

Clinical Development

LAP016A/ Lapatinib/Tykerb

Clinical Trial Protocol CLAP016A2410 / NCT02294786

**A Randomised, Multicentre, Open Label, Phase II study
of Prophylactic Octreotide to Prevent or Reduce the
Frequency and Severity of Diarrhoea in Subjects
Receiving Lapatinib with Capecitabine for the Treatment
of Metastatic Breast Cancer**

Statistical Analysis Plan (SAP)

Author:  Trial Statistician

Document type: SAP Documentation

Document status: Final 1.0

Release date: 28-Nov-2017

Number of pages: 41

Property of Novartis
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
28-Nov-2017		First Final version	NA	NA

Table of contents

Table of contents.....	3
List of abbreviations	5
1. Introduction.....	6
1.1 Study design.....	6
Table 1-3 Objectives and endpoints.....	10
2 Statistical methods.....	12
2.1 Data analysis general information.....	12
2.1.1 Data included in the analysis.....	12
2.1.2 General analysis conventions	13
2.1.3 General definitions	13
2.2 Analysis Populations.....	17
2.3 Patient disposition, demographics and other baseline characteristics.....	18
2.3.1 Patient disposition	18
2.3.2 Protocol deviations	19
2.3.3 Basic demographic and background data	19
2.3.4 Disease history and medical history	20
2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance).....	20
2.4.1 Study treatment and compliance	20
2.4.2 Concomitant medications	20
2.5 Analysis of the primary objective	21
2.5.1 Primary endpoint	21
2.5.2 Statistical hypothesis, model, and method of analysis	21
2.5.3 Handling of missing values/censoring/discontinuations	22
2.5.4 Supportive analyse.....	22
2.5.5 Subgroup analyses for the primary endpoint.....	22
2.6 Analysis of the secondary objective.....	22
2.6.1 Investigator-reported endpoints.....	22
2.6.2 Patient-reported outcomes	24
2.7 Safety analyses	24
2.7.1 Extent of Exposure	24
2.7.2 Adverse events (AEs).....	25
2.7.3 Adverse Events of Special Interest.....	26
2.7.4 Deaths and Serious Adverse Events.....	26
2.7.5 Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study.....	27
2.7.6 Clinical Trial Safety Disclosure	27

2.7.7	Pregnancies.....	27
2.7.8	Clinical Laboratory Evaluations.....	28
2.7.9	Other Safety Measures	30
2.8	Health outcomes analyses	32
2.8.1	Health Outcomes Assessments.....	32
2.9	Interim analysis	33
3	Sample size calculation.....	33
3.1	Sample size assumptions.....	33
3.2	Sample Size Sensitivity.....	33
3.3	Sample Size Re-estimation	34
4	Change to protocol specified analyses.....	34
5	Appendix.....	34
5.1	Imputation rules	34
5.1.1	AE date imputation.....	35
5.1.2	Concomitant medication and blood and blood supportive care products	36
5.1.3	Other imputations	38
5.2	AEs coding/grading.....	38
5.3	Statistical models	39
5.3.1	Analysis of binary data.....	39
5.3.2	Analysis of time to events data.....	40
6	Reference	40

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DMD	Diarrhoea Management Diary
eCRF	Electronic Case Report Form
FACIT-D	Functional Assessment of Chronic Illness therapy-Diarrhoea
FACT-G	Functional Assessment of Cancer Therapy-General
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
PRO	Patient-reported Outcomes
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class

1. Introduction

This statistical analysis plan (SAP) describes analyses required for a Clinical Study Report (CSR) to support a publication of study LAP016A2410, a randomised, multicentre, open label, phase II study of Prophylactic Octreotide to prevent or reduce the frequency and severity of diarrhoea in subjects receiving Lapatinib with Capecitabine for the treatment of metastatic breast cancer. This is a phase II study to evaluate the efficacy, safety [REDACTED] of prophylactic octreotide compared to no octreotide using a parallel group, open label, randomised study design.

As first interim analysis results showed study is futile and no patients will be recruited in the study. For final analysis abbreviated CSR will be done and it will include reduced analyses as compared to planned analyses in the protocol.

As planned in the protocol an interim analysis was performed after 62 patients enrolled using a cut-off date (30-Mar-2016) and an interim database lock on 16-Aug-2016. As the interim analysis results showed study was futile the DMC recommended to stop the study. Per protocol no further patients were enrolled in the study per IA cut-off.

For final analysis an abbreviated CSR will be done and it will include reduced analyses as compared to planned analyses in the protocol.

The content of this SAP is based on protocol CLAP016A2410 Amendment 02 dated 11 September 2015 (2012N152651_03).

The SAP was written by Novartis Statistician. The execution of the SAP will be undertaken by staff of [REDACTED] and the GSK layout standard will be used to generate all tables, figures, and listings.

All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a randomised, parallel group, multi-centre, open-label Phase II study in subjects with HER2-positive metastatic breast cancer which has progressed following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting. This study is not placebo controlled, and there is no active comparator.

Subjects must be screened for eligibility and informed consent must be given before any study-related procedures are conducted.

All subjects will receive treatment with lapatinib 1250mg once daily and capecitabine 1000mg/m² twice daily until disease progression. Lapatinib will be given every day; capecitabine will be given in 3 week cycles of two weeks treatment followed by one week off treatment. All subjects with episodes of diarrhoea will be encouraged to follow the diarrhoea management guidelines for subjects receiving lapatinib. One cycle of lapatinib and capecitabine equates to three study weeks.

Subjects will be randomised in a 1:1 ratio to receive either:

- Octreotide (Sandostatin long acting release (LAR)) 40mg 7 days before the start of treatment with lapatinib and capecitabine and again 28 days later, or

- No octreotide treatment.

For subjects randomised to receive octreotide, treatment with lapatinib and capecitabine will be initiated 7 days after the first dose of octreotide given as the LAR formulation. For subjects randomised to receive no octreotide, treatment with lapatinib and capecitabine will be initiated immediately following enrolment.

Subjects randomised to receive octreotide LAR must be given one 0.1mg dose of the standard formulation of octreotide subcutaneous (s.c.) to assess tolerability at least one hour before the first dose of the LAR formulation is administered. Subjects with significant intolerance to octreotide 0.1mg s.c. will not receive treatment with octreotide LAR, but will receive treatment with lapatinib and capecitabine as scheduled.

Study completion will be at the end of 24 weeks treatment with lapatinib and capecitabine, or disease progression, unacceptable toxicity or subject withdrawal if this is sooner. SAEs and other safety data will be reported beyond 24 weeks in subjects who continue treatment with lapatinib and capecitabine until disease progression in countries where the Sponsor is supplying lapatinib and capecitabine. SAEs will be followed up until resolution or stabilization of the event or until the subject is lost to follow-up.

The efficacy of prophylactic octreotide in reducing the frequency and severity of diarrhoea is the primary endpoint of this study. Each episode of diarrhoea will be recorded by the investigator as an AE in the eCRF in accordance with the standard AE reporting procedure. Actions associated with the management of diarrhoea (use of anti-diarrhoeal medication, unscheduled visits to healthcare professionals, treatment interruption, rehydration) will be recorded in the eCRF.

Subjects will complete the DMD and the FACIT-D to provide an additional perspective on the effects of treatment-associated diarrhoea.

Diarrhoea, nausea and vomiting, dermatological events, hepatobiliary, cardiovascular and respiratory events have been identified as events of special interest relating to lapatinib. Hand and foot syndrome has been identified as an event of special interest relating to capecitabine. There are no events of special interest relating to octreotide.

The schedule of all assessments is presented in [Table 1-1](#) for subjects who receive octreotide and [Table 1-2](#) for subjects who do not receive octreotide.

