

## TITLE PAGE

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**Information Type:** Protocol Amendment

<b>Title:</b>	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
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<p>In Amendment 01:</p> <ul style="list-style-type: none"> <li>• Prior treatment with lapatinib was added as an exclusion criterion;</li> <li>• Additional detail was provided for dermatological monitoring;</li> <li>• Secondary endpoints related to patient reported outcomes were updated;</li> <li>• The schedule for completion of the Diarrhoea Management Diary and FACIT-D was clarified;</li> <li>• The schedule of study visits relative to the week numbers and cycles of treatment with lapatinib and capecitabine was clarified;</li> <li>• The use of octreotide s.c. within the diarrhoea management guidelines was clarified.</li> </ul>		
2012N152651_02	2014-AUG-23	Republishing Amendment 1
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<p>In Amendment 02:</p> <ul style="list-style-type: none"> <li>• Details of planned interim analysis included in Protocol Summary, Study Assessments, for early assessment of the primary endpoint.</li> <li>• Recruitment Plan Section was included as an interim analysis was being incorporated.</li> <li>• Blinding Section was updated with further clarification to support addition of an interim analysis.</li> <li>• Number of subjects undergoing formal review of safety data was updated to reflect consistency with planned interim analysis.</li> <li>• Details of tertiary Sponsor Medical Monitor Contact Information added. Author list, Sponsor Signatory, address and telephone numbers of medical monitors updated</li> <li>• Instructive text presented in Appendix for Country Specific Requirements deleted.</li> <li>• Statement regarding application of amendment 01 to all participating sites added to improve the quality of the protocol.</li> </ul>		

**SPONSOR SIGNATORY**

\_\_\_\_\_  
[REDACTED], DO, [REDACTED]

\_\_\_\_\_  
Date

## SPONSOR INFORMATION PAGE

Clinical Study Identifier: LAP117314

### Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited  
980 Great West Road  
Brentford  
Middlesex, TW8 9GS  
UK

### Sponsor Contact Address

GlaxoSmithKline Research & Development Limited  
Stockley Park West,  
1-3 Iron Bridge Road,  
Uxbridge,  
Middlesex, UB11 1BU  
UK

Telephone: [REDACTED]

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

### Sponsor Medical Monitor Contact Information

[REDACTED], MD  
[REDACTED]  
Novartis Farmaceutica S. A., Madrid Site

Office: [REDACTED]  
Mobile: [REDACTED]  
e mail: [REDACTED]

### Sponsor Secondary Medical Monitor Contact Information:

[REDACTED], MD  
[REDACTED]  
Novartis Farma S. p. A.

Office: [REDACTED]  
Mobile: [REDACTED]  
e mail: [REDACTED]

**Sponsor Tertiary Medical Monitor Contact Information:**

[REDACTED]

Novartis Pharmaceuticals

Office: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

**Principal Investigator Information:**

Professor [REDACTED] MD PhD

[REDACTED]

Professor [REDACTED] BSc, D.Phil, [REDACTED]

[REDACTED]

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**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number LAP117314

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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## LIST OF ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	(the) American Society of Clinical Oncology
AST	Aspartate aminotransferase
CBR	Clinical benefit response
CI	Confidence interval
CR	Complete response
(e)CRF	(Electronic) Case report form
DMD	Diarrhoea Management Diary
DSS	Diarrhoea symptom subscale
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EWB	Emotional wellbeing
FACIT-D	Functional Assessment of Chronic Illness Therapy-Diarrhoea
FACT-G	Functional Assessment of Cancer Therapy-General
5-FU	5 Fluorouracil
FWB	Functional wellbeing
GCP	Good clinical practice
GSK	GlaxoSmithKline
hCG	Human chorionic gonadotrophin
HER2	Human epidermal growth factor receptor 2
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention to treat
IVR	Interactive voice response
LAR	Long acting release
LLN	Lower limit of the normal range
LTFU	Long term follow up
MBC	Metastatic breast cancer
m-ITT	Modified intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NE	Not evaluable
ORR	Overall response rate
PD	Progressive disease
PFS	Progression free survival
█	█

PP	Per protocol
PR	Partial response
PRO	Patient-reported outcome
PWB	Physical wellbeing
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Stable disease
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SPM	Study Procedures Manual
SRT	Safety Review Team
SWB	Social wellbeing
ULN	Upper limit of the normal range
VIP	Vasoactive intestinal polypeptide

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## PROTOCOL SUMMARY

### Rationale

The combination of lapatinib with capecitabine is approved for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer which has progressed following prior therapy, which must have included anthracyclines and taxanes and trastuzumab in the metastatic setting.

Diarrhoea is a common adverse event (AE) reported in studies of both lapatinib and capecitabine. Diarrhoea associated with cancer treatment is usually managed reactively, and standardised guidelines have been developed by the American Society of Clinical Oncology (ASCO); these guidelines have been modified by GlaxoSmithKline (GSK) for the management of diarrhoea associated with lapatinib use. Most episodes of diarrhoea reported in studies of lapatinib were mild to moderate in severity and uncomplicated, and were managed by dietary modification and by the use of loperamide, which is the first line approach recommended in both the ASCO and GSK diarrhoea management guidelines.

Octreotide is approved for the treatment of the severe diarrhoea and flushing episodes associated with metastatic carcinoid tumors and for the treatment of diarrhoea associated with vasoactive intestinal polypeptide-secreting tumours. Octreotide is effective in the treatment of diarrhoea associated with a number of conditions including carcinoid syndrome, short-bowel syndrome, and dumping syndrome. Octreotide provides effective control of chemotherapy-associated diarrhoea. Octreotide is also effective in the management of chemotherapy-associated diarrhoea which is unresponsive to treatment with loperamide, and is included as a second line agent in the ASCO and GSK guidelines for the management of more persistent diarrhoea.

Octreotide is available as a short acting formulation for subcutaneous injection, usually given three times daily, and as a long acting release (LAR) depot formulation for intramuscular injection, to be given once every 28 days. Treatment with octreotide is generally well tolerated, and the benefits and risks associated with the use of octreotide in its approved indications are described in the Octreotide SPC and the Octreotide LAR SPC. Gastrointestinal AEs are common, and include both diarrhoea and constipation. Adverse events related to the mechanism of action of octreotide have also been reported, including hyperglycaemia, hypoglycaemia, impaired glucose tolerance, hypothyroidism, thyroid dysfunction and cholelithiasis. However, these mechanism-related AEs are more usually associated with longer term treatment.

Diarrhoea associated with cancer therapy may affect the patients' sense of wellbeing and can result in treatment interruption or dose reduction, potentially reducing the therapeutic benefit of the cancer treatment. The frequency and severity of diarrhoea associated with cancer treatment has been extensively evaluated in clinical studies, but it is not known how accurately these data reflect the occurrence of diarrhoea in the wider patient population. It is also possible that diarrhoea is under-reported within the context of a clinical study, and that the effects of diarrhoea on patient wellbeing may not be reflected in the investigator-reported outcomes recorded in a clinical study. Furthermore it is

likely that diarrhoea might affect treatment compliance, which is known to be sub-optimal with many oral anti-cancer treatments, and episodes of diarrhoea might adversely influence the acceptability of subsequent cycles of treatment.

The prevention of diarrhoea associated with cancer treatment has the potential to benefit patients by reducing the frequency and severity of adverse events, improving patients' sense of wellbeing and improving treatment compliance. The efficacy of loperamide and octreotide in the treatment of chemotherapy-associated diarrhoea is established and has been included in the diarrhoea management guidelines developed by ASCO and by GSK. However, few studies have evaluated the efficacy of prophylactic loperamide or octreotide in the prevention of cancer treatment-associated diarrhoea, and no well controlled large studies have been conducted. The results of the few studies which have been reported are equivocal.

LAP117314 is an open label, randomised study to explore the potential benefit of the prophylactic use of octreotide in the prevention or reduction of diarrhoea associated with treatment with lapatinib and capecitabine. The primary endpoint of the study is investigator-reported diarrhoea with a severity of Grade 2 and above, as defined by the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE), version 4.03. The definition of AEs in accordance with the NCI CTCAE criteria is consistent with the definitions used in previous studies of lapatinib in combination with capecitabine. Diarrhoea with a severity of Grade 2 or more has a significant effect on the tolerability of treatment, the acceptability of continued treatment, and the subject's sense of wellbeing. Management of Grade 2 diarrhoea includes treatment interruption for capecitabine when the first episode occurs, and treatment interruption for lapatinib after the second episode. Secondary endpoints include other aspects of the frequency and severity of diarrhoea of all grades of severity and of the consequences and management of diarrhoea, which will be recorded by the investigator using standard methodology and also by patient reported outcome (PRO) measures in the study-specific Diarrhoea Management Diary (DMD) and in the Functional Assessment of Chronic Illness Therapy-Diarrhoea (FACIT-D). Inclusion of PROs in this study provides an opportunity to contrast and compare outcomes reported by investigators and by subjects within each treatment group, although differences between the electronic Case Report Form (eCRF) data and the PRO data will preclude formal comparisons. Disease progression measured as overall response rate and clinical benefit response is a secondary endpoint.

The prevention of diarrhoea associated with cancer treatment has the potential to improve treatment compliance and to improve the patients' sense of wellbeing. LAP117314 will evaluate the efficacy of the prophylactic use of octreotide in the prevention or reduction of diarrhoea associated with treatment with lapatinib and capecitabine.

## **Objectives**

The primary objective of this study will be to evaluate the efficacy of octreotide prophylaxis in reducing the proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above, as defined by the NCI CTCAE, version 4.03.

The secondary objectives will be to determine the efficacy of octreotide prophylaxis in reducing:

- the proportion of subjects experiencing diarrhoea with a severity of Grade 3 and above;
- the proportion of subjects experiencing at least one episode of diarrhoea of each grade of severity;
- the time to onset of the first episode of diarrhoea of any grade of severity;
- the duration of each episode of diarrhoea of any grade of severity;
- the proportion of subjects taking medication as a result of diarrhoea;
- the proportion of subjects making dietary changes to manage diarrhoea (PRO only);
- the proportion of subjects making unscheduled visits to healthcare professionals as a result of diarrhoea;
- the proportion of subjects making or requiring changes to treatment with lapatinib and capecitabine (missed doses, dose delays, dose reductions and treatment withdrawal) as a result of diarrhoea;
- the proportion of subjects requiring treatment with intravenous fluids as a result of diarrhoea;

and to determine the effect of octreotide prophylaxis on:

- compliance with treatment with lapatinib and capecitabine;
- treatment efficacy (overall response rate and clinical benefit response);
- quality of life;
- overall safety and tolerability of treatment with lapatinib and capecitabine.

Data will be recorded by the investigators in the eCRF at each study visit, and by subjects in the DMD every week and in the FACIT-D every 3 weeks. The eCRF, DMD and FACIT-D are considered to be independent sources of study data, and investigators **must not** use information collected in the DMD and FACIT-D to supplement data entry into the eCRF.



## Study Design

This is a randomised, parallel group, 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 advanced or metastatic breast cancer. This study is not placebo controlled, and there is no active comparator.

The study will enroll 140 women with histologically or cytologically confirmed HER2-positive advanced or metastatic breast cancer which has progressed following prior therapy, which must have included anthracyclines and taxanes and trastuzumab in the metastatic setting. LAP117314 is an exploratory Phase II study, and the sample size is not based on the number of subjects required to achieve a pre-specified reduction in the control incidence of diarrhoea. All subjects will receive treatment with lapatinib 1250mg once daily and capecitabine 1000mg/m<sup>2</sup> twice daily. The study duration is 24 weeks, but subjects will receive treatment with lapatinib and capecitabine 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. This treatment regimen and the subject population are consistent with the approved indication for the use of lapatinib with capecitabine in patients with advanced or metastatic breast cancer. Dose modification, treatment interruption and withdrawal from study treatment will be in accordance with the [Lapatinib SPC](#) and [Capecitabine SPC](#).

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

- Octreotide (Sandostatin LAR) 40mg 7 days before the start of treatment with lapatinib and capecitabine and again 28 days later, or
- No octreotide treatment.

Subjects randomised to receive octreotide LAR will be given octreotide 0.1mg in the subcutaneous (s.c.) formulation at least one hour before the first dose of octreotide in the LAR formulation is administered, to assess the tolerability of octreotide. 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.

The study subject population and the dosage regimen for lapatinib and capecitabine are consistent with the approved indication for the use of this combination in patients with metastatic breast cancer (MBC). The benefits and risks associated with lapatinib and capecitabine treatment in this study are presented in the Lapatinib SPC. Treatment with octreotide in this study is not consistent with the approved indications for octreotide.

## Study Assessments

The primary endpoint of LAP117314 is the proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above, as defined by the NCI CTCAE, version 4.03. The frequency and severity of episodes of diarrhoea will be recorded at each visit, by completion of the AE modules in the eCRF. Action taken as a result of diarrhoea (anti-diarrhoeal medication, unscheduled visits to healthcare professionals, dose reduction or

delay in treatment with lapatinib and capecitabine, treatment withdrawal, and intravenous fluid rehydration) will be recorded in the eCRF at each visit.

All subjects will complete the baseline DMD and FACIT-D during the 3 days prior to randomisation, before any study-related treatment is administered. Subjects randomised to receive octreotide will complete a second baseline DMD and FACIT-D before starting the first cycle of treatment with lapatinib and capecitabine. Subjects will then complete the DMD every week and the FACIT-D every 3 weeks until the end of 24 weeks of treatment with lapatinib and capecitabine or subject withdrawal, whichever is sooner. The DMD and FACIT-D will not be completed beyond 24 weeks of treatment.

Disease status will be assessed prior to the start of treatment with lapatinib and capecitabine in accordance with the Response Evaluation Criteria In Solid Tumours (RECIST), version 1.1. Disease progression will be evaluated by the investigator in accordance with local clinical practice during the course of treatment with lapatinib and capecitabine, and in accordance with RECIST version 1.1 at the end of study visit (subject withdrawal or at the end of 24 weeks of treatment with lapatinib and capecitabine, whichever is sooner). Treatment with lapatinib and capecitabine may continue beyond 24 weeks until disease progression occurs, but there will be no further data collection of disease progression beyond 24 weeks of treatment.

The safety and tolerability of treatment with octreotide, lapatinib and capecitabine will be evaluated by AE and serious AE reporting at each visit until subject withdrawal or the end of 24 weeks of treatment with lapatinib and capecitabine. Serious AEs and other specific safety assessments will be reported in subjects who continue treatment with lapatinib and capecitabine beyond 24 weeks. Serious AEs will be followed up until resolution or stabilisation of the event or until the subject is lost to follow-up.

All subjects with episodes of diarrhoea will be encouraged to follow the GSK diarrhoea management guidelines for subjects receiving lapatinib. The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range.

Cardiac function will be evaluated prior to the start of treatment, in accordance with the Lapatinib SPC. Physical examination findings, vital signs, clinical laboratory tests, clinical monitoring and observations will be reported at the start of the study in accordance with the protocol baseline and screening requirements, during the course of the study in accordance with local clinical practice and the requirements of the Lapatinib, Capecitabine and Octreotide SPCs, and at subject withdrawal or after 24 weeks of treatment with lapatinib and capecitabine, whichever is sooner, in accordance with the protocol. Dermatological monitoring and assessment will be conducted in accordance with the guidance provided in the Lapatinib SPC.



A GSK Safety Review Team will review safety data on an ongoing basis and at pre-defined points during the course of the study to protect the interests of subjects and to ensure their safety.

An interim analysis is planned when approximately 40% of the patients have been recruited and when those subjects have received 3 cycles of study treatment (lapatinib plus capecitabine), i.e. after 9 weeks of study treatment. The first safety review will take place at the same time as the interim analysis.

## 1. INTRODUCTION

### 1.1. Background

Breast cancer is the most common form of cancer in women in the USA and in Europe [[American Cancer Society](#), 2013; [Ferlay](#), 2013]. In the USA, there were more than 230,000 new cases of invasive breast cancer and over 39,000 deaths from breast cancer in 2011 [[American Cancer Society](#), 2013]. In Europe, there were an estimated 464,000 new cases and approximately 131,000 deaths from breast cancer in 2012 [[Ferlay](#), 2013].

Lapatinib is a reversible, orally active tyrosine kinase inhibitor that potently inhibits both epidermal growth factor receptor 1 (EGFR) and human epidermal growth factor receptor 2 (HER2) [[Lapatinib SPC](#)]. Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU) [[Capecitabine SPC](#)]. Lapatinib is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2, in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

The efficacy of lapatinib with capecitabine in subjects with metastatic breast cancer (MBC) was demonstrated in the registration study EGF100151, which compared the efficacy and tolerability of lapatinib with capecitabine to that of capecitabine alone [[Cameron](#), 2008]. The efficacy of lapatinib with capecitabine was greater than that of capecitabine alone with respect to time to progression (the interval between the date of randomisation and the earliest date of disease progression or death due to breast cancer), progression free survival (PFS; the time from randomisation until the earliest date of either disease progression or death due to any cause), response rate (the percentage of subjects achieving either a complete or partial tumour response) and clinical benefit response (the percentage of subjects with evidence of complete or partial tumor response or stable disease for at least 6 months; [Table 1](#)). Similar efficacy was shown for the combination of lapatinib with capecitabine in 271 subjects in a subsequent study, EGF111438 [GlaxoSmithKline Document Number [2012N144830\\_00](#)], in which the median duration of PFS was 6.60 months (95% confidence interval [CI]: 5.72-8.11 months), equivalent to 28.6 weeks (95% CI: 24.8-35.1 weeks).

**Table 1 EGF100151: Summary of efficacy (ITT Population)**

	<b>Lapatinib with capecitabine (n=198)</b>	<b>Capecitabine monotherapy (n=201)</b>	<b>Hazard ratio</b>	<b>p</b>
Time to disease progression, weeks (95% CI); Independent review	27.1	18.6	0.57 (0.43-0.77)	0.00013
Time to disease progression, weeks (95% CI) Investigator assessed	23.9	18.3	0.72 (0.56-0.92)	0.00762
Progression free survival, weeks (95% CI)	27.1 (24.1-36.9)	17.6 (13.3-20.1)	0.55 (0.41-0.74)	0.000033
			<b>Odds ratio</b>	
Response rate, % (95% CI) Independent review	23.7 (18.0-30.3)	13.9 (9.5-19.5)	1.9 (1.1-3.4)	0.017
Response rate, % (95% CI) Investigator assessed	31.8 (25.4-38.8)	17.4 (12.4-23.4)	2.2 (1.3-3.6)	0.002
Clinical benefit response, % (95% CI) Independent review	29	17	2.0 (1.2-3.3)	0.008
Clinical benefit response, % (95% CI) Investigator assessed	37	21		0.001

CI=confidence interval; ITT=Intention to treat; p=probability

The most common adverse events (AE) reported during treatment in EGF100151 were gastrointestinal (diarrhoea, nausea, and vomiting) or dermatologic (palmer plantar erythrodysesthesia and rash); most were [National Cancer Institute](#) common terminology criteria for adverse events (NCI-CTCAE) Grade 1 or 2 and were controlled by standard therapy. Published EGF100151 data [[Cameron, 2008](#)] are based on a safety population of 198 subjects who received treatment with lapatinib and capecitabine. Diarrhoea was reported by 65% of subjects overall, and diarrhoea with a severity of Grade 2 or more was reported by 34% of subjects.

Gastrointestinal and dermatological AEs in a later analysis of data based on 210 subjects who received lapatinib with capecitabine in EGF100151 are summarised in [Table 2](#). These data are taken from the EGF100151 clinical study report [GlaxoSmithKline Document Number [UM2004/00001/00](#)] and are cited in the Lapatinib Investigator's Brochure [Lapatinib Investigator's Brochure GlaxoSmithKline Document Number [RM2000/00481/12](#), 2013].

**Table 2 EGF100151: Summary of gastrointestinal and dermatological adverse events in subjects who received lapatinib with capecitabine (Safety Population; N=210)**

Lapatinib + Capecitabine Arm (N=210); n (%)						
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	TOTAL
Diarrhoea	64 (30)	48 (23)	31 (15)	2 (<1)	0	145 (69)
PPE	27 (13)	67 (32)	36 (17)	0	0	130 (62)
Nausea	62 (30)	31 (15)	5 (2)	0	0	98 (47)
Vomiting	36 (17)	22 (10)	5 (2)	0	0	63 (30)
Rash	41 (20)	18 (9)	2 (<1)	0	0	61 (29)
Decreased Appetite	31 (15)	12 (6)	1 (<1)	0	0	44 (21)
Stomatitis	25 (12)	12 (6)	0	0	0	37 (18)
Mucosal Inflammation	23 (11)	10 (5)	0	0	0	33 (16)
Abdominal Pain	18 (9)	10 (5)	3 (1)	0	0	31 (18)
Constipation	20 (10)	4 (2)	0	0	0	24 (11)
Dyspepsia	15 (7)	8 (4)	1 (<1)	0	0	24 (11)
Dry Skin	22 (10)	1 (<1)	0	0	0	23 (11)
Upper Abdominal Pain	11 (5)	9 (4)	0	0	0	20 (10)

PPE = Palmer plantar erythrodysesthesia

In EGF100151, diarrhoea was reported as a serious AE (SAE) in 15 subjects (7%) who received lapatinib with capecitabine and in 12 subjects (6%) who received capecitabine monotherapy [GlaxoSmithKline Document Number [UM2004/00001/00](#)]. Overall, episodes of diarrhoea were well managed, and only 9 subjects (5%) who received lapatinib with capecitabine and 5 subjects (3%) who received capecitabine monotherapy were withdrawn from study treatment due to diarrhoea.

Diarrhoea was reported by 121 subjects (45%) who received lapatinib with capecitabine in EGF111438 [GlaxoSmithKline Document Number [2012N144830\\_00](#)]. The majority of events were Grade 1 or 2, and were considered related to study medication ([Table 3](#)). Diarrhoea was reported as a SAE in 3 subjects (1%) and 1 subject (<1%) was withdrawn from study treatment due to diarrhoea.

**Table 3 EGF111438: Gastrointestinal adverse events occurring in at least 10% of subjects who received lapatinib with capecitabine (Safety Population, N=269)**

<b>Adverse event</b>	<b>Total n (%)</b>	<b>Treatment related</b>	<b>Grade 3 or 4</b>
Diarrhoea	121 (45)	116 (43)	16 (6)
Nausea	78 (29)	68 (25)	3 (1)
Vomiting	33 (12)	29 (11)	4 (1)
Decreased appetite	27 (10)	20 (7)	0

Most subjects in EGF111438 reported only one episode of diarrhoea. The median time to onset of the first episode of diarrhoea in EGF111438 was 12 days, and the median duration of the first episode of diarrhoea was 6 days. Treatment was interrupted in 16 subjects due to diarrhoea ([Table 4](#)).

**Table 4 EGF111438: Summary of characteristics of diarrhoea in subjects who received lapatinib with capecitabine (Safety Population; subjects who reported diarrhoea, N=121)**

	n (%)
<b>Number of occurrences</b>	
One	64 (53)
Two	23 (19)
Three or more	34 (28)
<b>Maximum Severity</b>	
Grade 1	67 (55)
Grade 2	38 (31)
Grade 3 or 4	16 (13)
<b>Number of study treatment interruptions</b>	
One	16 (13)
Two	1 (<1)
Three or more	2 (<1)
<b>Time to onset of diarrhoea (days)</b>	
1-14	67 (55)
15-28	22 (18)
>28	32 (26)
Mean (SD)	28.6 (55.30)
Median (Min-Max)	12.0 (1-411)
<b>Duration (days)</b>	
Number of subjects	113
1-5	53 (47)
6-10	16 (14)
>10	44 (39)
Mean (SD)	23.8 (43.01)
Median (Min-Max)	6.0 (1-253)

Duration is unknown for some events as not all were resolved

EGF100151 and EGF111438 are the only large studies which provide data on the incidence of diarrhoea with a severity of Grade 2 or more. The incidence of Grade 2 or more diarrhoea differs between these studies and also between subsequent analyses of data from EGF100151; 20% in EGF111438, 33% in EGF100151 based on 164 subjects [Geyer, 2006], 34% in EGF100151 based on 198 subjects [Cameron, 2008] and 39% in EGF100151 based on 210 subjects [GlaxoSmithKline Document Number UM2004/00001/00], possibly reflecting an increasing incidence of diarrhoea with a later onset as the duration of treatment within the study increases. Four additional

GlaxoSmithKline (GSK) studies (EGF105084, EGF107671, EGF109491 and EGF109749) [Lapatinib Investigator's Brochure, GlaxoSmithKline Document Number [RM2000/00481/12](#), 2013] and the LANDSCAPE study [[Bachelot](#), 2013] together report the incidence of diarrhoea associated with treatment with lapatinib and capecitabine in a total of 212 subjects. The EMILIA study [[Verma](#), 2012] reports the incidence of diarrhoea in 488 subjects who received treatment with lapatinib and capecitabine, but the incidence of diarrhoea with a severity of Grade 2 or more is not presented. The overall incidence of diarrhoea associated with treatment with lapatinib and capecitabine in these studies ranges from less than 40% to more than 80%. This variability may be due to a number of factors, such as differences in study populations, study durations, and implementation of active diarrhoea management guidelines.

Diarrhoea is a recognised adverse event associated with cancer treatment. Diarrhoea may affect the patients' sense of wellbeing and can result in treatment interruption or dose reduction, potentially reducing the therapeutic benefit of the cancer treatment. In rare cases, diarrhoea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency or electrolyte imbalances.

Diarrhoea should be managed actively during cancer treatment to avoid complications or worsening of the subject's condition. Standardised guidelines for treating chemotherapy-associated diarrhoea have been developed by ASCO [[Benson](#), 2004] and these guidelines have been modified by GSK for the management of diarrhoea associated with lapatinib use ([Appendix 1](#)). In general, mild to moderate diarrhoea can be managed by dietary modification and by the use of loperamide, which is the first line approach recommended in both the ASCO and GSK diarrhoea management guidelines.

Octreotide is included as a second line treatment in the ASCO and GSK diarrhoea management guidelines, for the management of more persistent diarrhoea which is refractory to treatment with loperamide and dietary modification. Octreotide is a cyclic octapeptide analogue of the natural hormone somatostatin. It has similar pharmacological properties to those of somatostatin, but has a longer duration of action than somatostatin. Octreotide is available as a solution for subcutaneous (s.c.) injection, usually given three times daily, and is approved for the treatment of symptoms associated with gastroenteropancreatic tumours, including carcinoid tumours with features of carcinoid syndrome, vasoactive intestinal polypeptide (VIP)-secreting tumours and glucagonomas [[Octreotide SPC](#)]. Octreotide is also available as a depot formulation (Sandostatin long acting release [LAR]) to be given by deep intramuscular injection once every 28 days, which is approved for use in patients in whom initial treatment with octreotide in the formulation for s.c. injection has been shown to be effective and well tolerated, for the long-term treatment of the severe diarrhoea and flushing episodes associated with metastatic carcinoid tumors and the long-term treatment of the profuse watery diarrhoea associated with VIP-secreting tumours [[Octreotide LAR SPC](#)].

Treatment with octreotide is generally well tolerated. Gastrointestinal AEs are common; diarrhoea, abdominal pain, nausea, constipation, flatulence, dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools and discolouration of faeces have been reported in clinical studies. Other AEs related to the mechanism of action of octreotide have also been reported, including hyperglycaemia, hypoglycaemia, impaired glucose

tolerance, hypothyroidism, thyroid dysfunction and cholelithiasis, but these mechanism-related AEs tend to be associated with chronic treatment with octreotide [[Octreotide SPC](#)].

Octreotide given by s.c. injection was effective in the control of diarrhoea associated with a number of conditions including carcinoid syndrome [[Kvols, 1986](#)], short-bowel syndrome [[Cooper, 1986](#)] and dumping syndrome [[Santangelo, 1987](#)]. Octreotide also provided effective control of diarrhoea associated with treatment with 5-FU [[Cascinu, 1993](#); [Gebbia, 1993](#) [Goumas, 1998](#); [Nikou, 1994](#); [Topkan, 2006](#); [Zidan, 2001](#)] and pelvic radiation therapy [[Yavuz, 2002](#)].

Octreotide 20mg LAR given once every 28 days by deep intramuscular injection was as effective as the s.c. formulation given three times daily in controlling the symptoms of carcinoid syndrome [[Rubin, 1999](#)], and in a summary of 11 case studies of patients with advanced cancer octreotide 30mg LAR provided complete resolution of severe diarrhoea which had not responded to treatment with loperamide and diphenoxylate-atropine [[Rosenhoff, 2004](#)].

Diarrhoea associated with cancer therapy may affect the patients' sense of wellbeing and can result in treatment interruption or dose reduction, potentially reducing the therapeutic benefit of the cancer treatment. The frequency and severity of diarrhoea associated with cancer treatment has been extensively evaluated in clinical studies, but it is not known how accurately these data reflect the occurrence of diarrhoea in the wider patient population. It is possible that diarrhoea is under-reported within the context of a clinical study, and that the effects of diarrhoea on patient wellbeing may not be reflected in the investigator-reported outcomes recorded in a clinical study [[Basch, 2010](#)]. Furthermore it is likely that diarrhoea might affect treatment compliance, which is known to be sub-optimal with many oral anti-cancer treatments [[Ruddy, 2009](#)], and episodes of diarrhoea might adversely influence the acceptability of subsequent cycles of treatment. Prophylactic treatment to prevent cancer treatment-associated diarrhoea has the potential to improve the overall tolerability of treatment and to improve treatment compliance. These effects together could improve treatment efficacy by reducing the frequency of treatment dose reductions and treatment interruptions.

Loperamide is recommended as a first-line agent for the treatment of chemotherapy-associated diarrhoea [[Benson, 2004](#)], and could be considered as a first choice agent for prophylactic management of cancer treatment-associated diarrhoea. Loperamide is inexpensive and is provided as a tablet formulation, and is therefore easy to self-administer. However, there are no published data from studies evaluating the efficacy of prophylactic loperamide in the prevention of cancer treatment-associated diarrhoea. In a small study to explore the efficacy and tolerability of lapatinib in combination with trastuzumab and paclitaxel, EGF104383, subjects received various combinations of dosages of these agents ([Table 5](#)), and prophylactic treatment with loperamide was included for subjects in treatment cohorts 2 and 3 [EGF104383 Clinical study report; GlaxoSmithKline Document Number [HM2009/00365/00](#)].

**Table 5 Treatment regimens in EGF104383**

	<b>Paclitaxel</b>	<b>Trastuzumab</b>	<b>Lapatinib</b>
<b>Cohort 1</b>	80mg/m <sup>2</sup> IV weekly for 3 weeks of a 4 week cycle	4 mg/kg IV loading dose and 2 mg/kg IV weekly	1000 mg PO daily
<b>Cohort 2</b>	70mg/m <sup>2</sup> IV weekly for 3 weeks of a 4 week cycle <sup>a</sup>	4 mg/kg IV loading dose and 2 mg/kg IV weekly	1000 mg PO daily
<b>Cohort 3</b>	80mg/m <sup>2</sup> IV weekly for 3 weeks of a 4 week cycle	4 mg/kg IV loading dose and 2 mg/kg IV weekly	750 mg PO daily <sup>b</sup>

a. Paclitaxel dose was to be systematically increased to 80 mg/m<sup>2</sup> after 2 cycles if 70mg/m<sup>2</sup> was tolerated

b. Lapatinib dose was to be systematically increased to 1000 mg after 2 cycles if 750mg was tolerated.

Overall, diarrhoea was reported by 28 subjects (97%) in cohort 1, 13 subjects (94%) in cohort 2 and 13 subjects (65%) in cohort3, which suggested that prophylactic treatment with loperamide had little effect on diarrhoea associated with this treatment regimen. Interpretation of data within this study was complicated by differences in treatment dosages of lapatinib and paclitaxel used in each cohort, and also by differences in the duration of follow up, which was shorter for subjects in cohort 3. However, there was an apparent trend towards less frequent and less severe diarrhoea in subjects in cohort 2 and cohort 3 who received prophylactic treatment with loperamide ([Table 6](#)).

**Table 6 Characteristics of diarrhoea adverse events in EGF104383**

	<b>Cohort 1 80/1000 N=29</b>	<b>Cohort 2 70/1000 N=14</b>	<b>Cohort 3 80/750 N=20</b>
Number of subjects with diarrhoea events; n (%)	28 (97)	13 (93)	13 (65)
Total number of diarrhoea events	358	90	37
Number of events per subject; n (%)	n=28	n=13	n=13
1	4 (14)	3 (23)	4 (31)
2	2 (7)	2 (15)	2 (15)
3 or more	22 (79)	8 (62)	7 (54)
Maximum severity; n (%)	n=28	n=13	n=13
Grade 1	4 (14)	2 (15)	4 (31)
Grade 2	6 (21)	4 (31)	5 (38)
Grade 3	18 (64)	7 (54)	4 (31)
Time to onset of first event (days)	n=28	n=13	n=13
Median (min-max)	4.0 (1-17)	9.0 (2-85)	15.0 (2-131)
Duration (days)	n=28	n=13	n=13
Median (min-max)	8.0 (1-233)	8.0 (1-231)	8.0 (1-277)

80/1000, 70/1000 and 80/750 refer to dosages of paclitaxel/lapatinib.

