DEVELOPMENT OF A NEW DEVICE FOR POINT-OF-CARE THAWING AND DOSING OF CELL THERAPY PRODUCTS

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International Society for Cellular Therapy ISCT
A-791
ISCT 2012
Seattle, US
June 04-08

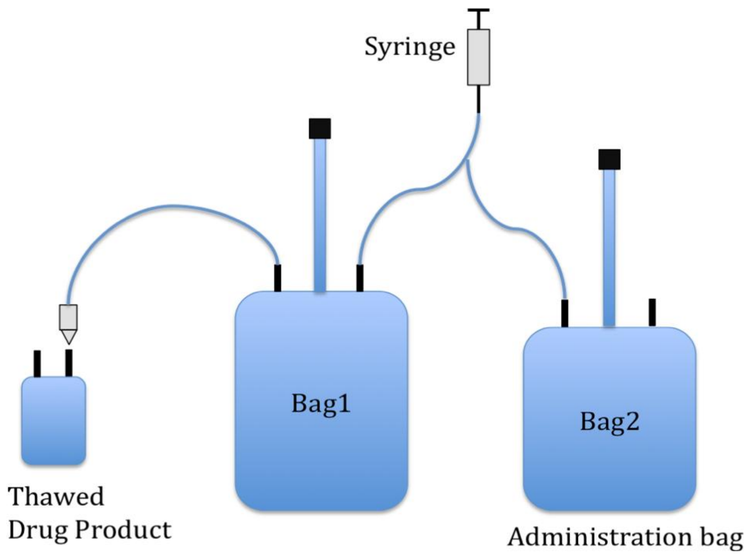
Background

Ovasave is a therapeutic cell based product consisting of autologous antigen-specific regulatory T cells. A phase I/II clinical trial has been performed in Crohn's Disease and showed good tolerability and positive signs of efficacy. Due to limited shelf life of T lymphocytes in classical infusion buffers, Ovasave was frozen and needs to be thawed, washed from cryoprotectants and adjusted at the required cell doses for the different patients cohorts. Due to regulatory constraints and to the fact that these procedures included open steps, they were performed in accredited Cell Therapy Units (CTU) distant from the point-of-care. For an open, uncontrolled phase I/II study with 6 centers in France, this continuation of events was acceptable but for further clinical development of Ovasave, a different method for cell procurement to the patient seems mandatory. Bearing in mind the constraints of clinical development (keeping the blind for physician and patients as well as for the sponsor/manufacturer), we developed a new device for on-site Ovasave thawing and dosing.

Methods

Ovasave was produced from patient's peripheral blood mononuclear cells (PBMC) exposed to ovalbumin with subsequent cloning and expansion in presence of S2 feeder cells [Brun et al, Journal of Int. Immunopharmacol, 2009].
Ovasave cells were frozen in vapour phase nitrogen in 5ml cryopreservation bags at 25.10^6 cells/ml in NaCl 0.9%, 4% Human Serum Albumin (HSA) + 10% DimethylSulfoxyde.
Dilution devices were produced by Charter Medical LTD using Clear-pak™ films made of a single web film in a multi-layer, co-extruded format with a Ultra Low Density Polyethylene Contact Layer (ULDPE), EVOH gas barrier layer, and Polyethylene (PE) outer layer. The thickness of the film is 13 mil. Clear-Pak™ is animal derivative free.

1- DEVICE CONCEPT



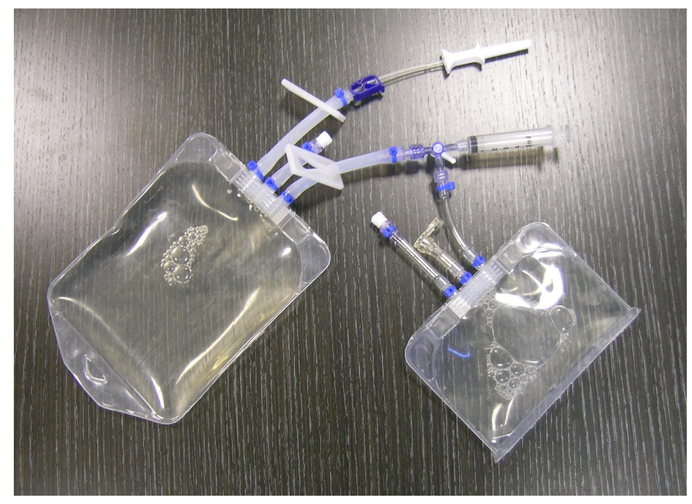
The dilution device is composed of:

- A first bag (dilution bag) prefilled with dilution buffer connected to a spike allowing connection to any cryopreservation bag.

- A syringe connected to the dilution bag and to a second bag allowing the sterile transfer of liquid volume from the first to a second bag

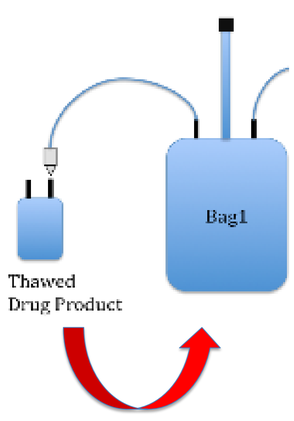
- A second bag (administration bag) prefilled with infusion buffer.

The whole kit represent a sterile closed system made of biocompatible material prefilled with sterile NaCl 0.9%, 4% human serum albumin (HSA), representing both dilution and administration buffers.



