| | |
|---|---|
| **Official Title of the study** | **PANOVA-3: Effect of Tumor Treating Fields (TTFields, 150 kHz) as Front-Line Treatment of Locally-advanced Pancreatic Adenocarcinoma Concomitant With Gemcitabine and Nab-paclitaxel** |
| **NCT number** | **NCT03377491** |
| **Document Date** | **October 16, 2024** |

# Statistical Analysis Plan

## Novocure GmbH

## EF-27

## PANOVA-3: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields, 150kHz) concomitant with gemcitabine and nab-paclitaxel for front-line treatment of locally-advanced pancreatic adenocarcinoma

[redacted] Study ID: [redacted]
Document Version: [redacted]
Document Date: [redacted]

[redacted]

# Table of Contents

# Reviewers

The following reviews of the SAP were conducted:

| Name and Title | Role | Version Last Reviewed | Company/ Organization |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

# Glossary of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| ADE | Adverse Device Effect |
| CA | Competent Authority |
| CA 19-9 | Carbohydrate Antigen 19-9 |
| CI | Confidence Interval |
| Cm | Centimeter |
| CR | Complete Response |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data and Monitoring Committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EORTC | European Organization for Research and Treatment of Cancer |
| FDA | Food and Drug Administration |
| ITT | Intent to Treat |
| mITT | Modified Intent to Treat |
| LDH | Lactatdehydrogenase |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PFS | Progression Free Survival |
| PR | Partial Response |
| PT | Preferred Term |
| QLQ C-30 | EORTC's Quality of life Questionnaire C-30 |
| QLQ PAN26 | Quality of life questionnaire Pancreatic Cancer Module |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAF | Safety Population |
| SOC | Standard of Care |
| TEAEs | Treatment-emergence adverse events |
| TTFields | Tumor Treating Fields |
| VAS | Visual Analogue Scale |

# 1. SOURCE DOCUMENTS

The Statistical Analysis Plan (SAP) was written based on the following documentation:

| Document | Date | Version |
|---|---|---|
| Protocol | [redacted] | [redacted] |
| eCRF | [redacted] | [redacted] |

# 2. PROTOCOL DETAILS

## 2.1. Study Objectives

### 2.1.1. Primary Objectives

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the overall survival of patients, compared to chemotherapy treatment alone.

### 2.1.2. Secondary Objectives

1. To determine if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the progression-free survival of patients, compared to chemotherapy treatment alone.
2. To determine if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the local progression-free survival of patients, compared to chemotherapy treatment alone.
3. To determine if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients leads to a higher rate of objective response rate, compared to chemotherapy treatment alone.
4. To determine if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients leads to a higher 1-year survival rate, compared to chemotherapy treatment alone.
5. To assess if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients affects the quality of life of patients, compared to chemotherapy treatment alone.
6. To evaluate if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients

prolongs the pain-free survival of patients, compared to chemotherapy treatment alone.

7. To determine if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the puncture-free survival of patients, compared to chemotherapy treatment alone.
8. To determine if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients increases the probability of the cancer becoming resectable (with a curative intention), compared to chemotherapy treatment alone.
9. To determine if TTFields in combination with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients is a safe treatment compared to chemotherapy treatment alone.

## 2.2. Overall Study Design

This is a pivotal, randomized, open-label, two-arm, multicenter study. This randomized study is designed to test the efficacy and safety of gemcitabine and nab-paclitaxel, with or without TTFields, using the NovoTTF-200T System as a front-line therapy for locally-advanced pancreatic adenocarcinoma patients. The study population are the patients with unresectable, locally-advanced adenocarcinoma of the pancreas, and with ECOG 0-2. Patients will be stratified as below:

[redacted]

1. Arm I: Patients receive TTFields using the NovoTTF-200T System together with gemcitabine and nab-paclitaxel.

2. Arm II: Patients receive gemcitabine and nab-paclitaxel alone.

[redacted]

[redacted]

[redacted]

Patients on both arms should also receive the best supportive care available at each site. Following progression patients may be offered standard pancreatic cancer-directed therapy and salvage therapy based on local practice at each site. Treatment may continue post-radiation therapy if radiation therapy is applied prior to local disease progression, as long as the skin has recovered from the radiation therapy according to the study investigator. Treatment may continue post-surgical resection if patient becomes resectable, as long as the skin has recovered from the surgical wounds according to the study investigator.