Although the efficacy of octreotide in the treatment of diarrhoea is established, few studies have assessed the efficacy of prophylactic octreotide in the prevention of diarrhoea. Prophylactic treatment with octreotide 20mg LAR did not prevent diarrhoea associated with pelvic radiation therapy [Martenson, 2008], and octreotide 30mg LAR was ineffective in a placebo-controlled study of 215 patients with rectal cancer receiving 5-FU based chemoradiation [Zachariah, 2010]. In addition, in a study of 139 patients with colorectal cancer treated with 5-FU and capecitabine with or without irinotecan, diarrhoea was reported in 76.1% of patients randomised to receive prophylactic treatment with octreotide 30mg LAR and in 78.9% of patients who received the physician's choice of treatment for diarrhea (loperamide in the majority of cases). In this study, no benefit from octreotide LAR was identified in terms of the need for diarrhoea treatment, use of opioids, intravenous hydration, the rate of hospitalisation, or quality-of-life [Hoff, 2012]. These controlled studies suggest prophylactic treatment with octreotide does not prevent chemotherapy-associated diarrhoea.

In a study of 124 evaluable chemotherapy-treated patients, severe diarrhoea was reported for 61.7% and 48.4% who received prophylactic treatment with octreotide 30mg LAR or 40mg LAR, respectively [Rosenhoff, 2006]. In a single arm study of 10 patients, octreotide 150 µg twice daily did not prevent diarrhoea associated with 5-FU plus leucovorin treatment [Meropol, 1998]. However, the efficacy of prophylactic octreotide in these uncontrolled studies cannot be assessed due to the lack of an active comparator group, such as placebo, loperamide or octreotide in the s.c. formulation to manage episodes of diarrhoea.

The evaluation of prophylactic octreotide in these controlled and uncontrolled studies is complicated by the characteristics of the subject populations and by differences in study design. It is possible that subjects with colorectal cancer, subjects receiving pelvic radiation therapy, and subjects with a prior history of diarrhoea associated with treatment may be pre-disposed to a more refractory type of treatment-associated diarrhoea, and the treatment regimens studied may be associated with a greater risk of more severe diarrhoea. Also, in studies of octreotide in the LAR formulation, there may not have been a sufficient interval between the administration of octreotide and the start of cancer treatment for the circulating concentration of octreotide to achieve clinically effective levels. Therefore, the results of these studies may not reflect the potential value of prophylactic treatment with octreotide for the prevention of diarrhoea in subjects with other types of cancer or receiving other combinations of anti-cancer agents.

The efficacy of octreotide LAR as a prophylactic treatment for diarrhoea associated with cancer treatment is not yet established, and has not been studied in patients with MBC. LAP117314 will explore the potential benefit of the prophylactic use of octreotide in the prevention and reduction of diarrhoea associated with treatment with lapatinib and capecitabine in subjects with MBC which has progressed following prior therapy. Patient reported outcome (PRO) measures may provide an alternative approach to the assessment of the tolerability of cancer treatment. Inclusion of PROs in this study provides an opportunity to contrast and compare outcomes reported by investigators and by subjects for each treatment group within a single study, although differences between the electronic Case Report Form (eCRF) data and the PRO data will preclude formal comparisons.

## 1.2. Study Rationale

Diarrhoea is the most commonly reported AE associated with lapatinib treatment, and is also commonly associated with capecitabine treatment. Although these events are generally mild to moderate in severity, diarrhoea adversely affects the tolerability of cancer treatment, and in severe cases diarrhoea has the potential to affect the efficacy of treatment due to poor compliance, or treatment interruption or withdrawal. Management of diarrhoea is currently reactive, and includes the use of loperamide and dietary modification for acute episodes of mild to moderate diarrhoea and the use of octreotide and rehydration therapy for more persistent diarrhoea.

The efficacy of octreotide in the management of cancer treatment-associated diarrhoea has not been extensively evaluated in large, well-controlled studies. Octreotide is available as a short acting formulation which is usually administered three times daily by s.c. injection and as a slow release (LAR) formulation which is given by deep intramuscular injection once every 28 days. This study will evaluate whether the prophylactic use of octreotide LAR offers a clinically meaningful benefit by reducing the frequency and severity of diarrhoea associated with treatment with lapatinib and capecitabine. Octreotide LAR will be administered 7 days prior to the start of treatment with lapatinib and capecitabine, then again 28 days later. All subjects with episodes of diarrhoea will be recommended to follow the standard guidelines for the management of diarrhoea ([Appendix 1](#)). The use of loperamide and other anti-diarrhoeal agents and other actions taken to manage diarrhoea will be secondary measures of the frequency of diarrhoea in both treatment groups. Subjects will receive treatment with lapatinib and capecitabine until disease progression, but study data will only be collected for up to a maximum of 24 weeks.

Therapeutically relevant circulating concentrations of octreotide should be achieved 7-14 days after the first dose of octreotide LAR, and should be maintained for at least four weeks following the second dose of octreotide LAR. The dose of octreotide LAR employed in LAP117314, 40mg, is higher than the standard starting dose of octreotide LAR, 20mg, in order to achieve clinically relevant circulating concentrations of octreotide more rapidly, reducing the delay required before the start of treatment with lapatinib and capecitabine. The primary analysis of efficacy will be based on data from the first three cycles of treatment with lapatinib and capecitabine (ie up to 9 weeks), when circulating concentrations of octreotide are predicted to be within the clinically relevant range. Supplementary analyses of efficacy will be based on the subsequent period of the study (ie nominally from week 12 to week 24) and for the total duration of the study (ie from the start of treatment with lapatinib and capecitabine to week 24).

It is unknown how accurately AE reporting within the context of a clinical study reflects the actual incidence of AEs. It is possible that the incidence of diarrhoea associated with cancer treatment is under-reported when recorded by investigators at each study visit, particularly if episodes of diarrhoea are mild or isolated. The completion of diaries by subjects to record episodes of diarrhoea may more accurately reflect the true incidence of these events.

In this study, the frequency and severity of diarrhoea will be recorded by the completion of AE forms in the eCRF by the investigator in a manner consistent with the method of AE recording used in previous studies. Episodes of diarrhoea and the effects of diarrhoea will also be evaluated indirectly by assessing the use of anti-diarrhoeal medication, treatment compliance, unscheduled visits to healthcare professionals, and the use of rehydration therapy as recorded in the eCRF.

In addition, subjects will complete the Diarrhoea Management Diary (DMD), which will collect information on the frequency and form of bowel movements, and information on the actions taken as a result of diarrhoea. Subjects will also complete the Functional Assessment of Chronic Illness Therapy-Diarrhoea (FACIT-D), which includes a sub-scale related to diarrhoea, to determine the effects of octreotide on quality of life during treatment with lapatinib and capecitabine.

The eCRF, the DMD and the FACIT-D are considered to be independent source data, and the investigator must not use the DMD and FACIT-D to supplement information recorded in the eCRF. This study provides an opportunity to compare and contrast investigator-reported outcomes and PROs for each treatment group within the setting of a single controlled clinical study, although differences between the eCRF data and the PRO data will preclude formal comparisons.

Diarrhoea is an AE associated with octreotide treatment in more than 10% of patients [Octreotide SPC]. Octreotide-associated diarrhoea usually occurs following the first dose of octreotide, and is usually mild in severity lasting only a few days [McKeage, 2003]. Diarrhoea associated with octreotide treatment could potentially confound the subsequent assessment of diarrhoea associated with treatment with lapatinib and capecitabine. The primary analysis of efficacy will be based on the total ITT population (Section 9.3.1). Supplementary analyses of efficacy will be based on a modified intent-to-treat (m-ITT) population, which will exclude subjects with diarrhoea reported following the first dose of octreotide LAR and prior to the first dose of lapatinib and capecitabine and will also exclude subjects with intolerance to the octreotide 0.1mg s.c. dose (Section 9.3.1).

The efficacy of prophylactic octreotide in the prevention of diarrhoea associated with treatment with lapatinib and capecitabine or in the management of diarrhoea associated with treatment of MBC is not known and is being explored for the first time in LAP117314. It is possible that prophylactic treatment with octreotide may provide no benefit for subjects, and could potentially worsen the frequency and severity of diarrhoea in this study. However, it is difficult to predict what the incidence or severity of octreotide-associated diarrhoea (and other AEs) might be in LAP117314, where subjects will receive only two doses of octreotide LAR, where the time taken to achieve clinically relevant circulating concentrations of octreotide is unknown, and where exposure to octreotide at clinically relevant doses is expected to last for no more than 12 weeks. A GSK Safety Review Team (SRT) will be established to review safety data in this study on an ongoing basis, in order to protect subjects' interests and to ensure their safety.

### 1.3. Benefit:Risk Assessment

LAP117314 will evaluate the efficacy and safety of octreotide used as a prophylactic treatment to prevent or reduce the frequency and severity of diarrhoea associated with treatment with lapatinib and capecitabine in subjects with HER2-positive MBC. Octreotide, lapatinib and capecitabine are all marketed products with approved indications and there is extensive post-approval experience of patient exposure. The overall benefits and risks associated with the use of octreotide, lapatinib and capecitabine are well established within the approved indications, and are presented in the [Octreotide SPC](#), [Lapatinib SPC](#) and [Capecitabine SPC](#).

Lapatinib is approved for use in combination with capecitabine in patients with histologically or cytologically confirmed HER2-positive breast cancer which has progressed following prior therapy, which must have included treatment with anthracyclines and taxanes and trastuzumab in the metastatic setting [[Lapatinib SPC](#)]. The subject population to be enrolled in LAP117314 and the treatment regimen for lapatinib and capecitabine are consistent with this approved indication. The benefits and risks associated with the use of lapatinib and capecitabine in LAP117314 are assumed to be consistent with the benefits and risks as described in the [Lapatinib SPC](#) and will not be discussed further in this analysis of benefit and risk.

Octreotide is approved for several indications; the most relevant of these with respect to LAP117314 is the treatment of symptoms (ie diarrhoea) associated with gastroenteropancreatic tumours, including carcinoid tumours with features of carcinoid syndrome, VIP-secreting tumours and glucagonomas [[Octreotide SPC](#)]. Octreotide is not approved for the treatment or prevention of diarrhoea associated with cancer treatment. The evaluation of prophylactic octreotide for the prevention or reduction of diarrhoea in LAP117314 is not within an approved indication, and octreotide is considered to be the exploratory agent in this study. However, the efficacy of octreotide in the treatment of chemotherapy-associated diarrhoea is established and has been included in the diarrhoea management guidelines developed by ASCO [[Benson, 2004](#)] and by GSK ([Appendix 1](#)).

Subjects in LAP117314 will be randomised in a 1:1 ratio to receive octreotide or to receive no octreotide. For subjects who receive no octreotide, the consideration of benefit and risk is consistent with the data presented in the [Lapatinib SPC](#). The additional risks and benefits for subjects who receive treatment with octreotide are considered in [Section 1.3.1](#) and [Section 1.3.2](#)

#### 1.3.1. Risk Assessment

The analysis of risk associated with octreotide treatment in LAP117314 is based primarily on potential risks identified in the [Octreotide SPC](#). These risks are considered relative to the subject population and study treatments and procedures in LAP117314.

Octreotide LAR is approved for use in patients in whom initial treatment with octreotide in the formulation for s.c. injection has been shown to be effective and well tolerated. Prior treatment with octreotide is not required for subjects to be enrolled in LAP117314, and the tolerance to treatment with octreotide is unlikely to be known for most subjects

prior to enrollment in the study. Subjects randomised to receive octreotide must receive one 0.1mg dose of octreotide by s.c. injection to assess tolerability at least one hour before the first dose of the LAR formulation is administered. Following s.c. administration of octreotide, peak circulating concentrations are achieved within 30 minutes, and the elimination half life of octreotide is approximately 100 minutes [Octreotide SPC]. This single s.c. dose of octreotide should identify subjects who have a hypersensitivity reaction to octreotide or its' excipients (the only contraindication for the use of octreotide).

Treatment with octreotide in both the s.c. and LAR formulations is generally well tolerated [McKeage, 2003]. Adverse events related to the mechanism of action of octreotide have been reported, including hyperglycaemia, hypoglycaemia, impaired glucose tolerance, hypothyroidism, thyroid dysfunction and cholelithiasis. These mechanism-related AEs tend to be associated with chronic treatment with octreotide [Octreotide SPC], and are therefore unlikely to be relevant within the context of LAP117314. In this study, octreotide will be administered as only one dose of the s.c. formulation and two doses of the LAR formulation over a period of 28 days, and the total duration of exposure to clinically relevant concentrations of octreotide is expected to be no more than 12 weeks.

Octreotide-associated gastrointestinal AEs are common, and are directly relevant to the conduct of LAP117314. Diarrhoea, abdominal pain, nausea, constipation and flatulence are reported to be very common (occurring in more than 10% of patients), and dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools and discolouration of faeces have been reported as common AEs (occurring in 1% to 10% of patients) [Octreotide SPC]. Diarrhoea and constipation are of particular relevance within the context of LAP117314, and additional guidance is provided for the management of these AEs. Diarrhoea will be managed in accordance with the GSK guidelines (Appendix 1); subjects with severe diarrhoea unresponsive to loperamide who have received octreotide LAR may receive further treatment with octreotide s.c. at the investigators discretion,. Subjects who report constipation with a severity of NCI CTCAE Grade 2 and above following the first dose of octreotide LAR must not receive the second dose of octreotide LAR, but will continue to receive treatment with lapatinib and capecitabine as scheduled.

Specific issues relating to warnings, precautions, contraindications and potential drug:drug interactions identified in the Octreotide SPC and the Octreotide LAR SPC are addressed in the inclusion criteria (Section 4.1.2), exclusion criteria (Section 4.1.3) and other eligibility considerations (Section 4.2). It is considered unlikely that drug:drug interactions between octreotide and lapatinib or capecitabine will occur based on the absorption, distribution, metabolism and excretion information provided in the Octreotide SPC , Lapatinib SPC and Capecitabine SPC or in published studies.

Subjects randomised to receive treatment with octreotide must wait a further 7 days to allow clinically relevant circulating concentrations of octreotide to be achieved before treatment with lapatinib and capecitabine is initiated. This delay is required as a consequence of the pharmacokinetic profile of the LAR formulation of octreotide. Following deep intramuscular injection of the LAR formulation, circulating concentrations of octreotide increase over a period of 7 to 14 days before a stable plateau

circulating concentration is achieved. The standard starting dose of octreotide LAR is 20mg; the dose of octreotide LAR used in LAP117314 is 40mg, to ensure clinically relevant circulating concentrations of octreotide will be achieved in most subjects within 7 days after dosing, and to minimise the delay before starting treatment with lapatinib and capecitabine.

The efficacy of octreotide in the prevention of diarrhoea associated with treatment with lapatinib and capecitabine is unknown. Octreotide-associated gastrointestinal AEs are common, and could potentially worsen the overall incidence of diarrhoea and other AEs in subjects who receive octreotide LAR together with lapatinib and capecitabine. An independent SRT will review safety data in this study on an ongoing basis, in order to protect subjects' interests and to ensure their safety (Section 10.8). There are no pre-specified stopping criteria in LAP117314, but the SRT can recommend changes to the study protocol to ensure the subjects' safety if necessary.

### **1.3.2. Benefit Assessment**

The objective of LAP117314 is to evaluate the potential efficacy of octreotide in preventing or reducing the frequency and severity of diarrhoea associated with treatment with lapatinib and capecitabine. Diarrhoea is a common AE reported in studies of both lapatinib and capecitabine [Lapatinib SPC; Capecitabine SPC]. Diarrhoea associated with cancer therapy may affect the patients' sense of wellbeing and can result in treatment interruption or dose reduction, potentially reducing the therapeutic benefit of the cancer treatment.

The efficacy of octreotide has been demonstrated in the treatment of diarrhoea associated with a number of conditions (Section 1.1). Diarrhoea associated with cancer treatment is usually managed reactively, but the experience of diarrhoea associated with cancer treatment may adversely influence the acceptability of subsequent cycles of treatment. Prophylactic treatment to prevent diarrhoea associated with cancer treatment has the potential to improve the overall tolerability of treatment and to improve treatment compliance. These effects together could potentially improve treatment efficacy by reducing the frequency of treatment dose reductions and treatment interruptions.

### **1.3.3. Overall Benefit:Risk Conclusion**

The potential benefits and risks associated with treatment with octreotide, lapatinib and capecitabine are considered to be acceptable within the context of LAP117314.

## 2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study are summarised in [Table 7](#).

**Table 7 Objectives and endpoints**

Objectives	Endpoints
<b>Primary: Investigator reported (eCRF)</b>	
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects experiencing diarrhoea with a severity of 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, recorded as AEs in the eCRF.
<b>Secondary: Investigator reported (eCRF)</b>	
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 AEs in the 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 reducing the duration of diarrhoea of any grade of severity.	Duration of diarrhoea of any grade of severity, 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.
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects taking anti-diarrhoeal medication.	Proportion of subjects taking anti-diarrhoeal medication, recorded in the eCRF.
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects making unscheduled visits to healthcare professionals as a result of diarrhoea.	Proportion of subjects making diarrhoea-related unscheduled visits to healthcare professionals, recorded in the eCRF.
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects requiring changes in cancer therapy (dose delays, dose reductions and treatment withdrawal) as a result of diarrhoea.	Proportion of subjects requiring diarrhoea-related lapatinib and capecitabine dose reduction, dose delay and treatment withdrawal, recorded in the eCRF.

Objectives	Endpoints
<b>Secondary: Investigator reported (eCRF)</b>	
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects requiring treatment with intravenous fluids resulting from diarrhoea.	Proportion of subjects requiring use of diarrhoea-related intravenous fluids for rehydration, recorded in the eCRF.
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.

Objectives	Endpoints
<b>Secondary: Patient<sup>1</sup> reported (DMD)</b>	
<p>To determine the effect of prophylactic octreotide on patient-reported diarrhoea.</p> <p>To determine the effect of prophylactic octreotide in delaying patient reported diarrhoea.</p> <p>To determine the effect of prophylactic octreotide in reducing the proportion of patients taking anti-diarrhoeal medication.</p> <p>To determine the effect of prophylactic octreotide in reducing the proportion of patients making dietary changes to control diarrhoea.</p> <p>To determine the effect of prophylactic octreotide on the proportion of patients contacting other non-hospital healthcare professionals to discuss diarrhoea.</p> <p>To determine the effect of prophylactic octreotide in reducing the proportion of patients reporting non-adherence due to diarrhoea.</p>	<p>Proportion of patients reporting changes in bowel movements from baseline (frequency and/or consistency), recorded in the DMD.</p> <p>Time to the first patient reported change in frequency and/or consistency of bowel movements from baseline, recorded in the DMD.</p> <p>Proportion of patients taking anti-diarrhoeal medication, recorded in the DMD.</p> <p>Proportion of patients making dietary changes due to diarrhoea, recorded in the DMD.</p> <p>Proportion of patients contacting other non-hospital healthcare professionals to discuss diarrhoea, recorded in the DMD.</p> <p>Proportion of patients reporting stopping completely or missing doses of anti-cancer tablets due to diarrhoea, recorded in the DMD.</p>
<b>Quality of Life (FACIT-D)</b>	
<p>To determine the effect of prophylactic octreotide on health-related quality of life.</p>	<p>Proportion of patients with changes in health-related quality of life, recorded by FACIT-D.</p> <p>Trial Outcomes Index will be the primary endpoint; FACT-G total, FACIT-D total, and sub-scales will be secondary endpoints..</p>

1. The term 'patient' refers to study subject in the context of DMD- and FACIT-D-related objectives and endpoints.

Consistent recording of diarrhoea AEs is a key component of this study. It is essential that the investigator understands fully the classification of diarrhoea and the definitions of severity used in this study (Table 8). For each diarrhoea AE report, the investigator should assess the change in stool form and frequency relative to the normal form and frequency for the subject to accurately ascertain the grade of diarrhoea.

**Table 8 National Cancer Institute common terminology criteria for grading diarrhoea adverse events**

Adverse Event Grade	Diarrhoea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
3	Increase of $\geq 7$ stools/day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death

Data will be recorded by the investigators in the eCRF at each study visit and by subjects in the DMD every week and in the FACIT-D every 3 weeks. These are considered to be independent sources of study data, and investigators must not use information collected in the DMD and FACIT-D to supplement data entry into the eCRF. Where comparable data are collected in the eCRF and in the DMD, secondary endpoints will be evaluated to contrast and compare these data within each treatment group, although differences between the eCRF data and the PRO data will preclude formal comparisons.

All subjects will complete the baseline DMD and the FACIT-D during the 3 days prior to randomisation, before any study-related treatment is administered. Subjects randomised to receive octreotide will complete a second baseline DMD and the FACIT-D before starting the first cycle of treatment with lapatinib and capecitabine. Hence, subjects randomised to receive octreotide will complete the baseline DMD and the FACIT-D (Week -1) prior to receiving the first dose of octreotide (0.1mg subcutaneous tolerability test dose), and all subjects will complete the baseline DMD and the FACIT-D prior to receiving the first dose of lapatinib and capecitabine (Week 0).

The DMD will be completed every week after the first dose of lapatinib and capecitabine is administered (Week 1, Week 2, Week 3, etc), until the end of study visit (Week 24, disease progression, unacceptable toxicity or subject withdrawal if this is sooner). The FACIT-D will be completed every 3 weeks during treatment with lapatinib and capecitabine (Week 3, Week 6, Week 9, etc), until the end of study visit (Week 24, disease progression, unacceptable toxicity or subject withdrawal if this is sooner). The DMD and FACIT-D will not be completed beyond 24 weeks of treatment.

The baseline DMD comprises 3 questions to record stool form and consistency. The DMD to be completed throughout the rest of the study comprises the 3 questions in the baseline DMD and a further 5 questions and 6 sub-questions to evaluate the consequences and management of diarrhoea. A copy of the baseline DMD and the DMD is included in the Study Procedures Manual (SPM).

The FACIT-D ([Appendix 2](#)) comprises the 27 item Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire which has physical (PWB), social (SWB), emotional (EWB) and functional wellbeing (FWB) subscales and an 11 item diarrhoea symptom subscale (DSS) which measures quality of life specific to diarrhoea. The primary endpoint derived from the FACIT-D will be the Trial Outcome Index, which is a summation of the PWB, FWB and diarrhoea symptom subscales. Secondary endpoints will be overall quality of life (total FACT-G), total FACIT-D and scores from each of the individual subscales.

Disease progression in accordance with RECIST version 1.1 is required only at the end of study visit. Disease assessments during the course of treatment with lapatinib and capecitabine may be conducted in accordance with local practice. The assessment of disease progression in LAP117314 is less rigorous than that employed in EGF100151 and EGF111438. LAP117314 is an exploratory study, and disease efficacy data may not be comparable with that reported in other studies.

### **3. INVESTIGATIONAL PLAN**

#### **3.1. 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.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Schedule ([Table 16](#), and [Table 17](#)), is essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

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/m<sup>2</sup> 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.

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

- Octreotide (Sandostatin 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 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.

All subjects with episodes of diarrhoea will be encouraged to follow the GSK diarrhoea management guidelines for subjects receiving lapatinib ([Appendix 1](#)). In subjects randomised to receive octreotide, episodes of mild diarrhoea which occur following the first dose of octreotide LAR should be managed in accordance with the diarrhoea management guidelines. The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range.

Subjects who report constipation with a severity of NCI CTCAE Grade 2 and above ([Table 9](#)) following the first dose of octreotide LAR must not receive the second dose of octreotide LAR, but will continue to receive treatment with lapatinib and capecitabine as scheduled.

**Table 9 National Cancer Institute common terminology criteria for grading constipation adverse events**

Adverse Event Grade	Constipation
1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
3	Obstipation with manual evacuation indicated; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

ADL=Activities of daily living

Dose reductions and dose delays are permitted during treatment with lapatinib and capecitabine. The procedures to be followed are described in Section 5.10 for lapatinib and in Section 5.11 for capecitabine.

Study completion will be the end of 24 weeks treatment with lapatinib and capecitabine, or disease progression, unacceptable toxicity or subject withdrawal if this is sooner. Serious AEs 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. Serious AEs 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 every week and the FACIT-D every 3 weeks during treatment with lapatinib and capecitabine 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. Management of dermatological events, gastrointestinal events, and cardiovascular and respiratory events is described in Section 5.12.1, Section 5.12.2, and Section 5.12.3, respectively. Dose delay and dose reduction guidance for lapatinib related to these events and to hepatobiliary events is described in Section 5.10. If future changes are made to this guidance, formal documentation will be created and stored with the study file. Any changes will be communicated to the investigative sites in the form of a letter and the revised version of the AE management or dose modification guidelines will be included in the SPM.

Hand and foot syndrome has been identified as an event of special interest relating to capecitabine. Management of this event is described in further detail in Section 5.12.4. Dose delay and dose reduction guidance for capecitabine related to this event is described in Section 5.11. If future changes are made to this guidance, formal documentation will be created and stored with the study file. Any changes will be communicated to the investigative sites in the form of a letter and the revised version of the AE management or dose modification guidelines will be included in the SPM.

There are no events of special interest relating to octreotide [[Octreotide SPC](#)].

The GSK SRT will review safety data from this study on an ongoing basis. A formal review of safety data will be conducted after the first 60 subjects (approximately 30 in each treatment arm) have received at least 9 weeks of treatment with lapatinib and capecitabine; subsequent reviews will be conducted at least every 12 weeks, or more frequently if required. It is anticipated that the SRT will meet at least three times during the course of the study. There are no pre-defined stopping rules for this study.

### 3.2. Discussion of Design

All subjects in this study will receive treatment with lapatinib and capecitabine consistent with the approved indication for this treatment combination. Diarrhoea is a recognised side effect of cancer treatment, and all subjects will be recommended to follow the standardised guidelines for diarrhoea management ([Appendix 1](#)). The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded, and investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR.

Subjects will be randomised in a 1:1 ratio to receive octreotide prophylaxis 7 days prior to starting treatment with lapatinib and capecitabine, or to start treatment with lapatinib and capecitabine immediately after enrolment. Treatment with octreotide is the key difference between the two groups of subjects with respect to the management of adverse events associated with cancer treatment. Therefore, any differences noted between the two groups of subjects with respect to efficacy or safety outcomes should be attributable to prophylactic treatment with octreotide.

This is an open label study, and no placebo for octreotide treatment will be used. It is possible that delaying treatment with lapatinib and capecitabine in subjects randomised to receive octreotide treatment may have a negative impact on disease outcome. The extent of risk associated with this delay is unknown, but it is considered to be a reasonable approach to disease management within the constraints of this study. Treatment with lapatinib and capecitabine would also need to be delayed in subjects who receive no octreotide if a placebo control was included, exposing subjects to an increased risk with no potential benefit. In addition, it is uncertain to what extent AEs associated with octreotide treatment will confound the assessment of AEs associated with treatment with lapatinib and capecitabine, and it is therefore uncertain to what extent the use of a placebo control for octreotide treatment would mitigate this complicating factor.

There are several common AEs associated with octreotide treatment, including diarrhoea, abdominal pain, nausea and constipation. Gastrointestinal AEs associated with octreotide treatment are generally mild and short lasting [[McKeage, 2003](#)], but there are no published data to provide information on the expected incidence, severity, time to onset or duration of gastrointestinal AEs following the first dose of octreotide LAR. In most patients, circulating concentrations of octreotide are below clinically relevant levels for the first 7 days after receiving the first dose of the LAR formulation, and plateau concentrations are achieved after about 14 days [[Octreotide LAR SPC](#)]. It is possible that circulating concentrations of octreotide will be below the levels required to elicit AEs during the first 7 days after the first dose of octreotide LAR in LAP117314.

It is also possible that the subjects' perception of the tolerability of lapatinib and capecitabine may be influenced by whether or not they receive octreotide, and by their expectations concerning the potential efficacy and tolerability of octreotide. This issue will be resolved at least in part by the information provided in the Informed Consent, to the effect that octreotide is an effective anti-diarrhoeal agent in other clinical settings, but that diarrhoea and other gastrointestinal AEs may also be associated with octreotide

treatment. In LAP117314 it is uncertain to what extent the predicted gastrointestinal AE profile associated with octreotide treatment will compromise the potentially beneficial effects of the prevention of diarrhoea associated with treatment with lapatinib and capecitabine. While it is recognised that the inclusion of a placebo control for octreotide would provide a more robust study design, it is uncertain to what extent this would resolve the complications associated with the efficacy and tolerability profile of octreotide.

The recommended dose for initiating treatment with octreotide LAR is 20mg, to be repeated every 28 days. There is a recognised delay of several days required for circulating concentrations of octreotide to achieve therapeutically relevant levels following the first dose of the LAR formulation [[Octreotide LAR SPC](#)]. During this period patients receiving octreotide LAR in clinical practice may also be treated with octreotide in the formulation for s.c. administration to manage episodes of diarrhoea. In this study, octreotide in the formulation for s.c. administration will not be provided prophylactically to prevent episodes of diarrhoea in subjects during the first 7 to 14 days after the first dose of octreotide LAR. This is primarily due to concerns that subjects are unlikely to be compliant with a regimen which requires self-administration of octreotide by s.c. injection three times daily, and uncertainty regarding the required duration of this treatment regimen. The dose of octreotide LAR to be used in this study is 40mg, and it is anticipated that this higher dose will reduce the time required for circulating concentrations of octreotide to achieve therapeutically relevant levels.

It is also acknowledged that a significant proportion of subjects who receive treatment with lapatinib and capecitabine do not report diarrhoea as an adverse event. There will, therefore, be a proportion of subjects randomised to receive treatment with octreotide who would not have reported diarrhoea as an adverse event and would not have required treatment with anti-diarrhoeal medication. The safety profile of octreotide is well established. Subjects randomised to receive octreotide LAR will first receive octreotide by s.c. administration to assess short term tolerability. Subsequently, subjects who report clinically significant constipation or other AEs which are considered likely to be related to octreotide treatment will not receive the second dose of octreotide LAR. This approach will minimise the risk associated with treatment with octreotide in this study.

Overall, 140 subjects will be enrolled. LAP117314 is an exploratory Phase II study, and the sample size is not based on the number of subjects required to achieve a pre-specified reduction in the control incidence of diarrhoea. While it is predicted that octreotide prophylaxis will reduce the frequency and severity of diarrhoea, the degree of benefit and the impact this might have on treatment compliance and on the subjects' quality of life are uncertain. The study should be of sufficient size to provide clinically meaningful data within a reasonable enrollment timeframe.

The primary endpoint of the study is the proportion of subjects reporting diarrhoea with a severity of Grade 2 or more. This represents an increase of at least four stools per day relative to baseline, and is considered to be sufficiently severe to have an impact on the subjects' sense of wellbeing. The recommended management of Grade 2 diarrhoea includes maintaining treatment with lapatinib on the first and second occurrence, with interruption of lapatinib treatment on subsequent occurrences ([Table 10](#)), and interruption

of treatment with capecitabine at the first occurrence, with restart at a reduced dose after the first occurrence if clinically indicated, restart at a reduced dose after the second and third occurrences, and treatment withdrawal after the fourth occurrence (Table 11). In addition to the diarrhoea management related dose interruptions, Grade 2 diarrhoea may also adversely affect the acceptability of subsequent cycles of treatment.

Secondary endpoints of the study provide a broader assessment of the incidence and severity of diarrhoea of all grades. It is possible that octreotide prophylaxis may not reduce the overall incidence of diarrhoea, but may reduce the severity of these incidences of diarrhoea. The proportion of subjects who report diarrhoea with a severity of Grade 3 or more will be summarised separately, as this represents diarrhoea which requires a significant clinical intervention.

The frequency and severity of diarrhoea will be recorded by the investigator in accordance with the standard process for AE reporting in the eCRF. In addition, 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. This methodology is broadly consistent with that used in clinical studies EGF100151 and EGF111438.

Further information concerning the frequency of diarrhoea and the consequences of diarrhoea will be recorded by the subjects in the DMD. The DMD, together with the FACIT-D, provides an alternative and complementary approach to recording the frequency of diarrhoea and to evaluating the impact of diarrhoea. The DMD is considered to be an independent source of study data, and investigators must not use information collected in the DMD to supplement data entry into the eCRF. The PROs recorded by completion of the DMD and the FACIT-D will provide an additional perspective on the impact of diarrhoea associated with treatment with lapatinib and capecitabine.

The management of the subjects' cancer will be conducted in accordance with local clinical practice, rather than according to a predefined schedule within the protocol. It is assumed that visits to the clinic will occur in three weekly cycles consistent with the cycles of treatment with lapatinib and capecitabine, and that the clinical management of subjects enrolled at different study sites will be broadly comparable.

### **3.3. Recruitment Plan**

The interim analysis will be triggered when approximately 40% (n=60) of the subjects that have completed 3 cycles of study treatment. In order to protect subjects from unnecessary exposure to octreotide, once 60 patients have been enrolled, recruitment will be temporarily halted to minimise potentially unnecessary further subjects being enrolled, whilst review of the interim analysis is being conducted. Therefore, once 60 patients have been recruited, investigator sites will receive communication from the sponsor to suspend any further recruitment and screening activities until the outcome of the interim analysis has been communicated to investigator sites. Subjects that are in screening during this period will still be considered for randomisation into the study.

## **4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA**

### **4.1. Subject Selection Criteria**

All subjects enrolled in LAP117314 will receive treatment with lapatinib and capecitabine in accordance with the approved indication for the use of this treatment combination as described in the Lapatinib SPC. It is the responsibility of the investigator to ensure all subjects enrolled in LAP117314 are eligible to receive treatment with lapatinib and capecitabine in accordance with the criteria described in the Lapatinib SPC. The investigator must also ensure that other factors have been considered, such as concurrent medications and medical conditions, which might affect the efficacy or safety of treatment with lapatinib, capecitabine or octreotide. Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information that may affect subject eligibility is provided in the Lapatinib, Capecitabine and Octreotide SPCs.

