Clinical Study Protocol	
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A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 mutation

Sponsor: Dizal (Jiangsu) Pharmaceutical Co., Ltd

Regulatory Agency Identifier Number(s)

IND: NCT03974022

EudraCT: 2019-003126-25

Dizal Research and Development Site Representative Signature

	Signature	Date
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Version History

Version 12.0, July 24, 2023
Summary of major changes from the previous version: 1) **Section 2.3.5 Clinical information of DZD9008, Section 3.2.2 Rationale for Part B, Dose Extension of DZD9008** and **Section 5.2.1 Potential benefit**: Clinical data are updated in accordance with Investigator's Brochure (IB) revision. 2) **Section 3.1 Overall study design and flowchart** and **Section 5.1 Treatment**: Supplementary information (including sample size and treatment) of the Part B optimal cohort is specified upon review and approval from IEC/IRB and/or local regulatory authority (as applicable) on the optimal RP2D selection. 3) **Section 4.2 Exclusion Criteria:** Per Canadian regulatory requirement to exclude mean resting corrected QT interval (QTc): > 470 msec for women or > 450 msec for men, obtained from 3 electrocardiograms (ECGs) at screening (Canada only). 4) **Section 5.1.5 Toxicity management and dose modification and Section 5.3 Discontinuation of investigational product and withdrawal from the study:** Per Canadian regulatory requirement to specify conditions on AE leading to permanent discontinuation and continuation of treatment beyond disease progression. 5) **Section 6.3.1 Enrolment and screening**: Added that subjects who have failed previous screening are permitted to be re-screened for once. 6) **Section 7.8 Analysis sets and Table 10 Analysis set definition:** • Definition of full analysis set was updated according to inclusion criteria to be "All randomized NSCLC patients with documented EGFR Exon20ins mutation in tumor tissue who were previously treated with platinum-based chemotherapy, received at least 1 dose of DZD9008 and have measurable disease at baseline as identified by IRC (applicable for Part B only)". 7) **Table 14 Study Plan of Part B Dose Extension:** Survival follow up is clarified to be performed within a visit window of ± 7 days. 8) **Appendix I (ophthalmic assessments):** Per Canadian regulatory requirement to advise patients referral to the ophthalmologist for AE management.

Version 11.0, December 21, 2022
Summary of major changes from the previous version: 1) **Section 1 Study objective:** The term '.a central laboratory confirmed diagnosis of..' was deleted to clarify the mutation diagnosis requirement for Part B.

2) **Section 2.1 Background of NSCLC** and **Section 3.2.2 Rationale of Part B:** These sections were updated to clarify current development of EGFR Exon20ins inhibitor treatment.
3) **Section 2.3.4 The key findings from Nonclinical toxicity studies:** Additional new data were provided to reveal no toxicity findings when dosing duration was extended.
4) **Section 2.3.5 Clinical information of DZD9008**: Food effect PK data were updated and added with a referral to the Investigator's Brochure (IB) for details.
5) **Section 3.2.2 Rationale of Part B, Dose Extension of DZD9008** and **Section 6.6.1 Exploratory analyses:** Name of Sponsor designated central laboratory in mainland China was added per regulatory requirement.
6) **Section 4.1.1 Core inclusion criteria:**
   - Criterion 7: The requirement of no evidence of progression was updated to provide clarity on at least 2 weeks after CNS-directed treatment as ascertained by clinical examination and brain imaging.
   - Criterion 8: Per updated safety risk assessment, the requirement was updated to creatinine $\leq$ 1.5 x ULN, or creatinine clearance $\geq$ 50 mL/min as measured or calculated by the Cockcroft-Gault method or others based on local practice.
7) **Section 4.1.2.2 Part B specific cohort inclusion criteria:**
   - To align with target population for drug launch, the requirement is updated for Part B subjects to have progressed on, or be intolerant of, at least one prior line with platinum-based chemotherapy.
   - Duplicated France specific requirement on therapy type of treatment in prior lines were deleted as it would be covered under newly changed requirement.
8) **Section 4.2 Exclusion criteria:**
   - Criterion 1: A typo in drug name: BDTX-198 was corrected. The exclusion was also added with patients who previously treated with furmonertinib which is an EGFR exon20ins inhibitor under development. Per updated clinical DDI study data, the required washout time was shortened for medications known to be potent inhibitors or inducers of CYP3A to within 1 week or 2 weeks respectively.
   - Criterion 4: To respect local practices for COVID-19, requirement of performing COVID-19 antigen testing to suspected subjects was removed.
   - Previous Criterion 14: Per updated safety risk assessment, the requirement "Requires anticoagulation and anti-platelet therapy, i.e., with warfarin, heparin etc." was removed.
   - Previous Criterion 15 had the order number updated to current Criterion 14 and variant spelling of hemorrhage was corrected.
   - Previous Criterion 16 had the number updated to current Criterion 15.
9) **Section 4.3 Restrictions** and **Section 5.2.2.10 Hemorrhage:** Safety management was added that subjects receiving anticoagulation or anti-platelet therapy while receiving DZD9008 should be monitored for any signs of bleeding.

10) **Section 4.3.1 Concomitant treatment** and **Section 5.2.2.9 CYP450 induction/inhibition:** Per updated food effect data, the washout period of CYP3A4 inducers and inhibitors was updated.
11) **Section 5.1 Treatment:** Per updated pharmacokinetics data, the accepted window for subject to take the missed dose was extended to 12 hours.
12) **Figure 3 Dose modification for toxicity related to DZD9008:** The figure was updated to clarify subjects either resuming same dose or at one dose level lower after dose interruption due to same AE in the past would have the exceptions to those already at the lowest possible dose.
13) **Section 6.3.3 Vital sign:** To respect local practices, siting position was added for measuring blood pressure and pulse rate.
14) **Section 6.4.4 Reporting of serious adverse events:** All SAEs was clarified to be recorded in both CRF and paper SAE form (Clinical Safety Event Report).
15) **Section 6.6.1 Exploratory analyses to support companion diagnostics development:**
    - This section was updated to clarify mutation test in Part B used in Sponsor designated central laboratory being developed as companion diagnostics for DZD9008.
    - All Part B patients being asked to provide plasma samples was clarified to be at screening.
    - Study Plan for reference was corrected to Table 14 Study Plan of Part B Extension (from previous Table 13).
16) **Section 6.6.2.1 Achieved tumor tissue or fresh biopsy for exploratory biomarker research:**
    - Duplicated reference to laboratory manual were deleted.
    - Sampling schedule in Part A had reference to Table 14 deleted as it was not applicable.
17) **Section 6.6.2.3. Blood sampling for other exploratory biomarker study**, **Table 14 Study Plan** and **Table 18 Lab visits and clinical monitoring:**
    - Based on tumor evaluation schedule, for Part B only, the blood samples collection plan was adjusted accordingly to be on Day 1 of each following odd Cycle (i.e., from previously even) until disease progression and updated table content.
    - Clarification on the exact subsequent sampling Cycle in both Part A and Part B was added.
    - Duplicated information of data be reported separately and not included in the Clinical Study Report was deleted as it had already been covered in **Section 6.6 Exploratory research**.
18) **Section 6.7.2 Handling, storage and destruction of biological samples** and **Section 6.7.2.4 Samples for pharmacogenetic study:** Maximum time for samples retention was clarified as to align with local regulatory requirements.

19) **Section 7.3 Calculation or derivation of safety variables:** Creatinine clearance calculation was updated with clarity that it can be done per local practice.
20) **Section 7.8 Analysis sets** and **Table 10 Analysis set definition:**
    - Definition of full analysis set was updated according to inclusion criteria to be "All randomized NSCLC patients with documented EGFR Exon20ins mutation in tumor tissue from a local CLIA certified laboratory who were previously treated with platinum-based chemotherapy, received at least 1 dose of DZD9008 and have measurable disease at baseline as identified by IRC (applicable for Part B only)".
    - Centrally confirmed EGFR Exon20ins analysis set was separated into two sets and re-named by tumor tissue and by plasma ctDNA with updated definition.
21) **Section 7.9.7 Efficacy**: Per new definition of analysis sets, the previous sensitivity analysis was updated to clarify as efficacy analysis in centrally confirmed EGFR Exon20ins by tumor tissue and by plasma ctDNA respectively.
22) **Section 7.9.7.2 Duration of response:** Analysis population was added with clarity to be in Part A and in FAS of Part B.
23) **Section 7.9.7.4 Progression free survival** and **Section 7.9.7.5 Overall survival:** Descriptions on survival analysis techniques was removed as it is not applicable.
24) **Section 7.9.7.5 Overall survival:** Analysis population was updated with clarity to be FAS of Part B only.
25) **Section 8.1 Medical emergencies and Sponsor contacts:** Contact person details were updated.
26) **Section 8.2 Overdose:** Reporting time for other overdoses was deleted to avoid confusion.
27) **Table 11 - 14 Study Plan:** Footnote for requirement on COVID-19 antigen testing for suspected COVID-19 infectious subjects was removed to respect local practices for COVID-19.
28) **Table 14 Study Plan of Part B Dose Extension** and **Table 18 Lab visits and clinical monitoring (Part B dose extension):** Per regulatory requirement on safety monitoring, footnote was updated for collecting additional serum or urine samples for pregnancy testing (Italy only).
29) **Table 16 Lab visits and clinical monitoring (Part A dose expansion):** Inconsistency to main text for PK sampling at pre-dose on C1D8 and C1D15, and at 3hr post-dose on C1D1 and C2D1 was filled out to correct.
30) **Table 18 Lab visits and clinical monitoring (Part B dose extension):** Inconsistency to main text for PK sampling at pre-dose on C4 onwards D1 was filled out to correct.
31) **Appendix A Signature:** The statement for investigators' signature included within the protocol to maintain consistency.

32) **Appendix H Guidance Regarding Potential Interactions with Concomitant Medication:** Per clinical DDI study data, CYP3A4 metabolism and withdrawal period required prior to DZD9008 administration was updated.

