AstraZeneca

**Amended Clinical Study Protocol**

| | |
|---|---|
| Drug Substance | ZACTIMA™ (ZD6474) |
| Study Code | D4200C00032 |
| Edition Number | 7.0 |
| Date | [redacted] |

# A Phase III, Randomized, Double-Blinded, Multi-Center Study to Assess the Efficacy of Docetaxel (TAXOTERE™) in Combination with ZD6474 (ZACTIMA™) versus Docetaxel (TAXOTERE™) in combination with Placebo in Patients With Locally Advanced or Metastatic (Stage IIIb – IV) Non-small Cell Lung Cancer (NSCLC) after Failure of 1st Line Anti-Cancer Therapy

**Sponsor:** AstraZeneca AB, 151 85 Södertälje, Sweden



**AstraZeneca Research and Development site representative**

[redacted] Date



**The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:**

| Amendment No. | Date of Amendment | Local Amendment No: | Date of Local Amendment |
|---|---|---|---|
| 1 | [redacted] | | |
| 2 | [redacted] | | |
| 3 | [redacted] | | |
| 4 | [redacted] | | |
| 5 | [redacted] | | |

| Administrative change No. | Date of Administrative Change | Local Administrative change No. | Date of local Administrative Change |
|---|---|---|---|
| 1 | [redacted] | | |
| 2 | [redacted] | | |
| 3 | [redacted] | | |
| 4 | [redacted] | | |

# PROTOCOL SYNOPSIS

## A Phase III, Randomized, Double-Blinded, Multi-Center Study to Assess the Efficacy of Docetaxel (TAXOTERE™) in Combination with ZD6474 (ZACTIMA™) versus Docetaxel (TAXOTERE™) in combination with Placebo in Patients With Locally Advanced or Metastatic (Stage IIIb – IV) Non-small Cell Lung Cancer (NSCLC) after Failure of 1st Line Anti-Cancer Therapy

**Principal Investigator**

[redacted]

**Study center(s) and number of subjects planned**

This multicenter study will be conducted in a minimum of 1380 subjects (690 per arm) with locally advanced or metastatic (IIIb-IV) non-small cell lung cancer (NSCLC) after failure of 1st line anti-cancer therapy. The prior regimen must have failed the subject because of unacceptable toxicity or progression of tumor during or subsequent to treatment.

| **Study period** | | **Phase of development** |
|---|---|---|
| Estimated date of first subject enrolled | [redacted] | III |
| Estimated date of last subject completed) | [redacted] | |

**Objectives**

The primary objective of the study is:

1. To demonstrate an improvement in progression-free survival (PFS) in the combination of ZACTIMA™ (ZD6474) with docetaxel compared with docetaxel plus placebo in subjects with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy

The secondary objectives of this study are the following:

1. To demonstrate an improvement in overall survival for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo

2. To demonstrate an improvement in the overall objective response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (DCR) (CR + PR + Stable Disease [SD] ≥ 6 weeks) and duration of response (DOR) for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo using modified Response Evaluation Criteria in Solid Tumors [RECIST] (Therasse et al, 2000)

3. To demonstrate a beneficial effect on disease-related symptoms, in subjects treated with ZACTIMA in combination with docetaxel, that is at least as good as those in subjects treated with docetaxel plus placebo based on the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) lung cancer subscale (LCS)

4. To demonstrate a quality of life (QoL) for ZACTIMA in combination with docetaxel-treated subjects that is at least as good as that for subjects treated with docetaxel plus placebo by assessment of the FACT-L and the Trial Outcome Index (TOI)

5. To demonstrate an improvement in time to deterioration of disease-related symptoms (TDS) based on the FACT-L LCS for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo

6. To study the tolerability and safety of ZACTIMA in combination with docetaxel in subjects with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy

7. To investigate the population pharmacokinetics (PK) of ZACTIMA in this subject population and assess the PK-QTc relationship, PK-safety relationship and PK-efficacy relationship

8. To investigate plasma levels of the N-desmethyl and N-oxide metabolites of ZACTIMA in this subject population

The exploratory objectives of this study are the following:

1. To investigate the correlation of epidermal growth factor receptor (EGFR) expression, gene amplification and mutations and other related biomarker status with efficacy in archival tumor samples in those subjects where such tumor material is available

2. To collect a blood sample for DNA extraction and storage for possible future testing by evaluation of single nucleotide polymorphism (SNP) status of genes involved in the response to ZACTIMA and its comparators (for example, EGFR, VEGF, VEGFR-2, eNOS and MDR-1)

3. To investigate in blood plasma samples, the correlation of levels of circulating protein biomarkers with efficacy

4. To investigate the amount of resource used by subjects in terms of inpatient stays and outpatient visits during the period of treatment with investigational therapy

5. To investigate subject health status index during the period of treatment with investigational therapy by assessment of the EuroQoL 5 Dimension Instrument (EQ5D)

6. To investigate the TDPS (time to deterioration in subject World Health Organization [WHO] Performance Status [PS]) during the period of treatment with investigational therapy

7. To investigate changes in subject weight

**Study design**

This is a parallel group, international, randomized, double-blind, placebo controlled, multi-center study design to assess whether the addition of ZACTIMA (100 mg daily) to docetaxel in subjects with locally advanced or metastatic NSCLC confers a statistically significant advantage in terms of PFS.

Subjects will be randomized in a 1:1 ratio to either ZACTIMA 100 mg plus docetaxel, or placebo plus docetaxel. No stratification at randomization will be made for this study. Docetaxel will be administered according to a 21-day cycle, up to a maximum of 6 cycles. ZACTIMA or placebo will be administered as a once daily tablet. Subjects may continue to receive study treatment as long as they are benefiting from treatment (in the Investigator's opinion, and they do not meet any other withdrawal criteria). There is a maximum of 6 cycles of docetaxel and no maximum duration of treatment for ZACTIMA/placebo. After 6 cycles of docetaxel, subjects will continue on ZACTIMA or placebo monotherapy until progression. Blinded ZACTIMA/placebo should not be combined with any other anti-cancer therapies, and should be discontinued following objective disease progression. The safety data from all subjects will be assessed on an ongoing basis.

Radiologic evaluation using RECIST will be performed at screening and then every 6 weeks after randomization. It is important to follow the assessment schedule as closely as possible. Subjects will be evaluated until objective disease progression, and will then be followed for survival, unless they withdraw consent. If a subject discontinues study medication prior to objective disease progression they should continue to be assessed by RECIST, as per the protocol schedule, until disease progression and then followed up for survival, unless they withdraw consent.

PK samples will be obtained from 440 subjects, and all Japanese subjects, for a total of 580 subjects randomized in the study.

Every attempt will be made to obtain archived tumor samples from all subjects randomized on the study, although tissue collection will not be mandatory.

### Target subject population

Male and female subjects aged 18 years or older with histologically or cytologically confirmed locally advanced or metastatic (IIIb-IV) NSCLC after failure of 1st line anti-cancer therapy and who have a performance status of 0 to 1 (WHO, Miller et al 1981).

### Investigational product, dosage and mode of administration

ZACTIMA (1 x 100 mg in tablet form) or matching placebo will be dosed orally, once daily, preferably at the same time of day each morning.

Subjects who experience Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicity that is considered related to ZACTIMA/placebo will have their trial medication stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the subject may restart treatment with a reduced dose of ZACTIMA in a blinded manner. The study evaluations should be continued as outlined in the trial plan. If the subject has been off treatment for greater than 3 weeks due to toxicity, the subject must be withdrawn from ZACTIMA/placebo. In the case of subjects who discontinue ZACTIMA/placebo therapy because of toxicity attributable to ZACTIMA/placebo, these subjects will continue to receive the scheduled treatment with docetaxel and will be followed for progression and survival.

### Docetaxel, dosage and mode of administration

Docetaxel, the registered, approved dose (60 mg/m$^2$ Japan only; 75 mg/m$^2$ all other countries), administered intravenously over at least a 1-hour period every 21 days.

Subjects should be premedicated with oral corticosteroids, such as dexamethasone, 8mg twice daily for 3 days starting 1 day before each administration of docetaxel. Investigators may choose an alternative corticosteroid premedication in accordance with approved local practice. In the event that the subject forgets to take the oral corticosteroid prior to Day 1 of each cycle, an IV dose can be given at the discretion of the Investigator. Additional doses of the IV dexamethasone, or alternative corticosteroid, can be given at the Investigator's discretion.

Subjects who experience CTCAE grade 3 or 4 toxicity that is considered related to docetaxel will have docetaxel stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the subject may restart treatment with a reduced dose of docetaxel. If docetaxel must be withheld for more than 3 weeks, after a scheduled treatment visit, for resolution of toxicity, the subject will not restart docetaxel treatment. In the case of subjects who discontinue combination therapy because of toxicity attributable to docetaxel, subjects may continue on ZACTIMA/placebo and will be followed for progression and survival.

### Duration of treatment

Docetaxel will be administered according to a 21-day cycle. ZACTIMA/placebo will be administered as a once daily tablet. Subjects may continue to receive study treatment as long as they are benefiting from treatment (in the Investigator's opinion, and they do not meet any other withdrawal criteria). There is a maximum of 6 cycles of docetaxel and no maximum

duration of treatment for ZACTIMA/placebo. After 6 cycles of docetaxel, subjects will continue on ZACTIMA/placebo monotherapy until progression. Blinded ZACTIMA/placebo should not be combined with any other anti-cancer therapies, and should be discontinued following objective disease progression.

**Outcome variables**

- **Efficacy**
  - **Primary outcome variable:**
    - PFS
  - **Secondary outcome variables:**
    - Overall survival
    - ORR, DCR and DOR
- **Safety**
    - Incidence and type of adverse events (AEs), clinically significant laboratory or vital sign abnormalities, and electrocardiographic (ECG) changes
- **Patient reported outcomes (PROs)**
    - Disease-related symptoms as measured by the LCS
    - TDS
    - QoL as measured by the FACT-L questionnaire (FACT-L and TOI scores)
- **Health economics**
    - EQ5D questionnaire
    - Inpatient stays and outpatient visits
- **Other subject measures**
    - Weight
    - WHO PS
    - TDPS
- **Pharmacokinetic**
    - To investigate the population PKs in this subject population and investigate correlations between exposure (area under the curve [AUC]), maximum concentration ($C_{max}$), and the average concentration at steady state ($C_{ss}$) with the QTc, AEs and the efficacy (survival, ORR, and PFS)
    - Plasma levels of the N-desmethyl and N-oxide metabolites of ZACTIMA, and their relationship to plasma levels of ZACTIMA

– **Pharmacodynamic**

- Plasma VEGF, VEGFR2 and basic fibroblast growth factor (bFGF)
- Expression levels of EGFR in archival tumor samples
- Gene Amplification of EGFR in archival tumor samples

– **Genetics**

- EGFR mutational status and mutational status of other candidate genes in archival tumor tissue (biopsy or archival fixed cell blocks from cytology samples)
- SNP status of genes involved in the response to ZACTIMA and its comparators

**Statistical methods**

There will be two co-primary analysis populations: the first will comprise all subjects; the second will comprise all female subjects. Therefore, a nominal 2-sided significance level of 2.5% will be used for all analyses, except for the primary endpoint of PFS and the secondary endpoint of overall survival, where the nominal significance will be adjusted to approximately 2.44% to allow for a single interim analysis.

In order to detect a 25% prolongation of overall PFS with >90% power at the 2-sided 2.44% significance level, a minimum of 1176 progression events are required. Assuming a median PFS of 3 months for docetaxel alone, a recruitment period of 19 months and minimum follow-up of 3 months, a minimum of 1380 subjects with locally advanced or metastatic (IIIb-IV) NSCLC after failure of 1st line anti-cancer therapy will be enrolled. The prior regimen must have failed the subject because of unacceptable toxicity or progression of disease.

A single interim analysis to assess futility and superiority of the PFS and overall survival endpoints will be performed when a minimum of 588 PFS events have occurred (using a nominal significance level of 0.14%).

The analysis of survival will be conducted at the time of analysis of the primary endpoint of PFS. It is estimated that 850 events (deaths) will have occurred at this time, in which case the power to detect a 25% prolongation of survival would be >80%.

PFS, overall survival (OS), TDS, and TDPS will be analyzed using a log-rank test. ORR and DCR will be analyzed using logistic regression.

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, and ECG changes which will be collected for all subjects. AEs (both in terms of Medical dictionary for regulatory activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by subject and summarized by treatment group.

In addition, subgroup analyses will be performed on the PFS and OS. The subgroups to be analyzed will include tumor stage, number of organs involved, prior Avastin™ (bevacizumab) therapy, histology, smoking history, gender, ethnic origin, EGFR expression and EGFR mutation status.

# TABLE OF CONTENTS PAGE

TITLE PAGE ..... 1
PROTOCOL SYNOPSIS ..... 2
TABLE OF CONTENTS ..... 9
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 14
1. INTRODUCTION ..... 18
1.1 Background ..... 18
1.1.1 Tumor angiogenesis ..... 18
1.1.2 ZACTIMA™ (ZD6474) ..... 19
1.1.2.1 Background ..... 19
1.1.2.2 Summary of adverse events (AEs) in previous studies ..... 19
1.1.3 Docetaxel (TAXOTERE™, Sanofi-Aventis) ..... 21
1.2 Rationale for this study ..... 21
2. STUDY OBJECTIVES ..... 23
2.1 Primary objective ..... 23
2.2 Secondary objectives ..... 23
2.3 Exploratory objectives ..... 24
3. STUDY PLAN AND PROCEDURES ..... 25
3.1 Overall study design and flow chart ..... 25
3.2 Rationale and risk/benefit assessment ..... 34
3.2.1 Rationale for study design, doses and control groups ..... 34
3.2.2 Risk/benefit and ethical assessment ..... 35
3.2.2.1 Docetaxel toxicity ..... 35
3.2.2.2 QTc prolongation ..... 35
3.2.2.3 Gastrointestinal toxicity ..... 37
3.2.2.4 Cutaneous toxicity ..... 38
3.2.2.5 Other toxicity ..... 38
3.3 Selection of study population ..... 41
3.3.1 Study selection record ..... 41
3.3.2 Inclusion criteria ..... 41
3.3.3 Exclusion criteria ..... 41
3.3.4 Restrictions ..... 43
3.3.5 Withdrawal from study and discontinuation of treatment ..... 44
3.3.5.1 Withdrawal from study ..... 44
3.3.5.2 Procedures for withdrawal from participation in the study ..... 44
3.3.5.3 Discontinuation of treatment ..... 44
3.3.5.4 Procedures for discontinuation from study treatment ..... 44
3.3.5.5 Procedures for discontinuation from genetic aspects of the study ..... 45

3.4 Treatments....45
3.4.1 Identity of investigational product and comparators....45
3.4.2 Doses and treatment regimens....46
3.4.2.1 ZACTIMA or placebo regimen....46
3.4.2.2 ZACTIMA dose reduction....46
3.4.2.3 Docetaxel....47
3.4.3 Labeling....47
3.4.4 Storage....48
3.4.5 Accountability....48
3.5 Method of assigning subjects to treatment groups....48
3.6 Blinding and procedures for unblinding the study....49
3.6.1 Methods for ensuring blinding....49
3.6.2 Methods for unblinding the study....49
3.6.3 Methods for breaking the blind for monitoring of the safety....49
3.7 Pre-study, concomitant and post-study treatment(s)....50
3.7.1 Treatment for cancer....50
3.7.1.1 Palliative Radiotherapy....50
3.7.2 Other concomitant treatment....50
3.8 Treatment compliance....51
4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES....52
4.1 Primary variable....52
4.2 Screening and demographic measurements....52
4.3 Patient-Reported Outcomes (PROs)....53
4.3.1 FACT-L questionnaire incorporating the LCS subscale....53
4.3.1.1 Methods of assessment....53
4.3.1.2 Derivation or calculation of variable....53
4.3.2 Time to deterioration of disease related symptoms (TDS)....54
4.3.2.1 Methods of assessment....54
4.3.2.2 Derivation or calculation of variable....54
4.3.3 Administration of ePRO/pPRO questionnaires....54
4.4 Health Economic measurements and variables....55
4.4.1 Resource data....55
4.4.1.1 Methods of assessment....55
4.4.1.2 Derivation or calculation of variable....55
4.4.2 EQ5D....55
4.4.2.1 Methods of assessment....55
4.4.2.2 Derivation or calculation of outcome variable....56
4.5 Pharmacokinetic measurements and variables....56
4.5.1 Collection of pharmacokinetic samples....56

4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters ....57
4.5.2.1 ZACTIMA ....57
4.5.2.2 N-desmethyl and N-oxide metabolites....57
4.6 Efficacy and pharmacodynamic measurement and variables ....58
4.6.1 Progression-free survival (PFS) ....60
4.6.1.1 Methods of assessment ....60
4.6.1.2 Derivation or calculation of outcome variable....60
4.6.2 Time to death ....60
4.6.2.1 Methods of assessment ....60
4.6.2.2 Derivation or calculation of outcome variable....60
4.6.3 Objective response, disease control and duration of response....60
4.6.3.1 Methods of assessment ....60
4.6.3.2 Derivation or calculation of outcome variable....62
4.6.4 Pharmacodynamic biomarker measurements and variables ....62
4.6.4.1 Methods of assessment ....62
4.6.4.2 Derivation or calculation of outcome variable....63
4.6.5 Time to deterioration in patient WHO Performance Status (TDPS) ....63
4.6.5.1 Methods of assessment ....63
4.6.5.2 Derivation or calculation of variable ....63
4.7 Safety measurements and variables ....64
4.7.1 Adverse events ....64
4.7.1.1 Definitions....64
4.7.1.2 Recording of adverse events ....66
4.7.1.3 Reporting of serious adverse events....68
4.7.2 Laboratory safety measurements and variables ....68
4.7.2.1 Methods of assessment ....68
4.7.2.2 Derivation or calculation of outcome variables ....69
4.7.3 ECG, Vital Signs and physical examination....69
4.7.3.1 12-lead ECG methods of assessment....69
4.7.3.2 12-lead ECG derivation or calculation of outcome variables ....71
4.7.3.3 Vital signs and physical examinations methods of assessment ....71
4.7.3.4 Vital signs and physical examinations derivation or calculation of outcome variables ....71
4.7.4 Other safety measurements and variables....71
4.8 Volume of blood sampling and handling of biological samples....71
4.8.1 Analysis of biological samples ....72
4.8.1.1 Clinical chemistry samples ....72
4.8.1.2 Pharmacokinetic samples....72
4.9 Genetic measurements and co-variables....72
5. DATA MANAGEMENT....72
5.1 Reporting of genotypic results ....73

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE ..... 73
6.1 Statistical evaluation – general aspects ..... 73
6.2 Description of outcome variables in relation to objectives and hypotheses ..... 73
6.3 Description of analysis sets ..... 75
6.4 Method of statistical analysis ..... 75
6.5 Determination of sample size ..... 77
6.6 Interim analyses ..... 78
6.7 Independent Data Monitoring Committee ..... 79
7. STUDY MANAGEMENT ..... 79
7.1 Monitoring ..... 79
7.2 Audits and inspections ..... 80
7.3 Training of staff ..... 80
7.4 Changes to the protocol ..... 80
7.5 Study agreements ..... 80
7.6 Study timetable and end of study ..... 81
8. ETHICS ..... 81
8.1 Ethics review ..... 81
8.2 Ethical conduct of the study ..... 82
8.3 Informed consent ..... 82
8.4 Subject data protection ..... 82
9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY ..... 83
9.1 AstraZeneca emergency contact procedure ..... 83
9.2 Procedures in case of medical emergency ..... 83
9.3 Procedures in case of overdose ..... 83
9.4 Procedures in case of pregnancy ..... 84
10. REFERENCES ..... 85