Table 1-1 Time and events schedule; Subjects who receive octreotide.

	Screen ¹	Octreotide Dose 1	Lapatinib and Capecitabine Cycle ^{9,10}			Withdrawal from Study Treatment or End of Study ¹⁴
			Cycle 1	Cycle 2 (Octreotide Dose 2)	Cycles 3 to 8	
Procedures						
Informed Consent	X					
Inclusion/Exclusion Criteria	x ²	x ²				
Demographics	X					
Breast Cancer Medical/Surgical and Treatment History	X					
Efficacy and Safety Assessments						

AE/Toxicity Assessment		x	x	x	x	x ¹⁵
Disease Assessment	x ³	(x) ⁵	(x) ⁵	(x) ⁵	(x) ⁵	x
PROs ⁶		x ⁷	x ¹¹	x	x	x
Concurrent Medications	X	x	x	x	x	x
Physical Exam	X					x
Weight, Height, Vital Signs (Temp, BP, pulse)	X					x
ECOG Performance Status	x ⁴					x
Cardiac function	X					x ¹⁶
ECG	X					(x) ¹⁷
Lab Assessments						
Liver function	X	(x) ⁵	(x) ⁵	(x) ⁵	(x) ⁵	x
Pregnancy Test	X					x
Study Treatments						
Administer Octreotide		x ⁸		x ¹³		
Dispense Lapatinib and Capecitabine			x	x	x	
Assess Lapatinib and Capecitabine Returned				x	x	x

1. Schedules for screening assessments are presented in Section [7.1.1] and Section [7.1.2] of the Study Protocol. All screening and baseline assessments must be completed prior to administration of the octreotide 0.1mg s.c. tolerability assessment dose.
 2. Inclusion and exclusion criteria are presented in Section [4.1.2] and Section [4.1.3] of the Study Protocol, and other considerations are presented in Section [4.2] of the Study Protocol. Investigators must ensure all subjects are eligible to receive treatment with lapatinib and capecitabine in accordance with the Lapatinib SPC and Capecitabine SPC, including evaluation of cardiac function.
 3. Disease assessment criteria are described in Section [7.1.11] of the Study Protocol.
 4. ECOG status may be assessed more than once prior to randomisation, but only the assessment within 3 days prior to randomisation will be recorded in the eCRF.
 5. Not mandatory at these visits, but should be conducted in accordance with local clinical practice, at the time of a scheduled 3 weekly visits when possible.
 6. PROs are the FACIT-D and the diarrhoea diary.
 7. To be completed before the octreotide 0.1mg s.c. tolerability assessment dose.
 8. First dose of octreotide LAR to be given 7 days before start of Cycle 1 treatment with lapatinib and capecitabine. Subjects must receive octreotide 0.1mg s.c. at least one hour before the first dose of octreotide LAR to assess tolerability.
 9. **Cycle 2 and Cycle 4 visits are mandatory.** Cycle 3, 5, 6, 7 and 8 visits are not mandatory; visits every 3 weeks would be preferred, but may be adapted to match local practice.
 10. Cycle 2 to be started 21 days (\pm 2 days) after the start of Cycle 1. Other cycles should be started within +/- 4 days of the 3 weekly treatment cycle intervals.
 11. To be completed before the first dose of lapatinib and capecitabine is administered.
-
13. Second dose of octreotide LAR to be given 28 days (+/- 2 days) after first dose of octreotide LAR.
 14. After 24 weeks treatment with lapatinib and capecitabine. Investigators should continue to treat subjects with lapatinib and capecitabine beyond 24 weeks in accordance with local clinical practice.
 15. Serious adverse events and other safety data as described in Section [7.4] of the Study Protocol should be reported for all subjects who continue treatment with lapatinib and capecitabine beyond the 24 week end of study assessment.
 16. If more than 12 weeks since the screening cardiac function assessment.

17. If clinically indicated.

Table 1-2 Time and events schedule; Subjects who receive no octreotide

	Screen ¹	Lapatinib and Capecitabine Cycle ^{9,10}		Withdrawal from Study Treatment or End of Study Visit ¹¹
		1	2 to 8	
Procedures				
Informed Consent	x			
Inclusion/Exclusion Criteria	x ²	x		
Demographics	x			
Medical/Surgical and Treatment History	x			
Efficacy and Safety Assessments				
AE/Toxicity Assessment		x	x	x ¹²
Disease Assessment	x ³	(x) ⁵	(x) ⁵	x
PROs ⁶		x ⁷	x	x
Concurrent Medications	x	x	x	x
Physical Exam	x			x
Weight, Height, Vital Signs (Temp, BP, pulse)	x			x
ECOG Performance Status	x ⁴			x
Cardiac function	x			x ¹³
ECG	x			(x) ¹⁴
Lab Assessments				
Liver function	x	(x) ⁵	(x) ⁵	x
Pregnancy Test	x			x
Study Treatments				
Dispense Lapatinib and Capecitabine		x	x	
Assess Lapatinib and Capecitabine Returned			x	x

- Schedules for screening assessments are presented in Section [7.1.1] and Section [7.1.2] of the Study Protocol. All screening and baseline assessments must be completed prior to the start of Cycle 1 of treatment with lapatinib and capecitabine.
- Inclusion and exclusion criteria are presented in Section [4.1.2] and Section [4.1.3] of the Study Protocol, and other considerations are presented in Section [4.2] of the Study Protocol. Investigators must ensure all subjects are eligible to receive treatment with lapatinib and capecitabine in accordance with the Lapatinib SPC and Capecitabine SPC, including evaluation of cardiac function.
- Disease assessment criteria are described in Section [7.1.11] of the Study Protocol.
- ECOG status may be assessed more than once prior to randomisation, but only the assessment within 3 days prior to randomisation will be recorded in the eCRF.
- Not mandatory at these visits, but should be conducted in accordance with local clinical practice, at the time of a scheduled 3 weekly visits when possible.
- PROs are the FACIT-D and the diarrhoea diary.
- To be completed before the first dose of lapatinib and capecitabine is administered.
- 
- Cycle 2 to be started 21 days (+/- 2 days) after the start of Cycle 1. Other cycles should be started within +/- 4 days of the 3 weekly treatment cycle intervals.
- Cycle 2 and Cycle 4 visits are mandatory.** Cycle 3, 5, 6, 7 and 8 visits are not mandatory; visits every 3 weeks would be preferred, but may be adapted to match local practice.

	Screen ¹	Lapatinib and Capecitabine Cycle ^{9,10}		Withdrawal from Study Treatment or End of Study Visit ¹¹
		1	2 to 8	

11. After 24 weeks treatment with lapatinib and capecitabine. Investigators should continue to treat subjects with lapatinib and capecitabine beyond 24 weeks in accordance with local clinical practice.
12. Serious adverse events and other safety data as described in Section [7.4] of the Study Protocol should be reported for all subjects who continue treatment with lapatinib and capecitabine beyond the 24 week end of study assessment.
13. If more than 12 weeks since the screening cardiac function assessment.
14. If clinically indicated.

One interim analysis was planned when at least 60 subjects have been randomised to treatment and completed their 9 week assessment or discontinued from study. The interim analysis allowed stopping the study early for lack of efficacy (futility) or safety. [Table 1-3](#) described the objectives and endpoints for final analysis. Since study was futile based on the interim analysis results, team decided to create abbreviated CSR for final analysis and hence removed some of the endpoints from final analysis.

The objectives and endpoints of the study are summarized in [Table 1-3](#).

Table 1-3 Objectives and endpoints

Objectives	Endpoints
Primary: Investigator reported	
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects experiencing diarrhoea with a severity of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 and above.	Proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above, as defined by the NCI-CTCAE, version 4.03.

