# Statistical Analysis Plan for 03TS Intrathecal Immunoglobulin for Treatment of Adult Patients With Tetanus: a Randomized Controlled 2x2 Factorial Trial.

## DATA SOURCES

The data-source for this analysis is **2-10-2020-\_03TS\_V1\_Data.xls** which contains multiple **tables** (eg. **ENR** contains patients’ enrollment information, **VENT** contains medical ventilation history etc). The study Data Management Plan, Standard Operating Procedures include further information.

In this analysis plan, we refer to variables within tables by separating them by a dot, e.g. **VENT**.TRACHE refers to the variable TRACHE in table **VENT** and indicates yes or no whether a patient had a tracheostomy.

## TRIAL DESIGN AND SAMPLE SIZE

### Trial design

Randomisation is 1:1:1:1 to the four treatment arms in the 2x2 factorial trial (intrathecal treatment and human intramuscular treatment, intrathecal treatment and equine intramuscular treatment, sham procedure and human intramuscular treatment, sham procedure and equine intramuscular treatment).

### Sample size

The target sample size for this trial is 272 subjects.

## ANALYSIS POPULATIONS

There are five main populations defined:

1. **The intrathecal intention to treat (IT-ITT) population** consists of all patients who have been randomised to the trial. (derived as **ENR**.RANDTC with a date, ie not missing data). Analysis will be according to the randomized treatment arm (from randomization list).
2. **The intramuscular intention to treat (IM-ITT) population** consists of all patients who have been randomised to the trial and **did not** receive IM antitoxin before arrival at HTD (they were not excluded in the protocol). (derived as **ADM**.PREHTIG =N). Analysis will be according to the randomized treatment arm (from randomization list).
3. The **Intrathecal per-protocol population (IT-PP)** consists of all patients who received the allocated intrathecal treatment. Excluded individuals will be supplied as a separate list. Analysis will be according to the randomized treatment arm (from randomization list).
4. The **Intramuscular per-protocol population (IM-PP)** consists of all patients in the IM-ITT population who received the allocated intramuscular treatment. Analysis will be according to the randomized treatment arm. Excluded individuals will be supplied as a separate list. Analysis will be according to the randomized treatment arm (from randomization list).
5. The **All Intramuscular population** (IM-ALL) consists of all patients who received intramuscular antitoxin, including those who received it at a previous hospital. Those receiving antiotixin at a previous hospital will be analyzed as a separate equine antitoxin group. (Derived as **ADM**.PREHTIG =Y). This group was not mentioned in the protocol.
6. Subjects recruited in the pilot phase will not be included in any of the analyses (Subject IDs P01-P05

## ANALYSIS

All analyses will be performed for the comparison of intrathecal vs. sham procedure (IT-ITT and IT-PP) and for the comparison of equine vs human antitoxin intramuscularly (IM-ITT, IM-PP and IM-ALL).

## Summary

1. **Tables**

**Summary of baseline characteristics**

Baseline characteristic**s** will be summarized as median (1st and 3rd quartile, lowest and highest value) for numeric data and n (%) for categorical data. No formal statistical comparison of baseline characteristics between the two study arms will be performed.

The following baseline characteristics will be summarized:

1. Patient details: sex, age (**ENR.**AGE **ENR.**SEX), BMI (**ADM**.WEIGHT/(**ADM**.HEIGHT)2)
2. Past medical history:

**ADM**.HYPERTENSION, **ADM.**MYOCARDIALINFART, **ADM.**ANGINA, **ADM**.PERIVASCULAR, **ADM.**CHRONICPUL, **ADM**.CONNECTIVETISSUE, **ADM**.MILDLIVER, **ADM**.HEMIPLEGIA, **ADM**.DIAWITHCHRONIC, **ADM**.SEVERELIVER, **ADM**.AIDS, **ADM**.CARDIACFAILUREIII, **ADM**.CARDIACFAILUREIV, **ADM**.CEREBROVASCULAR, **ADM**.SEVERERESP, **ADM**.PEPTICULCER, **ADM**.DIABETES, **ADM**.SEVEREKIDNEY, **ADM**.MALIGNANCY, **ADM**.TUMOUR, **ADM**.DEMENTIA, **ADM**.COMORBIDITYOTH1, **ADM**.COMORBIDITYOTH2

1. Recent surgery **ADM**.ELECTIVESURGERY, **ADM**.EMERGENCYSURGERY
2. Patient history

* Duration of illness (**ADM.**TIMETOADM)
* Incubation period (**ADM**.INCUBATIONPERIOD)
* Period of onset (**ADM**.INCUPERIODONSET)
* Wound (**ADM.**WOUND 1=deep, 2 – superficial/other)
* Difficulty breathing on admission (**ADM**.DIFFBREATH)
* Ablett Score on admission (**ADM**.ABLETT, values I, II, III or IV)
* ASA Score (**ADM**.ASA, values 1,2 3 or 4)
* Maximum temperature during 1st day (**ADM**.MAXTEMP)
* Respiratory Rate (**ADM**.RESP)
* FiO2 (**ADM**.FIO2)
* SpO2 (**ADM**.SPO2)
* PAO2 (**ADM.**PAO2)
* PH (**ADM**.PH)
* Platelet count (**ADM**.PLT)
* White blood cell count (**ADM**.WBC)
* Haematorcrit (**ADM**.HCT)
* Max HR (**ADM**.MAXHR)
* Min HR (**ADM**.MINHR)
* Max SBP (**ADM.**MAXSBP)
* Worst DBP (**ADM**.WORSTDBP)
* Worst SBP (**ADM**.WORSTSBP)
* Vasopressors (**ADM**.VASO)
* Bilirubin (**ADM**.BILI)
* Sodium (**ADM**.NA)
* Potassium (**ADM**.K)
* Creatinine (**ADM**.CREAT)
* Acute Renal failure **(ADM**.RENALFAILURE)
* Specific severity scores will be calculated from the above variables (See Appendix for details) Tetanus Severity Score, SOFA score, APACHE II score

