Local Clinical Study Protocol Amendment

Amendment Number	1 (United Kingdom)
Drug Substance	AZD9291
Study Code	D5160C00012
Protocol Dated	

A Phase I, Open-label, Non-randomised Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor) on the Pharmacokinetics of a Single Oral Dose of AZD9291 in Patients with EGFRm Positive NSCLC Whose Disease has Progressed on an EGFR TKI

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

Centres affected by the Amendment:

Centres in the United Kingdom

The protocol for the study is to be amended as follows:

Section of protocol affected:

List of appendices.

Previous text:

LIST OF APPENDICES

Appendix A Signatures

Appendix B Additional Safety Information

Appendix C IATA 6.2 Guidance Document

Appendix D Pharmacogenetics Research

Appendix E Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law

Appendix F Acceptable Birth Control Methods

Appendix G ECOG Performance Status Criteria

Appendix H Guidance Regarding Potential Interactions With Concomitant Medications

Revised text:

LIST OF APPENDICES

Appendix A Signatures **(Not applicable)**

Appendix B Additional Safety Information

Appendix C IATA 6.2 Guidance Document

Appendix D Pharmacogenetics Research

Appendix E Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law

Appendix F Acceptable Birth Control Methods

Appendix G ECOG Performance Status Criteria

Appendix H Guidance Regarding Potential Interactions With Concomitant Medications

Appendix I Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291

Reason for Amendment:

The list of appendices was updated to include Appendix I that has been added to the protocol. Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291 has been included in the protocol on the request of the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA).

Persons who initiated the Amendment:

AstraZeneca.

Section of protocol affected:

Section 6.7.1, Skin reactions, paragraph 1

Previous text:

Recommendations for appropriate management of skin reactions, including guidance on dose adjustments for clinically significant and/or intolerable skin reactions that are considered by the Investigator to be causally related to AZD9291 will be provided to Investigators.

Revised text:

Recommendations for appropriate management of skin reactions, including guidance on dose adjustments for clinically significant and/or intolerable skin reactions that are considered by the Investigator to be causally related to AZD9291 are **given in Appendix I.**~~will be provided to Investigators~~.

Reason for Amendment:

This change addresses the requirement for guidance on the management of skin reactions to be included in the protocol (Appendix I, Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291).

Persons who initiated the Amendment:

AstraZeneca.

Section of protocol affected:

Section 6.7.2, Diarrhoea, paragraph 1

Previous text:

Recommendations for appropriate management of diarrhoea, including dose adjustments for AEs of diarrhoea that are of CTCAE Grade ≥3 or that are clinically significant and/or intolerable and considered by the Investigator to be causally related to AZD9291, will be provided to Investigators.

Revised text:

Recommendations for appropriate management of diarrhoea, including dose adjustments for AEs of diarrhoea that are of CTCAE Grade ≥3 or that are clinically significant and/or intolerable and considered by the Investigator to be causally related to AZD9291, **are given in Appendix I**~~will be provided to Investigators~~.

Reason for Amendment:

This change addresses the requirement for guidance on the management of diarrhoea to be included in the protocol (Appendix I, Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291).

Persons who initiated the Amendment:

AstraZeneca.

Section of protocol affected:

Section 6.7.3, Worsening pulmonary symptoms, Paragraph 1

Previous text:

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca or representative study team should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters) will be sent to Investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study treatment permanently discontinued.

Revised text:

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca or representative study team should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters) will be sent to Investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study treatment permanently discontinued. **Recommendations for appropriate management of cases of ILD/pneumonitis are given in Appendix I.**

Reason for Amendment:

This change adds a reference to the guidance on the management of cases of interstitial lung disease/pneumonitis that is now included in Appendix I (Appendix I, Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291).

Persons who initiated the Amendment:

AstraZeneca.

Section of protocol affected:

New Appendix - Appendix I Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291.

Previous text:

Not applicable.

Revised text:

Guidance for the Management of Adverse Events in Studies using 80mg AZD9291

Skin Reactions

Diarrhoea

Ophthalmic Assessments

LVEF

ILD / Pneumonitis

A Guide for Investigators
Version 3.04:

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Contents

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Introduction

AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.

Clinical experience with 80mg AZD9291 has shown an association with the occurrence of dermatological adverse events (particularly rash and dry skin) and diarrhoea. The considerable majority of these events have been mild, transient events that have not always required treatment.

