Statistical Analysis Plan

Clinical trial protocol title:	Randomized, placebo-controlled trial of YF476, a gastrin receptor antagonist, in Barrett's esophagus
HMR code:	10-505
Sponsor code:	T-016
EudraCT no:	2014-002418-22
CRO details:	Hammersmith Medicines Research Cumberland Avenue London NW10 7EW
Sponsor details:	Trio Medicines Ltd Hammersmith Medicines Research Cumberland Avenue London NW10 7EW
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1 List of abbreviations

AE	Adverse Event
BE	Barrett's esophagus
BMI	Body Mass Index
BUN	Blood urea nitrogen
CCK2R	Cholecystokinin 2 receptor
CI	Confidence Interval
CgA	Chromogranin A
C_{max}	Peak Plasma Concentration
C_{trough}	Trough Plasma Concentration
CRF	Case Report Form
COX-2	Cyclooxygenase-2
CSR	Clinical Study Report
CV	Coefficient of variance
DCAMKL1	Doublecortin- and Ca^{2+}/calmodulin-dependent protein kinase-like protein 1
ECG	Electrocardiogram
ECL	Enterochromaffin-like
HMR	Hammersmith Medicines Research
HR	Heart Rate
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
ITT	Intent-to-treat
LDH	Lactase dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
N	Number of patients
N	Number of observations used in analysis
p53	Tumour protein 53
PK	Pharmacokinetic(s)
PP	Per protocol
PPI	Proton pump inhibitor
PR	Portion of the ECG from the beginning of the P wave to the beginning of the QRS complex, representing atrioventricular node function.
Q1	Lower quartile
Q3	Upper quartile
QRS	The QRS complex of the ECG reflects the rapid depolarization of the right and left ventricles.
qRT-PCR	Quantitative RT-PCR
QT	Portion of the ECG between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization.
QTc	Corrected portion of the ECG between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization.
QTcB	QTc interval with Bazett's correction method
QTcF	QTc interval with Fridericia's correction method
RBC	Red blood cells

RNAseq	RNA sequencing
RR	Portion of the ECG between consecutive R waves, representing the ventricular rate
RT-PCR	Reverse transcriptase polymerase chain reaction
SAP	Statistical Analysis Plan
SD	Standard deviation
SGOT/AST	Serum glutamic-oxaloacetic transaminase/aspartate amino transferase
SGPT/ALT	Serum glutamicpyruvic transaminase/ alanine aminotransferase
TEAE	Treatment Emergent Adverse Event
WBC	White blood cells
ΔKi67	Change in Ki67 expression

2 Signatures

The following persons have read and agreed the content of this Statistical Analysis Plan:

Stephen Sah ***Statistics Team Leader, HMR***	Signature	Date
Julian Abrams, MD MS ***Principal Investigator, Columbia University***	Signature	17-JAN-2019 Date
Professor Rebecca Fitzgerald ***Principal Investigator, MRC Cancer Unit***	Signature	21/01/2019 Date
Malcolm Boyce ***Trio Medicines Ltd***	Signature	23 Jan 2019 Date

3 Introduction

This Statistical Analysis Plan (SAP) is based on the current trial protocol (version 24, 26 April 2018. Where statistical methods differ substantially between this SAP and the protocol, that will be identified in this document.

This SAP describes the datasets and the statistical methods to be used for the reporting and analysis of all data collected during the trial except the efficacy data which will be reported separately. Serum gastrin and plasma CgA data will be included in this SAP.

The randomisation code will not be broken before this SAP is finalised. If a future protocol amendment necessitates a substantial change to the statistical analysis of the trial data, this SAP will be amended accordingly. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the integrated clinical study report (CSR). Any deviations from this SAP will be documented in the CSR.

This SAP has been written in consideration of the following guidelines:

- International Conference on Harmonization (ICH) E9, Guidance for Industry: Statistical Principles for Clinical Trials (ICH E9 1998)[1]; and
- ICH E3, Guidance for Industry: Structure and Content of Clinical Study Reports (ICH E3 1995)[2].

Statistical analysis will be done using SAS® 9.3 on a Windows PC.

4 Study Objectives and Endpoints

4.1 Study Objectives

4.1.1 Primary Objective

The primary objective of this study is to determine if administration of netazepide (a CCK2R antagonist) to patients with Barrett's esophagus (BE) decreases tissue Ki67 expression, a marker of cellular proliferation.

4.1.2 Secondary Objectives

The secondary objectives are to assess the effects of netazepide on:

- biomarkers potentially associated with esophageal adenocarcinoma, in particular, cyclooxygease-2 (COX-2), p53, CCK2R and DCAMKL1; and
- fasting serum gastrin, a marker of gastric acid suppression, and plasma chromogranin A (CgA), a marker of ECL cell hyperplasia.

We also aim to determine whether netazepide is safe in patients with BE.

4.2 Study Endpoints

4.2.1 Primary Endpoints

Change in Ki67 expression (ΔKi67) between baseline (Visit 2) and the Week 12 visit

4.2.2 Secondary Endpoints

- Biomarkers
    - Change from baseline at Week 12 in biomarkers potentially associated with esophageal adenocarcinoma, in particular:
        - Change in CCK2R mRNA levels (measured by qRT-PCR)
        - Change in DCAMKL1 expression (measured by IHC)
        - Change in DCAMKL1 mRNA levels (qRT-PCR)
        - Change in COX-2 mRNA levels (qRT-PCR)
        - Change in p53 expression (IHC)
    - Gene expression will be measured using RNA-Seq. Further examination of any changes in expression from baseline may be done using qRT-PCR and IHC
    - Reduction in PPI-induced increase in plasma CgA
    - Increase in PPI-induced hypergastrinaemia
- Safety
    - Vital signs, ECG, physical examination, laboratory safety tests: blood tests: red blood cells (RBC), haemoglobin, haematocrit, platelets, white blood cells (WBC, differential: neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils), sodium, potassium, magnesium, chloride, bicarbonate, creatinine, serum glucose, blood urea nitrogen (BUN), alkaline phosphatase, lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase/aspartate amino transferase (SGOT/AST), serum glutamicpyruvic transaminase/ alanine aminotransferase (SGPT/ALT), total bilirubin, total protein, albumin, calcium, amylase, lipase; and urine tests: pH, specific gravity, protein, glucose, ketones, blood.
    - Change in histology
- Tolerability: assessment of adverse events.
- Pharmacokinetics: trough and peak concentration of netazepide

4.3 Statistical Hypotheses

No formal statistical testing will be done

5 Study Design

A randomized, double-blind, placebo-controlled pilot study of netazepide, a cholecystokinin-2 receptor antagonist, in patients with Barrett's esophagus without dysplasia. Patients will take netazepide or placebo for 12 weeks.

