4 Potential impact

The BALANCE project has successfully upscaled the HepaRG-BAL to clinical size and has made preparations to start a clinical trial. Furthermore, proof of safety has been delivered in the pre-clinical experiments This implicates that the HepaRG-AMC-BAL is well underway to offer a long-expected solution for patients awaiting liver transplantation. The impact of this project is underlined by the following data:

Extending survival chances for patients on the donor liver waiting list

There are more than 30,000 patients on the liver transplant waiting list in Europe and the US. Besides the kidney waiting list (96,000 persons), the liver is the most demanded organ, followed at large distance by the heart (3,100 persons). Strikingly, there are only about 12,000 liver transplants a year in these countries and a significant share of patients dies while on the waiting list. An even larger share of patients suffers from the effects of late transplantation where early intervention has a much better clinical outcome. In BALANCE we aim to bring about an extracorporeal device that provides critical patients on the donor liver waiting list extended survival of about one week compared to standard treatment. This would be a major achievement considering that currently the median waiting time for patients with the most urgent need (Status 1, only several days to live) for liver transplantation is 7 days, and for the second most urgent group 20 days, while not all patients can wait this long (Table 2). Considering that a patient can be subsequently treated with two or three BALs, the availability of the HepaRG-BAL that offers one week extra survival suggest that the transplant rates, and thus survival rates, can be significantly higher.

Table 2: Liver transplantation statistics

	Transplant rate	Death rate	Median waiting time
Status 1	68%	38%	7 days
MELD 25+	62%	34%	20 days

Status 1 is the listing category reserved for patients awaiting liver transplantation who are at risk of imminent death. The Model for End-Stage Liver Disease (MELD): measure to prioritise patients on the donor liver waiting list. MELD 25+ patients are severely ill

Allowing injured livers to recover thus avoiding the need for costly and debilitating transplantation: In a week period of HepaRG-BAL treatment it is also possible that the patient's liver recovers, replacing the need for liver transplantation. In a previous trial with a BAL based on porcine cells 1 out of 14 patients experienced spontaneous recovery. Such patients would otherwise have received a liver transplant as the only life-saving alternative, and would be subjected to a surgical procedure and lifelong immunosuppression, which is associated with major resource cost and increased risk of death or complications. Furthermore, a donor liver that could be used in a more appropriate candidate would be lost. It is expected that the HepaRG-BAL system will have this result in at least 1 in 15 patients. This means that yearly at least 500 "unnecessary" liver transplantations in ALF and thousands in AoCLD can be prevented. When taking into account the transplantation cost of about €400.000 per patient for a single transplantation, the savings can be huge; up to €200 million in ALF and more than a billion Euros in AoCLD.

Higher survival rates for acute liver failure: The annual 7500 ALF patients in Europe and the U.S. will be the first group of patients benefiting from a clinically validated BAL system. Death rates are currently between 30 and 40%, mainly due to lack of timely availability of donor livers. A conservative estimate is that a week extra survival can reduce the death rates due to limited donor-liver availability at least by half; potentially saving thousands of lives.

Higher survival rates for acute on chronic liver disease: A large share of the annual 150.000 AoCLD patients can benefit from a powerful BAL system as death rates are >50% due to scarcity of donor livers. This means that annually more than 55.000 Europeans who currently die from AoCLD could benefit from HepaRG-BAL treatment. The impact of our BAL system on AoCLD healthcare is thus immense with the potential to offer thousands of patients a better outlook on surviving sudden liver failure and also to save hundreds of millions Euros on unnecessary transplantations.

In order to make sure that these target endpoints can be reached, several steps are still needed.

1. **A GMP production system** needs to be designed, based on the production process developed in the BALANCE project.

2. **Permission for a phase I/IIa clinical study*:*** Research covered by the National Medical Research Involving Human Subjects Act must be submitted to an accredited Medical Research Ethics Committee (MREC) for approval before it is carried out. The BALANCE has prepared most of the documents to start up a clinical Phase I/IIa in the Netherlands and the UK as soon as possible, provided that financing is arranged. In the case of an Advanced Therapy Medicinal Product as the HepaRG-BAL first approval from two executive agencies of the national Departments of Health, in the Netherlands the CCMO (Central Committee on Research inv. Human Subjects) and in the UK the MHRA (Medicines and Healthcare products Regulatory Agency), is required.

3. **Clinical safety and efficacy testing:** Safety and efficacy need to be proven in human clinical trials. A phase I/IIa study will be planned after BALANCE to gather safety and feasibility data and first proof of efficacy. Such trials are difficult to perform and to control properly due to the rarity of well- characterized patients, the heterogeneity of etiologies, varying levels of disease severity and varying access to transplantation. Therefore in this project we work with academic institutions with ample experience in liver diseases and related trials and to make sure that necessary number of patients will be recruited. In addition, working with a skilled CRO optimises our trial position. Following completion of a phase I/IIa study , a phase IIb/III study in ALF in a controlled clinical trial on approximately 180 ALF patients will be required to collect the clinical evidence that demonstrates that the BAL is sufficiently efficacious. This trial will be conducted in collaboration with several other hospitals specializing in liver disease and with industrial partners that have the resources and experience to carry out such costly trials. Business development activities for partnering are already ongoing (see also exploitation plan).

4. **Marketing approval:** The European Medicines Agency (EMA) has to grant marketing approval for the HepaRG-BAL system as Advanced Therapy Medicinal Product once the clinical phase has been finalised. Together with our future industrial partners we will collaborate closely with the EMA to smoothen the path towards approval. Our aim is to gain marketing authorisation for the BAL system in ALF and in a later stage in AoCLD. As ALF is designated as an orphan drug disease, the marketing approval trajectory will be markedly enhanced. The expectation is that AoCLD will also be considered as an orphan disease.

5. **Market introduction:** With EMA approval the European market can be penetrated. Nonetheless, for market acceptance it will be crucial that healthcare specialists are willing to apply the HepaRG-BAL system on their patients and that patients or their relatives feel comfortable with BAL treatment. Therefore we will collaborate with several clinical key opinion leaders (hepatologists) and with patient groups in BALANCE and have frequent meetings to receive feedback on the system and all related issues. By doing so, we cannot only optimise the system to their interest but also win their trust in the system which will radiate throughout the field and help to increase rapid market acceptance.

In order to take these steps new finances are required. To bring this project to the next level, i.e. to a successful clinical trial, the project will again rely on research funding from organizations as the EU. As the Balance project was successful in upscaling the HepaRG-BAL, the preparations of the clinical trial and the pre-clinical experiments showing safety, efficacy and feasibility of the therapy, we are confident that this next step can be taken.