Version 10.0, April 18, 2022

Summary of major changes from the previous version:

1) Section 1.1.2.2: secondary study objectives of Part B
   - Added endpoint/variable "DZD9008 metabolite concentration" to characterize the PK of DZD9008
   - Removed "to assess the effect of DZD9008 on patients' disease related symptoms and health related quality of life (HRQoL)" and endpoint/variable "the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaires" from secondary objectives.
2) Section 3.2.1 study design rationale: added "In Part A, radiological scans (including those at unscheduled visits, or outside visit windows) for patients with EGFR Exon20ins will be collected on an ongoing basis."
3) Section 3.2.2 study design rationale: updated enrollment of Part B NSCLC patients with EGFR Exon20ins which has been confirmed in a local CLIA-certified laboratory (or equivalent) or Sponsor designated central laboratory" and the description of tumor sample handling procedure.
4) Section 4.1.1 in the inclusion criteria:
   - Removed the restriction of ≥ 20 age for Japanese subjects.
   - Updated a time window of ≥ 2 weeks and ≥ 4 weeks is required respectively if BM has been treated with radiation or surgery.
5) Section 4.1.2.2 in Part B specific cohort inclusion criteria:
   - Updated mutation type confirmation for enrollment: "Patients must have histologically or cytologically confirmed locally advanced or metastatic NSCLC with documented EGFR Exon20ins mutation in tumor tissue from a local CLIA-certified laboratory (or equivalent) or Sponsor designated central laboratory. prior to the study entry".
   - Added the requirement on previous lines of treatment "The prior lines of treatment must include at least one platinum-based chemotherapy associated to an anti-PD-(L)1 therapeutic antibody" (France only)
6) Section 4.2 in the exclusion criteria:
   - Added mean resting corrected QT interval (QTc): > 470 msec for women or > 450 msec for men, obtained from 3 electrocardiograms (ECGs) at screening (France only).
7) Section 4.3.1: limited the restriction of blood transfusions and hematopoietic growth factors during the screening phase to Part A escalation only.

8) Section 5.1.5: clarified the AE related dose reduction and permanent discontinuation (France only)
9) Section 5.1: added the criteria for continuing treatment post progression (France only): (a) Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values) ; (b) Stable ECOG PS; (c) Absence of rapid progression of disease or of progressive tumor at critical anatomical sites that requires urgent alternative medical intervention; (d) Investigators must inform subjects that this practice is not considered standard in the treatment of cancer.
10) Section 6.3.4: added description of pregnancy test criteria for female subjects of childbearing potential (Italy only).
11) Section 6.5.2: added samples for determination of metabolite DZ0753 concentrations in plasma to be analyzed.
12) Section 6.9, 7.6.1, 7.9, Appendix J: removed the description and calculation for the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaires and removed previous Table 10 Visit Response for disease related symptoms and HRQoL.
13) Section 7.2.2: clarified determination of sample size in Part B extension cohorts.
14) Section 7.8 previous Table 11 (current Table 10) Analysis Set Definition:
    - updated the definition of full analysis set as “all randomized NSCLC patients who receive at least 1 dose of DZD9008 and have measurable disease at baseline as identified by IRC (applicable for Part B only)”
    - added definition of centrally confirmed EGFR Exon20ins analysis set as “all patients in full analysis set with EGFR Exon20ins mutations confirmed by central laboratory (applicable for Part B only)”.
15) Section 7.10: added the publication policy (Spain only).
16) Previous Table 15 (current Table 14) Study Plan of Part B Dose Extension: removed the schedule for the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaires.
17) Previous Table 15 (current Table 14) Study Plan of Part B Dose Extension and Table 19 (current Table 18) Lab visit and clinical monitoring (Part B dose extension): added the footnote clarification of collecting additional serum or urine samples for pregnancy testing (Italy only).
18) Appendix H: updated guidance regarding potential interaction with concomitant medication
19) Appendix I: updated advice for patients with CTCAE grade ≥ 2 ophthalmic AEs be referred to the ophthalmologist (France only).

Version 9.0, July 14, 2021
Summary of major changes from previous version: 1) Introduction: updated clinical study data to the cut-off date of 3 April 2021.

2) Section 1.1.2.3: added "To collect and store plasma samples to isolate circulating free tumor DNA (ctDNA) for EGFR Exon20ins mutation testing and necessary technical studies, for liquid biopsy companion diagnostic development and approval" to exploratory objectives.
3) Section 2.3.5: updated clinical study data to the cut-off date of 3 April 2021.
4) Section 6.3.5.1: added Cycle 1 Day 8 and Cycle 1 Day 15 into the ECG testing schedule.
5) Section 6.6.1: added the description of collecting plasma samples for liquid biopsy companion diagnostics development.
6) Section 7.1: added exploratory endpoints to Part B:
   - Collect and store tumor samples for diagnostics development and potential future exploratory research that may influence the development of DZD9008 (exploratory).
   - To collect and store plasma samples for EGFR Exon20ins mutation testing and necessary technical studies for liquid biopsy companion diagnostic development and approval (exploratory).
   - To collect and store blood-based samples for future exploratory research on genes/genetic aberrations that may influence response to DZD9008 treatment and/or susceptibility to DZD9008 (exploratory).
   - To collect and store blood sample for future exploratory research into genes/genetic variation that may influence PK or response to DZD9008 (Pharmacogenetics study, exploratory).
7) Table 15: added plasma sample collection for liquid biopsy companion diagnostic development; added Cycle 1 Day 8 and Cycle 1 Day 15 into the ECG assessment.

Version 8.0, April 29, 2021

Summary of major changes from previous version:

1) Study flow chart: added the Part A expansion cohort 6 (NSCLC with EGFR Exon20ins, previously treated with Amivantamab, dosing at 300 mg with low-fat meal); Part B extension was updated to have 2 dose cohort (dosing at 200 mg and 300 mg DZD9008 separately) for previously treated NSCLC with EGFR Exon20ins.
2) Section 1.1.2.2: updated the secondary study objectives of Part B by adding "to assess the impact of DZD9008 on patients' disease related symptoms and health related quality of life (HRQoL).
3) Section 3.1: added expansion cohort 6 in Part A; updated the design of Part B extension (a) by changing from 1 dose cohort of 300 mg to 2 dose cohorts of 200 mg and 300 mg (b) and added Simon two- stage design.

4) Section 3.2.2: RP2D was updated from 300 mg to both 200 mg and 300 mg selected for Part B.
5) Section 4.1.2.1: added inclusion criteria for Part A dose expansion cohort 6.
6) Section 4.1.2.2: removed treatment naïve from the patient population of Part B extension.
7) Added Table 3 to show the representative of dose intervention or modification. Updated the table listing.
8) Section 5.3 and 6.3.1: safety follow up period was updated from 14 days to 28 days.
9) Section 5.3.3: updated the interim analysis by adding futility analysis for Part B.
10) Section 6.9: added the EQ-5D-5L collection.
11) Section 7.2.2: updated the sample size calculation of Part B. Subjects will be randomized into two different dose cohorts. Each dose cohort uses a Simon two-stage design, and a sample size of 103 in each dose cohort is required to test a mull hypothesis of H_0: ORR $\leq$ 0.17 versus an alternative hypothesis of H_1: ORR $\geq$ 0.3 with a one-sided significance level of 0.0125 and 80% power.
12) Section 7.6: new added section to describe the calculation of derivation for EORTC QLQ-C30 and QLQ-LC13.
13) Section 7.7: new added section to describe the calculation of EQ-5D-5L.
14) Table 14 (study plan of Part A expansion): removed survival follow up from table to keep consistent with study objectives and assessment description.
15) Appendix J: added EQ-5D-5L.

Version 7.0, April 6, 2021
Summary of major changes from previous version: 1) Section 3.2.1 and section 5.1: updated the definition of low-fat meal (the low-fat meal is defined as approximatley 400 to 500 Kcal with about 25% of calories comes from 11-14 grams of fat) to keep it consistent with FDA guidance. 2) Appendix J: corrected the typing of answer to question of Nausea of CTCAE PRO

Version 6.0, March 5, 2021
Summary of major changes from previous version: 1) Updated study flow chart: In the Part A expansion cohort, added cohorts dosing with DZD9008 at 200 mg and 300 mg, respectively, with low-fat meal (cohort 3 and 4) and treatment naïve cohort (cohort 5). The 200 mg and 300 mg expansion cohorts dosing

under fasted condition in the previous flow chart (CSP version 4.0 and 5.0) are now the expansion cohort 1 and cohort 2.

2) Updated clinical data, including exposure, PK, safety and efficacy using new cut-off date of February 5, 2021 in section 2.3.5. Updated preliminary PK data from food effect cohort (high-fat meal).
3) Updated study objectives for Part A in section 1.1.1
   - Secondary objectives: added retrospective tumor assessment in patients with EGFR Exon20ins according to RECIST 1.1 by Independent Review Committee (IRC).
   - Exploratory objectives: added (a) To assess AEs of DZD9008 by using patient reported specific CTCAE symptoms and FACIT GP5 questionnaire. (b) To explore the relationship between DZD9008 exposure and selected endpoints (i.e., safety and efficacy), where deemed appropriate.
4) Section 4.1.2: updated the inclusion criteria for different cohorts of dose expansion part.
5) Section 5.1: updated the information of DZD9008 administration with low-fat meal.
6) Section 5.1.5: reworded the guidance for toxicity management and dose modification to make it clearer.
7) Section 6.3.5: added PRO-CTCAE and FACIT GP5 questionnaire in section 6.3.5.5 and 6.3.5.6, respectively.

Version 5.0, December 17, 2020

Summary of major changes from previous version:

1) Introduction and study flow chart
   - Updated study flow chart by only keeping cohort of NSCLC with EGFR Exon20ins and sample size of ~ 120.
   - Updated 13-week rat and dog toxicity study and genotoxicity study results.
   - Updated clinical study results of ongoing study of DZ2019E0001 and DZ2019E0002.
2) Section 1.1.2: updated the study objectives for Part B.
3) Section 2.1: added a paragraph of treatment status of NSCLC with EGFR Exon20ins.
4) Section 2.3.3: updated key data of nonclinical pharmacokinetics study.
5) Section 2.3.4: updated 13-week rat and dog toxicity study and genotoxicity study results.
6) Section 2.3.5: updated results of ongoing clinical studies of DZD9008.
7) Section 3.1: updated the study flow chart.
8) Section 3.2.2: updated study rationale and study cohort for Part B by only keeping EGFR Exon20ins cohort.
9) Section 4.1: updated inclusion and exclusion criteria.

- Added the description of stable brain metastasis
- Updated the inclusion criteria of Part B by removing cohort with EGFR uncommon mutation, HER2 Exon20ins and POM cohort.

10) Section 5.1.4: added the rationale for selecting 300 mg once daily as RP2D.
11) Section 5.1.5: added the maximum dose reduction for part B.
12) Section 5.2.1: added a paragraph of clinical efficacy data of DZD9008 from ongoing clinical studies.
13) Section 5.2.2: added a paragraph of clinical safety data of DZD9008 from ongoing clinical studies.
14) Section 5.3: updated the safety follow up time post last dosing from 28 days to 14 days.
15) Section 5.4: updated the end of study for part B.
16) Section 5.5: updated the post study access to study treatment. Updated the toxicity management for QTc prolongation.
17) Section 6.3.3: added the schedule for Part B.
18) Section 6.3.4: added Creatine phosphokinase into the lab testing in Table 3.
19) Section 6.3.5: added the ECG visiting and ECG central review for Part B of the study.
20) Section 6.3.6.3: updated the survival follow-up.
21) Section 6.4.3: updated the AE collection period to “from inform consent signed”.
22) Section 6.5.2 updated the pharmacokinetics sampling time for Part B extension in both text and Table 7 & Table 8.
23) Section 6.6 Exploratory research
    - Updated sample collection for tumor tissue.
    - Added a section for pharmacogenetics study.
24) Section 7.2.2: added the sample size calculation for Part B dose extension part.
25) Appendix H: added the gastric acid suppressive agents that may affect DZD9008 absorption.

