Statistical Analysis Plan

A Randomized Double-Blind Phase 2 Study Comparing the Efficacy, Safety, and Tolerability of Nitazoxanide Versus Placebo in Addition to Standard Care for the Treatment of Hospitalized Subjects with Severe Acute Respiratory Illness (NTZ-SARI)

(Based on Protocol Version 5 dated 16 September 2016)

Introduction

This document describes the content proposed for the primary statistical analysis of NTZ-SARI. The focus is on analyses that address the major randomized comparisons for key safety, tolerability and efficacy outcome measures, including those needed to address the study's primary objective as well as secondary objectives.

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Study Background and Objectives

Respiratory viruses are a significant cause of hospitalization for respiratory tract infections. Etiologic agents include influenza, parainfluenza virus, rhinovirus, adenovirus, metapneumovirus, respiratory syncytial virus (RSV), bocavirus and coronavirus. Of these, only influenza has a licensed treatment. Nitazoxanide (NTZ) is a licensed anti-infective agent with activity against many of these respiratory viruses. In a pediatric Phase 2 study of outpatient ILI, the NTZ cohort showed symptom resolution in 4 days versus 7 days in the placebo group. In a 624 person Phase 3 study of ILI, the NTZ cohort showed symptom resolution in 94 h compared to 108 h in the placebo group (p=0.0026). These benefits were observed in the entire cohort, not just those infected with influenza. If similar efficacy can be seen in the inpatient ILI population, there could be reductions in duration of hospitalization, morbidity, and costs.

The study is a multicenter, randomized, double-blind, placebo controlled trial to evaluate the efficacy of NTZ + standard of care (SOC) compared to placebo (PCB) + SOC in treating acute severe viral respiratory infections in adults and children ≥12 months old with SARI. It is anticipated that SOC would likely include antibiotics and may include treatment for influenza. The study is designed to enroll a total of 290 subjects who will be randomized in a 1:1 ratio. Subjects will be followed on Days 3, 7, 14, and 28. The subject will be discharged from the hospital when clinically indicated as determined by the treating physician – follow-up visits may occur as inpatients or as outpatients. Subjects still hospitalized on Day 28 will be followed until discharged from the hospital.

Study Objectives

Primary Objective: Evaluate the effect of NTZ in addition to SOC as compared to PCB + SOC in the treatment of SARI as measured by the time to hospital discharge

Secondary Objectives:

1. Evaluate the clinical efficacy of NTZ + SOC vs. PCB + SOC with regards to:
    - Percent hospitalized at Study Day 3, 7, 14 and 28
    - Death by Study Day 28
    - Duration of clinical symptoms (defined in Section 7.3.1.2)
    - Duration of fever
    - Use of supplemental oxygen (or increase greater than baseline oxygen requirement)
    - Admission to ICU
    - Intubation/mechanical ventilation
    - Proportion of subjects who develop complications including pneumonia, respiratory failure requiring mechanical ventilation, acute respiratory distress syndrome (ARDS), sepsis, or bronchiolitis.
    - Time to resumption of normal activity
    - Antibiotic/antiviral use during hospitalization
    - Systemic corticosteroid use during hospitalization
    - Re-hospitalization within 28 days

2. Evaluate the virologic efficacy of NTZ + SOC vs. PCB + SOC with regards to:
    - Percent cessation of viral shedding at Study Day 3

3. Evaluate the safety and tolerability of NTZ assessed by:
    - Cumulative incidence and severity of adverse events (AEs)
    - Cumulative incidence of serious AEs (SAEs)
    - Cumulative incidence of laboratory abnormalities on Study Days 3, 7 and 28

Study Endpoints:

Primary Endpoint:

- Duration of hospitalization (days and hours)

Secondary Endpoints:

Clinical Endpoints:

- Hospitalization on Study Days 3, 7, 14, and 28
- Date and time of hospital discharge
- Date of death, if applicable
- Clinical symptoms (measured daily through Study Day 14 and then again on Study Day 28)
- Temperature (measured daily through Study Day 14 and then again on Study Day 28)
- Oxygen use
- Date of admission to ICU and discharge from ICU, if applicable
- Date of intubation/extubation, if applicable
- Presence of complications during study (pneumonia, respiratory failure requiring mechanical ventilation, ARDS, sepsis, or bronchiolitis)
- Global assessment (measured daily through Study Day 14 and then again on Study Day 28) (defined in Section 7.3.1.3)
- Antibiotic/antiviral use during hospitalization (number and duration)
- Re-hospitalization within 28 days
- Use of systemic corticosteroids

