STATISTICAL ANALYSIS PLAN (SAP)

Study No.:	**CLN-01-1011 (NEOART)**
Study Title:	**A Prospective, randomized, controlled multi-center study of ArtiFascia® Dural repair patch compared with commercially available dural substitutes.**
Device:	**ArtiFascia®**
Intended Use:	**ArtiFascia® is indicated as a dural substitute for the repair of dura matter.**
Date:	**14AUG2022**
Version:	**Version 2.0**
NCT	**04145544**
Sponsor:	**Nurami Medical Ltd.** **Hanamal 36, Haifa, 3303203, Israel**

Statistical Considerations

Randomization

Eligible Subject will be randomly allocated into one of the two treatment groups by Interactive Response Technology (IRT) in a 2:1 allocation ratio of ArtiFascia and control group respectively, using blocks stratified by study sites and surgery in posterior fossa area or not.

The primary endpoint will be absence of CSF fistula (drainage from wound or sinus) and pseudo-meningocele within 6 months post-operative evaluated by Magnetic Resonance Imaging evaluation and physical examination of the surgical site.

Sample Size Rationale

The sample size for this study is calculated assuming the following assumptions: power of 80%, 5% one-sided significance level, 2:1 allocation ratio of ArtiFascia and control groups respectively, the absence of CSF leak rate in both the ArtiFascia and control groups is 97%, non-inferiority margin of -10% and the Chi-square test statistics.

Assuming the above assumptions a sample size of 81 subjects will be required in total. Allowing for a potential 10% dropout, 90 subjects should be randomized (60 in the ArtiFascia® group and 30 in the control group).

Blinded Sample Size Reassessment

To examine whether the assumed absence of CSF leak rate of 97% in the sample size calculation, a non-comparative assessment of the pooled absence of CSF leak rate will be performed after 50% of the randomized subjects will complete the study.

In case that the pooled absence of CSF leak rate will be less than the assumed 97%, the sample size will be upsized accordingly.

Primary Efficacy Endpoint Analysis

The primary endpoint: CSF leakage absence at month 6 will be tested for non-inferiority of the CSF leakage absence rate in the ArtiFascia group, to that in the control group, using a non-inferiority margin of -10%.

The estimated rates of CSF leakage absence at month 6 for each treatment group and the difference between the treatment groups (ArtiFascia - Control) will be calculated.

Exact one-sided 95% confidence interval will be calculated for the difference between the treatment groups in CSF leakage absence rates at month 6 using the Farrington-Manning method.

Non-inferiority will be concluded if the lower limit of the one-sided 95% exact confidence interval of the difference between the two study arms of CSF leakage absence rate at month 6 will be above the non-inferiority margin of -10%.

Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be compared between the study treatment groups using Fisher exact test (for endpoints with more than 2 categories, collapsing of categories with low frequency will be considered):

1. Wound healing assessment (Clean and/or fully healed vs. Infected),) which will be considered as key secondary efficacy end point
2. Device Handling Characteristics (Ease of Use, Strength, Suturability, Seal Quality)
3. Magnetic Resonance Imaging at the 6-month follow-up, to determine the presence or absence of the following measures:
    - Adhesion formation
    - New tissue formation
    - Brain edema adjacent to device implant site