2-PRODUCT DILUTION/PREPARATION PROCEDURE

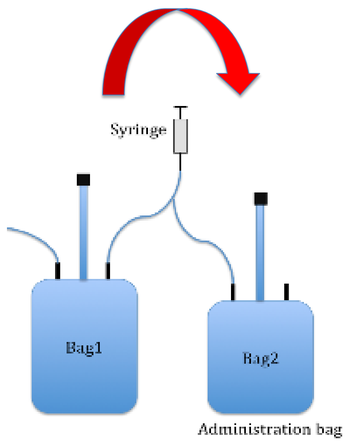
Step 1- Thawing and dilution



Rapid thawing of the cryo-preserved cell therapy product followed by complete dilution of the product in the first dilution bag prefilled with NaCl 0.9%, 4%HSA.

Thawing performed using a 37°C water bath.
Dilution in closed system under a biosafety cabinet.

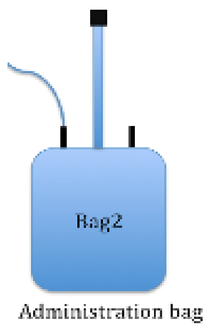
Step 2- Cell Transfer



Transfer of the required amount of cells from the first bag to the second bag using the connected syringe.

Transfer in closed system under a biosafety cabinet.

Step 3- Disconnection of final infusion bag



Sterile disconnection of the second bag prefilled with HSA and containing the required amount of cells for patient injection.

Transfer to patient's bed for cell therapy treatment.

First part of the kit can be discarded or used for additional quality controls of the product to be injected.

3- DEVICE VALIDATION PACKAGE

Biocompatibility

Biocompatibility studies on Charter Medical Clear-Pak™ films have been successfully performed including

- Extractables/leachables study
- Cytotoxicity study
- Absence of Endotoxin release

Aseptic Filling with HSA

Further validation of the kit will include

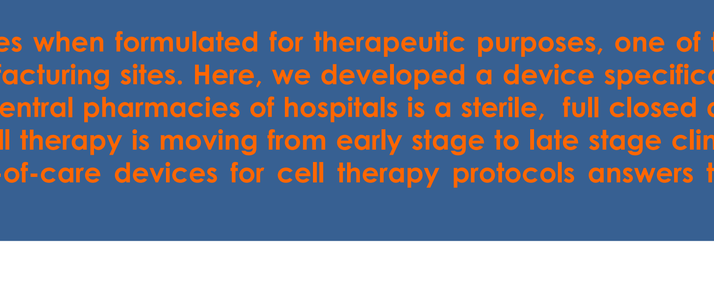
- Validation of aseptic filling with NaCl 0.9%, 4%HSA
- Stability of HSA overtime after filling (3-6-12 months)
- Impact of 3-6-12 months prefilled kit on cell characteristics.

Regulatory pathway

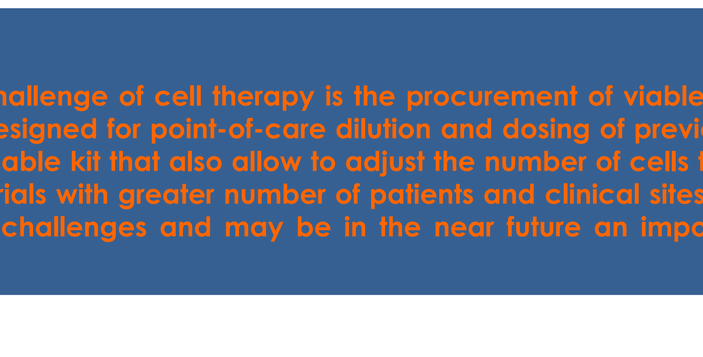
Validation of the use of the dilution device for cell therapy protocols will be performed during a Phase IIb clinical trialwith Ovasave in severe, refractory Crohn's Disease patients.

Kit interaction with Ovasave

Dilution and dosing (from 25.10^6 cells to 10^6 and 10^7 cells in the administration bag) of Ovasave cells after thawing using the dilution device do not alter cell number, viability and phenotype compared to cells taken immediately after thawing.



Diluted cells are stable for several hours after preparation using the dilution kit.



4- DEVICE ADVANTAGES

The key advantages of this kit are the following.

1. Full sterile point-of-care closed system that can be used in hospital pharmacies
2. Avoid the use of dedicated cell therapy unit for cell therapy product preparation
3. Useful for products with low shelf life
4. Rapid thawing/dilution procedure (approx 5min)
5. Rapid dilution of cryo-protectants such as DMSO in the first dilution bag
6. Allow to adjust the number of cells to be injected in a blind way for manufacturers, physicians and patients.
7. Allow to adjust the number of cells to be injected according to a clinical cohort, patient weight, body volume or any other parameter few minutes before injection.
8. Disposable kit.

CONCLUSION QND DISCUSSION

Due to low shelf-life of several cell populations such as lymphocytes when formulated for therapeutic purposes, one of the challenge of cell therapy is the procurement of viable and functional cells at patient's point-of-care usually distant from manufacturing sites. Here, we developed a device specifically designed for point-of-care dilution and dosing of previously thawed cell therapy products. This device designed to be used in central pharmacies of hospitals is a sterile, full closed disposable kit that also allow to adjust the number of cells to be administrated several minutes before injection to patients. Since cell therapy is moving from early stage to late stage clinical trials with greater number of patients and clinical sites, fast and secured procurement of cells to patients are needed. Point-of-care devices for cell therapy protocols answers these challenges and may be in the near future an important component of the cell therapy field development.

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