There are 2 research sites, Columbia University and the MRC Cancer Unit at the University of Cambridge.

Patients will be randomised (1:1 ratio) to receive either 25 mg netazepide or matching placebo.

6 Time and Events Table

	Baseline Testing/ Prestudy Evaluation		Study treatment		Follow-up period
	Visit 1[1]	**Visit 2**	**Week 6 visit**	**Week 12 visit**	**Follow–up**
Evaluation/ Procedure	Registration	Randomization, & Endoscopy	Week 6	Week 12	Follow Up Visit 4 weeks after stopping treatment
Informed consent	X				
Assess eligibility	X				
Central pathology review[2]	X				
Medical history	X				
Physical exam	X				
Vital signs	X	X[5]	X	X	X
Height and weight/ waist circumference	X				
Smoking history	X				
Medication history	X				
Blood and urine collection for safety tests	X	X[5]	X	X	X
Urine pregnancy test[4]	X	X[5]	X	X	X
ECG	X	X[5]	X	X	X
Blood for YF476 assay[3]			X	X	
Blood for assay of fasting serum gastrin and plasma CgA, and serum for storage		X	X	X	X
EGD (Upper GI endoscopy)		X		X	
Biopsies		X		X	
Concomitant medication assessment		X	X	X	
Dispense study medication		X	X		
Collect study medication			X	X	
Compliance assessment			X	X	
AE assessment		X	X	X	X

1. There may be up to a 2-week gap between Visits 1 and 2.
2. Review of patient's history to obtain histological confirmation of the patient's eligibility to participate in the trial.
3. Plasma YF476 assay: patients fast overnight. For the Week 6 and 12 visits, patients bring their container of study medication with them, and take study medication only after collection of blood samples for trough YF476, fasting serum gastrin and CgA levels, and endoscopy (if applicable). Patients stay for 1 h after dosing for collection of a blood sample for peak YF476 level.
4. Pre-menopausal women only.
5. These tests may be omitted if Visit 2 occurs on the same day as Visit 1.

7 Planned Analyses

7.1 Interim Analyses

No interim analyses are planned.

7.2 Final Analysis

The database will be locked once all patients have completed the study, data have been entered and all queries resolved. The final analysis will be carried out following database lock and unblinding.

7.2.1 Persons responsible for analysis

Steven Whaley (HMR)	Statistician
Nick Jackson (HMR)	SAS Programmer
Jyoti Ambhir (HMR)	Data Manager

8 Sample Size Considerations

8.1 Sample Size Assumptions

Based on preliminary data, a mean baseline Ki67 index of 45–50%, with a common SD of 14–18% was estimated. Assuming a two-sided type I error rate of 0.05, a sample size of 20 (10 per arm) has 98% power to detect a 30% absolute difference in ΔKi67 between the two arms if the common SD is 16%, and 97% power for a 25% difference with a 14% common SD (see Table 1).

Table 1. Power calculations based on 20 patients (10 per arm)			
	$\Delta Ki67_{YF} - \Delta Ki67_{pl}$		
SD	**0.25**	**0.30**	**0.35**
0.14	97%	99%	>99%
0.16	91%	98%	>99%
0.18	84%	94%	98%

9 Analysis Populations

The following populations will be identified:

Screened Population: All patients screened for the study.

Safety Population: All patients who are randomised and received at least one dose of the study drug. In this population, treatment will be assigned based upon the treatment patients actually receive regardless of the treatment to which they were randomized.

Intent-to-Treat (ITT) Population: All randomised patients who receive at least one dose of study medication and had at least one post-baseline assessment. In this population, treatment will be assigned based upon the treatment to which subjects were randomised regardless of which treatment they actually received.

Per Protocol (PP) Population: All randomized patients who receive at least one dose of study medication and had at least one post-baseline assessment and did not have any major protocol deviations.

In all populations (apart from ITT) treatment will be assigned based upon the treatment patients actually receive regardless of the treatment to which they were randomised.

The primary endpoint will be analysed using the ITT population.

9.1 Analysis Datasets

All analysis datasets will be based on observed data, except as outlined in Section 12.2.

10 Treatment Comparisons

The treatment comparison of interest is active (netazepide) versus placebo.

11 General Considerations for Data Analyses

11.1 Data Display Treatment and Other Subgroup Descriptors

The sort order for treatment groups will be placebo, then study treatment. When a total column is included, it immediately follows the treatment groups which it aggregates.

Listings of data will be sorted and displayed by treatment group, patient number, and also by date and time if applicable.

The treatment descriptions to be used on all tables and listings are:

Treatment Groups
Placebo
Netazepide 25 mg

11.2 Conventions for Summary Statistics and Data Displays

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error), median, minimum, and maximum. 95% confidence intervals will be presented where appropriate for data interpretation.

Categorical data will be summarised in frequency tables with n and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented with the same number of decimal places as the raw data collected on the CRF (or to 3 significant figures for derived parameters less than 100 and as integers for values more than 99). The mean and percentiles (e.g. median, Q1, and Q3) will be presented using one additional decimal place. The standard deviation and standard error will be presented using two additional decimal places.

