**NEU-HORIZONS**

**The neuroprotection and therapeutic use of riluzole for the prevention of oxaliplatin neurotoxicity study**

**Statistical Analysis Plan**

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# Introduction

The aim of the Neu-Horizons is to evaluate the neuroprotective effect of riluzole in adult patients with colorectal or gastric cancer receiving oxaliplatin chemotherapy.

The study is a blinded phase II screening trial randomising eligible patients to either Riluzole 50mg b.d. or matched placebo. Randomisation is performed in a 1:1 ratio stratified by frequency of oxaliplatin treatment (2-weekly or 3-weekly treatment schedules). Allocated treatment is to commence 7-10 days prior to first oxaliplatin dose and continue through to 2 weeks after the last oxaliplatin dose.

The primary objective of Neu-Horizons is to determine the effect of riluzole on the Total Neuropathy Score (TNS) during the post-oxaliplatin follow-up. The secondary objectives are to determine the effect of riluzole during the post-oxaliplatin follow-up on: limb dexterity (9 hole peg tests); nerve conduction (sural amplitude, tibial amplitude); peripheral nerve excitability (sensory amplitude superexcitability, threshold electrotonus 90-100, refractoriness 2.5ms); and quality of life (FACT-GOG-NTX-13). Two additional objectives listed in the Neu-Horizons protocol (v3) relating to severity of acute neurotoxicity and tumour response rate have been removed. Following discussions with other investigators in the area, the focus of the project shifted to assessment of chronic neuropathy. Due to difficulties with recruitment, it was clear that the study would not be adequately powered to provide accurate data on response rate.

This statistical analysis plan (SAP) was developed and finalised blinded to treatment. The information herein supersedes the statistical considerations section of the protocol including the section that describes a previously considered primary endpoint of development of grade 2 neuropathy (Yes/No). The primary endpoint was changed from the binary variable of “grade 2 neuropathy (Y/N)” to “Total Neuropathy Score” (based on a suggestion by the HREC) as the protocol was being finalised but the associated edits to the statistical section were not implement due to an administrative error. A further consideration in the development of this SAP was the lower than expected amount of outcome information available for analysis due to (1) a short-fall in accrual (the trial was terminated before reaching its target of N=90 due to insufficient funds), and the appreciable rates of missing data (due to patient withdrawal/death etc). In an effort to maximise the statistical power of the study, given the short-fall in outcome data, a mixed model for repeated measures modelling approach has been specified (where applicable). This makes use of all available data (e.g. all randomised patients with at least one post-baseline assessment are included) in the estimation of the treatment effect on the primary analysis.

# Outcome Measures

## Total Neuropathy Score (TNS)

The Total Neuropathy Score (reduced)[[1]](#footnote-2) is an amalgamation of evaluations made on a series of (0-5) scales of: (1) sensory symptoms, (2) motor symptoms, (3) autonomic symptoms, (4) pin sensibility, (5) vibration sensibility, (6) muscle strength, (7) deep tendon reflexes, (8) compound muscle action potential amplitude, and (9) sensory action potential amplitude.

The TNS is administered at baseline, prior to the 10th and 12th cycle of oxaliplatin, and at 4 and 12 weeks post final cycle of oxaliplatin.

## Nine hole peg test

The nine hole peg test (NHPT) requires the patient to insert, with one hand only, 9 pegs into corresponding holes in a horizontal board[[2]](#footnote-3). The time (in seconds) taken to complete the task was recorded for the left hand and for the right hand. An average of the two results was taken to derive the analysis variable. The NHPT was administered according to same schedule as the TNS.

## Nerve Conduction

Sural sensory and tibial motor amplitudes was to be assessed using standard nerve conduction techniques. Action potential amplitude was documented in both nerves.

Nerve conduction is measured according to same schedule as the TNS.

## Peripheral Nerve Excitability

Hyperpolarizing threshold electrotonus hyperpolarizing 90–100 ms (TEh 90–100 ms) was measured as the threshold change following the onset of hyperpolarizing current. Recovery cycle parameters were assessed according to the changes in threshold following a supramaximal stimulus. Specifically refractoriness was assessed at 2.5 ms and superexcitability at 7ms. Peripheral nerve excitability was to be measured at baseline, prior to oxaliplatin cycles 2, 4, 6, 8, 10 and 12, and at 4 and 12 weeks post final cycle of oxaliplatin. A composite measure of peripheral nerve excitability was constructed by summing the absolute change from baseline in superexcitability, refractoriness at 2.5 ms, and TEh 90–100 ms over patient’s last 3 visits (i.e. for each patient, the composite measure comprises up to nine individual change from baseline values).

## Quality of Life (FACT-GOG-NTX-13)

The FACT-GOG\_NTX-13 is a validated instrument that includes a specific assessment of the intensity of neuropathy symptoms across 13 items [[3]](#footnote-4). The degree of concern associated with each item is graded by the patient on a 0-4 response scale (ranging from ‘no concern’ to ‘very much concerned’). The responses to the items are aggregated to form an overall score.

The FACT-GOG\_NTX-13 is administered according to same schedule as the TNS.

## Safety

Details of serious adverse events considered to be secondary to study drug were to be collected.