Version 4.0, January 16, 2020

Summary of major changes from previous version:

1) Study flow chart and Figure 1: updated with new chart. Add Part A expansion into the chart. Change “Part B expansion” to “Part B extension”.
2) Updated the list of abbreviations and definition of terms.
3) Section 1.1.1.3: added “to investigate any change in the ratio of 4β-hydroxycholesterol to total cholesterol as a biomarker of cytochrome P450 (CYP)3A4 induction by DZD9008” into exploratory objectives.
4) Section 2.3: added clinical information of DZD9008 under 2.3.5.
5) Section 3.1 and section 3.2.1: added a paragraph to describe Part A expansion.
6) Inclusion criteria

- Section 4.1.2.1 added the cohort specific inclusion criteria of Part A dose expansion.
- Section 4.1.2.2: changed the mutation "determination by next generation sequencing (NGS) assay in Clinical Laboratory Improvement Amendments (CLIA) certified laboratories (USA sites) or other similarly certified laboratories (outside of USA)" to "determined by central lab testing".

7) Section 4.2: exclusion criteria
   - Added exclusion criteria for Part B "prior malignancy within 2-3 years requires active treatment, except for adequately treated basal cell skin carcinoma, in situ cervical carcinoma, or other cancer type has been disease free for > 2 years with life expectancy > 2years".
   - Updated the exclusion criteria. For Expansion cohort of Part A and cohort 1, 2, 4 of Part B: Patients who have received prior Poziotinib or TAK788 or other EGFR/HER2 exon20ins inhibitors treatment should be excluded.
   - "Prior history of atrial fibrillation" is updated with "Prior history of atrial fibrillation within 6 months of first administration of DZD9008".
   - Added the exclusion criteria of: Known history of bleeding diathesis, i.e., hemophilia, Von Willebrand disease.
   - Removed the paragraph "Grapefruit, grapefruit juice, and orange marmalade CYP3A4" from exclusion criteria. This paragraph is described in Section 4.3 Restriction.
8) Section 5.1: updated the drug supply, packaging and labeling of DZD9008 by adding 150 mg and 200 mg strength of tablet.
9) Section 5.1.1.1: added a paragraph to describe Part A expansion. Added a paragraph to describe the prior setting of Bayesian logistic regression model.
10) Updated Figure 2 with detailed description of treatment period 1 & 2.
11) Section 6.5.1.1, Table 5 and Table 9: add pre-dose on Cycle 2 Day 1 to PK time point of Part A food effect cohort.
12) Section 7.2.1: updated the sample size for Part A.
13) Section 7.7: updated the definition for PK analysis set.
14) Table 9: change the Cycle 1 duration from 28 days to 21 days.

Version 3.1, October 9, 2019
Summary of changes from previous version: 1) Section 5.3, "Procedures for withdrawal from the exploratory research are outlined in Section 5.4.2": corrected the typing error from Section 5.4.2 to Section 5.3.2. 2) Section 5.3, "Patients incorrectly initiated on investigational product (Section 5.4.1): corrected the typing error from Section 5.4.1 to Section 5.3.1.

3) Section 6.4.2, “For definition of other significant adverse event (OAE), see section 7.3.1”: corrected the typing error from Section 7.3.1 to Section 7.3.
4) Table 9, RECIST assessments: corrected the typing error from Section 6.9.1 to Section 6.8.1.
5) Appendix F, Methods of measurement: corrected the link by removing “Table 13”.

Version 3.0, September 6, 2019

Summary of major changes from previous version:

1) Title page: removed investigators’ name, information and space for signature as there are too many investigators participating the study. The signature from each investigator will be obtained separately.
2) Section 1.1.2.2: removed urine PK from the secondary objectives. The reason is to keep consistency with that described in section 6.5.1.1.
3) Section 3.1, Part B, dose escalation: removed HER2 Exon20ins from Cohort 4. This is to align with that pEGFR is the applied PoM biomarker.
4) Section 4.1.1.2:
   - Added “per local regulation/IRB requirement” to ensure the age fulfills local requirement.
   - Added “International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (APTT) ≤ 1.5 x ULN; Serum amylase ≤ 1.5 x ULN and serum lipase ≤ 1.5 x ULN” into inclusion criteria per risk assessment based on DZD9008’s activity on BTK in updated Investigator’s Brochure.
5) Section 4.2:
   - Exclusion criteria: changed “before screening” to “before the first dose of DZD9008”. This is to ensure patients staying untreated for a relatively shorter time while meeting the requirement for washout from prior treatment.
   - Added “Requires anticoagulation therapy with Warfarin, heparin etc.” into exclusion criteria per risk assessment based on DZD9008’s BTK activity
   - Added “prior history of atrial fibrillation” and “history of stroke or intracranial hemorrhage within 6 months before the first dose of DZD9008” into exclusion criteria per risk assessment based on DZD9008’s BTK activity.
   - 4.2.12: changed QTcF to QTc, as the QTc interval will be measured by either Fridericia’s or Bazett’s formula.
6) Section 4.3 and section 4.3.1: to make consistency that patients must avoid concomitant use of medications, herbal supplements and/or ingestions of foods with known potent inducer/inhibitory effects on CYP3A4 activity whenever feasible. Changed the wording “Such drugs must have been discontinued for an appropriate period before patients enter into screening and for 3 weeks prior to first administration of DZD9008” to “Such

drugs must have discontinued for a period of 2 weeks (CYP3A4 inhibitors) or 3 weeks (CYP3A4 inducers) prior to first administration of DZD9008".

7) Section 5.1 Drug administration:
   - Added "If a subject miss taking a scheduled dose, within a window of 4 hours, it is acceptable to take the dose. If it is more than 4 hours after the dose time, the missed dose should not be taken, protocol deviation will be recorded, and patients should be instructed to take the dose at the next scheduled time. If a subject vomits after taking their DZD9008, they should not make up for this dose, but should take the next scheduled dose".
   - Changed "Whether the patients in Part B will take the study treatment in a fasted or fed condition will be based on the data from the food effect cohort in Part A" to "Enrollment of patients into Part B will be triggered by RP2D being defined, and patients may take DZD9008 under fast condition until the data from dose effect cohort is available". This is to clarify the trigger of Part B.
8) Table 1: corrected some errors of number.
9) Section 5.1.4 Toxicity management
   - Changed the wording to "If a further episode of the same AE subsequently requires dose interruption, patient should restart at one dose level lower (except cohort 1 dose, restart at cohort 1 dose level)". This is to keep the wording consistent with that in Figure 3.
   - Patients experiencing any of the following will not be permitted to restart study treatment: removed "QTc interval prolongation > 500 msec absolute or a > 60 msec increase from baseline or with serious signs/symptoms" from this paragraph. This is to keep consistent with the main paragraph of "toxicity management and dose modification" and figure 3.
10) Section 5.1.5: changed the "21" into "28" day evaluation period of Cycle 1 of Part A, to make consistency across different parts.
11) Section 5.2: added section 5.2.2.10 Hemorrhage and a whole paragraph description of this potential risk per risk assessment based on DZD9008's BTK activity.
12) Table 3: updated the laboratory safety assessments list by adding S/P- magnesium, lipase and amylase into the clinical chemistry list, adding Coagulation test (include APTT and INR) into the laboratory measurement list per updated risk assessment, and removing S/P Cystatin C from chemistry list considering there are S/P creatine and urine nitrogen already included for renal function testing.
13) Section 6.3.5
   - ECG: removed "will be transferred electronically for central analysis as described in the study specific ECG manual". This is to keep consistency across the protocol and considering no cardiac risk of QT prolongation from preclinical safety assessment.
   - Ophthalmologic examination: removed "Photographs should be performed to record any clinically significant findings. These photographs should be available for

central review by Dizal representatives if necessary". The eye examination is done by ophthalmologist and not mandatory for Dizal representative to review.

- Echocardiogram/MUGA Scan: changed the assessment frequency to "Echocardiogram or MUGA scan to assess LVEF will be conducted at baseline (prior to first dose of DZD9008), on Cycle 3 Day 1 (± 7 days), then every 6 weeks (± 1 week) and whenever clinically indicated".
- Pulmonary function tests (PFTs): changed the assessment frequency to "PFTs (including spirometry and DLCO) will be performed at baseline (prior to first dose of DZD9008), on Cycle 3 Day 1 (± 7 days), and then every 6 weeks (± 1 week) and whenever clinically indicated".

14) Section 6.7.1: updated the volume of blood due to additional coagulation test added into the laboratory variables.
15) Section 6.8.1.1 Imaging assessment: changed the assessment frequency to "Imaging assessments will be performed using CT scan or MRI to assess extracranial lesions, such as chest, abdomen (including liver and adrenal glands), and MRI for the brain if brain metastasis presents at baseline (within 28 days of treatments start, ideally as close as possible to the start of study treatment), on Cycle 3 Day 1 (± 7 days) and then every 6 weeks ± 7 days (relative to first dose of multiple dosing) until objective disease progression or withdrawal from study".
16) Section 7.3
    - ECG changes: added Bazett's to the formula of QTc calculation.
    - Creatine clearance: updated the calculation formula by adding the formula based on creatinine value in mg/dL.
17) Section 7.4: updated the PK calculation by adding more PK parameter for calculation and adding more detailed description to the calculation.
18) Secrion 7.5 Investigator RECIST based assessments: removed the paragraph of scaling up rule if ≤ 1/3 TL is missing. This will be included in the review charter of independent image review for Part B study.
19) Section 7.8.4: updated the PK summary by adding more PK parameter and the detailed description.
20) Table 4, 5, 6, 8, 9, 10: corrected some error to make it consistency between the description and tables; added foot note to clarify the visit or testing window; add HBV/HCV/HIV and APTT/INR into table 8, 9, 10.
21) Table 11, 12 and 13: added APTT/INR into tables.