Secondary: Investigator reported	
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects experiencing diarrhoea with a severity of NCI-CTCAE Grade 3 and above.	Proportion of subjects experiencing diarrhoea with a severity of Grade 3 and above, as defined by the NCI-CTCAE, version 4.03, recorded as adverse events (AEs) in the electronic Case Report Form (eCRF).
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects experiencing diarrhoea of any grade of severity.	Proportion of subjects experiencing diarrhoea of any grade of severity as defined by the NCI-CTCAE, version 4.03, recorded as AEs in the eCRF.
To determine the efficacy of prophylactic octreotide in increasing the time to onset of the first episode of diarrhoea of any grade of severity.	Time to onset of the first episode of diarrhoea of any grade of severity, recorded as an AE in the eCRF.

Objectives	Endpoints
Secondary: Investigator reported	
To determine the effect of prophylactic octreotide on compliance with lapatinib and capecitabine treatment.	Number of lapatinib and capecitabine tablets dispensed and returned, recorded in the eCRF.
To determine the effect of prophylactic octreotide on the efficacy of treatment with lapatinib and capecitabine.	Overall response rate and clinical benefit response measured in accordance with the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1.
To determine the effect of prophylactic octreotide on the safety and tolerability of cancer treatment.	Proportion of subjects with AEs and SAEs, recorded in the eCRF.
Secondary: Patient reported Diarrhoea Management Diary (DMD)	
To determine the effect of prophylactic octreotide on patient reported diarrhoea.	Patients reporting changes in bowel movements from baseline (frequency and/or consistency), recorded in the DMD.
Quality of Life – FACIT-D	
To determine the effect of prophylactic octreotide on health-related quality of life.	Trial Outcomes Index will be the primary measure; the sub-scales, Total FACT-G score and Total FACIT-D score will be secondary measures.

2 Statistical methods

2.1 Data analysis general information

Data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

The final analyses will be performed by [REDACTED]. The currently supported version of Statistical Analysis System (SAS®) will be used to perform all data analyses, and generate tables, figures, and listings.

2.1.1 Data included in the analysis

All data up to the time of study completion (i.e. 24 weeks of lapatinib and capecitabine treatment) or withdrawal from the study will be included in the final analysis, regardless of duration of treatment.

All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data

collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations. For the final analysis the database lock date will be used as cut-off date.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ‘continuing at the cut-off date’. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

2.1.2 General analysis conventions

Unless specified otherwise, categorical data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population as the denominator. Continuous data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, minimum, median, and maximum) by treatment group.

Unless specified otherwise, all listings will be sorted by treatment group, center, subject number, and then by visit date and time, if applicable. Only visits at Cycle 2 and 4 are mandated, other visits are as per clinical practice. All available data will be included in listings, including data from unscheduled visits.

All laboratory data will be presented in GSK’s standard units for reporting.

Planned (nominal) assessment times relative to study drug dosing will be used in all summaries and analyses.

Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

Note: although octreotide is administered twice, once 7 days before the first cycle of lapatinib and capecitabine and then 28 days later, assessments will be entered as cycles to correspond to the lapatinib plus capecitabine assessments. For this purpose a cycle corresponds to 3 weeks of lapatinib and capecitabine.

Deviations from the analyses in the SAP will be identified in the CSR.

2.1.3 General definitions

2.1.3.1 Investigational drug and study treatment

Investigational drug, will refer to the Octreotide only. Whereas, *study treatment* will refer to Octreotide + Lapatinib + Capecitabine and Lapatinib + Capecitabine.

The following treatment descriptors will be used on all applicable displays:

Table 2-1 Treatment descriptors of investigational drug

Treatment Group Description	Data Display	Order of Treatment Groups
Octreotide+Lapatinib+Capecitabine	Octreotide+Lap+Cap	1

Lapatinib+ Capecitabine	Lap+Cap	2
-------------------------	---------	---

2.1.3.2 Reference start date

There are three reference start dates:

- Age is an eligibility requirement and therefore the reference start date for age is the date of screening.
- The safety reference start date is the date of a subject receiving the first dose of study treatment (i.e., octreotide, lapatinib or capecitabine).
- The efficacy reference start date is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics.

The reference start date for all other, non-safety assessments (i.e., tumor assessment, death, disease progression, tumor response, ECOG performance status, and patient reported outcomes (PRO)) is the date of randomization.

2.1.3.3 Date of first/last administration of study drug/study treatment

• **Date of first administration of study drug**

The date of first administration of investigational drug is defined as the first date when a nonzero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of study drug will also be referred as start of investigational drug.

• **Date of last administration of study drug**

The date of last administration of investigational drug is defined as is the last date when a nonzero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

• **Date of first administration of study treatment**

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the Dosage Administration (e)CRF. (Example: if 1st dose of Octreotide is administered on 05-Jan-2015, and 1st dose of combination partner is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015).

• **Date of last administration of study treatment**

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per Dose Administration (e)CRF. (Example: if the last Octreotide dose is administered on 15-Apr-2014, and the last dose of a combination partner is administered on 17-May-2014, then the date of last administration of study treatment is on 17-May-2014).

2.1.3.4 Study day

The study day, describes the day of the event or assessment date, relative to the reference start date. There is no study day 0.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date if event precedes the reference start date.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.3.5 Duration/Elapsed Time/Time unit

Durations (e.g., the duration of an adverse event, duration of exposure, duration of episodes of diarrhoea) are calculated as the stop date minus the start date +1.

For elapsed time (e.g., the time since initial diagnosis):

- If the reference start date is on or after the event date, then the elapsed time is the reference start date minus the event date + 1.
- If the reference start date is before the event date then the elapsed time is the reference start date minus the event date.

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.1.3.6 Baseline

Baseline is defined as the most recent, non-missing value prior to receiving the first dose of study treatment (octreotide, lapatinib or capecitabine).

For subjects who did not receive any study treatment (i.e. octreotide, lapatinib or capecitabine) during the study, baseline will be defined as the latest, non-missing collected value.

If patients have no value as defined above, the baseline result will be missing.

2.1.3.7 Change from baseline

Change from baseline will be presented for safety data as described in the relevant sections.

Change from baseline is calculated as:

- visit value - baseline value, if records occur after baseline, or
- missing, if either the baseline or visit value is missing.

2.1.3.8 Multiple assessments

All data will be analysed according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report worst-case post-baseline.

If multiple assessments on different days are reported for the same scheduled assessment, then the latest assessment for that scheduled assessment will be analysed.

If multiple assessments are reported on the same date for the same scheduled planned time, then the mean of the multiple measurements reported for the same date will be analysed. For example, for ECG data where 3 assessments are collected for each scheduled planned time, the first 3 measures will be used to compute the mean values for ECG intervals at each scheduled planned time.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

2.1.3.9 Last contact date

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the last complete date among the following:

- “When was subject last seen or heard alive?” collected on the ‘DEATH’ eCRF.
- All assessment dates (e.g. tumor assessment, laboratory collection dates, vital signs assessment, performance status/PRO assessment, ECG assessment). Note, only a true on study assessment date or patient contact date will be used. If there is a visit date without evidence of any actual assessment performed that date will not be used.
- Medication dates including study medications, concomitant medications, and anti-neoplastic therapies administered after study treatment discontinuation (with non-missing medication/procedure term).
- Adverse event dates (with non-missing verbatim AE term present).
- Randomization date.
- Date of subject discontinuation from ‘Conclusion Details’ eCRF.

The last contact date is defined as the latest complete date from the above list or the cut-off date whichever comes first. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from ‘Death’ eCRF.

The last contact date will be used for censoring of subjects in the analysis of overall survival.

2.1.3.10 On-treatment assessment/event

All on-treatment assessments/events are any assessments/events obtained in the time interval:

[date of first administration of study treatment, date of last administration of study treatment +28 days], i.e., inclusive lower and upper limit.