## LIST OF TABLES PAGE

Table 1 Table of assessments (study plan): Screening to discontinuation of docetaxel ..... 28
Table 2 Table of assessments (study plan): After Discontinuation of Docetaxel ..... 31

Table 3 Table of assessments (study plan): Discontinuation of both ZACTIMA/placebo and docetaxel ....33

Table 4 Summary of guidance on the management of toxicity for ZACTIMA/placebo and docetaxel ....39

Table 5 Formulation numbers of ZACTIMA ....45

Table 6 Dose reduction ....46

Table 7 PK endpoints related to each objective ....56

Table 8 Objectives and outcome variables....58

Table 9 Blood plasma schedule for pharmacodynamic biomarker analysis ....63

Table 10 Laboratory safety variables ....69

Table 11 Volume of blood to be drawn from each subject ....71

Table 12 Objectives and outcome variables ....73

## LIST OF FIGURES PAGE

Figure 1 Study flow chart ....27

Figure 2 Flow chart detailing management of QTc prolongation ....36

## LIST OF APPENDICES & SUPPLEMENTS

Appendix A Signatures

Appendix B Additional Safety Information

Appendix C WHO Performance Status

Appendix D Medications known to prolong QT

Appendix E Definitions of measurable, non-measurable, target and non-target lesions and objective response criteria based on the revised RECIST criteria (Therasse et al, 2000)

Appendix F FACT-L quality of life questionnaire

Appendix G Cockcroft-Gault formula

Appendix H Docetaxel (TAXOTERE™, Sanofi-Aventis) Label

Appendix I EQ5D questionnaire

Appendix J New York Heart Association (NYHA) classification of heart disease

Appendix K Pharmacogenetics as exploratory objective

Supplement 1 Study Team Contacts in the Event of Emergency Situations, Overdose or Pregnancy

Supplement 2 Investigators and Study Administrative Structure

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event (see definition in Section 4.7.1.1) |
| ALT | Alanine aminotransferase |
| ALP | Alkaline phosphatase |
| ANC | Absolute neutrophil count |
| APTT | Activated partial thromboplastin time |
| Assessment | An observation made on a variable involving a subjective judgment |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{ss}$ | Area under plasma concentration-time curve during any dosing interval at steady state |
| bFGF | Basic fibroblast growth factor |
| BUN | Blood urea nitrogen |
| °C | Degree Centigrade |
| $C_{max}$ | Maximum concentration |
| $C_{ss}$ | Concentration of drug at steady state |
| $C_{ss, max}$ | Maximum steady state plasma concentration |
| CI | Confidence Interval |
| CL/F | Total body clearance of drug from plasma after an oral dose |
| CR | Complete response (RECIST criteria) |
| CRC | Colorectal cancer |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events (National Institutes of Health, National Cancer Institute) |
| D | Day |
| DCR | Disease control rate |
| DMPK | Drug Metabolism Pharmacokinetics |
| DNA | Deoxyribonucleic Acid |
| DOR | Duration of response |
| ECG | Electrocardiogram |

| Abbreviation or special term | Explanation |
|---|---|
| eCRF | electronic Case Report Form |
| EGFR | Epidermal Growth Factor Receptor |
| eNOS | endothelial Nitric Oxide Synthase |
| EQ5D | EuroQoL 5 Dimension Instrument |
| EWB | Emotional well-being (FACT-L) |
| FACT-L | Functional Assessment of Cancer Therapy for Lung Cancer |
| FWB | Functional well-being (FACT-L) |
| GCP | Good Clinical Practice |
| HR | Hazard ratio |
| IB | Investigator's Brochure |
| $IC_{50}$ | Inhibitory concentration |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| INR | International normalized ratio |
| International Co-ordinating Investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally. |
| IRB | Institutional Review Board |
| IV | Intravenous |
| IVRS | Interactive Voice Response System |
| KDR | Kinase insert domain receptor |
| LBBB | Left bundle branch block |
| LCS | Lung cancer subscale |
| LD | Longest diameter |
| LDH | Lactate dehydrogenase |
| LQTS | Long QT Syndrome |
| MAb | Monoclonal antibody |
| MDR-1 | Multidrug resistance gene |
| Measurement | An observation made on a variable using a measurement device. |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mmHg | Millimeter of mercury |

| Abbreviation or special term | Explanation |
|---|---|
| msec | Millisecond |
| NCI | National Cancer Institute |
| nM | Nanomolar |
| NSCLC | Non-small cell lung cancer |
| NYHA | New York Heart Association |
| OAE | Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.7.1.1). |
| ORR | Objective response rate |
| OS | Overall survival |
| Outcome variable | A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective. |
| Parameter | A quantity (usually unknown) that characterizes the distribution of a variable in a population of subjects. |
| PD | Progressive disease (RECIST criteria) |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PR | Partial response (RECIST criteria) |
| Principal Investigator | A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a Principal Investigator. |
| PSI | Pulmonary Symptom Index |
| PVC | Premature ventricular contraction |
| PWB | Physical well-being (FACT-L) |
| QoL | Quality of Life |
| QT | The interval between Q and T on ECG |
| QTc | QT interval corrected for heart rate by the Bazett's method |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| rhuMAb | Recombinant humanized monoclonal antibody |
| SAE | Serious adverse event (see definition in Section 4.7.1.1). |
| SAP | Statistical Analysis Plan |
| SAS | Statistical analysis software |
| SD | Stable disease (RECIST criteria) |
| SDOS | Study Delivery Operations Specialist |

| **Abbreviation or special term** | **Explanation** |
|---|---|
| SDV | Source Data Verification |
| SMQ | Special MedDRA Query |
| SNP | Single nucleotide polymorphism |
| SVC | Superior vena cava |
| SWB | Social well-being (FACT-L) |
| TDPS | Time to deterioration in patient WHO PS |
| TDS | Time to deterioration of disease-related symptoms |
| TKI | Tyrosine kinase inhibitor |
| TOI | Trial outcome index |
| TTD | Time to death |
| ULRR | Upper limit of reference range |
| VEGF | Vascular endothelial growth factor |
| VEGFR | Vascular endothelial growth factor receptor |
| VEGFR2 | Vascular endothelial growth factor receptor-2 |
| WBC | White blood count |
| WBDC | Web-based data capture |
| WHO | World Health Organization |
| WHO PS | World Health Organization Performance Status |

# 1. INTRODUCTION

Investigators should be familiar with the ZACTIMA™ (ZD6474) Investigator's Brochure (IB).

## 1.1 Background

### 1.1.1 Tumor angiogenesis

Therapies that inhibit the growth of new blood vessels, so called angiogenesis inhibitors, offer considerable promise as anticancer agents. The link between angiogenesis and tumor progression and spread was first established some 30 years ago by Judah Folkman (Folkman, 1971). Folkman noted that without new blood vessels, many tumors only grow to a few millimeters in size. He also found that while a tumor may remain small, its cells continue to proliferate, a situation brought about by a balance between cell rate of proliferation and apoptosis (programmed cell death). These observations led to the concept of an "angiogenic switch", a complex process by which a tumor mass expands and overtakes the rate of internal apoptosis by developing blood vessels, thereby changing into an angiogenic phenotype. Evidence has emerged that suggests this change is a result of a shift in net balance of stimulators and inhibitors of angiogenesis within the tumor microenvironment in which the inhibitors are down regulated (Hanahan et al, 1996). It is now recognized that the growth of most solid tumors and the formation of metastases are dependent on this process.

Vascular endothelial growth factor (VEGF) has been shown to play a pivotal role in tumor angiogenesis (Stacker et al, 1999). VEGF is a mitogen for vascular endothelial cells derived from arteries, veins, and lymphatics and induces a strong angiogenic response in a variety of in vivo models; it also functions as a survival factor for endothelial cells (Leung et al, 1989; Ferrara, 1999). In addition, it has been proposed that a major function of VEGF is the induction of plasma protein leakage because of its ability to induce vascular leakage (Dvorak et al, 1995). Other properties of VEGF include promotion of monocyte chemotaxis, inhibition of functional maturation of dendritic cells, and vasodilatation (Ferrara, 1999). The discovery of VEGF was followed by the identification of specific VEGF receptors (VEGFR) that constituted a new subfamily of tyrosine-kinase receptors (Neufeld et al, 1999). Of the 2 receptors identified on endothelial cells, only signaling of VEGFR2 (Kinase insert domain receptor [KDR]) was found to induce endothelial cell proliferation. Most solid tumors express high levels of VEGF, and the VEGF receptors appear predominantly in endothelial cells of vessels surrounding or penetrating the malignant tissue (Siemeister et al, 1998). Interestingly, a correlation between VEGF expression and prognosis has been noted for several cancers (Gasparini et al, 1997; Maeda et al, 1996). Increased levels of VEGF expression in non-small cell lung cancer (NSCLC) cells are associated with poor prognosis, local invasion, advanced stage, and lymph node involvement (Niklinska et al 2001, Shou et al 2001). The importance of VEGF in tumor angiogenesis was revealed in experiments of abrogation of VEGF activity by neutralizing antibodies or by the introduction of dominant negative VEGF receptors into

endothelial cells of tumor-associated blood vessels. This resulted in inhibition of tumor growth and in tumor regression (Kim et al, 1993; Millauer et al, 1994).

In many cases, prevention of angiogenesis by VEGF receptor inhibition will be cytostatic. Therefore, the combination of anti-angiogenesis agents with cytotoxic chemotherapy may provide the ideal effect on tumor killing.

### 1.1.2 ZACTIMA™ (ZD6474)

#### 1.1.2.1 Background

ZACTIMA is an inhibitor of the tyrosine kinase domain of the VEGF receptor-2 (KDR or VEGFR2). It is expected that this molecule may be beneficial in a broad range of human malignancies, and perhaps other diseases, that are dependent upon VEGF-mediated angiogenesis. ZACTIMA has shown excellent reversible inhibition of tumor cell growth in a broad range of pre-clinical models, including lung cancer xenografts. Regression of some established tumors in animals were observed following oral administration. Pre-clinical toxicology shows the agent to be well tolerated after 6 months of daily administration. ZACTIMA also inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase, though at an inhibitory concentration ($IC_{50}$) of 500 nanomolar (nM), which was higher than that for VEGFR2 (40 nM) (Ciardiello et al, 2003; Wedge et al, 2002). Two Phase I studies were conducted in the West and in Japan, which demonstrated a maximum tolerated dose of 300 mg, with common adverse events (AEs) being diarrhea, rash, and asymptomatic QTc prolongation. Subsequently, a randomized double-blind study was conducted to compare ZACTIMA at 100 mg or 300 mg in combination with docetaxel to docetaxel plus placebo. The results of this study demonstrated that ZACTIMA combined with docetaxel prolonged progression-free survival (PFS) in subjects with NSCLC.

#### 1.1.2.2 Summary of adverse events (AEs) in previous studies

Please refer to the latest IB for the most up to date information.

The most common AEs associated with ZACTIMA in the phase I and other monotherapy studies included rash, diarrhea and asymptomatic QTc prolongation. In Study 6474IL/0006, subjects with advanced or metastatic NSCLC were enrolled after failure of prior platinum-based chemotherapy. Subjects were randomized to treatment with a standard dose of docetaxel and either placebo or 100 mg of ZACTIMA or 300 mg of ZACTIMA. The median duration of therapy for each arm (docetaxel/placebo, docetaxel /ZACTIMA 100 mg, and docetaxel /ZACTIMA 300 mg) was 65 days, 91days, and 61.5 days, respectively. More subjects discontinued therapy as a result of AEs for those who received 300 mg ZACTIMA (22.7%) compared to those who received 100 mg (4.8%) or placebo (12.6%).

The AE profile was similar for all three treatment arms, although somewhat higher frequencies were observed for the 100 mg ZACTIMA arm compared with placebo, and for the 300 mg ZACTIMA arm compared with 100 mg ZACTIMA.

The most frequent AEs observed in this study were similar to those observed in prior trials for ZACTIMA or reported for docetaxel in the literature. The most common AEs and their frequencies as reported in the 300 mg ZACTIMA, 100 mg ZACTIMA and placebo arms, respectively, were diarrhea (50.0%, 38.1%, 24.4%), fatigue (45.5%, 40.5%, 26.8%), neutropenia (31.8%, 26.2%, 19.5%) and nausea (29.5%, 26.2%, 19.5%). Rash was observed in 15.9%, 16.7% and 9.8% of subjects in the three arms.

Gastrointestinal events (77.3%, 59.5%, 41.5%), and skin events (72.7%, 64.3%, 41.5%) were more common in the ZACTIMA-containing arms. For all arms the majority of these events were common toxicity criteria (CTC) grade 1 and 2; however CTC grade 3/4 event were more prominent in the ZACTIMA 300 mg arm. Cardiac disorders occurred more frequently in ZACTIMA-containing arms (15.9%, 14.3%, 2.4%). The majority were CTC grade 1/2 and included a variety of terms, none ventricular. The frequency of respiratory events (50.0%, 57.1%, 46.3%) was similar in all arms. Neutropenia (31.8%, 26.2%, 19.5%) and related terms were more common in ZACTIMA-containing arms, but this did not result in an increase in infection. There was little difference in frequency of other hematologic events.

Approximately 10% of subjects receiving ZACTIMA developed an AE of hypertension. The majority of events were CTC grade 1 or 2, and no events were CTC grade 4. There were no serious adverse events (SAEs) of hypertension. The maximum median rise in both systolic and diastolic blood pressure was approximately 8 mm Hg in subjects who received ZACTIMA 300 mg, and approximately 4 mm Hg in subjects who received ZACTIMA 100 mg.

For the analysis of AEs that might have been caused by QT prolongation, AstraZeneca utilized the broad Special Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) for QT prolongation. The terms queried included electrocardiogram (ECG) QT corrected interval prolonged, ECG QT interval abnormal, ECG QT prolonged, long QT syndrome, long QT syndrome congenital, Torsades de Pointes, ventricular tachycardia, cardiac death, sudden cardiac death, sudden death, cardiac arrest, cardiac fibrillation, cardiorespiratory arrest, ECG repolarization abnormality, ECG J wave abnormality, ECG U-wave abnormality, loss of consciousness, syncope, syncope vasovagal, ventricular arrhythmia, ventricular fibrillation, and ventricular flutter. The only event that was actually reported in the randomized phase was ECG QT (corrected) interval prolonged, which occurred in 7, 5, and 2 subjects treated with ZACTIMA 300 mg, ZACTIMA 100 mg, and placebo, respectively.

In addition, AstraZeneca reviewed the data for subjects who experienced a confirmed prolongation of the ECG QTc interval, as specified in the protocol. Seven subjects had confirmed QTc prolongation in this study. Five occurred on the ZACTIMA 300 mg/docetaxel arm, 4 of which occurred in the first 28 days and 1 at day 70. Two occurred on the ZACTIMA 100 mg /docetaxel arm, at days 22 and 43. No subjects with confirmed QTc prolongation in study 6474IL/0006 experienced a potentially relevant AE. One subject in the run-in phase of trial 6 had received ZACTIMA 300 mg plus docetaxel, was hospitalized with a post-obstructive pneumonia as well as hypokalemia resulting from prednisone and fluorinef given to treat adrenal insufficiency resulting from adrenal metastases. He was noted to have a

QTc interval of 626 milliseconds (msec). During this hospitalization he developed a 12 beat run of ventricular tachycardia, which was asymptomatic and resolved without treatment.

### 1.1.3 Docetaxel (TAXOTERE™, Sanofi-Aventis)

Docetaxel (TAXOTERE™, Sanofi-Aventis) is indicated for the treatment of subjects with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy. At a dose of 75 mg/m$^2$, docetaxel had a significant beneficial effect on overall survival compared with best supportive care, and a significantly higher 1 year survival compared to the control arm of vinorelbine or ifosfamide (Shepherd et al 2000, Fossella et al 2000). Expected toxicities include hypersensitivity reactions, neutropenia, peripheral neuropathy, and fluid retention. The incidence of severe fluid retention can be reduced by treatment with oral corticosteroids such as dexamethasone for 3 days beginning the day before docetaxel administration. Investigators may choose an alternative corticosteroid premedication in accordance with approved local practice. Dexamethasone, or alternative corticosteroid, should be given orally. Additional doses of IV dexamethasone, or alternative corticosteroid, can be given at the Investigator's discretion. Prescribing information may vary between countries and should be confirmed with the local dispensary or with the manufacturer at the address given in Appendix H.

## 1.2 Rationale for this study

The outlook for subjects with refractory advanced NSCLC is poor, with a median survival of approximately 6 months at time of failed first treatment.

There are now several reports on the use of novel targeted therapies with unique mechanisms of action, which have provided proof of the concept in the clinical trials. Avastin™ (bevacizumab), an anti-VEGF recombinant humanized monoclonal antibody (rhuMAb), showed improved efficacy in stage IIIb/IV NSCLC when combined with paclitaxel/carboplatin (Sandler AB et al, 2005) and in advanced colorectal cancer (CRC) when combined with Irinotecan/5 Fluorouracil/Leucovorin (Hurwitz H et al, 2004). Agents such as EGFR-tyrosine kinase inhibitors (TKIs) (eg, Tarceva™), and anti-EGFR monoclonal antibodies (MAbs) (eg Erbitux™) have shown efficacy in refractory NSCLC and refractory CRC, respectively.

Combination therapies have been reported with these novel agents. Herbst et al reported on a Phase I/II trial of Avastin and Tarceva in subjects with NSCLC having shown an increased response rate and PFS (Herbst et al, 2005), suggesting that EGFR and VEGFR blockade may have significant activity in NSCLC even without chemotherapy.

ZACTIMA has both EGFR & VEGFR TKI activity. Hence, ZACTIMA may have potential utility as a novel agent containing both EGFR and VEGFR inhibition in one compound.

In a Japanese ZACTIMA Phase I study with doses ranging from 100 mg to 400 mg, objective tumor response was seen from 4 of 9 subjects with NSCLC. In a Phase II study (ZD6474IL/0006), ZACTIMA combined with docetaxel showed prolonged PFS in subjects with NSCLC. In study ZD6474IL/0006 a total of 127 subjects were randomized from 27

centers in the Czech Republic, Hungary, and USA. At the data cut-off of 30 November 2004, the median follow-up was approximately 9.5 months and minimum follow-up approximately 4.5 months. Treatment groups were generally well balanced for key baseline variables. The overall median age was 59 years; approximately 55% of subjects were male; 90% were Caucasian; 50% had adenocarcinoma; 75% had stage IV disease; 90% were current or previous smokers; and 65% were performance status 1 (the remainder were performance status 0).

At the data cutoff, approximately 75% of subjects had experienced a progression event, and approximately 45% had died. The estimated hazard ratios (HRs) for PFS (ZACTIMA + docetaxel : docetaxel alone) were 0.64 (2-sided 95% CI 0.30-1.05; p=0.07) for ZACTIMA 100 mg + docetaxel, and 0.83 (2-sided 95% CI 0.50-1.36; p=0.42) for ZACTIMA 300 mg + docetaxel. The estimated median PFSs were 19 weeks for ZACTIMA 100 mg + docetaxel; 17 weeks for ZACTIMA 300 mg + docetaxel, and 12 weeks for docetaxel alone.