Virologic Endpoints:

- Presence of virus on nasopharyngeal (NP) swab (or aspirate) at Study Day 3 (same virus as Day 0)

Safety Endpoints:

- AEs
- SAEs
- Chemistry and hematologic laboratory assessments on Study Days 3, 7 and 28

Analysis Plan

Subject Populations

Here we give the definitions for the populations that will be referred to for different analyses.

- Enrolled: all subjects that signed consent
- Intention to Treat (ITT) population: per protocol defined as all participants who are randomized and received at least 1 dose of the study drug, and for analysis the treatment group will be assigned as randomized.
- ITT age subgroups (only on specified analyses):
    - Adults ≥ 18 years
    - Children aged <18 years
- ITT pediatric formulation subgroups (only on specified analyses; may be omitted depending on the number of subjects enrolled in each pediatric subgroup):
    - Children ≥ 13 years and <18 years (children that take the adult tablet formulation)
    - Children aged <13 years (as this is the age for pediatric formulation)
- ITT virology subgroups (only on specified analyses):
    - Influenza A or B
        - Influenza A
        - Influenza B
    - RSV
    - Human Metapneumovirus
    - Rhinovirus/Enterovirus
    - Adenovirus
    - Mycoplasma pneumoniae
    - Chlamydophila pneumoniae
    - Legionella pneumophila
    - Bordetella pertussis
    - Parainfluenza
    - Bocavirus
    - Coronavirus

Table and Figure presentation
Results in figures and tables will be presented

- all subjects (total)
- by randomized arm

Number in brackets [] represents corresponding table number

1. Accrual, eligibility violations and exclusions from analyses (Enrolled)

- Table: Number enrolled: overall and by month/year and by institution. Dates of first and last subjects screened. [14.1.1.1]
- Figure: Number enrolled, by month/year
- Table: Screen failures, and number of subjects for each inclusion and exclusion criteria. [14.1.1.2]
- List: description of subjects screened and excluded from the ITT: Randomized arm, study drug received (yes or no), site, age, subject ID, subject's study status (completed study, died, discontinued early from study), reason for exclusion.

2. Accrual, eligibility violations and exclusions from analyses (ITT and ITT age subgroup)

- Table: Number randomized: overall and by month/year and by institution. Dates of first and last randomizations. [14.1.1.3]
- Figure: Number randomized, by month/year. Note the date of data lock for interim efficacy analysis.
- List: Description of violations of eligibility criteria among subjects randomized: Randomized arm, study drug received (yes or no), site, age, subject ID, subject's study status (completed study, died, discontinued early from study), reason for violation as noted by site.

3. Selected characteristics of participants at baseline (Day 0) (ITT)
Baseline is defined as the last observation prior to study drug administration. P-values using the test of means for continuous variables, test of proportions for binary endpoints or chi-square tests for categorical endpoints

- Demographics [14.1.3]
  - Table: Age (median, 25th and 75th percentile, mean, min, max)
  - Table: number randomized by age group (<2 years, ≥2 years to <8 years, ≥8 years to <13 years, ≥13 years to <18 year, ≥18 years to <65 years, ≥65 years).
  - Sex (%)
  - Self-reported NIH race/ethnicity (%)
  - Medical History (occurring in 5% or more of the study population)
  - BMI for adults age ≥18 years
  - Z score for age <18 years
  - Smoking History
- Baseline Disease Characteristics [14.1.4.1, 14.1.4.2, 14.1.4.3, 14.1.4.4]
  - Influenza vaccination history (categorical - vaccinated the season of enrollment)
  - Confirmed pathogen by multiplex PCR (i.e. Respifinder®). Include totals for pathogen type (e.g. all influenzas), and for each strain (e.g., H1N1 influenza)
  - Days since onset of symptoms (onset of symptoms to randomization).
  - Days since onset of symptoms to first dose.
  - SaO2