2.1.3.11 Study Time Periods for Concomitant Medications and Blood and Blood Supportive Care Products

Concomitant Medication and Blood and Blood Supportive Care Product start and end dates will be assigned to study time periods in relation to first dose of study treatment (octreotide, lapatinib or capecitabine as applicable). The start date reference time flag variables and end

date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

- **Start relative to treatment:** Assign to 'BEFORE' if start date is prior to first dose of study treatment start date, if subject has not taken any study treatment, or start date is missing and end date is before study treatment start date. Else assign to 'DURING' if the start date falls into the on-therapy period (defined as the time from first dose of study treatment to the last dose date of study treatment) or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period.
- **End relative to treatment:** Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if start date falls into the on-therapy period or if subject is ongoing (not all study treatment discontinuation records completed) or end date is missing and start relative to treatment not 'AFTER'. Else assign to 'AFTER' if start date is after the on-therapy period or end date is missing and start relative to treatment='AFTER'.

Only on-therapy blood and blood supportive care products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product summaries. Therefore, for summary tables, include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER'). All data will be reported in listings.

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- **Summary of Concomitant Medications:** This summary will contain medications including those with start date prior to study treatment start date and which continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment in ('DURING','AFTER').

2.2 Analysis Populations

Intent-to-Treat Population

The Intent-to-Treat (ITT) population will comprise all randomised subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomised. Any subject who receives a treatment randomization number will be considered to have been randomised. The primary analysis of disease efficacy and all diarrhoea-related efficacy endpoints will be analysed using the ITT population.

Modified ITT

The modified ITT (m-ITT) population will comprise all subjects in the ITT population and under Octreotide arm this population will include subjects who do not show intolerance to octreotide in the s.c. formulation and who do not have non treatment related diarrhoea recorded

as an AE after the first dose of octreotide LAR and prior to the start of treatment with lapatinib and capecitabine. A sensitivity analysis of diarrhoea-related primary efficacy endpoint will be conducted using the m-ITT population.

Per Protocol Population

The Per-Protocol (PP) population will comprise all randomised subjects who receive at least one dose of study treatment and who comply closely with the protocol (that is subjects who are not excluded from PP set as per PDMP). The PP population will not be analysed if this population comprises more than 95% or less than 50% of the ITT population. The analysis of primary efficacy endpoint will be repeated using the PP population.

Subjects with potential PDs will be excluded from PP population based on Protocol Deviation Management Plan (PDMP).

Safety Population

The Safety population will comprise all randomised subjects who receive at least one dose of study treatment and will be based on the actual treatment received if this differs from that to which the subject was randomised. This population will be used for the analysis of clinical safety data. Moreover, if a subject who was randomised to Octreotide arm, showed intolerance to octreotide in the s.c. formulation, and took at least one dose of lapatinib or capecitabine, then subject will be included in no Octreotide arm for safety analysis.

2.3 Patient disposition, demographics and other baseline characteristics

The Intent-to-Treat (ITT) population will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment group labeled as specified in [Table 2-1](#) and for all subjects and listings will be reported by treatment group to assess baseline comparability. No inferential statistics will be provided.

2.3.1 Patient disposition

A summary of the number of subjects in each of the analysis populations described in [Section 2.2](#) will be provided. A listing of analysis populations in which each subject will be included or excluded will be provided as well.

A summary of study treatment status (octreotide, lapatinib and capecitabine) will be provided. This display will show the number and percentage of subjects who completed all doses of Octreotide, completed 24 weeks of treatment with lapatinib and capecitabine and a summary of the primary reason for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF.

A separate table of a summary of study status will be provided with frequency and percentages for patients died and withdrawn from study will be provided. Reasons for withdrawal will be presented in the order they are displayed in the eCRF.

Listing of patient disposition will be provided including details on study treatment discontinuation and study discontinuation.

2.3.2 Protocol deviations

The number (%) of patients in the ITT population with any important protocol deviation will be tabulated by deviation category, total, and by treatment group for the ITT population. All important protocol deviations will be listed and deviations leading to exclusion from per protocol population will be flagged in the listing. The important protocol deviation will be categorized as below as per GSK SOP:

- those who entered the study even though they did not satisfy the entry criteria;
- those who developed withdrawal criteria during the study but were not withdrawn;
- those who received the wrong treatment or incorrect dose;
- those who received an excluded concomitant treatment
- Any study specific procedure or assessment deviation, which the study team determines may compromise subject rights, safety, or well being, or has a significant impact on study conclusions

Protocol deviations are listed / described in the Protocol Deviation Management Plan, (PDMP). All protocol deviations will be summarized and listed. Protocol deviations will be classified by criteria - Deviations are/aren't important or/and Deviations that do/don't require exclusion from per-protocol population.

2.3.3 Basic demographic and background data

Demographics data and background data at baseline (including key efficacy variables) will be summarized by treatment for all Intent-to-Treat subjects (ITT).

Categorical variables will be summarized by frequency counts and percentages.

The category "Missing" will be displayed if data is missing

Continuous variables will be summarized by n (number of subjects with a non-missing value), mean, standard deviation, minimum (Min.), median, and maximum (Max.).

Demographics data summary includes the following variables:

- (continuous) Age (years) at Screening
- (categorical) Age group at Screening:
 - <18 years
 - >= 18 years - <65 years
 - >= 65 years - <75 years
 - >=75 years
- (categorical) Sex
- (categorical) Ethnicity:
- (categorical) Geographic Ancestry
- (continuous) Baseline Height (cm) at Screening
- (continuous) Baseline weight (kg) at Screening

- (categorical) Baseline ECOG performance status at Screening

A by-subject listing of all demographic characteristics will be produced.

2.3.4 Disease history and medical history

Cardiovascular medical history / risk factors assessed at screening, disease characteristic for the primary tumor type under study at screening and biomarker assessment at screening will be summarized and listed.

In addition, prior anti-cancer therapies are summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment and compliance

A listing of percentage overall compliance for octreotide, lapatinib and capecitabine based on the exposure data will be produced. **Overall compliance (octreotide) is calculated as:**

$$\text{Overall compliance (\%)} = \frac{\text{total cumulative actual dose}}{\text{total cumulative planned dose}} \times 100.$$

where total cumulative planned dose of octreotide will be 80mg if the subject is continuing in the study at the Cycle 2 visit or 40mg otherwise.

Overall compliance (lapatinib) is calculated as:

$$\text{Overall compliance (\%)} = \frac{\text{total cumulative actual dose}}{\text{total cumulative planned dose}} \times 100.$$

where total cumulative actual (or planned) dose is the summation of all actual (or planned) daily doses (mg) of lapatinib in the duration of lapatinib which is last dose date-first dose date +1.

Overall compliance (capecitabine) is calculated as:

$$\text{Overall compliance (\%)} = \frac{\text{total cumulative actual dose}}{\text{total cumulative planned dose}} \times 100.$$

where total cumulative actual (or planned) dose is the summation of all actual (or planned) daily doses (mg/m²) of capecitabine in the duration of lapatinib which is last dose date-first dose date +1.

In addition, summaries of exposure to study medication (octreotide, lapatinib and capecitabine) and dose modifications (e.g., number of dose reductions, escalations, and interruptions) will further characterize compliance. These analyses are described in [Section 2.7.1](#) 'Extent of Exposure'.

2.4.2 Concomitant medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be

summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxicillin on two separate occasions, the subject is counted only once under the ingredient “Amoxicillin”.

2.5 Analysis of the primary objective

The primary objective of the study is to determine the efficacy of prophylactic octreotide in reducing the proportion of subjects experiencing diarrhoea with a severity of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 and above during the first 3 cycles of treatment with lapatinib and capecitabine.