Response evaluation criteria in solid tumors (RECIST)-confirmed objective responses (PR [partial response]) were observed in 11/42 subjects randomized to ZACTIMA 100 mg + docetaxel (26%), in 8/44 subjects randomized to ZACTIMA 300 mg + docetaxel (18%), and in 5/41 subjects randomized to docetaxel alone (12%). Rates of disease control for at least 6 weeks were 83% for ZACTIMA 100 mg + docetaxel, 64% for ZACTIMA 300 mg + docetaxel, and 56% for docetaxel alone.

The analysis of survival gave estimated HRs (ZACTIMA + docetaxel : docetaxel alone) of 1.14 (2-sided 95% CI 0.57-2.28; p=0.72) for ZACTIMA 100 mg + docetaxel, and 1.49 (2-sided 95% CI 0.77-2.88; p=0.24) for ZACTIMA 300 mg + docetaxel. The median time to death could not be estimated for ZACTIMA 100 mg + docetaxel at the time of the data cut-off but was estimated as 8.2 months for ZACTIMA 300 mg + docetaxel, and 11.5 months for docetaxel alone. In this study, the addition of ZACTIMA to docetaxel did not confer an advantage in terms of survival. This may be explained, in part, by the immaturity of the data, the small sample size and the confounding effects of subsequent cancer therapy. No evidence could be found of a systematic adverse safety effect of ZACTIMA which could explain the lack of survival advantage.

Docetaxel is indicated for the 2$^{nd}$-line treatment of subjects with locally advanced or metastatic NSCLC who have failed platinum-based chemotherapy. This trial will determine if the daily administration of ZACTIMA provides a significant prolongation of PFS when compared with docetaxel in combination with placebo in subjects whom have failed a 1$^{st}$ line anti-cancer therapy and will include subjects that have not received a platinum-based chemotherapy.

The dose of ZACTIMA in this study was selected following review of the efficacy, safety and pharmacokinetic (PK) data to date. In study 006, the 100 mg dose in combination with docetaxel demonstrated superior tolerability compared to the 300 mg dose in combination with docetaxel, and was not markedly different from the tolerability of docetaxel plus placebo. While both doses of ZACTIMA provided superior efficacy (PFS, response rate) in combination with docetaxel compared to docetaxel plus placebo, the 100 mg dose of

ZACTIMA was superior to the 300 mg dose. Therefore, ZACTIMA 100 mg is the appropriate dose for future study in combination with docetaxel.

Exploratory subgroup analyses of progression and survival data from the previous Phase II study (ZD6474IL/0006) have generated a hypothesis that the advantage for ZACTIMA 100 mg plus docetaxel over docetaxel alone may be most pronounced in female subjects. In order to test this hypothesis, this trial will incorporate two co-primary analysis populations: the first will comprise all subjects; the second will comprise all female subjects. Accordingly, a nominal significance level of 2.5% will be used for each of the two analysis populations.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

The primary objective of this study is to demonstrate an improvement in PFS in the combination of ZACTIMA with docetaxel compared with docetaxel plus placebo in subjects with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy

## 2.2 Secondary objectives

The secondary objectives of the study are to:

- To demonstrate an improvement in overall survival for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo

- To demonstrate an improvement in the overall objective response rate (ORR) (complete response [CR] + PR), disease control rate (DCR) (CR + PR + Stable Disease [SD] ≥ 6 weeks) and duration of response (DOR) for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo using modified RECIST (Therasse et al, 2000, Appendix E)

- To demonstrate a beneficial effect on disease-related symptoms, in subjects treated with ZACTIMA in combination with docetaxel, that is at least as good as those in subjects treated with docetaxel plus placebo based on the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) lung cancer subscale (LCS)

- To demonstrate a quality of life (QoL) for ZACTIMA in combination with docetaxel-treated subjects that is at least as good as that for subjects treated with docetaxel plus placebo by assessment of the FACT-L and the Trial Outcome Index (TOI)

- To demonstrate an improvement in time to deterioration of disease-related symptoms (TDS) based on the FACT-L LCS for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo

- To study the tolerability and safety of ZACTIMA in combination with docetaxel in subjects with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy

- To investigate the population PKs of ZACTIMA in this subject population and assess the PK-QTc relationship, PK-safety relationship and PK-efficacy relationship

- To investigate plasma levels of the N-desmethyl and N-oxide metabolites of ZACTIMA in this subject population

## 2.3 Exploratory objectives

The exploratory objectives of the study are to:

- To investigate the correlation of EGFR expression, gene amplification and mutations and other related biomarker status, in archival tumor samples, with efficacy in those subjects where such tumor material is available

- To collect a blood sample for DNA extraction and storage for possible future testing by evaluation of single nucleotide polymorphism (SNP) status of genes involved in the response to ZACTIMA and its comparators (for example, EGFR, VEGF, VEGFR-2, eNOS and MDR-1)

- To investigate in blood plasma samples, the correlation of levels of circulating protein biomarkers with efficacy

- To investigate the amount of resource used by subjects in terms of inpatient stays and outpatient visits during the period of treatment with investigational therapy

- To investigate health status index during the period of treatment with investigational therapy by assessment of the EuroQoL 5 Dimension Instrument (EQ5D)

- To investigate the TDPS (time to deterioration in patient World Health Organization [WHO] Performance Status [PS]) during the period of treatment with investigational therapy

- To investigate changes in subject weight

# 3. STUDY PLAN AND PROCEDURES

## 3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This is a parallel group, international, randomized, double-blind, placebo controlled, multi-center study design to assess whether the addition of ZACTIMA (100 mg daily) to docetaxel in subjects with locally advanced or metastatic NSCLC confers an advantage in terms of PFS. A minimum of 1380 subjects will be enrolled in the clinical study, with 420 subjects in EU Directive implementing countries (20 in Austria, 30 in Belgium, 50 in Denmark, 70 in France, 70 in Germany, 30 in Greece, 50 in Italy, 30 in Netherlands, 30 in Portugal, and 40 in Spain).

Subjects will be randomized in a 1:1 ratio to either ZACTIMA 100 mg plus docetaxel, or placebo plus docetaxel. No stratification at randomization will be made for this study. Docetaxel will be administered according to a 21-day cycle up to a maximum of 6 cycles. ZACTIMA/placebo will be administered as a once daily tablet. Subjects may continue to receive study treatment as long as they are benefiting from treatment (in the Investigator's opinion and they do not meet any other withdrawal criteria). There is a maximum of 6 cycles of docetaxel and no maximum duration of treatment for ZACTIMA/placebo. After 6 cycles of docetaxel, subjects will continue on ZACTIMA/placebo monotherapy until progression. Blinded ZACTIMA/placebo should be discontinued following objective disease progression.

The safety data from all subjects will be assessed on an ongoing basis. Subjects who experience Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicity (Section 3.2.2.) that is considered related to ZACTIMA/placebo will have their trial medication stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the subject may restart treatment with a reduced dose of ZACTIMA in a blinded manner. The study evaluations should be continued as outlined in the trial plan. If the subject has been off treatment for greater than 3 weeks due to toxicity, the subject must be withdrawn from ZACTIMA/placebo. In the case of subjects who discontinue ZACTIMA/placebo therapy because of toxicity attributable to ZACTIMA/placebo, these subjects will continue to receive the scheduled treatment with docetaxel and will be followed for progression and survival.

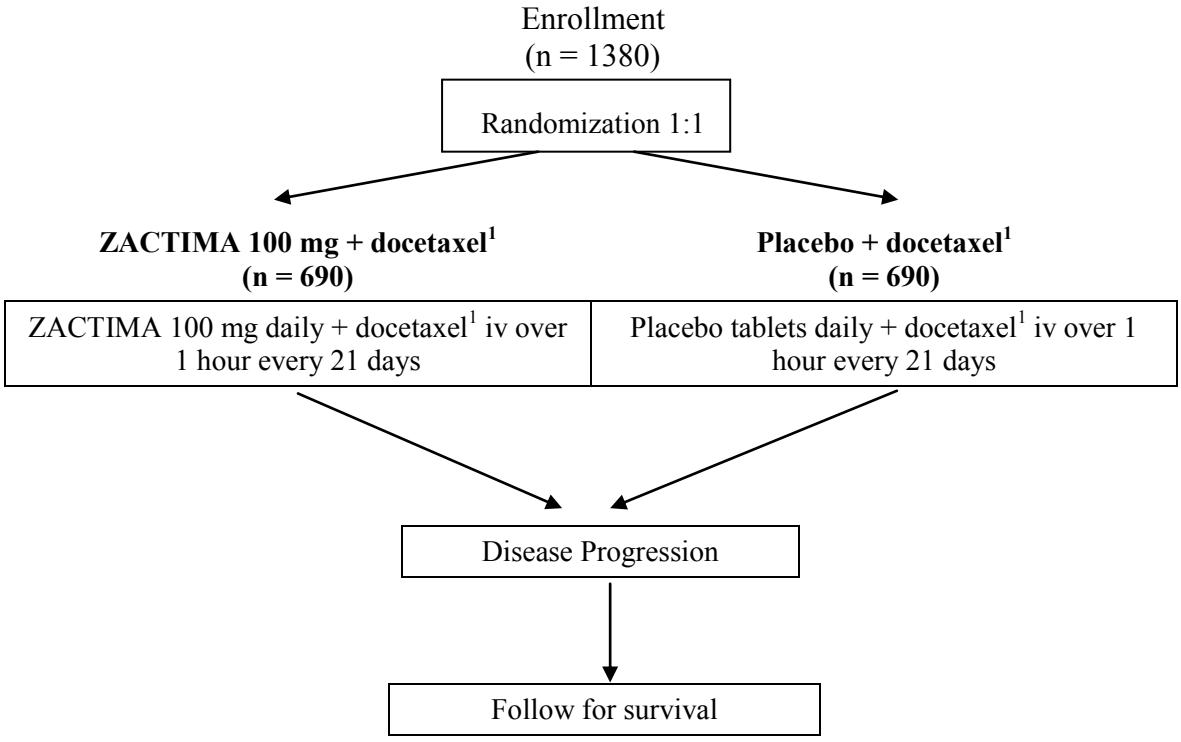
Subjects who experience CTCAE grade 3 or 4 toxicity (Section 3.2.2) that is considered related to docetaxel will have docetaxel stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the subject may restart treatment with a reduced dose of docetaxel. If docetaxel must be withheld for more than 3 weeks, after a scheduled treatment visit, for resolution of toxicity, the subject will not restart docetaxel treatment. In the case of subjects who discontinue docetaxel because of toxicity attributable to docetaxel (Section 3.2.2.1), subjects may continue on ZACTIMA/placebo and will be followed for progression and survival.

Radiologic evaluation using RECIST will be performed at screening and then every 6 weeks after randomization. It is important to follow the assessment schedule as closely as possible. Subjects will be evaluated until objective disease progression, and will then be followed for survival, unless they withdraw consent. If a subject discontinues study medication prior to objective disease progression they should continue to be assessed by RECIST, as per the protocol schedule, until disease progression and then followed up for survival, unless they withdraw consent.

PK samples will be obtained from 440 subjects, and all Japanese subjects, for a total of 580 subjects randomized in the study.

Every attempt will be made to obtain archived tumor samples from all consenting subjects randomized on the study, although tissue collection will not be mandatory.

**Figure 1 Study flow chart**




1 – Up to 6 cycles of docetaxel at the registered, approved dose of 75 mg/m$^2$ (60 mg/m$^2$ Japan only)

| **Table 1** | **Table of assessments (study plan): Screening to discontinuation of docetaxel** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle** | **Screen** | | **1** | | | **2** | | | **3** | **4** | **5** | **6** |
| **Day** | **-21 – 0** | **-7 – 0** | **1** | **8** | **15** | **22/1** | **8** | **15** | **22/1** | **22/1** | **22/1** | **22/1** |
| **Visit** | **1** | | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** |
| **Visit window** | | | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** |
| Informed consent | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | | |
| Physical examination | | X | | | | X | | | X | X | X | X |
| Vital signs[a] | | X | X | X | X | X | X | X | X | X | X | X |
| Electrocardiogram | X[b] | | X[c] | X[c] | | X[c] | | | X[c] | | X[c] | |
| PK assessments[d] | | | | X | | X | | | X | | X | |
| Hematology/ clinical chemistry[e] | X | | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | | X | X | | | X | | | X | X | X | X |
| Pregnancy test | | X[f] | | | | | | | | | | |
| WHO Performance Status | | X | | | | X | | | X | X | X | X |
| FACT-L QoL questionnaire[g] | | X | | | | X | | | X | X | X | X |
| EQ5D[g] | | X | | | | X | | | X | X | X | X |
| RECIST[h] | X | | | | | | | | X | | X | |
| Randomization | | | X | | | | | | | | | |
| Study medication dispensing | | | X[i] | | | X | | | X | X | X | X |
| Tolerability/AE reporting | X | | X | X | X | X | X | X | X | X | X | X |
| Concurrent medication | | X | X | X | X | X | X | X | X | X | X | X |
| Plasma biomarker blood sample[j] | | X | | | | X | | | X | X | X | X |
| Resource use | | | | | | X | | | X | X | X | X |
| Genetic blood sample (optional) | X[k] | | | | | | | | | | | |
| Archival samples (optional) | X[k] | | | | | | | | | | | |

**All assessments are to be performed before administration of docetaxel unless otherwise indicated. At the Baseline Visit (Visit 2, day 1), vital signs, ECGs, hematology, clinical chemistry and urinalysis should be performed prior to administration of ZACTIMA/placebo and docetaxel. Assessments and treatment should be carried out as specified in the study plan. If the scheduled study day falls on a weekend or holiday, every attempt should be made to have the treatment or assessment carried out within 3 calendar days of the scheduled day.**

Abbreviations: AE = adverse event; d = day; EQ5D = EuroQoL 5 Dimension Instrument; FACT-L = Functional Assessment of Cancer Therapy for Lung Cancer; PK = pharmacokinetic; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

(a) Vital signs include blood pressure, pulse, temperature and weight (and height at screening).

(b) A single 12-lead ECG must be performed at screening (within 21 days before the first dose). The screening QTc must be <480 msec. If the single screening QTc is ≥480 msec (≥460 msec for subjects who are receiving one of the drugs listed in Appendix D, Table 2 – see Exclusion Criteria #18), then the Investigator has the option to perform up to an additional 2 ECGs so that a maximum of 3 ECGs (each at least 24 hours apart) may be obtained at screening. The QTc value used to determine eligibility would be the average of the QTc values obtained at screening.

(c) On day 1, cycle one, 12-lead ECGs are to be performed pre-infusion. Baseline QTc will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) on day 1. When possible, ECGs should be performed at the same time throughout the study (performed 4-8 hours after the subject takes their oral medication) at Visits 3, 5, 8, 10 (weeks 2, 4, 7, 13), and then every 3 months up to and including discontinuation of ZACTIMA/placebo. If QTc prolongation occurs at one of the usual assessment times, or at any other time, please refer to Section 3.2.2.2 for further details. Subjects who are receiving one of the drugs listed in Appendix D, Table 2, at the time of study treatment must have an additional ECG obtained 4-8 hours after the first dose of ZD6474.

(d) PK sampling will be taken close to or at the same time as the ECGs performed in Visits 3, 5, 8, 10 (weeks 2, 4, 7, 13), and then every 3 months up to and including discontinuation of ZACTIMA/placebo. No PK sample is required with the baseline ECG. PK samples will be obtained from 440 subjects, and all Japanese subjects, for a total of 580 subjects. ZACTIMA concentrations will be determined in all samples, and metabolite determination will be done in weeks 2 & 13 and 6-month samples, from a minimum of 60 subjects identified as being on ZACTIMA.

(e) Hematology and clinical chemistry should be performed at each visit until the end of docetaxel treatment. After discontinuation of docetaxel, hematology and clinical chemistry should be performed at least every 3 weeks. During the period of study treatment, more frequent assessment of hematology and clinical chemistry should be performed if clinically indicated, based on the Investigator's judgment. [For example, it is important to maintain patient's electrolytes within normal limits (see section 3.2.2.3) and some patients with diarrhea may require more frequent assessment of clinical chemistry to monitor for electrolyte abnormalities]. Hematology and clinical chemistry need only be assessed at Day 1 if the screening assessments were taken more than 7 days before.

(f) Premenopausal women of child bearing potential must have a negative pregnancy test within 3 days before first dose of study medication.

(g) FACT-L & EQ5D questionnaires are to be administered at screening (within 7 days before the 1st dose) and every 3 weeks until discontinuation. The FACT-L & EQ5D questionnaires should be completed before the subject receives docetaxel (even when delayed) and before the subject is given the results of their tumor assessments.

(h) RECIST is carried out at screening (within 3 weeks before the 1st dose) and every 6 weeks following randomization until objective disease progression per RECIST. If a subject discontinues study treatment prior to objective disease progression they should continue to be assessed for progression per RECIST every 6 weeks according to the protocol schedule, until disease progression and then followed up for survival, unless they withdraw consent. Scans performed for RECIST will be expected to cover abdomen and chest (pelvic imaging is only required if clinically indicated). Bone

lesions identified by CT, MRI or X-ray at baseline, covering abdomen, chest (and pelvis if clinically indicated), should be recorded as non-target lesions and followed as per study schedule. Any additional bone lesions not covered by the protocol scans do not require regular isotopic bone scans. If new or worsening bone symptoms occur and a bone scan is performed then worsening of disease needs to be confirmed by X-ray, CT or MRI and recorded as a new lesion. For subjects with cerebral metastases, regular cranial CT/MRI scans are not required. If new or worsening symptoms occur and a CT/MRI scan is performed, then worsening of disease needs to be recorded as a new lesion. If docetaxel is delayed, the RECIST assessment should be delayed in-line with docetaxel. RECIST assessments should be performed preceding administration of docetaxel, at the cycles indicated in the study plan (i.e. preceding cycles 3 and 5).

(i) Docetaxel and ZACTIMA/placebo are both started on Day 1. If docetaxel is delayed, all subsequent visit assessments, including RECIST and ECGs, should be delayed in-line with docetaxel.

(j) Plasma biomarker blood samples should be taken prior to administration of docetaxel either before or after administration of ZACTIMA/placebo. Plasma samples should only be taken on subjects who qualify at screening for entry into the study.

(k) Archival paraffin-embedded tumor sections and blood samples for genetic analysis should be collected from all consenting randomized subjects if available. The archival paraffin-embedded tumor sections and blood samples can be obtained at any time during the study.

| **Table 2 Table of assessments (study plan): After Discontinuation of Docetaxel** | | | |
|---|---|---|---|
| **Treatment Period** | **Every 3 Weeks** | **Every 6 Weeks** | **Every 3 Months** |
| Physical examination | X | | |
| Vital signs[a] | X | | |
| Electrocardiogram[b] | | | X |
| Hematology/clinical chemistry | X | | |
| Urinalysis | X | | |
| PK assessments[c] | | | X |
| WHO Performance Status[d] | X | | |
| FACT-L QoL questionnaire[e] | X | | |
| EQ5D[e] | X | | |
| RECIST[f] | | X | |
| Study medication dispensing | X | | |
| Tolerability/AE reporting | X | | |
| Concurrent medication | X | | |
| Resource use | X | | |

**Assessments and treatment should be carried out as specified in the study plan. If the scheduled study day falls on a weekend or holiday, every attempt should be made to have the treatment or assessment carried out within 3 calendar days of the scheduled day. If a subject discontinues ZACTIMA/placebo, but continues to receive docetaxel (up to 6 cycles), then ECG and PK assessments are no longer required. All other assessments should continue as outlined in the study plan.**

Abbreviations: AE = adverse event; EQ5D = EuroQoL 5 Dimension Instrument; FACT-L = Functional Assessment of Cancer Therapy for Lung Cancer; PK = pharmacokinetic; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

(a) Vital signs include blood pressure, pulse, temperature and weight. Weight must be obtained until progression, unless the subject has withdrawn consent.