Subject selection criteria are based on the Lapatinib, Capecitabine and Octreotide SPCs current at the effective date for this protocol. Investigators will be informed of any changes to the SPCs which affect subject selection criteria, and formal documentation will be created and stored with the study file.

#### **4.1.1. Number of Subjects**

Approximately 140 subjects will be randomised, 70 will receive octreotide and 70 will receive no octreotide. See Section [9.2.1](#) for sample size assumptions.

#### **4.1.2. Inclusion Criteria**

Deviations from the inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Signed written informed consent.
2. Histologically or cytologically confirmed HER2-positive advanced or metastatic breast cancer which has progressed following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.
3. Females age  $\geq 18$  years old.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 ([Appendix 4](#)).
5. Life expectancy of at least 12 weeks.
6. Able to swallow and retain oral medications.

7. Incapable of becoming pregnant, or not pregnant and using an adequate form of contraception, i.e. a female who is of:
  - a. non-childbearing potential (physiologically incapable of becoming pregnant), including any female who has had hysterectomy, bilateral oophorectomy, bilateral tubular ligation or is post-menopausal (total cessation of menses for at least 1 year);
  - b. childbearing potential must have a negative serum pregnancy test within 7 days prior to treatment with octreotide if randomised to receive octreotide or the first dose of lapatinib with capecitabine if randomised to receive no octreotide, preferably as close to the first dose as possible, and must agree to use adequate contraception (intrauterine device, birth control pills unless clinically contraindicated, or barrier device) during the study and continuing for at least 4 weeks after the final dose of treatment with lapatinib and capecitabine. Acceptable contraceptive methods are described in Section 7.5.1.
8. Subjects must complete all screening assessments as outlined in the protocol.
9. Subjects must complete the FACIT-D and diarrhoea diary before receiving the first dose of octreotide if randomised to receive octreotide. All subjects must complete the FACIT-D and diarrhoea diary before receiving the first dose of lapatinib with capecitabine.
10. Prior treatment with other chemotherapeutic agents or endocrine therapy is permitted. All prior treatment related toxicities, except diarrhoea and alopecia, must be NCI CTCAE (version 4.03)  $\leq$  Grade 1 at the time of randomisation. Subjects with diarrhoea with any grade of severity within 14 days prior to randomisation are excluded from LAP117314.
11. Prior treatment with radiation therapy is permitted provided that at least 2 weeks have elapsed since the last fraction of radiation therapy prior to treatment with octreotide if randomised to receive octreotide or the first dose of lapatinib with capecitabine if randomised to receive no octreotide, and all radiation therapy related AEs are  $\leq$  Grade 1 at the time of randomisation.

**French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category. Other country-specific criteria are included in [Appendix 5](#).

#### **4.1.3. Exclusion Criteria**

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Concurrent treatment with an investigational agent or concurrent participation in another clinical study.

2. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, prior to treatment with octreotide for subjects randomised to receive octreotide or the first dose of lapatinib and capecitabine for subjects randomised to receive no octreotide.
3. Treatment with octreotide within the 3 months prior to randomisation.
4. Concurrent chemotherapy, radiation therapy, immunotherapy, biologic therapy (including an EGFR and/or HER2 inhibitor), or hormonal therapy for treatment of cancer.
5. Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent, unless a legally acceptable representative could provide informed consent (if in accordance with the policies of the local Ethics Committee).
6. Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical or psychiatric disorder that would interfere with the subject's safety or compliance with study procedures.
7. Diarrhoea with any grade of severity within 14 days prior to treatment with octreotide for subjects randomised to receive octreotide or within 14 days prior to the first dose of lapatinib and capecitabine for subjects randomised to receive no octreotide.
8. Malabsorption syndrome, inflammatory bowel disease (ulcerative colitis, Crohn's disease), irritable bowel syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel.
9. Pregnant or lactating subjects.
10. Prior treatment with lapatinib.

**French subjects:** the French subject has participated in any study using an investigational drug during the previous 30 days or 5 half-lives, whichever is longer, preceding the first dose of protocol treatment.

## 4.2. Other Eligibility Criteria Considerations

It is the responsibility of the investigator to ensure all subjects enrolled in LAP117314 are eligible to receive treatment with lapatinib and capecitabine, and meet other criteria described in the Lapatinib, Capecitabine and Octreotide SPCs. In addition to the inclusion criteria (Section 4.1.2) and exclusion criteria (Section 4.1.3), the contraindications, special warnings and precautions for use, and other information included in the Lapatinib, Capecitabine and Octreotide SPCs should be taken into consideration.

Lapatinib, capecitabine and octreotide are contraindicated in subjects with a history of allergic reactions to these drugs, compounds with a similar chemical composition, or excipients associated with these drug formulations. Capecitabine is contraindicated in

subjects with severe leucopenia, neutropenia or thrombocytopenia, or dihydropyrimidine dehydrogenase deficiency.

Caution should be taken in subjects with moderate or severe hepatic impairment. Investigators should consider the subjects hepatic function measures relative to the guidance provided for the management of hepatobiliary AEs in Section 5.13. It is recommended that hepatic function measures prior to randomisation should meet the following criteria:

- Albumin  $\geq 2.5$  g/dL
- Serum bilirubin  $\leq 1.5$  x the upper limit of the normal range (ULN) or  $\leq 2.5$  x ULN with Gilbert's Syndrome
- AST and ALT  $\leq 3 \times$  ULN

Caution should be taken in subjects with severe renal impairment.

Caution should be taken in subjects with conditions that could impair cardiac function, including conditions that could result in prolongation of QTc, arrhythmias and angina pectoris. Subjects with hypertension who are randomised to receive octreotide must be monitored to manage the potential risk of bradycardia associated with octreotide use.

Information on potential interactions with other medicinal products is presented in the Lapatinib, Capecitabine and Octreotide SPCs and in Section 6.2.

Correction of electrolytes (most importantly, potassium, magnesium and calcium) to within normal ranges should take place prior to study entry and during study conduct as clinically indicated.

### **4.3. Permanent Discontinuation from Study Treatment and Subject Completion Criteria**

#### **4.3.1. Discontinuation from Treatment with Octreotide**

Subjects randomised to receive octreotide must be given one 0.1mg dose of the standard formulation of octreotide s.c. to assess tolerability at least one hour before the first dose of the LAR formulation is administered. Subjects who show any evidence of intolerability to octreotide administered s.c. **must not** receive treatment with the LAR formulation; these subjects should receive treatment with lapatinib and capecitabine and should not be withdrawn from the study.

Subjects randomised to receive octreotide will be given prophylactic octreotide (Sandostatin LAR) 40mg 7 days before the start of treatment with lapatinib and capecitabine and again 28 days later. Episodes of mild diarrhoea which occur following treatment with octreotide LAR should be managed in accordance with the diarrhoea management guidelines ([Appendix 1](#)). The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in

subjects randomised to receive treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range. Subjects who report constipation with a severity of NCI CTCAE Grade 2 and above (Table 9) or other adverse events which are considered likely to be related to octreotide treatment following the first dose of octreotide LAR must not receive the second dose of octreotide LAR, but should continue to receive lapatinib and capecitabine and should not be withdrawn from the study.

#### **4.3.2. Discontinuation from Treatment with Lapatinib and Capecitabine**

Subjects may withdraw from the study at any time.

Study treatment may be permanently discontinued for any of the following reasons:

- liver chemistry meeting the stopping criteria described in Section 5.13.1
- deviation(s) from the protocol
- disease progression
- request of the subject or proxy
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and the study eCRF. If the subject voluntarily discontinues treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation in the eCRF.

Subjects who require permanent discontinuation of either lapatinib or capecitabine must permanently discontinue both treatments in that combination and the reason for discontinuation must be recorded. Once a subject has permanently discontinued treatment with lapatinib and capecitabine, the subject will not be allowed to be re-treated and must be withdrawn from the study.

All subjects who discontinue treatment with lapatinib and capecitabine will have safety assessments at the time of discontinuation as specified in the Time and Events Schedule (Table 16 and Table 17) and in Section 7.1.8.

#### **4.3.3. Subject Completion**

A subject will be considered to have completed the study if the subject completes 24 weeks of treatment with lapatinib and capecitabine, or if cancer progresses or the subject dies during treatment, whichever is sooner. The cause of death must be recorded in the eCRF. A subject will be considered to have withdrawn from the study prematurely if

treatment is permanently stopped due to toxicity, or the subject has withdrawn consent, or the subject is no longer being followed at the investigator's discretion.

## **5. STUDY TREATMENTS**

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

The mechanism for providing lapatinib and capecitabine will vary by centre and by country, depending on drug reimbursement status. Lapatinib and capecitabine will be provided locally by each centre, and if this is not possible lapatinib and capecitabine will be provided by GSK. Only subjects enrolled in the study may receive study-related treatment, in accordance with all applicable regulatory requirements. Only the site pharmacist or authorized site personnel may supply or administer study-related treatment.

Octreotide will be provided by GSK for all sites.

Prescribing information and patient information documents for lapatinib, capecitabine and octreotide will be sourced locally, in the local language.

The content of the treatment labels will be in accordance with all applicable regulatory requirements. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request. Under normal conditions of handling and administration, study-related treatment is not expected to pose significant safety risks to site staff.

### **5.1. Lapatinib**

Lapatinib is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab in the metastatic setting. The approved dose of the combination is lapatinib 1250mg once daily and capecitabine 1000mg/m<sup>2</sup> twice daily.

Lapatinib is supplied as 250mg tablets that are oval, biconvex, and orange film-coated with one side plain and the opposite side debossed with FG HLS, or as 250mg tablets that are oval, biconvex, and yellow film-coated with one side plain and the opposite side debossed with GS XJG. Each tablet contains 405mg of lapatinib ditosylate monohydrate, equivalent to 250mg lapatinib free base. For more information regarding the physical and chemical properties of the drug substance and the list of excipients refer to the Lapatinib SPC.

### 5.1.1. Lapatinib Dosage and Administration

Lapatinib will be dispensed to the subject after it has been confirmed that the subject meets all eligibility criteria and all screening assessments have been completed and the results reviewed. Subjects will receive their re-supply of lapatinib therapy at the time of a scheduled visit.

Study staff will carefully instruct subjects on how to take lapatinib and the correct dose to take. Subjects are to receive 1250 mg per day of lapatinib, so will be instructed to take 5 x 250 mg tablets per day. Subjects will be instructed to take lapatinib therapy either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Lapatinib is taken every day, including during the week that capecitabine is not taken. A record of therapy administered to each subject must be maintained in the source documents.

Lapatinib dose modification guidelines are outlined in Section 5.10 and should be used for the management of treatment-related toxicities. Subjects should be carefully instructed when any dose modifications occur.

NOTE: Lapatinib should NOT be taken with grapefruit or grapefruit juice. Grapefruit and grapefruit juice is not permitted for the duration of the study.

If a subject vomits after taking lapatinib, the subject should be instructed not to retake the dose. Subjects should take the next dose of lapatinib therapy as scheduled. If vomiting persists then the subject should contact the investigator.

## 5.2. Capecitabine

Capecitabine (Xeloda) is indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen. Capecitabine is supplied as a biconvex, oblong, light peach or peach colored film-coated tablet for oral administration. Each light peach colored tablet contains 150mg capecitabine and each peach colored tablet contains 500mg capecitabine. For more information regarding the physical and chemical properties of the drug substance and the list of excipients refer to the Capecitabine SPC.

Capecitabine is also available in generic form. The characteristics of generic capecitabine tablets may differ from those as described for capecitabine (Xeloda). Generic capecitabine may be used in LAP117314 if capecitabine (Xeloda) cannot be provided.

### 5.2.1. Capecitabine Dosage and Administration

The capecitabine dose schedule is an intermittent regimen consisting of 2 weeks of treatment followed by a 1 week drug-free period. The starting dose of capecitabine in combination with lapatinib will be 2000mg/m<sup>2</sup>/day. This is to be divided to 1000 mg/m<sup>2</sup> per dose and given twice daily orally, 12 hours apart, for 14 days, every 21 days. Study staff will carefully instruct subjects on how to take capecitabine and the correct dose to be taken.

The capecitabine morning dose must be taken with food or within 30 minutes after a breakfast meal with approximately 200ml of water. The capecitabine evening dose should be taken approximately 12 hours after the morning dose and should be taken with food, or within 30 minutes after food, with approximately 200ml of water.

### **5.3. Octreotide**

Octreotide is the acetate salt of a cyclic octapeptide. It has pharmacologic properties mimicking those of the natural hormone somatostatin, but has a longer duration of action than somatostatin. Octreotide is not an anti-tumour agent.

Octreotide is indicated for the relief of symptoms associated with gastroenteropancreatic tumours, including carcinoid tumours with features of carcinoid syndrome, VIP-secreting tumours and glucagonomas. Octreotide is provided as a 0.1mg/mL solution for s.c. injection.

Octreotide is also available as a depot formulation (Sandostatin LAR), which is indicated in patients in whom initial treatment with octreotide injection has been shown to be effective and tolerated, for the long-term treatment of the severe diarrhoea and flushing episodes associated with metastatic carcinoid tumors and the long-term treatment of the profuse watery diarrhoea associated with VIP-secreting tumors. Sandostatin LAR may only be administered by deep intragluteal injection.

Sandostatin LAR is available as sterile 5mL vials delivering 10mg, 20mg or 30mg octreotide as the free peptide. When mixed with diluent (approximately 2mL or 2.5 mL) it becomes a suspension that is given as an intramuscular injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

For more information regarding the physical and chemical properties of the drug substance and the list of excipients refer to the Octreotide and Octreotide LAR SPCs.

#### **5.3.1. Octreotide Dosage and Administration**

Octreotide in the formulation for s.c. injection will be administered as a 0.1mg dose (1mL) at the study site to assess tolerability at least one hour before the first 40mg dose of the LAR formulation is administered. The LAR formulation must not be administered to any subjects who show signs or symptoms of intolerance to octreotide following administration of the 0.1mg s.c. dose.

The 40mg dose of the LAR formulation will be given as two 20mg doses, each of approximately 2.5mL. The mixing instructions for this formulation should be followed carefully to ensure the suspension is properly prepared. Octreotide in the LAR formulation will be administered at the study site 7 days prior to starting the first cycle of treatment with lapatinib and capecitabine, and repeated 28 days later.

#### **5.4. Handling and Storage of Study Treatment**

Study-related treatment must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of study-related treatment will be limited to the investigator and authorized site staff. Study-related treatment must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

#### **5.5. Treatment Assignment**

Subjects will be identified by a unique subject number that will remain constant for the duration of the study. Investigators or designated staff will telephone the GSK interactive voice response (IVR) system called RAMOS (Registration and Medication Ordering System) to register and record subject activity. To randomize the subject, the study staff will enter the subject number to obtain a randomisation number and treatment group assignment. All calls to RAMOS are confirmed with a fax, which will be sent to the site on the completion of each call. Study-specific instructional worksheets will be provided for the use of the IVR system.

#### **5.6. Blinding**

This is an open label study; however, effort will be made to maintain the blind for key internal sponsor personnel working on the study.

To preserve the integrity of the study at the interim analysis (Section 9.3.4), the treatment assignment will be obtained by an independent statistician, (who has access to the randomisation system RandAll NG), and provided to an external statistics group (to be appointed) to allow the required pre-defined analyses and data summaries to be produced. These analyses and data tables will be clearly documented in the Reporting Analysis plan. These data tables will then be provided to the independent review committee for their review. The results of the interim analyses will only be known by the independent review committee and not disclosed to the study team. There will be a secure firewall put in place to ensure that the study team remain blinded to the interim data and results. The recommendation from the independent review committee will be communicated to the study team and, in the event of a recommendation to halt the trial early, also to the appropriate regulatory agencies. If the independent review committee recommends the study continue, the study team will continue to remain blinded to interim results and treatment assignments until final analysis.

#### **5.7. Product Accountability**

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of octreotide, lapatinib and capecitabine dispensed and/or administered to study subjects, the amount of lapatinib and capecitabine returned by study subjects, and the amount received from and returned to GSK, when applicable. Recording of drug accountability is

required regardless of whether the Institution or GSK are providing lapatinib and capecitabine. Product accountability records must be maintained throughout the course of the study. Further detailed instructions on product accountability are included in the SPM.

## 5.8. Treatment Compliance

Compliance with treatment with lapatinib and capecitabine will be assessed through querying the subject during the site visits and will be recorded in the source documents and in the eCRF.

A record of the number of lapatinib and capecitabine tablets dispensed to and returned by each subject must be maintained and reconciled with treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

Treatment delays and/or dose reductions will also be recorded by subjects in the DMD. The eCRF and the DMD are considered to be independent source data, and information recorded in the DMD should not be used to supplement information recorded in the eCRF.

Octreotide will be administered to subjects at the study site. Administration will be recorded in the source documents and in the eCRF.

## 5.9. Dose Adjustment

Dose adjustment will be considered for lapatinib (Section 5.10) and capecitabine (Section 5.11), and the dose of either agent may be adjusted independently of the other. All subjects who may require discontinuation of either lapatinib or capecitabine must discontinue both treatments. Subjects should be carefully instructed when any dose modifications occur.

Treatment with lapatinib and capecitabine may be delayed up to 2 weeks, to allow for resolution of toxicity except in the event of a  $\geq$  Grade 3 relative decrease in left ventricular ejection fraction, interstitial pneumonitis or hepatotoxicity. Guidelines for the management of these events are presented in Section 5.12.3 (cardiovascular and respiratory) and Section 5.13 (hepatobiliary).

No dose reduction or dose delay is permitted for octreotide. Subjects who show intolerance to the s.c. injection of octreotide must not receive treatment with octreotide LAR. Episodes of mild diarrhoea which occur following the first dose of octreotide LAR and prior to the first dose of lapatinib and capecitabine should be managed in accordance with the diarrhoea management guidelines (Appendix 1). The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range.

Subjects who report constipation with a severity of NCI CTCAE Grade 2 and above (Table 9) or other adverse events which are considered likely to be related to octreotide treatment following the first dose of octreotide LAR must not receive the second dose of octreotide LAR.

#### **5.10. Dose Delays and Reductions for Lapatinib**

Dose modification guidelines for lapatinib have been developed for the management of selected AEs (Table 10). The investigator must consult the Medical Monitor prior to continuing therapy for any subject requiring a delay of treatment of more than two weeks for any reason, but in general in these circumstances subjects should be withdrawn from treatment permanently.

**Table 10 Dose modification rules for lapatinib**

Toxicity NCI-CTCAE Grade	During Course of Therapy	Lapatinib Dose Change
<b>Grade 1</b>	Maintain dose	No change
<b>Specific Events of Grade 2/3</b> <b>Haematology</b> Absolute Neutrophil Count (ANC) <1.5 × 10 <sup>9</sup> /L Platelet count is <100.0 × 10 <sup>9</sup> /L Haemoglobin is <9.0 g/dL (after transfusion if needed) <b>Chemistry</b> For liver AE refer to Section 5.13 Serum Creatinine ≥1.5 mg/dL Calculated Creatinine Clearance <40mL/mins (Appendix 6)	Interrupt treatment until resolved to Grade 0-1, up to 14 days.  If toxicity does not resolve, consult GSK Medical Monitor to determine if it is in the best interest of the subject to continue in the study	1 <sup>st</sup> appearance Resume 100%  2 <sup>nd</sup> appearance Resume 100% or dose reduce to 1000mg/day.  3 <sup>rd</sup> appearance-Resume 100% or dose reduce to 1000mg/day.
<b>Grade 2-Any other event</b> For Cardiac Ejection Fraction and interstitial pneumonitis AEs, refer to Section 5.12.3. For liver AE refer to Section 5.13. For rash refer to Section 5.12.1. For diarrhoea refer to Section 5.12.2 and to Appendix 1	Maintain dose for 1 <sup>st</sup> and 2 <sup>nd</sup> appearance  Interrupt treatment until resolves to Grade 0-1, up to 14 days for 3 <sup>rd</sup> and 4 <sup>th</sup> appearance	1 <sup>st</sup> appearance-Maintain dose- No change 2 <sup>nd</sup> appearance- Maintain dose No change 3 <sup>rd</sup> appearance – Resume 100% or dose reduce to 1000mg/day 4 <sup>th</sup> appearance – Resume with a dose reduction to 1000mg/day.
<b>Grade 3 – Any other event</b> For Cardiac Ejection Fraction and interstitial pneumonitis AEs, refer to Section 5.12.3. For liver AE refer to Section 5.13. For rash refer to Section 5.12.1. For diarrhoea refer to Section 5.12.2 and to Appendix 1	Interrupt treatment until resolves to Grade 0-1, up to 14 days.	Any appearance-Resume 100% or Reduce dose to 1000mg permitted in consultation with GSK Medical Monitor.
<b>Grade 4</b> For Cardiac Ejection Fraction and interstitial pneumonitis AEs, refer to Section 5.12.3 For liver AE refer to Section 5.13. For rash refer to Section 5.12.1. For diarrhoea refer to Section 5.12.2 and to Appendix 1	Interrupt treatment until resolves to Grade 0-1, up to 14 days.	Consult with GSK Medical Monitor to determine if in the best interest of the subject to continue at a dose reduction.

Toxicity grading system according to NCI-CTCAE V4.03

### 5.11. Dose Delays and Reductions for Capecitabine

Dose modification guidelines for capecitabine have been developed for the management of selected AEs (Table 11).

**Table 11 Dose modification rules for capecitabine**

Toxicity NCI-CTCAE Grade	During Course of Therapy	Capecitabine Dose Change
<b>Grade 1</b>	Maintain dose	No change
<b>Specific Events of Grade 2/3</b> <b>Haematology</b> ANCs $<1.5 \times 10^9/L$ Platelet count is $<100.0 \times 10^9/L$ Haemoglobin is $<9.0$ g/dL (after transfusion if needed) <b>Chemistry</b> For liver AE refer to Section 5.13. Serum Creatinine $\geq 1.5$ mg/dL. Calculated Creatinine Clearance $<40$ mL/mins (Appendix 6)	Interrupt treatment until resolved to Grade 0-1, up to 14 days.  If toxicity does not resolve, consult GSK Medical Monitor to determine if it is in the best interest of the subject to continue in the study.	1 <sup>st</sup> appearance -Resume at 100% or Resume at 75% (rounded to nearest 150mg) as clinically indicated 2 <sup>nd</sup> appearance Resume at 75% (rounded to nearest 150mg) 3 <sup>rd</sup> appearance-Resume at 50% of starting dose rounded to nearest 150mg) 4 <sup>th</sup> appearance-Discontinue permanently
<b>Grade 2-Any other event</b> For liver AE refer to Section 5.13. For diarrhoea refer to Section 5.12.2 and to Appendix 1	Interrupt treatment until resolved to Grade 0-1, up to 14 days.	1 <sup>st</sup> appearance -Resume at 100% or Resume at 75% (rounded to nearest 150mg) as clinically indicated 2 <sup>nd</sup> appearance Resume at 75% (rounded to nearest 150mg) 3 <sup>rd</sup> appearance-Resume at 50% of starting dose rounded to nearest 150mg) 4 <sup>th</sup> appearance-Discontinue permanently
<b>Grade 3 – Any other event</b> For liver AE refer to Section 5.13. For diarrhoea refer to Section 5.12.2 and to Appendix 1	Interrupt until resolves to Grade 0-1, up to 14 days.	1 <sup>st</sup> appearance-Resume 75% of starting dose (rounded to nearest 150mg) 2 <sup>nd</sup> appearance- Resume 50% of starting dose (rounded to nearest 150 mg) 3 <sup>rd</sup> appearance- Discontinue treatment permanently
<b>Grade 4</b> For liver AE refer to Section 5.13. For diarrhoea refer to Section 5.12.2 and to Appendix 1	Interrupt until resolves to Grade 0-1, up to 14 days.	Consult GSK Medical Monitor to determine if it is in the best interest of the subject to continue at a dose level lower than the original capecitabine dose

Toxicity grading system according to NCI-CTCAE V4.03

## 5.12. Guidelines for Events of Special Interest and Dose Modifications

The severity of AEs will be graded in accordance with the NCI CTCAE version 4.03. Guidelines for dose modifications and interruptions for management of common toxicities associated with the treatment with lapatinib and capecitabine are provided in this section. Any future changes made to this guidance will be communicated to the investigative sites in the form of a letter and the revised version will be included in the SPM.

## 5.12.1. Dermatological Events

### 5.12.1.1. Dermatological Monitoring

As part of their physical examination, subjects must have a thorough skin examination prior to the start of study treatment or randomisation. The examination may include the scalp, previously irradiated areas, hair, and nails. In addition, if clinically indicated an examination of the oral/genital mucosa may also be included.

Subsequent dermatological evaluations should be performed as clinically indicated. Any serious and/or clinically relevant dermatological AEs must be followed until resolution to grade one (or better), or until there is no further improvement.

Subjects must also have a skin examination as part of the physical examination at the end of 24 weeks of treatment with lapatinib and capecitabine, or disease progression, treatment discontinuation due to unacceptable toxicity or subject withdrawal, whichever is sooner.

The purpose of dermatological monitoring is:

- to facilitate dermatological safety throughout the trial in all subjects receiving lapatinib;
- to assess whether a holding/stopping rule imposed during the course of treatment leads to less dermatological toxicity;
- to identify the incidence of dermatological adverse events (AEs) for lapatinib, or the combination of lapatinib with other agents.

### 5.12.1.2. Frequency Evaluation and Grading Guide of Dermatological AEs

The frequency of dermatological adverse events occurring in 2,093 patients with locally advanced or metastatic cancer who participated in nine completed phase II and III lapatinib clinical trials is shown in [Table 12](#). This patient population included 1,413 patients with breast cancer and 680 patients with other cancers. Patients were treated with lapatinib as monotherapy (n = 926) or in combination with paclitaxel (n=293) or capecitabine (n = 491). Patients who were not exposed to lapatinib but received paclitaxel, capecitabine, or hormonal agents served as controls (n = 676).

**Table 12 Most Common Dermatological AEs Occurring in Patients Receiving Lapatinib (NCI-CTCAE versions 2.0 and 3.0)**

Skin event	CTC grade, %															
	All L <i>n</i> = 1,417		L <i>n</i> = 926		L + C <i>n</i> = 198		L + P <i>n</i> = 293		No L <sup>a</sup> <i>n</i> = 676		C <i>n</i> = 191		P <i>n</i> = 286		Hormonal <i>n</i> = 199	
	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3
Rash	43	4	47	3	13	2	50	8	14	<1	8	<1	25	<1	5	<1
Hand-foot syndrome	8	2	<1	<1	54	14	1	<1	14	4	51	14	0	0	0	0
Hair disorder	3	<1	<1	0	<1	0	14	1	16	2	<1	0	37	5	2	0
Dry skin	3	<1	3	<1	2	0	3	0	3	0	2	0	2	0	5	0
Pruritus/Urticaria	3	<1	3	<1	<1	0	5	<1	4	<1	<1	0	7	<1	2	0
Skin disorder	1	0	2	0	<1	0	1	0	<1	<1	2	0	1	<1	0	0
Skin infection	<1	<1	<1	0	<1	<1	0	0	<1	0	0	0	<1	0	0	0
Nail disorder	<1	<1	1	<1	0	0	1	0	<1	0	<1	0	<1	0	<1	0

There were no grade 4 dermatologic events

CTC: National Cancer Institute Common Toxicity/Terminology Criteria for Adverse Events; L: lapatinib; C: capecitabine; P: paclitaxel

<sup>a</sup> No lapatinib is monotherapy with either hormones (*n* = 199), capecitabine (*n* = 191), or paclitaxel (*n* = 286)

The NCI CTCAE descriptions and grades of severity of dermatological AEs is presented in [Table 13](#).

**Table 13 NCI-CTCAE dermatological reactions**

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Rash: Acne/acneiform (Acne)	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local super infection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive super infection with IV antibiotics indicated; life-threatening consequences	Death

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Nail Loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localised intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Pruritus/itching (Pruritus)	Mild or localised; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	
Alopecia	Hair loss of up to 50% of normal for that individual that	Hair loss of >50% normal for that individual	-	-	

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact			
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death

Lapatinib-related severe dermatological events ( $\geq$ Grade 3) are infrequent (1-3%). Despite the rarity of lapatinib associated severe dermatological events, it is recommended that subjects who present with a severe dermatological event be assessed for the following: shortness of breath, angioedema, or generalised mucosal/cutaneous affection with blisters or ulcers, suggestive of Type I hypersensitivity and/or NCI-CTCAE Grade 4 dermatological event, manifested as toxic epidermal necrolysis or Stevens-Johnson Syndrome etc. If a Grade 4 dermatological event occurs, lapatinib must be permanently discontinued.

### 5.12.1.3. Stopping and holding rules

If any Grade 4 dermatological event occurs, lapatinib must be permanently discontinued.

#### 5.12.1.3.1. Holding rule

Lapatinib should be held for 14 days, in all patients who experience either a grade 3 dermatological reaction or a grade 2 dermatological reaction, which is unimproved after two-weeks of medical management. After the 14 day interruption, and provided the dermatological reaction improves to grade 1 or better, lapatinib may be restarted at the previous dose.

If the investigator considers continuation of lapatinib without interruption, it is required that he/she discusses the individual case with the GSK medical monitor before taking any decision on study treatment. In some cases, resolution of grade 2 or greater dermatological reactions occurred without interruption of lapatinib. For those subjects

that interrupted lapatinib, many were able to resume lapatinib therapy at the same dose after resolution of the dermatological event.

#### **5.12.1.3.2. Re-challenge**

One re-challenge may be considered, if indicated in the opinion of the investigator, for subjects who present with NCI-CTCAE Grade 3 dermatological events which recover to NCI-CTCAE Grade 1 or better (within 14 days) after holding lapatinib.

#### **5.12.1.3.3. Stopping rules**

Lapatinib must be permanently discontinued for:

- Recurrent Grade 3 dermatological reactions
- All Grade 4 dermatological reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.

#### **5.12.1.4. Treatment**

There is no standard treatment proven to be effective for lapatinib-induced dermatological reactions. Therefore it is recommended that subjects who develop Grade 2 dermatological reactions that are unresponsive to initial treatment may be referred to a dermatologist for evaluation and management. For subjects with Grade 3 or 4 dermatologic events, or chronic, persistent or recurring lower grade skin events, a dermatology consultation is strongly encouraged.

There are some general precautions for subjects receiving lapatinib therapy. Subjects are recommended to avoid exposure to bright sunlight. When going out into bright sunlight, a broad spectrum sunscreen (containing titanium dioxide or zinc oxide) with an SPF of at least 30 should be applied.

A variety of agents may be used to manage dermatological reactions. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, immunomodulators, hypoallergenic moisturisers, and emollients.

The need for oral or topical antibiotics and topical steroids is a clinical decision. For **pruritic** lesions oral antihistamine agents may be effective. For **paronychia** antiseptic bath and local potent corticosteroids in addition to tetracycline therapy is recommended. If no improvement occurs, a dermatology or surgery consultation is recommended. For **infected** lesions appropriate, culture driven treatment with systemic or topical antibiotics is recommended as clinically indicated.

Oral retinoids are not recommended because of theoretical concerns about negative effects on lapatinib's mechanism of action. Topical steroids may result in skin irritation and severe xerodermia (dryness). Oral steroids may be used for a short treatment course (maximum of 14 days).

## 5.12.2. Gastrointestinal Events

If gastrointestinal AEs are not appropriately managed, they may be associated with the development of dehydration.

### 5.12.2.1. Nausea and vomiting

In subjects who vomit and are unable to retain lapatinib and/or capecitabine, every attempt should be made to control nausea and vomiting. If a subject vomits after administration of study drug, the subject should be instructed not to retake the dose. Subjects should take the next dose as scheduled. If vomiting persists, then the subject should contact the investigator.

### 5.12.2.2. Diarrhoea

Diarrhoea is the primary efficacy endpoint of this study. It is essential that the investigator understands fully the classification of diarrhoea and the definitions of severity used in this study (Table 8). For each diarrhoea AE report, the investigator should assess the change in stool form and frequency relative to the normal form and frequency for the subject to accurately ascertain the grade of the diarrhoea AE.

In rare cases, diarrhoea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances. Diarrhoea should be managed proactively to avoid complications such as dehydration, renal insufficiency, and electrolyte imbalances or worsening of the subject's condition.

Standardised guidelines for treating chemotherapy-associated diarrhoea have been developed by ASCO [Benson, 2004], and these have been used to develop specific guidelines for the management of diarrhoea associated with lapatinib use (Appendix 1). These guidelines should be used in combination with the treatment delay and dose reduction rules described in Section 5.10 and in Section 5.11.

## 5.12.3. Cardiac and Respiratory Events

### Asymptomatic Cardiac Events

Subjects who have a  $\geq 20\%$  decrease in left ventricular cardiac ejection fraction relative to baseline, and an ejection fraction below the institution's lower limit of the normal range (LLN), should have a repeat evaluation of ejection fraction 1-2 weeks later while still receiving treatment with lapatinib and capecitabine.

If the repeat ejection fraction evaluation confirms a  $\geq 20\%$  decrease in left ventricular cardiac ejection fraction, and the ejection fraction is below the institution's LLN, then treatment with lapatinib and capecitabine should be temporarily discontinued.