2.5.1 Primary endpoint

The primary efficacy endpoint is proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above during the first 3 cycles of treatment with lapatinib and capecitabine, as defined by the NCI-CTCAE, version 4.03 (see Appendix 1 Table 1 of the study protocol).

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Diarrhoea of Grade 2 and above during the first 3 cycles treatment

This study is designed to test the superiority of prophylactic octreotide vs. no prophylactic octreotide in reducing the proportion of subjects experiencing diarrhoea with a severity of 2 or higher during the first 9 weeks (i.e., 3 cycles treatment) of lapatinib and capecitabine. Superiority will be assessed using data from the Intent-to-Treat population. The following statistical hypothesis will be tested to address the primary efficacy objective:

$$H_0: \delta = 0 \text{ vs. } H_a: \delta < 0,$$

where δ is the difference in the incidence of Grade 2 or higher diarrhoea between prophylactic vs. no prophylactic octreotide during the first 3 cycles of lapatinib and capecitabine.

The AE term ‘diarrhoea’ will be used to select episodes of diarrhoea.

Episodes of diarrhoea ‘during the first 3 cycles of treatment’ are defined as those with an onset date on or after the efficacy reference start date as defined in [Section 2.1.3.2](#) and before the Cycle 4 visit date.

Subjects who withdraw from the study on or prior to the Cycle 4 visit date will be assumed to have experienced diarrhoea (non-responder imputation) of grade 2 or higher.

The superiority of prophylactic octreotide compared to no prophylactic octreotide will be assessed using a Pearson chi-square test in ITT population. The implementation of the Pearson chi-square test is specified in [Section 5.3.1](#). The proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 2 or higher in each treatment group, the difference in proportions between the treatment groups, the corresponding 95% confidence interval and the two-sided p-value from the chi-square test will be presented.

2.5.2.2 Diarrhoea of Grade 2 and above during the entire treatment period

The proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 2 or higher during the entire treatment period will be summarised using the same methods as described for [Section 2.5.2.1](#). There will not be any statistical test performed for this endpoint.

Episodes of diarrhoea ‘during the entire treatment period’ are defined as those with an onset date on or after the efficacy reference start date as defined in [Section 2.1.3.2](#) and on or before the End of Study/Withdrawal visit date.

2.5.3 Handling of missing values/censoring/discontinuations

Diarrhoea with a severity of 2 or higher during the first 9 weeks (i.e., 3 cycles treatment): Subjects who withdraw from the study on or prior to the Cycle 4 visit date will be assumed to have experienced diarrhoea (non-responder imputation) of grade 2 or higher. Such an imputation techniques will be used for the ITT and m-ITT population analysis of the primary endpoint. No imputation will be performed for the Per Protocol analyses.

Diarrhoea with a severity of 2 or higher during the entire treatment period: Subjects who do not have diarrhea event prior to the End of Study/Withdrawal visit date will be considered as non-responders and no imputation will be done in such cases.

2.5.4 Supportive analyse

Supportive analyses of the primary endpoint will be conducted using the m-ITT and PP populations, using the same methods as defined for the primary analysis. The primary endpoint will be summarized using the m-ITT and PP populations, but there will not be any statistical test performed for these populations.

No imputation will be used for the PP analysis, i.e., patients without any diarrhea event on or before desired timepoint will not be imputed and considered as non-responders.

2.5.5 Subgroup analyses for the primary endpoint

Not Applicable.

2.6 Analysis of the secondary objective

2.6.1 Investigator-reported endpoints

These analyses will be based on data reported by the investigator in the eCRF. Analyses of secondary diarrhoea-related endpoints and disease efficacy will be conducted for the ITT population.

2.6.1.1 Diarrhoea of Grade 3 and above

The proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 3 or higher during the entire treatment period will be summarised using the same methods as described for [Section 2.5.2](#), diarrhoea of Grade 2 and above.

2.6.1.2 Diarrhoea of any grade

The proportion of subjects experiencing at least one episode of diarrhoea of any grade of severity during the entire treatment period will be summarised using the same methods as described for [Section 2.5.2](#) diarrhoea of Grade 2 and above.

A by-subject listing of all diarrhoea events will be presented in the form of an adverse event listing, including the duration and time to onset of each event.

2.6.1.3 Time to onset of the first episode of diarrhoea

The time to onset (in days) of the first episode of diarrhoea of any grade of severity will be derived as ((date of first episode of diarrhoea – date of first dose of lapatinib and capecitabine) + 1) and it will be summarised by treatment group using Kaplan-Meier methods. Subjects who complete the study or withdraw prematurely without experiencing an episode of diarrhoea will be censored at the date of withdrawal or study completion.

The Kaplan-Meier estimate of the proportion of subjects experiencing an episode of diarrhoea will be presented for each 3 week cycle of lapatinib and capecitabine by treatment group. Estimates and 95% confidence intervals for the 25th percentile, median and 75th percentile will be provided by treatment group.

2.6.1.4 Study treatment compliance

Inference of the efficacy of prophylactic octreotide will be made by summarising compliance to lapatinib and capecitabine separately by treatment group. Compliance will be derived as described in [Section 2.4.1](#).

A summary of compliance with prophylactic octreotide will be presented. Compliance will be derived as described in [Section 2.4.1](#).

2.6.1.5 Response

Response is a secondary aim of this study, as the sample size is relatively small and the study is not powered to detect a statistically significant difference in the response rate or the efficacy of lapatinib and capecitabine for octreotide vs. no octreotide subjects. However, overall response rate and clinical benefit response rate will be presented for interest. RECIST data to assess tumour size and new tumours will be collected as per clinical practice throughout the study. Data will be collected at baseline (screening) and end of 24 weeks of lapatinib and capecitabine treatment. Therefore overall response rate will be presented as response following 24 weeks of treatment, as subjects will not be followed up to progression or death. Therefore, the results of this analysis should be treated with caution and are for interest and exploratory purposes.

Overall response rate (ORR)

Overall response rate (ORR) is defined as the percentage of subjects achieving either a confirmed complete (CR) or partial (PR) tumour response at the end of the study (End of Study/Withdrawal visit). This will be based on the investigator's assessment of overall response.

Subjects with a not evaluable (NE) or missing response will be treated as non-responders; i.e. they will be included in the denominator when calculating the percentage.

The 95% CI for response rates in each group will be provided for the difference in response rates, as for the primary endpoint.

Clinical benefit response

Clinical benefit response (CBR) is defined as the percentage of subjects with a CR, PR or stable disease (SD) for at least 24 weeks. The CBR will be calculated using the investigator's assessment of response. Subjects who do not have measurable disease, or who have a missing or NE response will be treated as non-responders. The CBR in each treatment group and corresponding 95% confidence interval will be presented.

2.6.2 Patient-reported outcomes

These analyses will be based on data reported by the patient in the DMD and FACIT-D (see [Section 2.6.2.1](#) and [Section 2.8.1](#)). Analyses of secondary patient-reported diarrhoea-related endpoints will be presented for the ITT populations for patients completing the baseline and at least one post-baseline assessments. Missing data will be treated as missing, i.e. there will be no imputation of missing data.

2.6.2.1 DMD

A by-patient listing of all DMD data will be presented.

2.7 Safety analyses

Unless otherwise specified, all the safety analyses will be based on the Safety population and summaries will include all events or assessments collected during the study. All the summaries will be presented by treatment group.

2.7.1 Extent of Exposure

Extent of exposure to octrotide, lapatinib and capecitabine will be summarized separately.