12 Data Handling Conventions

12.1 Premature Withdrawal and Missing Data

All patients who withdraw prematurely from the study or study drug will be included in the statistical analyses.

If a patient completes the treatment period but has missing data, then this will be made apparent in the patient listings. Missing data will not be imputed except for as outlined in Section 12.2.

If the study is prematurely discontinued, all available data will be listed and a review will be carried out to assess which statistical analyses are still considered appropriate.

Data collected at unscheduled time points during the study will not be used in the summaries or data analyses. They will be included in the listings.

If time information (i.e. hours and/or minutes) for adverse events or concomitant medication is missing, but the day is present, then the time will be calculated in days. If date information is partial or missing, then any derived times (e.g. AE start time from last study medication) will be listed as missing.

12.2 Derived and Transformed Data

Baseline will be considered to be the latest value obtained before study drug administration (e.g. Visit 2; or Visit 1 if not recorded elsewhere).

Laboratory data will be reported in standard units. Out-of-range laboratory tests may be repeated. If a test is out-of-range at a baseline timepoint and repeated before dosing, the latest repeat value before dosing will be used as baseline. However, if a test is out-of-range and repeated at any other time during the study, the out-of-range value (not the repeat value) will be included in statistical summaries.

12.3 Assessment Windows

There is a +/- 4 day window for clinic visits. Visit 2 can take place on the same day as visit 1, or up to 2 weeks later.

For the safety and ITT populations, all data will be analysed as recorded (regardless of the assessment windows).

12.4 Values of Potential Clinical Importance

Laboratory results identified as 'clinically significant' in the CRF will be considered to be potentially clinically important.

QT, QTcB or QTcF > 450 msec and increases in QT, QTcB or QTcF from baseline (Visit 2) of > 30 msec will be considered to be potentially clinically important.

13 Study Population

13.1 Disposition of Patients

The disposition of all patients in the safety population will be summarised (by site and overall) including number of patients randomised, number completing the study by treatment, and number withdrawn from the study. The number of screen failures will also be summarised and listed.

All patients who withdraw or are withdrawn from the study will be listed by treatment, with the reason for withdrawal.

A listing of analysis populations will be provided.

13.2 Protocol Deviations

Before closing the database, data listings will be reviewed to identify any significant deviations and determine whether the data should be excluded from any analysis populations.

Major protocol deviations include patients who:

- Entered the study even though they did not satisfy the entry criteria.
- Met the criteria for withdrawal from the study but were not withdrawn.
- Received the wrong treatment or incorrect dose.
- Received an excluded concomitant therapy.
- Received investigational product(s) past the expiration date.
- Had their treatment assignment unblinded.
- Visits outside of assessment windows

13.3 Baseline Characteristics and Concomitant Medication

Demographic and baseline characteristics (e.g. , vital signs and ECGs) will be listed and summarised.

Patients who take concomitant medication will be listed and summarised.

Proton Pump Inhibitor use data will be listed.

Medical history including history of Barrett's Esophagus data will be listed and summarised

13.4 Treatment Compliance

The percentage treatment compliance at each visit will be listed and summarised.

14 Safety Analyses

Summaries and listings of safety data will use the safety population.

14.1 Extent of Exposure

The dates and times of first and last treatment dosing will be listed to indicate exposure to the study medication.

14.2 Adverse Events

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) which is current at the time of database lock (version 20.1 or higher).

All adverse events will be listed.

The number of patients with at least one treatment-emergent adverse event (TEAE) will be tabulated by actual treatment and MedDRA system organ class. A treatment-emergent adverse event is defined as an event emerging during treatment having been absent pre-treatment or having worsened relative to pre-treatment[1].

For each of the following, the number of adverse events and number of patients with adverse events will be summarised by treatment:

- TEAEs by system organ class and preferred term
- Drug-related ("possibly", "probably" or "definitely" as recorded by the Investigator) TEAEs by system organ class and preferred term

Patients with more than one TEAE will be counted only once, at the greatest severity or causality, for each system organ class/preferred term. Multiple TEAEs in a patient will be

counted once per system organ class and preferred term. Adverse events with missing severity and/or causality will be treated as severe and definitely related, respectively.

Summaries will be sorted by system organ class and decreasing total incidence of preferred term.

14.3 Deaths, Serious Adverse Events and Other Significant Adverse Events

Deaths and serious adverse events will be listed separately (fatal events separate from non-fatal events). Other significant adverse events, as identified by the investigator in the CRF, will be listed separately.

14.4 Adverse Events Leading to Withdrawal from the Study

Adverse events leading to withdrawal will be listed separately.

14.5 Clinical Laboratory Evaluations

Data from haematology, clinical chemistry and urinalysis will be summarised by treatment group.

All laboratory values of potential clinical importance will be listed and all related laboratory results (i.e. haematology or clinical chemistry) for patients with values of potential clinical importance will be listed, separately. Frequencies of laboratory values of potential clinical importance will be summarised.

Urinalysis parameters will also be listed.

14.6 Other Safety Measures

14.6.1 Vital signs

Vital signs evaluation at each planned visit, and change in vital signs from baseline (Visit 2 or Visit 1 if not recorded elsewhere) at each planned post-baseline visit, will be summarised by treatment group.

14.6.2 ECG

QT interval data will be presented using Bazett's (QTcB) and Fridericia's (QTcF) corrections.

ECG data will be summarised by treatment and visit. Differences from baseline (Visit 2) will be summarised by treatment and visit.

The number of patients with a potentially clinically important ECG value will be summarised by actual treatment and visit, giving the numbers of patients with QT, QTcB or QTcF > 450 msec, > 480 msec and > 500 msec, and the numbers of patients with increases in QT, QTcB or QTcF from baseline of > 30 msec and > 60 msec[3]. A supporting listing of all patients with an ECG value of potential clinical importance and a separate listing of ECG findings classified as abnormal by the Investigator will also be provided.

