A Clinical Investigation Evaluating Efficacy of a Full-Thickness Placental Allograft (Revita®) in Lumbar Microdiscectomy Outcomes

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STATISTICAL ANALYSIS PLAN

RANDOMIZATION
Subjects who meet all inclusion and exclusion criteria will be randomized on Treatment Day in a 1:1 ratio to either the Treatment Group or the Control Group, in accordance with a computer-generated schedule prepared by a biostatistician. The randomization schedule will be incorporated into the OBERD system. Randomization will then be performed by study personnel directly in the OBERD system. Study personnel will be instructed not to randomize until subject has been confirmed to meet all inclusion/exclusion criteria on treatment day.

SAMPLE SIZE JUSTIFICATION
Sample Size Calculations
The following type I error rates and decision boundaries for the study are specified:
- primary outcomes are ODI and SF-12 scores
- null hypothesis: $\mu_{\text{Revita}} = \mu_{\text{SOC}}$
- type I error rate: $\alpha=0.05$
- sampling ratio: $\kappa=1$
- effect size: 0.45

Power Analysis

<table>
<thead>
<tr>
<th>Power, 1-(\beta^*)</th>
<th>0.70</th>
<th>0.75</th>
<th>0.80</th>
<th>0.85</th>
<th>0.90</th>
<th>0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>124</td>
<td>140</td>
<td>158</td>
<td>182</td>
<td>210</td>
<td>291</td>
</tr>
</tbody>
</table>

*Power, 1-\(\beta\), is defined as the likelihood of correctly detecting an effect when an effect exists. When power is high, probability of Type II error (i.e. concluding there is no effect when an effect exists) goes down.

Loss to follow-up
Possibility of loss to follow-up at 12 months postoperative is moderate and can be assumed at 15%, adjusting the sample size calculation at 80% power to $n=158+24=182$.

Recommendation
The sample size was calculated on the basis of the null hypothesis ($H_0$: $\mu_{\text{Revita}} = \mu_{\text{SOC}}$). In a previous study [Anderson DG, et al. Cryopreserved amniotic membrane improves clinical outcomes following microdiscectomy. Clin Spine Surg 2017;30(9):413-418], patients treated with a cryopreserved amniotic (cAM) tissues during elective lumbar microdiscectomy surgery experienced a significantly higher improvement in pain, disability, and quality of life compared to those receiving no tissue as standard of care.

For a fixed sample size design, the sample size required to achieve a power of 1-\(\beta\)=0.80 for a two-sided t-test at level $\alpha=0.05$ under these assumptions amounts to a total of 158 patients, or 79 patients in each treatment group. This calculation also provides adequate
power for two-sided equivalency chi-squared tests of secondary outcomes between treatment groups.

As the study outcome for the primary endpoint are available 2 years after treatment, the drop-out rate is expected to be moderate. A potential dilution of the treatment effect due to drop-outs is take into account (e.g. loss to follow-up); it is assumed that this can be compensated by additional 15% of patients to be enrolled, and therefore the total sample size required for a fixed sample size design is n=158+24=182 patients, or 91 patients in each treatment group.

**Primary Endpoint**
Low back and leg pain as measured by the Oswestry Disability Index (ODI), 12-Item Short Form Survey (SF12)

**Secondary Endpoints**
Reherniation rate.

All analyses will be performed using per-protocol population as well as intention-to-treat population (to include subjects who are withdrawn prematurely or randomized but not treated per randomization arm).