2.7.1.1 Octreotide

The number and percentage of subjects who received a given number of infusions of octreotide (an infusion is defined as one dose of 20mg, patients should have two 20 mg infusions per dose) (0, 1, 2, 3, 4, >4 20mg infusions) will be reported. The duration of exposure to study treatment in days, calculated as (last dose of octreotide – first dose of octreotide +1), will also be summarised.

Dose intensity (total dose delivered i.e. two 20 mg infusions per dose) will be summarized using mean, median, standard deviation, minimum, and maximum.

The number of subjects with dose reductions, dose escalation, dose delays or missed doses will be summarized using frequency and percentages.

2.7.1.2 Lapatinib and capecitabine

The duration of exposure to lapatinib and capecitabine in weeks will be derived as described in [Section 2.1.3.5](#) and will be summarised. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for weeks on study treatment. Moreover, time on study treatment will be categorized in different time periods: ≤ 3 weeks, $>3-6$ weeks, $>6-9$ weeks, $>9-12$ weeks, $>12-24$ weeks, >24 weeks.

The subject's average daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarized. In addition, summary of the population level daily dose will also be provided. In this analysis, a dose on each day for each subject will be treated as an observation and the summary will be based on the dose on each individual day for all subjects.

Dose reductions will be summarised by number of reductions and reasons for reductions. Dose escalations will be summarised by number of escalations and reasons for escalation. Dose interruptions will be summarised by number of interruptions and reasons for the interruptions. The mean, standard deviation, median, minimum, and maximum will be computed for the duration of interruptions. The summaries of dose modifications will be provided only if there is sufficient data.

All the dose reductions, dose escalations, missed doses and dose delays will be listed separately for octreotide, lapatinib and capecitabine.

2.7.2 Adverse events (AEs)

AEs will be graded by the investigator according to the NCI-CTCAE, Version 4.03. Adverse events will be coded to the PT level using Medical Dictionary for Regulatory Activities (MedDRA).

The following adverse event summaries will be produced by treatment group: overview of adverse events and deaths (number and % of subjects who died, any AE, any SAE, any dose reductions/interruptions, AEs related to study treatment, SAEs related to study treatment, AEs leading to treatment discontinuation, AEs requiring additional therapy, AEs leading to withdrawal), AEs by SOC and PT summarized by relationship (all AEs and AEs related to study treatment), SAEs by SOC and PT.

A summary of all AEs that occurred in strictly 5% or higher of all the subjects will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g., event with 4.9% incidence rate should not be included in this table). The summary will be displayed by preferred term (PT) and maximum grade.

The summary will use the following algorithms for counting the subject:

- **Preferred term row:** Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row:** Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

These summaries are displayed in descending order of Octreotide+Lap+Cap group by SOC and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as “Yes”. A worst case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study treatment as ‘Yes’ or missing. The summary table will be displayed in descending order of Octreotide+Lap+Cap group by SOC and PT

A listing for all AEs will be provided including seriousness, relatedness, action taken.

2.7.3 Adverse Events of Special Interest

Adverse events of special interest are:

- diarrhoea,
- hepatobiliary events
- cardiac events

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the SRT agreements in place at the time of reporting.

Summaries of the number and percentage of subjects with these events of special interest will be provided for each type of event separately by SOC and PT.

The worst case approach will be applied at subject level for the event outcome and maximum grade, i.e. a subject will only be counted once as the worst case from all the events experienced by the subject.

In addition, AEs of special interest will be listed separately.

2.7.4 Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process.

Separate summaries for on-treatment and all deaths (on-treatment and post-treatment) will be produced. All deaths will be summarized by treatment arm and primary cause of death. All deaths will be listed, post treatment deaths will be flagged.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related SAEs. The summary tables will be displayed in descending order of Octreotide+Lap+Cap group by SOC and PT.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as “Yes”. A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as ‘Yes’ or missing.

SAEs are included in the listing of all adverse events with flag for fatal AEs.

2.7.5 Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study

The following categories of AEs will be summarized separately in descending order of Octreotide+Lap+Cap group by SOC and PT and separate supportive listings will be generated with subject level details for those subjects:

- AEs leading to discontinuation of octreotide
- AEs leading to discontinuation of lapatinib
- AEs leading to discontinuation of capecitabine
- AEs leading to withdrawal from the study

2.7.6 Clinical Trial Safety Disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.7 Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

2.7.8 Clinical Laboratory Evaluations

The assessment of laboratory toxicities will examine the following laboratory tests:

Hematology:

- Hemoglobin (HGB),
- Hematocrit (HCT),
- Red Blood Cell (RBC) count,
- White Blood Cell (WBC) count,
- Total Neutrophils,
- Lymphocyte count
- Monocytes
- Eosinophils
- Basophils
- Platelet count.

Hematocrit, monocytes, eosinophils, basophils and RBC are not gradable by NCI-CTCAE v4.03.

Clinical Chemistry:

- Sodium,
- Potassium,
- Ionised Calcium,
- Glucose,
- Urea/Blood Urea Nitrogen (BUN)
- Creatinine,
- Estimated Creatinine Clearance,
- Albumin,
- Total Protein

Estimated Creatinine Clearance and Total Protein are not gradable by CTCAE v4.03. For Sodium, Potassium, Ionised Calcium and Glucose there will be two bi-directional parameters (hyper and hypo) created, and the tests will be graded by NCI-CTCAE v4.03 in both directions.

Liver Function Tests (LFT):

- Aspartateaminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Total bilirubin (total)

- Direct bilirubin.

All these tests are gradable by NCI-CTCAE v4.03.

Coagulation Tests:

- Prothrombin time (PT)
- International Normalized Ratio (INR)
- Activated partial thromboplastin time (APTT).

INR and APTT are gradable by NCI-CTCAE v4.03 and PT is not.

Urinalysis:

Dipstick urinalysis; if dipstick urinalysis showed $\geq 2+$ urine protein, then a 24-hour urine protein must be assessed. It is not gradable by NCI-CTCAE v4.03.

Laboratory grades will be reported using NCI-CTCAE v4.03.

Summaries of lab data by maximum toxicity grade will be provided.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by NCI-CTCAE v4.03. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by NCI-CTCAE v4.03, summaries of worst case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the “Decrease to Low” categories and the “Increase to High” categories. In addition, the summary will include worst case changes from baseline with respect to normal range by scheduled visits.

Separate summary tables for hematology, chemistry and liver function laboratory tests will be produced.

A supporting listing of laboratory data for subjects with abnormalities of potential clinical concern will be provided. A separate listing of laboratory data with character values will also be provided.

Detailed derivation of baseline assessment is specified in [Section 2.1.3.6](#).

Unless otherwise specified, the denominator in percentage calculation will be based on the number of subjects with non-missing value at each particular visit.

2.7.8.1 Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided.

Possible Hy's law cases are defined as any elevated $ALT > 3 \times ULN$, total bilirubin $\geq 2 \times ULN$ and $ALP < 3 \times ULN$ /missing. Total bilirubin $\geq 2 \times ULN$ can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be $\geq 35\%$ of total bilirubin. $ALP < 3 \times ULN$ /missing means the criteria is satisfied unless the ALP is $\geq 3 \times ULN$ at any time of bilirubin elevation within the 28 days window.

2.7.8.2 Lab values of Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign grades to the relevant laboratory parameters.

For laboratory data which are not listed in the NCI-CTCAE v4.03, a summary of values outside the normal range will be provided.

2.7.9 Other Safety Measures

Unless otherwise specified, the denominator in percentage calculation will be based on the number of subjects in safety set.

Vital Signs

In addition vital signs values will be categorized as follows:

- Systolic BP (mmHg): Grade 0 (< 120), Grade 1 (≥ 120 - < 140), Grade 2 (≥ 140 - < 160) and Grade 3 (≥ 160)
- Diastolic BP (mmHg): Grade 0 (< 80), Grade 1 (≥ 80 - < 90), Grade 2 (≥ 90 - < 100), and Grade 3 (≥ 100)
- Heart rate (beats/min): < 60 , 60-100, and > 100

Summaries of increase in vital signs from the baseline with respect to the categories defined above will be performed. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 at the worst case post-baseline.