15 Efficacy Analyses

Efficacy data (serum gastrin and CgA) will be summarised using the ITT and PP populations. Summaries based on the PP population will only be produced if there is a difference between the ITT and PP populations

Serum gastrin and plasma CgA data at each planned visit, and change in Serum gastrin and plasma CgA from baseline at each planned post-baseline visit, will be summarised by treatment group and visit. Individual values will be presented by patient

Mean profile plots for serum gastrin and CgA will also be produced. Each plot will contain all results for all subjects in the active and placebo arms

16 Pharmacokinetic Analyses

Analytics Services International Ltd. will measure the plasma concentrations of netazepide. The pharmacokinetic analysis will be done by HMR.

PK data will be summarised using the safety population for patients who received netazepide 25 mg.

For all variables N (number of patients receiving the treatment in the population), n (number of observations), arithmetic mean, median, minimum, maximum, SD, %CV, and the 95% confidence interval for the arithmetic mean will be provided.

16.1 Pharmacokinetic Concentration Data

The peak (C_{max}) and trough (C_{trough}) plasma concentration will be listed, presented graphically and summarised by treatment.

We will produce scatterplots to examine the relationship between peak PK concentrations and plasma CgA concentration or serum gastrin concentration.

17 Changes from the Protocol Specified Statistical Analysis

After the study was submitted to the regulatory authorities and ethics committee the following changes were made to the analyses:

- Section 13.1 Analysis Sets of the protocol states "The pharmacokinetic analysis set will include all patients who receive at least one dose of study medication, and yield at least one plasma concentration for netazepide." This definition is not included in the SAP as the population is not required.

18 References

1. International Conference on Harmonization, 1998. Statistical Principles for Clinical Trials - ICH Harmonised Tripartite Guideline. Guidance for Industry, E9, FDA federal register, Vol 63, 1998, p49583. Available at: http://www.fda.gov/cder/guidance.
2. International Conference on Harmonization, 1995. Structure and Content of Clinical Study Reports - ICH Harmonised Tripartite Guideline. Guidance for Industry, E3, FDA federal register, Vol 61, 1996, p37320. Available at: http://www.fda.gov/cder/guidance.
3. International Conference on Harmonisation, 2005. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Concept paper, Guidance for Industry, E14, Center for Drug Evaluation and Research (CDER). Available at: http://www.fda.gov/cder/guidance/6922fnl.htm.

19 ATTACHMENTS

19.1 Table of Contents for Data Display Specifications

For overall page layout refer to Appendix B.

The numbering in the tables below will take precedence over the numbering in the shells.

The following tables and figures will be produced (templates provided in Section 19.2.1 and 19.2.2):

Table	Description	Population	Source Listing	Template (Shells below)
10.1	Summary of patient disposition	Safety	16.2.1.2 16.2.3.1	T_SD1
10.2.1	Summary of concomitant medications	Safety	16.2.4.2	T_CM1
10.2.2	Summary of medical history: barrett's esophagus	Safety	16.2.4.3	T_MH1
10.2.3	Summary of treatment compliance	Safety	16.2.5.1	T_COMP1
14.1	DEMOGRAPHIC DATA			
14.1	Summary of demographic characteristics	Safety	16.2.4	T_DM1
14.2	PHARMACOKINETIC and EFFICACY			
14.2.1	Summary of netazepide plasma peak and trough concentration data	Safety	16.2.6.1	T_PK1
14.2.2.1	Summary of serum gastrin and plasma CgA data (ITT)	ITT	16.2.6.2	T_EG2
14.2.2.2*	Summary of serum gastrin and plasma CgA data (PP)	PP	16.2.6.2	T_EG2
14.3	SAFETY DATA			
14.3.1.1	Summary of treatment-emergent adverse events	Safety	16.2.7.1	T_AE1
14.3.1.2	Summary of drug-related treatment-emergent adverse events	Safety	16.2.7.1	T_AE1
14.3.2.1	Listing of fatal adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.2.2	Listing of non-fatal serious adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.2.3	Listing of other significant adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.3	Narratives of deaths, other serious and significant adverse events	Safety	-	-
14.3.4	Summary of laboratory values of potential clinical importance	Safety	16.2.8.1, 16.2.8.3	T_LB1
14.3.5.1	Summary of chemistry laboratory values	Safety	16.4	T_LB2
14.3.5.2	Summary of haematology laboratory values	Safety	16.4	T_LB2
14.3.5.3	Summary of urinalysis results	Safety	16.4	T_UR1
14.3.6.1	Summary of vital signs	Safety	16.4	T_VS1
14.3.7.1	Summary of ECG values	Safety	16.4	T_EG2
14.3.7.2	Summary of ECG values and changes in ECG values of potential clinical importance	Safety	16.4	T_EG3

Figure	Description	Population	Source Listing	Template (Shells below)
14.3	SAFETY AND EFFICACY DATA			
14.3.1	Individual netazepide plasma concentration plots	Safety	16.2.6.1	F_PK1
14.3.2.1.1	Mean ± SD serum gastrin – time plot (ITT)	ITT	16.2.6.2	F_PK4
14.3.2.1.2*	Mean ± SD serum gastrin – time plot (PP)	PP	16.2.6.2	F_PK4
14.3.2.2.1	Mean ± SD plasma CgA – time plot (ITT)	ITT	16.2.6.2	F_PK4
14.3.2.2.2*	Mean ± SD plasma CgA – time plot (PP)	PP	16.2.6.2	F_PK4

*Only produce if there is a difference between ITT and PP populations

The following listings will be produced (templates found in section 19.2.3)