(b) When possible, ECGs should be performed at the same time throughout the study (performed 4-8 hours after the subject takes their oral medication). If docetaxel is discontinued within the first 12 weeks of treatment, ECGs must be performed at weeks 1, 2, 4, 7, 13, and then every 3 months up to and including discontinuation of ZACTIMA/placebo.

(c) PK samples will be obtained from 440 subjects, and all Japanese subjects, for a total of 580 subjects. The PK sample will be taken close to or at the same time as the ECG is performed every 3 months, and at discontinuation of ZACTIMA/placebo. If docetaxel is discontinued within the first 12 weeks of treatment, PK samples should be performed at weeks 1, 2, 4, 7, 13, and then every 3 months up to and including discontinuation of ZACTIMA/placebo.

(d) WHO PS must be obtained until progression, unless the subject has withdrawn consent.

(e) The FACT-L & EQ5D questionnaires should be completed before the subject is given results of their tumor assessments.

(f) RECIST is carried out every 6 weeks. Subjects will be evaluated until objective disease progression, unless they have withdrawn consent. If a subject discontinues study medication prior to objective disease progression they should continue to be assessed by RECIST, as per the protocol schedule,

until disease progression and then followed up for survival, unless they withdraw consent. Bone lesions identified by CT, MRI or X-ray at baseline, covering abdomen, chest (and pelvis if clinically indicated), should be recorded as non-target lesions and followed as per study schedule. Any additional bone lesions not covered by the protocol scans do not require regular isotopic bone scans. If new or worsening bone symptoms occur and a bone scan is performed then worsening of disease needs to be confirmed by X-ray, CT or MRI and recorded as a new lesion. For subjects with cerebral metastases, regular cranial CT/MRI scans are not required. If new or worsening symptoms occur and a CT/MRI scan is performed then worsening of disease needs to be recorded as a new lesion.

| **Table 3** | **Table of assessments (study plan): Discontinuation of both ZACTIMA/placebo and docetaxel** | | | |
|---|---|---|---|---|
| **Cycle** | **Discontinuation** | **30-day f/u** | **60-day f/u[a]** | **Survival** |
| **Visit window** | **±3 days** | **±3 days** | **±3 days** | **±3 days** |
| Electrocardiogram | X | | | |
| Hematology/clinical chemistry | X | | | |
| Urinalysis | X | | | |
| Vital Signs[b, c] | X | X[c] | | |
| PK assessments[d] | X | | | |
| FACT-L QoL questionnaire[e] | X | X | | |
| EQ5D[e] | X | X | | |
| WHO Performance Status[c] | X | X | | |
| RECIST[g] | X | | | |
| Tolerability/AE reporting | X | X | X | |
| Concurrent medication | X | X | X | |
| 1st & Subsequent therapies | | X | X | X |
| Survival[f] | | | | X |
| Plasma biomarker blood sample | X | | | |
| Resource use | X | X | | |

**Assessments and treatment should be carried out as specified in the study plan. If the schedule study day falls on a weekend or holiday, every attempt should be made to have the treatment or assessment carried out within 3 calendar days of the scheduled day.**

Abbreviations: AE = adverse event; EQ5D = EuroQoL 5 Dimension Instrument; FACT-L = Functional Assessment of Cancer Therapy for Lung Cancer; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

(a) The 60-day follow-up visit may be conducted via telephone contact.

(b) Vital signs include blood pressure, pulse, temperature and weight.

(c) Weight and WHO PS must be collected every 6 weeks until progression for subjects who discontinue both ZACTIMA/placebo and docetaxel prior to disease progression, unless they have withdrawn consent.

(d) PK samples will be obtained from 440 subjects, and all Japanese subjects, for a total of 580 subjects. The PK sample will be taken close to or at the same time as the ECG is performed at discontinuation of ZACTIMA/placebo.

(e) The FACT-L & EQ5D questionnaires should be completed before the subject is given results of their tumor assessments. The FACT-L & EQ5D questionnaires do not need to be collected at the 30-day follow-up visit for subjects who discontinue both ZACTIMA/placebo and docetaxel prior to disease progression.

(f) Assessments for survival should be made every 6 weeks. Survival information may be obtained via telephone contact.

(g) If a subject discontinues study medication prior to objective disease progression they should continue to be assessed by RECIST, as per the protocol schedule (every 6 weeks), until disease progression, and then followed up for survival, unless they withdraw consent.

## 3.2 Rationale and risk/benefit assessment

### 3.2.1 Rationale for study design, doses and control groups

A randomized, double blind, placebo controlled Phase III study will be appropriate to assess whether ZACTIMA plus docetaxel confers a longer PFS benefit when compared with placebo plus docetaxel in subjects with refractory, advanced NSCLC. The population for this study will consist of subjects who failed 1st-line anti-cancer therapy and for whom docetaxel is therefore an appropriate therapeutic option (2nd-line subjects). The study is based on the results of a randomized, double-blind, phase II study in 2nd-line NSCLC (study 6474IL/0006), which compared ZACTIMA 100 mg or 300 mg in combination with docetaxel to docetaxel plus placebo. In this study, both doses of ZACTIMA provide superior efficacy in combination with docetaxel when compared to docetaxel plus placebo, but the 100 mg dose of ZACTIMA was superior to the 300 mg dose. The median PFS for subjects who received ZACTIMA 100 mg plus docetaxel was 18.7 weeks, compared to 12.0 weeks for docetaxel plus placebo, with 2–sided p=0.07. While this advantage in PFS did not meet statistical significance, the study was powered so that $p<0.2$ was considered evidence of activity worthy of further study. In addition to the advantage of PFS, subjects who received ZACTIMA 100 mg in combination with docetaxel had a higher response rate (26% vs 12%) and DCR at 6 weeks (83% vs 56%) compared to subjects who received docetaxel plus placebo. The survival data were immature at the time of the data cutoff, and the results were likely confounded by differences in subsequent therapy. Common AEs experienced by subjects who received ZACTIMA included rash, diarrhea, and asymptomatic QTc prolongation, though the toxicity profile for ZACTIMA 100 mg in combination with docetaxel was not markedly different from that for docetaxel alone. Therefore, the dose of ZACTIMA that will be studied in combination with docetaxel in the current study is 100 mg.

The primary endpoint of PFS in this study, rather than overall survival, is justified by the increasing prevalence of 3rd-line therapies that are available for subjects who have disease progression after 2nd-line treatment. These subsequent therapies are likely to impact the overall survival outcome, independent of the effects of ZACTIMA in the 2nd-line setting. Furthermore, regional and other variations in the standard of care may result in imbalances in the subsequent therapy received by subjects in the 2 treatment arms of the study. The survival outcomes for subjects in the Phase II study 6474IL/0006 demonstrate the potential confounding nature of these subsequent therapies. This study will include overall survival as a secondary endpoint, and all subjects will be followed for survival. In addition, the study will include other measures of clinical benefit, including response rate, DCR, and measures of quality of life, to provide supportive data of the benefit of ZACTIMA.

The use of placebo control in this study will provide for a robust assessment of the benefit of ZACTIMA in combination with docetaxel, and is considered appropriate in this subject

population because docetaxel is approved for use as a single-agent in the 2nd-line treatment of subjects with NSCLC. By blinding subjects and Investigators, using a placebo control, and assessing tumor measurements on a fixed and frequent schedule, the risk of bias that could affect the interpretation of the PFS endpoint should be reduced.

### 3.2.2 Risk/benefit and ethical assessment

All toxicities will be graded according to the National Cancer Institute (NCI) CTCAE, Version 3. Management of toxicities including dose modifications are detailed below and summarized in Table 4.

#### 3.2.2.1 Docetaxel toxicity

In the event of the following toxicities, docetaxel should be withheld and when the toxicity has resolved (to CTCAE grade 1 or baseline), docetaxel may be administered at 75% of the original dose (i.e. 55mg/m$^2$) [In Japan only, docetaxel may be administered at a reduced dose of 50 mg/m$^2$], unless the subject withdraws consent:

- Absolute neutrophil count (ANC) <0.5 x $10^9$/L for more than 7 days
- Febrile neutropenia or CTCAE grade 4 infection
- CTCAE grade 3 or 4 cutanous reactions
- CTCAE grade 3 or 4 edema
- Other CTCAE grade 3 or 4 non-hematologic toxicity

For CTCAE grade 3 or 4 peripheral neuropathy, docetaxel should be stopped and not restarted. Docetaxel should be stopped for a grade 3 or 4 allergic reaction/hypersensitivity that is clearly related to docetaxel. A re-challenge is permitted at the Investigator's discretion.

For other toxicity, if docetaxel must be withheld for more than 3 weeks for resolution of toxicity, or if CTCAE grade 3 or 4 toxicity recurs following the dose reduction, the subject will not restart docetaxel treatment.

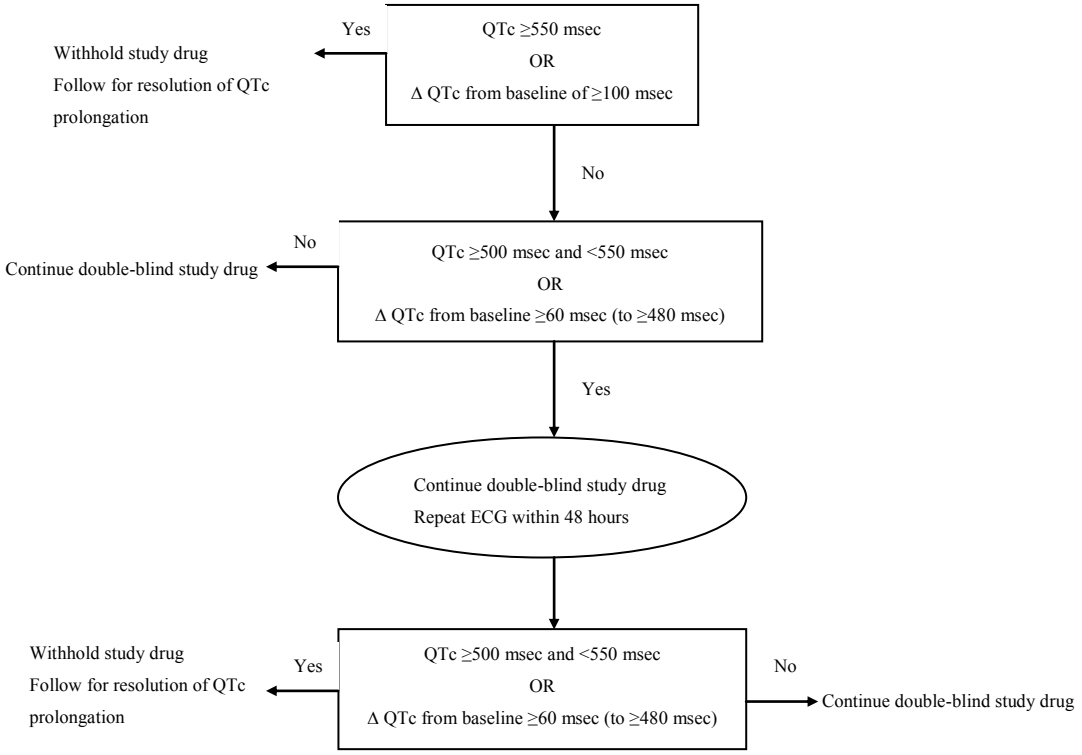
Subjects should not be retreated with subsequent cycles of docetaxel until platelets recover to a level ≥100 x $10^9$/L.

#### 3.2.2.2 QTc prolongation

Subjects will have ECGs performed to monitor the QTc interval (using Bazett's correction). The screening QTc must be <480 msec (<460 msec for subjects who are receiving one of the drugs listed in Appendix D, Table 2 –see Exclusion Criteria #18). Up to 3 ECGs may be obtained at screening, and the mean QTc value used to determine eligibility. If a subject is receiving one of the medications in Appendix D, Group 2 prior to study entry, and it cannot be discontinued before study treatment, then the screening QTc must be <460msec, and an additional ECG must be obtained 4-8 hours after the first dose of ZD6474. Baseline QTc will

be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1.

**Figure 2 Flow chart detailing management of QTc prolongation**




For this study QTc prolongation is defined as:

- A single QTc value of ≥550 msec or an increase of ≥100 msec from baseline;

**OR**

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs):

  - A QTc interval ≥500 msec, but <550 msec;

  **OR**

  - An increase of ≥60 msec, but <100 msec from baseline QTc to a QTc value ≥480 msec

**Management of subjects with QTc prolongation**

For a single QTc value of ≥550 msec or an increase of ≥100 msec from baseline, ZACTIMA/placebo must be withheld. ECGs and electrolytes (including potassium and magnesium) should be followed 3 times a week until QTc falls below 480 msec or baseline, whichever is higher. ZACTIMA/placebo treatment may be resumed at a lower dose after the QTc recovers to <480 msec or baseline.

For a QTc interval ≥500 msec, but <550 msec, or an increase of ≥60 msec but <100 msec from baseline QTc to a QTc value ≥480 msec, ZACTIMA/placebo may be continued but a repeat ECG (in triplicate, within 5-10 minutes of one another) must be obtained within 48 hours. If QTc prolongation is confirmed, ZACTIMA/placebo should be withheld. ECGs and electrolytes (including potassium and magnesium) should be checked 3 times a week until QTc falls below 480 msec or baseline, whichever is higher. ZACTIMA/placebo treatment may be resumed at a lower dose after the QTc recovers to <480 msec or baseline. If the subject does not meet the criteria for QTc prolongation at the repeat ECG then the subject should continue treatment with double blind study medication and resume the ECG schedule as outlined in the Study Plan.

Subjects who experience QTc prolongation may be given ZACTIMA 100 mg/placebo every other day, after the QTc recovers to <480 msec or baseline. If ZACTIMA/placebo is restarted after the QTc prolongation has resolved, ECGs should be performed 1, 2, 4, 7, 13 weeks and then every 3 months after treatment is restarted. After week 2, the timing of these ECGs can be adjusted to correspond with the docetaxel schedule, where relevant. If ZACTIMA/placebo must be withheld for >3 weeks to allow for QTc prolongation to recover <480 msec or baseline, the subject will not be restarted on study medication. If QTc prolongation recurs after the dose reduction as detailed, the subject must permanently discontinue treatment with ZACTIMA/placebo.

### 3.2.2.3 Gastrointestinal toxicity

Nausea, vomiting, or both may be controlled with antiemetic therapy. In subjects who have emesis and are unable to retain the ZACTIMA/placebo, every attempt should be made to obtain control of nausea and vomiting. The dose of ZACTIMA/placebo may be repeated if emesis occurs within 30 minutes of taking the tablet.

Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation and regular laboratory monitoring should be used, when appropriate, to maintain electrolytes (including potassium, magnesium) within normal limits and prevent an increased risk of QTc prolongation. No dose modifications will be made because of grade 1 or 2 diarrhea. If grade 3 diarrhea develops, ZACTIMA/placebo and docetaxel should be withheld until diarrhea resolves to grade 1 or baseline. Subjects who are clinically unstable because of diarrhea or other intercurrent medical illness must be admitted and evaluated using telemetry, until clinically stable. Upon recovery, treatment may resume at a permanently reduced dose (of ZACTIMA/placebo 100 mg given every other day. Docetaxel should be reduced to 50 mg/m$^2$ Japan only; 75% of the original dose [55 mg/m$^2$] all other countries, at the

discretion of the Investigator. If ZACTIMA/placebo must be withheld for more than 3 weeks for resolution of diarrhea, the subject will not restart ZACTIMA/placebo. If grade 3 or 4 diarrhea recurs after this dose reduction, the subject must permanently discontinue ZACTIMA/placebo.

#### 3.2.2.4 Cutaneous toxicity

It is strongly recommended that all subjects follow a program of sun protective measures while receiving study therapy and for 3-4 weeks after discontinuing study therapy. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study therapy.

If a subject develops a skin rash, the following actions are recommended to the Investigator for the management of this reaction:

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

- The rash should be graded as soon as possible according to the CTCAE cutaneous toxicity criteria (NCI CTCAE, Version 3).

- If a rash of CTCAE grade 2 or higher is detected, immediate symptomatic treatment should be provided.

- If a rash of CTCAE grade 3 or higher is detected, ZACTIMA/placebo and docetaxel should be withheld until recovery to grade 1 or baseline. The following actions should be instituted:

    - Docetaxel should be reduced to 50 mg/m$^2$ in Japan, 55 mg/m$^2$ in all other countries (at the discretion of the Investigator)

    - ZACTIMA/placebo should be reduced to 100 mg/placebo every other day

If severe cutaneous toxicity (CTCAE grade 3 or higher) recurs at reduced dose of ZACTIMA/placebo, the subject will permanently discontinue study treatment of ZACTIMA/placebo. The subject may remain on 50 mg/m$^2$ of docetaxel, Japan only, and 55 mg/m$^2$ of docetaxel, all other countries, at the discretion of the study Investigator, once the rash has recovered to grade 1 or baseline.

If ZACTIMA/placebo or docetaxel must be withheld for >3 weeks due to cutaneous toxicity, the subject will be discontinued.

#### 3.2.2.5 Other toxicity

If any other grade 3 or 4 toxicity that is not outlined in Sections 3.2.2.1 to 3.2.2.4 develops and is attributable to either ZACTIMA/placebo or docetaxel, ZACTIMA/placebo and

docetaxel should be withheld until the toxicity resolves to grade 1 or baseline. Upon recovery, treatment may resume at a permanent reduced dose (ZACTIMA should be reduced to 100 mg/placebo every other day; docetaxel should be reduced to 50/55 mg/m$^2$ at the discretion of the Investigator). If ZACTIMA/placebo must be withheld for more than 3 weeks for resolution of toxicity attributable to ZACTIMA/placebo, the subject will not restart ZACTIMA/placebo. If grade 3 or 4 toxicity recurs after dose reduction, the subject must permanently discontinue ZACTIMA/placebo. Docetaxel may be discontinued at the discretion of the Investigator. Subjects who develop CTCAE grade 3 hypertension may continue on therapy if blood pressure is controlled on antihypertensive medication. If blood pressure cannot be stabilized with increased antihypertensive medication, ZACTIMA/placebo must be discontinued and cannot be resumed until blood pressure is controlled to baseline level. Subjects with CTCAE grade 4 hypertension should discontinue ZACTIMA/placebo and cannot resume therapy until blood pressure is controlled to baseline level. If study treatment must be interrupted for more than 3 weeks to allow for toxicity to resolve, the subject's participation in the part of the study will be discontinued.