    - Severity of illness score
        - Sequential Organ Failure Assessment (SOFA) score for subjects ≥ 24 months of age
        - Tal bronchiolitis score for subjects < 24 months of age
    - Charlson comorbidity index.
    - Chronic oxygen use
    - Oxygen requirement (yes/no)
    - ICU requirement (yes/no)
- Presence of Complications
    - Pneumonia (clinical diagnosis supported by radiographic data)
    - Respiratory failure requiring mechanical ventilation (documentation of mechanical ventilation)
    - ARDS (clinical diagnosis supported by radiographic data)
    - Sepsis (clinical diagnosis)
    - Bronchiolitis (clinical diagnosis)
- Presence of symptoms for each of the following (defined as 2 or 3 = symptoms present):
    - Cough
    - Sore throat
    - Fatigue
    - Headache
    - Myalgia
    - Rhinorrhea
    - Nausea
    - Vomiting
    - Diarrhea
- CBC with differential white cell count (to include neutrophil, lymphocyte, and eosinophil percentages), hemoglobin, hematocrit, and platelets
- Blood chemistries (creatinine, ALT/GPT, AST/GOT, total bilirubin, LDH, CRP)
- Global Assessment
    - Adult
        - Overall question
        - Function question
    - Pediatric
        - Activity
        - Diet

4. Study status of participants and loss to follow-up (ITT)

- Table: Number (%) for the following categories: [14.1.2]
    - Off study: completed study (completed day 28 visit or died prior to 28 days of follow-up)
    - Off study: died
    - Off study: lost to follow-up before completing 28 days of follow-up
        - subcategories for each of the reasons for early discontinuation
- List: subjects lost of follow-up and last date

5. Study drug receipt (ITT) [14.2.1]

- Table showing number (%) in following categories

  - Full planned treatment
  - Partial treatment (by doses received – 9,8,7…etc.)
- Listing of subjects that did not receive full planned treatment: subject ID, site, age, at request of study team, reason for not receiving full planned treatment.

6. Concomitant medications (ITT)

- Anti-influenza antivirals during first 5 days [14.3.4.1]
  - Table of influenza antivirals taken (y/N)
  - If yes: number (%) for each specific drug
- Antibiotic during first 5 days [14.3.4.2]
  - Table of if antibiotics taken (Y/N)
  - If yes: number (%) for each specific drug
    - Grouping by family
    - Grouping by pathogens targeted (gram positive, gram negative, atypical, anaerobic)
      (note – groupings will be decided after study is closed to new enrollment by looking at pooled data but before study unblinding)
- Systemic steroids during first 5 days [14.3.4.3]
  - Table of systemic steroids taken (y/N)
  - If yes: number (%) for each specific drug

7. Mortality (ITT and ITT age subgroups)

- Table: [14.3.3]
  - number (%) total deaths
  - deaths in first 5 days
- List of deaths: Randomized arm, days from randomization to death, subject ID, site, age, primary cause of death, relatedness to study intervention. Sort by randomized arm, days from randomization to death and subject ID.
- Figure and Analysis: Kaplan-Meier plot of time from randomization to death (censoring at 28 days if completed follow-up, or at date of last contact if lost to follow-up prior to 28 days), with associated table showing: number censored and number (%) dying, median time to death and associated 95% confidence interval; p-value from log-rank test. The estimated hazard ratio and associated 95% confidence interval comparing randomized arms will be obtained using a proportional hazards model applied to the times of death with censoring as above.

8. Serious Adverse Events (ITT)

- Table: [14.3.2.1] Number (%) of subjects with an SAE by MedDRA System Organ Class (SOC) and Preferred Term (PT); number (%) of subjects with any SAE. In these tables, subjects with SAEs will be counted (e.g. counting a subject with multiple SAEs with the same PT only once for that PT).

- Table: [14.3.2.2]Number of SAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT); number (%) of SAEs. In these tables, SAEs will be counted (e.g. counting multiple SAEs with the same PT within the same subject).