Listing	Description	Template (Shells below)
16.2.1	Study dates & disposition of patients	
16.2.1.1	Listing of study dates	L_SD1_PG
16.2.1.2	Listing of reasons for withdrawal	L_SD2_PG
16.2.1.3	Listing of screen failures	L_SD3_PG
16.2.2	Protocol deviations	
16.2.2.1	Listing of patients with inclusion/exclusion criteria deviations	L_DV1_PG
16.2.2.2	Listing of patients with other protocol deviations	L_DV2_PG
16.2.3	Analysis sets, including patients excluded from analysis	
16.2.3.1	Listing of analysis populations	L_AN1_PG
16.2.4	Demographic data & concomitant medication	
16.2.4.1	Listing of demographic characteristics	L_DM1_PG
16.2.4.2	Listing of concomitant medications	L_CM1_PG
16.2.4.3	Listing of medical history: barrett's esophagus	L_MH1_PG
16.2.4.4	Listing of proton pump inhibitor use	L_PP1_PG

Listing	Description	Template (Shells below)
16.2.5	Study drug administration	
16.2.5.1	Listing of study drug administration and treatment compliance	L_EX_PG
16.2.6	Pharmacokinetic and Efficacy data	
16.2.6.1	Listing of netazepide plasma pharmacokinetic data	L_PK1_PG
16.2.6.2	Listing of serum gastrin and plasma CgA data	L_PK4_PG
16.2.7	Adverse events	
16.2.7.1	Listing of all adverse events	L_AE1_PG
16.2.7.2	Listing of serious adverse events	L_AE1_PG
16.2.7.3	Listing of adverse events leading to withdrawal from study	L_AE1_PG
16.2.8	Laboratory values	
16.2.8.1	Listing of clinical chemistry abnormalities of potential clinical importance	L_LB1_PG
16.2.8.2	Listing of all clinical chemistry laboratory data for patients with PCI abnormalities	L_LB2_PG
16.2.8.3	Listing of haematology abnormalities of potential clinical importance	L_LB1_PG
16.2.8.4	Listing of all haematology laboratory data for patients with PCI abnormalities	L_LB2_PG
16.2.8.5	Listing of urinalysis results	
16.2.9	ECG variables	
16.2.9.1	Listing of ECG values of potential clinical importance	L_EG1_PG
16.2.9.2	Listing of abnormal ECG findings	L_EG2_PG

Complete listings of all data collected in this study will also be produced.

19.2 Data Display Specifications

19.2.1 Table Outlines

Template T_SD1

Table 10.1 Summary of Patient Disposition

Population	Status	Reason for Withdrawal	Treatment 1			Etc	All Patients		
			Columbia n (%)	Cambridge n (%)	All Sites n (%)		Columbia n (%)	Cambridge n (%)	All Sites n (%)
Screened	Included		xx	xx	xx		xx	xx	xx
Safety	Included		xx	xx	xx		xx	xx	xx
	Completed		xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
	Withdrawn								
		Death	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Adverse Events	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Withdrawal by patient	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Physician decision	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Protocol violation	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Pregnancy	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Study terminated by Sponsor	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Lost to follow-up							
		Other	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
Intent to Treat	Included		xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
	Completed		xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
	Withdrawn								
		Death	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Adverse Events	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Withdrawal by patient	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Physician decision	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)
		Protocol violation	xx (xx)	xx (xx)	xx (xx)		xx (xx)	xx (xx)	xx (xx)

		Pregnancy	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
		Study terminated by Sponsor	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
		Lost to follow-up						
		Other	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Per Protocol	Included		xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

Source: Listing 16.2.xx

Programming notes: Continued with all treatment groups

Template T_CM1

Table 10.2.2 Summary of Concomitant Medications

Generic Term	Treatment 1 (N=xx)		Treatment 2 (N=xx)	
	n	%	n	%
Any medication				
Medication 1				
Medication 2				
Medication 3				
Medication 4				

Source: Listing 16.2.xx

Programming notes: Continued with all treatment groups

Template T_COMP1

Table 10.2.2 Summary of Treatment Compliance

Variable	Treatment	Visit	n	Mean	SD	Median	Min	Max
Compliance (%)	Treatment 1 (N=xx)							

Programming notes: *Continued with all treatment groups*

Template T_MH1

Table 10.2.2 Summary of Medical History: Barrett's Esophagus

Barrett's mucosa	Treatment 1 (N=xx)		Treatment 2 (N=xx)	
	n	%	n	%
Circumferential				
Non-circumferential				

Template T_DM1

Table 14.1 Summary of Demographic Characteristics

Variable	Statistics	Screen Failures (N=xx)	Treatment 1 (N=xx)	Treatment 2 (N=xx)	Etc	All Treated Patients (N=xx)
Age (y)	n					
	Mean					
	SD					
	Median					
	Min					
	Max					
Gender	N					
	Female					
	Male					
Race	American Indian					
	Asian/ Pacific Islander					
	Black					
	Hispanic					
	White					
	Other					
Height (cm)	n					
	Mean					
	SD					
	Median					
	Min					
	Max					
Weight (kg)	n					
	Mean					
	SD					
	Median					
	Min					
	Max					

Variable	Statistics	Screen Failures (N=xx)	Treatment 1 (N=xx)	Treatment 2 (N=xx)	Etc	All Treated Patients (N=xx)
BMI (kg/m2)	n					
	Mean					
	SD					
	Median					
	Min					
	Max					
Waist circumference (cm)	n					
	Mean					
	SD					
	Median					
	Min					
	Max					
Cigarettes* (daily)	n					
	Mean					
	SD					
	Median					
	Min					
	Max					
Alcohol* (units/week)	n					
	Mean					
	SD					
	Median					
	Min					
	Max					

*includes only those patients who smoke/drink alcohol

Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups and additional demographic characteristics*

Template T_AE1

Table 14.3.3.xx Summary of Treatment-Emergent Adverse Events

System Organ Class	Preferred Term	Treatment 1 (N=xx) n (%)	Treatment 2 (N=xx) n (%)	Etc
Number of patients with AEs		x (xx.x)	x (xx.x)	
Gastrointestinal disorders	Total number of patients	x (xx.x)	x (xx.x)	
	Abdominal discomfort	x (xx.x) [xx]	x (xx.x) [xx]	
	Abdominal pain	x (xx.x) [xx]	x (xx.x) [xx]	
	↓			
Nervous system disorders	Total number of patients			
	Dizziness			
	Headache			
	↓			
↓	↓			

n = number of patients (patients with ≥1 adverse event are counted only once per system organ class and preferred term)
[ ] = number of TEAEs
Based on MedDRA version xx.x

Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups*
SOCs and PTs are sorted in decreasing order of frequency
Presented for all applicable MedDRA system organ classes and terms.