If the left ventricular ejection fraction recovers during the next 3 weeks, after consultation and approval of the medical monitor, the subject may be restarted on treatment with lapatinib and capecitabine at a reduced dose of lapatinib. For such subjects, monitoring of left ventricular ejection fraction will then be performed 2 weeks and 4 weeks after rechallenge, and then every 4 weeks thereafter.

If repeat ejection fraction evaluation still shows a  $\geq 20\%$  decrease in left ventricular ejection fraction relative to baseline, and the value is below the institution's LLN, then the subject should be withdrawn from treatment with lapatinib and capecitabine.

### Symptomatic Respiratory and Cardiac Events

Subjects should be monitored for symptoms of pulmonary toxicity (dyspnoea, cough, fever, interstitial pneumonitis) or cardiotoxicity, and subjects who experience pulmonary symptoms or left ventricular systolic dysfunction which are NCI CTCAE Grade 3 or greater must be withdrawn from treatment with lapatinib and capecitabine.

#### 5.12.4. Hand and Foot Syndrome

The frequency of hand and foot syndrome among patients receiving capecitabine has led the US regulatory agency, in conjunction with the manufacturer, to arrive at the capecitabine-specific toxicity rating scale shown in [Table 14](#).

**Table 14** Hand and Foot toxicity rating scale

Criteria for grading palmar-plantar erythrodysesthesia (hand and foot) syndrome	
Toxicity Grade	Manifestations
Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling, or erythema of the hands and/or feet that causes discomfort but does not disrupt normal activities of daily living
Grade 2	Painful erythema and swelling of the hands and/or feet that results in discomfort affecting normal activities of daily living
Grade 3	Moist desquamation, ulceration, blistering, and severe pain of the hands and/or feet and/or severe discomfort that causes inability to work or perform activities of daily living
Source: Capecitabine SPC	

In the event the subject presents with hand-foot syndrome, follow the recommended dose modification guidelines for capecitabine described in Section 5.11. If Grade 2 or 3 hand-foot syndrome occurs, administration of lapatinib and capecitabine should be stopped until resolution to Grade 0-1.

### 5.13. Monitoring, Interruption, and Stopping Criteria for Hepatobiliary Events

If alanine aminotransferase (ALT) is  $\geq 3xULN$  and bilirubin  $\geq 2xULN$ , and serum bilirubin fractionation is not immediately available, the subject must discontinue study treatment. Serum bilirubin fractionation should be performed if testing is available.

If serum bilirubin testing is unavailable, the presence of detectable urinary bilirubin on a dipstick test is indicative of direct bilirubin elevations and suggests liver injury may be present.

A safety algorithm detailing stopping and follow up criteria for hepatobiliary AEs is presented in [Appendix 7](#).

#### 5.13.1. Liver Chemistry Stopping Criteria

Phase II study liver chemistry stopping and follow up criteria have been designed to assure subject safety and to evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, [www.fda.gov](http://www.fda.gov)).

Phase II liver chemistry stopping criteria 1-5 are defined as follows and are presented in a Figure in [Appendix 7](#):

1. ALT  $\geq 3xULN$  **and** bilirubin  $\geq 2xULN$  ( $>35\%$  direct bilirubin) (or ALT  $\geq 3xULN$  and INR  $>1.5$ , if INR measured)

**NOTE:** If serum bilirubin fractionation is not immediately available, and if ALT  $\geq 3xULN$  **and** bilirubin  $\geq 2xULN$  discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT  $\geq 5xULN$ .
3. ALT  $\geq 3xULN$  if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. ALT  $\geq 3xULN$  persists for  $\geq 4$  weeks
5. ALT  $\geq 3xULN$  and cannot be monitored weekly for 4 weeks

**When any of the liver chemistry stopping criteria 1-5 is met, do the following:**

- **Immediately discontinue subject from** study treatment
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE

- All events of ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN (>35% direct bilirubin) (or ALT $\geq$ 3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed ‘Hy’s Law’, **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
- NOTE: if serum bilirubin fractionation is not immediately available, and if ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Withdraw the subject from the study after completion of the liver chemistry monitoring as described below.
- Subjects meeting criterion 5 should be monitored as frequently as possible.

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 5.13.1.1), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, Aspartate aminotransferase [AST], alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For subjects meeting any of the liver stopping criteria 2-5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (refer to Section 5.13.1.1)
- Monitor subjects weekly until liver chemistries (ALT, aspartate aminotransferase (AST), alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
- Subjects meeting criterion 5 should be monitored as frequently as possible.

All subjects who meet the liver chemistry criteria requiring permanent discontinuation of treatment with lapatinib and capecitabine must complete the study assessments and procedures as defined in the Time and Events Schedule (Table 16 and Table 17).

### 5.13.1.1. Liver event follow up assessments

For subjects meeting any of the liver chemistry stopping criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A immunoglobulin M (IgM) antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody;
- Blood sample for pharmacokinetic (PK) analysis, obtained within one week of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase and lactate dehydrogenase;
- Fractionate bilirubin if total bilirubin  $\geq 2xULN$ .
- Complete blood count with differential to assess eosinophilia;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, decreased appetite, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash or eosinophilia as relevant on the AE form;
- Record use of concomitant medications, such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form;
- Record alcohol use on the liver event alcohol intake form.

The following assessments are required for subjects with ALT  $\geq 3xULN$  and bilirubin  $\geq 2xULN$  ( $>35\%$  direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG) or gamma globulins)
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

- Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [[James](#), 2009]. **NOTE: not required in China**)
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE:** if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed [[Le Gal](#), 2005]).

### 5.13.2. Liver Chemistry Monitoring Criteria

For subjects with ALT  $\geq 3xULN$  **but**  $< 5xULN$  **and** bilirubin  $< 2xULN$ , without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety
- Continue treatment with lapatinib and capecitabine
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time the subject meets any of the liver chemistry stopping criteria (Section [5.13.1](#)), proceed as described above
- If, after 4 weeks of monitoring, ALT  $< 3xULN$  and bilirubin  $< 2xULN$ , monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

An algorithm of liver chemistry monitoring, interruption stopping and follow up criteria is presented in [Appendix 7](#).

## 6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

### 6.1. Permitted Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

The following will be recorded on the appropriate eCRF pages:

- A complete list of prescription and over-the-counter medications (including herbal medications) that have been taken **within two weeks** prior to treatment with octreotide for subjects randomised to receive octreotide or **within two weeks** prior to the first dose of lapatinib and capecitabine for subjects randomised to receive no octreotide.

- All treatments related to supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeal medications and analgesics.
- All other concomitant medications (including over-the-counter medications) taken during the study.

**NOTE:** Lapatinib is likely to increase exposure to concomitantly administered drugs which are metabolized by CYP3A4 or CYP2C8. Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. **Caution** should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. Refer to [Table 15](#) for a list of CYP3A4 Inducers and Inhibitors that are prohibited during this study.

Concurrent treatment with bisphosphonates is permitted; however treatment must be initiated prior to the first dose of study treatment. Prophylactic use of bisphosphonates in subjects without bone disease is not permitted, except for the treatment of osteoporosis.

## 6.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited:

- Anti-cancer therapy should not be given until disease progression or withdrawal from investigational treatment. Subjects who receive concurrent anti-cancer therapy (i.e. cytotoxic or biologic) will not be allowed to continue treatment with lapatinib and capecitabine. Subjects who require an alternative anti-cancer therapy may withdraw from the study at any time;
- Concurrent radiation therapy and surgery for metastatic breast cancer, including resection of non-dominant metastases. Radiotherapy will ONLY be allowed for palliation of pain for bone metastases and for spinal cord decompressions;
- Hormonal therapy(ies), other than physiologic replacement;
- Any other investigational drug;
- All herbal supplements, because the composition, pharmacokinetics and metabolism of many herbal supplements are unknown;
- Inducers and inhibitors of CYP3A4, because they may alter the metabolism of lapatinib. The list of CYP3A4 inducers and inhibitors that are prohibited from screening through to discontinuation from study treatment is presented in [Table 15](#).
- allopurinol, dipyridamole, folinic acid, trimethoprim, leucovorin, sorivudine and its' analogues, because they are contraindicated with capecitabine or associated with 5-FU interactions.

Pre-treatment with a proton pump inhibitor (esomeprazole) decreased lapatinib exposure by an average of 27% (range: 6% to 49 %). This effect decreases with increasing age from approximately 40 to 60 years. Therefore, caution should be used when lapatinib is used in subjects pre-treated with a proton pump inhibitor.

Anticoagulation with coumarin or derivatives other than in low doses (e.g.  $\leq 1$  mg coumarin daily) for catheter prophylaxis is prohibited. Subjects taking coumarin at doses  $\leq 1$  mg daily should be monitored regularly for alteration in their coagulation parameters (prothrombin time or international normalized ratio [INR]).

Concomitant administration of octreotide and bromocriptine increases the bioavailability of bromocriptine.

Octreotide reduces the intestinal absorption of cyclosporin and delays that of cimetidine. Cimetidine is a prohibited medication due to its known effect on liver enzymes, and the potential for interaction with lapatinib.

Information on potential interactions with other medicinal products is presented in the Lapatinib, Capecitabine and Octreotide SPCs.

**Table 15 CYP3A4 inducers and inhibitors**

Drug Class	Specific Agents	Wash-out <sup>1</sup>
CYP3A4 Inducers		
rifamycin antibiotics	rifampicin, rifabutin, rifapentine	2 weeks
anticonvulsants	phenytoin, carbamazepine, barbiturates (e.g., phenobarbital)	
antiretrovirals	efavirenz, nevirapine, tipranivir, etravirine	
glucocortical steroids (oral only)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg) <sup>2</sup>	
other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
antibiotics	clarithromycin, erythromycin, troleandomycin, flucloxacillin	1 week
antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
antiretrovirals	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir, atazanavir	
calcium channel blockers	verapamil, diltiazem	
antidepressants	nefazodone, fluvoxamine	
gastrointestinal agents <sup>3</sup>	cimetidine	
fruit juices	grapefruit, star fruit and papaw	
other	amiodarone	6 months
Miscellaneous		
antacids	Mylanta, Maalox, Tums, Rennies	1 hour before and after dosing
herbal supplements <sup>4</sup>	ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	2 weeks

1. Time period between last dose of listed drug and first dose of lapatinib, required to avoid drug-drug interaction potential for toxicity (inhibitors) or loss of efficacy (inducers) that could make the subject unevaluable. Clinically appropriate substitution of drugs not on the list is recommended.
2. A standard 3-5 day course of dexamethasone at a dose following the institutions standard of care for the prevention and/or treatment of platinum-induced nausea and vomiting is allowed. Glucocortical steroid oral dose equivalents (in parentheses) to dexamethasone 1.5 mg (or less) given daily are allowed. Intravenous dosing should be considered if clinically appropriate.
3. Emetogenic chemotherapy may require 3-4 daily doses of aprepitant. CYP3A4 inhibition by oral (not IV) aprepitant may require a concurrent dose reduction of 1-2 lapatinib tablets.
4. This list is not all-inclusive; therefore, for herbal supplements not listed, please contact a GSK Medical Monitor or Clinical Scientist.

NOTE: If future changes are made to the list of prohibited medications, formal documentation will be created and stored with the study file. Any changes will be communicated to the investigative sites in the form of a letter and revised version included in the SPM.

### 6.3. Treatment after Discontinuation of the 24 Week Study Treatment or Withdrawal from/Completion of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment.

In countries and centres where lapatinib and capecitabine are reimbursed and have been sourced locally, lapatinib and capecitabine should also be sourced locally for continuation

of treatment post-study. These subjects are considered to have completed the study after 24 weeks of treatment with lapatinib and capecitabine, and post-study care should be conducted in accordance with local best practice.

In countries and centres where lapatinib and capecitabine are provided by GSK, these drugs will also be provided by GSK for continuation of treatment post-study. After completing 24 weeks of treatment with lapatinib and capecitabine, these subjects will enter the long term follow up (LTFU) phase of the study and will continue to receive treatment with lapatinib and capecitabine until disease progression, unacceptable toxicity or death.

Upon discontinuation from treatment with lapatinib and capecitabine, subjects may receive additional (non protocol) anti-cancer therapy at the discretion of the treating physician. Every effort should be made to complete the required withdrawal evaluations and follow up evaluations relating to resolution or stabilization of SAEs prior to initiating further anti-cancer therapy or dosing of an investigational agent (see [Table 16](#) and [Table 17](#) for end of study and follow-up assessments and procedures).

#### **6.4. Treatment of Study Treatment Overdose**

There is no specific antidote for the inhibition of EGFR and/or HER2 tyrosine phosphorylation. The maximum oral doses of lapatinib that have been administered to date are 1800 mg once daily and 900 mg twice daily. Serum concentrations following 900 mg twice daily dosing are approximately twice that of 1800 mg once daily.

Subjects with suspected lapatinib overdose should be monitored until drug can no longer be detected systemically (at least 2.5 days). Follow-up physical examination with laboratory testing should be performed between 10 and 14 days after drug concentrations are undetectable and before the subject is discharged from the investigator's care.

Lapatinib is not significantly renally excreted and is highly bound to plasma proteins, therefore haemodialysis would not be expected to be an effective method to enhance the elimination of lapatinib. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

If an overdose with octreotide should occur, the investigator, site pharmacist or authorized site personnel should refer to the Sandostatin SPC for instruction.

Any SAEs that occur as a result of an overdose of treatment with lapatinib or capecitabine should be reported to the GSK Medical Monitor and through the usual SAE reporting process as described in [Section 7.4.9](#).

## 7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments.

The schedule of all assessments is presented in [Table 16](#) and [Table 17](#). Details of the efficacy and safety assessments are presented in [Section 7.2](#) and [Section 7.3](#), respectively. Details of health outcomes [REDACTED] are presented in [Section 7.7](#) and [Section 7.8](#), respectively. Further details of study procedures and assessments can be found in the SPM.

Procedures conducted as part of the subject's routine clinical management (e.g., liver function) and obtained prior to the signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe of the study.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

**Table 16 Time and events schedule; Subjects who receive octreotide**

	Screen <sup>1</sup>	Octreotide Dose 1 (Week -1)	Lapatinib and Capecitabine Cycle <sup>10</sup>			Withdrawal from Study Treatment or End of Study <sup>15</sup>
			Cycle 1	Cycle 2 <sup>13</sup> (Octreotide Dose 2)	Cycles 3 to 8 <sup>13</sup>	
<b>Procedures</b>						
Informed Consent	x					
Inclusion/Exclusion Criteria	x <sup>2</sup>	x <sup>2</sup>				
Demographics	x					
Breast Cancer Medical/Surgical and Treatment History	x					
<b>Efficacy and Safety Assessments</b>						
AE/Toxicity Assessment		x	x	x	x	x <sup>16</sup>
Disease Assessment	x <sup>3</sup>	(x) <sup>5</sup>	(x) <sup>5</sup>	(x) <sup>5</sup>	(x) <sup>5</sup>	x
PROs <sup>6</sup>		x <sup>7</sup>	x <sup>11</sup>	x	x	x
Concurrent Medications	x	x	x	x	x	x
Physical Exam	x					x
Dermatological Exam	x	(x) <sup>8</sup>	(x) <sup>8</sup>	(x) <sup>8</sup>	(x) <sup>8</sup>	x
Weight, Height, Vital Signs (Temp, BP, pulse)	x					x
ECOG Performance Status	x <sup>4</sup>					x
Cardiac function	x					x <sup>17</sup>
ECG	x					(x) <sup>8</sup>
<b>Lab Assessments</b>						

	Screen <sup>1</sup>	Octreotide Dose 1 (Week -1)	Lapatinib and Capecitabine Cycle <sup>10</sup>			Withdrawal from Study Treatment or End of Study <sup>15</sup>
			Cycle 1	Cycle 2 <sup>13</sup> (Octreotide Dose 2)	Cycles 3 to 8 <sup>13</sup>	
<b>Procedures</b>						
Liver function	x	(x) <sup>5</sup>	(x) <sup>5</sup>	(x) <sup>5</sup>	(x) <sup>5</sup>	x
Pregnancy Test	x					x
<b>Study Treatments</b>						
Administer Octreotide		x <sup>9</sup>		x <sup>14</sup>		
Dispense Lapatinib and Capecitabine			x	x	x	
Assess Lapatinib and Capecitabine Returned				x	x	x

- Schedules for screening assessments are presented in Section 7.1.1 and Section 7.1.2. All screening and baseline assessments must be completed prior to administration of the octreotide 0.1mg s.c. tolerability assessment dose.
- Inclusion and exclusion criteria are presented in Section 4.1.2 and Section 4.1.3, and other considerations are presented in Section 4.2. 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.
- 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 DMD.
- Week -1 baseline PROs to be completed prior to randomisation, before the octreotide 0.1mg s.c. tolerability assessment dose.
- If clinically indicated, in accordance with the Lapatinib SPC.
- 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.
- Visits at the start of Cycle 2 and Cycle 4 are mandatory.** Visits at the start of Cycle 3, 5, 6, 7 and 8 are not mandatory; visits every 3 weeks would be preferred, but may be adapted to match local practice.
- Week 0 baseline PROs to be completed before the first dose of lapatinib and capecitabine is administered.
- 
- Cycle 2 to be started 21 days ( $\pm 2$  days) after the start of Cycle 1. Other cycles should be started within  $\pm 4$  days of the 3 weekly treatment cycle intervals.
- Second dose of octreotide LAR to be given 28 days ( $\pm 2$  days) after first dose of octreotide LAR.
- 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.
- Serious adverse events and other safety data as described in Section 7.4 should be reported for all subjects who continue treatment with lapatinib and capecitabine beyond the 24 week end of study assessment.
- If more than 12 weeks since the screening cardiac function assessment.

**Table 17 Time and events schedule; Subjects who receive no octreotide**

	Screen <sup>1</sup>	Lapatinib and Capecitabine Cycle		Withdrawal from Study Treatment or End of Study Visit <sup>12</sup>
		Cycle 1	Cycle 2 <sup>10,11</sup> to 8	
<b>Procedures</b>				
Informed Consent	x			
Inclusion/Exclusion Criteria	x <sup>2</sup>	x		
Demographics	x			
Medical/Surgical and Treatment History	x			
<b>Efficacy and Safety Assessments</b>				
AE/Toxicity Assessment		x	x	x <sup>13</sup>
Disease Assessment	x <sup>3</sup>	(x) <sup>5</sup>	(x) <sup>5</sup>	x
PROs <sup>6</sup>		x <sup>7</sup>	x	x
Concurrent Medications	x	x	x	x
Physical Exam	x			x
Dermatological Exam	x	(x) <sup>8</sup>	(x) <sup>8</sup>	x
Weight, Height, Vital Signs (Temp, BP, pulse)	x			x
ECOG Performance Status	x <sup>4</sup>			x
Cardiac function	x			x <sup>14</sup>
ECG	x			(x) <sup>8</sup>
<b>Lab Assessments</b>				
Liver function	x	(x) <sup>5</sup>	(x) <sup>5</sup>	x
Pregnancy Test	x			x
<b>Study Treatments</b>				
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. 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, and other considerations are presented in Section 4.2. 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.
- 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 DMD.
- Week 0 baseline PROs to be completed prior to randomisation, before the first dose of lapatinib and capecitabine is administered.
- If clinically indicated, in accordance with the Lapatinib SPC.
- 
- Cycle 2 to be started 21 days ( $\pm 2$  days) after the start of Cycle 1. Other cycles should be started within  $\pm 4$  days of the 3 weekly treatment cycle intervals.
- Visits at the start of **Cycle 2 and Cycle 4 are mandatory**. Visits at the start of Cycle 3, 5, 6, 7 and 8 are not mandatory; visits every 3 weeks would be preferred, but may be adapted to match local practice.
- 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.

13. Serious adverse events and other safety data as described in Section 7.4 should be reported for all subjects who continue treatment with lapatinib and capecitabine beyond the 24 week end of study assessment.
14. If more than 12 weeks since the screening cardiac function assessment.

## **7.1. Assessments and Procedures**

Following randomisation subjects will be followed according to the Time and Events Schedules (Table 16 and Table 17). Under exceptional circumstances and with prior documented agreement between the principal investigator and the medical monitor, the timing of assessments may be adjusted to ensure subject safety or scientific integrity.

### **7.1.1. Critical Baseline Assessments**

All subjects enrolled in LAP117314 must be eligible to receive treatment with lapatinib and capecitabine. The investigator must confirm that all subjects have histologically or cytologically confirmed HER2-positive breast cancer which has progressed following prior therapy, which must have included anthracyclines and taxanes and trastuzumab in the metastatic setting.

Cardiovascular medical history/risk factors will be assessed at baseline.

### **7.1.2. Screening and Baseline Assessments and Procedures**

Baseline and screening assessments should be completed prior to the first dose of octreotide for subjects randomised to receive octreotide and prior to the first dose of lapatinib and capecitabine for subjects randomised to receive no octreotide.

Subjects who meet the inclusion and exclusion criteria for the study must complete the Informed Consent Form before any study-specific procedures are conducted.

### **Within 4 Weeks prior to First Dose of Study Treatment**

- Disease assessment, in accordance with RECIST version 1.1 [Eisenhauer, 2009]:
  - Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
  - Pathological lymph nodes with <15mm and but  $\geq 10$ mm short axis are considered non measurable.
  - Pathological lymph nodes with  $\geq 15$ mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
  - Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

**Note:** Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

**Note:** Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by computerized tomography (CT) or magnetic resonance imaging (MRI) can be considered measurable. Bone scans, fluorodeoxyglucose-positron emission tomography scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.
- Disease characteristics and breast cancer history:
  - Details of the primary tumor: oestrogen and progesterone receptor status (performed by immunohistochemical [IHC] methods), and HER2 status, including IHC and /or fluorescence in-situ hybridization (FISH) analysis;
  - Clinical characteristics: date of diagnosis, stage and histology at initial diagnosis, date of documented diagnosis of metastatic disease by CT or MRI (if applicable), site(s) of metastases, lines of therapy completed;
  - Prior treatment history: adjuvant or neoadjuvant chemotherapy received (agent(s), date of last dose), biologic therapy, immunotherapy or hormonal therapy received.
- Current medical conditions.
- ECOG performance status (as defined in [Appendix 4](#)). This should not be recorded in the eCRF.
- Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin). Other haematology and clinical chemistry tests should be conducted in accordance with local clinical practice, but should only be recorded in the eCRF if associated with an AE or SAE.
- Electrocardiogram (12-lead ECG).
- Cardiac function: left ventricular ejection fraction (LVEF) measurement by echocardiogram or Multiple Gated Acquisition Scan (MUGA).

### **Within 7 days prior to First Dose of Study Treatment**

- Pregnancy test: serum human chorionic gonadotrophin ( $\beta$ -hCG) pregnancy test for women of childbearing potential. Test to be performed within 7 days prior to treatment with octreotide if randomised to receive octreotide or within 7 days prior to the first dose of lapatinib with capecitabine if randomised to receive no octreotide, but preferably as close to the start of treatment as possible. The results must be reviewed prior to initiating treatment.

### 7.1.3. Prior to Randomisation

These assessments are to be performed within 3 days prior to treatment with octreotide if randomised to receive octreotide or within 3 days prior to the first dose of lapatinib with capecitabine if randomised to receive no octreotide:

- Demographic data: year of birth, race, ethnicity, gender.
- Physical examination.
- Dermatological examination.
- Vital signs (body temperature, blood pressure and pulse rate).
- Height and weight.
- Review Current Medical Conditions.
- Review of screening liver function test results. If any result is outside the normal range the laboratory screening will be repeated (prior to the first dose of study medication) at the discretion of the Principal Investigator.
- Evaluation of diarrhoea occurring within the previous 2 weeks.
- Concomitant Medication: Record all medication(s) received within 2 weeks prior to the first dose of study treatment and note if the medication is continuing.
- ECOG performance status, as defined in [Appendix 4](#) This must be recorded in the eCRF.  
**Note:** if the subject's performance status score is  $>2$ , the subject will be excluded from the study.
- FACIT-D questionnaire and the baseline DMD. These must be completed before the first dose of any study treatment.

After all screening and baseline evaluations have been completed, determine if the subject is eligible for the study by reviewing the inclusion and exclusion criteria (Section [4.1.2](#) and Section [4.1.3](#)). Any changes in the subject's mental or physical condition since the time of screening that would make the subject ineligible for the study should be considered.

### 7.1.4. Post-Randomisation

Subjects will be randomised to receive octreotide or to receive no octreotide.

For subjects randomised to receive octreotide:

- Administer the octreotide 0.1mg s.c. tolerability assessment dose, monitor for at least one hour and record any AEs associated with this dose.
- Administer first dose of octreotide 40mg LAR (only in subjects who have not shown intolerance to the octreotide 0.1mg s.c. tolerability assessment dose).

For subjects randomised to receive no octreotide:

- Dispense lapatinib and capecitabine to the subject with instructions for taking therapy.

All subjects will be given advice concerning the management of diarrhoea. It is recommended that subjects should be provided with loperamide for the prompt management of diarrhoea.

#### **7.1.5. One Week after the First Dose of Octreotide LAR (Subjects Randomised to Receive Octreotide only)**

These assessments and procedures are to be performed 7 days after the first dose of octreotide LAR in subjects randomised to receive octreotide only.

- Record any AEs and SAEs and assign appropriate toxicity grade (NCI CTCAE, version 4.03).
- Dermatological examination, if clinically indicated.
- FACIT-D questionnaire and the baseline DMD. These must be completed before the first dose of lapatinib and capecitabine.
- Record all concomitant medications added and/or changed.
- Record visits to/contact with healthcare professionals associated with diarrhoea AEs.
- Record intravenous rehydration associated with diarrhoea AEs.
- Dispense lapatinib and capecitabine to the subject with instructions for taking therapy.

Other assessments, such as haematology, clinical chemistry, liver function tests and change in disease status should be conducted in accordance with the local standard of care. Liver function tests and change in disease status should be recorded as required in the relevant modules of the eCRF. Haematology and other clinical chemistry tests should be recorded in the eCRF only if associated with an AE or SAE.

#### **7.1.6. Assessments Every 3 Weeks**

These assessments are to be performed every 3 weeks or as close to these intervals as possible. **Assessments at the start of Cycle 2 and Cycle 4 of treatment with lapatinib and capecitabine are mandatory**; assessments at the start of Cycles 3, 5, 6, 7 and 8 should be performed in accordance with local clinical practice. Assessments at the end of the 24 week study treatment period (i.e. Cycle 8 of treatment with lapatinib and capecitabine) or at withdrawal from study treatment before the end of the 24 week study treatment period are described in 'Assessments at Study Completion or Early Withdrawal from Study and/or Study Treatment' (Section 7.1.8).

- Record any AEs and SAEs and assign appropriate toxicity grade (NCI CTCAE, version 4.03).
- Dermatological examination if clinically indicated.
- Record all concomitant medications added and/or changed.

- Record visits to/contact with healthcare professionals associated with diarrhoea AEs.
- Record intravenous rehydration associated with diarrhoea AEs.
- Record treatment delays or dose reductions associated with diarrhoea AEs.
- Assess compliance of taking lapatinib and capecitabine since the previous study visit; the importance of compliance should be reviewed and emphasised.
- Dispense lapatinib and capecitabine to the subject with instructions for taking therapy.
- Confirm completion of FACIT-D questionnaire and DMDs.

Subjects randomised to receive octreotide only, start of Cycle 2 only:

- Administer octreotide 40mg LAR dose 2.

Other assessments, such as haematology, clinical chemistry, liver function tests and change in disease status should be conducted in accordance with the local standard of care. Liver function tests and change in disease status should be recorded as required in the relevant modules of the eCRF. Haematology and other clinical chemistry tests should be recorded in the eCRF only if associated with an AE or SAE.

#### **7.1.7.      **Unscheduled Visits****

Unscheduled visits must be recorded in the eCRF. There are no formal requirements for assessments and procedures to be conducted at unscheduled visits. All data relevant to this study must be recorded, such as reason for the visit and actions taken as a consequence of the visit.

#### **7.1.8.      **Study Completion (24 weeks) or Early Withdrawal from Study and/or Study Treatment****

- Record any AEs and SAEs and assign appropriate toxicity grade (NCI CTCAE, version 4.03).
- Record all concomitant medications added and/or changed.
- Record visits to/contact with healthcare professionals associated with diarrhoea AEs.
- Record intravenous rehydration associated with diarrhoea AEs.
- Assess compliance of taking lapatinib and capecitabine since the previous study visit; the importance of compliance should be reviewed and emphasised.
- Record treatment delays or dose reductions associated with diarrhoea AEs.
- Confirm completion of FACIT-D questionnaires and DMDs.
- Liver function tests; ALT, AST, alkaline phosphatase, total bilirubin, fractionated bilirubin (if total bilirubin  $\geq 2 \times$  ULN).
- Echocardiogram or MUGA scan if the last cardiac assessment was >12 weeks previously.

- Physical examination.
- Dermatological examination.
- Vital signs; blood pressure, pulse rate.
- Body weight.
- ECOG performance status, as defined in [Appendix 4](#).
- Disease assessment, in accordance with RECIST version 1.1 [[Eisenhauer, 2009](#)].
- Pregnancy test: serum human chorionic gonadotrophin ( $\beta$ -hCG) pregnancy test for women of childbearing potential.

#### **7.1.9. Assessments after Study Completion: Long Term Follow Up**

Following completion of the 24 week study treatment period subjects may continue to receive treatment with lapatinib and capecitabine until disease progression or the occurrence of AEs leading to treatment discontinuation.

In countries and centres where lapatinib and capecitabine are provided by the study centre, subjects will continue to receive treatment with lapatinib and capecitabine in accordance with local practice. Post-study assessments of efficacy and safety will be performed in accordance with the local standard of medical care and the [Lapatinib](#) and [Capecitabine](#) SPCs.

In countries and centres where lapatinib and capecitabine are provided by GSK subjects will enter the LTFU phase of the study. Investigators will be required to collect and report the following safety information until lapatinib discontinuation:

- Adverse events (AEs) leading to lapatinib discontinuation.
- Other reasons leading to lapatinib discontinuation.
- Date of lapatinib discontinuation.

Additionally, investigators will be required to collect and report the following safety information, until 30 days following lapatinib discontinuation:

- Serious adverse events (SAEs) including AEs of special interest defined as SAEs will continue to be collected (as defined in Section [7.1.8](#) per protocol specific SAEs: cardiac, hepatic and pneumonitis).
- Pregnancies.
- Other AEs the investigator deems medically necessary to report.

Subjects with abnormal clinical or laboratory findings believed to be treatment-related will be followed until the condition resolves or until laboratory findings are not considered to be clinically significant.

### 7.1.10. Procedures and Assessments: Additional Information

At mandated visits laboratory assessments may be performed  $\pm$  3 days from the date of actual visit to the site in order to allow for flexibility in scheduling. Procedures, examinations, and laboratory assessments may be performed more frequently, if clinically indicated or part of routine clinical practice. GSK recommend that all laboratory tests with values that become significantly abnormal while the subject is participating in the study or within 5 days after the last dose of study-related treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor medical monitor notified.

Severity of diarrhoea will be determined according to the NCI CTCAE version 4.03 definitions (Table 8) and each episode will be recorded as an AE in the eCRF. It is essential that the frequency and form of stools are assessed relative to baseline to ensure accurate assessment of the severity of each episode of diarrhoea.

### 7.1.11. Disease Assessments

Disease assessments and response evaluations will be determined according to the definitions established in RECIST version 1.1 [Eisenhauer, 2009]. The frequency and methodology of disease assessments will be in accordance with local clinical practice during treatment with lapatinib and capecitabine, but disease assessments in accordance with RECIST version 1.1 must be conducted at the early withdrawal or study completion visit.

Overall response will be determined at the end of study treatment or at early withdrawal. The possible combinations of tumour responses are described in Table 18 and in Table 19.

**Table 18 Evaluation of overall response for subjects with measurable disease at screening**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

**Table 19 Evaluation of overall response for subjects with non-measurable only disease at screening**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response, PD=progressive disease, and NE=Not Evaluable		

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

## 7.2. Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above, as defined by the NCI CTCAE, version 4.03. Other aspects of the frequency and severity of diarrhoea and of the consequences of diarrhoea are secondary endpoints.

Overall response rate and clinical benefit response are secondary endpoints. Disease status will be defined in accordance with RECIST version 1.1 [Eisenhauer, 2009], and will be categorized in accordance with the definitions outlined in [Table 18](#) and [Table 19](#).

## 7.3. Safety Endpoints

LAP117314 will evaluate the effect of prophylactic treatment with octreotide on the tolerability of treatment with lapatinib and capecitabine. Reduction of the frequency and severity of diarrhoea are efficacy endpoints. Changes in the frequency and severity of other AEs will be used to evaluate the effects of prophylactic treatment with octreotide on the safety and tolerability of treatment with lapatinib and capecitabine.

## 7.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### 7.4.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

“Lack of efficacy” or “failure of expected pharmacological action” per se is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from “lack of efficacy” will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.

#### 7.4.2. Definition of a SAE

A SAE is any untoward medical occurrence that, at any dose:

a. Results in death

NOTE: Death due to disease under study is to be recorded on the Death eCRF form and does not need to be reported as an SAE.