Based on experience with other EGFR and HER2 inhibitors, decreases in LVEF; anterior ocular effects and ILD/pneumonitis should be monitored for.

Some guidance is provided in this document regarding these events.

The purpose of these treatment guidelines is:

- To prevent tolerable adverse events becoming intolerable for the patient and leading to discontinuation of treatment.
- To promote consistency of treatment for specific adverse events across the AZD9291 clinical development programme.

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Skin Effects – Rashes & Acnes

- Skin effects may occur at any time, but most likely to start within 2 weeks of starting study treatment
- **Patients may consider applying over-the-counter moisturising cream to face, hands and feet twice daily from the start of study.**
- Treatment administered should be recorded in the **MED** module
- Any occurrence of a skin event should be recorded as an Adverse Event by completing the **AELOG** CRF, and the severity captured using the CTCAE(v4) grading system.
- Please also complete the **SKNREAC** CRF to record details of the rash. This will help future management of these events.
- AstraZeneca will be reviewing dermatological adverse events on an ongoing basis and may ask for additional information to be provided

You can request additional expert advice on management of dermatological reactions via AstraZeneca particularly if:

- A patient has not responded to dermatological intervention and permanent discontinuation of AZD9291 is being considered

Email:
Please provide anonymised

- description of reaction: time to onset, anatomical location, associated symptoms, dermatological interventions already implemented
- patient age, comorbidities and concomitant medications

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Skin Effects - Rash Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- **<10% body surface area (BSA)** papules/pustules
- with or without symptoms of pruritus or tenderness

Emollient cream application
and/or
Topical steroid moderate strength bid
and/or
Topical antibiotic bid

CTCAE(v4) Grade 2

- **10 to 30% BSA** papules/pustules with or without symptoms of pruritus or tenderness
- **psychosocial impact**
- **limiting instrumental activities of daily living (ADL)**

- Treatment same as Grade 1
- Consider using oral antibiotic for 6 weeks

CTCAE(v4) Grade ≥3

- **>30% BSA** papules/pustules with or without symptoms of pruritus or tenderness
- **limiting self-care ADL**
- **associated with local superinfection**

Topical steroid moderate strength bid
and
Oral antibiotic for 6 weeks
Switch to broad spectrum/gram negative cover if infection suspected (yellow crusts, purulent discharge, painful skin / nares)
Consider skin swab for bacterial culture

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Dry Skin / Xerosis Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- <10% body surface area (BSA)
- No associated erythema or pruritus

- Face/Hands/Feet: over-the-counter moisturising cream or ointment bid
- Body: ammonium lactate 12% cream bid or salicylic acid 6% cream bid

CTCAE(v4) Grade 2

- 10 to 30% BSA
- Associated with erythema or pruritus
- Limiting instrumental activities of daily living (ADL)

- Treatment same as Grade 1

CTCAE(v4) Grade ≥3

- >30% BSA
- Associated with erythema or pruritus
- Limiting self-care ADL

- Treatment same as Grade 1/2, plus:
- Eczematous areas of body: topical steroid moderate strength bid

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Pruritus Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- Mild or localised
- Topical intervention indicated

- Topical steroid moderate strength bid or topical antipruritic bid

CTCAE(v4) Grade 2

- Intense or widespread
- Intermittent
- Skin changes from scratching (e.g. oedema, papulation, excoriation, lichenification, oozing/crusts)
- Oral intervention indicated
- Limiting instrumental ADL

- Topical steroid moderate strength bid or topical antipruritic bid
- Oral antihistamine

CTCAE(v4) Grade ≥3

- Intense or widespread
- Limiting self-care ADL or sleep
- Oral corticosteroid or immunosuppressive therapy indicated

- Oral antihistamine
- GABA agonist (gabapentin 300 mg or pregabalin 50-75 mg every 8 hours)

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Paronychia Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- Nail fold oedema or erythema
- Disruption of the cuticle

- Topical antibiotic bid and vinegar soaks#

CTCAE(v4) Grade 2

- Localised intervention indicated
- Nail fold oedema or eythema with pain
- Associated with discharge or nail plate separation
- Limiting instrumental activities of daily living (ADL)

- Topical antibiotic bid and vinegar soaks#
- Topical silver nitrate weekly

CTCAE(v4) Grade ≥3

- Surgical intervention or IV antibiotics indicated
- Limiting self-care ADL

- Topical antibiotic bid and vinegar soaks#
- Topical silver nitrate weekly
- Consider nail avulsion / removal

Soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day

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Key Points for Dermatological Guidance

- Patients may consider applying over-the-counter moisturising cream to face, hands and feet bid from the start of study.
- Investigators may consider issuing a prescription for topical treatment to patients. However, topical steroids and topical or oral antibiotics should not be implemented prophylactically and treatment should only be started when confirmed with Investigator.
- **As soon as an acneiform / papulopustular rash occurs, treatment with moderate strength topical steroids and antibiotics should be implemented.**
- Use of topical benzoyl peroxides and other irritating anti-acne agents should be avoided.
- **Patients should be instructed to contact the site if the skin reaction changes (e.g. if it spreads or becomes painful)**
- Investigators should record skin effects in the **AELOG** and **SKNREAC** CRF modules.
- The occurrence of non-papulopustular skin reactions should be treated appropriately, as defined by the treating physician, and in consultation with a dermatologist where necessary
- Photographs of skin reactions should be sent to the AstraZeneca study team, which may be used for external expert dermatological review if required.

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Diarrhoea Treatment Guidance

Uncomplicated CTCAE (v4) Grade ≤2 diarrhoea:

- Dietetic measures:
  - Stop all lactose-containing products
  - Drink 8 to 10 large glasses of clear liquids per day
  - Eat frequent small meals
  - Recommend low fat regimen enriched with rice, bananas, and apple sauce
- Pharmacological treatment:
  - Administer loperamide: initial dose 4mg, followed by 2mg every 4 hours or after every unformed stool.
  - Grade 1 intermittent diarrhoea may not require treatment
  - Consider continuation of loperamide until diarrhoea-free for 12h
  - Consider electrolyte replacement, as appropriate

CTCAE (v4) Grade ≥3 or any Grade with complications (dehydration, fever and/or Grade ≥3 neutropenia):

- Dietetic measures:
  - As per Grade ≤2 diarrhoea
- Pharmacological treatment:
  - As per Grade ≤2 diarrhoea
  - If dehydration is severe, administer octreotide and use intravenous fluids as appropiate.
  - Consider prophylactic antibiotics, especially if diarrhoea is persistent beyond 24h or there is fever or Grade 3-4 neutropenia
  - Consider electrolyte replacement, as appropriate, and consider more frequent measurement of electrolytes until AE resolves

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Advice for Patients: Skin Reactions and Diarrhoea

- It is important that patients are fully informed that skin reactions or diarrhoea may occur during treatment with AZD9291
- Patients should be informed that skin reactions and diarrhoea:
  - Are not contagious
  - Do not result from allergy to treatment
- Patients should be encouraged to report any instances of skin reaction or diarrhoea as soon as they arise so that appropriate treatment can be promptly initiated
- Patients should be instructed to contact the site if a skin reaction changes (e.g. if it spreads or becomes painful)
- It may be beneficial to avoid irritating skin products (e.g. irritating soaps, products containing retinol or retinoic acid)
- Camouflage make-up (non-comedogenic or non-pore blocking) can be used during study treatment

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Introduction – Ophthalmic Assessments

AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.

There have been no keratitis or ulcerative events with **clinical experience with AZD9291**, but an association between the use of other EGFR TKIs and the occurrence of ophthalmic adverse events has been reported.[1]

As a result, AstraZeneca has chosen to include the following in the clinical study:

- baseline slit-lamp assessments for all patients
- follow-up assessments for those patients reporting any clinically significant and/or persistent ophthalmic symptom

The purpose of these guidelines is to:

- provide guidance on when to perform follow-up ophthalmic assessments
- promote consistency of assessment across the study

[1] Tullo et al., Eye, 2005; 19:729-738

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Ophthalmic Assessments

Baseline

- Slit lamp examination performed by an ophthalmologist (or appropriately qualified individual)
- Date of assessment should be recorded on the **VISUAL** CRF
- Results should be recorded in the patient's notes

Follow-up

- If the patient reports any eye symptoms during treatment with AZD9291 or if signs are observed during a study visit, the Investigator should perform a clinical examination including a repeat best corrected near and distant visual acuity assessment if appropriate
- Findings should be documented in the patient's notes