Template T_LB1

Table 14.3.4.xx Summary of Laboratory Values of Potential Clinical Importance

Laboratory Test (units)	Treatment	Visit	n (%)
	Treatment 1 (N=xx)		

Source: Listing 16.2.xx

Programming notes: Continued with all tests, treatment groups and time points. n = total number of results for that parameter

Template T_LB2

Table 14.3.5.xx Summary of Chemistry Laboratory Values

									Change from Baseline					
Laboratory Test (units)	Treatment	Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: Continued with all treatments and time points For Ki67 Expression data exclude first column

Template T_UR1

Table 14.3.5.xx Summary of Urinalysis Results

			Treatment 1 (N=xx)		Treatment 2 (N=xx)	
Laboratory Test	Visit	Result	n	%	n	%
	Time 1	Positive	X	x		
		Negative	X	X		
		Not Done	x			
	Time 2	Positive				
		Negative				
		Not Done				

Source: Listing 16.2.xx

Programming notes: *Results recorded as received, e.g. Negative, Trace, etc; urine pH summarized as <5, 5-8, >8*
Continued with all treatment groups and time points. The n's sum to N but the calculated percentages exclude Not Done.

Template T_VS1

Table 14.3.6.xx Summary of Vital Signs

									Change from Baseline					
Variable (units)	Treatment	Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Systolic BP (mmHg)	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all variables, treatments and time points*

Template T_EG2

Table 14.3.7.xx Summary of ECG Values

									Change from Baseline					
Variable (units)	Treatment	Visit	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Heart Rate (bpm)	Treatment 1 (N=xx)													
	Treatment 2 (N=xx)													
PR Interval (msec)	Treatment 1 (N=xx)													
	Treatment 2 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups and time points*
Do not summarise RR or QRS axis

Template T_EG3

Table 14.3.7.xx Summary of ECG Values and Changes in ECG Values of Potential Clinical Importance

			451 – 480 msec		481 – 500 msec		> 500 msec		>30-60 msec Increase		>60 msec Increase	
Variable	Treatment	Visit	n	%	n	%	n	%	n	%	n	%
QT interval	Treatment 1	Time 1										
	(N=xx)	Time 2										
		Time 3										
	Treatment 2	Time 1										
	(N=xx)	Time 2										
		Time 3										
QTcB interval	Treatment 1	Time 1										
	(N=xx)	Time 2										
		Time 3										
	Treatment 2	Time 1										
	(N=xx)	Time 2										
		Time 3										
QTcF interval	Treatment 1	Time 1										
	(N=xx)	Time 2										
		Time 3										

Source: Listing 16.2.xx

Programming notes: Continued with all treatments and time points. n = total number of results for that parameter

Template T_PK1

Table 14.2.xx Summary of Netazepide Plasma Pharmacokinetic Peak and Trough Concentration Data

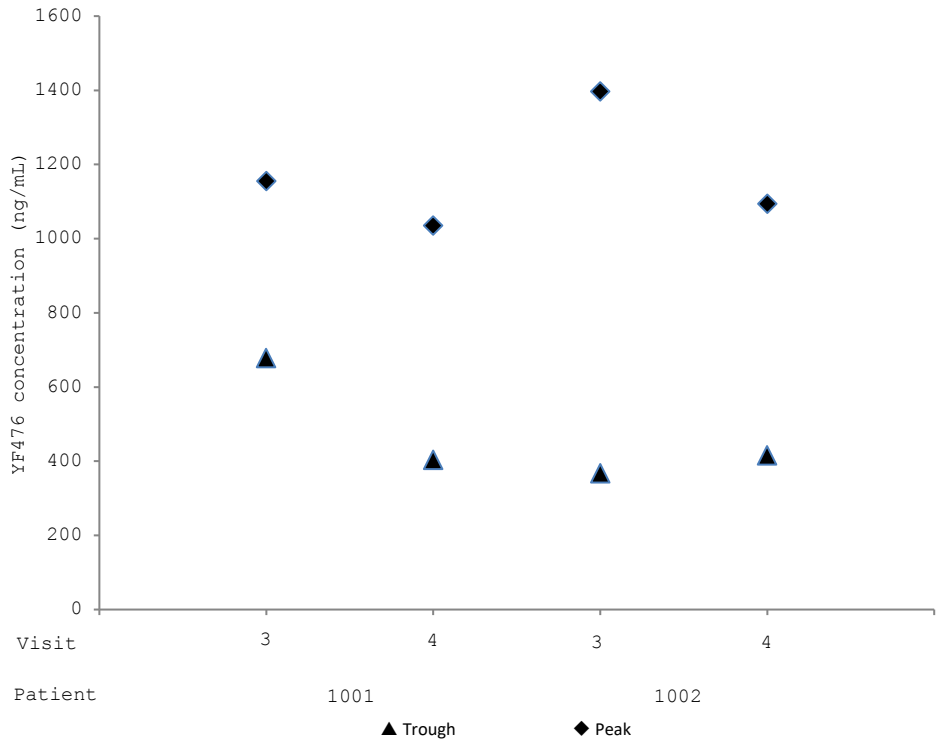
Measurement (units)	Treatment	Visit	n	Mean	SD	%CVb	Median	Min	Max	Geom Mean	95% CI (Lower,Upper)
Peak	Treatment 1	Visit 3	x	xxxx.x		xx.x	xxxx.x	xxxx	xxxx		(xxxx.x,xxxx.x)
	(N=xx)	Visit 4	x	xxxx.x	xx.xx	xx.x	xxxx.x	xxxx	xxxx		(xxxx.x,xxxx.x)
											(xxxx.x,xxxx.x)
Trough	Treatment 1	Visit 3	x	xxxx.x		xx.x	xxxx.x	xxxx	xxxx		
	(N=xx)	Visit 4	x	xxxx.x	xx.xx	xx.x	xxxx.x	xxxx	xxxx		