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign categories that align with the grades for ‘Sinus bradycardia’, ‘Sinus tachycardia’, ‘Supraventricular tachycardia’, and ‘Ventricular tachycardia’.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Decrease from baseline Heart Rate	Decrease to <60	bpm
Increase from baseline Heart Rate	Increase to >100	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign categories that align with the grades for ‘Hypertension’.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed overall at baseline and at 24 week end.

Listings of abnormal ECG findings will be provided.

LVEF

Absolute and relative change from baseline in LVEF will be summarized at 24 week end. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline.

LVEF results will also be listed with subject level details including absolute/relative change from baseline and abnormal ECHO / MUGA findings.

To identify LVEF values of potential clinical importance, NCI-CTCAE v4.03 will be used to assign categories that align with the grades for ‘Ejection fraction decreased’.

LVEF Parameter	Potential Clinical Importance (PCI) Range	Unit
Relative change from baseline LVEF	≥20 decrease and below LLN	%

Liver Events

For any liver events that occur during the study, the liver event information will be summarized, including

- whether the subject was age 55 or over,
- whether the subject became pregnant,
- whether a liver imaging was normal or not,
- whether a biopsy was taken or not,
- whether there was fasting or significant dietary change,
- whether the subject took any unconventional medications, if yes, timing when the unconventional medications taken (on treatment or after stopping treatment)
- summary statistics for time from first dose to start of liver event
- summary statistics for time from last dose to start of liver event.

If the number of events does not support a summary, then only listings will be produced.

For subjects with multiple events, the first event will be used for the summary tables. All events with subject level details will be displayed in a supporting listing.

2.8 Health outcomes analyses

The health outcome endpoint of this study is subject-reported quality of life.

2.8.1 Health Outcomes Assessments

Quality of life will be assessed using the FACIT-D questionnaire. Patients randomised to receive treatment with octreotide will complete the FACIT-D immediately before receiving the first dose of octreotide. All patients will complete the FACIT-D immediately before the start of treatment with lapatinib and capecitabine, then every three weeks through to withdrawal from the study or the end of the 24 week period of treatment with lapatinib and capecitabine, whichever is sooner.

The FACIT-D (version 4) consists of the FACT-G and a diarrhoea-specific subscale, and measures multidimensional quality of life in patients with cancer. FACT-G includes 27 general questions relating to four subscales: physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing, and the diarrhoea-specific subscale includes 11 questions. Patients assess how true each statement has been for them in the previous 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). Higher scores on the FACIT-D scales indicate a better quality of life. In psychometric testing, the FACT/FACIT system has shown good test-retest reliability and sensitivity to change when compared with ECOG performance status.

The following scores will be calculated, using the standard scoring algorithms and methods to deal with missing data:

- Trial Outcome Index (includes diarrhoea subscale)
- Physical subscale,

- Social/Family subscale,
- Emotional subscale
- Functional Wellbeing subscale,
- FACT-G total,
- FACIT-D total.

A by-patient listing of total scores and each of the 4 subscales will be presented. Each of these 7 scores will be listed by visit and treatment group.

2.9 Interim analysis

It was planned to have one formal interim analysis. The results were reviewed by the independent DMC. Based on the interim analysis DMC meeting (09-Sep-2016) it was recommended to stop the trial for futility.

3 Sample size calculation

3.1 Sample size assumptions

It is planned that a total of 140 subjects will be randomised in a 1:1 ratio i.e. 70 subjects in each treatment group. LAP117314 is an exploratory Phase II study, and the sample size is not based on the number of subjects required to achieve a statistically significant pre-specified reduction in the control incidence of diarrhoea. The sample size for this study was based on considerations of cost and feasibility of completing the trial in a timely manner.

The overall incidence of diarrhoea associated with treatment with lapatinib and capecitabine ranges from less than 40% to more than 80% across a number of studies (see Protocol). Only limited data are available on the incidence of diarrhoea with a severity of Grade 2 or more which can be used as a basis for sample size estimation. It is likely that the implementation of active diarrhoea management guidelines will limit the incidence of more severe diarrhoea which develops as a progression from inadequately treated mild diarrhoea. Therefore, a conservative approach has been taken in LAP117314, and data from study EGF111438, which shows the lowest incidence of diarrhoea with a severity of Grade 2 or more (20%), has been used as the basis for the power calculations. In addition, power calculations have been conducted based on a less conservative approach using data from EGF100151, in which diarrhoea management guidelines were not implemented and in which the incidence of diarrhoea with a severity of Grade 2 or more was 32%.

3.2 Sample Size Sensitivity

Based on the results of EGF111438, an incidence of 20% of Grade 2 or higher diarrhoea is assumed for subjects who receive lapatinib and capecitabine with no prophylactic octreotide. The power for the analysis to detect a reduction in the incidence of Grade 2 or higher diarrhoea from 14% to 8% ranges from 69% to 25%, if the assumed incidence in the control group is 20%, using a one-sided test with an alpha level of 0.025 ([Table 3-1](#)).

Table 3-1 Sensitivity of sample size based on 20% control incidence of Grade 2 or more diarrhoea

Incidence, no prophylactic octreotide	20%	20%	20%	20%	20%
Incidence, prophylactic octreotide	6%	7%	8%	10%	12%
Estimated Statistical Power	69%	61%	53%	37%	25%
Subjects per Treatment group	70	70	70	70	70

Based on the results of EGF100151, an incidence of 32% of Grade 2 or higher diarrhoea is assumed for subjects who receive lapatinib and capecitabine with no prophylactic octreotide. The power for the analysis to detect a reduction in the incidence of Grade 2 or higher diarrhoea from 20% to 12% ranges from 82% to 36%, if the assumed incidence in the control group is 32%, using a one-sided test with an alpha level of 0.025 ([Table 3-2](#)) [Table 3-2](#).

Table 3-2 Sensitivity of sample size based on 32% control incidence of Grade 2 or more diarrhoea

Incidence, no prophylactic octreotide	32%	32%	32%	32%	32%
Incidence, prophylactic octreotide	12%	14%	16%	18%	20%
Estimated Statistical Power	82%	72%	60%	48%	36%
Subjects per Treatment group	70	70	70	70	70

Power calculations were performed using nQuery software version 7.0.

3.3 Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

4 Change to protocol specified analyses

Since final CSR will be an abbreviated CSR, not all endpoints will be analysed. [Table 1-3](#) contains reduced list of endpoints as compared to protocol.

Secondary endpoint Patient reported Diarrhoea Management Diary (DMD) is reported using a listing of patients reporting changes in bowel movements from baseline (frequency and/or consistency), recorded in the DMD.

5 Appendix

5.1 Imputation rules

Octreotide will be administered 7 days before the start of treatment with lapatinib and capecitabine and again 28 days later. The primary endpoint is the reduction of treatment-induced diarrhoea for subjects taking lapatinib and capecitabine over 3 cycles. Subjects withdrawing prior to the end of Cycle 3 of lapatinib and capecitabine will be considered to be non-responders. For responder endpoints, subjects withdrawing before the Cycle 4 assessment, i.e. before completing 3 cycles of treatment with lapatinib and capecitabine, will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

In the event that the study is terminated, all available data will be listed and a review carried out by the study team to assess which statistical analyses are still considered appropriate.

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”.

Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables.