- List of SAEs: Randomized arm, days from randomization to first SAE experienced by a subject, subject ID, site, age, days from start of study drug to SAE, SAE (MedDRA SOC and PT, and verbatim description), severity grade, relatedness to study intervention, outcome (sort by randomized arm, subject ID, MedDRA SOC and PT and, if a subject has multiple SAEs, days from randomization to SAE). This listing will include any SAE that occur after day 28 and are reported.
- Listing of SAE after enrollment (informed consent) and not included in the ITT

9. Adverse Events (ITT)

- Table: [14.3.1.1] Number (%) of subjects with an AE by MedDRA System Organ Class (SOC) and Preferred Term (PT) and severity grade; number (%) of subjects with any AE. In this table, subjects with AEs will be counted (e.g. counting a subject with multiple AEs with the same PT only once for that PT).

- Table: [14.3.1.2] Number of AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) and severity grade; number (%) of AEs. In this table, AEs will be counted (e.g. counting multiple AEs with the same PT within the same subject).

- List of AEs: Randomized arm, days from randomization to first AE experienced by a subject, subject ID, site, age, days from start of study drug to AE, AE (MedDRA SOC and PT, and verbatim description), severity grade, relatedness to study intervention, outcome (sort by randomized arm, subject ID, MedDRA SOC and PT and, if a subject has multiple AEs, days from randomization to AE). This listing will include any AE that occur after day 28 and are reported.
- Listing of AE after enrollment (informed consent) and not included in the ITT

10. Laboratory Values (ITT and ITT age subgroups)

The following should be performed for the protocol specified collection days of 0, 3, 7, and 28. Figure and table that includes the min, 25%tile , 50%tile, 75%tile, max, change from baseline and % change from baseline at each day for each of the following lab values.

- CBC with differential white cell count (to include neutrophil, lymphocyte, and eosinophil percentages), hemoglobin, hematocrit, and platelets [14.3.5.1.x]
- Blood chemistries (creatinine, ALT/GPT, AST/GOT, total bilirubin, LDH, CRP) [14.3.5.2.x]

11. Primary Endpoint (ITT, ITT age subgroups, ITT pediatric formulation subgroups, ITT virology subgroups)

Table to show the completeness of the primary endpoint should include number (%) with [14.2.2]:

- Complete data (Day of hospitalization and discharge or death)
- Incomplete data (missing day of hospitalization or discharge/death

The following table and figure provide descriptive statistics of the primary endpoint. The table and figures should impute values of 28 days for patients who died and should censor patients with missing discharge date at the time of last follow up.

- Figure: Kaplan-Meier plot of time to hospital discharge/death (only ITT and ITT age subgroups)
- Table: with the following estimates from the Kaplan-Meier curves- 25^{th} , 50^{th} and 75^{th} percentile along with min and max values in hours [14.2.3.1.x]

  - The between group difference in median time to discharge will be used to estimate the treatment effect and will be reported along with a 95% two-sided confidence interval.
  - Additionally, data from median, min, max converted to "days, hours"
- The p-value for the 2 group comparison of the primary endpoint analysis will be performed using the Shaw-Fay method as described in appendix 1.
- Sensitivity analyzes to exam effect of missing death or discharge data. (only ITT and ITT age subgroups)
  - Figure with Kaplan-Meier curves and Shaw-Fay p-values on the ITT only where missing death or discharge dates are imputed in the placebo group as censored at the time of last follow up and in the experimental group are imputed as events at day 28.
  - Figure with Kaplan-Meier curves and Shaw-Fay p-values on the ITT only where missing death or discharge dates are imputed in both groups as events at day 28.
  - For any imbalance seen in baseline characteristics ($p<.05$) perform a cox proportional hazards model with deaths receiving event times of 28 days. Missing discharge dates will be censored at last follow up time.

12. Secondary Endpoint (ITT and ITT age subgroups)

For secondary endpoints that test proportion:

- Deaths are always counted as worst case (i.e. deaths are counted as being hospitalized through Day 28).
- Missing data is analyzed in two ways:
  - Missing data is excluded after date of last follow-up. i.e. any analysis after the date of last follow up will exclude the missing subject from the denominator. This represents the "best case" for the missing data.
  - Missing data is assigned the worst case. i.e. for hospitalization, this missing data would be assumed to be hospitalized through Day 28. This represents the "worst case" scenario for the missing data.