The overall schedule of the study is as follows:

[redacted]

[redacted]

## 2.3. Sample Size and Power

[redacted]

[redacted]

# 3. EFFICACY AND SAFETY VARIABLES

## 3.1. Primary Efficacy Endpoint

Overall survival (OS) of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to overall survival of patients treated with chemotherapy alone.

OS will be measured from the date of randomization to the date of death (in months).

[redacted]

[redacted]

## 3.2. Secondary Efficacy Endpoints

### 3.2.1. Progression-free survival (PFS)

PFS of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone, using the RECIST V1.1 Criteria.

Progression-free survival is defined as the time from the date of randomization until the date of disease progression for the entire body according to RECIST Criteria Version 1.1 or death (by any cause in the absence of progression). [redacted]

### 3.2.2. Local progression-free survival

Local disease progression is defined as Progressive Disease per revised RECIST version 1.1 in the absence of distant metastasis [redacted]

Local progression-free survival is defined as the time from the date of randomization until the date of local disease progression as defined above (by any

cause in the absence of local disease progression) or death[redacted]

[redacted]

[redacted]

[redacted]

### 3.2.3. Objective response rate (ORR)

The objective response to the tumor will be assessed using CT scans and according to the revised RECIST Criteria V1.1. Objective response rate is defined as the proportion of patients with best response of partial-response (PR) or complete response (CR) between the time of randomization and the time of disease progression or death. [redacted]

### 3.2.4. One-year survival rate

One-year survival rate of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to the one-year survival rate of patients treated with chemotherapy alone. [redacted]

### 3.2.5. Quality of life

Quality of life of patients are assessed using the EORTC QLQ C30 questionnaire with the PAN26 addendum.

[redacted]

[redacted]

### 3.2.6. Pain-free survival

Pain-free survival measures the duration between the time of randomization until a greater than or equal to [redacted] points increase, which means pain increase, from baseline measurement of a patient self-reported visual analogue scale (VAS) is recorded or death, whichever occurs first. [redacted]

### 3.2.7. Puncture-free survival

Puncture-free survival will be measured as the duration between randomization until the first need for paracentesis as data collected on the ascitic fluid drainage

eCRF or death, whichever occurs first. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

### 3.2.8. Resectability rate

Resectability rate will be measured as the percentage of patients whose tumors were deemed resectable. [redacted]

[redacted]

[redacted]

| PT terms | MEDDRA codes |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

## 3.3. Safety Variables

### 3.3.1. Extend of Exposure [redacted]

#### 3.3.1.1. Extend exposure to NovoTTF-200T

Extend of exposure to NovoTTF-200T will be summarized descriptively for the patients who randomized to the NovoTTF-200T arm as:

[redacted]

[redacted]

### 3.3.1.2. Exposure to Standard of Care

Standard of care in this study contains two drugs: Nab-paclitaxel and Gemcitabine. For each drug, the following variables will be determined:

[redacted]

- [redacted]

### 3.3.2. Adverse Events (AEs)

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary [Version 20.1-23.0]. The adverse event reporting period will begin immediately following randomization. Adverse events will be collected until last study follow up visit and for [redacted] following treatment termination

Treatment-emergence adverse events (TEAEs) are events with start date on or after the first date of any study treatment (including SOC or TTFields), or events with start date prior to the date of first treatment whose severity worsens on or after the date first treatment.