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Protocol-Specific SAEs:

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT  $\geq 3 \times \text{ULN}$  **and** bilirubin  $\geq 2 \times \text{ULN}$  with  $>35\%$  direct (or ALT  $\geq$

3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events. (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

- NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin  $\geq 2xULN$ , then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations  $>1.5$  suggest severe liver injury.
- Any new primary cancers.

Cardiovascular events have been seen in subjects taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines, and interstitial pneumonitis has been reported in subjects taking compounds that inhibit ErbB1. As a precaution, the following will be reported as an SAE:

- Cardiac dysfunction, defined as any signs or symptoms of deterioration in left ventricular cardiac function that are Grade 3 (NCI CTCAE) or a  $\geq 20\%$  decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal.
- Any signs or symptoms of pneumonitis that are Grade 3 (NCI CTCAE) (defined as radiographic changes and requiring oxygen).
- Hepatobiliary event leading to permanent discontinuation of study-related treatment.

#### **7.4.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs**

Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as an SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

#### **7.4.4. Cardiovascular Events**

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

#### **7.4.5. Death Events**

A specific death data collection tool is to be completed for all deaths, whether or not they are considered SAEs. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded within one week of when the death is first reported.

#### **7.4.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs**

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE.

Death due to disease under study is to be recorded on the Death eCRF form and does not need to be reported as SAE.

However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

#### **7.4.7. Time Period and Frequency of Detecting AEs and SAEs**

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of treatment with the first dose of octreotide for subjects randomised to receive octreotide and treatment with the first dose of lapatinib and capecitabine for subjects randomised to receive no octreotide until 30 days following the end of the 24 week study period or discontinuation of study-related treatment, whichever is sooner, regardless of initiation of a new cancer therapy or transfer to hospice.

Serious AEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.4.9.

Serious AEs, AEs of special interest, AEs leading to treatment discontinuation and pregnancies will be collected for all subjects who enter the LTFU phase of the study (Section 7.1.9).

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment.

#### **7.4.8. Method of Detecting AEs and SAEs**

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

#### **7.4.9. Prompt Reporting of SAEs and Other Events to GSK**

SAEs, pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in Table 20 once the investigator determines the event meets the protocol definition for that event.

**Table 20 Adverse events to be reported promptly to the study sponsor**

Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
CV events or death	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	“CV events” and/or “death” data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated “CV events” and/or “death” data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
<b>Liver chemistry abnormalities Phase II:</b>				
ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct) (or ALT $\geq$ 3xULN and INR>1.5, if INR measured) <sup>3</sup>	24 hours <sup>1</sup>	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable <sup>2</sup>	24 hours	Updated SAE data collection tool. Updated Liver Event CRF <sup>2</sup>
ALT $\geq$ 5xULN; ALT $\geq$ 3xULN with hepatitis or rash or 3xULN $\geq$ 4 weeks	24 hours <sup>1</sup>	Liver Event CRF <sup>2</sup>	24 hours	Updated Liver Event CRF <sup>2</sup>
ALT $\geq$ 3xULN and <5xULN and bilirubin <2xULN	24 hours <sup>1</sup>	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks <sup>2</sup>		

1. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
2. Liver Event Documents (i.e., “Liver Event CRF” and “Liver Imaging CRF” and/or “Liver Biopsy CRF”, as applicable) should be completed as soon as possible
3. .INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Liver chemistry stopping criteria are described in Section 5.13.1.

Methods for detecting, recording, evaluating, and following up on AEs and SAEs and procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs and SAEs are provided in the SPM.

#### **7.4.10. Regulatory Reporting Requirements for SAEs**

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### **7.5. Pregnancy Testing, Prevention and Reporting**

#### **7.5.1. Pregnancy Test and Prevention**

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

**A female of non-childbearing potential** (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal with total cessation of menses for at least 1 year.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy. In questionable cases, the subject must have a follicle stimulating hormone value >40 mIU/mL and an oestradiol value < 40pg/mL (<140 pmol/L).

**A female of child-bearing potential** is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum  $\beta$ -hCG pregnancy test performed within 7 days prior to treatment with octreotide if randomised to receive octreotide or the first dose of lapatinib with capecitabine if randomised to receive no octreotide, but preferably as close to the start of treatment as possible. Subjects with a

positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below during the study until 30 days following the end of the 24 week study period or until 30 days following the last dose of lapatinib and capecitabine for subjects who enter the LTFU phase of the study. Subjects who continue treatment with lapatinib and capecitabine beyond the 24 week study period but do not enter the LTFU phase of the study should continue to use an acceptable contraceptive method in accordance with the Lapatinib and Capecitabine SPCs.

GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomised partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to first dose of study-related treatment, through the dosing period, and for at least 30 days following the end of the 24 week study period or until 30 days following the last dose of lapatinib and capecitabine for subjects who enter the LTFU phase of the study.  
**UK subjects:** In the UK, sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).
- Implants of levonorgestrel where not contraindicated for this subject population or per local practice.
- Injectable progesterone where not contraindicated for this subject population or per local practice.
- Oral contraceptives (either combined or progesterone only) where not contraindicated for this subject population or per local practice.

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and 30 days following the end of the 24 week study period or until 30 days following the last dose of lapatinib and capecitabine for subjects who enter the LTFU phase of the study. Subjects who continue treatment with lapatinib and capecitabine beyond the 24 week study period but do not enter the LTFU phase of the study should discontinue nursing in accordance with the Lapatinib and Capecitabine SPCs.

## **7.5.2. Pregnancy Reporting**

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

## **7.6. Laboratory Assessments**

All laboratory assessments will be performed by a local laboratory. Prior to administration of the first dose of study drug, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator. A subject with a laboratory value outside the reference range(s) or ranges for tests which relate to inclusion criteria (Section 4.1.2) and exclusion criteria (Section 4.1.3), the contraindications, special warnings and precautions for use, and other information included in the Lapatinib, Capecitabine and Octreotide SPCs may be included only if the investigator and GSK Medical Monitor agree that it is unlikely to introduce additional risk factors and will not interfere with study procedures.

All laboratory tests with values that are significantly abnormal during participation in the study or within 30 days following the end of the 24 week study period or until 30 days following the last dose of lapatinib and capecitabine for subjects who enter the LTFU phase of the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

## **7.7. Health Outcomes**

### **7.7.1. Health Outcomes Endpoints**

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

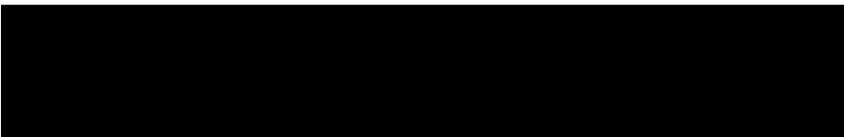
### **7.7.2. Health Outcomes Assessments**

Quality of life will be assessed using the FACIT-D ([Appendix 2](#)). Detail concerning the methods of collecting and returning FACIT-D data are included in the SPM.

All subjects will complete the baseline FACIT-D prior to randomisation, before any study related treatment is administered. Subjects randomised to receive treatment with octreotide will also complete the FACIT-D immediately before receiving the first dose of

lapatinib and capecitabine. All subjects will complete the FACIT-D every three weeks during treatment with lapatinib plus capecitabine 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; [Appendix 2](#)) consists of the FACT-G [[Webster, 2003](#)] and a diarrhoea-specific subscale, and measures multidimensional quality of life in subjects with cancer. FACT-G includes 27 general questions relating to four subscales, PWB, SWB, EWB and FWB, and the DSS includes 11 questions. Subjects 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 FACIT-D has been translated and validated in many languages, and the translations have been shown to have cross-cultural acceptability.



## 8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. AEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. Electronic CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

The PRO data (FACIT-D and DMD) will be entered in a non-GSK database. This database will be used for the sole purpose of the LAP117314 study. Only authorised personnel will have access to the PRO database, and all personnel are obliged to fully comply with The Data Protection Act 1998. All electronic PRO data will be kept in a dedicated database in a secure data vault, on a dedicated database server. Access to the database will be password and access right controlled.

In all cases, subject initials will not be collected or transmitted to GSK in accordance with GSK policy.

## 9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

### 9.1. Hypotheses

The primary objective of this study is to evaluate and compare whether administering prophylactic octreotide vs. no prophylactic octreotide reduces the incidence of cancer treatment-associated diarrhoea in subjects taking lapatinib plus capecitabine.

The study is designed to provide evidence to support the null hypothesis  $H_0: \delta \geq 0$  or to reject it in favour of the alternative hypothesis  $H_A: \delta < 0$ , where  $\delta$  is the difference in the incidence of Grade 2 or higher diarrhoea between prophylactic octreotide vs. no prophylactic octreotide.

### 9.2. Study Design Considerations

#### 9.2.1. 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 arm. 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 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 (Section 1.1). 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%.

#### 9.2.2. 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 arm is 20%, using a one-sided test with an alpha level of 0.025 (Table 21).

**Table 21 Sensitivity of sample size based on 20% control incidence of Grade 2 or more diarrhoea**

Incidence, placebo	20%	20%	20%	20%	20%
Incidence, prophylactic octreotide	6%	7%	8%	10%	12%
Power	69%	61%	53%	37%	25%
Subjects per Treatment Arm	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 arm is 32%, using a one-sided test with an alpha level of 0.025 (Table 22).

**Table 22 Sensitivity of sample size based on 32% control incidence of Grade 2 or more diarrhoea**

Incidence, placebo	32%	32%	32%	32%	32%
Incidence, prophylactic octreotide	12%	14%	16%	18%	20%
Power	82%	72%	60%	48%	36%
Subjects per Treatment Arm	70	70	70	70	70

Power calculations were performed using nQuery software version 7.0.

### 9.2.3. Sample Size Re-estimation

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

## 9.3. Data Analysis Considerations

### 9.3.1. Analysis Populations

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 randomisation number will be considered to have been randomised. The primary analysis of disease efficacy and all diarrhoea-related efficacy endpoints will be conducted using the ITT population.

The modified ITT (m-ITT) population will comprise all subjects in the ITT population who do not show intolerance to octreotide in the s.c. formulation and who do not have diarrhoea recorded as an AE after the first dose of octreotide LAR and prior to the start of treatment with lapatinib and capecitabine. The supplementary analysis of all diarrhoea-related efficacy endpoints will be conducted using the m-ITT 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. Major protocol violations that would exclude subjects from the PP population will be defined and documented in the Reporting and Analysis Plan (RAP) prior to database release. The PP population will not be analysed if this population comprises more than 95% of the ITT 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.

### **9.3.2. Analysis Data Sets**

The primary data set for assessing disease efficacy will be the ITT population as defined in Section 9.3.1.

The primary data set for assessing diarrhoea-related efficacy will be the ITT population as defined in Section 9.3.1.

The primary data set for assessing safety will be the Safety population as defined in Section 9.3.1.

### **9.3.3. Treatment Comparisons**

#### **9.3.3.1. Primary comparison of interest**

The primary objective will be supported through the test for superiority of prophylactic octreotide vs. no prophylactic octreotide in relation to reducing the incidence of Grade 2 or higher diarrhoea in subjects after 9 weeks of treatment with lapatinib plus capecitabine, using the ITT population.

#### **9.3.3.2. Other comparisons of interest**

This is an exploratory study, and the sample size may be insufficient to demonstrate statistical significance for the primary objective. The diarrhoea-related secondary objectives of the study will provide additional perspective to support the primary objective.

Assessment of disease progression in accordance with RECIST version 1.1 is required only at the end of study visit. Disease assessments during the course of treatment with lapatinib and capecitabine may be conducted in accordance with local practice, and there

will be some inconsistency between the data provided by different sites at these visits. The assessment of disease progression in LAP117314 will be limited by the sample size and by the variability in response assessments prior to the end of study visit, and may not be comparable with that reported in other studies.

#### **9.3.4. Interim Analysis**

An interim analysis will be conducted to assess the futility of octreotide in relation to reducing the incidence of Grade 2 diarrhoea after 9 weeks of treatment. This analysis will take place when at least 60 subjects have been randomised to treatment and completed their 9 week assessment. At this analysis a review of both the accumulating safety and efficacy data will be conducted by an independent review committee to assure the safety of the patients in the trial and to provide an opportunity to terminate the study if:-

- There is overwhelming clinical evidence of a negative imbalance in the safety profile of either treatment group
- There is not sufficient evidence of an effect of efficacy in the reduction of Grade 2 diarrhoea as described by the stopping rules in Section 9.3.4.2.

The independent review committee will review the accumulating safety data and also the analysis of the primary endpoint, the incidence of Grade 2 diarrhoea. There will be full treatment disclosure at the interim analysis to the Senior Management team, but the study team will remain blinded to treatment assignment and the results of the interim analysis.

##### **9.3.4.1. Interim Review of Safety Profile**

The data to be reviewed by the independent review committee will be the accumulated safety and diarrhoea response data. These safety data will include, at minimum, all AEs, SAEs and any deaths. The safety review committee will evaluate these data and make a clinical judgement as whether the study can progress as planned based on the welfare of the subjects. At least one interim review of this safety data will occur.

##### **9.3.4.2. Futility Analysis of Primary Endpoint**

A futility analysis of the incidence of Grade 2 diarrhoea, the primary endpoint, comparing this incidence between the group of subjects who receive lapatinib and capecitabine to the group of subjects who receive no prophylactic octreotide will be performed. This will take place at a single interim analysis after approximately 40% of subjects (60 subjects) have had at least 9 weeks of study treatment.

Early termination of the study will be considered by the independent review committee. Their recommendation will be based on the following points:-

- Whether it would be possible to draw any meaningful conclusions if the study were to continue to planned completion given the:-

- The clinical relevance of the observed incidence of Grade 2 diarrhoea.
- The conditional power based on data from approximately 40% of the patients
- The totality of the evidence observed.

For example:

- If the diarrhoea rate is 30% in the control arm, in order for the conditional power (under the current trend) to be around 50% to see a positive result at the end of the trial, we would need to see a diarrhoea rate of 16% or lower in the octreotide arm. (Equating to a difference in 14% in incidence between treatment arms)
- If the diarrhoea rate is 20% in the control arm, in order for the conditional power (under the current trend) to be around 70% to see a positive result at the end of the trial, we would need to see a diarrhoea rate of 6% or lower in the octreotide arm. (Equating to a difference of 14% in incidence between treatment arms)

The conditional power will need to be re-calculated based on the actual incidence and actual percentage of patients evaluated at the time of the interim analyses.

It is envisaged that if at least a modest improvement in the diarrhoea rate in the octreotide arm is not seen with a conditional power of at least 50% at the interim analysis, it is unlikely that the trial would justify octreotide use in clinical practice. Further confidence intervals around the estimate of the observed difference in incidence of Grade 3 diarrhoea will be provided to aid clinical judgement.

### **9.3.5. Key Elements of Analysis Plan**

The final analysis will take place when all subjects have completed the study.

Data will be listed and summarised according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion (24 weeks or early withdrawal from the study) will be included in the summaries, regardless of the duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of treatment will vary between subjects. Non-responder imputation will be used in the case of missing data for the analysis of the primary endpoint based on the ITT population. Subjects who withdraw from the study prior to the Week 9 visit without experiencing Grade 2 diarrhoea or above will be assumed to have experienced Grade 2 diarrhoea or above for the purpose of the analysis. Similar imputation techniques will be

used for the m-ITT population analysis of the primary endpoint. No imputation will be performed for the Per Protocol analyses. Imputation methods for the secondary endpoints will be considered and detailed as appropriate in the RAP.

Demographic and screening characteristics will be summarised.

Details on the determination of tumour response are given in Section 7.1.11. There will be no adjustments for multiplicity.

Details on efficacy summaries are provided in Section 9.3.5.1 and details on safety summaries are provided in Section 9.3.5.2.

### **9.3.5.1. Efficacy analyses**

The ITT population will be used for the analyses of diarrhoea-related endpoints and for the analysis of disease efficacy. The m-ITT population will be used for the supplementary analysis of diarrhoea-related endpoints. The primary analysis of diarrhoea-related endpoints will be based on data recorded in the eCRF. Secondary analyses of diarrhoea-related endpoints will be based on data recorded in the eCRF and in the DMD.

#### **9.3.5.1.1. Primary endpoint analysis**

The primary efficacy endpoint is the proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 2 or higher during the first 9 weeks of treatment with lapatinib and capecitabine in the ITT population. The AE terms diarrhoea and frequent bowel movements will be aggregated to form the term diarrhoea in accordance with the Aggregation Guidelines for AE Terms in Lapatinib Studies. The superiority of prophylactic octreotide compared to no prophylactic octreotide will be assessed using a chi-square test. The proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 2 or higher in each treatment arm, the reduction in proportions between the treatment arms, the corresponding 95% confidence interval for the reduction and the two-sided p-value from the chi-square test will be presented.

Secondary analyses of the primary endpoint will be conducted based on the proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 2 or higher during the period of treatment with lapatinib and capecitabine after 9 weeks and up to 24 weeks (nominally weeks 12-24), and also for the entire 24 week treatment period (nominally weeks 0-24).

Supplementary analyses of the primary endpoint will be conducted in the m-ITT and PP populations, using the same lapatinib and capecitabine treatment intervals as described for the m-ITT population.

**9.3.5.1.2. Secondary endpoint analysis: Investigator-reported endpoints**

These analyses will be based on data reported by the investigator in the eCRF. Analyses of secondary diarrhoea-related endpoints will be conducted for the ITT and m-ITT populations using the same lapatinib and capecitabine treatment intervals as described for the analysis of the primary endpoint in Section 9.3.5.1.1. Disease efficacy will be assessed in the ITT and m-ITT populations over the total 24 week treatment period. For the secondary endpoints, 95% confidence intervals and two-sided tests will be presented.

**Diarrhoea of Grade 3 and above**

The proportion of subjects experiencing at least one episode of diarrhoea of Grade 3 and above will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint.

**Diarrhoea of any grade**

The proportion of subjects experiencing at least one episode of diarrhoea of any grade of severity will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint.

**Duration of diarrhoea of any grade of severity**

The maximum duration of episodes of diarrhoea of any grade of severity will be calculated for each subject and will be summarised by treatment arm using descriptive statistics (including lower quartile, median and upper quartile) and the treatment arms will be compared using the Wilcoxon Rank Sum test. The median maximum duration of episodes in each treatment arm, the Hodges-Lehmann estimate for the difference between treatment arms, corresponding 95% confidence interval for the Hodges-Lehmann estimate and the p-value from the Wilcoxon Rank Sum test will be presented. It should be noted that if episodes of diarrhoea are ongoing at the time of study completion or premature withdrawal from the study, the duration of these episodes will be censored at that point, and therefore the resulting summary statistics and analyses may be subject to bias.

**Time to onset of the first episode of diarrhoea**

The time to onset of the first episode of diarrhoea of any grade of severity will be summarised by treatment arm 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 patients experiencing an episode of diarrhoea will be presented for each 3-week time interval by treatment group. Estimates and 95% confidence intervals for the 25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile will be provided by treatment group. Treatment groups will be compared using the log-rank test, or the Wilcoxon test in the case of non-proportional hazards.

**Anti-diarrhoeal medication**

The proportion of subjects taking medication at least once as a result of diarrhoea will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint.

**Unscheduled visits to/contact with healthcare professionals**

The proportion of subjects requiring an unscheduled visit to or contact with a healthcare professional at least once as a result of diarrhoea will be summarised and analysed using the same method as described in Section 9.3.5.1.1 for the primary endpoint.

**Changes in study treatment**

The proportion of subjects requiring changes in study treatment (lapatinib or capecitabine) as a result of diarrhoea will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint. Summaries will be performed separately for each type of change in study treatment (i.e. dose delays, dose reductions and treatment withdrawal) as well as overall.

Dose intensity of study treatment (lapatinib or capecitabine) will be calculated daily (i.e. total dose of lapatinib or capecitabine divided by the number of days on lapatinib or capecitabine). Dose intensity will be summarised and analysed using the same methods as described above for frequency of diarrhoea of any grade of severity.

## **Intravenous fluids**

The proportion of subjects requiring treatment with intravenous fluids at least once as a result of diarrhoea will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint.

## **Study treatment compliance**

Inference of the efficacy of prophylactic octreotide will be made by summarising overall compliance to the study treatment (lapatinib plus capecitabine) by treatment arm.

A summary of compliance with prophylactic octreotide will be presented for the ITT and m-ITT populations.

## **Overall Response Rate**

Overall response rate (ORR) is defined as the percentage of subjects achieving either a confirmed complete (CR) or partial (PR) tumour response. The ORR will be calculated from the investigator's assessment of response. Subjects who do not have measurable disease or have an unknown or a missing response will be treated as non-responders when calculating the percentages and will contribute to the response rate-based analyses for the evaluation of CR, PR, stable disease (SD) and progressive disease. The ORR in each treatment arm and corresponding 95% confidence interval will be presented.

## **Clinical Benefit Response**

Clinical benefit response (CBR) is defined as the percentage of subjects with a CR, PR or SD for at least 24 weeks. The CBR will be calculated using the same methods as described for the ORR, i.e. from the investigators assessment of response, subjects who do not have measurable disease, missing or unknown will be treated as non-responders. The CBR in each treatment arm and corresponding 95% confidence interval will be presented.

### **9.3.5.1.3. Secondary analyses: Patient-reported endpoints**

These analyses will be based on data reported in the DMD. Analyses of secondary diarrhoea-related endpoints will be presented for the ITT and m-ITT populations for patients completing the baseline and at least one post-baseline DMD.

## **Diarrhoea**

The proportion of patients reporting an increase in the frequency and/or worsening in consistency of bowel movements will be summarised and analysed using Generalised Estimating Equations (GEE), using a repeated statement, the binary response is the patient reported increase in frequency or worsening in consistency, as defined in the RAP, in addition individual patient data will be plotted.

**Time to onset of first patient-reported increase in frequency and/or worsening in consistency of bowel movements**

The time to onset of the first patient-reported increase in frequency and/or worsening of consistency of bowel movements will be summarised by treatment arm using Kaplan-Meier methods. Patients who complete the study or withdraw prematurely without experiencing an increase in the frequency and/or worsening in consistency of bowel movements will be censored at the date of withdrawal or study completion. The Kaplan-Meier estimate of the proportion of patients reporting an increase in the frequency and/or worsening of consistency of bowel movements will be presented for each weekly time interval by treatment group. Estimates and 95% confidence intervals for the 25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile will be provided by treatment group. Treatment groups will be compared using the log-rank test, or the Wilcoxon test in the case of non-proportional hazards.

**Additional anti-diarrhoeal medication**

The proportion of patients taking any extra medication not prescribed by the hospital-doctor to help with diarrhoea will be summarised and analysed using the same GEE analysis and plots as described for patient-reported diarrhoea.

**Impact of dietary changes**

The proportion of patients making dietary changes to help with the diarrhoea will be summarised and analysed using the same GEE analysis and plots as described for patient-reported diarrhoea.

**Contact with any other healthcare professionals**

The proportion of patients contacting a health care professional other than the hospital doctors/nurses to discuss diarrhoea will be summarised and analysed using the same GEE analysis as and plots as described for patient-reported diarrhoea..

**Reduction / stopping of anti-cancer treatment**

The proportion of patients reducing or completely stopping the number of anti-cancer tablets to help with diarrhoea will be summarised and analysed using the same GEE analysis and plots as described for patient-reported diarrhoea. Summaries will be performed separately for each type of change in anti-cancer tablets (i.e. reducing tablets and stopping completely) as well as overall.

**9.3.5.2. Safety analyses**

The Safety population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP. Summaries will be presented by treatment arm and overall unless specified otherwise. Safety endpoints are described in Section 2 and Section 7.3.

**9.3.5.2.1. Extent of exposure**

The number of subjects administered prophylactic octreotide will be summarised according to the duration of therapy. The extent of exposure to prophylactic octreotide will be presented.

The extent of exposure to treatment with lapatinib and capecitabine may be increased if prophylactic octreotide is effective in reducing the incidence of Grade 2 or higher diarrhoea. Exposure to lapatinib and capecitabine will be summarised by treatment arm.

**9.3.5.2.2. Adverse events**

Adverse events (AEs) will be coded using the standard GSK Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 4.03).

The AE terms diarrhoea and frequent bowel movements will be aggregated to form the term diarrhoea in accordance with the Aggregation Guidelines for AE Terms in Lapatinib Studies.

The number and percentage of subjects experiencing adverse events will be summarised by system organ class and preferred term. Separate summaries will be given for all AEs, drug-related AEs, SAEs and AEs leading to discontinuation of study treatment.

If the AE is listed in the NCI CTCAE (version 4.03) table, the maximum grade will be summarised.

Characteristics (e.g. number of occurrences, action taken, grade and severity) of the following AEs of special interest will be summarised separately: diarrhoea, rash, nausea, vomiting, hepatobiliary events, cardiac events, and pneumonitis.

The incidence of deaths and the primary cause of death will be summarised.

**9.3.5.2.3. Clinical laboratory evaluations**

Haematology and clinical chemistry data will be summarised at each scheduled assessment according to NCI CTCAE grade (version 4.03). The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in “overall” and “any post-screening” summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment. Further details will be provided in the RAP.

**9.3.5.2.4. Other safety measures**

The results of scheduled assessments of physical examination, body height and weight, vital signs, (temperature, blood pressure, pulse), 12-lead ECG, echocardiogram (or

MUGA scan) and ECOG performance status will be summarised. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). All data will be listed. Further details will be provided in the RAP.

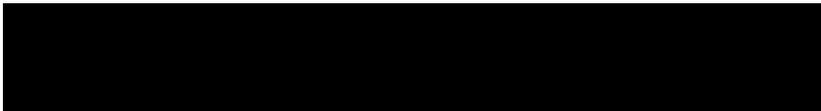
### **9.3.5.3. Health Outcomes analyses**

The primary endpoint for the FACIT-D will be the Trial Outcome Index (TOI) comprised of the PWB, FWB and the DSS. Secondary endpoints will be:

- Total FACT-G (i.e. PWB, SWB, EWB and FWB subscales);
- Total FACIT-D (i.e. PWB, SWB, EWB and FWB subscales and the DSS);
- Each individual subscale score.

Scores will be summarised by visit and treatment arm. Changes from baseline (prior to randomisation) and changes from baseline (prior to start of lapatinib and capecitabine) will also be summarised at each post-baseline visit as appropriate. Proportions of subjects in each treatment arm who achieve a clinically meaningful improvement or decline will be compared at each time point using the chi-square test. A responder criterion can be defined as a 6 or more point change from baseline on the TOI, a 7 or more point change from baseline for the Total FACT-G, a 7 or more point change from baseline for the Total FACIT-D, a 3 or more point change from baseline for the individual subscales (PWB, EWB, SWB, FWB), and a 4 or more point change from baseline for the DSS. For the total scores and each of the subscale scores, the difference between the treatment arms in terms of the change from baseline at each study visit will be analysed using a two sample t-test. Treatment effect over time will be evaluated. Further details will be provided in the RAP.

The calculation of scores and methods to deal with missing data will be handled according to the standard scoring guidelines. Full details of all the FACIT-D analyses will be provided in the RAP.



## **10. STUDY CONDUCT CONSIDERATIONS**

### **10.1. Posting of Information on Publicly Available Clinical Trial Registers**

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

### **10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments [REDACTED] described in [Appendix 3](#), unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

### **10.3. Quality Control (Study Monitoring)**

In accordance with applicable regulations, GCP, and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### **10.4. Quality Assurance**

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified

### **10.5. Study and Site Closure**

The end of the study will occur when the last subject has completed the last visit, and all SAEs have been followed up as required.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and GSK Standard Operating Procedures (SOPs).

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

GSK also reserves the right to close sites which fail to enroll subjects within a predefined timeframe, as described in the SPM.

## **10.6. Records Retention**

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

## **10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Upon completion of the clinical study report, GSK will ensure public disclosure of the clinical trial research results via the GSK Clinical Study Register. GSK will also publish the results of the study to be searchable on the internet according to the GSK policy and SOP.

The results summary will be posted to the GSK Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer-reviewed journal for publication no later than 18 months after the last subject's last visit. When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

## **10.8. Safety Review Team**

The SRT includes GSK representatives from Biostatistics, Clinical and Global Clinical Safety and Pharmacovigilance. Representatives from other disciplines may be involved in the SRT meetings on an ad hoc basis as required to provide additional expertise. All members of the SRT must be independent of the LAP117314 study team, and must have no other role or responsibility within the broader scope of the study. The primary role of the SRT is to provide an internal and independent review of safety data to protect the interests of subjects and to ensure their safety.

The SRT will review safety data on an ongoing basis. The first formal review of safety data will be conducted after the first 60 subjects have received at least 9 weeks of treatment with lapatinib and capecitabine. Subsequent formal review will be conducted at least every 12 weeks, or more frequently if required. It is anticipated that the SRT will meet to conduct formal review of the safety data at least three times during the course of the study. Unblinded study data will be provided to the SRT by a statistician independent of the LAP117314 study team. All efforts will be made to maintain the study integrity and validity of study data.

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## 12. APPENDICES

### 12.1. Appendix 1 Diarrhoea Management Guidelines

Experience thus far suggests that when lapatinib is used as monotherapy most diarrhoea presents as uncomplicated NCI CTCAE Grade 1 or 2 (G1 54%, G2 20%, G3 15%, G4<1%).

In rare cases, diarrhoea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances.

Standardised and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhoea [Benson, 2004]. Presented in the sections below are the recommended guidelines for the management of diarrhoea in subjects receiving lapatinib-based therapy; these guidelines were derived from the recommendations published by the ASCO panel [Benson, 2004].

Early identification and intervention is critical for the optimal management of diarrhoea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

**It is strongly recommended to give subjects receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhoea as per the recommendations outlined below.**

**Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhoea of any severity.**

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhoea can be identified. Subjects should be educated on signs and symptoms of diarrhoea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhoea episodes and its characteristics. They should also include information on any dietary changes or other observations that may be useful in the evaluation of their diarrhoea history.

If subjects present with diarrhoea of any grade, check they are taking lapatinib correctly, i.e. single daily dose, rather than splitting it through the day. . Obtain information on food (solid and liquid) and over the counter (OTC) medication, including herbal supplements, taken during the lapatinib treatment period.

## Definitions

National Cancer Institute (NCI) guidelines define diarrhoea compared to baseline ([Appendix 1 Table 1](#))

**Appendix 1 Table 1 NCI Common terminology criteria for grading diarrhoea adverse events (version 4.03)**

Adverse Event Grade	Diarrhoea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
3	Increase of $\geq 7$ stools/day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living (ADL)
4	Life-threatening consequences; urgent intervention indicated
5	Death

**Uncomplicated diarrhoea** is considered mild-to-moderate and defined as CTCAE Grade 1 or 2 with no complicating signs or symptoms.

**Complicated diarrhoea** is severe and defined as any CTCAE Grade 3 or 4 diarrhoea, or Grade 1 or 2 with one or more of the following signs or symptoms:

- Moderate to severe abdominal cramping
- Nausea/vomiting  $\geq$ Grade2
- Decreased performance status
- Fever
- Sepsis
- Neutropenia
- Frank bleeding (red blood in stool)
- Dehydration

## Management Guidelines for Subjects Receiving Lapatinib Alone or as Combination Therapy

### A) Uncomplicated Diarrhoea

#### I. CTCAE Grade 1

**NOTE: Subject should be instructed to: start supportive care immediately at the first episode of diarrhoea (i.e., unformed stool) and call their physician.**

1. Administer loperamide

- a. Initial dose 4mg followed by 2mg after every unformed stool. Re-evaluate after 24 hours, if:
    - i. Diarrhoea is resolving:
      - Continue loperamide treatment at 2mg dose after every unformed stool until diarrhoea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours.
        - If diarrhoea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
    - ii. Diarrhoea is not resolving:
      - Administer loperamide at 2mg every 4 hours for the next 24 hour. Re-evaluate after 24 hours. If diarrhoea is resolving, administer loperamide at 2mg after every unformed stool until diarrhoea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours. If diarrhoea is not resolving continue loperamide treatment at 2mg every 4 hours and re-evaluate every 24 hours.
  - b. If Grade 1 diarrhoea persists for more than 1 week with loperamide treatment, consider treatment with second-line agents (octreotide, budesonide or tincture of opium).
2. Dietary modifications which are essential in the management of diarrhoea include the following recommendations (American Cancer Society; National Cancer Institute):
- a. Stop all lactose containing products and eat small meals
  - b. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber
    - i. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
  - c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
  - d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
    - i. Avoid acidic drinks such as tomato juice and fizzy soft drinks
  - e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots) , evaluate their impact on diarrhoea due to the fiber content (e.g., apricots)
1. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhoea has resolved (diarrhoea free for 12 hours/bowel pattern return to baseline). Once diarrhoea has resolved, the subject can begin to gradually re-introduce foods from their normal diet.

If diarrhoea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications. Continue with study treatment.

If Grade 1 diarrhoea persists for  $\geq 2$  weeks, refer to the management guidelines for Persistent Grade 2 Diarrhoea.