Source: Listing 16.2.xx

19.2.2 Figure Outlines

Template F_PK1

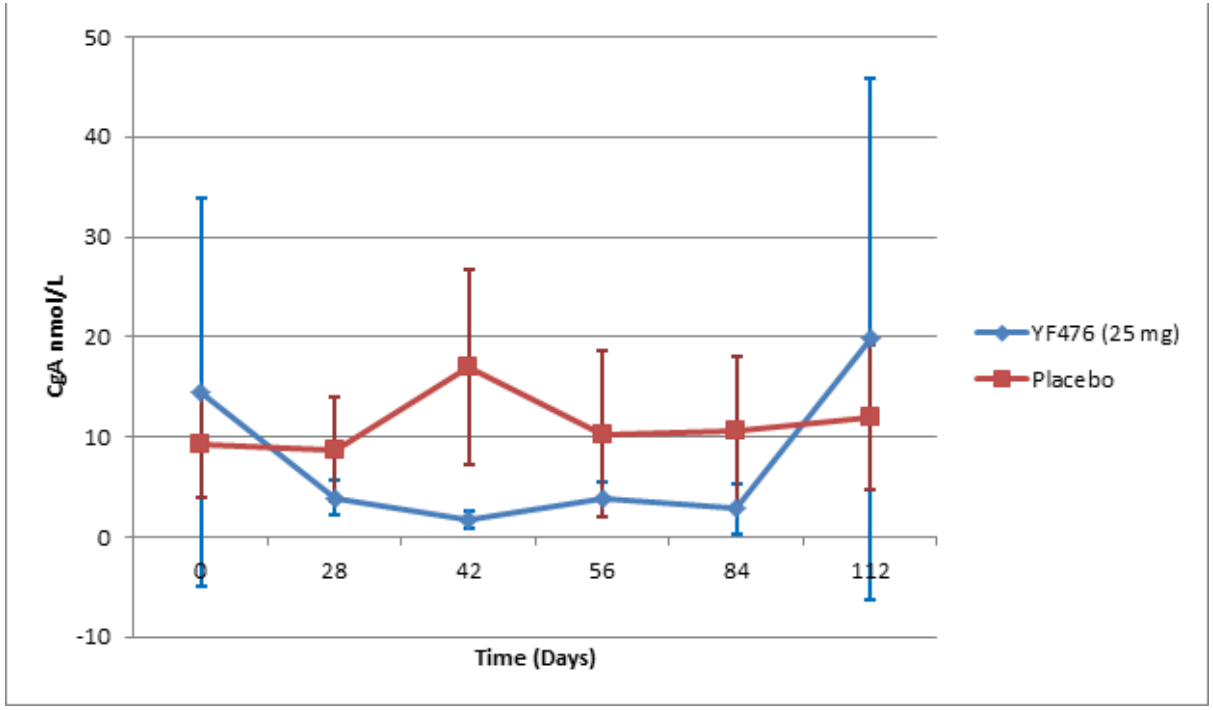
Figure 14.3.1 Individual Netazepide Plasma Concentration-Time Plots



Programming notes: *All patients will be displayed in the same graph on one page.*

Template F_PK4

Figure 14.3.4 Mean ± SD serum gastrin – time plot (ITT)



19.2.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of Study Dates

Treatment	Patient	Visit 1	Visit 2	Week 6 Visit	Week 12 Visit	Follow Up

Programming notes: *Lists dates for screening, each dosing period and follow up*
For crossover studies use Sequence instead of Treatment

Template L_SD2_PG

Listing 16.2.x.xx Listing of Reasons for Withdrawal

Treatment	Patient	Date of Withdrawal	Study Day	Reason

Programming notes: *Reason for withdrawal is concatenation of reason and details*

Template L_SD3_PG

Listing 16.2.x.xx Listing of Screen Failures

Patient	Date of Screen Failure	Failure Category	Details

Template L_DV1_PG

Listing 16.2.x.xx Listing of Patients with Inclusion/Exclusion Criteria Deviations

Treatment	Patient	Type	Criterion
		Inclusion	
		Exclusion	

Template L_DV2_PG

Listing 16.2.x.xx Listing of Patients with Other Protocol Deviations

Treatment	Patient	Protocol Deviation

Template L_AN1_PG

Listing 16.2.x.xx Listing of Analysis Populations

Treatment	Patient	Screened Population	Safety Population	ITT Population	PP Population

Template L_DM1_PG

Listing 16.2.x.xx Listing of Demographic Characteristics

Treatment	Patient	Date of visit	Date of birth	Age (y)	Gender	Race	Ethnic origin	Height (cm)	Weight (kg)	BMI (kg/m2)	Etc (units)
Treatment 1 ↓											

Programming notes: *A by-patient listing of demographic characteristics including:*

Treatment

Patient

Date of visit

Date of birth

Age

Gender

Race / Ethnic Origin

Height (if collected only once during the study)

Weight (if collected only once during the study)

Smoking History

Alcohol Consumption

Additional study-specific demography characteristics included on the CRF

Template L_CM1_PG

Listing 16.2.x.xx Listing of Concomitant Medications

Treatment	Patient	Drug Name/ Indication	Dose/ Freq/Route	Date/time Started/ Date Stopped	Time Since Last Dose	Started Pre-Trial?	Ongoing Medication?