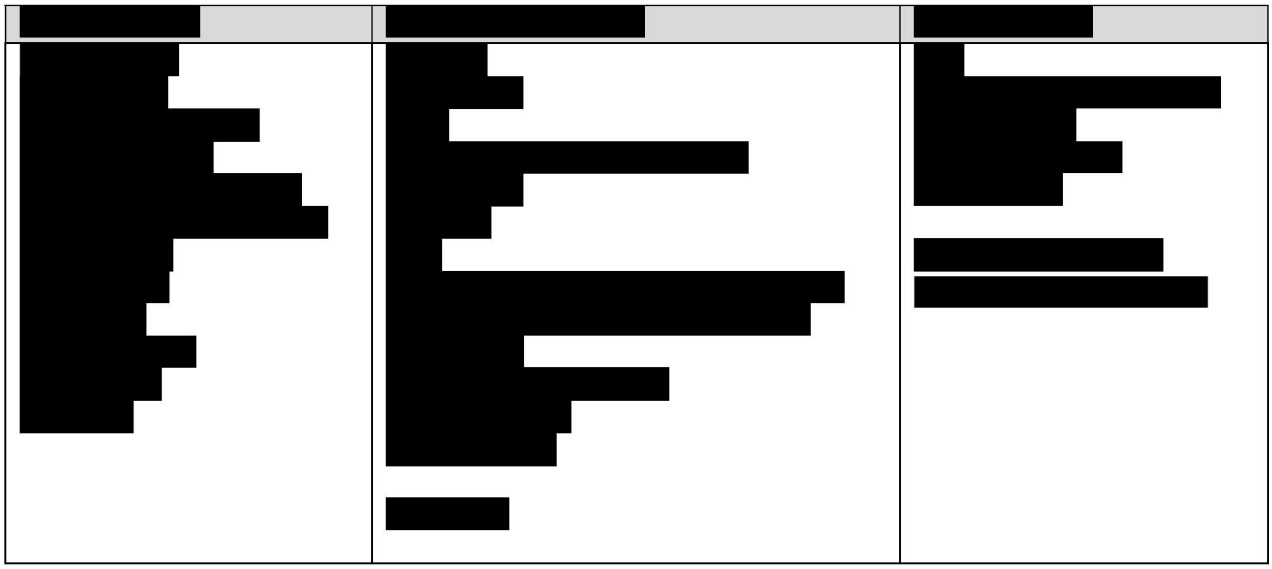
Assessment of AE severity will be based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The relationship between an AE and study device is assessed as definite, probable, possible, unlikely, or none. A device-related AE is an AE considered by the investigator as definitely, possibly, or probably related to study device. [redacted]

### 3.3.3. Laboratory Evaluations

[redacted]

[redacted]



### 3.3.4. Vital Signs

The following vital signs will be evaluated [redacted]

### 3.3.5. Physical Examination

Physical examination assessments including [redacted] will be performed according to the study schedule. [redacted].

## 4. PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

Not applicable.

# 5. ANALYSIS POPULATIONS

## 5.1. Intent-to-treat Population

The Intent-to-treat (ITT) will consist of all randomized subjects regardless of treatment receipt. ITT subjects are analyzed according to their randomized treatment.

## 5.2. Modified Intent-to-treat Population

The Modified Intent-to-treat (mITT) will consist of all patients who received at least one complete cycle of study treatments.

[redacted]

## 5.3. Safety Population

The safety population (SAF) will include all patients who received any amount of study Standard of Care drugs or TTFields in the experimental arm, and any amount of study Standard of Care drugs in the control arm. [redacted]

# 6. DATA HANDLING

## 6.1. Time points and Visit Windows

[redacted]

## 6.2. Handling of Dropouts, Missing Data, and Outliers

[redacted]

# 7. STATISTICAL METHODS

## 7.1. General Principles

All data processing, summarization and analyses will be performed using [redacted] of the SAS® statistical software package.

[redacted]

[redacted]

**Table 1 Statistical Analysis General Principles**

| Principle | Value |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

| Principle | Value |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

## 7.2. Subject Disposition and Data Sets Analyzed

Subject disposition will include all subjects and will be listed and summarized by treatment group and overall and will include [redacted]

[redacted]

## 7.3. Protocol Deviations

All protocol deviations will be listed [redacted]

## 7.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for ITT populations.

Standard descriptive statistics will be presented for the continuous variable of:

[redacted]

The total counts and percentages of subjects will be presented for the categorical variables of:

- Gender (Female, Male);
    - Childbearing potential (Yes, No), if female;
    - If no, reason (Surgically sterile, Post-menopausal, Other).

- Race [redacted]
- Ethnicity [redacted]
- Cigarette smoking status [redacted]
- ECOG performance status [redacted]

[redacted] Region [redacted]

[redacted]

[redacted]

### 7.4.1. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 20.1-23.0]. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for safety population by system organ class (SOC) and preferred term (PT) for each treatment group and overall. [redacted]

### 7.4.2. Previous and Concomitant Medications

A listing of prior treatments and procedures for pancreatic cancer will be presented.