## II. CTCAE Grade 2

**NOTE: Subject should be instructed to call physician at first episode of diarrhoea and start supportive care immediately**

1. Administer loperamide
  - a. Initial dose 4mg followed by 2mg every 4 hours or after every unformed stool. Re-evaluate after 24 hours. If:
    - i. Diarrhoea is resolving, continue loperamide treatment at 2mg dose after every unformed stool until diarrhoea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours
      - If diarrhoea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
    - ii. Diarrhoea is not resolving, consider loperamide dose of 2mg every 2 hours for 24 hours. If Grade 2 diarrhoea persists after total of 48 hours of loperamide treatment, start second-line agents (octreotide, budesonide or tincture of opium).
      - Consider performing stool work-up, CBC, electrolytes and other tests as appropriate
2. Dietary modifications which are essential in the management of diarrhoea include the following recommendations (American Cancer Society; National Cancer Institute):
  - a. Stop all lactose containing products and eat small meals
  - b. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber
    - i. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
  - c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
  - d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
    - ii. Avoid acidic drinks such as tomato juice and fizzy soft drinks
  - e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots), evaluate their impact on diarrhoea due to the fiber content (e.g., apricots)
2. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhoea has resolved (diarrhoea free for 12 hours/bowel pattern return to baseline). Once diarrhoea has resolved, the subject can begin to gradually re-introduce foods from their normal diet. Refer to Section IV “Recurrent Diarrhoea” for study treatment guidelines.

If diarrhoea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications.

**III. Persistent ( $\geq 3$  days/72 hours) Grade 2 Diarrhoea:** hold lapatinib and chemotherapy (if applicable) until diarrhoea resolves ( $<$ Grade 1/return to baseline bowel pattern). If supportive care measures and the interruption of study treatment (i.e., lapatinib and if applicable chemotherapy) are ineffective in treating persistent Grade 1 or Grade 2 diarrhoea, perform stool work-up, CBC, electrolytes and other tests as appropriate, consider consulting with a gastrointestinal specialist.

After diarrhoea resolves ( $\leq$ Grade 1), resume treatment with lapatinib and chemotherapy (if applicable).

**IV. Recurrent Diarrhoea (more than 1 occurrence of Grade 2 diarrhoea):** once the 2<sup>nd</sup> occurrence of Grade 2 diarrhoea resolves to  $\leq$ Grade 1, consider reducing the dose of lapatinib by 250mg or 1 tablet, unless the lapatinib dose already had been reduced to 750mg. No further dose reduction is recommended for subjects taking lapatinib at 750mg.

3. Consider a dose reduction for chemotherapy (if applicable)

## **B) Complicated Diarrhoea**

**1. CTCAE Grade 3 or Grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration)**

- a. Subject **must** call physician immediately for any complicated severe diarrhoea event
- b. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool
- c. Refer to the dietary modification recommendations for Grade 1 and Grade 2 uncomplicated diarrhoea
- d. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
- e. Perform stool work-up, CBC, electrolytes and other tests as appropriate
- f. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhoea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia
- g. Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to  $\leq$ Grade 1 and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750mg, contact medical monitor for further guidance)

- i. Consider a dose reduction for chemotherapy (if applicable)
4. Supportive care and other interventions should be continued until diarrhoea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
5. Intervention may require hospitalisation for subjects most at risk for life threatening complications

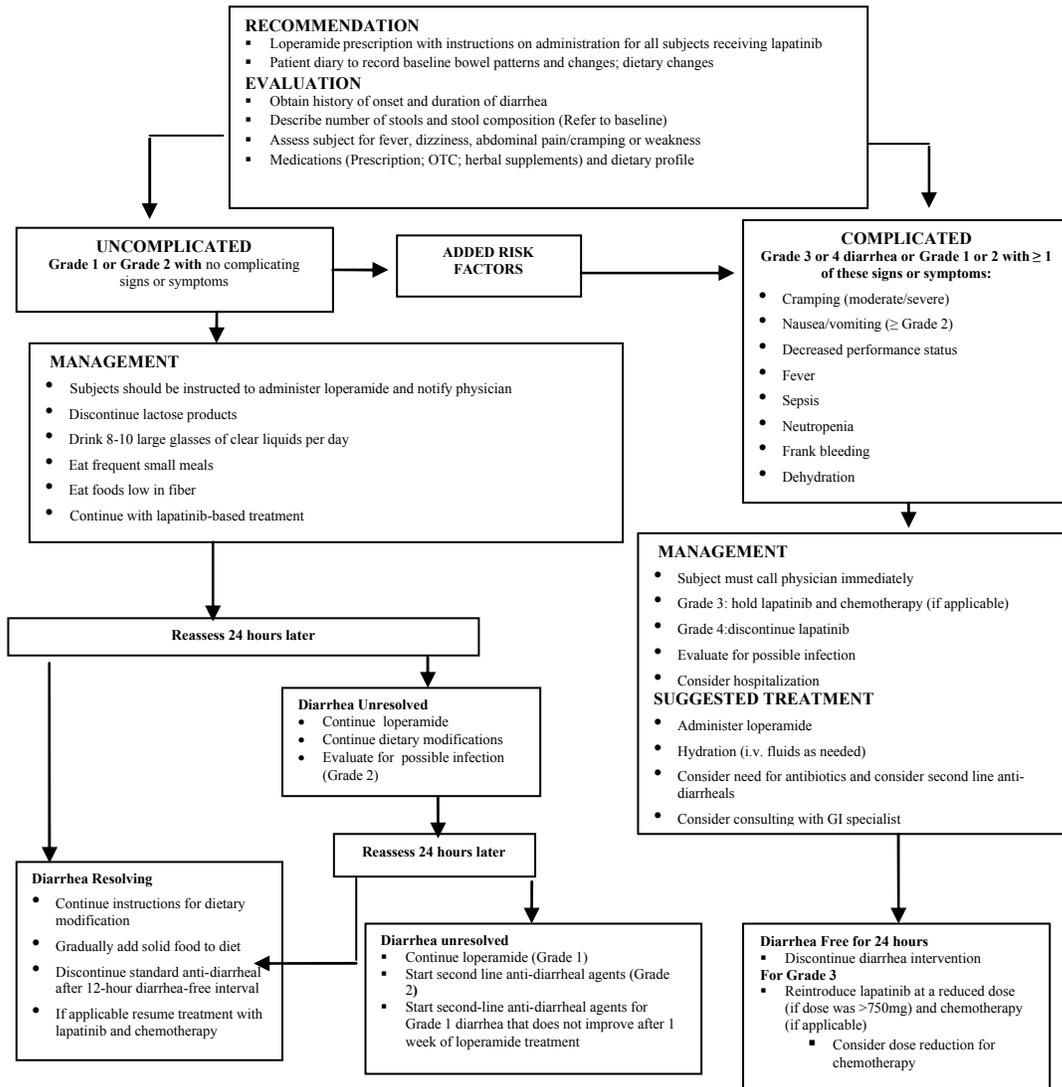
## **II CTCAE Grade 4**

Subject must call physician immediately for any Grade 4 diarrhoea event

1. Discontinue treatment with lapatinib, hold chemotherapy (if applicable)
2. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool
3. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
4. Perform stool work-up, CBC, electrolyte and other tests as appropriate
5. Recommend consulting with gastrointestinal specialist
6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhoea is persistent beyond 24 hours or there is fever or Grade 3/4 neutropenia
7. Supportive care and other intervention should be continued until diarrhoea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
8. Intervention may require hospitalisation for subjects most at risk for life threatening complications

Refer to and follow the recommended supportive care guidelines in the previous sections and as depicted in [Appendix 1 Figure 1](#).

**Appendix 1 Figure 1 Algorithm for the management of diarrhoea in subjects treated with lapatinib-based therapy**



1. For Grade 1 diarrhoea that persists for 2 weeks or longer, refer to Section III
2. For Grade 2 diarrhoea that persists longer than 3 days/72 hours, refer to Section III
3. For recurrent diarrhoea, refer to Section IV for further management guidelines

## References

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Dia[http://www.cancer.org/docroot/MBC/content/MBC\\_2\\_3X\\_Diarrhoea.asp](http://www.cancer.org/docroot/MBC/content/MBC_2_3X_Diarrhoea.asp)

Benson A, Jaffer AA, Catalano RB, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhoea. *Journal of Clinical Oncology* 2004; 22:2918-2926.

Charma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. *Lancet/Oncology* 2005; 6:93-102

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<http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/Subject>

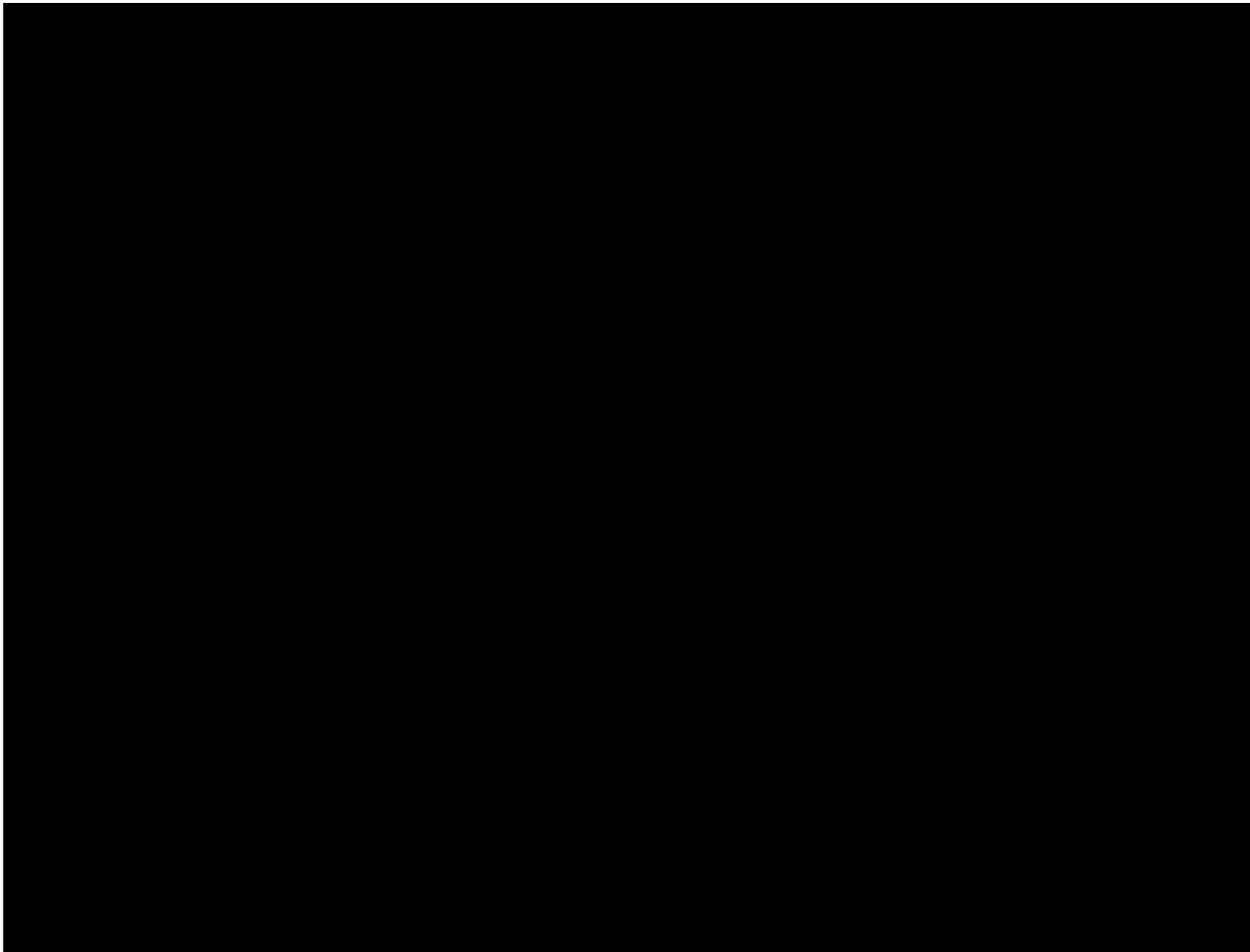
Saltz LB. Understanding and Managing Chemotherapy-Induced Diarrhoea. *Journal of Supportive Oncology* 2003; 1:35-46.

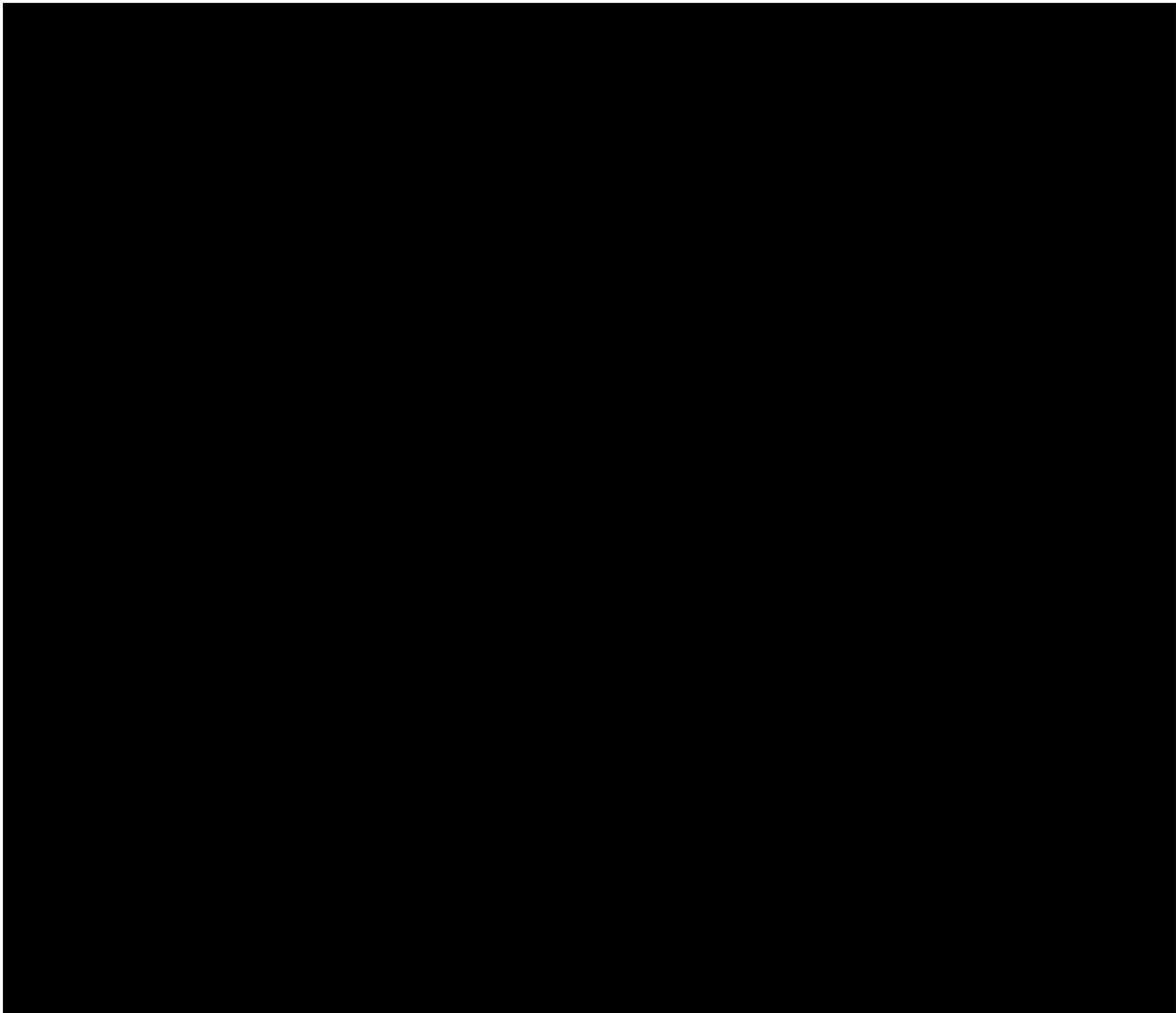
## 12.2. Appendix 2 FACIT-D Questionnaire

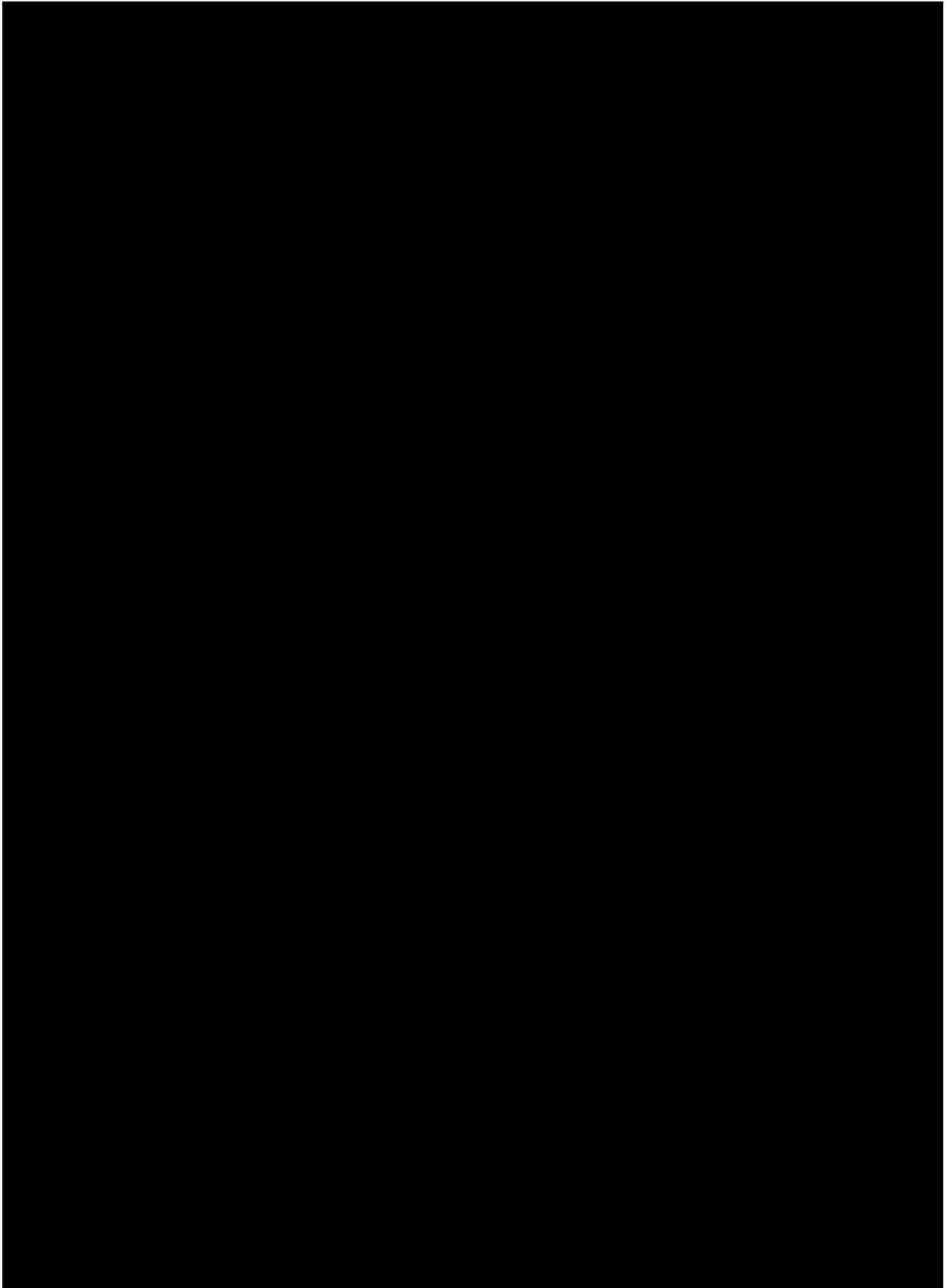
The FACIT-D questionnaire (version 4, English original) is available in two forms with different dates: '16 Nov 2007' and '09 June 2013'. These two forms have minor differences in question phrasing and format. Both forms are fully validated and the minor differences between two forms do not affect the quality of data collection and analysis. In this study, the languages translated based on 'English FACIT-D version 4 (dated 16 Nov 2007)' are Arabic, French, Hebrew, Italian and Polish. The languages translated based on 'English FACIT-D version 4 (dated 09 June 2013)' are Czech, Greek, Russian and Traditional Chinese.

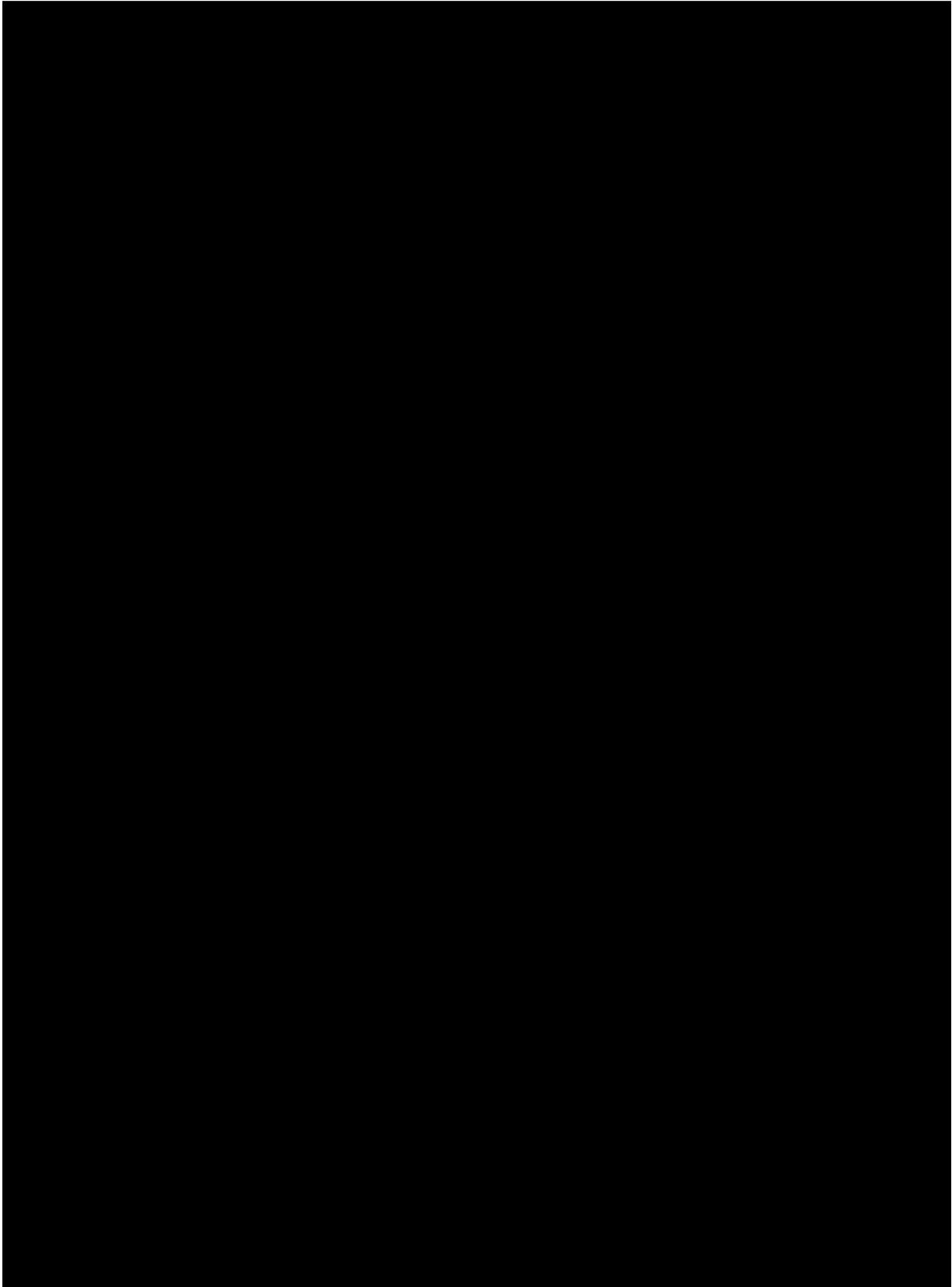
This appendix provides an example of the questionnaire 'English FACIT-D version 4 (dated 09 June 2013)'.

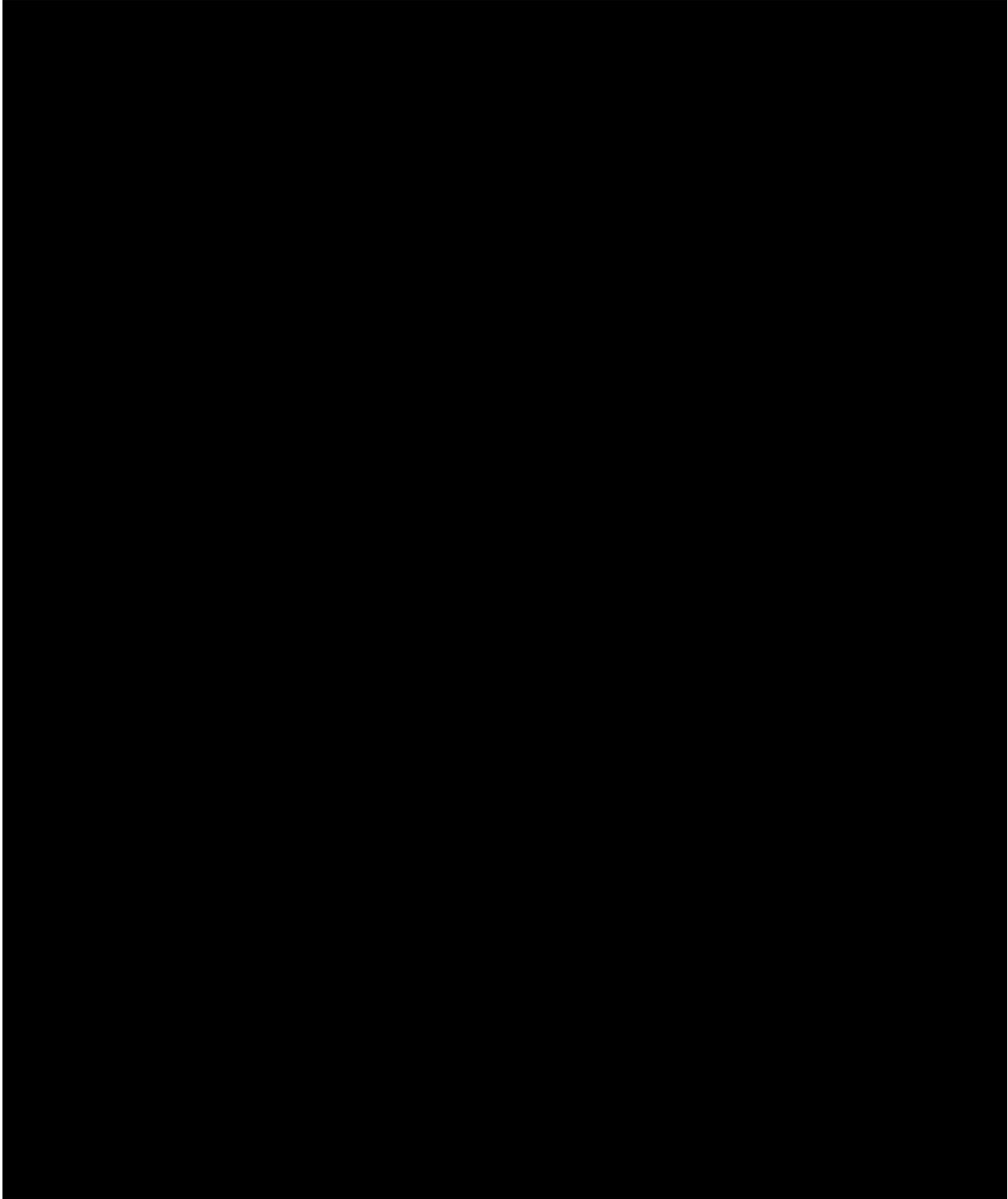
Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