Version 2.0, March 8, 2019
Summary of major changes from previous version: 1) Study flow chart:

- Removed previous cohort 1 (TKI treatment naïve EGFR sensitizing mutation or T790M mutation positive without Osimertinib treatment) from current Part B

2) Section 1.1.2.1: added Independent Central Review for ORR and DOR.
3) Section 2.3.4: added the new data of pathology analysis of 14 days dog DRF study into the summary.
4) Section 3.1: removed the previous study flow chart and updated as above
   - Part A: removed "Expansion of cohort size at any dose level to further confirm safety or/and efficacy will be allowed as agreed by SRC".
   - Part B: removed cohort 1, change total patient number from ~ 140 to ~ 120; remove "Additional patients may be enrolled into each cohort to further evaluate anti-tumor efficacy signals and/or assess safety".
5) Section 3.2.2: removed cohort 1 (TKI treatment naïve EGFR sensitizing mutation or T790M mutation positive without Osimertinib treatment)
6) Section 4.1.1.4: removed "collection of plasma samples from patients with EGFR L858R, 19del and T790M mutation diagnosed using plasma samples".
7) Section 4.1.2.1 Part A: Patients must have documented histologically or cytologically confirmed locally advanced or metastatic NSCLC with EGFR or HER2 mutations, and have relapsed from, been refractory or intolerant to at least one line of standard therapy.
8) Section 4.1.2.2 Part B: removed previous cohort 1. Patient enrolment in Part B using Next Generation Sequence (NGS) assay for mutation detection.
9) Section 4.2: for exclusion criteria 2-8, changed "first dosing of DZD9008" to "screening".
10) Section 5.5.1.1: added additional point to starting dose justification rationale "The predicted human free AUC and Cmax at 50 mg once daily are 0.12 μM*hr and 0.006 μM, respectively, which are comparable or below the drug exposure at NOAEL in preclinical toxicity studies of rat and dog". Added new table (exposure of DZD9008 at NOAEL from preclinical toxicity studies and margin to the predicted drug exposure in human at 50 mg once daily) into current protocol (Table 1).
11) Section 5.1.1.2 DLT criteria:
    - Removed "present for continuous 4 days" from DLT criteria of Haematological toxicity that is Common Terminology Criteria for Adverse Events (CTCAE 5.0) grade 4
    - Added "Grade 3 platelet count decrease associated with clinically significant bleeding" to the DLT criteria
    - Added "Grade 4 laboratory abnormalities per CTCAE 5.0 including life-threatening consequences" to the DLT criteria.
12) Section 5.1.1.5: Changed DLT period from 21 day to 28 day (Cycle 1 of Part A).
13) Section 5.1.2 The effect of food on PK of DZD9008:
    - Updated "the washout time of each treatment period might be updated in light of human PK data. In general, after single dose, at least 7 days or 5 x half-life whichever is longer will be allowed for drug elimination".

- Updated Fasted condition as "Patients must fast for ≥1 hours prior to taking a dose and to ≥2 hour post dose".
- Updated Fed condition as "Patients should start ingestion of a recommended meal 30 minutes prior to administration of DZD9008. Patients should finish this meal within 30 minutes or less; however, DZD9008 should be administered at 30 minutes after start of high fat meal".

14) Section 5.1.3: removed previous cohort 1 from Part B
15) Section 5.2.2.8: added renal effect.
    - Patients with abnormal renal function as defined by creatinine >1.5 x upper limit of normal (ULN) concurrent with creatinine clearance < 50 mL/min at screening are excluded from participating in the study. During the study, kidney function tests (creatinine, urea nitrogen and Cystatin C) will be monitored regularly during the study and recorded at discontinuation.
16) Section 5.3.3: updated as "In Part B, when the first 20 patients of cohort 1 or 2 complete at least 12-week repeated dosing of DZD9008, and have two consecutive RECIST assessment available, interim data analysis will be performed to evaluate clinical efficacy and safety. Ongoing patients will be able to continue DZD9008 treatment if they are still deriving clinical benefit".
17) Section 7.2.2.: changed sample size of Part B from ~140 to ~ 120.
18) Section 7.5: added Independent Review Committee (IRC) and investigator RECIST based assessment

Independent Central Review of RECIST based assessments (Part B)

The Independent Central Review of all radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be provided to the IRC. Prior radiotherapy reports for patients (at baseline) and information on biopsied lesions will also be provided to the IRC to allow the selection of appropriate target lesions. The imaging scans will be reviewed by two independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. For each patient, the IRC will define the overall visit response data (CR, PR, SD, PD or NE) and the relevant scan dates for each time point (i.e. for visits where response or progression is/is not identified). If a patient has had a tumor assessment which cannot be evaluated then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD). Endpoints (ORR, DoR, DCR, PFS) will be derived from the overall visit response date and the scan dates. ORR will only include patients whose response has been confirmed by a second scan at least 4 weeks after the initial response. The endpoint of tumor shrinkage will be assessed from tumor size measurements based on the primary independent radiologist assessment.

Investigator RECIST based assessments

From the investigators review of the imaging scans, the RECIST tumour response data will be used to determine each subject's visit response according to RECIST version

1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD). 19) Section 7.8.6.1: added “Data will be analyzed by subgroup (taken into consideration of the prior treatment) in each dose cohort”. 20) Updated Table 8, 9, 10 to align with section 6.3.3, 6.3.4, 6.3.5.

Version 1.0, January 16, 2019
Initial creation

INTRODUCTION & STUDY FLOW CHART

A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 mutation

Study center (s) and number of patients planned:

Part A: 130 - 150 patients, Part B: ~206 patients (providing approximately 103 patients are enrolled to the optimal RP2D cohort)

Epidermal growth factor receptor (EGFR) Exon 20 insertions (Exon20ins), human epidermal growth factor receptor 2 (HER2) Exon20ins and EGFR uncommon mutations occurred in about 7% patients with non-small cell lung cancer (NSCLC). Chemotherapy is the standard of care (SoC) for patients carrying EGFR or HER2 Exon20ins, but median progression free survival (PFS) and overall survival (OS) were only around 6 months and 24 months, respectively. For EGFR uncommon mutations, afatinib was approved as 1st line therapy in some regions, but there was no effective treatment after disease relapse. Therefore, there is an unmet medical need to develop more effective therapy.

DZD9008 is an oral, potent, selective and irreversible EGFR tyrosine kinase inhibitor (TKI) targeting EGFR sensitizing mutation, T790M resistance mutation, Exon20ins and uncommon mutations as well as HER2 Exon20ins mutation, with weak activity against wild type EGFR. *In vitro*, DZD9008 modulates pEGFR with IC_{50} of [redacted] in tumor cells carrying EGFR L858R, exon 19 deletion (Exon19del), L858R/T790M, Exon20ins or uncommon mutations, and inhibits pHER2 with IC_{50} of [redacted] in tumor cells engineered with different subtypes of HER2 Exon20ins. DZD9008 suppresses cell proliferation with GI_{50} of [redacted] in tumor cells carrying EGFR L858R, Exon19del, L858R/T790M, Exon20ins or uncommon mutations, and GI_{50} of [redacted] in tumor cells engineered with HER2 Exon20ins. *In vivo*, DZD9008 induces profound tumor regression in standard or patient derived xenograft models expressing EGFR Exon19del, L858R/T790M, Exon20ins or uncommon mutations, but demonstrates modest effect in a xenograft model carrying wild type EGFR. In addition, there is a good correlation between plasma PK and pEGFR modulation in tumor tissues of xenograft models.

DZD9008 has favorable drug metabolism and pharmacokinetics (DMPK) properties for oral dosing. Pharmacokinetic exposure increased approximately in proportion to oral dosing in rat and dog. Accumulation in terms of AUC was less than 2- folds on multiple daily dosing in rat and dog. *In vitro* data have indicated that CYP3A4/5 are the principal P450 isozymes responsible for human metabolism. Incubations with hepatocytes from rat, dog and humans have indicated that glutathione conjugation may be alternative/additional elimination pathways. Based upon *in vitro* data, DZD9008 DDI risk is considered unlikely to cause clinically significant hepatic drug interactions at clinically relevant concentrations through inhibition or induction of cytochrome P450 enzyme activity.

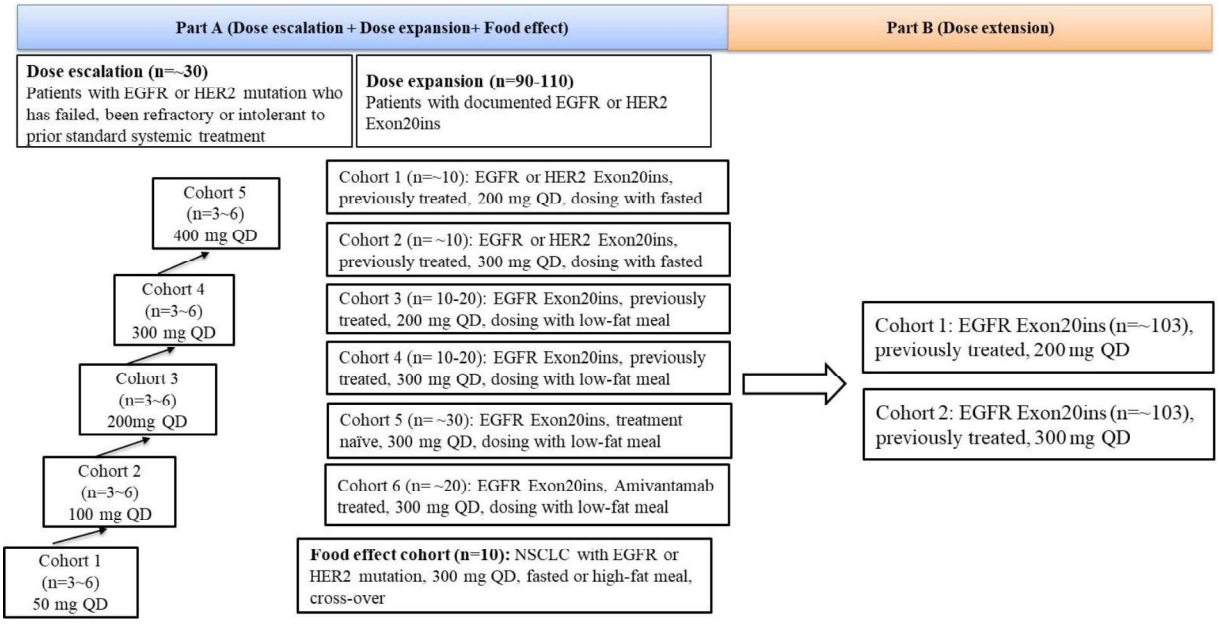
The key findings from the non-clinical toxicity studies were: diarrhea, low food intake and body weight loss. Histopathological findings include: gastrointestinal tract (inflammation,

hemorrhage, ulcer, erosion, necrosis, gland dilatation), thyroid (follicular atrophy), lacrimal gland (acinal cell atrophy), vagina (epithelial atrophy), tongue/esophagus (epithelial atrophy/erosion/neutrophilic infiltrate), eye (cornea epithelial atrophy), pancreas (acinar atrophy, acinar cell secretory depletion), skin (crust formation in the epidermis), lung (alveolar infiltrates of macrophages), kidney (cortical tubular dilatation) and mandibular salivary gland acinar cell secretory depletion, which are considered EGFR inhibition related; lymphoid depletion of immune organs (thymus, spleen and lymph nodes) and adrenal gland hypertrophy were likely due to the stress; bone marrow myeloid hypercellularity could be the inflammatory response to gastrointestinal tract change; pancreas fibrosis was likely DZD9008 BTK inhibition related. Majority of findings observed during the 1-month studies were not present following 1-month recovery period, with the exception of pancreas fibrosis. The results from preclinical toxicology studies support progression of DZD9008 into clinical trials in patients with advanced cancer.

