Online Resource 3

Details of adverse events by cohort

A total of 29 out of the 36 subjects (80.6%) who received study treatment with either MultiStem therapy or placebo experienced a total of 76 TEAEs during the study. Out of these, a total of 38 events in 21 subjects were considered serious (SAEs). The occurrence of TEAEs was higher in the MultiStem groups compared to placebo (91.3% for all subjects treated with the 900 million cells MultiStem dose compared to 60.0% for placebo), but the occurrence of serious TEAEs was similar in both groups (60.9% for all subjects treated with the 900 million cells MultiStem dose compared to 60.0% for placebo).
A sinjgle possibly related TEAE was reported in the MultiStem group in Cohort 3 but all the other TEAEs were considered either unrelated or unlikely to be related to the IMP and reflect the complexity of the condition. The majority of reported TEAEs were multiorgan falure, pyrexia, deep vein thrombosis, hypernatraemia] moderate or severe in intensity (see table below).

Summary of TEAEs Reported in ≥ 2 Subjects in Study B04-01

	MultiStem Therapy			Cohort 3	Total at
	Cohort 1	Cohort 2	Cohort 3	Placebo	Selected Dose
	N = 3	N = 3	N = 20	N = 10	N = 23
	n (%)	n (%)	n (%)	n (%)	n (%)
TEAEs	2 (66.7)	3 (100.0)	18 (90.0)	6 (60.0)	21 (91.3)
Respiratory failure	1 (33.3)	0	3 (15.0)	0	3 (13.0)
Sepsis	1 (33.3)	0	1 (5.0)	1 (10.0)	1 (4.3)
Pneumonia	1 (33.3)	0	2 (10.0)	0	2 (8.7)
Pleural effusion	1 (33.3)	0	1 (5.0)	0	1 (4.3)
Cardiac arrest	1 (33.3)	0	0	1 (10.0)	0
Multi-organ failure	0	0	2 (10.0)	0	2 (8.7)
Pyrexia	0	0	2 (10.0)	0	2 (8.7)
Deep vein thrombosis	1 (33.3)	0	1 (5.0)	0	1 (4.3)
Hypernatremia	1 (33.3)	0	1 (5.0)	0	1 (4.3)

Cohort 1: received 300 million cells MultiStem therapy via i.v. infusion.
Cohort 2: received 900 million cells MultiStem therapy via i.v. infusion.
Cohort 3: subjects randomized 2:1 to receive MultiStem therapy or placebo via i.v. infusion. In Cohort 3, MultiStem therapy was administered at the highest tolerated dose from Cohorts 1 and 2 (i.e., 900 million cells).
TEAE = treatment-emergent adverse event

Centres involved in this trial:

UK

Cambridge University Hospital:
Manchester Royal Infirmary:
Oxford University Hospitals:
St. George's University Hospitals:
University College London Hospitals:
University Hospitals Birmingham:
Wythenshawe Hosp. – Manchester Univ.:

USA

Iowa University Hospital:
University Hospitals Cleveland:
University of Pennsylvania:
University Pittsburgh Medical Center:
Northwestern Memorial Hospital:

Further details on cell preparation

Individual dose preparation of the cell product formulation used in the MUSTARDS trial required specialized cell lab personnel to perform dilution, cell counts, and assessments of cell viability. The MultiStem diluted product for infusion was prepared from MultiStem drug product cryobags by diluting the cryobag contents with Plasma-Lyte A (1:1) and passed through a 200 µm blood filter prior to infusion. The final diluted product consisted of Plasma-Lyte A, DMSO (5%) and HSA (2.5%), to produce a final IV bag for patient administration with the targeted cell dose. Storage of the final diluted product is 2-8°C prior to the infusion.

Cell viability was assessed for each prepared dose just prior to delivery to patients for infusion. Cell labs removed 0.5ml of diluted cell suspension to perform a nucleated cell count (for example Beckman Coulter automated impedance cell counters) and viability assessment (for example trypan blue dye exclusion assay using a microscope and haemocytometer) according to their internal SOPs. Assay results were compared to listed specifications to confirm product release criteria were met. Adequacy of participating site cell lab assay qualification, training, and SOPs were carefully evaluated and documented prior to approval of site initiation.

Currently available vialized formulations of MAPC used in ongoing trials of MultiStem for the treatment of ischemic stroke, trauma and ARDS do not require processing in cell labs, and can be thawed and diluted into Plasma-Lyte for infusion by pharmacy staff or other appropriate staff competent with basic aseptic technique.