1. Treatment details

* Time from hospital admission to intramuscular antitoxin calculated from admission date and time (**ADM**.ADMDTC **ADM**.ADMTIME) and time and date of intrathecal procedure (**ADM**.DATEHTIG and **ADM**.TIMEHITG); [Excluding those with intramuscular anditoxin before admission (**ADM**.PREHTIG= Y) [ for patient ID 03-057 onwards – before this answer is blank, which should be set to N]
* Time from hospital admission to intrathecal antitoxin calculated from admission date and time (**ADM**.ADMDTC **ADM**.ADMTIME) and Date intrathecal procedure (**ADM**.DATEIT); Time intrathecal procedure (**AMD**.TIMEIT);
* Proportion of patients with nasogastric tube (*AE.SAE DATA SHEET*  **SAE\_GRID\_AE.** CTCAENAME = “Nasogastric tube”
* Proportion of patients with tracheostomy tube ( *AE.SAE DATA SHEET* **SAE\_GRID\_AE.** CTCAENAME= “Tracheostomy”
* Proportion of patients with urinary catheter (*AE.SAE DATA SHEET* **SAE\_GRID\_AE.** CTCAENAME = “Urinary Catheter”

**Summary of adverse events**

Adverse events (AE) have been derived by study physicians who were blind to the treatment allocations. We consider “any adverse event” as well as each AE separately. Tables will be generated to summarize the proportion of individuals with the adverse event, tabulating adverse events by grade (I-IV) and whether these events were judged to be related or possibly related to the treatment intervention. [*AE.SAE DATA SHEET* **SAE\_GRID\_AE.**CTCAENAME, **SAE\_GRID\_AE.**CTCAEGRADE, POSRELUNREL , “POSREL” or “REL”]. The following events will be excluded from adverse event reporting *AE.SAE DATA SHEET:* **SAE\_GRID\_AE.**CTCAENAME = “Nasogastric tube”; “Urinary Catheter”; “Tracheostomy”; “Mechanical ventilation” and “ANSD”

Tables will be generated separately for severe adverse events for IT-ITT, IM-PP, IM-ITT, IM-PP and IM-ALL,[*AE.SAE DATA SHEET* **SAE\_GRID\_SAE.** SAECATEGORY]. Comparisons of the proportions will be done with the chi-square test for independence; if the expected number is <= 1 in at least one of the cells, Fisher’s exact test is used. AE and SAE data will be supplied as a separate file [*AE.SAE DATA SHEET*].

1. **Plots**

**Histogram plots**

1. **Pipecuronium**:
   * Total dose during hospital stay (ventilated patients).
   * Duration of use (ventilated patients).
2. **Diazepam**:
   * Total dose during hospital stay.
3. **Midazolam**:
   * Total dose during hospital stay.
4. **Benzodiazepines**:
   * Total dose as diazepam equivalent.
   * Total duration of use.

• Total dose of pipecuronium during hospital stay for patients who are ventilated (**VENT**. VENSTART=Y) (sum of the values of **DAILY\_DAILY.**PIPECURONIUM per patient over the days) (not mentioned in protocol)

* Duration of pipecuronium during hospital stay in patients who are ventilated (**VENT**. VENSTART=Y) (length of **DAILY\_DAILY.**PIPECURONIUM per patient) (not mentioned in protocol). The value is zero for those that did not receive pipecuronium.

• Total dose of diazepam during hospital stay (**DAILY\_DAILY**.DIAZEPAMIM, + **DAILY\_DAILY**.DIAZEPAMORAL, (not mentioned in protocol)

• Total dose of midazolam during hospital stay (**DAILY\_DAILY**.MIDAZOLAM) (not mentioned in protocol)

• Total dose of benzodiazepines during hospital stay [as diazepam equivalent dose] calculated as total **DAILY\_DAILY**. DIAZEPAMIM, + **DAILY\_DAILY**.DIAZEPAMORAL + (4.17\*( **DAILY\_DAILY**.MIDAZOLAM)) (sum of the values per patient; not mentioned in protocol)

* Total duration of benzodiazepines (**DAILY\_DAILY**.DIAZEPAMIM, **DAILY\_DAILY**.DIAZEPAMORAL , **DAILY\_DAILY**.MIDAZOLAM)) (length of the column per patient; not mentioned in protocol).

**Line plots**

Create a line plot of the daily maximum temperature for each patient during the first 7 days after admission. Use one colour for each treatment arm and make the mean temperature for each day bold for each patient.

• Daily maximum temperature (**DAILY\_DAILY.** MAXTEMP) during first 7 days in hospital (not mentioned in protocol)