For secondary endpoints that are time to events, the Fay-Shaw method accounts for deaths and missing data. In cases where the Fay-Shaw method is not appropriate, the Log-Rank p-value will be reported.

- Percent hospitalized at Study Day 3, 7, 14 and 28 [14.2.3.2.x]
  - Table N (%) hospitalized at Study Day 3, 7, 14 and 28 and test of proportions
  - Figure of proportions at each time point
- Duration of clinical symptoms [14.2.4.1.x]
  Subjects with 0-1 on all symptoms on Day 0 are considered to have a time of 0 hours.
  - Table: time (in hours) from symptom onset to symptom free (symptom free is 0-1 on all symptoms that last at least 2 days), noting min, 25%tile, 50%tile, 75%tile
    - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
  - Figure using Kaplan-Meier plot.

- Duration of fever- defined as temperature ≥ 38.0 C [14.2.4.2.x]
  - Table: v with min, 25%tile, 50%tile, 75%tile, max.
    - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)

- Figure using Kaplan-Meier plot.

- Use of supplemental oxygen (or increase greater than baseline oxygen requirement) [14.2.5.1.x]
  - Resolution is defined as off oxygen Subjects without stop date will be censored at 28 days. A time of 00:00 will be imputed for subjects with a stop date but missing stop time.
  - Table N (%) of use of oxygen (Y/N) at any point during the study, and at each time point
    - P-value obtained using test of proportions
  - Figure of proportions at each time point
  - Table duration of oxygenation: defined as time of oxygen first administered, to time off oxygen (in hours) noting min, 25%tile, 50%tile, 75%tile, max [14.2.5.2.x]
    - Table includes all subjects – where subjects not requiring oxygen have 0 hours.
    - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
  - Table duration of oxygenation: defined as time of oxygen first administered, to time off oxygen (in hours) noting min, 25%tile, 50%tile, 75%tile, max [14.2.5.3.x]
    - Table is restricted to those requiring oxygen at any point during the study.
    - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
  - Figure using Kaplan-Meier plot
    - Figure includes all subjects – where subjects not requiring oxygen have 0 hours.
    - Figure is repeated, but restricted to those requiring oxygen at any point during the study.

- Admission to ICU
  - Table N (%) of requiring ICU (Y/N) at any point during the study, and at each time point [14.2.6.1.x]
    - P-value obtained using test of proportions
  - Figure of proportions at each time point
  - Table duration of ICU: defined as time subject admitted to ICU, to time discharged from ICU (in hours) noting min, 25%tile, 50%tile, 75%tile, max [14.2.6.2.x]
    - Table includes all subjects – where subjects not requiring ICU have 0 hours.
    - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
  - Table duration of ICU: defined as time subject admitted to ICU, to time discharged from ICU (in hours) noting min, 25%tile, 50%tile, 75%tile, max [14.2.6.3.x]
    - Table is restricted to those requiring ICU at any point during the study.
    - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
  - Figure using Kaplan-Meier plot
    - Figure includes all subjects – where subjects not requiring ICU have 0 hours.
    - Figure is repeated, but restricted to those requiring ICU at any point during the study

- Intubation/mechanical ventilation
  - Table N (%) of requiring mechanical ventilation (Y/N) at any point during the study, and at each time point [14.2.7.1]

        - P-value obtained using test of proportions
    - Figure of proportions at each time point
    - Table duration of mechanical ventilation: defined as time subject placed on mechanical ventilation, to time extubated (removed from mechanical ventilation) noting min, 25%tile, 50%tile, 75%tile, max [14.2.7.2.x]
        - Table includes all subjects – where subjects not requiring mechanical ventilation have 0 hours.
        - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
    - Table duration of mechanical ventilation: defined as time subject placed on mechanical ventilation, to time extubated (removed from mechanical ventilation) noting min, 25%tile, 50%tile, 75%tile, max [14.2.7.3.x]
        - Table is restricted to those requiring mechanical ventilation at any point during the study.
        - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
    - Figure using Kaplan-Meier plot
        - Figure includes all subjects – where subjects not requiring mechanical ventilation have 0 hours.
        - Figure is repeated, but restricted to those requiring mechanical ventilation at any point during the study