There are three clinical studies of DZD9008 monotherapy for which efficacy analysis has been conducted in NSCLC subjects with EGFR Exon20ins post platinum-based chemotherapy: (DZ2019E0001, and DZ2019E0002 and DZ2020E0001).

DZ2019E0001 (ClinicalTrials.gov Identifier: NCT03974022) is a phase 1/2 study in NSCLC with EGFR or HER2 mutations, which is being conducted in US, Australia, Taiwan, and South Korea, etc. This study consists of two parts: Part A (dose escalation, food effect and dose expansion) and Part B (dose extension). In Part A, advanced NSCLC patients with EGFR or HER2 mutations who relapsed from or were refractory, or intolerant to standard systemic therapy will be enrolled for dose escalation. These patients will receive one single dose, and after a wash-out period, then multiple doses of DZD9008 with the objective to investigate its safety and tolerability, MTD, and preliminary anti-tumor efficacy. A separated cohort at defined dose level will be enrolled to evaluate food effect on PK. Further expansion of Part A will be triggered at well tolerated dose(s) with observed anti-tumor effect in patients with EGFR Exon20ins or HER2 Exon20ins mutant NSCLC. In Part B, advanced NSCLC patients with EGFR Exon20ins who have relapsed from or were refractory, or intolerant to 1 - 3 lines of prior systemic treatment will be enrolled. The objective of this part of study is to further assess anti-tumor efficacy, safety and tolerability of DZD9008 at the Recommend Phase 2 Dose(s) (RP2Ds) of 200 mg and 300 mg. Following review and approval from IEC/IRB and/or local regulatory authority (as applicable) on the optimal RP2D selection, eligible patients can be enrolled into the optimal RP2D cohort. The results of Part B is planned to be used to support an NDA submission for accelerated approval of DZD9008 in NSCLC with EGFR Exon20ins.

Study flow chart (DZ2019E0001)



- Patients will be dosed at 200 mg or 300 mg once daily in two separate cohorts in phase 2 for Part B, but only the optimal RP2D cohort remains open for enrolling patients following review and approval from IEC/IRB and/or local authority (as applicable).
- About 10 patients may participate in the proof-of-mechanism (PoM) study in each dose cohort of Part B.
- Expansion cohort 5 will be triggered after the emerging data shows DoR of EGFR Exon20ins patients reaches 6 months, and the food effect cohort data is available.

DZ2019E0002 (Chinadrugtrial identifier: CTR 20192097) is a phase 1 study in Chinese NSCLC with EGFR or HER2 mutations. This study consists of dose escalation and expansion cohorts. Enrolled patients will first receive a single oral dose of DZD9008, followed by a 7-day wash out, then repeated daily dosing until disease progression, intolerable AEs, a discontinuation criterion is met or withdrawal of consent. The dose expansion will be initiated from the dose level where anti-tumor activity (PR or CR in patients with EGFR or HER2 Exon20ins) is observed. Data from dose escalation and dose expansion will be used to define RP2D.

As of data cut-off date April 3, 2023, in 74 prior platinum-based chemotherapy treated NSCLC subjects with EGFR Exon20ins, the confirmed ORR assessed by investigators was [redacted] across all dose levels. At the dose level of 200 mg and 300 mg, the confirmed ORR was [redacted] and [redacted] respectively.

DZ2020E0001 (Clinicaldrugtrial identifier: CTR20211009) is a phase 2, single arm, pivotal study in Chinese NSCLC with EGFR Exon20ins mutations.. As of April 3, 2023, in 97 patients of efficacy analysis set, the confirmed ORR was [redacted] and the confirmed DCR was [redacted] as

assessed by IRC. The median DoR was [redacted] months. The longest DoR already reached [redacted] months, and subject is still responding.

By the same DCO, a total of 313 advanced NSCLC subjects with EGFR or HER2 mutations were included in the safety analysis set. The most common (≥ 20%) TEAEs across all dose levels were diarrhea, rash, anemia, blood creatine phosphokinase increased, paronychia, decreased appetite, vomiting, nausea, blood creatinine increased, and weight decreased. Refer to the current DZD9008 Investigator's Brochure (IB) for a complete summary of nonclinical and clinical information including safety, efficacy, and pharmacokinetics.

TABLE OF CONTENTS PAGE

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
Ae	Cumulative amount of unchanged drug excreted into urine
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time zero to 24 hours
$AUC_{(0-72)}$	Area under the plasma concentration-time curve from time zero to 72 hours
$AUC_{(0-168)}$	Area under the plasma concentration-time curve from time zero to 168 hours
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to t [amount·time/volume]
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{ss}	Area under the plasma concentration-time curve during any dosing interval at steady state [amount· time/volume]
BOR	Best Overall Response
ctDNA	Circulating free tumor deoxyribonucleic acid
CL/F	Total body clearance of drug from plasma after an oral dose
CL_{ss}/F	Total body clearance of drug from plasma after an oral dose at steady state
CL_R	Renal clearance of drug from plasma
C_{max}	Maximum plasma concentration
CLIA	Clinical Laboratory Improvement Amendments
CPP	Clinical Pharmacology and Pharmacometrics
CR	Complete response
CRF	Case Report Form (electronic/paper)

Abbreviation or special term	Explanation
CSP	Clinical Study Protocol
$C_{ss,max}$	Maximum plasma concentration at steady state
$C_{ss,min}$	Minimum plasma concentration at steady state
CSR	Clinical Study Report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG	Eastern Co-operative Oncology Group
EGFR	Epidermal growth factor receptor
Exon19del	Exon 19 deletion
Exon20ins	Exon 20 insertion
Fe	Percentage of the dose excreted unchanged in urine
FFPE	Formalin-fixed paraffin-embedded
FTIP	First Time in Patients
GCP	Good Clinical Practice
GI_{50}	The concentration of a test agent for 50% of maximal inhibition of cell proliferation
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HNSTD	Highest non-seriously toxic dose
HRQoL	Health related quality of life
IATA	International Air Transport Association
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration (the concentration of a test agent needed to inhibit a biological process or response by 50%)

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
IRC	Independent Review Committee
INR	International normalized ratio
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition scan
NE	Not evaluable
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective Response Rate
PD	Progression of disease
PFS	Progression free survival
PK	Pharmacokinetics
PoM	Proof of Mechanism
PR	Partial response
PRO	Patient Reported Outcomes
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcB	QTc interval with Bazett's correction
QTcF	QTc interval with Fredericia’s correction
R_{AC}	Extent of accumulation on multiple dosing
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation or special term	Explanation
RP2D	Recommended Phase II Dose
SAE	Serious adverse event
SD	Stable disease
SRC	Safety Review Committee
STD_{10}	10% of the Severely Toxic Dose in rodents
λ_z	terminal rate constant
$t_{½\lambda z}$	Terminal half-life
TL	Target lesion
TKI	Tyrosine kinase inhibitor
t_{max}	Time to maximum plasma concentration
$t_{ss\ max}$	Time to maximum plasma concentration at steady state
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
V_{ss}/F	Apparent volume of distribution
WBDC	Web Based Data Capture
WHO	World Health Organization
~	Approximately

Clinical Study Protocol

A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 mutation

Part A: ~130 - 150 patients, Part B: ~206 patients (providing approximately 103 patients are enrolled to the optimal RP2D cohort)

1. STUDY OBJECTIVES

Part A of the study is a first time in human study to assess safety, tolerability, pharmacokinetics and anti-tumor efficacy of DZD9008 in advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) or human epidermal growth factor receptor 2 (HER2) mutations, with preferential focusing on patients with EGFR and HER2 Exon20ins. Part B extension is a phase 2 study to assess the efficacy and safety of DZD9008 in NSCLC patients with EGFR Exon20ins mutation, who have relapsed from 1-3 lines of prior systemic therapy.

This study includes two parts: Part A (dose escalation, food effect and dose expansion) and Part B (dose extension).

1.1 Objectives

1.1.1 Part A

1.1.1.1 Primary objectives

Objectives	Endpoint/Variable
To investigate the safety and tolerability of DZD9008 when given orally to patients with advanced NSCLC with EGFR or HER2 mutations	• Adverse Events (AEs)/Serious Adverse Events (SAEs) • Laboratory data • Vital signs • Electrocardiogram (ECG) • Physical examination • Echocardiogram/MUGA • Pulmonary function test
To establish Maximum Tolerated Dose (MTD) (if possible) and Recommended Phase 2 Dose (RP2D) of DZD9008 when given orally in patients with advanced NSCLC with EGFR or HER2 mutations	• Dose Limiting Toxicities (DLTs) • AEs/SAEs

1.1.1.2 Secondary objectives

Objectives	Endpoint/Variable
To characterize the pharmacokinetics (PK) of DZD9008 following a single oral dosing and at steady state after multiple oral dosing in the fasted state, and renal excretion of DZD9008	• Plasma and urine DZD9008 concentrations, and derived PK parameters
To evaluate the effect of food on the exposure of DZD9008 at the defined doses	• Plasma DZD9008 concentrations, and derived PK parameters
To assess preliminary anti-tumor activity of DZD9008 according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator	• Objective Response Rate (ORR) • Best Overall Response (BOR) • Duration of Response (DoR) • Disease Control Rate (DCR) • % Change in Size of tumor lesion • Progression Free Survival (PFS)
To retrospectively assess anti-tumor activity of DZD9008 in patients with EGFR Exon20ins according to RECIST 1.1 by Independent Review Committee (IRC)	• ORR, DCR, DoR by IRC

1.1.1.3 Exploratory objectives

- To collect and store diagnostic tumor samples (archived) or any fresh tumor biopsies (if archived tumor sample is not available) to confirm EGFR and HER2 mutations by central lab retrospectively, support the development of diagnostic test for pre-market approval by regulatory authorities and potential future exploratory research into factors that may influence development of DZD9008 in NSCLC and/or tumor response to DZD9008.