With the exception of date of birth on the Demography analysis dataset and exposure end date on the Exposure analysis dataset, imputed dates will also not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition partial dates may be imputed for ‘slotting’ data to study time periods or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

5.1.1 AE date imputation

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	Start Date	day, month,	No Imputation for completely missing dates

Dataset	Date	Missing Element	Rule
		and year	
		day, month	<ul style="list-style-type: none"> • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: <ul style="list-style-type: none"> ◆ If year of start date = year of study treatment start date then <ul style="list-style-type: none"> - If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. - Else set start date = study treatment start date. ◆ Else set start date = January 1.
		day	<ul style="list-style-type: none"> • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: <ul style="list-style-type: none"> ◆ If month and year of start date = month and year of study treatment start date then <ul style="list-style-type: none"> - If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. - Else set start date = study treatment start date. ◆ Else set start date = 1st of month.
	End Date		No imputation for partial end dates will be performed

5.1.2 Concomitant medication and blood and blood supportive care products

Concomitant medication and blood and blood supportive care products are defined as any medications taken 2 weeks prior to the start of octreotide for subjects randomised to octreotide and 2 weeks prior to the start of lapatinib and capecitabine for subjects randomised to no octreotide.

Impute start and end dates for use in derivation of the reference variables concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but do not permanently store the imputed start and end dates in the analysis datasets. The reference variables will be used to differentiate before, during and after for the concomitant medication or blood or blood supportive care start and end dates. The derived time in relation to treatment variables are not needed for reporting of these data.

Dataset	Date	Missing Element	Rule
Concomitant Medication Blood and Blood Supportive Care Products	Start Date	day, month, and year	No Imputation for completely missing dates
		day, month	<ul style="list-style-type: none"> • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: <ul style="list-style-type: none"> ◆ If year of start date = year of study treatment start date then <ul style="list-style-type: none"> - If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. - Else set start date = study treatment start date. ◆ Else set start date = January 1.
		day	<ul style="list-style-type: none"> • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: <ul style="list-style-type: none"> ◆ If month and year of start date = month and year of study treatment start date then <ul style="list-style-type: none"> - If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. - Else set start date = study treatment start date. ◆ Else set start date = 1st of month.
	End Date	day, month, and year	<ul style="list-style-type: none"> • No Imputation for completely missing dates
		day, month	<ul style="list-style-type: none"> • If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
		day	<ul style="list-style-type: none"> • If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact (MSTONE.LCONTD).)

5.1.3 Other imputations

5.1.3.1 Date of birth

Due to data protection rules, only a subject's year of birth (YOB) can be collected, therefore date of birth (DOB) will be imputed as, 30th June YOB, for the calculation of age in the demography dataset

5.1.3.2 Missing exposure end date imputation

In general, completely missing dates are not imputed. However, subjects completing 24 weeks of lapatinib and capecitabine may still be on lapatinib and capecitabine and so may have missing exposure end dates in their last dosing record. Missing exposure end dates for subjects who are still on lapatinib and capecitabine at the time of analysis will be imputed as the date of the End of Study/Withdrawal visit.

For subjects with missing exposure end dates at the time of data cut-off, i.e. for SRT summaries, the exposure end date will be imputed to be the earliest of: the date of the data cut-off, the date of End of Study/Withdrawal visit, or the death date. The imputed exposure end date will be used to calculate cumulative dose and exposure duration. The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. Imputed exposure end dates will also be stored on the study treatment end date variable.

For subjects who have missing end dates in their last exposure record because they are still on lapatinib and capecitabine, the on-therapy indicator variables (time in relation to lapatinib and capecitabine) are assigned to on-therapy for all records where the 'dataset'.date' is after or on the lapatinib and capecitabine start date.

5.1.3.3 Missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute max [(1 mmm-yyyy), min(last contact date+1 , cutoff date)].
- If both day and month are missing, then impute max [(1 Jan-yyyy, min (last contact date +1, cutoff date)].

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

The NCI-CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. NCI-CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily

proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The NCI-CTCAE grade of 5 (death) is not used; rather, ‘fatal’ is collected as AE outcome and death information is also collected on a separate (e)CRF page.

5.3 Statistical models

5.3.1 Analysis of binary data

Analysis of the proportion difference

The null hypothesis of equal proportion of subjects who have a specific event (e.g., the Grade 2 or higher diarrhoea) in the two treatment group will be tested against one-sided alternative.

The statistical hypotheses are:

$$H_0: \delta = 0 \text{ vs. } H_a: \delta < 0,$$

where δ is the difference in proportions of subjects who have a specific event (e.g., the Grade 2 or higher diarrhoea) between two treatment groups, i.e., $\delta = \pi_1 - \pi_2$, where π_1 and π_2 are proportions of subjects who have a specific event in prophylactic octreotide and no prophylactic octreotide group respectively.

The Pearson chi-square test (implemented via SAS procedure FREQ with CHISQ option in the TABLES statement) will be used to test the difference in proportions of subjects who have a specific event between the treatment groups. The two-sided p-value corresponding to the chi-square test will be used which follows a Chi-square distribution with one degree of freedom. The difference in proportions and its corresponding 95% confidence interval will be estimated by using the Wald method (implemented via SAS procedure FREQ with RISKDIFF option in the TABLES statement).

If the sampling assumptions for chi-square test is not met (i.e., the expected values should exceed 5 for all of the table cells.), the exact Pearson chi-square test will be used (implemented via SAS procedure FREQ with the TABLES statement and a CHISQ option in the EXACT statement) for the estimation of the two-sided p-value. The corresponding 95% confidence interval of the difference of proportions between two groups will be estimated by the exact unconditional confidence limits which will be implemented via SAS procedure FREQ with the TABLES statement and RISKDIFF option in the EXACT statement. The approach of exact unconditional confidence limits estimation eliminates nuisance parameters by maximizing the p-value over all possible values of the nuisance parameters [Santner and Snell 1980].

The SAS syntax is specified as follows:

```
PROC FREQ DATA = <input_dataset>;  
  TABLES <treat_var> * <response>/CHISQ RISKDIFF;  
  EXACT CHISQ RISKDIFF;  
RUN;
```

Confidence interval for response rate

Response rate is defined as the percentage of subjects who have a specific event (e.g., experiencing diarrhoea). The $100(1 - \alpha)\%$ confidence interval of a response rate will be

estimated by using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

The SAS syntax is specified as follows:

```
PROC FREQ DATA = <input_dataset>;  
  BY <treat_var>;  
  TABLES <response>/BINOMIAL (EXACT) ;  
RUN;
```

where treat_var = treatment group
response = response (e.g., diarrhoea)

5.3.2 Analysis of time to events data

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

25th, 50th, and 75th percentile survivals for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized.

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties.

6 Reference

1. Agresti, A. A Survey of Exact Inference for Contingency Tables. *Statistical Science*, 1992; 7(1),131–177.
2. Bernstein L, Anderson J, Pike M. Estimation of the proportional hazard in two-treatment-group clinical trials. *Biometrics*, 1981; 37:513-519.
3. Berry G, Kitchen R, Mock P. A Comparison of two simple hazard ratio estimators based on the Logrank Test. *Statistics in Medicine*, 1991; 10:749-755.
4. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*, 1982; 38:29-41.
5. Carroll KJ. Back to basics: Explaining sample size in outcome trials, are statisticians doing a thorough job? *Pharmaceutical Statistics*, 2009; 8(4):333-345.
6. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrical*, 26, 404-413.
7. Santner, T. J. and Snell, M. K., Small-Sample Confidence Intervals for p_1-p_2 and p_1/p_2 in 2 X 2 Contingency Tables. *Journal of the American Statistical Association*, (1980; 75, 386–394.

8. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 1987; 15(6):657-80.
9. Hollander M, Wolfe DA. *Nonparametric Statistical Methods*. 2nd ed. New York: John Wiley & Sons; 1999.