Referral to Ophthalmologist

- Patients with ophthalmic AEs of CTCAE Grade ≥ 3 or eye symptoms that are clinically significant and/or persistent (>7 days) should be referred to the ophthalmologist. For example:
  - Deterioration in near or distant visual acuity by more than one level
  - Persistence or worsening of:
    - Burning/ irritation/ smarting
    - Itching
    - Redness with or without discharge
    - Light sensitivity (photophobia)
    - Blurred vision
- Ophthalmology examination findings should be documented in the patient's notes and reported to AstraZeneca if required

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Post-baseline Ophthalmic Findings

- Any clinically significant post-baseline ophthalmic findings, including those confirmed by the ophthalmologist, must be recorded as an Adverse Event by completing the **AELOG** module, and the severity captured using the CTCAE(v4) grading system.

- In addition, a report should be provided to AstraZeneca detailing:
  - ophthalmic examinations performed
  - findings
  - photographic record of appropriate findings

- Treatment administered should be captured on the **MED** CRF

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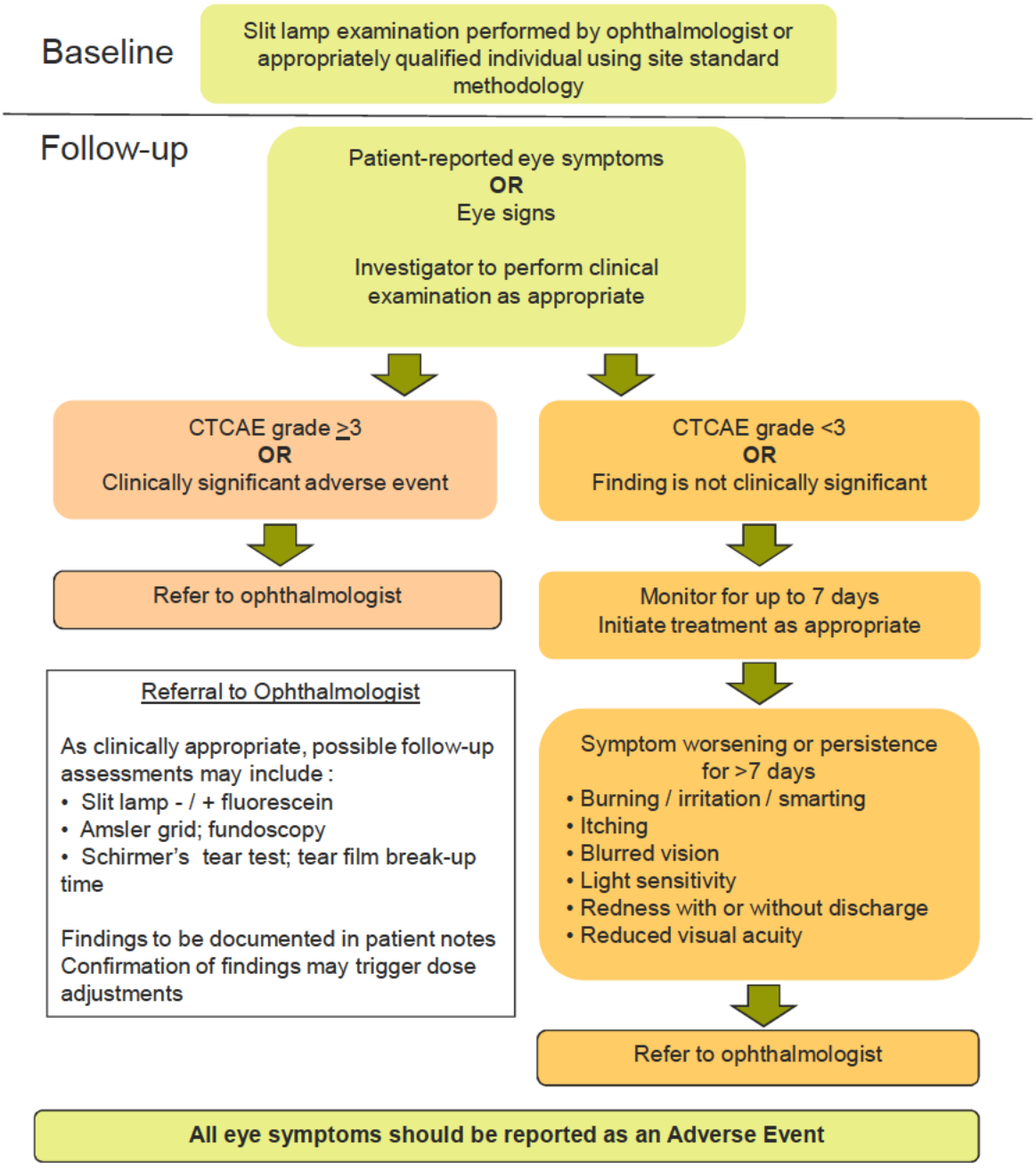
Ophthalmic Assessments Flow Chart



