Commercialisation of Allogeneic Mesenchymal Precursor Cells

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Agenda

- About Mesoblast
- Mesenchymal Precursor Cells
- Nonclinical considerations
- Key issues for allogeneic use in humans
About Mesoblast
About Mesoblast

- Global HQ in Melbourne, Australia
- Offices in New York and Austin, USA, including wholly-owned subsidiary Angioblast
- Listed on ASX (MSB)
- Primarily focussed on development of adult stem cells (Mesenchymal Precursor Cells; MPCs)
- Development at an advanced stage for a wide range of indications
Mesenchymal Precursor Cells
We own the intellectual property on MPCs

- Bone marrow + antibody
- Magnetic beads

MPC highly-expandable + non-immunogenic

- Isolated cells
- Culture-expanded cells

- US composition patent granted
- US manufacturing process patent granted

Global use patents file

- Bone
- Cartilage
- Heart muscle
- Pancreas

Products for orthopaedic diseases
Products for eye diseases
Products for cardiac diseases and diabetes
Our industrial scale manufacturing process

- Homogeneous cell population
- Well-controlled cell expansion
- Efficient large-scale expansion
- Lower costs of cell culture process
- Batch-to-batch consistency
- Stringent release criteria
- Greater potency of expanded product

Bone marrow plus MPC-binding antibody
Magnetic beads
Magnet
Final product
“Off-the-shelf” product portfolio

<table>
<thead>
<tr>
<th>Lead products</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Bone marrow transplantation</td>
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<td>Congestive heart failure</td>
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<td>Spinal fusion</td>
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<td>Knee osteoarthritis</td>
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<td>Long bone fracture repair</td>
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<td>Acute myocardial infarction</td>
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<td>Intervertebral disc repair</td>
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<td>Eye disease (AMD)</td>
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<tr>
<td>Diabetes</td>
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<td>Neurodegenerative diseases</td>
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*Partnered with Cephalon*
Very promising clinical efficacy data: heart failure

<table>
<thead>
<tr>
<th>Event</th>
<th>MPC treatment (N=45) No. patients with event (%)</th>
<th>Controls (N=15) No. patients with event (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious Adverse Cardiac Event (SAE)</td>
<td>20 (44.4%)</td>
<td>14 (93.3%)</td>
<td>0.001</td>
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<tr>
<td>Any Major Adverse Cardiac Event (MACE¶)</td>
<td>3 (6.7%)</td>
<td>6 (40%)</td>
<td>0.005</td>
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<td>Cardiac deaths</td>
<td>0 (0.0%)</td>
<td>2 (13.3%)</td>
<td>0.059</td>
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<tr>
<td>All cause deaths</td>
<td>2 (4.4%)</td>
<td>2 (13.3%)</td>
<td>0.26</td>
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<tr>
<td>MACE¶ or any hospitalization for heart failure</td>
<td>6 (13.3%)</td>
<td>6 (40%)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Interim data analysis December 2010, after all patients have reached 6 months follow-up (average 18 months)

¶MACE defined as composite of MI, revascularization, or cardiac death
Very promising clinical efficacy data (2)

- In patients with non-healing fractures:
  - Significant new bone growth observed in all fractures
  - Clinical & radiographic union of fractures observed in >80%

- In patients with haematological malignancies:
  - Composite efficacy endpoint of 100 day survival with sustained engraftment of both neutrophils and platelets
  - 80% transplanted with MPC-expanded cord blood met this endpoint, c.f. 38% in controls
  - Incidence of severe graft-versus-host disease lower in those transplanted with MPC-expanded cord blood
Allogeneic Cell Therapy: Nonclinical considerations
Nonclinical considerations (1)

- Standard regulatory guidance (incl ICH) often not applicable
- Availability of relevant and/or feasible animal models for human derived cells?
- Safety studies may need to be conducted in animal disease models rather than healthy animals
Nonclinical considerations (2)

- Human cells would elicit a xenogeneic response in immunocompetent animals
- Use of nude mice etc is an option, but has limitations
- Studies with allogeneic animal cells can be more informative
Key issues for allogeneic use in humans
Donor selection (1)

- Need clearly defined criteria to select suitable donors
- Must meet relevant regulatory requirements, e.g.:
  - 21 CFR Part 1271 (US)
  - Directive 2006/17/EC (EU)
- In addition, may want to specify additional criteria – e.g. age, race?
Donor selection (2)

- Selection process will typically involve detailed medical history, physical exams & lab tests
- Samples should be retained for retrospective testing
- Full traceability from donor to recipient is essential, without compromising anonymity of donor
- Comparability between donors also important
Donor selection (3)

- Typical exclusions:
  - Malignancy
  - Current systemic infection
  - Positive test for HIV, Hep B/C, HTLV I/II, Treponema pallidum, CMV
  - High risk of infection with communicable diseases
  - Known/suspected TSE
  - Autoimmune diseases
  - Unexplained health issues
Immunogenicity

- Crucial regulatory and commercial consideration for allogeneic use
- Mesoblast has demonstrated that MPCs do not initiate an immune response in unrelated recipients
- This facilitates “off the shelf” use just like classic pharmaceutical drugs
- Prior to first in human – risk assessment/nonclinical data
- In clinical trials – monitor for immune response
Logistical considerations (1)

- Fresh-released products have very short shelf life: requires either manufacturing close to point of use or cryopreservation
- Need to establish that cryopreservation does not adversely affect cells
- May need to demonstrate safety of cryoprotectant for human use
Logistical considerations (2)

- Cryopreserved products have special storage, distribution and handling requirements
- Investigational sites likely to need specific training
- Re-labelling of product difficult if not impossible
- However, if appropriate procedures are put in place, supply worldwide from a single manufacturing facility is feasible
Thank you.

Questions?

This document was accompanied by an oral presentation, and is not a complete record of the discussion held.

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For more information, please contact info@mesoblast.com