**Table 4 Summary of guidance on the management of toxicity for ZACTIMA/placebo and docetaxel**

| Toxicity | Docetaxel | ZACTIMA (100 mg)/placebo |
|---|---|---|
| QTc value ≥550 msec or prolonged ≥100 msec from baseline | No change | Withhold dose; if QTc recovers to <480 msec or baseline, then reduce dose to 100 mg every other day. If QTc does not recover to <480 msec or baseline within 3 weeks, subject will permanently discontinue ZACTIMA. |
| QTc value ≥500 msec or prolonged ≥60 msec from baseline | No change | Continue dosing; repeat ECG (in triplicate) within 48 hours; if repeat ECG meets criteria, withhold dose; then if QTc recovers to <480 msec or baseline, reduce dose to 100 mg every other day. If QTc does not recover to <480 msec or baseline within 3 weeks, subject must permanently discontinue treatment with study medication. Or, if the repeat ECG does not meet criteria, subject should continue study medication. |
| Hematological toxicity as specified in section 3.2.2.1 | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 50 mg/m$^2$ Japan, 55 mg/m$^2$ all other countries. | No change |
| Platelets <100 x $10^9$/L | Withhold dose until platelets recover to ≥100 x $10^9$/L. | No change |

**Table 4 Summary of guidance on the management of toxicity for ZACTIMA/placebo and docetaxel**

| Toxicity | Docetaxel | ZACTIMA (100 mg)/placebo |
|---|---|---|
| Grade 3 or 4 diarrhea | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 50 mg/m$^2$ Japan, 55 mg/m$^2$ all other countries. If withheld for >3 weeks, subject should not restart study medication. | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then permanently reduce dose to 100 mg every other day. If withheld for >3 weeks, subject should not restart study medication. If grade 3 or 4 diarrhea recurs, subject should permanently discontinue study treatment. |
| Grade 3 or 4 cutaneous | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 50 mg/m$^2$ Japan, 55 mg/m$^2$ all other countries. | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then permanently reduce dose to 100 mg every other day. |
| Grade 3 or 4 Peripheral neuropathy | Stop docetaxel | No change |
| Grade 3 or 4 allergic reaction/hypersensitivity that is clearly attributable to docetaxel | Stop docetaxel. Docetaxel can be rechallenged at the discretion of the Investigator. | No change |
| Severe fluid retention (grade 3 or 4 edema) | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 50 mg/m$^2$ Japan, 55 mg/m$^2$ all other countries. | No change |
| Other grade 3 or 4 toxicity related to docetaxel and/or ZACTIMA/placebo | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 50 mg/m$^2$ Japan, 55 mg/m$^2$ all other countries. | Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 100 mg every other day. |

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; QTc = QT interval corrected for heart rate by the Bazett's method (QT = the interval between Q and T on ECG)

## 3.3 Selection of study population

### 3.3.1 Study selection record

Investigator(s) must keep a record of subjects who were considered for enrolment but were never enrolled eg, subject screening log. This information is necessary to establish that the subject population was selected without bias.

### 3.3.2 Inclusion criteria

For inclusion in the study treatment period, subjects must fulfill all of the following criteria:

1. Provision of informed consent

2. Female or male aged 18 years and over

3. Histologic or cytologic confirmation of locally advanced or metastatic NSCLC (IIIb-IV) on entry into study

4. Failure of 1st line anti-cancer therapy (either radiological documentation of disease progression or due to toxicity) or subsequent relapse of disease following 1st line therapy

5. WHO PS 0 – 1

6. One or more measurable lesions at least 10 mm in the longest diameter (LD) by spiral CT scan or 20 mm with conventional techniques according to RECIST criteria

7. Negative pregnancy test for women of childbearing potential

8. Life expectancy of 12 weeks or longer

### 3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Mixed small cell and non-small cell lung cancer histology

2. Subjects who have received 2nd-line anti-cancer therapy

3. Prior treatment with docetaxel (prior treatment with paclitaxel is acceptable)

4. Prior treatment with VEGFR TKIs (previous treatment with bevacizumab [Avastin] is permitted)

5. The last dose of prior chemotherapy or other anti-cancer therapy is discontinued less than 4 weeks before the start of study therapy (6 weeks for nitrosoureas, mitomycin, and suramin)

6. The last radiation therapy within 4 weeks before the start of study therapy, not including local palliative radiation (previously irradiated lesions will not be considered measurable and should be recorded as non-target lesions)

7. Major surgery within 4 weeks before the start of study therapy, or incompletely healed surgical incision

8. Any unresolved toxicity > CTCAE grade 2 from previous anti-cancer therapy

9. Neutrophils $<1.5 \times 10^9$/L and/or platelets $<100 \times 10^9$/L

10. Serum bilirubin greater than upper limit of reference range (ULRR)

11. Creatinine clearance <30 mL/minute (calculated by Cockcroft-Gault formula [see Appendix G])

12. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x ULRR or alkaline phosphatase >2.5 x ULRR

13. Significant cardiovascular event (eg. myocardial infarction, superior vena cava [SVC] syndrome, New York Heart Association [NYHA] classification of heart disease ≥2 [See Appendix J]) within 3 months before entry, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia

14. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) which is symptomatic or requires treatment (CTCAE grade 3) or asymptomatic sustained ventricular tachycardia. Atrial fibrillation, controlled on medication is not excluded.

15. Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age

16. QT prolongation with other medications that required discontinuation of that medication

17. Presence of left bundle branch block (LBBB)

18. QTc with Bazett's correction unmeasurable or ≥480 msec on screening ECG (Note: If a subject has QTc interval ≥480 msec on screening ECG, the screen ECG may be repeated up to 2 additional times, with each ECG at least 24 hours apart. The average QTc from up to three screening ECGs must be <480 msec in order for the subject to be eligible for the study.) Subjects who are receiving a drug that has a risk of QTc prolongation (see Appendix D, Table 2) are excluded if the screening QTc is ≥460 msec.

19. Potassium <4.0 mmol/L despite supplementation; serum calcium (ionized or adjusted for albumin), or magnesium out of normal range despite supplementation

20. Women who are pregnant or breast feeding

21. Any concomitant medications that may cause QTc prolongation or induce Torsades de Pointes (see Appendix D for the lists of medications in Table 1 & Table 2) or induce CYP3A4 function (see Section 3.7.2) within 2 weeks of start of study treatment. Drugs listed in Appendix D, Table 2, that in the Investigator's opinion cannot be discontinued, are allowed (additional criteria must also be met – see Exclusion Criteria #18)

22. Brain metastases or spinal cord compression, unless treated at least 4 weeks before the start of study treatment, and stable without steroid treatment for 10 days

23. Hypertension not controlled by medical therapy (systolic blood pressure greater than 160 millimeter of mercury [mmHg] or diastolic blood pressure greater than 100 mmHg)

24. Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix and adequately treated basal cell or squamous cell carcinoma of the skin

25. Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the Investigator's opinion makes it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol

26. Previous randomization in the present study

27. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational site)

28. Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment

### 3.3.4 Restrictions

1. Subjects who are blood donors should not donate blood during the trial and for 3 months following their last dose of trial treatment.

2. Due to the experimental nature of ZACTIMA, female subjects must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide). In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation are allowed. Male subjects must be surgically sterile or using an acceptable method of contraception during their participation in this study.

### 3.3.5 Withdrawal from study and discontinuation of treatment

#### 3.3.5.1 Withdrawal from study

Subjects will be considered to have withdrawn from the study only in the event of death, loss to follow-up, or informed consent is withdrawn. In this case, no data will be collected after the date of withdrawal of informed consent.

Subjects may withdraw consent at any time without prejudice to further treatment.

#### 3.3.5.2 Procedures for withdrawal from participation in the study

The reason for withdrawal from participation in the study should be recorded on the appropriate eCRF(s). This is also applicable to screening failures (subjects who were enrolled but were never randomized into the study due to failure of inclusion/exclusion criteria) and their reason for withdrawal should be recorded as incorrect enrollment (ie, subject does not meet the required inclusion/exclusion criteria). The Investigator should immediately notify AstraZeneca of a subject's withdrawal from the study.

#### 3.3.5.3 Discontinuation of treatment

Discontinuation from study treatment is when a subject no longer receives study medication but continues to be followed up for objective disease progression and/or survival.

Specific reasons for discontinuing study treatment are:

- Voluntary discontinuation by the subject who is at any time free stop study medication, without prejudice to further treatment
- Safety reasons as judged by the Investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca
- Subject lost to follow-up
- Disease progression

#### 3.3.5.4 Procedures for discontinuation from study treatment

Subjects who discontinue from the study treatment should always be asked about the reason(s) for their discontinuation and the presence of any AEs. If possible, they should be seen and assessed by an investigator(s). AEs are to be followed for 60 days; diary cards (if applicable), questionnaires (eg, for subject reported outcomes) and investigational products should be returned by the subject. The discontinuation visit should take place after the last dose of ZACTIMA/placebo or chemotherapy, whichever comes last. Following the discontinuation visit, there is a 30-day and 60-day follow-up visit that should also take place. Subjects should be contacted for survival status every 6 weeks following the discontinuation visit.

Subjects who discontinue the study treatment prior to disease progression must be assessed for progression by RECIST once every 6 weeks until objective disease progression, and should

then be contacted for survival status every 6 weeks. These subjects must also have both weight and WHO PS assessments every 6 weeks until objective disease progression. Subjects who discontinue due to disease progression should be contacted for survival status every 6 weeks following the discontinuation visit.

Survival status should be collected by telephone contact with the subject, subject's family, or by contact with the subject's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

All ongoing AEs and SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease. All new AEs and all SAEs occurring up to 60 days after the last dose of ZACTIMA/placebo or chemotherapy, whichever was dosed last, must be reported to AstraZeneca and must be followed until resolution where possible.

All subjects who have any CTCAE grade 3 or 4 laboratory values at the time of discontinuation must have further tests performed and the results recorded on the appropriate electronic case report form (eCRF) until the lab values have returned to CTCAE grade 1, unless these values are not likely to improve because of the underlying disease.

#### 3.3.5.5 Procedures for discontinuation from genetic aspects of the study

See Appendix K for details.

## 3.4 Treatments

Additional packaging details for this clinical study material are described in the Clinical Supply Action Plan on file with AstraZeneca Investigational Products Section.

### 3.4.1 Identity of investigational product and comparators

Descriptive information for docetaxel can be found in Appendix H.

Additional descriptive information for ZACTIMA can be found in the IB. ZACTIMA and matching placebo will be supplied as white film-coated tablets. The formulation numbers and descriptions are provided below:

**Table 5 Formulation numbers of ZACTIMA**

| Tablet strength (mg) | Formulation number |
|---|---|
| ZACTIMA 100 mg tablet | F013025 |
| Placebo to match ZACTIMA 100 mg tablet | F013044 |

AstraZeneca Pharmaceuticals Investigational Products will pack ZACTIMA/placebo trial material. ZACTIMA/placebo will be packed into white high-density polythene (HDPE) bottles with child resistant, tamper evident closures. Trial medication must be kept out of the

reach of children. Subjects will be supplied with sufficient medication to continue treatment between each visit.

### 3.4.2 Doses and treatment regimens

#### 3.4.2.1 ZACTIMA or placebo regimen

Subjects will be given single oral doses of 100 mg ZACTIMA or placebo daily. ZACTIMA or placebo tablets must be taken whole and they must not be broken or crushed and dissolved. There are no food restrictions for the administration of ZACTIMA or matching placebo. Subjects can continue to receive treatment as long as they are benefiting from treatment in the opinion of the Investigator, and they do not meet the criteria of discontinuation. There is no maximum duration of treatment for ZACTIMA/placebo. After 6 cycles of docetaxel, subjects will continue on blinded ZACTIMA/placebo monotherapy until progression.

Blinded ZACTIMA/placebo should not be combined with any other anti-cancer therapies, and should be discontinued following objective disease progression. See Table 1 and 2 for schedule of assessments.

Subjects enrolled in the trial will be dispensed bottles of blinded ZACTIMA tablets; each bottle will contain ZACTIMA 100 mg, or placebo tablets as determined by the randomization scheme. Subjects will take 1 tablet per day at the same time of day each morning. ZACTIMA/placebo should be taken prior to the administration of docetaxel due to the timings of the required ECGs and PK samples. As stated in Table 1, footnote j, these samples can be taken before or after ZACTIMA/placebo.

If the subject inadvertently does not take the dose in the morning, he or she may take that day's dose any time up to 10 p.m. that same day. However, if a subject misses taking their scheduled dose and is unable to take the missed dose on the same day, he or she must take the next scheduled dose and the missed dose will not be made up. The missed dose must be documented on the appropriate eCRF. The dose of study treatment may be repeated if vomiting occurs within 30 minutes of taking the study treatment.

#### 3.4.2.2 ZACTIMA dose reduction

There will be no intrasubject dose escalation in this study. Subjects who have toxicity related to ZACTIMA/placebo may have their dose reduced (see Section 3.2.2 for guidance on management of toxicity). If the subject experiences toxicity, they can be given 100 mg ZACTIMA/placebo every other day. If the subject experiences toxicity attributed to ZACTIMA/placebo on the reduced dose, the subject will discontinue ZACTIMA/placebo treatment. Dose reduction will be managed in blinded manner.

**Table 6 Dose reduction**

| ZACTIMA dose | ZACTIMA or placebo tablet | Tablets per daily dose |
|---|---|---|
| 100 mg | 1 x 100 mg | 1 |

| **Table 6** | **Dose reduction** | |
|---|---|---|
| **ZACTIMA dose** | **ZACTIMA or placebo tablet** | **Tablets per daily dose** |
| 100 mg dose reduction | 1 x 100 mg | 1 every other day |

### 3.4.2.3 Docetaxel

The registered, approved dose of docetaxel (60 mg/m$^2$ Japan only; 75 mg/m$^2$ all other countries) will be administered intravenously over at least a 1-hour period every 21 days, up to a maximum of 6 cycles. If toxicity is seen, docetaxel will be reduced (to 50 mg/m$^2$ Japan only; 75% of the original dose [55 mg/m$^2$] all other countries [as outlined in Section 3.2.2.1]).

Subjects should be premedicated with oral corticosteroids such as dexamethasone 8 mg twice daily for 3 days starting one day before each dose of docetaxel. Investigators may choose an alternative corticosteroid premedication in accordance with approved local practice. In the event that the subject forgets to take the oral corticosteroid prior to Day 1 of each cycle, an IV dose can be given at the discretion of the Investigator. Additional doses of IV dexamethasone, or alternative corticosteroid, may be given at the Investigators discretion. Antiemetics may be used for the prevention or management of nausea and vomiting. Pegfilgrastim (Neulasta®) or filgrastim (Neupogen®) may also be administered, and as with all concomitant medications given during the course of the study, must be recorded on the appropriate eCRF.

Standard cytotoxic handling procedures must be used when preparing docetaxel for administration. Skin reactions associated with the accidental exposure to docetaxel may occur; the use of gloves is recommended.

Any unused diluted infusion solutions of docetaxel must be discarded.

The dose will be calculated on the basis of the height and weight of the subject, recorded at baseline. Body surface area (BSA) should be calculated using the Mosteller method {BSA (m²) = ([Ht (cm) x Wt (kg)]/ 3600)$^{½}$} or the DuBois and DuBois formula [BSA (m²) = 0.20247 x Ht (m)$^{0.725}$ x Wt (kg)$^{0.425}$]. If the subject's weight changes by more than 10% from that used in the previous calculation of BSA during the study, the Investigator should recalculate the BSA and amend the dose accordingly.

### 3.4.3 Labeling

One bottle of ZACTIMA/placebo should be dispensed to subjects every 3 weeks.

Information on the bottle labels will indicate the trial number, unique material code, blinded contents, caution, and storage conditions and will have blank spaces for the E-code and dispensing date (to be written in by the site personnel at the center at the time of dispensing). Dosing instructions will be included on the label.

### 3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product bottle label.

### 3.4.5 Accountability

The trial treatment(s) must be used only as directed in the protocol. Records of overall dispensing and returns will be maintained by each center, separately from the eCRFs recording the treatment dispensed to individual subjects.

Subjects must return all unused medication and empty containers to the Investigator, who will retain these until they are collected by AstraZeneca Pharmaceuticals authorized personnel, along with any trial treatments not dispensed.

The Investigator must maintain accurate records accounting for the receipt of the investigational products and for the disposition of the material. This record keeping consists of a dispensing record including the identification of the person to whom the drug was dispensed, the quantity and date of dispensing, and any unused drug returned to the Investigator. This record is in addition to any drug accountability information recorded on the eCRFs. At the termination of the trial or at the request of the sponsor, the Investigator must send any unused supplies for destruction in liaison with their AstraZeneca Study Delivery Operations Specialist (SDOS).

## 3.5 Method of assigning subjects to treatment groups

As subjects are screened for the study, they must be allocated an E-code. The E-code is a 7-digit number made up of the center number and the subject number within that particular center (eg, the first subject screened at center number 0001 would be assigned the E-code E0001001, the second subject screened would be E0001002 and so on). This number is the subject's unique identifier and is used to identify the subject on the eCRFs. For this study, an Interactive Voice Response System (IVRS) system will be used. When a subject is entered into screening, the Investigator should contact the Centralized Registration/Randomization Center by telephone to register the subject. Subjects will be randomized in a 1:1 ratio. All screened subjects are assigned an E-code irrespective of whether or not they are subsequently randomized to receive study treatment.

The actual treatment given to individual subjects will be determined by a randomization scheme. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating random numbers. Randomization numbers will be allocated to centers in balanced blocks. The block size will be such that the randomization scheme will effectively be stratified by center.

If a subject discontinues from the study, the subject E-code number will not be reused, and the subject will not be allowed to re-enter the study.

Subject eligibility will be established before treatment randomization. Subjects will be randomized strictly sequentially, as subjects are eligible for randomization. Once the eligibility of a subject has been confirmed, the Investigator (or nominated assistant) should contact the Centralized Registration/Randomization Center by telephone for the issue of a subject randomization code and allocation of randomized therapy. Subjects will be identified to the Centralized Registration/Randomization Center using subject initials, E-code, and date of birth. The Centralized Registration/Randomization Center will inform the Investigator of the subject randomization number and treatment to be allocated. The subject randomization number will correspond to either docetaxel plus ZACTIMA or docetaxel plus placebo.

## 3.6 Blinding and procedures for unblinding the study

### 3.6.1 Methods for ensuring blinding

Medication will be labeled using a unique material pack code which is linked to the randomization scheme. The Centralized Registration/ Randomization Center will assign the bottle of study material to be dispensed to each subject at each visit. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the medication.

### 3.6.2 Methods for unblinding the study

The subject's randomization code break will be available to the Investigator at the study center through IVRS.

The treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomization. The Investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Subjects should be counseled by their Investigator on the relevant contacts if they experience AEs or toxicity and are being evaluated outside of the Investigative site.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented. Unblinded PK data will not be accessed by AstraZeneca staff affiliated with the conduct of the study prior to study completion.

### 3.6.3 Methods for breaking the blind for monitoring of the safety

An Independent Data Monitoring Committee (IDMC) will be in place before the start of the study to monitor emerging toxicity.

The blind should be maintained for personnel at AstraZeneca, such as biometrics personnel, who are responsible for analysis and interpretation of the results at the study's conclusion.

## 3.7 Pre-study, concomitant and post-study treatment(s)

### 3.7.1 Treatment for cancer

At entry to the study and while the subject remains on study medication (ZACTIMA or placebo), subjects must not be given any concurrent cancer therapy, including cytotoxic agents, radiotherapy (except for palliative radiotherapy), biological response modifiers, hormonal therapy, or any other investigational agents. Cytokines are permitted for the prophylaxis and management of neutropenia. Systemic anticancer therapy or other investigational agents must have been stopped at least 4 weeks before study treatment; nitrosoureas, mitomycin C and suramin must have been stopped at least 6 weeks before study treatment. Previous treatment with bevacizumab for NSCLC is permitted.