Medications received prior to or concomitantly with treatment will be coded using the WHO Drug Dictionary [March 2016], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

[redacted]

[redacted]

## 7.5. Efficacy

### 7.5.1. Primary Efficacy Analysis

The primary endpoint is to compare overall survival (OS) of patients treated with TTFields concomitant with standard of care of chemotherapy (SOC) versus patients treated with SOC alone.

The null hypothesis is that the OS is the same in the two study groups, *i.e.,* hazard ratio=1. The alternative hypothesis is that the OS is not the same, i.e., hazard ratio≠1.

The primary endpoint will be summarized using Kaplan-Meier (KM) estimate. The treatment difference will be tested using a [redacted] in ITT population in order to allow for two efficacy analyses of the primary endpoint (interim analysis and final analysis [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

### 7.5.2. Secondary Efficacy Analysis

[redacted]The secondary endpoint of progression free survival will be tested if the primary endpoint of OS met its significance level. Thus, the entire alpha of 0.05 will be allocated to the progression free survival endpoint and no adjustment will be made for multiple hypothesis testing.

#### 7.5.2.1. Progression-free Survival

A [redacted] test at an alpha level of 0.05 will be used to compare the difference of progression-free survival between the patients treated with TTFields concomitant with SOC and the patients treated with SOC alone[redacted]

The median, 25th and 75th percentiles of progression-free survival with 95% CIs will be estimated using the Kaplan-Meier method for the two treatment groups[redacted]

[redacted]

[redacted]

### 7.5.2.2. Local Progression-free Survival

A [redacted] test at an alpha level of 0.05 will be used to evaluate if the local PFS will be significantly greater in the TTFields + SOC arm than in the SOC alone arm [redacted]

The median, 25th and 75th percentiles of local progression-free survival with 95% CIs will be estimated using the Kaplan-Meier method for the two treatment groups. [redacted]

[redacted]

### 7.5.2.3. One Year Overall Survival Rate

One-year overall survival (OS) rate is the proportions of patients who are alive at 12 months in each arm of the study. The Kaplan-Meier estimates of survival at Year 1 will be presented with number at risk, number with events, and estimated survival probability.

The one-year OS rates will be compared using [redacted]

### 7.5.2.4. Objective Radiological Response Rate

Objective radiological response rate (ORR) and its two-sided 95% confidence interval, which is based on [redacted]), will be presented.

[redacted]

### 7.5.2.5. Quality of Life Questionnaire Scores

Scores from 0-100 will be derived for all multi-item or single item scales of the EORTC QLQ-C30 and QLQ-PAN26.

[redacted]

**Table 2. Clinically meaningful change and categories**

| Questionnaire | Score | Change from baseline | Visit |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

### 7.5.2.6. Pain-free Survival

A [redacted] test at an alpha level of 0.05 will be used to evaluate if TTFields + SOC prolongs the pain-free survival of patients, compared to SOC treatment alone. [redacted]

The median, 25th and 75th percentiles of pain-free survival with 95% CIs will be estimated using the Kaplan-Meier method for the two treatment groups. [redacted]

### 7.5.2.7. Puncture-free Survival

A [redacted] test at an alpha level of 0.05 will be used to evaluate if TTFields + SOC prolongs the puncture-free survival of patients, compared to SOC

treatment alone[redacted]

The median, 25th and 75th percentiles of puncture-free survival with 95% CIs will be estimated using the Kaplan-Meier method for the two treatment groups[redacted]

[redacted]

[redacted]

#### 7.5.2.8. Resectability Rate

Resectability rate and its [redacted], which is based on the [redacted] will be presented.

The resectability rate between the patients treated with TTFields concomitant with SOC and the patients treated with SOC alone will be compared using [redacted] assuming the TTFields plus the chemotherapy arm would have a higher resectability rate than the chemotherapies alone arm.

### 7.5.3. Sensitivity Analysis

[redacted]

### 7.5.4. Subgroup Analysis

[redacted]

[redacted]

## 7.6. Safety

### 7.6.1. Extent of Exposure [redacted]

#### 7.6.1.1. Exposure to NovoTTF–200T

[redacted] usage will be summarized descriptively for the patients who randomized to the NovoTTF arm. The total counts and percentages of subjects will be presented for the categorical variables of:

[redacted]

### 7.6.1.2. Exposure to Standard of Care

Standard of care in this study contains two drugs: Nab-paclitaxel and Gemcitabine. For each drug, total dose administered, and duration of exposure will be summarized by each treatment group in safety population using continuous descriptive statistics. Duration of exposure will be calculated as the total number of weeks from the first date of dose to the last date of dose plus 1 day:

[redacted]

### 7.6.2. Adverse Events

An overview table will summarize the number and percentage of subjects with at least one of the following AEs by treatment group and overall, where subjects with more than one AE in a particular category are counted only once in that category:

[redacted]

A similar overall table summarizing treatment emergent AE will also be created.