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Guidance on Ophthalmic Dose Adjustments

Confirmed CTCAE Grade ≥3
OR
clinically significant or persistent (present for >7 days) Adverse Event
and considered causally related to AZD9291

Initiate ophthalmic treatment as appropriate and withhold dose for up to 3 weeks

- **If adverse event improves to CTCAE Grade ≤1 within 3 weeks reinstate AZD9291 at the current dose maintaining treatment as appropriate**
- **If adverse event improves to CTCAE Grade 2 within 3 weeks, consider reinstating AZD9291 at a reduced dose* (1 dose level) maintaining treatment as appropriate**
- **Where a CTCAE Grade ≥3 or clinically significant or persistent adverse event does not improve to a lower CTCAE Grade within 3 weeks of AZD9291 interruption, AZD9291 should be permanently discontinued.**

*** Note dose reduction requirements in CSP**

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Summary of Ophthalmic Guidance

- It is important that patients are fully informed that ophthalmic events may occur during treatment with AZD9291.
- AZD9291 should not be administered on the first scheduled day if the patient has any clinically significant eye symptoms.
- Patients should be encouraged to report any instances of ophthalmic symptoms and/or vision changes to allow the appropriate treatment to be initiated. Symptoms may include:
  - Burning / itching / irritation / smarting
  - Redness with / without discharge
  - Blurred vision
  - Light sensitivity
- Patients who wear contact lenses must discontinue wearing them if they have any mild to moderate eye symptoms (CTCAE grade ≤2) until at least one week after symptoms have resolved.
- Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after AZD9291 has been permanently discontinued.
- If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events they must discontinue wearing their contact lenses until at least one week after treatment with AZD9291 is permanently discontinued.
- **Ulcerative events must result in permanent discontinuation from study**

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LVEF Guidance

- AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.

- AZD9291 and its active metabolite may also inhibit HER2. For this reason, LVEF measurements are being taken at baseline and every 12 weeks to monitor for potential decreases in LVEF.

- For high quality data and best assessment of risk:
  - The same method must be used for each patient (i.e. ECHO throughout, or MUGA throughout)
  - Please use the same machine for each assessment
  - Wherever possible, the scans must be performed by the same operator

- Consult cardiologist or AstraZeneca for abnormal LVEF results, at the Investigator's discretion

- *ad hoc* measurement of LVEF should be performed if the investigator has clinical suspicion of new onset impaired cardiac function

- Patients are to be managed clinically according to local practice

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ILD / Pneumonitis Guidance

- AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.

- A number of unconfirmed pneumonitis like events have been seen in patients dosed with 80mg AZD9291. Causality has not been established.

- If you have clinical suspicion of interstitial lung disease (ILD), dosing with AZD9291 should be interrupted whilst further investigations are performed.

- Please complete the eCRF and inform AstraZeneca as soon as a potential pneumonitis event is identified. The Study Team will send a pneumonitis questionnaire to you, in order to collect more information about the event for full review and reporting.

- All Imaging conducted throughout the study (including High Resolution CTs (HRCT) at time of pneumonitis diagnosis and follow up) will be requested to be sent to AstraZeneca for independent review.

- A diagnostic workup (including HRCT, blood and sputum culture, laboratory parameters) should be performed, to exclude conditions such as lymphangitic carcinomatosis, infection, allergy or pulmonary haemorrhage.