After the subject withdraws from study medication, the details of the first and subsequent therapies for cancer, after study medication withdrawal, will be collected.

#### 3.7.1.1 Palliative Radiotherapy

A subject may receive local/regional radiotherapy to a symptomatic target and/or non-target lesion(s) in the absence of disease progression, which must be confirmed by objective evaluation. This information must be recorded on the RECIST eCRFs. This treatment will affect the analysis of these lesions, as described in Section 4.6.3.1.

Currently, limited information is available regarding the safety and therapeutic benefit of the combination of ZACTIMA and radiotherapy. Thus the investigator may use his/her own discretion of whether to stop or continue ZACTIMA during the radiation therapy ensuring careful safety monitoring.

### 3.7.2 Other concomitant treatment

Subjects should be premedicated with oral corticosteroids such as dexamethasone 8 mg twice daily for 3 days starting one day before each dose of docetaxel or according to local practices. Investigators may choose an alternative corticosteroid premedication in accordance with approved local practice. In the event that the subject forgets to take the dexamethasone, or alternative corticosteroid, prior to Day 1 of each cycle, an IV dose can be given at the discretion of the Investigator. Additional doses of IV dexamethasone, or alternative corticosteroid, can be given at the Investigator's discretion.

Supportive care measures and symptomatic treatment for any treatment-associated toxicity may be instituted once the first signs of toxicity occur.

Concomitant use of the known potent inducers of CYP3A4: rifampicin, phenytoin, carbamazepine, barbiturates and St John's Wort are not allowed within 2 weeks of start of study treatment or during the study.

Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (see Appendix D Table 1) are not allowed within 2 weeks of start of study treatment

or during study. These drugs should also be avoided for up to 4 weeks following discontinuation of ZACTIMA/placebo.

The following medications can be taken by subjects, but require additional monitoring:

- Co-administration of drugs that in some reports might be associated with Torsades de Pointes but at this time lack substantial evidence of Torsades de Pointes (see Appendix D, Table 2) should be avoided if possible. However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the subject must be closely monitored including regular checks of QTc and electrolytes (including potassium, magnesium). If a subject is receiving one of the medications in this group prior to study entry, and it cannot be discontinued before study treatment, then the screening QTc must be <460msec, and an additional ECG must be obtained 4-8 hours after the first dose of ZD6474. For subjects who start on one of the drugs in this group while on the study, the ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the subject remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no ECG prolongation has been noted during 4 weeks of co-administration of a drug from Appendix D, Table 2. The electrolytes should be maintained within the normal range using supplements if necessary.

- Warfarin is allowed in therapeutic and low-doses and these subjects should be monitored regularly for changes in their International Normalized Ratio (INR), at the discretion of the Investigator.

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the eCRF).

## 3.8 Treatment compliance

It is the Investigator or institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure the following:

- Deliveries of such products from AstraZeneca Pharmaceuticals are correctly received by a responsible person (eg, a pharmacist)

- Such deliveries are recorded

- Study treatments are handled and stored safely and properly

- Study treatments are only dispensed to study subjects in accordance with the protocol

- Any unused products are returned for destruction in liaison with the AstraZeneca project team

At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist.

Subjects should be given clear instructions on how and when to take their study treatment. Their tablet returns should be counted to check for compliance. Discrepancies between the number of tablets returned and the expected number of tablets returned should be discussed with the subject and the reasons for non-compliance documented.

If the subject is not compliant after counseling on the importance of taking study medication as instructed, the Investigator may withdraw the subject from study treatment.

# 4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

## 4.1 Primary variable

- PFS (see Section 6 for Statistical methods and determination of sample size)

## 4.2 Screening and demographic measurements

Before they enter the study, consenting subjects will be assessed to ensure that they meet eligibility criteria (see Sections 3.3.2 and 3.3.3). Subjects who do not meet these criteria must not be allowed to enroll.

The following must be assessed within 3 weeks before the first dose of study medication is administered:

- Radiological and clinical tumor assessment (per RECIST) (note: Baseline RECIST assessments should be obtained within 21 days prior [but no more than 28 days prior] to the first dose of ZACTIMA/placebo)

- Medical history, including all previous but now resolved significant medical conditions; additional data includes detailed smoking history, date of diagnosis, chemotherapy and other anti-cancer therapy history, collection of historical tumor biomarker status (EGFR mutation, EGFR protein expression, EGFR gene amplification and k-ras mutation), tumor stage and number of organs involved, prior radiation and radiation site, oncology surgical history, reason from withdrawal from prior chemotherapy and most recent date of disease progression

- 12-lead ECG

- Collection of optional genetic blood sample
- Collection of optional archival tumor sample
- Full hematology and biochemistry testing

The following must be assessed within 7 days before the first dose of study medication is administered:

- Physical examination, including vital signs, height, and weight
- Concurrent therapy
- WHO PS
- FACT-L questionnaire
- EQ5D questionnaire
- Full urinalysis testing
- Collection of blood for pharmacodynamic biomarker testing

The following must be assessed within 3 days before the first dose of study medication is administered:

- Serum or urine pregnancy test in women of childbearing potential

## 4.3 Patient-Reported Outcomes (PROs)

The methods for collecting Patient Reported Outcomes (PRO) data are presented below.

### 4.3.1 FACT-L questionnaire incorporating the LCS subscale

#### 4.3.1.1 Methods of assessment

QoL data will be assessed by use of the FACT-L questionnaire (see Appendix F). FACT-L will be assessed as outlined in the study plan. Symptoms will be assessed using the LCS, a section of the FACT-L focusing on symptoms of lung cancer (see Appendix F). FACT-L has been validated with respect to its psychometric properties and sensitivity to clinical changes (Cella et al 1993, 1995, 2002).

#### 4.3.1.2 Derivation or calculation of variable

The following scores will be derived from the FACT-L questionnaire:

- The 7-item LCS total score
- The 4-item Pulmonary Symptom Index (PSI) score

- The total FACT-G score, made up of the sum of the 4 individual subscale scores from the core FACT-L questionnaire: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB) and functional well-being (FWB)

- The TOI, made up of the sum of PWB, FWB, and LCS scores

- The overall score for the FACT-L questionnaire

- Individual subscale scores from the core questionnaire: PWB, SWB, EWB and FWB

For each subscale, if less than 50% of the subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If at least 50% of the items are missing, that subscale also will be treated as missing. The reason for any missing data will be identified. If data is missing at random, the above techniques will be used. If there is evidence that the missing data is systematic, missing values will be handled to ensure that any possible bias is minimized.

### 4.3.2 Time to deterioration of disease related symptoms (TDS)

#### 4.3.2.1 Methods of assessment

Symptoms will be assessed using the LCS, a section of the FACT-L focusing on symptoms of lung cancer (see Appendix F).

#### 4.3.2.2 Derivation or calculation of variable

Baseline LCS is defined as the FACT-L questionnaire closest to, but not subsequent to, the first dose of ZACTIMA/placebo or docetaxel with a non-missing LCS score. At a given time point, deterioration in LCS is defined as $\leq$ -3 change from baseline score.
TDS based on FACT-L LCS is defined as the interval from the date of randomization to the first assessment of 'deterioration' without an improvement within the next 21 days.

If a deterioration of disease-related symptoms has not been observed at the time of analysis, time to deterioration LCS will be censored as of the last non-missing LCS assessment date.

### 4.3.3 Administration of ePRO/pPRO questionnaires

FACT-L should be given to subjects at baseline and as detailed in the study plan, before assessments, prior to administration of docetaxel, and before imparting any news about the status of their disease. If docetaxel is delayed, the FACT-L questionnaire should be completed preceding the next administration of docetaxel. Subjects should be allowed to complete the electronic or paper questionnaire in their own time, and without any help from relatives or clinic staff. An electronic form will be completed by the clinic staff to detail if an ePRO/pPRO questionnaire has been completed at each QoL visit, and if not, the reason will be recorded.

Each center must allocate responsibility for the FACT-L questionnaire to a specific individual (ie, a Research Nurse). The AstraZeneca Study Delivery Team will provide training for relevant personnel in the administration of the FACT-L questionnaire, which will be collected using either an Interactive Voice Response System (IVRS) or as paper questionnaires. It is also important that the significance and relevance of the data are explained carefully to participating subjects so that they are motivated to comply with data collection (Fallowfield et al 1987).

The instructions for completion of the FACT-L questionnaire are:

- The subject must complete it in private in his or her own time
- The subject must complete it before any investigations or discussions about their disease with the clinic staff (including administration of docetaxel treatment)

Help should not be given from relatives or clinical staff unless the subject is blind or illiterate. In this case, the subject can receive help from a study nurse in reading the instructions and questions. However, under no circumstances should help in interpreting the questions or in selecting responses be provided.

## 4.4 Health Economic measurements and variables

The methods for collecting Health Economic data are presented below.

### 4.4.1 Resource data

#### 4.4.1.1 Methods of assessment

Health care resource data will be collected at each cycle after baseline until progression and at the 30 day follow-up visit, including at each unscheduled visit, which requires the subject to see a clinician. Resource data will include inpatient stays and outpatient visits.

#### 4.4.1.2 Derivation or calculation of variable

Data will be presented as means and standard deviations for each treatment arm.

### 4.4.2 EQ5D

#### 4.4.2.1 Methods of assessment

The EQ5D descriptive system is a standardized instrument for use in the measurement of health outcome, applicable to a wide range of health conditions and treatment (EuroQoL 1990).

The EQ5D (EuroQoL group 1990) will be self-administered along with the FACT-L. The EQ5D is a utility measure designed to provide an assessment of general health status of the individual. This instrument is extensively validated and is available in several languages that facilitate its use in multinational studies.

#### 4.4.2.2 Derivation or calculation of outcome variable

The EQ5D descriptive system comprises 5 questions (see Appendix I) which generate possible health states which can be converted into a weighted health status index by applying scores from the appropriate available 'value sets'.

The responses on EQ5D will be used to derive a unique EuroQoL health state. For each EuroQoL health state there exists a corresponding valuation. This valuation will be used for health economic issues.

## 4.5 Pharmacokinetic measurements and variables

The table below shows the relationship between the PK endpoints and analysis of this study and the study objectives.

**Table 7 PK endpoints related to each objective**

| Objective | Variable(s) |
|---|---|
| To generate individual PK parameters (predicted plasma concentrations, AUCss, Css, max, CL/F) and investigate the relationships between these and subject AEs, efficacy and QTc prolongation | PK<br>AUCss, Css, max, CL/F, predicted Cmax, predicted plasma concentration, half-life<br>Safety<br>AEs, QTc<br>Efficacy<br>PFS, Survival, and ORR |
| Individual plasma levels of the N-desmethyl and N-oxide metabolites | Accumulation ratio and ratio to ZACTIMA |

Abbreviations: AE = adverse event; $AUC_{ss}$ = area under plasma concentration-time curve during any dosing interval at steady state; $C_{max}$ = maximum concentration; $C_{ss, max}$ = maximum steady state plasma concentration; CL/F = total body clearance of drug from plasma after an oral dose; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic; QTc = QT interval corrected for heart rate by the Bazett's method (QT is the interval between Q and T on the ECG)

The methods for collection of biological samples and derivation of PK variables are presented below in Sections 4.5.1 and 4.5.2.

### 4.5.1 Collection of pharmacokinetic samples

Venous blood will be taken at the sampling times shown in the study plan, into tubes containing lithium heparin anticoagulant and thoroughly mixed. The blood samples will then be centrifuged within 15 minutes of collection by spinning at 1000 G for 10 minutes. The plasma should be taken off immediately and stored in a plain tube at -20 ºC before transportation to the central holding laboratory. The date and the time of collection will be recorded on the appropriate eCRF. Further details on collection, labeling, and shipping are in the central laboratory manual.

### 4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters

A validated high performance liquid chromatography method with tandem mass spectrometric detection will be used to measure the plasma concentration of ZACTIMA and the N-desmethyl and N-oxide metabolites.

#### 4.5.2.1 ZACTIMA

The PK data will be analyzed using non-linear mixed effects models (Beal and Sheiner, 1988-1998). The PK structural models will be developed in addition to inter- and intra-individual variance models. Assumptions of the pharmacokinetics will be based on previous data and the exact nature of the structural, inter-individual variance and intra-individual variance models will be base on examination of the diagnostic scatter plots (predicted versus observed concentrations, weighted residual versus predicted concentrations, weighted residuals versus time, final parameter estimates, standard error of the parameter estimates, estimated objective function and structure of the variance/covariance matrix). If data from the study proves limited and is identified as insufficient to define the pharmacokinetics (large standard errors, non-identifiable PK profile), additional data will be included from previous clinical trials. Depending on the definition of the PK model parameter, estimates for all subjects will be calculated using Bayesian based methodology. Parameters will include plasma drug clearance, estimated maximum drug concentration, half-life, and volumes of distribution. Once the PK model is defined, covariates (including age, weight, race, gender, etc) will be added in a step-wise manner, and the statistical significance tested via a relevant change in the objective function, depending on the statistical significance level. The clinical relevance of all covariates included in the model will be explored and discussed, through simulation.

With the derivation of the parameters, estimates and accurate predictions of the plasma concentration, modeling of the pharmacodynamics, (QTc, AEs, and efficacy end points will then be undertaken. In a similar manner to the pharmacokinetics model, accuracy will be undertaken through diagnostic plots.

A PK analysis plan will be prepared prior to the commencement of this analysis.

#### 4.5.2.2 N-desmethyl and N-oxide metabolites

For 60 subjects on ZACTIMA that attain 6 months on study, of the 580 PK subjects, the plasma levels of the N-desmethyl and N-oxide metabolites of ZACTIMA will be determined in the samples taken during weeks 2 and 13 and at 6 months. Accumulation ratios will be determined at week 13 and at 6 months from the week 13 and 6 month concentrations divided by the week 2 concentration. The ratio of each metabolite to ZACTIMA will be determined by dividing each metabolite by the ZACTIMA concentration for the weeks 2 and 13 and 6 month samples.

Individual plasma concentrations, accumulation ratios and ratios of ZACTIMA to metabolites will be listed and summarized by sample time.

## 4.6 Efficacy and pharmacodynamic measurement and variables

The objectives and outcome variables for the randomized phase are listed in the table below.

**Table 8 Objectives and outcome variables**

| Objective | Variable(s) |
|---|---|
| Primary | |
| To demonstrate an improvement in PFS in the combination of ZACTIMA with docetaxel compared with docetaxel plus placebo in subjects with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy | PFS |
| Secondary | |
| To demonstrate an improvement in overall survival for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo | Overall survival |
| To demonstrate an improvement in the overall ORR (CR + PR), DCR (CR + PR + SD ≥ 6 weeks) and DOR for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo using modified RECIST (Therasse et al, 2000) | ORR by RECIST, DCR and DOR |
| To demonstrate a beneficial effect on disease-related symptoms, in subjects treated with ZACTIMA in combination with docetaxel, that is at least as good as those in subjects treated with docetaxel plus placebo based on the FACT-L LCS | LCS |
| To demonstrate a QoL for ZACTIMA in combination with docetaxel-treated subjects that is at least as good as that for subjects treated with docetaxel plus placebo by assessment of the FACT-L and the TOI | FACT-L and TOI |
| To demonstrate an improvement in time to deterioration of disease related symptoms based on the FACT-L LCS for ZACTIMA in combination with docetaxel compared with docetaxel plus placebo | TDS |
| To study the tolerability and safety of ZACTIMA in combination with docetaxel in subjects with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy | AEs, laboratory data, vital signs, and ECG changes |

**Table 8 Objectives and outcome variables**

| Objective | Variable(s) |
|---|---|
| To investigate the population PK of ZACTIMA in this subject population and assess the PK-QTc relationship, PK-safety relationship and PK-efficacy relationship | Population PK, AEs, survival, ORR, and PFS |
| Exploratory | |
| To investigate the correlation of EGFR expression, gene amplification and mutations and other related biomarker status, in archival tumor samples, with efficacy in those subjects where such tumor material is available | EGFR mutational status, gene amplification and expression levels of EGFR and other related biomarker |
| To collect a blood sample for DNA extraction and storage for possible future testing by evaluation of single nucleotide polymorphism (SNP) status of genes involved in the response to ZACTIMA and its comparators (for example, EGFR, VEGF, VEGFR-2, eNOS and MDR-1) | DNA sequence of EGFR, VEGF, VEGFR-2, eNOS, MDR-1 |
| To investigate in blood plasma samples, the correlation of levels of circulating protein biomarkers with efficacy | Levels of soluble VEGF, bFGF, VEGFR2 and other biomarkers to assess surrogate markers of tumor angiogenesis |
| To investigate the amount of resource used by subjects in terms of in subject stays and out subject visits during the period of treatment with investigational therapy | Inpatient stays and outpatient visits |
| To investigate health status index during the period of treatment with investigational therapy | EQ5D |
| To investigate the TDPS during the period of treatment with investigational therapy | WHO PS and TDPS |
| To investigate changes in subject weight | Weight |

Abbreviations: AE = adverse event; bFGF = basic fibroblast growth factor; CR = complete response; DCR = disease control rate; DNA = deoxyribonucleic Acid; DOR = duration of response; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; EQ5D = EuroQoL 5 Dimension Instrument; FACT-L = Functional Assessment of Cancer Therapy for Lung Cancer; LCS = lung cancer subscale; NSCLC = non-small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SNP = single nucleotide polymorphism; TDS = Time to deterioration of disease related symptoms; TDPS = Time to deterioration in subject WHO PS; TOI = Trial Outcome Index; VEGF = vascular endothelial growth factor; VEGFR2 = vascular endothelial growth factor receptor-2; WHO PS = World Health Organization Performance Status

### 4.6.1 Progression-free survival (PFS)

#### 4.6.1.1 Methods of assessment

PFS is determined using data from RECIST assessments performed at baseline, during treatment and during the follow-up period.

#### 4.6.1.2 Derivation or calculation of outcome variable

PFS will be defined from the date of randomization to the date of objective progression or death (by any cause in the absence of progression). Subjects who have not progressed or died at the time of statistical analysis will be censored at the time of their latest objective tumor assessment. This includes subjects who are lost to follow-up or have withdrawn consent. For subjects lost to follow-up without having progressed, death within a further 3 months will be considered an event, otherwise the subject will be censored for PFS at the time of their last tumor assessment date.

### 4.6.2 Time to death

#### 4.6.2.1 Methods of assessment

Subjects survival status throughout the course of the study will be used to determine overall survival (OS).

#### 4.6.2.2 Derivation or calculation of outcome variable

OS is calculated from the date of randomization to the date of death. Subjects who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

### 4.6.3 Objective response, disease control and duration of response

#### 4.6.3.1 Methods of assessment

The RECIST criteria will be used to perform the objective tumor assessments and determine a subject's PFS and best overall objective tumor response; details are given in Appendix E.

Baseline radiological tumor assessments should be performed within 21 days prior (but no more than 28 days prior) to the first dose of ZACTIMA/placebo, before study treatment, and at all time points defined in the study plan.

Previously irradiated lesions will not be considered measurable.

All measurable lesions, up to a maximum of 10 lesions and representative of all involved organs (maximum of 5 lesions per organ), should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or "present with progression".

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the eCRF in the same order as they were recorded at screening. Details of any new lesions will also be collected.

