main deliverables and to attract financing for next (clinical) phases the attractiveness of the market was analysed. In addition the needed follow on finance and a Proposition for Investment was established; a Business Plan has been finalized.