Programming notes: *Include dose and units (e.g. 5 mg)/Freq/Route*

Template L_PP1_PG

Listing 16.2.x.xx Listing of Proton Pump Inhibitor Use

Treatment	Patient	Date/Time	Is patient taking proton pump inhibitor?	Have they been taking it for at least 12 months?	How often does the patient take the PPI?	Generic name	Dose	Date Started
Treatment 1	1001	01JAN2002	Yes	Yes	Once daily			

Template L_MH1

Listing 16.2.x.xx Listing of Medical History: Barrett's Esophagus

Treatment	Patient	Date/Time	Endoscopy	Most recent endoscopy date	Intestinal metaplasia and no dysplasia	Is Barrett's mucosa circumferential	Maximum measurement of Barrett's mucosa (cm)
Treatment 1	1001	01JAN2002	Yes		Yes	Yes	

Template L_EX1_PG

Listing 16.2.x.xx Listing of Study Drug Administration

Treatment	Patient	Start Date/ Start Time of Dose	Stop Date/ Stop Time of Dose	Dur-ation (days)	Dose	Dose Unit	Formulation/ Route	Frequency	Visit 3 Compliance (%)	Visit 4 Compliance (%)
Treatment 1	1001	01JAN2002 23:59	15FEB2002 15:30	46	25	mg	Tablet/ Oral	2xday		

Template L_AE1_PG

Listing 16.2.x.xx Listing of All Adverse Events

Treatment	Patient	System Organ Class / Preferred Term/ Verbatim Text	Outcome/ Onset Date/Time/ Resolved Date/Time/ Duration	Time Since Last Dose	Severity/ Serious/ Withdrawal	Frequency/ Action Taken (1)/ Other Action Taken	Related to Study Drug/ Treatment Emergent?
Treatment 1	1001	Gastrointestinal Disorders / Intestinal Spasm / Entero-spasm	Resolved/ 24SEP2003 13:05/ 27OCT2003 7:50/ 34d 4h 5m	10d 7h 3m	Mild/ No/ Yes	Intermittent/ Dose not changed/ None	Possibly/ Yes

(1) Action Taken with Study Treatment

Programming notes: *For the listing of "other significant AEs" include (from ICH E3) AEs leading to withdrawal, AEs leading to dose reduction (including drug withdrawn, interrupted, reduced or similar) and AEs with AEOSE=Y. If AEOSE has not been collected then use "Otherwise significant" in the CRF.*

Template L_LB1_PG

Listing 16.2.x.xx Listing of clinical chemistry abnormalities of potential clinical importance

Treatment	Subject	Laboratory test (units)	Planned Relative Time	Date/Time	Study Day	Value	Reference Interval	Clinically Significant?
Treatment 1	1001	Alk Phos (U/L)	Time 1	01JAN2002 13:34	-1	64.00	32.0 - 92.0	Y
			Time 2	01APR2002 07:22	85	84.00	32.0 - 92.0	Y
		ALT (U/L)	Time 1	01JAN2002 18:56	-1	29.00	10.0 - 40.0	Y
			Time 2	01APR2002 09:22	85	70.00	10.0- 40.0	Y

Programming notes: *Lists only* Laboratory results identified as 'clinically significant' in the CRF

Template L_LB2_PG

Listing 16.2.x.xx Listing of all clinical chemistry laboratory data for subjects with PCI abnormalities

Treatment	Subject	Planned Relative Time	Date/Time	Alkaline Phosphatase (IU/L) Result	Alanine Amino Transferase (IU/L) Result	Aspartate Amino Transferase (IU/L) Result	Total Bilirubin (UMOL/L) Result
				xx*	x.xx		

Treatment	Subject	Planned Relative Time	Date/Time	Chloride (MMOL/L) Result	Glucose (MMOL/L) Result	Potassium (MMOL/L) Result	Sodium (MMOL/L) Result

Treatment	Subject	Planned Relative Time	Date/Time	Calcium (MMOL/L) Result	Creatinine (UMOL/L) Result	Etc. Result

* Value of potential clinical significance

Programming notes: *Lists only subjects identified as* 'clinically significant' in the CRF
Include all parameters for the study following the order from the lab report (above is a guide only)

Template L_EG1_PG

Listing 16.2.x.xx Listing of ECG Values of Potential Clinical Importance

								QT Int. (msec)		QTcB (msec)		QTcF (msec)	
Treatment	Patient	Planned Relative Time	Date/Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	QRS Axis (deg)	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
		24 H	26SEP2012:09:57	63	148	78	50	390	32.7 *	399	-27.7	396	-6.5

* Value of potential clinical importance

Programming notes: *Do not list RR*

Template L_EG2_PG

Listing 16.2.x.xx Listing of Abnormal ECG Findings

Treatment	Patient	Planned Relative Time	Date/Time	ECG Finding	Comment on Clinical Significance

Programming notes: *Lists only values with Normal variant='No' or with comment on ECG result*
ECG Finding contains Physician's Opinion from CRF and relates to whole trace (not individual parameters), e.g. Normal, Abnormal - NCS or Abnormal - CS

Template L_PK1_PG

Listing 16.2.6.xx Listing of Netazepide Plasma Pharmacokinetic Parameters

Treatment	Patient	Date	Planned Relative Time	Concentration (units) Peak (C_{max})	Trough (C_{min})

Template L_PK4_PG

Listing 16.2.6.xx Listing of serum gastrin and plasma CgA data

Treatment	Patient	Date	Planned Relative Time	Serum Gastrin	Plasma Cg

Appendix A: Sample Page Layout

Trio Medicines Ltd : T-016 Page x of y*

Population: [Pop]

Table [number] [title]

Column headers

Main body of output

Source: Listing [16.2.xx]

Footnotes about the table or listing text go here.

Program: [Prog Name] [Date] HMR 10-505

Produced By:[Username]

*y = last page of individual output

Font size will be Arial 9.5pt. The following margins will be used: Left: 1", Right: 1", Top: 1", Bottom: 1"