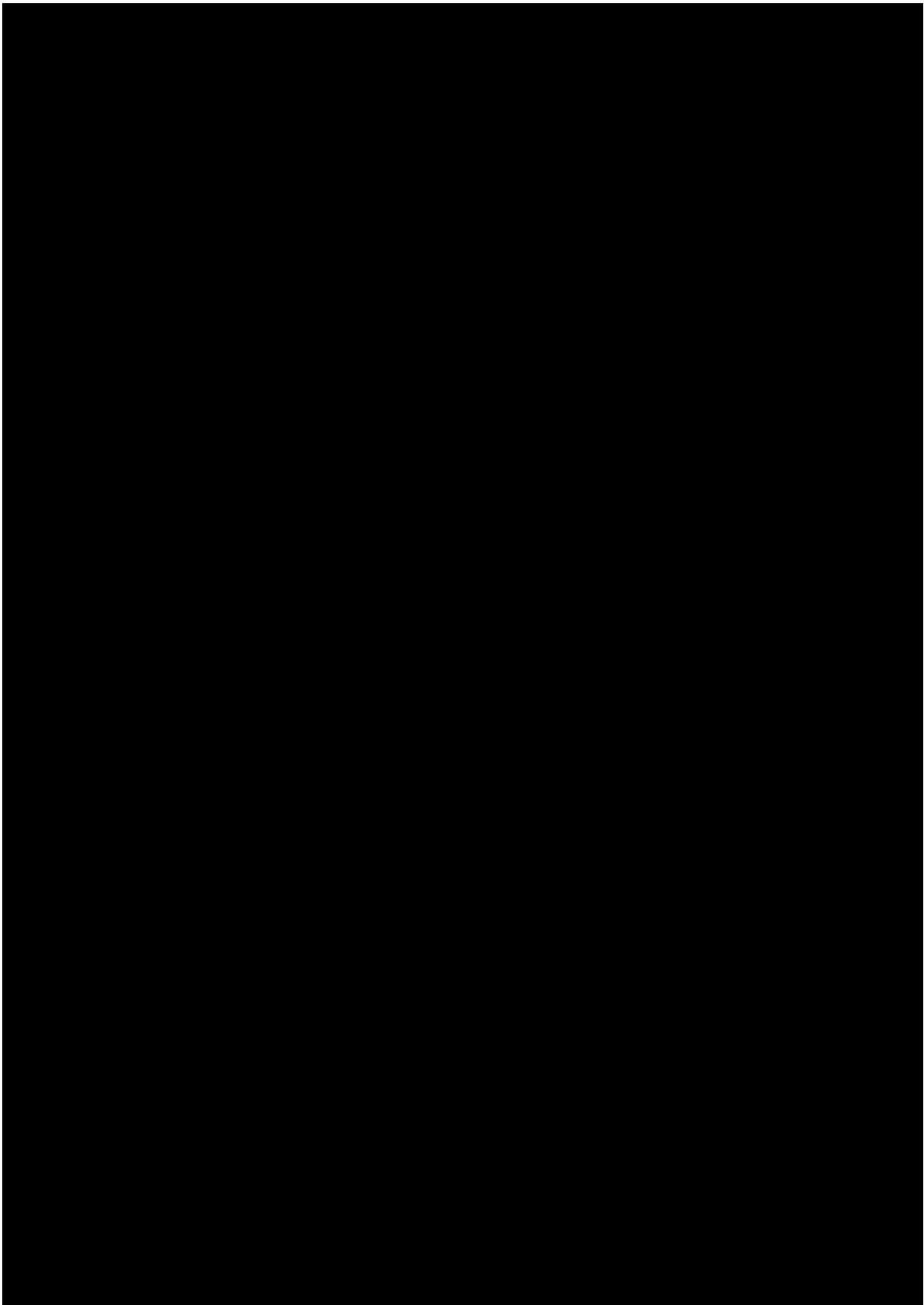


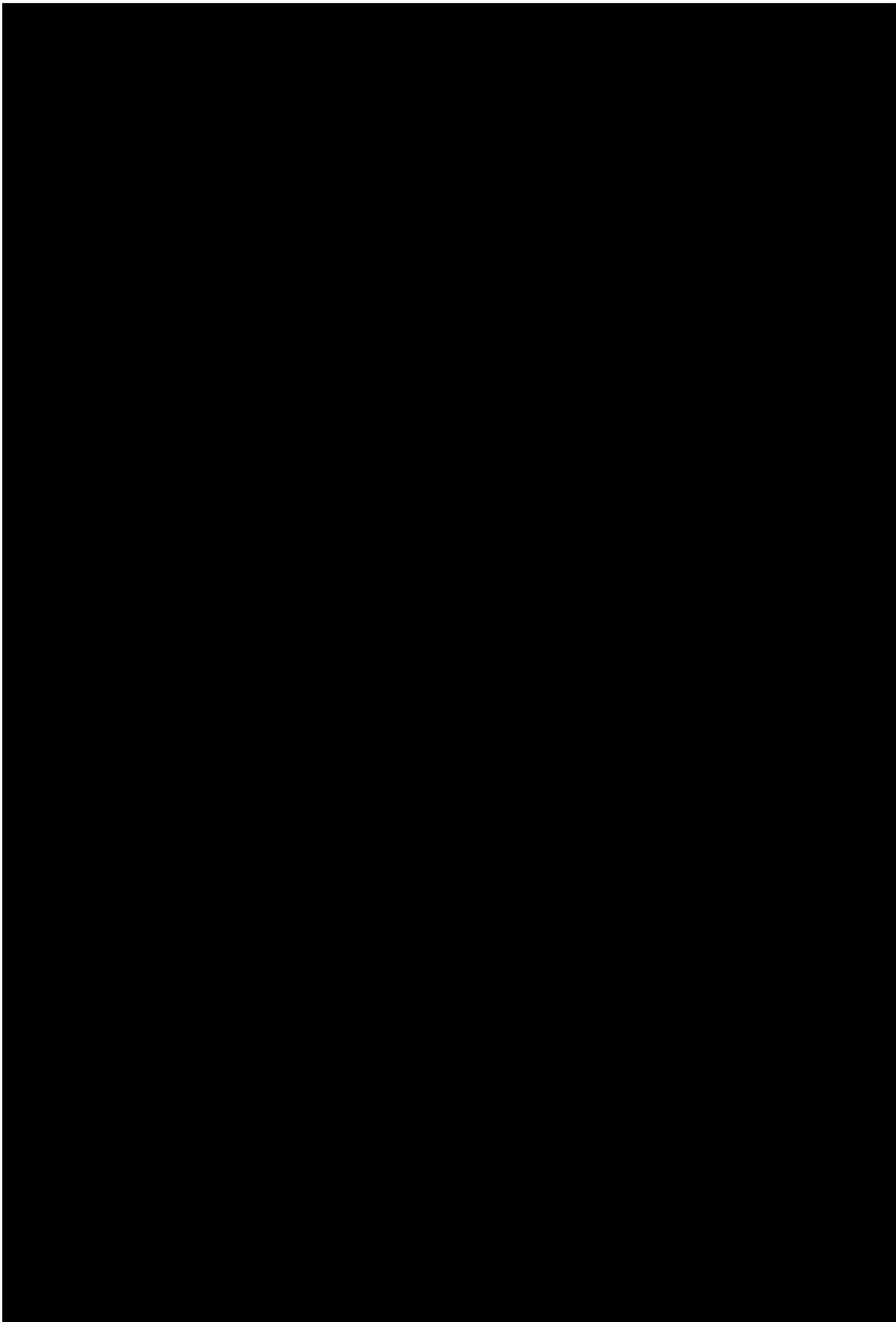


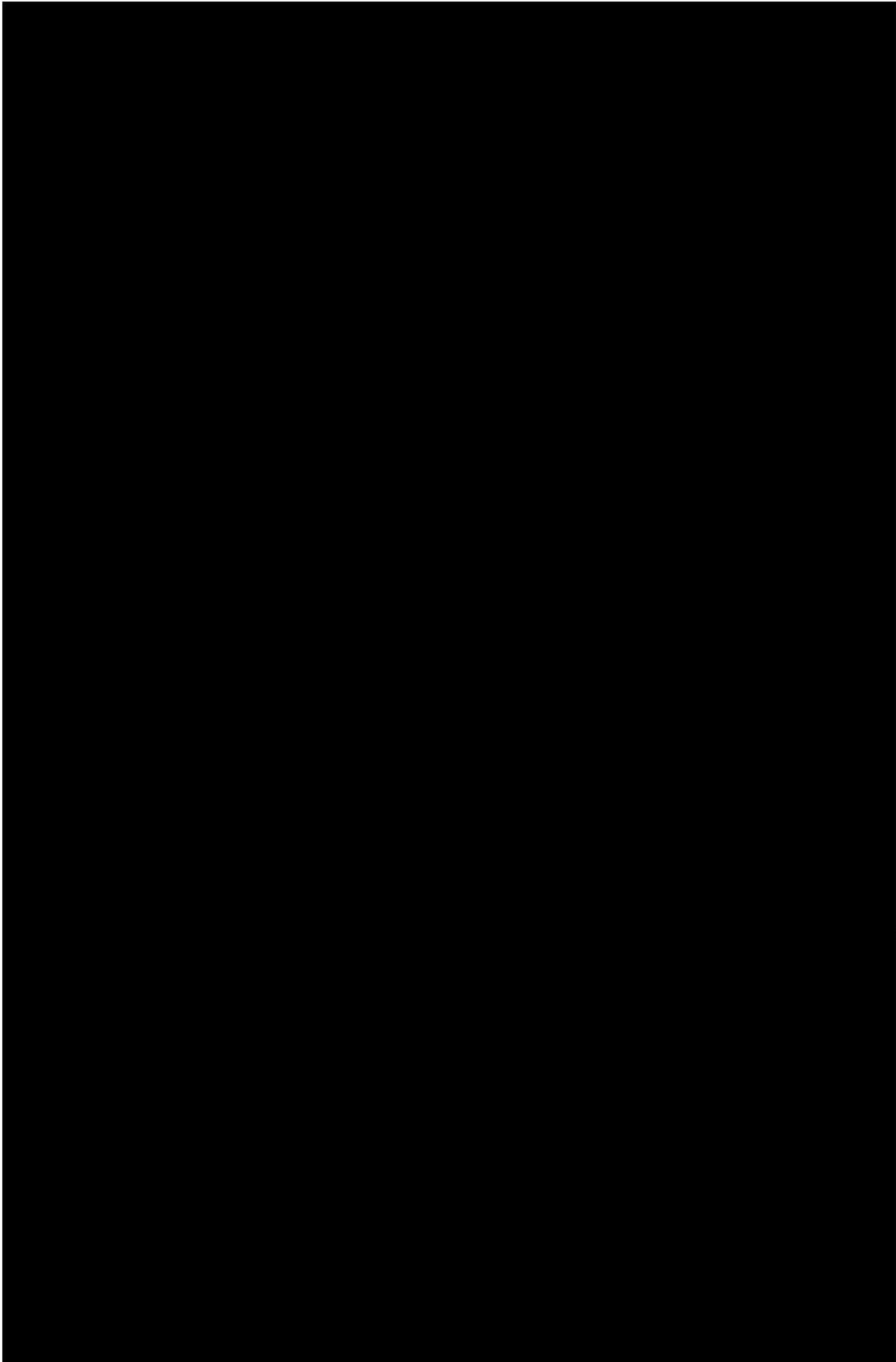






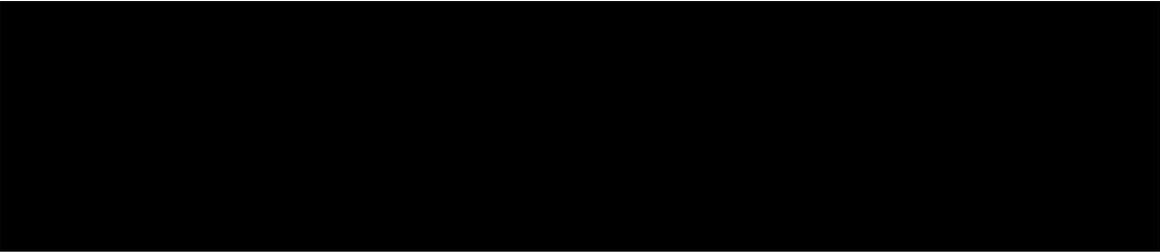






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Ferrell PB, McLeod HL. Carbamazepine, HLA-B\*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics.* 2008; 9: 1543-46.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet.* 2002; 359:1121-2.

Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; 22: 1382-1388.

Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS. UGT1A1\*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. *Cancer.* 2008; 112: 1932-40.

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Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A; PREDICT-1 Study Team. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008; 358: 568-78

Schulz C, Heinemann V, Schalhorn A, Moosmann N, Zwingers T, Boeck S, Giessen C, Stemmler HJ. UGT1A1 gene polymorphism: Impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. *World J. Gastroenterol.* 2009; 15: 5058-66.

## 12.4. Appendix 4 Eastern Cooperative Oncology Group Performance Status

The scale and criteria summarised [Appendix 4 Table 1](#) are designed to assess how a subject's disease is progressing and to assess how the disease affects activities of daily living of the subject.

**Appendix 4 Table 1 Eastern Cooperative Oncology Group performance status grading criteria**

Grade	Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Abbreviations: ECOG = Eastern Cooperative Oncology Group

## References

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5:649-655, 1982

## **12.5. Appendix 5 Country Specific Requirements**

No country-specific requirements exist.

## 12.6. Appendix 6 Cockcroft-Gault Equation for Calculating Creatinine Clearance

Creatinine clearance can be calculated from serum creatinine values by two formulas.

To calculate as mg/dL:

$$\begin{aligned} \text{Calculated creatinine} \\ \text{clearance (mL/min)} = & \frac{(140 - \text{age [years]}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \\ \text{Female subjects: multiply by 0.85} \end{aligned}$$

To calculate as  $\mu\text{mol/L}$ :

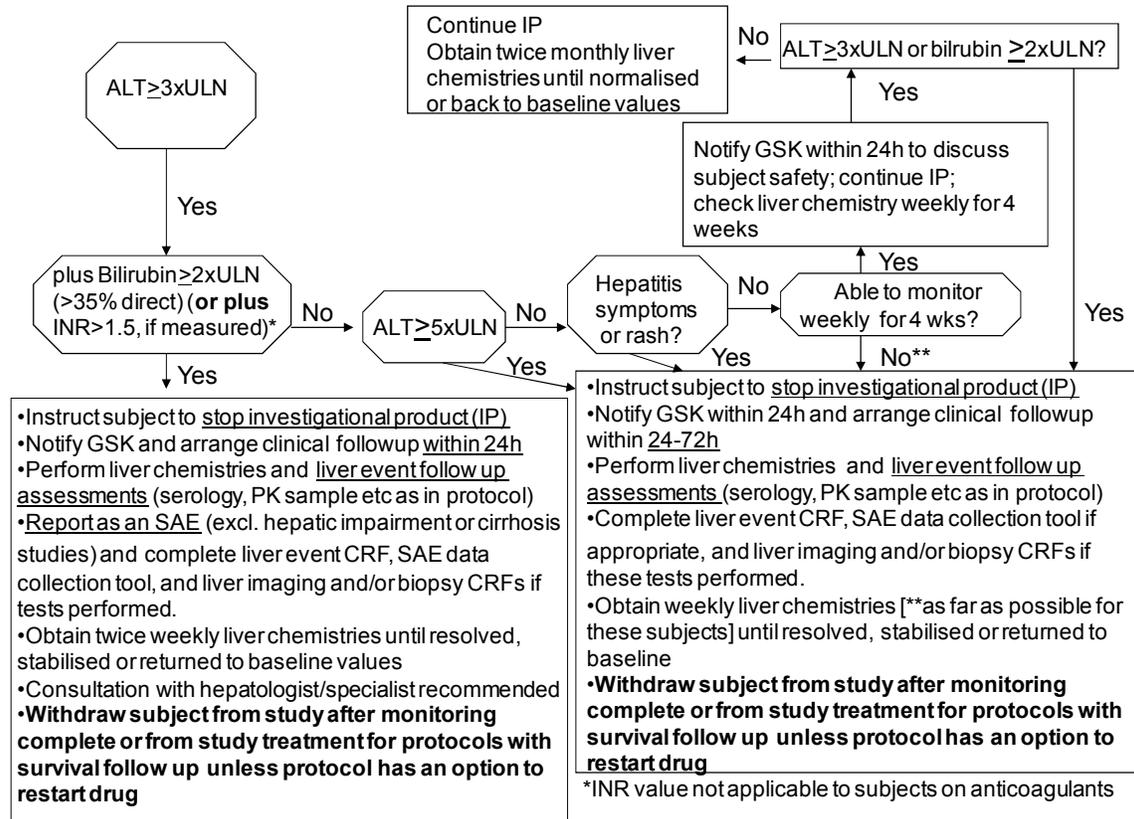
$$\begin{aligned} \text{Calculated creatinine} \\ \text{clearance (mL/min)} = & \frac{(140 - \text{age [years]}) \times \text{weight (kg)} \times 88.4}{72 \times 1 \times \text{serum creatinine } (\mu\text{mol/L})} \\ \text{Female subjects: multiply by 0.85} \end{aligned}$$

### References

Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. *Nephron* 16: 31-41, 1976

## 12.7. Appendix 7 Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Appendix 7 Figure 1 Liver safety algorithm



## 12.8. Appendix 8 Protocol Changes

### Amendment 1

**Protocol Amendment 01 applies to all site(s) participating in the conduct of the study**

#### Summary of changes and rationale:

Change	Rationale
Prior treatment with lapatinib was added as an exclusion criterion.	It is possible that prior treatment with lapatinib might influence the subjects' perception of the tolerability of lapatinib, or the subjects' susceptibility to lapatinib-associated diarrhoea.
Additional detail was provided for dermatological monitoring.	The protocol was updated to include the GSK lapatinib dermatological assessment guidelines (version 4.0, 10 March 2014). The frequency of skin examination was modified to be consistent with recommendations in the lapatinib SPC.
Secondary endpoints related to patient reported outcomes were updated.	The Diarrhoea Management Diary was revised after the LAP117314 protocol was finalised (17 February 2014). The patient-reported endpoints and objectives were amended to be consistent with the revised Diarrhoea Management Diary.
The schedule for completion of the Diarrhoea Management Diary and FACIT-D was clarified.	Information has been provided to describe and clarify the schedule for completion of the Diarrhoea Management Diary and FACIT-D at the baseline visits and during treatment with lapatinib and capecitabine.
The schedule of study visits relative to the week numbers and cycles of treatment with lapatinib and capecitabine was clarified	The Diarrhoea Management Diary and FACIT-D refer to 'Week' of treatment and the protocol Time and Events table refers to 'Cycle' of treatment. Information has been provided to describe and clarify the relationship between 'Week' and 'Cycle' of treatment.
The use of octreotide s.c. within the diarrhoea management guidelines was clarified	The protocol includes the GSK diarrhoea management guidelines, which recommend the use of octreotide as a second line treatment option for diarrhoea refractory to treatment with loperamide. Additional guidance has been provided concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR.

Change	Rationale
Typographical errors have been corrected; Time and Events table content has been update; format changes have been made.	These changes have been made to improve the quality of the protocol, and are listed in detail in this appendix.

### Detail of changes

- The detail of changes is presented in the order in which the change appears in the protocol.
- ‘Original’ refers to content of the protocol dated 17 February 2014.
- ‘Amended’ refers to the content of the protocol as updated in Amendment 01.
- Text deleted from the original protocol is presented as a ~~strikethrough~~ font.
- The location of the changes in the text of the protocol is identified by section number and title, followed by paragraph number and sentence number if required.
- Minor changes to table content are identified by table number, followed by row number and column number.
- More extensive changes to tables are presented as ‘Original’ table content, followed by ‘Amended’ table content.
- Changes to section numbers and table numbers subsequent to amendment changes are not recorded in the appendix, unless this clarifies the location of the change.

### Title page

[REDACTED] were added as authors.

### Sponsor Information page

Item	Original	Amended
[REDACTED] position updated	[REDACTED]	Tykerb/Tyverb [REDACTED]
[REDACTED] position updated	<del>Tykerb/Tyverb</del> [REDACTED]	Tykerb/Tyverb [REDACTED]
[REDACTED] address updated	[REDACTED]	[REDACTED]
[REDACTED] telephone number updated	[REDACTED]	[REDACTED]
[REDACTED] fax number deleted	[REDACTED]	n/a

Item	Original	Amended
[REDACTED] added as Principal Investigator	n/a	[REDACTED]
[REDACTED] added as Principal Investigator	n/a	[REDACTED]

### Table of contents

The Table of Contents was updated.

### List of abbreviations

Added:

DMD	Diarrhoea Management Diary
DSS	Diarrhoea symptom subscale

Deleted:

<del>IWR</del>	<del>Interactive web response</del>
<del>NG</del>	<del>Next generation</del>

### Minor Typographical changes

These changes may also occur in sections of text which have been more extensively modified, summarised in other sections of this appendix.

‘Diarrhoea diary’ has been changed to ‘Diarrhoea Management Diary’ or ‘DMD’ in the following locations:

Location	Paragraph	Line
Protocol Summary: Rationale	7	15/16

<b>Location</b>	<b>Paragraph</b>	<b>Line</b>
Protocol Summary: Objectives	3	2, 4
Section 1.2 Study rationale	6	1
Section 1.2 Study rationale	7	1, 2
Section 2 Objectives and Endpoints	3	2, 4, 5
Section 3.1 Study design	14	1
Section 3.2 Discussion of design	12	2, 4, 6, 7
Section 5.8 Treatment compliance	3	2, 3
Time and Events Table 16	Footnote	6
Time and Events Table 17	Footnote	6
Section 7.1.6 Assessments every 3 weeks	Bullet list	Bullet point 9
Section 7.1.8 Study completion or early withdrawal	Bullet list	Bullet point 7
Section 8 Data Management	3	1
Section 9.3.5.1 Efficacy analyses	1	6

The term ‘every week’ was added to clarify the frequency for completing the DMD in the following locations:

<b>Location</b>	<b>Paragraph</b>	<b>Line</b>
Protocol Summary: Objectives	3	2
Section 2 Objectives and Endpoints	3	2
Section 3.1 Study design	14	1

The term ‘every 3 weeks’ was added to clarify the frequency for completing the FACIT-D in the following locations:

Location	Paragraph	Line
Protocol Summary: Objectives	3	2
Section 2 Objectives and Endpoints	3	2
Section 3.1 Study design	14	1

### Protocol Summary: Study design

Original text, paragraph 3:

~~All subjects with episodes of diarrhoea will be encouraged to follow the GSK diarrhoea management guidelines for subjects receiving lapatinib.~~

### Protocol Summary: Study assessments

Original text, paragraph 2:

~~Subjects randomised to receive octreotide will complete the diarrhoea diary and FACIT-D before receiving the first dose of octreotide. All subjects will complete the diarrhoea diary and FACIT-D immediately before starting the first cycle of treatment with lapatinib and capecitabine. Subjects will then complete a diarrhoea diary and the FACIT-D at regular intervals until the end of 24 weeks of treatment or subject withdrawal, whichever is sooner. PROs will not be collected beyond 24 weeks of treatment.~~

Amended text, paragraph 2:

All subjects will complete the baseline DMD and FACIT-D during the 3 days prior to randomisation, before any study-related treatment is administered. Subjects randomised to receive octreotide will complete a second baseline DMD and FACIT-D before starting the first cycle of treatment with lapatinib and capecitabine. Subjects will then complete the DMD every week and the FACIT-D every 3 weeks until the end of 24 weeks of treatment with lapatinib and capecitabine or subject withdrawal, whichever is sooner. The DMD and FACIT-D will not be completed beyond 24 weeks of treatment.

New text inserted, paragraph 5:

All subjects with episodes of diarrhoea will be encouraged to follow the GSK diarrhoea management guidelines for subjects receiving lapatinib. The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and

capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range.

New text inserted, last sentence of original paragraph 5, amended paragraph 6:

Dermatological monitoring and assessment will be conducted in accordance with the guidance provided in the Lapatinib SPC.

### **Section 1.3.1 Risk assessment**

Original text, paragraph 4, sentence 4:

~~Diarrhoea will be managed in accordance with the GSK guidelines (Appendix 1), with the exception that subjects with severe diarrhoea unresponsive to loperamide who have received octreotide LAR should not receive further treatment with octreotide, but should receive supportive care as second line management of diarrhoea.~~

Amended text, paragraph 4, sentence 4:

Diarrhoea will be managed in accordance with the GSK guidelines (Appendix 1); subjects with severe diarrhoea unresponsive to loperamide who have received octreotide LAR may receive further treatment with octreotide s.c. at the investigators discretion,

### **Section 2 Objectives and Endpoints, Table 7**

Original text, Row 2 '~~Primary: Investigator reported~~'

Amended text, Row 2 'Primary: Investigator reported (eCRF)'.

Original text Row 3, Endpoints column, '~~Proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above, as defined by the NCI CTCAE, version 4.03~~'.

Amended text Row 3, Endpoints column 'Proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above, as defined by the NCI CTCAE, version 4.03, recorded as AEs in the eCRF.'

Original text Row 4, '~~Secondary: Investigator reported~~',

Amended text Row 4 'Secondary: Investigator reported (eCRF)'.

Original text, Rows relating to Secondary: Subject-reported endpoints and objectives.

<b>Secondary: Subject reported</b>	
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, recorded in the diarrhoea diary.
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 in the diarrhoea diary.
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects taking anti-diarrhoeal medication.	Proportion of subjects taking anti-diarrhoeal medication, recorded in the diarrhoea diary.
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects making dietary changes as a result of diarrhoea.	Proportion of subjects making dietary changes due to diarrhoea, recorded in the diarrhoea diary.
To determine the effect of prophylactic octreotide on the proportion of subjects making unscheduled visits to healthcare professionals as a result of diarrhoea.	Proportion of subjects making unscheduled visits to healthcare professionals due to diarrhoea, recorded in the diarrhoea diary.
To determine the efficacy of prophylactic octreotide in reducing the proportion of subjects making changes to cancer therapy as a result of diarrhoea.	Proportion of subjects missing doses of lapatinib and capecitabine due to diarrhoea, recorded in the diarrhoea diary.
<b>Quality of Life</b>	
To determine the effect of prophylactic octreotide on quality of life.	Proportion of subjects with improvement in quality of life, recorded by FACIT-D. Trial Outcomes Index will be the primary measure; sub-scales will be secondary measures.

Amended text, Rows relating to Secondary: Patient-reported endpoints and objectives.

<b>Secondary: Patient<sup>1</sup> reported (DMD)</b>	
To determine the effect of prophylactic octreotide on patient-reported diarrhoea.	Proportion of patients reporting changes in bowel movements from baseline (frequency and/or consistency), recorded in the DMD.
To determine the effect of prophylactic octreotide in delaying patient reported diarrhoea.	Time to the first patient reported change in frequency and/or consistency of bowel movements from baseline, recorded in the DMD.
To determine the effect of prophylactic octreotide in reducing the proportion of patients taking anti-diarrhoeal medication.	Proportion of patients taking anti-diarrhoeal medication, recorded in the DMD.
To determine the effect of prophylactic octreotide in reducing the proportion of patients making dietary changes to control diarrhoea.	Proportion of patients making dietary changes due to diarrhoea, recorded in the DMD.
To determine the effect of prophylactic octreotide on the proportion of patients contacting other non-hospital healthcare professionals to discuss diarrhoea.	Proportion of patients contacting other non-hospital healthcare professionals to discuss diarrhoea, recorded in the DMD.
To determine the effect of prophylactic octreotide in reducing the proportion of patients reporting non-adherence due to diarrhoea.	Proportion of patients reporting stopping completely or missing doses of anti-cancer tablets due to diarrhoea, recorded in the DMD.
<b>Quality of Life (FACIT-D)</b>	
To determine the effect of prophylactic octreotide on health-related quality of life.	Proportion of patients with changes in health-related quality of life, recorded by FACIT-D. Trial Outcomes Index will be the primary endpoint; FACT-G total, FACIT-D total, and sub-scales will be secondary endpoints..

1. The term 'patient' refers to study subject in the context of DMD- and FACIT-D-related objectives and endpoints.

## Section 2 Objectives and endpoints

Amended text, new paragraphs inserted after paragraph 3:

All subjects will complete the baseline DMD and the FACIT-D during the 3 days prior to randomisation, before any study-related treatment is administered. Subjects randomised to receive octreotide will complete a second baseline DMD and the FACIT-D before starting the first cycle of treatment with lapatinib and capecitabine. Hence, subjects randomised to receive octreotide will complete the baseline DMD and the FACIT-D (Week -1) prior to receiving the first dose of octreotide (0.1mg subcutaneous tolerability

test dose), and all subjects will complete the baseline DMD and the FACIT-D prior to receiving the first dose of lapatinib and capecitabine (Week 0).

The DMD will be completed every week after the first dose of lapatinib and capecitabine is administered (Week 1, Week 2, Week 3, etc), until the end of study visit (Week 24, disease progression, unacceptable toxicity or subject withdrawal if this is sooner). The FACIT-D will be completed every 3 weeks during treatment with lapatinib and capecitabine (Week 3, Week 6, Week 9, etc), until the end of study visit (Week 24, disease progression, unacceptable toxicity or subject withdrawal if this is sooner). The DMD and FACIT-D will not be completed beyond 24 weeks of treatment.

The baseline DMD comprises 3 questions to record stool form and consistency. The DMD to be completed throughout the rest of the study comprises the 3 questions in the baseline DMD and a further 5 questions and 6 sub-questions to evaluate the consequences and management of diarrhoea. A copy of the baseline DMD and the DMD is included in the Study Procedures Manual (SPM).

Original text, paragraph 4:

~~The FACIT-D (Appendix 2) comprises the 27 item Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire which has physical (PWB), social (SWB), emotional (EWB) and functional wellbeing (FWB) subscales and an 11 item subscale which measures quality of life specific to diarrhoea. The primary PRO endpoint will be the Trial Outcome Index, which is a summation of the PWB, FWB and diarrhoea subscales. Secondary PRO endpoints will be overall quality of life (total FACT-G), total FACIT-D and scores from each of the individual subscales. The FACIT-D will be completed every 3 weeks.~~

Amended text, paragraph 7 (replaces original paragraph 4):

The FACIT-D (Appendix 2) comprises the 27 item Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire which has physical (PWB), social (SWB), emotional (EWB) and functional wellbeing (FWB) subscales and an 11 item diarrhoea symptom subscale (DSS) which measures quality of life specific to diarrhoea. The primary endpoint derived from the FACIT-D will be the Trial Outcome Index, which is a summation of the PWB, FWB and diarrhoea symptom subscales. Secondary endpoints will be overall quality of life (total FACT-G), total FACIT-D and scores from each of the individual subscales.

Original text, paragraph 5 (amended text paragraph 8), line 5, mis-spell 'efficiacy' corrected to 'efficacy'.

### **Section 3.1 Study design:**

Original text paragraph 3, sentence 1, ~~Study Procedures Manual (SPM)~~

Amended text 'paragraph 3, sentence 1, SPM.

Original text: paragraph 5, sentence 3, 'All subjects with episodes of diarrhoea will be encouraged to follow the diarrhoea management guidelines for subjects receiving lapatinib (Appendix 1).

Original text: paragraph 9

~~Episodes of mild diarrhoea which occur following the first dose of octreotide LAR and prior to the first dose of lapatinib and capecitabine should be managed in accordance with the diarrhoea management guidelines (Appendix 1). Episodes of severe diarrhoea which occur following any dose of octreotide should be managed by taking supportive measures, but should not include further use of octreotide.~~

Amended text (new paragraph):

All subjects with episodes of diarrhoea will be encouraged to follow the GSK diarrhoea management guidelines for subjects receiving lapatinib (Appendix 1). In subjects randomised to receive octreotide, episodes of mild diarrhoea which occur following the first dose of octreotide LAR should be managed in accordance with the diarrhoea management guidelines. The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range.

Original text, paragraph 14:

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

Amended text, paragraph 15 (replaces original paragraph 14)

Subjects will complete the DMD every week and the FACIT-D every 3 weeks during treatment with lapatinib and capecitabine to provide an additional perspective on the effects of treatment-associated diarrhoea.

Original text, paragraph 15, sentence 5

~~Any changes will be communicated to the investigative sites in the form of a letter and revised version will be included in the SPM.~~

Amended text, paragraph 16, sentence 5 (replaces original paragraph 15, sentence 5)

Any changes will be communicated to the investigative sites in the form of a letter and the revised version of the AE management or dose modification guidelines will be included in the SPM.

Original text, paragraph 16, sentence 5

~~Any changes will be communicated to the investigative sites in the form of a letter and revised version will be included in the SPM.~~

Amended text, paragraph 17, sentence 5 (replaces original paragraph 16, sentence 5)

Any changes will be communicated to the investigative sites in the form of a letter and the revised version of the AE management or dose modification guidelines will be included in the SPM.

### **Section 3.2 Discussion of design**

Original text, paragraph 1

~~All subjects in this study will receive treatment with lapatinib and capecitabine consistent with the approved indication for this treatment combination. Diarrhoea is a recognised side effect of cancer treatment, and all subjects will be recommended to follow the standardised guidelines for diarrhoea management (Appendix 1).~~

Amended text, paragraph 1

All subjects in this study will receive treatment with lapatinib and capecitabine consistent with the approved indication for this treatment combination. Diarrhoea is a recognised side effect of cancer treatment, and all subjects will be recommended to follow the standardised guidelines for diarrhoea management (Appendix 1). The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded, and investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR.

Original text, paragraph 6, sentence 4

~~In this study, all subjects will be recommended to follow the standardised guidelines for management of diarrhoea associated with lapatinib use, and octreotide in the formulation for s.c. administration will not be provided to manage episodes of diarrhoea in subjects randomised to receive octreotide LAR.~~

Amended text, paragraph 6, sentence 4

In this study, octreotide in the formulation for s.c. administration will not be provided prophylactically to prevent episodes of diarrhoea in subjects during the first 7 to 14 days after the first dose of octreotide LAR.

#### **Section 4.1.2 Inclusion criteria**

Amended text, bullet 7b, 'Acceptable contraceptive methods are described in Section 7.5.1.' was added.

#### **Section 4.1.3 Exclusion criteria**

Amended text, bullet point 10, 'Prior treatment with lapatinib' was added.

## Section 4.2 Other eligibility criteria considerations

Original text, paragraph 3

~~Caution should be taken in subjects with moderate or severe hepatic impairment or severe renal impairment. Caution should be taken in subjects with conditions that could impair cardiac function, including conditions that could result in prolongation of QTc, arrhythmias and angina pectoris. Subjects with hypertension who are randomised to receive octreotide must be monitored to manage the potential risk of bradycardia associated with octreotide use.~~

Amended text, paragraph 3

Caution should be taken in subjects with moderate or severe hepatic impairment. Investigators should consider the subjects hepatic function measures relative to the guidance provided for the management of hepatobiliary AEs in Section 5.13. It is recommended that hepatic function measures prior to randomisation should meet the following criteria:

- Albumin  $\geq 2.5$  g/dL
- Serum bilirubin  $\leq 1.5$  x the upper limit of the normal range (ULN) or  $\leq 2.5$  x ULN with Gilbert's Syndrome
- AST and ALT  $\leq 3 \times$  ULN

Caution should be taken in subjects with severe renal impairment.

Caution should be taken in subjects with conditions that could impair cardiac function, including conditions that could result in prolongation of QTc, arrhythmias and angina pectoris. Subjects with hypertension who are randomised to receive octreotide must be monitored to manage the potential risk of bradycardia associated with octreotide use.

### Section 4.3.1 Discontinuation from treatment with octreotide

Original text, paragraph 2, sentence 2 and sentence 3

~~Episodes of mild diarrhoea which occur following the first dose of octreotide LAR and prior to the first dose of lapatinib and capecitabine should be managed in accordance with the diarrhoea management guidelines (Appendix 1). Episodes of severe diarrhoea occurring at any time during the first three cycles of treatment with lapatinib and capecitabine should be managed by taking supportive measures, but should not include further use of octreotide.~~

Amended text, paragraph 2, sentence 2 and sentence 3

Episodes of mild diarrhoea which occur following treatment with octreotide LAR should be managed in accordance with the diarrhoea management guidelines (Appendix 1). The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive

treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range.

#### **Section 4.3.2 Discontinuation from treatment with lapatinib and capecitabine**

Amended text, inserted before original text sentence 1

Subjects may withdraw from the study at any time.

#### **Section 5.3 Octreotide**

Original text, paragraph 2, sentence 2

~~Octreotide is provided as a 0.1mg/mL solution for s.c. injection, which may be diluted for intravenous infusion.~~

Amended text, paragraph 2, sentence 2

Octreotide is provided as a 0.1mg/mL solution for s.c. injection.

#### **Section 5.3.1 Octreotide dosage and administration**

Original text, paragraph 3

~~Episodes of mild diarrhoea which occur following the first dose of octreotide LAR and prior to the first dose of lapatinib and capecitabine should be managed in accordance with the diarrhoea management guidelines (Appendix 1). Episodes of severe diarrhoea should be managed by taking supportive measures, but should not include further use of octreotide. Subjects who report constipation with a severity of NCI CTCAE Grade 2 and above (Table 9) or other adverse events which are considered likely to be related to octreotide treatment following the first dose of octreotide LAR must not receive the second dose.~~

There is no amended text for this deletion.

#### **Section 5.5 Treatment assignment**

Original text, sentence 2

~~Investigators or designated staff will telephone the GSK interactive voice response (IVR) system called RAMOS (Registration and Medication Ordering System) or will contact the GSK interactive web response (IWR) system called RAMOS NG (Next Generation) to register and record subject activity.~~

Amended text, sentence 2

Investigators or designated staff will telephone the GSK interactive voice response (IVR) system called RAMOS (Registration and Medication Ordering System) to register and record subject activity.

Original text, sentence 5

~~Study-specific instructional worksheets will be provided for the use of the IVR and IWR systems.~~

Amended text, sentence 5

Study-specific instructional worksheets will be provided for the use of the IVR system.

### **Section 5.7, Product accountability**

Amended text, inserted after sentence 1.

Recording of drug accountability is required regardless of whether the Institution or GSK are providing lapatinib and capecitabine.

### **Section 5.9, Dose adjustment**

Original text, paragraph 3, sentence 3.

~~Episodes of severe diarrhoea should be managed by taking supportive measures, but should not include further use of octreotide.~~

Amended text, paragraph 3, sentence 3.

The use of octreotide in the s.c. formulation for the management of diarrhoea refractory to treatment with loperamide is not excluded. Investigators should use their clinical judgement concerning the use of octreotide s.c. in subjects randomised to receive treatment with octreotide LAR, particularly during Week 2 through to Week 12 of treatment with lapatinib and capecitabine, when circulating concentrations of octreotide should already be within the clinically effective range.