- To investigate the presence, and/or identity of the drug metabolites of DZD9008 in plasma and urine samples, if appropriate, characterize their PK.

- To investigate any change in the ratio of 4β-hydroxycholesterol to total cholesterol as a biomarker of cytochrome P450 (CYP)3A4 induction by DZD9008.

- To collect and store blood-based samples for future exploratory research on genes/genetic aberrations that may influence response to DZD9008 treatment and/or susceptibility to DZD9008.

- To assess AEs of DZD9008 by using patient reported specific CTCAE symptoms (PRO-CTCAE) and FACIT GP5 questionnaire.

- To explore the relationship between DZD9008 exposure and selected endpoints, (i.e., safety and efficacy), where deemed appropriate.

1.1.2 Part B

1.1.2.1 Primary objectives

Objectives	Endpoint/Variable
To evaluate anti-tumor activity of DZD9008 in advanced NSCLC patients with EGFR Exon20ins at defined dose(s) by assessment of Objective Response Rate (ORR)	• Objective Response Rate (ORR) according to RECIST 1.1 by an Independent Review Committee (IRC).

1.1.2.2 Secondary objectives

Objectives	Endpoint/Variable
To assess anti-tumor efficacy of DZD9008 using additional endpoints	• DoR, Progression Free Survival (PFS), DCR, BOR and % of Change in Size of tumor lesion according to RECIST 1.1 using assessments performed by an IRC • DoR, PFS, DCR, BOR and % of Change in Size of tumor lesion using investigators assessments according to RECIST 1.1 • Description of OS
To determine the safety and tolerability of DZD9008	• AEs/SAEs • Laboratory data • Vital signs • Physical examination • ECG • Echocardiogram/MUGA • Pulmonary function test
To characterize the PK of DZD9008	• Plasma DZD9008 and metabolite concentration and derived PK parameters if deemed appropriately

1.1.2.3 Exploratory objectives

- To collect and store archived tumor samples (if more than one formalin-fixed paraffin-embedded (FFPE) block from a patient, tissue from the most recent one is preferred) or any fresh tumor biopsies (if archived tumor sample is not available) for EGFR Exon20ins confirmation in central laboratory and necessary technical studies

for companion diagnostics development and approval and potential future exploratory research into factors that may influence development of DZD9008.

- To collect and store plasma samples to isolate circulating free tumor DNA (ctDNA) for EGFR Exon20ins mutation testing and necessary technical studies, for liquid biopsy companion diagnostic development and approval.
- To collect and store blood-based samples for future exploratory research on genes/genetic aberrations that may influence response to DZD9008 treatment and/or susceptibility to DZD9008.
- To investigate the effect of DZD9008 on proof-of-mechanism (PoM) biomarkers in tumor biopsy (e.g., EGFR phosphorylation (pEGFR).
- To explore the relationship between DZD9008 exposure and selected endpoints (which may include efficacy, safety, QTc interval etc.), where deemed appropriate.
- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response to DZD9008, (i.e., absorption, distribution, metabolism, excretion, safety and efficacy).
- To explore the impact of DZD9008 treatment and disease state on health state utility by using EQ-5D-5L health state utility index based on patient reported data.
- To assess AEs of DZD9008 by using subjects reported specific CTCAE symptoms (PRO-CTCAE) and FACIT GP5 questionnaire.

2. BACKGROUND

2.1 NSCLC with EGFR Exon20ins, HER2 Exon20ins, and EGFR uncommon mutation

Lung cancer is the most common cancer type in the world for several decades. It is also one of the most common causes of cancer death. NSCLC represents approximately 80% to 85% of all lung cancer.

EGFR tyrosine kinase inhibitors (TKIs) have been proved to be effective therapy for NSCLC patients with EGFR sensitizing mutations, such as L858R and exon 19 deletion (Exon19del), and resistance mutation, T790M (1-9). However, beyond L858R, Exon19del and T790M, EGFR or HER2 Exon20ins, which together with EGFR G719X, S768I and L861Q uncommon mutations comprise of about 7% of NSCLC (10). Although amivantamab (JNJ-61186372), an EGFR and MET bispecific antibody, and mobocertinib (TAK-788), an EGFR TKI, both have recently received accelerated approval for NSCLC patients with EGFR Exon20ins, but the efficacy and safety of these two drugs should be further validated in phase 3 confirmatory studies with larger cohorts. Post-hoc analysis of afatinib phase 2 and phase 3 trials LUX-Lung

2, LUX-Lung 3 and LUX-Lung 6 demonstrated clinical activities in 1st line patients in certain types of uncommon EGFR mutations, such as G719X, S768I and L861Q, while there was no effective treatment after disease relapse. In addition, afatinib is not effective in patients with Exon20ins (11).

There is no standard regimen for the treatment of patients with EGFR Exon20ins. Platinum-based doublet chemotherapies are commonly used in the clinic, however the treatment effect is not optimal. The first to third generation of EGFR TKIs as well as onco-immune therapy provides limited treatment effect in the above mentioned population. Real-world data showed that ORR of patients receiving the 2nd line therapies was ~ 14% (7% to 24%), and median PFS was ~ 3.7 months. In another retrospective real-world analysis of 165 Chinese NSCLC patients harboring EGFR Exon20ins who were diagnosed with advanced disease between 2015 and 2018, data showed that ORR of 1st line platinum-based chemotherapy was 19.2%, DCR at 6 months was 41.3%, and median PFS was 6.4 months (95% confidence interval: 5.7 to 7.1 months). The ORR for 2nd line chemotherapy was 17.6%, ORR for 2nd line EGFR TKIs was 5.9%. The median PFS for 2nd line chemotherapy was 4 months and for EGFR TKIs was 2 months (12-13). These data suggest that highly effective targeted therapy against EGFR Exon20ins is urgently needed in the clinic.

2.2 Investigational agent

DZD9008 is an oral, potent, selective and irreversible EGFR TKI targeting EGFR sensitizing mutations, EGFR T790M mutation, EGFR Exon20ins, HER2 Exon20ins and EGFR uncommon mutations. DZD9008 demonstrates potent activities against all known EGFR or HER2 mutations with less potent activity against wild type EGFR.

2.3 Non-clinical and clinical information of DZD9008

2.3.1 The key data from primary pharmacology studies were as follows:

- DZD9008 is a potent and selective irreversible EGFR TKI that targets various EGFR Exon20ins, uncommon mutation, or classical mutation with enzymatic IC50 of [redacted].

- DZD9008 shows good selectivity against kinase panel of 117 kinases. In addition to EGFR (L858R/T790M), only 14 other kinases were inhibited by greater than 50% at 1 μM of DZD9008 (ranging from 51% - 96% inhibition). DZD9008 does not hit IGF1R (insulin growth factor receptor 1) and InsR (insulin receptor), demonstrated by both low kinase activity (IC50 > 100 nM) and low cellular pIGF1R and pInsR modulation activity (IC50 of ~ 5000 nM).

- DZD9008 downregulates pEGFR with IC50 ranging from [redacted] in tumor cells expressing EGFR L858R, Exon19del, L858R/T790M, Exon20ins or uncommon mutations, and pHER2 with IC50 of [redacted] in tumor cells engineered with different subtypes of HER2 Exon20ins. In contrast, DZD9008 was less potent in modulating pEGFR in tumor cells expressing wild type EGFR, with IC50 of [redacted]

- In cell proliferation assays, DZD9008 suppresses cell proliferation with GI50 of [redacted] in tumor cells carrying EGFR L858R, Exon19del, L858R/T790M, Exon20ins or uncommon mutations, and GI50 of [redacted] in tumor cells engineered with different subtypes of HER2 Exon20ins.

- In a number of standard and patient derived tumor xenograft models, DZD9008 induces profound tumor regression in a dose dependent manner, while demonstrates only modest effect in xenograft model carrying wild type EGFR.

2.3.2 The key findings in the secondary and safety pharmacology studies were as follows:

- In secondary pharmacology screening, DZD9008 had activity (a defined IC50 value) against 55 targets. No targets had activity within 50 folds of wild type EGFR biochemical enzyme activity IC50 ([redacted]).

- DZD9008 inhibits the function of the hERG potassium channel with IC50 value of [redacted] Using manual patch clamping, DZD9008 showed activity at three other cardiac ion [redacted]

- There were no notable effects on the cardiovascular system in conscious telemetered dogs following administration of single doses up to 30 mg/kg DZD9008.

- There were no notable effects on the respiratory and central nervous system (CNS) in rats following administration of single doses up to 100 mg/kg DZD9008.

2.3.3 The key data from Nonclinical pharmacokinetics were as follows:

- DZD9008 has favorable drug metabolism and pharmacokinetics (DMPK) properties for oral dosing. Pharmacokinetic exposure approximately increased in proportion to oral dose in rats and dogs. Accumulation in terms of AUC was less than 2 folds on multiple daily dosing in rat and dog.

- In vitro data have indicated that CYP3A4/5 are the principal P450 isozymes responsible for human metabolism. Thus, co-administration with CYP3A4/5 perpetrators may alter the exposure of DZD9008. The metabolism of DZD9008 in hepatocytes from mouse, rat, dog and human was primarily to N-dealkylated and N-oxidative products with direct conjugation to a range of glutathione, cysteine and glucuronide conjugates. Glutathione conjugation may be an important pathway in DZD9008 metabolism in rat, dog and human.

- Based upon in vitro data and clinical exposure, DZD9008 DDI risk is considered unlikely to cause clinically significant hepatic drug interactions at clinically relevant concentrations through inhibition or induction of cytochrome P450 enzyme activity. Combination of In vitro data and DZD9008 clinical exposure indicated that

DZD9008 is likely a perpetrator of DDI through inhibition of P-gp, BCRP and OATP1B1 transporters, and induction of CYP3A4, CYP2C enzymes.

- Following intravenous and oral administration of [14C]-DZD9008 in intact and bile-duct cannulated rats, the major route of excretion was via feces and/or biliary route, with urinary elimination being a minor component. Excretion was rapid in rats, with the majority radioactivity recovered in the first 48 hours.

- Concentration of radioactivity in tissues were quantified from the whole body auto-radiography, using a validated image analysis system. Following oral administration of [14C]-DZD9008 to male and female non-pigmented rats in a QWBA study, drug related material was widely distributed to all tissues, with highest concentrations of radioactivity between 2 and 6 hours with elimination - GI tract, spleen, liver, kidney, lung and glandular tissue. Radioactivity in the brain and spinal cord remained below the limit of quantification. Following a single oral administration of [14C]-DZD9008 to male partially-pigmented rats, distribution of radioactivity followed a similar pattern to that observed in the non-pigmented animals. Terminal half-life of radioactivity in tissues ranges from 2 to 1043 days. Radioactivity in the melanin-containing uveal tract and meninges was measurable up to and including 60 days after dose administration, indicating affinity of the test material for melanin.