For subjects who have target lesions that have been subjected to local/regional radiotherapy for symptom control (palliative radiotherapy) during the course of the study the following rules will be applied. The subject will not be allowed a response of CR or PR following radiotherapy. The subject will be assessed for evidence of disease progression. If there is no evidence of disease progression, the subject can be assigned a response of stable disease.

A subject is determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions or the appearance of one or more new lesions (see Appendix E). Progression of target lesions is defined as at least a 20% increase in the sum of the LD of target lesions taking as references the smallest sum of LD recorded. Death will be regarded as a progression event in those subjects who die before documented disease progression. Unequivocal malignant disease identified on additional anatomical imaging e.g. CT or MRI or bone scan confirmed by x-ray, prompted by symptoms is considered disease progression and should be recorded as new lesions. If the Investigator is in doubt as to whether progression has occurred, particularly with respect to non-target lesions and the appearance of a new lesion then it is advisable to pursue treatment until the next scheduled visit, or earlier if felt appropriate by the Investigator (and then repeat the RECIST assessment to confirm progression).

Categorization of the objective tumor response assessments will be based on the RECIST criteria for target and non-target lesions. Response will be assigned as CR, PR, SD or progressive disease (PD) at each scheduled visit by the Investigator. For the purposes of analysis the sponsor will determine visit and overall response using the lesion assessments recorded on the eCRF.

It is important to follow the assessment schedule as closely as possible as PFS is the primary endpoint and biases in analysis can occur if 1 treatment group is examined more often or sooner than the other. If an unscheduled radiological and clinical tumor assessment is performed, and the subject has not progressed, the next scheduled tumor assessment should still be performed at the planned time (as detailed in the study plan). This is in order to minimize any unintentional bias caused by some subjects being monitored at a different frequency than other subjects.

Subjects who discontinue study treatment prior to objective disease progression should continue to have RECIST assessments every 6 weeks as per protocol schedule until progression is documented, unless the subject withdraws consent.

After discontinuation of the study treatment, and completion of the 30-day and 60-day follow-up visits, subjects should be followed for survival every 6 weeks, as outlined in the study plan, unless the subject withdraws consent. Adherence to the study plan should be observed whenever possible.

For subjects with objective response of CR or PR, confirmation of response by repeat imaging should be performed at the next scheduled RECIST visit at 6 weeks and not earlier than 4 weeks following date of response.

#### 4.6.3.2 Derivation or calculation of outcome variable

The overall best ORR will be calculated as the percentage of subjects with CR or PR. The DCR will be calculated as the percentage of subjects with CR or PR or SD ≥ 6 weeks.

DOR will be calculated for those subjects who have a best response of CR or PR only. DOR will be defined in two ways:

1. from date of randomization until the date of documented disease progression or death from any cause in the absence of documented progression, and

2. from the date of first documentation of response until date of documented disease progression or death from any cause in the absence of documented progression.

### 4.6.4 Pharmacodynamic biomarker measurements and variables

Blood plasma samples will be collected as outlined in the Study Plan and assessed for pharmacodynamic biomarkers. Archival tumor tissue will be collected from consenting subjects and assessed for pharmacodynamic biomarkers. Archival tumor tissue may be derived from tumor resections, tumor biopsies, pleural effusions, or other cytology samples, but should be presented as formalin fixed paraffin embedded blocks or slides. Pharmacodynamic biomarkers will be investigated for possible correlation with clinical outcomes (survival, response, and PFS) and for the effects of the study medication.

Since this is a rapidly evolving and complex area of investigation, and as yet not completely understood, pharmacodynamic biomarker data obtained in this study will not be definitive, but may generate hypotheses that are likely to require further testing in additional clinical studies.

#### 4.6.4.1 Methods of assessment

**Plasma samples**

Plasma will be prepared from venous blood (10 mL) collected at screening, at Day 1 of cycles 1 through 6, and at withdrawal (see Table 9 for details). Plasma protein levels of VEGF, bFGF and VEGFR2 will be determined. If the current assays become more sensitive, we will investigate other potential protein biomarkers associated with tumor angiogenesis in these plasma samples (see central laboratory manual for further details regarding sample collection, preparation and shipment).

| **Table 9** | **Blood plasma schedule for pharmacodynamic biomarker analysis** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening** | | **Cycle 1** | | | **Cycle 2** | | | **Cycle 3+** | | | **Discon-tinuatio n** |
| **Specimen Required** | **-21 – 0** | **-7 – 0** | **Day 1** | **Day 8** | **Day 15** | **Day 1** | **Day 8** | **Day 15** | **Day 1** | **Day 8** | **Day 15** | |
| VEGF, bFGF, VEGFR2 (Plasma) | | X[a] | | | | X | | | X[b] | | | X |

Abbreviations: bFGF = basic fibroblast growth factor; VEGF = vascular endothelial growth factor; VEGFR2 = vascular endothelial growth factor receptor-2

a – Plasma should only be taken on subjects who qualify at screening for entry into the study. Therefore, this assessment can be done anytime between screening and Day 1, as long as it is performed prior to first dose of study medication.

b – Cycle 3, Day 1 and Day 1 of cycles 4, 5 and 6

**Archival tumor samples**

In subjects where samples are available, archival, paraffin-embedded tumor samples should be collected for consenting subjects for analysis of (i) EGFR expression, and related signal transduction, proliferation and apoptosis markers, (ii) mutation status of the EGFR gene, (iii) gene amplification, and (iv) other related biomarkers (see central laboratory manual for further details regarding sample collection, preparation and shipment). Archival tumor tissue may be derived from tumor resections, tumor biopsies, pleural effusions, or other cytology samples, but should be presented as formalin fixed paraffin embedded blocks or slides.

**Genetics**

Refer to Appendix K for details.

#### 4.6.4.2 Derivation or calculation of outcome variable

Appropriate summaries of plasma sample data correlates with PFS and OS and appropriate summaries of tumor sample data correlates with PFS and OS will be produced.

### 4.6.5 Time to deterioration in patient WHO Performance Status (TDPS)

#### 4.6.5.1 Methods of assessment

WHO PS is recorded according to the study plan (see Tables 1, 2, and 3).

#### 4.6.5.2 Derivation or calculation of variable

Baseline WHO PS is defined as the measurement recorded closest to, but not subsequent to, the first dose of ZACTIMA/Placebo or docetaxel. At a given time point, deterioration in WHO PS is considered to be ≥1 change from baseline score.

TDPS is defined as the interval from the date of randomization to the first assessment of 'deterioration.'

If a deterioration of WHO PS has not been observed at the time of analysis, TDPS will be censored as of the last non-missing WHO PS assessment date.

## 4.7 Safety measurements and variables

The methods for collecting safety data are described below. For a complete list of the safety objectives and outcome variables, please see Table 8 in Section 4.6.

### 4.7.1 Adverse events

#### 4.7.1.1 Definitions

The definitions of AEs, SAEs, and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

All AEs will be graded according to the NCI CTCAE, Version 3.0.

Any events that are unequivocally due to progression of disease must not be reported as an AE.

**Adverse event**

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

For the purposes of this study, any detrimental change in a subject's condition subsequent to them entering the study and during the 60-day follow-up period should be considered an AE. When there is a deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that study treatment contributed to the deterioration or local regulations state to the contrary the deterioration should be considered a lack of efficacy. Signs and symptoms of disease progression are therefore not considered AEs.

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the subject into the clinical study.

**Serious adverse event**

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

**Any event or hospitalization that is unequivocally due to progression of disease must not be reported as an SAE.**

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the Investigator(s), who in completing the relevant eCRF must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?". For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes". SAE causality may be attributed either to docetaxel or ZACTIMA/placebo alone, to the combination of both drugs, or to neither drug. Toxicities that are expected with docetaxel in combination with placebo include hematologic, peripheral neuropathy, and fluid retention.

SAEs will be collected from the time of informed consent and will be followed up until resolution or up to 60 days after administration of the last dose of trial treatment.

**Other Significant Adverse Events**

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

**Deaths**

All deaths that occur during the study and follow-up period (both cancer-related and other) must be reported. All deaths except those due to unequivocal progression of disease that occur within the study period or within 60 days after the administration of last dose of study treatment must be reported to the study monitor for the purposes of SAE reporting. Deaths as a result of disease progression are not considered SAEs, but must be collected on the appropriate eCRF. The site should continue to follow all subjects for survival beyond the 60-day period after the administration of last dose of study treatment and collect information around the death on the appropriate eCRF.

An AE form should be completed for all deaths except those due to unequivocal progression of disease. The AE causing death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Death as a result of progression of disease alone should be reported to the study monitor at the next monitoring visit and should be documented on the relevant eCRF, but should not be reported as an AE or SAE.

#### 4.7.1.2 Recording of adverse events

AEs and SAEs will be collected throughout the study, from the time of informed consent until 60 days after the last administration of study treatment and will be followed up to resolution.

The following variables will be recorded for each AE: onset, resolution, action taken, outcome, causality (yes or no), and whether it constitutes an SAE or not. The NCI CTCAE, Version 3.0 grade should be recorded where applicable.

All AEs will be recorded on the eCRFs provided. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment, other treatment given, and follow-up tests) and outcome, should be provided along with the Investigator's assessment of causality (the relationship to the study treatment). AEs will also be graded according to the NCI CTCAE, Version 3.0, and changes tracked on the relevant eCRF.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE (see Appendix B for guidelines on interpretation of causality).

**(a) Disease progression**

Any events that are unequivocally due to progression of disease must not be reported as an AE.

**(b) Lack of efficacy**

When there is deterioration in the condition for which the study treatment is being used (i.e., NSCLC), there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that the study treatment contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

**(c) Abnormal laboratory values/vital signs**

The reporting of laboratory / vital signs abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:

- Any criterion for an SAE is fulfilled
- The laboratory / vital signs abnormality causes the subject to discontinue from the study treatment
- The laboratory / vital signs abnormality causes the subject to interrupt the study treatment
- The laboratory / vital signs abnormality causes the subject to modify the dose of study treatment
- The laboratory / vital signs abnormality requires intervention
- The Investigator believes that the abnormality should be reported as an AE

If an abnormal laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE and the associated laboratory result or vital sign should be considered additional information that must be collected on the relevant eCRF. AEs will be coded using the MedDRA.

A vendor to be selected by AstraZeneca will evaluate ECGs centrally, and results will be communicated to each site within 72 hours. If a QTc prolongation is recorded, the vendor will inform the Investigator and AstraZeneca within 24 hours. Any clinically significant abnormal findings and QTc prolongations during the treatment period will be recorded as AEs.

**(d) Overdose**

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

**(e) Pregnancy**

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

**(f) Handling unresolved AE/SAEs at completion/withdrawal**

All study-related toxicities and SAEs must be followed until resolution or for 60 days after the last administration of study treatment, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

AEs will be coded using the MedDRA.

#### 4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

Follow-up information on SAEs must also be reported by the Investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that become serious but which is not fatal or life-threatening a report should be received within 5 days.

The AstraZeneca representative will work with the Investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by Day 1 for all fatal and life-threatening cases and by Day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. The Investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca (see section 8.1).

### 4.7.2 Laboratory safety measurements and variables

A central laboratory vendor to be selected by AstraZeneca will be utilized for laboratory procedures.

#### 4.7.2.1 Methods of assessment

Routine hematology and biochemistry assessments will be performed at the central laboratory for the study center.

All subjects who have any CTCAE grade 3 or 4 laboratory values (NCI CTCAE, Version 3.0 Booklet, provided by AstraZeneca) at the time of withdrawal must be followed up until they have returned to CTCAE grade 1 or baseline, unless the values are not likely to improve because of the underlying disease. Additional samples may be taken, as clinically indicated.

The following laboratory parameters will be investigated. See Table 11 for total volume of blood samples to be collected.

**Table 10 Laboratory safety variables**

| Type of assessment | Variables |
|---|---|
| Hematology | hemoglobin, platelet count, WBC[a], APTT[b], INR[c] |
| Clinical chemistry | |
| Hepatic function | ALP, ALT, AST, total bilirubin |
| Renal function | BUN, creatinine |
| Other | Albumin, inorganic phosphate, magnesium, potassium, sodium, calcium, chloride, bicarbonate, total protein, glucose, LDH |
| Urinalysis | Proteins, blood, glucose |

Abbreviations: ALP = alkaline phosphatase; ALT = Alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransaminase; BUN = blood urea nitrogen; INR = International Normalized Ratio; LDH = lactate dehydrogenase; WBC = white blood cell count

a total, with manual or automated differentiation, according to study plan
b at screening only, unless subject is on anticoagulation therapy and requires additional evaluation
c at screening only, unless subject is on anticoagulation therapy and requires additional evaluation

#### 4.7.2.2 Derivation or calculation of outcome variables

Section 4.7.1.2 provides details on how AEs based on laboratory tests will be recorded and reported.

### 4.7.3 ECG, Vital Signs and physical examination

#### 4.7.3.1 12-lead ECG methods of assessment

A single 12-lead ECG must be performed at screening (within 21 days of first dose). The screening QTc must be <480 msec. If the single screening QTc is ≥480 msec (≥460 msec for subjects who are receiving one of the drugs listed in Appendix D, Table 2 –see Exclusion Criteria #18), then the Investigator has the option to perform up to an additional 2 ECGs so that a maximum of 3 ECGs (each at least 24 hours apart) may be obtained at screening. The QTc value used to determine eligibility would be the average of the QTc values obtained at screening. If a subject is receiving one of the medications in Appendix D, Group 2 prior to

study entry, and it cannot be discontinued before study treatment, then the screening QTc must be <460msec, and an additional ECG must be obtained 4-8 hours after the first dose of ZD6474.

Baseline QTc (using the Bazett's correction) will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1.

When possible ECGs should be performed at the same time throughout the study. ECGs must be performed 4-8 hours after the subject takes their oral medication on assessment day at Visits 3, 5, 8, 10 (weeks 2, 4, 7, 13), and then every 3 months until discontinuation of ZACTIMA/placebo. An additional ECG must be performed at discontinuation. If ZACTIMA/placebo has been discontinued, the ECG assessments are not required. In the event of QTc prolongation, the QTc will be re-evaluated within 48 hours with no less than 3 consecutive ECGs (within 5-10 minutes of one another). The criteria for QTc prolongation are:

- A single QTc value of ≥550 msec, or an increase of ≥100 msec from baseline;

**OR**

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs):
  - A QTc interval of ≥500 msec, but <550 msec;

    **OR**

  - An increase of ≥60 msec, but <100 msec from baseline QTc, to a value ≥480 msec

In the event of a QTc prolongation see Section 3.2.2.2.

PK sampling will be taken close to or at the same time as the ECGs. The time of each visit does not have to be exactly the same; only the assessment (i.e., ECG and PK) sample at a particular visit needs to be taken at the same time. Whenever possible the assessments should be carried out at the same time of day.

A vendor to be selected by AstraZeneca will evaluate ECGs. A cardiologist at the vendor will review all ECGs for the presence of QTc prolongation or other abnormalities, in particular any changes in the T-wave morphology that would suggest a higher likelihood for the development of any arrhythmia. Any clinically significant abnormal findings or QTc prolongations during this period will be recorded as AEs.

#### 4.7.3.2 12-lead ECG derivation or calculation of outcome variables

Any clinically significant abnormal findings observed and recorded during the treatment period will be recorded as AEs. The following parameters will be recorded for each ECG: date and time of ECG, heart rate (beats/min), QRS duration (ms), PR interval (ms), QT interval (ms), QTcB interval (ms), QTcF interval (ms), sinus rhythm (yes/no) and overall evaluation (normal/abnormal).

#### 4.7.3.3 Vital signs and physical examinations methods of assessment

Full physical examinations will be performed including height (screening only), weight, blood pressure, pulse, and temperature at the screening visit and as outlined in the study plan. Blood pressure should be measured after the subject has been sitting for 5 minutes.

Performance status will be assessed using the WHO criteria (Appendix C) at baseline and as outlined in the study plan. The same observer should assess performance status each time.

#### 4.7.3.4 Vital signs and physical examinations derivation or calculation of outcome variables

Any new conditions reported during the study will be recorded on the AE forms. Only those findings that are in addition to the condition being treated will be recorded as AEs, see Section 4.7.1.2 for reporting of AEs. Conditions that are considered by the Investigator to be unequivocally disease-related will not be recorded as AEs.

### 4.7.4 Other safety measurements and variables

Not applicable.

## 4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each subject in this study is as follows (based on Tables 1 and 3 only [additional samples may be required]):

**Table 11 Volume of blood to be drawn from each subject**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| Pharmacodynamic biomarkers | VEGF, VEGFR2 and bFGF | 10 | 7 | 70 |
| Pharmacokinetic | ZACTIMA | 7 | 5 | 35 |
| Safety | Clinical chemistry | 6 | 12 | 72 |
| | Hematology | 6.5 – Visit 1<br>2 – Visit 2 onward | 12 | 28.5 |
| Genetics (optional) | Genes | 10 | 1 | 10 |
| **Total** | | 25 – 39.5 | 36 – 37 | 205.5 – 215.5 |

The number of samples and total volume of blood are calculated on the basis of the subject completing 6 cycles. PK sampling will be conducted on 440 subjects and all Japanese subjects for a total of 580 subjects.
Abbreviations: bFGF = basic fibroblast growth factor; mL = milliliter; VEGF = vascular endothelial growth factor

If in the opinion of the treating physician there is a need for additional blood sampling, this may be undertaken as clinically indicated.

### 4.8.1 Analysis of biological samples

#### 4.8.1.1 Clinical chemistry samples

The analyte stability limits defined by the central laboratory vendor will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory vendor will not analyze samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central laboratory vendor may be amended in accordance with its Standard Operating Procedures. The central laboratory vendor will inform AstraZeneca of the stability limits relevant to this study before the first subject gives informed consent to take part in the study.

If the central laboratory vendor chooses to sub-contract the analytical work to another laboratory, the central laboratory vendor must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analyzed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first subject gives informed consent to take part in the study.

#### 4.8.1.2 Pharmacokinetic samples

The long-term stability of the analyte(s) should be documented in method validation produced by AstraZeneca DMPK. Results from analyses of samples stored longer than the time period for which stability has been demonstrated should not be reported unless complementary analyte(s) stability data is acquired and amended to the relevant method validation report. Stability of ZACTIMA has been documented for 12 months in work done by AstraZeneca. Samples stored for longer than 12 months will not be analyzed.

## 4.9 Genetic measurements and co-variables

Refer to Appendix K for details.

# 5. DATA MANAGEMENT

Data will be entered in the web-based data capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the Investigator Instructions Manual. The Investigator Instructions Manual will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to

a central database and changes tracked to provide an audit trail. When data have been entered reviewed, edited and Source Data Verification (SDV) performed the Principal Investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the eCRF will be archived at the study site.

Appropriate documentation will accompany the PK samples during shipment. The PK data (plasma concentrations) will be fully validated by the Drug Metabolism Pharmacokinetics (DMPK) at AstraZeneca, then sent in the form of a protected Excel spreadsheet directly to the study team programmer for loading into AstraZeneca's statistical analysis software (SAS).

The plasma concentration data and doses for the subjects will be tabulated by the study team programmer and forwarded to Clinical Pharmacokinetics, who will complete the derived parameters and return to the programmer for loading into SAS.

Unblinded PK and pharmacodynamic biomarker data will not be accessed by AstraZeneca staff affiliated with the conduct of the study prior to database lock.

## 5.1 Reporting of genotypic results

Refer to Appendix K for details.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before unblinding of the data.

## 6.2 Description of outcome variables in relation to objectives and hypotheses

Please refer to the table below for a description of the relationship between specific study objectives and outcome variables.