The number and percentage of subjects reporting each AE will be summarized [redacted] for the Safety population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

[redacted]

[redacted]

[redacted]

### 7.6.3. Laboratory Evaluations

Data for the following [redacted] analyses recorded in the eCRF will be listed and summarized [redacted].

| [redacted] | [redacted] | [redacted] |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

All laboratory data will be reported in International System of Units (SI) units. [redacted]

Laboratory data will be summarized [redacted] for the Safety population. [redacted]

[redacted]

For each laboratory analytic, [redacted]

### 7.6.4. Vital Signs

The following vital signs [redacted]

Vital signs data and changes from baseline in vital signs will be summarized [redacted] for the Safety population. [redacted]

### 7.6.5. Physical Examination

Physical examination data will be listed. [redacted].

## 7.7. Interim Analysis

One interim analysis will be performed on the OS data available [redacted]

## 8. CHANGES IN PLANNED ANALYSIS

[redacted]

## 9. REFERENCES

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3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-1703. doi:10.1056/NEJMoa1304369.
4. Anne AE, Paul K, Mithat G, et al. Psychometric Validation of the EORTC QLQ-PAN26 Pancreatic Cancer Module for Assessing Health Related Quality of Life after Pancreatic Resection. J Pancreas. 2017; 1027;18(1):19-25

# 10. APPENDICES

## 10.1. Scoring algorithm for the EORTC-QLQC30

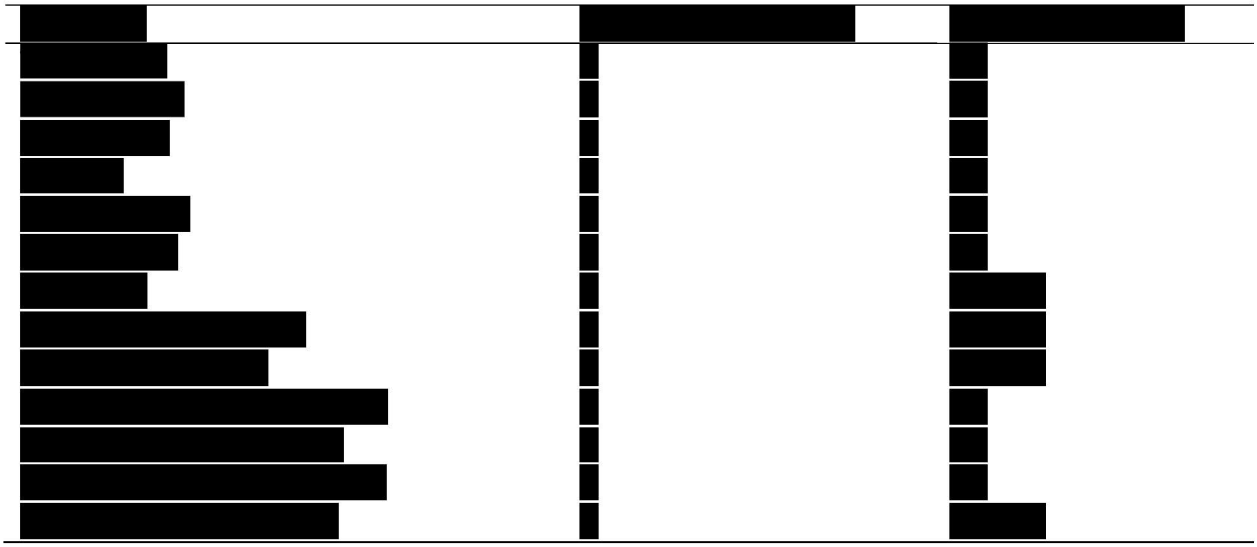
[redacted]

[redacted]

[redacted]

## 10.2. Scoring algorithm for the PAN26

[redacted]



[redacted]