### **Section 5.12.1 Dermatological events**

Original text

~~The NCI CTCAE descriptions and grades of severity of dermatological AEs is presented in Table 12.~~

**Table 12** — NCI-CTCAE dermatological reactions

Adverse Event (Short name)	Grade 1	Grade 2	Grade 3	Grade 4
Rash / desquamation* (Rash)	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation* or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation* covering $\geq$ 50% BSA.	Generalized exfoliative, ulcerative, or bullous dermatitis.
Rash: Acne/acneiform (Acne)	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration or desquamation	-
Nail changes (Nail changes)	Discoloration; ridging (koilonychias; pitting) Paronychia: no intervention indicated	Partial or complete loss of nail(s); pain in nailbed(s) Paronychia: intervention indicated	Interfering with Activities of Daily Living (ADL)	-
Pruritus/itching (Pruritus)	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Dry skin (Dry skin)	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	-
Hair loss/alopecia (scalp or body)	Thinning or patchy	Complete	-	-
Photosensitivity (Photosensitivity)	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling

Significant skin AEs (Grade 3 or more) resulting from lapatinib are rare, occurring in only 1-3% of subjects.

For NCI-CTCAE Grade 4 rash manifested as toxic epidermal necrolysis (i.e. Stevens-Johnson's Syndrome, etc) lapatinib must be permanently discontinued.

Subjects with poorly tolerated skin AEs may be successfully managed by providing a brief (up to 14 days) therapy interruption. However, the rash may improve without the need for interrupting therapy with lapatinib.

A variety of agents can be used to manage skin rashes. These agents include mild to moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, and occasionally, retinoid creams.

Amended text

#### 5.12.1.1 Dermatological Monitoring

As part of their physical examination, subjects must have a thorough skin examination prior to the start of study treatment or randomisation. The examination may include the scalp, previously irradiated areas, hair, and nails. In addition, if clinically indicated an examination of the oral/genital mucosa may also be included.

Subsequent dermatological evaluations should be performed as clinically indicated. Any serious and/or clinically relevant dermatological AEs must be followed until resolution to grade one (or better), or until there is no further improvement.

Subjects must also have a skin examination as part of the physical examination at the end of 24 weeks of treatment with lapatinib and capecitabine, or disease progression, treatment discontinuation due to unacceptable toxicity or subject withdrawal, whichever is sooner.

The purpose of dermatological monitoring is:

- to facilitate dermatological safety throughout the trial in all subjects receiving lapatinib;
- to assess whether a holding/stopping rule imposed during the course of treatment leads to less dermatological toxicity;
- to identify the incidence of dermatological adverse events (AEs) for lapatinib, or the combination of lapatinib with other agents.

#### 5.12.1.2 Frequency Evaluation and Grading Guide of Dermatological AEs

The frequency of dermatological adverse events occurring in 2,093 patients with locally advanced or metastatic cancer who participated in nine completed phase II and III lapatinib clinical trials is shown in Table 12. This patient population included 1,413 patients with breast cancer and 680 patients with other cancers. Patients were treated with lapatinib as monotherapy (n = 926) or in combination with paclitaxel (n=293) or capecitabine (n = 491). Patients who were not exposed to lapatinib but received paclitaxel, capecitabine, or hormonal agents served as controls (n = 676).

**Table 12 Most Common Dermatological AEs Occurring in Patients Receiving Lapatinib (NCI-CTCAE versions 2.0 and 3.0)**

Skin event	CTC grade, %															
	All L <i>n</i> = 1,417		L <i>n</i> = 926		L + C <i>n</i> = 198		L + P <i>n</i> = 293		No L <sup>a</sup> <i>n</i> = 676		C <i>n</i> = 191		P <i>n</i> = 286		Hormonal <i>n</i> = 199	
	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3
Rash	43	4	47	3	13	2	50	8	14	<1	8	<1	25	<1	5	<1
Hand-foot syndrome	8	2	<1	<1	54	14	1	<1	14	4	51	14	0	0	0	0
Hair disorder	3	<1	<1	0	<1	0	14	1	16	2	<1	0	37	5	2	0
Dry skin	3	<1	3	<1	2	0	3	0	3	0	2	0	2	0	5	0
Pruritus/Urticaria	3	<1	3	<1	<1	0	5	<1	4	<1	<1	0	7	<1	2	0
Skin disorder	1	0	2	0	<1	0	1	0	<1	<1	2	0	1	<1	0	0
Skin infection	<1	<1	<1	0	<1	<1	0	0	<1	0	0	0	<1	0	0	0
Nail disorder	<1	<1	1	<1	0	0	1	0	<1	0	<1	0	<1	0	<1	0

There were no grade 4 dermatologic events

CTC: National Cancer Institute Common Toxicity/Terminology Criteria for Adverse Events; L: lapatinib; C: capecitabine; P: paclitaxel

<sup>a</sup> No lapatinib is monotherapy with either hormones (*n* = 199), capecitabine (*n* = 191), or paclitaxel (*n* = 286)

The NCI CTCAE descriptions and grades of severity of dermatological AEs is presented in Table 13.

**Table 13 NCI-CTCAE dermatological reactions**

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Rash: Acne/acneiform (Acne)	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local super infection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive super infection with IV antibiotics indicated; life-threatening consequences	Death
Nail discoloration	Asymptomatic; clinical or	-	-	-	-

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	diagnostic observations only; intervention not indicated				
Nail Loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localised intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Pruritus/itching (Pruritus)	Mild or localised; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	
Alopecia	Hair loss of up to 50% of normal for that individual that is not obvious from a distance but only	Hair loss of >50% normal for that individual that is readily apparent to	-	-	

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact			
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death

Lapatinib-related severe dermatological events ( $\geq$ Grade 3) are infrequent (1-3%). Despite the rarity of lapatinib associated severe dermatological events, it is recommended that subjects who present with a severe dermatological event be assessed for the following: shortness of breath, angioedema, or generalised mucosal/cutaneous affection with blisters or ulcers, suggestive of Type I hypersensitivity and/or NCI-CTCAE Grade 4 dermatological event, manifested as toxic epidermal necrolysis or Stevens-Johnson Syndrome etc. If a Grade 4 dermatological event occurs, lapatinib must be permanently discontinued.

#### 5.12.1.3 Stopping and holding rules

If any Grade 4 dermatological event occurs, lapatinib must be permanently discontinued.

##### 5.12.1.3.1 Holding rule

Lapatinib should be held for 14 days, in all patients who experience either a grade 3 dermatological reaction or a grade 2 dermatological reaction, which is unimproved after two-weeks of medical management. After the 14 day interruption, and provided the dermatological reaction improves to grade 1 or better, lapatinib may be restarted at the previous dose.

If the investigator considers continuation of lapatinib without interruption, it is required that he/she discusses the individual case with the GSK medical monitor before taking any decision on study treatment. In some cases, resolution of grade 2 or greater dermatological reactions occurred without interruption of lapatinib. For those subjects that interrupted lapatinib, many were able to resume lapatinib therapy at the same dose after resolution of the dermatological event.

#### 5.12.1.3.2 Re-challenge

One re-challenge may be considered, if indicated in the opinion of the investigator, for subjects who present with NCI-CTCAE Grade 3 dermatological events which recover to NCI-CTCAE Grade 1 or better (within 14 days) after holding lapatinib.

#### 5.12.1.3.3 Stopping rules

Lapatinib must be permanently discontinued for:

- Recurrent Grade 3 dermatological reactions
- All Grade 4 dermatological reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.

#### 5.12.1.4 Treatment

There is no standard treatment proven to be effective for lapatinib-induced dermatological reactions. Therefore it is recommended that subjects who develop Grade 2 dermatological reactions that are unresponsive to initial treatment may be referred to a dermatologist for evaluation and management. For subjects with Grade 3 or 4 dermatologic events, or chronic, persistent or recurring lower grade skin events, a dermatology consultation is strongly encouraged.

There are some general precautions for subjects receiving lapatinib therapy. Subjects are recommended to avoid exposure to bright sunlight. When going out into bright sunlight, a broad spectrum sunscreen (containing titanium dioxide or zinc oxide) with an SPF of at least 30 should be applied.

A variety of agents may be used to manage dermatological reactions. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, immunomodulators, hypoallergenic moisturisers, and emollients.

The need for oral or topical antibiotics and topical steroids is a clinical decision. For **pruritic** lesions oral antihistamine agents may be effective. For **paronychia** antiseptic bath and local potent corticosteroids in addition to tetracycline therapy is recommended. If no improvement occurs, a dermatology or surgery consultation is recommended. For **infected** lesions appropriate, culture driven treatment with systemic or topical antibiotics is recommended as clinically indicated.

Oral retinoids are not recommended because of theoretical concerns about negative effects on lapatinib's mechanism of action. Topical steroids may result in skin irritation and severe xeroderma (dryness). Oral steroids may be used for a short treatment course (maximum of 14 days).

### Section 5.13. Monitoring, Interruption, and Stopping Criteria for Hepatobiliary Events

Original text, paragraph 1, sentence 1

~~the upper limit of the normal range (ULN)~~

Amended text, paragraph 1, sentence 1

ULN

## **Section 6.2. Prohibited Medications and Non-Drug Therapies**

Amended text, added after bullet point 1, sentence 2

Subjects who require an alternative anti-cancer therapy may withdraw from the study at any time.

Amended text, paragraph added after paragraph 5

Information on potential interactions with other medicinal products is presented in the Lapatinib, Capecitabine and Octreotide SPCs.

**Section 7, Study Assessments and Procedures.** Original Table 15, Amended Table 16.

Column 3, row 1-2, inserted text 'Week -1'.

Below row 13 (Physical Exam) insert new row, Dermatological Exam, with 'x' and '(x)<sup>8</sup>' in relevant columns to show schedule of assessment.

Original text Table footnote 7

~~To be completed before the octreotide 0.1mg s.c. tolerability assessment dose.~~

Amended text Table footnote 7

Week -1 baseline PROs to be completed prior to randomisation, before the octreotide 0.1mg s.c. tolerability assessment dose.

New footnote inserted, Table footnote 8

If clinically indicated, in accordance with the Lapatinib SPC.

Original Table footnotes 8 and 9 were renumbered as Table footnotes 9 and 10.

Original text Table footnote 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.~~

Amended text Table footnote 10

Visits at the start of Cycle 2 and Cycle 4 visits are mandatory. Visits at the start of 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.

Original text Table footnote 10

~~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.~~

Original text Table footnote 11

~~To be completed before the first dose of lapatinib and capecitabine is administered.~~

Amended text Table footnote 11

Week 0 baseline PROs to be completed before the first dose of lapatinib and capecitabine is administered.

Amended text inserted, new Table footnote 13

Cycle 2 to be started 21 days ( $\pm$  2 days) after the start of Cycle 1. Other cycles should be started within  $\pm$  4 days of the 3 weekly treatment cycle intervals.

Original Table footnotes 13, 14, 15 and 16 were renumbered as Table footnotes 14, 15, 16 and 17.

Original Table footnote 17

~~If clinically indicated.~~

Superscript numbers linking table cells to table footnotes were updated in accordance with the updated footnote numbers.

**Section 7, Study Assessments and Procedures.** Original Table 16, Amended Table 17.

Column 3, row 2, inserted text 'Cycle'.

Column 4, row 2, inserted text 'Cycle'.

Below row 13 (Physical Exam) insert new row, Dermatological Exam, with 'x' and '(x)<sup>8</sup>' in relevant columns to show schedule of assessment.

Original text Table footnote 7

~~To be completed before the first dose of lapatinib and capecitabine is administered.~~

Amended text Table footnote 7

Week 0 baseline PROs to be completed prior to randomisation, before the first dose of lapatinib and capecitabine is administered.

New footnote inserted, Table footnote 8

If clinically indicated, in accordance with the Lapatinib SPC.

Original Table footnotes 8 and 9 were renumbered as Table footnotes 9 and 10.

Original text Table footnote 10

~~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.~~

Amended text Table footnote 11

Visits at the start of Cycle 2 and Cycle 4 visits are mandatory. Visits at the start of 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.

Original Table footnote 14

~~If clinically indicated.~~

Superscript numbers linking table cells to table footnotes were updated in accordance with the updated footnote numbers.

### **Section 7.1.3 Prior to randomisation**

Paragraph 1, new bullet point inserted after bullet point 2

Dermatological examination.

Original text, paragraph 1, original bullet point 10, amended bullet point 11

~~diarrhoea diary~~

Amended text, paragraph 1, original bullet point 10, amended bullet point 11

baseline DMD

### **Section 7.1.5, One Week after the First Dose of Octreotide LAR (Subjects Randomised to Receive Octreotide only).**

Paragraph 1, new bullet point inserted after bullet point 1

Dermatological examination, if clinically indicated.

Original text, paragraph 1, original bullet point 2, amended bullet point 3

~~diarrhoea diary~~

Amended text, paragraph 1, original bullet point 2, amended bullet point 3

baseline DMD

Original text, paragraph 1, original bullet point 4, amended bullet point 5

~~Record visits to healthcare professionals associated with diarrhoea AEs.~~

Amended text, paragraph 1, original bullet point 4, amended bullet point 5

Record visits to/contact with healthcare professionals associated with diarrhoea AEs.

#### **Section 7.1.6 Assessments every 3 weeks**

Paragraph 1, new bullet point inserted after bullet point 1

Dermatological examination, if clinically indicated.

Original text, paragraph 1, original bullet point 3, amended bullet point 4

~~Record visits to healthcare professionals associated with diarrhoea AEs.~~

Amended text, paragraph 1, original bullet point 3, amended bullet point 4

Record visits to/contact with healthcare professionals associated with diarrhoea AEs.

#### **Section 7.1.8 Study Completion (24 weeks) or Early Withdrawal from Study and/or Study Treatment**

Original text, paragraph 1, bullet point 3

~~Record visits to healthcare professionals associated with diarrhoea AEs.~~

Amended text, paragraph 1, bullet point 3

Record visits to/contact with healthcare professionals associated with diarrhoea AEs.

Paragraph 1, new bullet point inserted after bullet point 10

Dermatological examination.

#### **Section 7.4.2 Definition of a SAE**

Format change, bullet point g, sub-bullet point 4, beginning ‘Cardiovascular events have been seen...’; bullet point removed and text changed to ‘Normal’ format.

#### **Section 7.5.1 Pregnancy test and prevention**

Paragraph 6, new text inserted at the end of bullet point 3

UK subjects: In the UK, sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

#### **Section 7.7.2 Health outcomes assessments**

Original text, paragraph 2

~~Subjects randomised to receive treatment with octreotide will complete the FACIT-D immediately before receiving the first dose of octreotide. All subjects will complete the FACIT-D immediately before the start of treatment with lapatinib plus 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.~~

Amended text, paragraph 2

All subjects will complete the baseline FACIT-D prior to randomisation, before any study related treatment is administered. Subjects randomised to receive treatment with octreotide will also complete the FACIT-D immediately before receiving the first dose of lapatinib and capecitabine. All subjects will complete the FACIT-D every three weeks during treatment with lapatinib plus capecitabine through to withdrawal from the study or the end of the 24 week period of treatment with lapatinib and capecitabine, whichever is sooner.

Original text, paragraph 3, sentences 1 and 2

~~The FACIT-D (version 4; Appendix 2) consists of the FACT-G [Webster, 2003] and a diarrhoea-specific subscale, and measures multidimensional quality of life in subjects 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.~~

Amended text, paragraph 3, sentences 1 and 2

The FACIT-D (version 4; Appendix 2) consists of the FACT-G [Webster, 2003] and a diarrhoea-specific subscale, and measures multidimensional quality of life in subjects with cancer. FACT-G includes 27 general questions relating to four subscales, PWB, SWB, EWB and FWB, and the DSS includes 11 questions.

#### **Section 9.3.5.1.2. Secondary endpoint analysis: Investigator-reported endpoints**

Original bold heading 6 and paragraph 7

##### **~~Unscheduled visits to healthcare professionals~~**

~~The proportion of subjects requiring an unscheduled visit to a health care professional at least once as a result of diarrhoea will be summarised and analysed using the same method as described in Section 9.3.5.1.1 for the primary endpoint.~~

Amended bold heading 6 and paragraph 7

##### **Unscheduled visits to/contact with healthcare professionals**

The proportion of subjects requiring an unscheduled visit to or contact with a healthcare professional at least once as a result of diarrhoea will be summarised and analysed using the same method as described in Section 9.3.5.1.1 for the primary endpoint.

#### **Section 9.3.5.1.3.**

Original section title

~~Secondary analyses: Subject reported endpoints~~

Original text

~~These analyses will be based on data reported by the subject in the diarrhoea diary. Analyses of secondary diarrhoea-related endpoints will be presented for the ITT and m-ITT populations using the same lapatinib and capecitabine treatment intervals as described for the summaries of the primary endpoint in Section 9.3.5.1.1.~~

### **~~Diarrhoea at any grade~~**

~~The proportion of subjects experiencing at least one episode of diarrhoea, of any grade of severity, will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint.~~

### **~~Time to onset of diarrhoea of any grade of severity~~**

~~The time to onset of the first episode of diarrhoea of any grade of severity will be summarised by treatment arm 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 patients experiencing an episode of diarrhoea will be presented for each weekly time interval by treatment group. Estimates and 95% confidence intervals for the 25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile will be provided by treatment group. Treatment groups will be compared using the log-rank test, or the Wilcoxon test in the case of non-proportional hazards.~~

### **~~Anti-diarrhoeal medication~~**

~~The proportion of subjects taking medication at least once as a result of diarrhoea will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint.~~

### **~~Dietary changes~~**

~~The proportion of subjects making dietary changes at least once as a result of diarrhoea will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint.~~

### **~~Unscheduled visits to healthcare professionals~~**

~~The proportion of subjects making an unscheduled visit to a health care professional at least once as a result of diarrhoea will be summarised and analysed using the same method as described in Section 9.3.5.1.1 for the primary endpoint.~~

### **~~Changes in study treatment~~**

~~The proportion of subjects making changes to study treatment (lapatinib or capecitabine) as a result of diarrhoea will be summarised and analysed using the same methods as described in Section 9.3.5.1.1 for the primary endpoint. Summaries will be performed separately for each type of change in study treatment (i.e. dose delays, dose reductions and treatment withdrawal) as well as overall.~~

Amended section title

Secondary analyses: Patient-reported endpoints

Amended text

These analyses will be based on data reported in the DMD. Analyses of secondary diarrhoea-related endpoints will be presented for the ITT and m-ITT populations for patients completing the baseline and at least one post-baseline DMD.

### **Diarrhoea**

The proportion of patients reporting an increase in the frequency and/or worsening in consistency of bowel movements will be summarised and analysed using Generalised Estimating Equations (GEE), using a repeated statement, the binary response is the patient reported increase in frequency or worsening in consistency, as defined in the RAP, in addition individual patient data will be plotted.

#### **Time to onset of first patient-reported increase in frequency and/or worsening in consistency of bowel movements**

The time to onset of the first patient-reported increase in frequency and/or worsening of consistency of bowel movements will be summarised by treatment arm using Kaplan-Meier methods. Patients who complete the study or withdraw prematurely without experiencing an increase in the frequency and/or worsening in consistency of bowel movements will be censored at the date of withdrawal or study completion. The Kaplan-Meier estimate of the proportion of patients reporting an increase in the frequency and/or worsening of consistency of bowel movements will be presented for each weekly time interval by treatment group. Estimates and 95% confidence intervals for the 25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile will be provided by treatment group. Treatment groups will be compared using the log-rank test, or the Wilcoxon test in the case of non-proportional hazards.

#### **Additional anti-diarrhoeal medication**

The proportion of patients taking any extra medication not prescribed by the hospital-doctor to help with diarrhoea will be summarised and analysed using the same GEE analysis and plots as described for patient-reported diarrhoea.

#### **Impact of dietary changes**

The proportion of patients making dietary changes to help with the diarrhoea will be summarised and analysed using the same GEE analysis and plots as described for patient-reported diarrhoea.

### **Contact with any other healthcare professionals**

The proportion of patients contacting a health care professional other than the hospital doctors/nurses to discuss diarrhoea will be summarised and analysed using the same GEE analysis as and plots as described for patient-reported diarrhoea..

### **Reduction / stopping of anti-cancer treatment**

The proportion of patients reducing or completely stopping the number of anti-cancer tablets to help with diarrhoea will be summarised and analysed using the same GEE analysis and plots as described for patient-reported diarrhoea. Summaries will be performed separately for each type of change in anti-cancer tablets (i.e. reducing tablets and stopping completely) as well as overall.

### **Section 9.3.5.3 Health Outcomes analyses**

#### Original text

~~The following scores will be calculated: Total diarrhoea subscale, individual Physical, Social/Family, Emotional and Functional Wellbeing subscales, FACT-G total and FACIT-D total. Each score will be summarized by visit and treatment arm. Changes from baseline (prior to randomisation) and changes from baseline (prior to start of lapatinib and capecitabine) will also be summarized at each post-baseline visit as appropriate. Proportions of subjects in each treatment arm who achieve a clinically meaningful improvement or decline will be compared at each time point using the chi-square test. A responder criterion can be defined as a 5 or more point change from baseline on the FACT-G and FACIT-D and a 2 or more change from baseline for the individual subscales [Cella, 2002; Eton, 2004]. For the total scores and each of the 4 subscale scores, the difference between the treatment arms in terms of the change from baseline at each study visit will be analysed using a two sample t test. Treatment effect over time will be evaluated. Further details will be provided in the RAP.~~

~~The calculation of scores and methods to deal with missing data will be handled according to the standard scoring guidelines. Full details of all the health outcomes analyses will be provided in the RAP.~~

#### Amended text

The primary endpoint for the FACIT-D will be the Trial Outcome Index (TOI) comprised of the PWB, FWB and the DSS. Secondary endpoints will be:

- Total FACT-G (i.e. PWB, SWB, EWB and FWB subscales);
- Total FACIT-D (i.e. PWB, SWB, EWB and FWB subscales and the DSS);
- Each individual subscale score.

Scores will be summarised by visit and treatment arm. Changes from baseline (prior to randomisation) and changes from baseline (prior to start of lapatinib and capecitabine) will also be summarised at each post-baseline visit as appropriate. Proportions of subjects in each treatment arm who achieve a clinically meaningful improvement or decline will be compared at each time point using the chi-square test. A responder criterion can be defined as a 6 or more point change from baseline on the TOI, a 7 or more point change from baseline for the Total FACT-G, a 7 or more point change from baseline for the Total FACIT-D, a 3 or more point change from baseline for the individual subscales (PWB, EWB, SWB, FWB), and a 4 or more point change from baseline for the DSS. For the total scores and each of the subscale scores, the difference between the treatment arms in terms of the change from baseline at each study visit will be analysed using a two sample t-test. Treatment effect over time will be evaluated. Further details will be provided in the RAP.

The calculation of scores and methods to deal with missing data will be handled according to the standard scoring guidelines. Full details of all the FACIT-D analyses will be provided in the RAP.

## **Appendix 2 FACIT-D**

New text inserted

The FACIT-D questionnaire (version 4, English original) is available in two forms with different dates: '16 Nov 2007' and '09 June 2013'. These two forms have minor differences in question phrasing and format. Both forms are fully validated and the minor differences between two forms do not affect the quality of data collection and analysis. In this study, the languages translated based on 'English FACIT-D version 4 (dated 16 Nov 2007)' are Arabic, French, Hebrew, Italian and Polish. The languages translated based on 'English FACIT-D version 4 (dated 09 June 2013)' are Czech, Greek, Russian and Traditional Chinese.

This appendix provides an example of the questionnaire 'English FACIT-D version 4 (dated 09 June 2013)'.

Original FACIT-D copy was deleted.

Amended FACIT-D copy was inserted.

**End of Amendment 01 record of changes.**

## Amendment 2

### Protocol Changes for Amendment 2 (DD-MMM-YYYY) from the Protocol Amendment 1 (23-Aug-2014)

Protocol Amendment 02 applies to all site(s) participating in the conduct of the study

#### Summary of changes and rationale:

Change	Rationale
Incorporation of a planned Interim Analysis	An interim analysis for futility is being incorporated into this study to allow an early assessment of the primary endpoint, that is the proportion of subjects experiencing diarrhoea with a severity of Grade 2 and above, as defined by the NCI CTCAE, version 4.03, recorded as AEs in the eCRF. The diarrhoea data from the eCRF will be summarised / analysed and reviewed by an independent review committee.
Number of subjects undergoing formal review of safety data was updated in Section Study Design and Section Safety Review Team.	An interim analysis and first safety review is planned when approximately 40% (n=60) of the patients have been recruited, change made for consistency and practicality.
Recruitment Plan Section included.	To include a recruitment plan as an interim analysis is being incorporated.
Blinding Section updated.	The addition of an interim analysis requires further clarification to preserve the integrity of the study.
Details of tertiary Sponsor Medical Monitor Contact Information was added, Author list, Sponsor Signatory, address and telephone numbers of medical monitors updated	Details have been added based on administrative change.
Appendix for Country Specific Requirements was updated	Instructive text presented was deleted to improve the quality of the protocol.
Appendix for Protocol Changes was updated	Statement regarding application of amendment 01 to all participating sites added to improve the quality of the protocol.

## Detail of changes

- The detail of changes is presented in the order in which the change appears in the protocol.
- ‘Original’ refers to content of the protocol dated 23-Aug-2014.
- ‘Amended’ refers to the content of the protocol as updated in Amendment 02.
- Text deleted from the original protocol is presented as a ~~striketrough~~ font and underlining to identify Amended text.
- The location of the changes in the text of the protocol is identified by section number and title, followed by paragraph and sentence number if required.

## List of Specific Changes

### Title Page

Added:

[REDACTED]

### Sponsor Signatory

Original text:

[REDACTED], MD

Tykerb/Tyverb [REDACTED]

Amended text:

[REDACTED], DO, [REDACTED]  
[REDACTED]

### Sponsor Information page

Original text:

### ~~Sponsor Medical Monitor Contact Information~~

[REDACTED], MD

Tykerb/Tyverb [REDACTED]

~~GlaxoSmithKline SA~~

~~C/ Severo Ochoa, 2~~

~~28760~~

~~Tres Cantos,~~

Madrid  
Spain

Office: [Redacted]  
Mobile: [Redacted]  
Fax: [Redacted]  
e-mail: [Redacted]

**Sponsor Secondary Medical Monitor Contact Information:**

[Redacted], MD  
Tykerb/Tyverb [Redacted]  
GlaxoSmithKline  
[Redacted]  
[Redacted]

Office: [Redacted]  
Mobile: [Redacted]  
e-mail: [Redacted]

Amended text:

**Sponsor Medical Monitor Contact Information**

[Redacted], MD  
[Redacted]  
Novartis Farmaceutica S. A., Madrid Site

Office: [Redacted]  
Mobile: [Redacted]  
e-mail: [Redacted]

**Sponsor Secondary Medical Monitor Contact Information:**

[Redacted], MD  
[Redacted]  
Novartis Farma S. p. A.

Office: [Redacted]  
Mobile: [Redacted]  
e-mail: [Redacted]

Added:

**Sponsor Tertiary Medical Monitor Contact Information:**

[REDACTED]

Novartis Pharmaceuticals

Office:

Mobile:

Email:

**Protocol Summary, Study Assessments**

Added, last paragraph :

An interim analysis is planned when approximately 40% of the patients have been recruited and when those subjects have received 3 cycles of study treatment (lapatinib plus capecitabine), i.e. after 9 weeks of study treatment. The first safety review will take place at the same time as the interim analysis.

**Section 3 Investigational Plan**

**Section 3.1 Study Design**

Original text, last paragraph, Sentence 2:

A formal review of safety data will be conducted after the first ~~50~~ subjects (approximately ~~25~~ in each treatment arm) have received at least 9 weeks of treatment with lapatinib and capecitabine; subsequent reviews will be conducted at least every 12 weeks, or more frequently if required.

Amended text, last paragraph, Sentence 2:

A formal review of safety data will be conducted after the first 60 subjects (approximately 30 in each treatment arm) have received at least 9 weeks of treatment with lapatinib and capecitabine; subsequent reviews will be conducted at least every 12 weeks, or more frequently if required.

Added:

### **Section 3.3 Recruitment Plan**

The interim analysis will be triggered when approximately 40% (n=60) of the subjects that have completed 3 cycles of study treatment. In order to protect subjects from unnecessary exposure to octreotide, once 60 patients have been enrolled, recruitment will be temporarily halted to minimise potentially unnecessary further subjects being enrolled, whilst review of the interim analysis is being conducted. Therefore, once 60 patients have been recruited, investigator sites will receive communication from the sponsor to suspend any further recruitment and screening activities until the outcome of the interim analysis has been communicated to investigator sites. Subjects that are in screening during this period will still be considered for randomisation into the study.

### **Section 5.6 Blinding**

Added, Paragraph 2:

To preserve the integrity of the study at the interim analysis (Section 9.3.4), the treatment assignment will be obtained by an independent statistician, (who has access to the randomisation system RandAll NG), and provided to an external statistics group (to be appointed) to allow the required pre-defined analyses and data summaries to be produced. These analyses and data tables will be clearly documented in the Reporting Analysis plan. These data tables will then be provided to the independent review committee for their review. The results of the interim analyses will only be known by the independent review committee and not disclosed to the study team. There will be a secure firewall put in place to ensure that the study team remain blinded to the interim data and results. The recommendation from the independent review committee will be communicated to the study team and, in the event of a recommendation to halt the trial early, also to the appropriate regulatory agencies. If the independent review committee recommends the study continue, the study team will continue to remain blinded to interim results and treatment assignments until final analysis.

### **Section 9.3.4 Interim Analysis**

Original text:

~~No interim efficacy analyses are planned for this study.~~

~~The GSK Safety Review Team (SRT) will review safety data on an ongoing basis. The first formal review of safety data will be conducted after the first 50 subjects have received at least 9 weeks of treatment with lapatinib and capecitabine. Subsequent formal review will be conducted at least every 12 weeks, or more frequently if required. There are no formal stopping criteria for this study, and in the absence of significant unexpected safety findings the SRT review of the study data should have no effect on study conduct or data integrity.~~

Amended text:

An interim analysis will be conducted to assess the futility of octreotide in relation to reducing the incidence of Grade 2 diarrhoea after 9 weeks of treatment. This analysis will take place when at least 60 subjects have been randomised to treatment and completed their 9 week assessment. At this analysis a review of both the accumulating safety and efficacy data will be conducted by an independent review committee to assure the safety of the patients in the trial and to provide an opportunity to terminate the study if:-

- There is overwhelming clinical evidence of a negative imbalance in the safety profile of either treatment group
- There is not sufficient evidence of an effect of efficacy in the reduction of Grade 2 diarrhoea as described by the stopping rules in section 9.3.4.2.

The independent review committee will review the accumulating safety data and also the analysis of the primary endpoint, the incidence of Grade 2 diarrhoea. There will be full treatment disclosure at the interim analysis to the Senior Management team, but the study team will remain blinded to treatment assignment and the results of the interim analysis.

#### **Section 9.3.4.1 Interim Review of Safety Profile**

The data to be reviewed by the independent review committee will be the accumulated safety and diarrhoea response data. These safety data will include, at minimum, all AEs, SAEs and any deaths. The safety review committee will evaluate these data and make a clinical judgement as whether the study can progress as planned based on the welfare of the subjects. At least one interim review of this safety data will occur.

#### **Section 9.3.4.2 Futility Analysis of Primary Endpoint**

A futility analysis of the incidence of Grade 2 diarrhoea, the primary endpoint, comparing this incidence between the group of subjects who receive lapatinib and capecitabine to the group of subjects who receive no prophylactic octreotide will be performed. This will take place at a single interim analysis after approximately 40% of subjects (60 subjects) have had at least 9 weeks of study treatment.

Early termination of the study will be considered by the independent review committee. Their recommendation will be based on the following points:-

- Whether it would be possible to draw any meaningful conclusions if the study were to continue to planned completion given the:-
  - The clinical relevance of the observed incidence of Grade 2 diarrhoea.
  - The conditional power based on data from approximately 40% of the patients
  - The totality of the evidence observed.

For example:

- If the diarrhoea rate is 30% in the control arm, in order for the conditional power (under the current trend) to be around 50% to see a positive result at the end of the trial, we would need to see a diarrhoea rate of 16% or lower in the octreotide arm. (Equating to a difference in 14% in incidence between treatment arms)
- If the diarrhoea rate is 20% in the control arm, in order for the conditional power (under the current trend) to be around 70% to see a positive result at the end of the trial, we would need to see a diarrhoea rate of 6% or lower in the octreotide arm. (Equating to a difference of 14% in incidence between treatment arms)

The conditional power will need to be re-calculated based on the actual incidence and actual percentage of patients evaluated at the time of the interim analyses.

It is envisaged that if at least a modest improvement in the diarrhoea rate in the octreotide arm is not seen with a conditional power of at least 50% at the interim analysis, it is unlikely that the trial would justify octreotide use in clinical practice. Further confidence intervals around the estimate of the observed difference in incidence of Grade 3 diarrhoea will be provided to aid clinical judgement.

### **Section 10.8 Safety Review Team**

Original text, paragraph 2, Sentence 2:

The first formal review of safety data will be conducted after the first 50 subjects have received at least 9 weeks of treatment with lapatinib and capecitabine.

Amended text, paragraph 2, Sentence 2:

The first formal review of safety data will be conducted after the first 60 subjects have received at least 9 weeks of treatment with lapatinib and capecitabine.

### **Section 12.5 Appendix 5 Country Specific Requirements**

Original text:

~~This blank appendix is handled modularly by each participating CMD and serves as a place holder for CMD to add standard text authorized for that country prior to distribution within that country. If standard authorized text for that country does not exist, then use the following wording:~~

### **Section 12.8 Appendix 8 Protocol Changes**

Added, paragraph 1 and paragraph 2:

#### Amendment 1

Protocol Amendment 01 applies to all site(s) participating in the conduct of the study

**End of Amendment 02 record of changes.**