**Table 12 Objectives and outcome variables**

| Objective/outcome variable type | Outcome variable(s) |
|---|---|
| Primary/efficacy | PFS |
| Secondary/efficacy | ORR by RECIST |
| | Disease control |
| | DOR |
| | Overall survival |
| Secondary/PRO | LCS |

**Table 12 Objectives and outcome variables**

| Objective/outcome variable type | Outcome variable(s) |
|---|---|
| | FACT-L |
| | TOI |
| | TDS |
| Secondary/safety | Incidence, CTCAE grade and type of AEs, clinically significant laboratory abnormalities or changes in vital signs, and ECG changes |
| Secondary/PK | ZACTIMA: |
| | AUCss, Clearance, Cmax, Cmin |
| Secondary/PK-Pharmacodynamics | Exploration of the relationship between ZACTIMA exposure and measures of safety and efficacy |
| | Plasma levels of the N-desmethyl and N-oxide metabolites of ZACTIMA |
| Exploratory | Pharmacodynamic biomarkers |
| | VEGF, VEGFR2 and bFGF and other candidate proteins from plasma samples |
| | EGFR expression, gene amplification and mutational status from archived tumor samples |
| | Expression status and mutational status of other candidate genes from archived tumor samples |
| | K-ras mutational status |
| | SNP analysis |
| | Inpatient stays |
| | Outpatient visits |
| | EQ5D |
| | Vital signs |
| | WHO PS |
| | TDPS |
| | Subject weight |

Abbreviations: AE = adverse event; $AUC_{ss}$ = area under the plasma concentration-time curve; bFGF = basic fibroblast growth factor; $C_{max}$ = maximum concentration; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; EQ5D = EuroQoL 5 Dimension Instrument; FACT-L = Functional Assessment of Cancer Therapy for Lung Cancer; LCS = lung cancer subscale; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SNP = Single Nucleotide Polymorphism; TDPS = Time to deterioration in subject WHO PS; TDS = Time to deterioration of disease-related symptoms; TOI = Trial Outcome Index; VEGF = vascular endothelial growth factor; VEGFR2 = vascular endothelial growth factor receptor

## 6.3 Description of analysis sets

Efficacy data from this study will be analyzed on an intention-to-treat basis using randomized treatment. There will be two co-primary analysis populations: the first will comprise all subjects; the second will comprise all female subjects.

In addition, a per protocol analysis excluding significant protocol deviators will be carried out for the primary analysis of PFS and OS. This will be done for both co-primary analysis populations.

The safety data for this study will be summarized using treatment received. The analysis population will consist of all subjects who received at least one dose of ZACTIMA/placebo.

## 6.4 Method of statistical analysis

At the time of the final analysis of the primary endpoint of PFS, OS will also be analyzed.

The analyses for PFS, OS, TDS, and TDPS will be performed using the log-rank test (unadjusted model with treatment factor only) in the ITT population.

For PFS, OS, TDS, and TDPS, a Cox's proportional hazards regression model will also be performed as a secondary analysis. The model will allow for the effect of treatment and will also include terms for tumor stage, number of organs involved, prior Avastin failures, histology, smoking history, gender (except for the co-primary analysis population assessing female subjects only), ethnic origin, EGFR expression, EGFR gene amplification and EGFR mutation status. The conclusion will be based on the unadjusted analysis, which is considered as primary. If the unadjusted analysis and the adjusted analysis yield different results, the consequences of the covariate adjustment will be explored.

A global test for the presence of the treatment by baseline covariate interactions will be performed at the 1% level of significance by including all the 2-way treatment by baseline covariate interactions in the model. The assumptions of proportionality will also be investigated with a time-dependent exploratory variable, which is defined as treatment *{log(time to event)}. If the p-value from the Wald Chi-squared statistic for this variable is less than 5% there is evidence of a departure from the adjusted model assumptions. In this case, the reason will be explored and reported in the statistical text.

The comparison of treatments will be estimated using the HR together with the corresponding two-sided 97.5% confidence interval (CI) and p-value.

In addition, subgroup analyses will be performed on PFS and OS. The subgroups to be explored will be the same factors included as covariates in adjusted Cox's proportional hazard model, as described above.

PFS, OS, TDS, and TDPS will be summarized using Kaplan-Meier methods. Kaplan-Meier plots and Kaplan-Meier estimates of median time to event will be presented by randomized treatment group.

The primary analysis of ORR will be analyzed using logistic regression including treatment factor only. A secondary analysis will also be performed where the logistic regression model will allow for the effect of treatment and will also include terms for tumor stage, number of organs involved, prior Avastin failures, histology, smoking history, gender (except for the co-primary analysis population assessing female subjects only), ethnic origin, EGFR expression and EGFR mutation status. The conclusion will be based on the unadjusted analysis, which is considered as primary. If the unadjusted analysis and the adjusted analysis yield different results, the consequences of the covariate adjustment will be explored. The results of the analyses will be presented in terms of odds ratios together with associated CIs and 2-sided p-values. The estimates of the differences in the response rates and the corresponding 2-sided 97.5% CIs will also be presented.

Duration of response will be summarized in 2 ways (see Section 4.6.3.2) using the Kaplan-Meier method. Kaplan-Meier plots and Kaplan-Meier estimates of the median duration of response will be presented for the responders in each treatment group.

The focus of the statistical analysis of QoL assessments will be on the LCS and the TOI scores. Other QoL scores (individual subscales scores and the total FACT-L scores) will be summarized only. These analyses are exploratory in nature. Data will be summarized over time in terms of mean, median, standard deviation, minimum and maximum and number of subjects for each treatment group. Graphical displays will also be presented. For LCS and TOI scores, a mixed model using the repeated measures approach will be fitted to the data. The analysis will include all non-missing visit scores and the model will include terms for treatment, baseline score, time of assessment, tumor stage, number of organs involved, prior Avastin failures, histology, smoking history, gender, ethnic origin, EGFR expression and EGFR mutation status. The results of the analyses will be presented in terms of adjusted means for each treatment, estimated effect for the treatment comparison, associated CI and p-value. In addition, summary tables will be produced to investigate the relationship between TDS and duration of PFS.

WHO PS scores will be summarized over time for each treatment group using appropriate summary statistics. In addition, summary tables will be produced to investigate the relationship between TDPS and duration of PFS.

Safety and tolerability data will be presented by treatment received. Appropriate summaries of these data will be presented. Safety and tolerability will be assessed in terms of AEs, laboratory data, and ECG changes which will be collected for all subjects. Data from all cycles and treatment periods will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade), laboratory data and ECG data will be listed individually by subject and summarized by treatment received. For subjects who have a dose modification, all AE data (due to toxicity or otherwise) will be assigned to the initial treatment received group. ECG changes will be summarized for each treatment group.

Vital signs data will be listed for each subject and changes in vital signs will be summarized for each treatment group.

Please see Section 4.5.2 for a summary of the methodology to be used in the PK analysis.

## 6.5 Determination of sample size

The primary endpoint of this study is PFS. Two trials have been used to estimate the median PFS for docetaxel alone. Based on the Phase II, second-line, randomized trial, ZD6474IL/0006, assessing docetaxel alone versus docetaxel in combination with ZACTIMA 100 mg, a median time to progression of 3 months was observed for the docetaxel alone treatment arm. Similarly, based on the docetaxel study 317 (Shepherd et al, 2000) the median PFS in this study was also approximately 3 months for docetaxel alone. Therefore for the sample size estimation a median PFS of 3 months has been assumed for the docetaxel alone arm.

The final analysis of PFS will be performed when a minimum of 1176 events have been observed. The nominal 2-sided significance level for all analyses will be 2.5%, except for the primary endpoint of PFS and the secondary endpoint of overall survival, where the nominal significance level will be adjusted to approximately 2.44% to allow for a single interim analysis.

In order to detect a 25% prolongation of progression with >90% power, assuming a non-linear recruitment period of 19 months and a minimum follow-up of 3 months; i.e. the total length of trial is estimated to be 22 months to observe the required number of events, a minimum of 1380 subjects with locally advanced or metastatic (IIIb-IV) NSCLC after failure of 1$^{st}$ line anti-cancer therapy will be recruited. This equates to 3-week improvement in the median time to progression; i.e. a 3.75-month median PFS on the docetaxel in combination with ZACTIMA 100 mg arm.

Feasibility assessment in Japan suggests that 140 subjects can be recruited within the time-frame of the overall study. If the treatment effect in Japan differs from the treatment effect for subjects recruited outside of Japan such that there is a 25% prolongation of PFS for ZD6474 plus docetaxel compared to docetaxel alone in subjects recruited outside of Japan and a 25% deficit for subjects recruited in Japan (or vice versa), then a study which includes 140 subjects recruited in Japan and 1240 subjects recruited outside of Japan will have >80% power to detect this interaction at a 2-sided significance level of 10%. The recruitment of 140 subjects in Japan would represent approximately 10% of the overall total of 1380 subjects.

In the event of a treatment by country interaction with Japan, the power of the analysis to detect a 25% prolongation of PFS for subjects recruited outside of Japan would be >90%.

Chinese regulatory requirements state that 100 subjects per group are required to gain registration in this country. In the event of a treatment by country interaction with China, the power of the analysis to detect a 25% prolongation of progression would be >90% for subjects recruited outside of China.

In the event of a treatment by country interaction with both Japan and China the power of the analysis to detect a 25% prolongation of progression would be >80% for subjects recruited outside of Japan and China.

It is assumed that the ratio of female:male subjects in this study will be 1:1. In the co-primary analysis population assessing females there will be >90% power to detect a 37.5% prolongation of progression, assuming the same recruitment details as the overall population. This equates to a 4.875 week improvement in the median time to progression in female subjects; i.e. a 4.125 month median PFS on the docetaxel in combination with ZACTIMA 100 mg arm.

In the event of a treatment by country interaction with Japan, the power of the analysis to detect a 37.5% prolongation of progression would be >90% for female subjects recruited outside of Japan.

In the event of a treatment by country interaction with China, the power of the analysis to detect a 37.5% prolongation of progression would be >90% for female subjects recruited outside of China.

In the event of a treatment by country interaction with both Japan and China, the power of the analysis to detect a 37.5% prolongation of progression would be >80% for female subjects recruited outside of Japan and China.

Based on the docetaxel study 317 (Shepherd et al, 2000) and 320 (Fossella et al, 2000) the median OS in these studies were 7.5 months (n=55) and 5.7 months (n=125), respectively. Therefore it is estimated that the median OS in this study will be 6 months for docetaxel alone. The analysis of survival will be conducted at the time of the analysis of the primary endpoint of PFS. It is estimated that 850 events (deaths) will have occurred at this time, and the power to detect a 25% prolongation of survival would be >80%. This equates to a 1.5 month improvement in the median overall survival; ie a 7.5 month median OS on the docetaxel in combination with ZACTIMA 100 mg arm.

## 6.6 Interim analyses

The IDMC will review the study data every three months, and could recommend terminating the study at any stage if in the committee's judgment, the relationship between potential benefits and risks to subjects were to become unacceptable.

A single interim analysis to assess superiority of the PFS and overall survival endpoints will be performed when approximately 588 PFS events have occurred in the overall population. If exactly 588 events overall are reported at the time of the interim analysis, the nominal significance levels for these tests will be 0.14% (O'Brien et al, 1979, S+SEQTRIAL, 2002). The exact nominal significance level will be determined based on the exact number of events at the time of the interim analysis.

The statistician of the IDMC will perform the interim analysis and will present the results to the other members of the IDMC. The IDMC will then make a recommendation that the study be stopped, amended or continue unchanged.

## 6.7 Independent Data Monitoring Committee

This trial will use an external IDMC, comprising of at least 3 individuals who are not employed by AstraZeneca, and do not have major conflicts of interest. The remit and function of the IDMC is specified in Supplement 2.

# 7. STUDY MANAGEMENT

## 7.1 Monitoring

Before first subject into the study, a representative of AstraZeneca will visit the investigational study site to:

- determine the adequacy of the facilities
- discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the Investigator

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

- provide information and support to the Investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- perform SDV (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information and advice.

## 7.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including SDV. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her center.

## 7.3 Training of staff

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

## 7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be notified to or approved by each IRB or IEC, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular center's Informed Consent Form, then AstraZeneca and the center's IRB or IEC must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB or IEC is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each Principal Investigator(s), who in turn is responsible for the distribution of these documents to his or her IRB or IEC, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

## 7.5 Study agreements

The Principal Investigator at each center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

## 7.6 Study timetable and end of study

Before a subject's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- approval of the study by the IRB/IEC
- approval of the study, if applicable, by the regulatory authority

The approximate date of enrollment of the first subject is expected in March 2006 and the approximate date when the last subject is expected to have completed the study is February 2008. The Investigator will be notified by AstraZeneca when recruitment is completed. The end of study will be declared once a program has been established that allows all remaining subjects still receiving ZACTIMA study treatment to receive open-label supplies after the final analysis of the trial has occurred.

# 8. ETHICS

## 8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to AstraZeneca before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC annually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

For all countries except the US, AstraZeneca will provide IECs and Principal Investigators with safety updates/reports according to local requirements. For the US, each PI is responsible for submitting all safety updates/reports to the IRB for their study site.

## 8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

## 8.3 Informed consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The Principal Investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

## 8.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by subject number, study code, and subject initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IRB or IEC may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

# 9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

## 9.1 AstraZeneca emergency contact procedure

| Role in the study | Name | Address & telephone number |
|---|---|---|
| CST Leader responsible for the protocol at central R&D site | [redacted] | [redacted] |
| CST Physician responsible for the protocol at central R&D site | [redacted] | [redacted] |
| 24-hour emergency cover at central R&D site | [redacted] | [redacted] |
| The local AstraZeneca representative can be found in Supplement 1, 'Study Team Contacts in the Event of Emergency Situations, Overdose or Pregnancy' | | |

## 9.2 Procedures in case of medical emergency

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

## 9.3 Procedures in case of overdose

There is currently no known antidote to ZACTIMA. In the event of an overdose (> 1 dose within 24 hours), symptomatic and supportive care should be given, and all details should be recorded.

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRFs.

- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

- An overdose without associated symptoms should not be recorded as an AE in the eCRFs. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form"

In the event of an overdose of docetaxel, appropriate measures must be taken in accordance with the prescribing information of docetaxel

## 9.4 Procedures in case of pregnancy

In the event of pregnancy occurring while a subject is receiving ZACTIMA/placebo, the study drug should be discontinued and AstraZeneca should be contacted for advice.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

As for docetaxel, refer to the prescribing information.

# 10. REFERENCES

Beal, SL, and Sheiner, LB (1988-1998). NONMEM Users Guides. Part I-VIII. NONMEM Project Group C255, University of California at San Francisco.

Cella D, Bonomi A, Lloyd S, Tulsky D, Kaplan E, Bonomi P, et al. Reliability and validity of the Functional Assessment of Cancer Therapy - Lung (FACT-L) quality of life instrument. Lung Cancer 1995; 12:199-220.

Cella D, Eton D, Fairclough D, Bonomi P, Heyes A, Silberman C, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy - Lung (FACT-L) Questionnaire? Journal of Clinical Epidemiology 2002; 55:285-295.

Cella D, Tulsky D, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy Scale: Development and Validation of the General Measure. Journal of Clinical Oncology 1993; 11(3):570-579.

Ciardiello F, Caputo R, Damiano V, Caputo R, Troiani T, Vitagliano D, Carlomagno F, Veneziani BM, Fontanini G, Bianco AR, Tortora G. Antitumor effects of ZD6474, a small molecule vascular endothelial growth factor receptor tyrosine kinase inhibitor, with additional activity against EGFR tyrosine kinase. Clin Cancer Res 2003 Apr; 9(4):1546-56.

Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol 1995; 146:1029-1039.

The EuroQoL Group. EuroQoL – a new facility for the measurement of health-related quality of life. Health Policy 1990; 16 (3):199-208.

Fallowfield LJ, Baum M, Magquire GP. Do psychological studies upset patients? J of the Royal Society of Medicine, 80:59, 1987.

Ferrara N. Molecular and biological properties of vascular endothelial growth factor. J Mol Med 1999; 77:527-543.

Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285:1182-1186.

Fossella FV et al. Randomized Phase III Trial of Docetaxel Versus Vinorelbine or Ifosfamide in patients With Advanced Non-Small-Cell Lung Cancer Previously Treated With Platinum-Containing Chemotherapy Regimens. J Clin Oncol 2000; 18:2354-2362.

Gasparini G et al. Prognostic significance of vascular endothelial growth factor protein in node-negative breast carcinoma. J Natl Cancer Inst 1997; 89:139-147.

Hanahan D and Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996; 86:353-364.

Herbst R, Johnson DH, Mininberg E, Carbone DP, Henderson T, Kim ES, Blumenschein G, Lee JJ, Liu DD, Truong MT, Hong WK, Tran H, Tsao A, Xie D, Ramies DA, Mass R, Seshagiri S, Eberhard DA, Kelley SK, Sandler A. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/EGFR tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. Journal of Clincal Oncology 2005; 23:2544-2555.

Hurwitz H et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350(23):2335-42.

Kim KJ, Li B, Winer J, Armanini M, Gillet N, Phillips HS and Ferrara N. Inhibition of vascular endothelial growth factor induced angiogenesis suppresses tumor growth in vivo. Nature 1993; 62:841-844.

Leung DW, Cachianes G, Kuang WJ, Goeddel DV and Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989; 246:1306-1309.

Maeda K, Chung Y-S, Ogawa Y, Takatsuka S, Kang SM, Ogawa M, Sawada T and Sowa M Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. Cancer 1996; 77:858-863.

Millauer B, Shawver LK, Plate KH and Risau W. Glioblastoma growth inhibited in vivo by a dominant negative Flk-1 mutant. Nature 1994 Feb 10; 367:576-579.

Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47:207-14.

Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 1999 Jan; 13(1):9-22.

Niklinska W, Burzykowski T, Chyczewski L and Niklinski J. Expression of vascular endothelial growth factor (VEGF) in non-small cell lung cancer (NSCLC): association with p53 gene mutation and prognosis. Lung Cancer December 2001; 34 Suppl 2:S59-64.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-556.

S+SEQTRIAL 2 User's Manual, Insightful Corporation, Seattle, WA, 2002.

Sandler AB, Gray R, Brahmer J, Dowlati A, Schiller JH, Perry MC, Johnson DH. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) trial - E4599. Abstract No. LBA4. 2005 ASCO Annual Meeting Proceedings.

Shepherd FA et al. Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients With Non-Small-Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy. J Clin Oncol 2000; 18:2095-2103.

Shou Y, Hirano T, Gong Y, Kato Y, Yoshida K, Ohira T, Ikeda N, Konaka C, Ebihara Y, Zhao F and Kato H. Influence of angiogenetic factors and matrix metalloproteinases upon tumour progression in non-small-cell lung cancer. British Journal of Cancer 2001 (Nov 30); 85(11):1706-12.

Siemeister G, Martiny-Baron G and Marmé D. The pivotal role of VEGF in tumor angiogenesis: Molecular facts and therapeutic opportunities. Cancer Metastasis Rev 1998; 17:241-248.

Stacker SA and Achen MG. The vascular endothelial growth factor family: Signaling for vascular development. Growth Factors 1999; 17:1-11.

Therasse P Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. Journal of the National Cancer Institute 2000 Feb 2; 92(3):205-216.

Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 2002 Aug 15; 62(16):4645-55.