2.3.4 The key findings from Nonclinical toxicity studies were as follows:

- In both dog and rat toxicity studies, most observations and findings are consistent with consequences of the pharmacological inhibition of wild type EGFR by DZD9008 or sequelae to primary effects. A wide range of organs and tissues containing epithelial cell lineages were affected with changes spanning epithelial atrophy through to erosion, inflammation and necrosis. Dose-limiting toxicity was principally deterioration of the animals from low food intake and body weight loss as a consequence of gastrointestinal (GI) toxicity resulting from effects of EGFR inhibition by DZD9008.

- In the 14-day dose range finding (DRF) study in dog, toxicity findings were associated to pharmacological inhibition of EGFR or sequelae secondary to primary effects. Doses of 50 and 75 mg/kg were not tolerated and associated with moribund, notable body weight loss and decreased appetite, severe clinical signs (including moribund, weakness, deep breathing, lethargy, thin, decreased activity, diarrhea, oral mucosa color change, emesis); and macroscopic findings of diffused/multifocal dark red in GI tract. Besides, altered clinical pathology parameters related to liver/kidney injury/inflammation at moribund condition were noted at 50 and 75 mg/kg. Major target organs identified by histology are: gastrointestinal tract (hemorrhage, ulcer, erosion, gland dilatation), thyroid (follicular atrophy), lacrimal gland (acinar cell atrophy), vagina (epithelial atrophy), tongue/esophagus (epithelial atrophy/erosion/neutrophilic infiltrate), eye (cornea epithelial atrophy), pancreas (acinar cell secretory depletion), kidney (cortical tubular dilatation), and mandibular

salivary gland acinar cell secretory depletion, which are considered EGFR inhibition related; Lymphoid depletion of immune organs (thymus, spleen and lymph nodes) and adrenal gland hypertrophy were likely due to the stress; bone marrow myeloid hypercellularity could be the inflammatory response to gastrointestinal tract change. At lower doses of 15 and 25 mg/kg, similar but milder or less findings presented.

- In the 4-week GLP dog study, dogs were dosed at 3, 6, 12/8 (males) or 12 (females) mg/kg. The toxicity findings were similar with 14-day DRF dog study. Up to 12 mg/kg was tolerated in female dogs, while one female at 12 mg/kg showed severe body weight loss, low food consumption and diarrhea. Twelve mg/kg was intolerable in males due to EGFR inhibition related effects (including diarrhea, body weight loss and notable low food intake); when the dosage reduced to 8 mg/kg, males were well tolerated. Mild ectasia of the glands of the colon was observed at one female dog given 12 mg/kg/day DZD9008. Though exposure (C_{max} and AUC_{last}) was comparable with peers, one male dog dosed at 6 mg/kg showed EGFR inhibition related effect in the first two weeks including diarrhea, yellow/reddish mucus in feces, low food intake, body weight loss, and thin appearance, but these findings relieved in late stage of dosing phase. The GI findings are dose-limiting and reversible. NOAEL is defined as 3 mg/kg and 6 mg/kg for males and females, respectively.

- In the 13-week GLP dog study, dogs were dosed at 1, 3 or 6 mg/kg/day for 13 weeks and well tolerated at all dose levels, with clinical signs limited to a non-adverse increase in the incidence of loose or liquid feces at 3 or 6 mg/kg/day, which were reversible during the treatment-free period. Slight decreases in primary red cell parameters at 6 mg/kg/day and slight decreases in potassium and albumin concentrations at 3 or 6 mg/kg/day at the end of the dosing period were reversible and considered not to be adverse. There were no pathology findings to indicate target organ toxicity. NOAEL is 6 mg/kg/day.

- In the 4-week DRF rat study, male rats were dosed with 25, 50, 100 or 200 mg/kg DZD9008 for up to 28 days. Dose level of 100 and 200 mg/kg were not tolerated. Moribund, notable body weight loss and adverse clinical signs (soft/watery feces) were observed at 100 and 200 mg/kg. Reduction of alkaline phosphatase (47%), total cholesterol (16%) and triglyceride (48%) were observed at 100 mg/kg. Slightly decreases of albumin was noted at 50 mg/kg. DZD9008-related microscopic findings were present in the skin (crust formation in the epidermis), GI tract (erosion of mucosal epithelium, necrosis and inflammation), eye (corneal epithelial atrophy), thymus (lymphoid decrease) and pancreas (acinar atrophy) in 100 mg/kg or 200 mg/kg dosing groups. Rats were well tolerated at 25 and 50 mg/kg.

- In the 4-week GLP rat study, animals were dosed at 25, 50/15, 65/35 mg/kg. Similar to findings in 4-week DRF rat study, GI related changes (soft stool, low food intake, body weight loss) are dose limiting. High dosage (65 and 50 mg/kg) was intolerable due to remarked body weight loss and after 5 - 6 day dosing, doses were reduced to 35 and 15 mg/kg, respectively. Animals were well tolerated at ≤ 35 mg/kg. Minimal

persistent pupillary membrane, iris synechia, or opacity of anterior lens capsule were observed at all dose levels. Minor clinical pathology changes (decreases in albumin, total protein, red blood cell count, hematocrit and/or hemoglobin concentration) along with minor histopathology findings in lung (diffuse, multifocal or focal alveolar infiltrates of macrophages in the lung, both sexes) and pancreas (focal or multifocal fibrosis, males only) were noted at all dose levels. Except for pancreas fibrosis, all above findings were not observed at the end of recovery phase. NOAEL is defined as 35 mg/kg.

- In the 13-week GLP rat study, DZD9008 administered to animals at 15, 25 or 35 mg/kg/day for 13 weeks resulted in reduced body weight gain at all dose levels and non-adverse clinical signs (flaky tails, tail riding and head scabbing) at 35 mg/kg/day. Slight changes in primary red cell parameters, neutrophil counts and liver, kidney and spleen weights were reversible and considered not to be adverse. Target organs were identified as the mesenteric lymph nodes, lungs and mammary gland (males only) but based on the severity of the changes and apparent reversibility they were considered not to be adverse under the conditions of this study. NOAEL is 35 mg/kg/day.

- When dosing duration was extended from 4 weeks to 13 week, no new toxicity findings were noted. In addition, the severity and frequency of the toxicity findings did not change when the dosing duration increased.

- DZD9008 showed no evidence of genotoxicity potential in AMES, in vitro chromosome aberration assay or in vivo micronucleus assay in rat studies.

- DZD9008 showed no evidence of phototoxic potential in an in vitro 3T3 cell phototoxicity assay conducted in the presence or absence of UV light.

- The results from the toxicology studies support progression into clinical trials in patients with advanced NSCLC.

- Further details are provided in the Investigator's Brochure (IB).

2.3.5 Clinical information of DZD9008

There are three clinical studies of DZD9008 monotherapy for which efficacy analysis has been conducted in NSCLC subjects with EGFR Exon20ins post platinum-based chemotherapy: (DZ2019E0001, and DZ2019E0002 and DZ2020E0001).

As of April 3, 2023, in 74 prior platinum-based chemotherapy treated NSCLC subjects with EGFR Exon20ins from studies DZ2019E0001 and DZ2019E0002, the confirmed ORR assessed by investigators were [redacted] across all dose levels. At the dose level of 200 mg and 300 mg, the confirmed ORR was [redacted] and [redacted] respectively.

In another phase 2 pivotal study DZ2020E0001 in Chinese NSCLC with EGFR Exon20ins, in 97 subjects of efficacy analysis set, the confirmed ORR was [redacted] and the confirmed DCR was

[redacted] as assessed by IRC. The median DoR was [redacted] months. The longest DoR already reached [redacted] months, and subject is still responding.

By the same DCO, a total of 313 advanced NSCLC subjects with EGFR or HER2 mutations were included in the safety analysis set. The most common (≥ 20%) TEAEs across all dose levels were diarrhea, rash, anemia, blood creatine phosphokinase increased, paronychia, decreased appetite, vomiting, nausea, blood creatinine increased, and weight decreased.

As the bioanalytical sample cut-off dates of February 15, 2021 for study DZ2019E0001 and September 9, 2020 for study DZ2019E0002, preliminary PK analysis showed that the median t_{max} occurred about [redacted] post-dose. Following a single oral dosing, DZD9008 exhibited low to moderate apparent clearance (CL/F) and extensive volume of distribution (V/F). Following once daily dosing, steady state was achieved by day[redacted] DZD9008, with an accumulation of around[redacted] folds in AUC which was expected based on around 50-hour half-life. At steady state, DZD9008 has flat PK profile and there was limited fluctuation between $C_{ss,max}$ and $C_{ss,min}$, which is desirable PK properties to maintain effective concentrations during the dosing interval. DZD9008 exhibited approximately dose-proportional increases in exposure across the dose range investigated (50 - 400 mg) on multiple-dose. The impact of high-fat meal on the bioavailability of DZD9008 has been evaluated in healthy subjects (n = 20, study DZ2021E0004) as well as in NSCLC patients (n = 12) in this study at the 300 mg dose with the tablet (the proposed commercial formulation). Both studies showed high-fat meal has no to negligible effect on the C_{max} and AUC of DZD9008. Since food might help to mitigate the GI related toxicity, it is recommended that DZD9008 be taken with food in this study.

Refer to the current DZD9008 Investigator's Brochure (IB) for a complete summary of nonclinical and clinical information including safety, efficacy, and pharmacokinetics.