- In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

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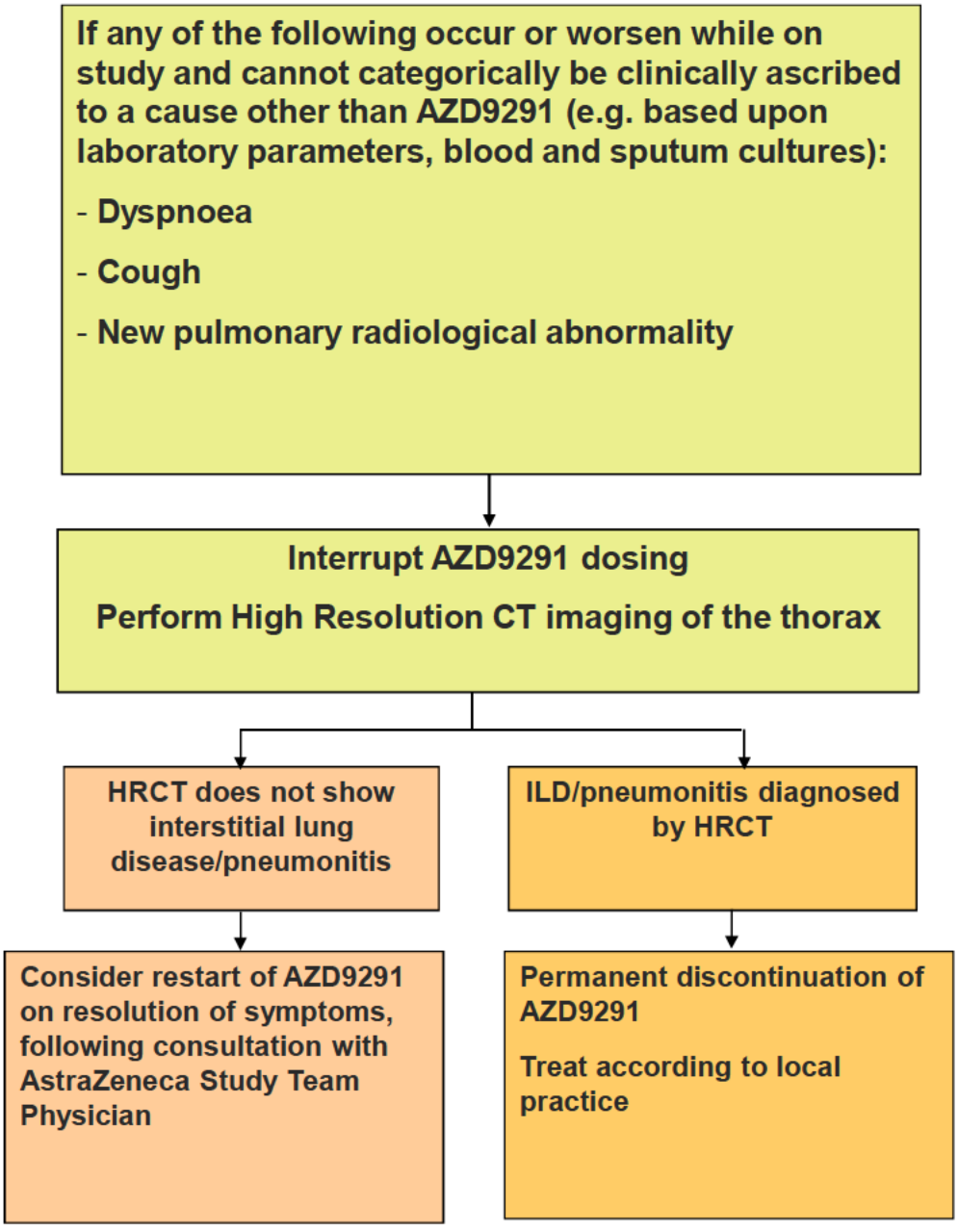
ILD & Pneumonitis Guidance



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Reason for Amendment:

This change addresses the requirement for guidance on the management of skin reactions and diarrhoea to be included in the protocol (Appendix I, Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291).

Persons who initiated the Amendment:

AstraZeneca.

Clinical Study Protocol Local Amendment No 1
Appendix A (United Kingdom)

Drug Substance	AZD9291
Study Code	D5160C00012
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase I, Open-label, Non-randomised Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor) on the Pharmacokinetics of a Single Oral Dose of AZD9291 in Patients with EGFRm Positive NSCLC whose Disease has Progressed on an EGFR TKI

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment..

AstraZeneca Research and Development site representative

Signing on behalf of:

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

SIGNATURE OF NATIONAL CO-ORDINATING INVESTIGATOR

A Phase I, Open-label, Non-randomised Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor) on the Pharmacokinetics of a Single Oral Dose of AZD9291 in Patients with EGFRm Positive NSCLC whose Disease has Progressed on an EGFR TKI

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

International Co-ordinating Investigator:

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