# Analysis Sets

All randomized subjects will be eligible for inclusion in the full analysis set in accordance with the intention-to-treat analysis principle. Any patients that are deemed ineligible for inclusion on blinded central clinical review will be reported.

Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis.

# Data Analysis and Presentation

This is a randomised phase II study that aims to gather preliminary evidence on the efficacy and safety of riluzole for the prevention of ON using the Phase II Screening Trial design of Rubinstein[[4]](#footnote-5). This design is used to gather estimates that are sufficiently precise to determine whether larger scale confirmatory phase III testing is warranted and employs a less conservative threshold for the type I error rate (alpha) than would be used in any subsequent confirmatory phase III trial. A two-sided type I error rate of 10% was selected a-priori as being appropriate for this phase II study.

Sensitivity of conclusions obtained from the primary analysis method for each outcome measure (described below) to adjustment for baseline covariates that may be prognostic (of outcome) may be investigated; particularly if noteworthy chance imbalances arise between randomised groups. Note that whilst randomisation was stratified according by frequency of oxaliplatin treatment (2-weekly or 3-weekly treatment schedules), this will not be accounted for in the analyses because virtually all patients was assigned the same level (i.e. 2-weekly schedule) as determined by blinded data review.

## Subject Disposition

Details of the analysis sets along with reasons for exclusions will be presented along with reasons for withdrawals.

## Demographic and Clinical Characteristics at Baseline

Descriptive statistics will be prepared to summarise baseline characteristics of the study participants by treatment allocation. Variables to be summarised are: age, gender, type of cancer, planned frequency of oxaliplatin, and diabetes comorbidity.

## Exposure to Study Medication

The duration of exposure to study medication (riluzole or placebo) will be tabulated by treatment group using descriptive statistics.

## Oxaliplatin Treatment

The number of oxaliplatin cycles delivered, and the total cumulative oxaliplatin dose, of will be tabulated by treatment group. A Wilcoxon Rank-Sum Test will be used to compare these endpoints between the two groups.

## Total Neuropathy Score (TNS)

The TNS data will be analysed using a mixed model for repeated measures (MMRM) that includes covariates for baseline, treatment arm, post-baseline time-point, and a treatment-by-time point interaction. The primary endpoint is the TNS at 4 weeks post final cycle of oxaliplatin. The effect of riluzole on this endpoint will be estimated from the MMRM. The p-value for that comparison will be evaluated at the 0.1 level of significance (as per the explanation provided in Section 3). A variety of covariance structures (including compound symmetry and autoregressive) will be evaluated when performing the MMRM analysis and that with the best fit (according to AIC) will be used.

TNS from the post-oxaliplatin period (i.e. 4 weeks post final cycle and 12 weeks post final cycle) will be combined to derive an alternative endpoint on which randomised groups will be compared in a secondary analysis. The combined score will be based on the average TNS value obtained during the post-oxaliplatin period. That score will be analysed using a linear model with treatment allocation and baseline score fitted as covariates.

This ‘secondary analysis approach’ will be elevated to ‘primary analysis approach’ if a suitably well fitted MMRM cannot be constructed (e.g. model does not converge, standard errors are highly inflated, etc.).

Rectifying transformations (e.g. log, normal transform, etc.) will be applied as necessary to deal with highly skewed data. If a rectifying transformation cannot be found, the variable will be categorised (e.g. split at the median value) and that categorical variable will become the analysis endpoint. The approaches described above would be adapted to accommodate the categorical data (i.e.

a generalised linear model applying a logit link function would be used).

## Nine Hole Peg Test

The average result on the left hand and right hand administrations of the Nine Hole Peg Test will be derived to obtain a single metric for each patient at each assessment time point.

These data will analysis using the same approach described above for the TNS.

## Nerve Conduction

The sural amplitude and tibial amplitude results will be analysed separately using the same approach described above for the TNS.

## Peripheral Nerve Excitability

Treatment arms will be compared on the composite measure of peripheral nerve excitability using an ANCOVA model adjusting for the overall mean at baseline of superexcitability, refractoriness at 2.5 ms, and TEh 90–100 ms measures. A rectifying transformation (e.g. log, normal transform, etc.) will be applied as necessary to deal with highly skewed data. If a satisfactory transformation cannot be found, the variable will be categorised (e.g. split at the median value) and a logistic regression would be performed (with the baseline included as a covariate).

## Quality of Life (FACT-GOG-NTX-13)

The overall score from the FACT-GOG\_NTX-13 will be analysed separately using the same approach described above for the TNS.

## Safety Data Analysis

Details of serious adverse events considered to be secondary to study drug will be listed by treatment arm.

1. Cavaletti G et al. J Peripher Nerv Syst 2006;11:135–141 [↑](#footnote-ref-2)
2. Carvalho de Almeida L, et al. Neurosci Lett. 2017;659:54-59 [↑](#footnote-ref-3)
3. Park SB et al. CA Cancer J Clin. 2013;63(6):419-37 [↑](#footnote-ref-4)
4. Rubinstein LV et al. Design Issues of Randomized Phase II Trials and a Proposal for Phase II Screening Trials Journal of Clinical Oncology 2005 23:28, 7199-7206 [↑](#footnote-ref-5)