- Proportion of subjects who develop complications including pneumonia, acute respiratory distress syndrome (ARDS), sepsis, or bronchiolitis at Day 3, 7, 14 and 28
    - Table for any complication: restricted to those subjects without any at baseline [14.2.8.1.x]
    - Figure of proportions at each time point
    - Table for each complication: restricted to those subjects without that complication at baseline [14.2.8.2.x]
        - Pneumonia
        - Respiratory failure requiring mechanical ventilation
        - ARDS
        - Sepsis
        - Bronchiolitis
    - Figure of proportions at each time point

- Global assessment [14.2.9.x]
    - Table duration (days) from enrollment until stating the first affirmative to global assessment questions
        - P-value obtained using Shaw-Fay method (here only treat deaths as worst rank and missing as censored)
    - Figure using Kaplan-Meier plot (time until stating the first affirmative).
    - There are two global assessment questions for adults and two global assessment questions for children. Each of these four questions will be analyzed separately.

- Antibiotic/antiviral use during hospitalization [14.2.10]

  - Table N (%) of subjects with an antibiotic starting on or after Day 3
    - P-value obtained using test of proportions

- Systemic steroids use during hospitalization [14.2.10]
  - Table N (%) of subjects with systemic steroids starting after Day 3
    - P-value obtained using test of proportions

- Re-hospitalization within 28 days [14.2.10]
  - Table N (%) of subjects with rehospitalization within 28 days
    - P-value obtained using test of proportions
  - Listing of rehospitalizations: Randomized arm, days from randomization to re-hospitalization, subject ID, site, age, (sort by randomized arm, day from randomization)

- Evaluate the virologic efficacy of NTZ + SOC vs. PCB + SOC with regards to:
  Restricted to those with virus detectable on Day 0
  - Table N (%) of subjects that had any virus detectable on Day 0, and no longer had any virus detectable on Day 3 [14.2.11]
    - If more than one virus was present on Day 0, both viruses must be cleared to be considered as no detectable virus. If Day 3 has a virus that was not detected on Day 0 (day 0 had virus A and Day 3 virus B), this is not considered as having no detectable virus.
    - P-value obtained using test of proportions
  - Table N (%) of subjects that had virus detectable on Day 0, and had a different virus detectable on Day 3.

Appendix 1

The primary endpoint is time to hospital discharge or death within 28 days. The primary analysis will follow the intent to treat principal where all patients randomized will be used in the analysis and analyzed according to treatment assignment. Observations will be censored at 28 days if discharge or death does not occur before 28 days.

The Shaw-Fay methodology uses ranks to form the test statistic. The following ranking system will be followed if no loss to follow up occurs. Patients who die will be given worse ranks than those who are alive. Among those who die, early deaths receive worse ranks than those who are alive and among those alive the order of ranking from worst to best is no discharge, late, than early discharge. Table 1 gives an example of rankings for an invented data set.

Table 1. Example of rankings for invented data set. C indicates censored at day 28 or censored due to death. Larger ranks are worse than smaller ranks.

Person	Day of discharge	Day of Death	Rank
1	C	5	8
2	C	10	7
3	3	15	6
4	C	C	5
5	15	C	4
6	5	C	3

7	2	C	1.5
8	2	C	1.5

The test statistics is the sum of the ranks for patients in the Nitazoxanide group. Treatment labels will be permuted to calculate the probability of obtaining a test statistic as extreme as the observed sum of the ranks of the experimental group.

If patients are lost to follow up (i.e. withdraw consent) prior to day 28 the Shaw-Fay formulation of the 2 sample Mann-Whitney Wilcoxon rank-sum statistic will be formed. Ranks for observed data will be as described above and ranks for those with missing data will be as described in Shaw-Fay. R code will be provided that calculates the ranks for those patients who are lost to follow up. The rank based permutation test as described above will be used to calculate the test statistics.

Reference: Shaw, Pamela A., and Michael P. Fay. "A rank test for bivariate time-to-event outcomes when one event is a surrogate." Statistics in Medicine 2016; 35(19): 3413-3423.