3. STUDY DESIGN AND RATIONALE

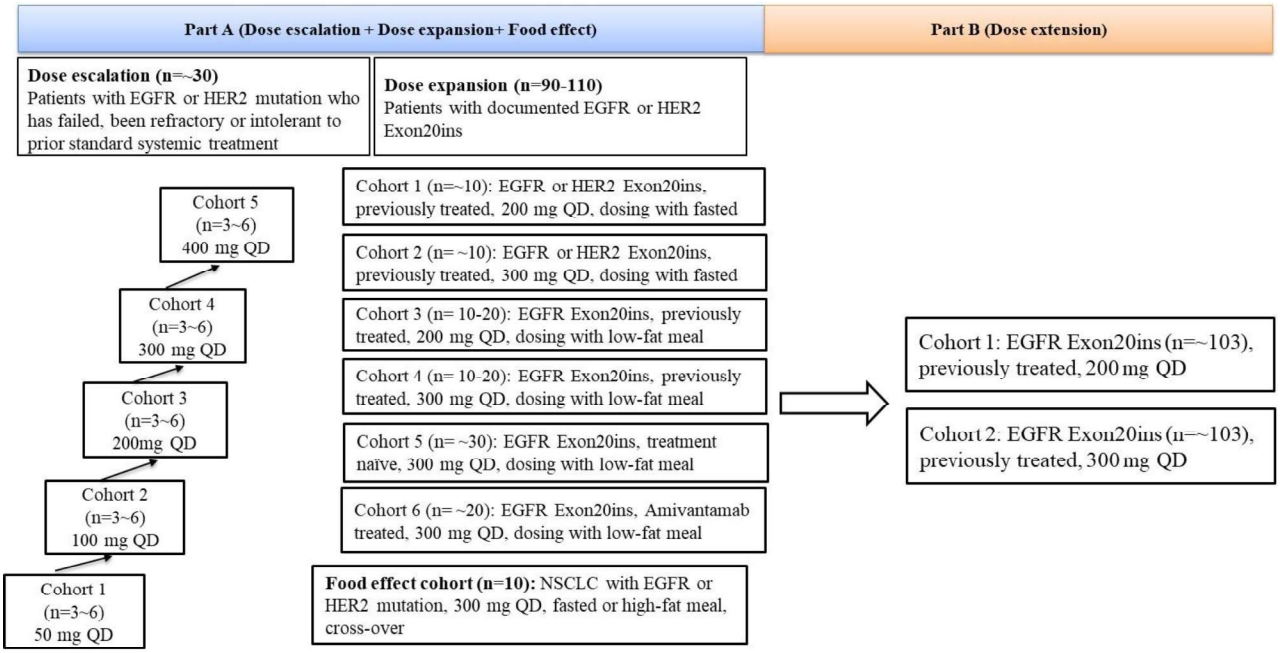
The clinical study protocol has finished peer review within Dizal Pharmaceuticals.

3.1 Overall study design and flowchart

This is a phase 1/2, open-label, multicenter study of DZD9008 administered orally in patients with advanced stage NSCLC with EGFR or HER2 mutation. The study design allows a dose escalation of DZD9008, with intensive safety monitoring to ensure the safety of the patients, followed by dose expansion at selected dose (s) in Part A, then move into cohort of patients with EGFR Exon20ins in Part B at defined RP2D.

There are two parts in this study. Part A, Dose escalation, dose expansion and food effect, and Part B, Dose extension. Approximately a total of 130 - 150 patients and ~206 patients are expected to be enrolled into Part A and Part B, respectively. Part B will be triggered when RP2D is defined. Following review and approval from IEC/IRB and/or local regulatory authority (as applicable) on the optimal RP2D selection, eligible patients can be enrolled into the optimal RP2D cohort to ensure approximately 103 patients be enrolled into this cohort.

Figure 1 Study Flowchart



Part A, dose escalation

The number of patients will depend upon the number of dose escalation necessary and potential expansion. Approximately 30 evaluable patients with advanced EGFR or HER2 mutant NSCLC who relapsed from or were refractory, or were intolerant to standard systemic therapy will be enrolled.

Part A, food effect

A separated cohort of ~10 evaluable patients will be enrolled to assess the effect of high-fat meal on PK of DZD9008 at a defined dose (i.e. predicted efficacious dose or RP2D).

Part A, dose expansion

To further evaluate safety, tolearbility, PK and preliminary anti-tumor efficacy of DZD9008 and help define RP2D, a total of approximately 90 - 110 additional patients with EGFR or HER2 Exon20ins will be enrolled into 6 different cohorts (see details in the study flow chart). There is no DLT assessment period for patients in Part A expansion cohorts. However, the incidence and type of DLT like toxicities will be taken into consideration by the SRC in determining dose escalation steps and RP2D.

- Dose expansion cohort 1 (n = ~10): patients with EGFR Exon20ins or HER2 Exon20ins, previously treated with at least one line of systemic therapy, dose at 200 mg in fasted state.

- Dose expansion cohort 2 (n = ~10): patients with EGFR Exon20ins or HER2 Exon20ins, previously treated with at least one line of systemic therapy, dose at 300 mg in fasted state.

- Dose expansion cohort 3 (n = 10 ~ 20): patients with EGFR Exon20ins, previously treated with at least one line of systemic therapy, dose at 200 mg with low-fat meal.

- Dose expansion cohort 4 (n = 10 ~ 20): patients with EGFR Exon20ins, previously treated with at least one line of systemic therapy, dose at 300 mg with low-fat meal.

- Dose expansion cohort 5 (n = ~ 30): patients with EGFR Exon20ins, treatment naïve, dose at 300 mg with low-fat meal. This cohort will be triggered when the emerging data shows DoR reaches 6 months, and the food effect cohort data is available.

- Dose expansion cohort 6 (n= ~ 20): patients with EGFR Exon20ins, previously treated with at least one line of systemic therapy, and patients should be refractory to, relapsed from or intolerant to amivantamab treatment, DZD9008 will be dose at 300 mg with low-fat meal.

Part B, dose extension

Part B is a phase 2, open-label, randomized pivotal study with 2 dose cohorts to evaluate the anti-tumor efficacy of DZD9008. Approximately 206 NSCLC patients with EGFR Exon20ins will be enrolled into 2 separate cohorts of this part of study. Simon two-stage design (14) will be used within each dose cohort respectively. When both dose cohorts pass stage 1, the response rate of two cohorts will be compared to identify the more effective arm. Alternatively, Dizal may trigger the earlier discussion with regulatory on the optimal RP2D selection upon emerging efficacy and safety data.

Eligible patients will be stratified by the brain metastasis at baseline (Yes, No) and number of regimens of prior anti-cancer systemic therapy (<3, 3) and randomized to the DZD9008 200 mg or 300 mg arm at the ratio of 1:1.

- Cohort 1: patients with EGFR Exon20ins, previously treated with at least one line but no more than 3 lines of systemic therapy, DZD9008 will be dosed at 200 mg with food.

- Cohort 2: patients with EGFR Exon20ins, previously treated with at least one line but no more than 3 lines of systemic therapy, DZD9008 will be dosed at 300 mg with food.

Following review and approval from IEC/IRB and/or local regulatory authority (as applicable) on the optimal RP2D selection, eligible patients can be enrolled into the optimal RP2D cohort to ensure approximately 103 subjects be enrolled into this cohort.

3.2 Rationale for conducting this study and for study design

3.2.1 Part A, Dose escalation, dose expansion and food effect of DZD9008

Part A, Dose escalation

This is a first time in patient study for DZD9008. The primary purpose of this part of the study is to assess safety, tolerability and determine MTD and/or RP2D of DZD9008.

The preclinical data suggest DZD9008 has broad inhibition effect against different types of EGFR or HER2 mutations, including EGFR sensitizing mutation, T790M, EGFR and HER2 Exon20ins, EGFR uncommon mutation etc. Thus, the target patient population of Part A includes any patients with locally advanced or metastatic NSCLC with all types of documented EGFR or HER2 mutations who have progressed despite prior systemic anti-cancer therapy (i.e. chemotherapy, with or without prior EGFR or HER2 target therapy), are relapsed or intolerant to current standard therapy.

The starting dose, dose escalation and cohort size are based upon accepted methology for phase I oncology studies defined by the United States, European, Japanese and Chinese regulation (Section 5.2). This part of study will determine the MTD based upon assessment of the safety, tolerability and pharmacokinetic data collected during the first 28 days of daily dosing. The 28-day assessment period was selected as the major toxicities leading to cessation of dose escalation in such studies (haematological, gastrointestinal, liver enzymes) are anticipated to present within this duration. The dose escalation method will utilize a Bayesian adaptive design, where the model provides a recommendation of the next dose (see Section 5.1.1 for more details).

Part A, Food effect

A cohort of NSCLC patients with EGFR or HER2 mutation (Food effect cohort, n = ~10) will be enrolled at the defined dose (ie. predicted efficacious dose etc) to evaluate the effect of high-fat meal on exposure of DZD9008. Food effect study can be run in parallel with dose extension, and the emerging results from food effect study will guide optimization of dose scheme in Part B. The detailed process is specified in Section 5.1.1.2.

Part A, Dose Expansion

To further evaluate safety, tolerability, PK and preliminary anti-tumor efficacy of DZD9008 in fasted state or with low-fat meal (approximately 400 to 500 Kcal with about 25% of calories comes from 11-14 grams of fat), to help define and optimize RP2D, a total of approximately 90~ 110 additional patients with EGFR or HER2 Exon20ins will be enrolled into 6 different cohorts (see details in the study flow chart). Cohort 6 aims to specifically evaluate the anti-tumor activity of DZD9008 in amivantamb treated patients. There is no DLT assessment period for patients in Part A expansion cohorts. However, the incidence and type of DLT like toxicities will be taken into consideration by the SRC in determining dose escalation steps and RP2D.

Preliminary results (n = 3) from the food effect study at 300 mg have shown that high-fat meal had limited effect on bioavailability of DZD9008. Hence, 300 mg once daily taken with low-fat meal is not anticipated to increase the exposure of DZD9008 to clinically relevant extent, and is unlikely to increase safety risk. Additionally, experience from other TKIs showed that drug administered with food could improve GI tolerability (15).

In Part A, Dizal plans to collect archived tumor tissue or fresh tumor biopsy to confirm the EGFR or HER2 mutation status retrospectively. This could be used to support the development of companion diagnostics.

In Part A, radiological scans (including those at unscheduled visits, or outside visit windows) for patients with EGFR Exon20ins will be collected on an ongoing basis for retrospective reviews by the Independent Review Committee.

For specific part, Japan will follow Japan local CSP addendum in Part A.

3.2.2 Part B, Dose Extension of DZD9008

Although amivantamab (JNJ-61186372) and mobocertinib (TAK-788) have recently received accelerated approval for NSCLC patients with EGFR Exon20ins, the efficacy and safety of thse two drugs should be further validated in phase 3 confirmatory studies with larger cohorts.

From the real-world data analysis, current clinical treatment provides minimal benefit to NSCLC patients with EGFR Exon20ins. Platinum-based doublet chemotherapy is commonly used in the clinic, however, ORR was only around 14% (7.0% - 24.4%) and median PFS is around 3.7 months (2.6 - 5.9 months) for patients received prior treatment (13). In another real-world study of Chinese patients with EGFR Exon20ins, ORR for patients received first-line and second line chemotherapy were 19.2% and 17.6%, respectively; median PFS for patients received first-line and second line chemotherapy were 6.4 months (5.7 - 7.1 months) and 4.0 months (3.2 - 4.8 months), respectively (12). Current available EGFR TKIs only confer ORR of around 8.7% and 5.9%, and median PFS of 2.9 months and 2.0 months for patients received first line and second line treatment, respectively (16). Data from Korea and Japan etc. shows similar results (17).

Given the unmet medical need in the aforementioned patient population alongside with the lack of well-proven treatment options, and the encouraging efficacy (BoR of [redacted] and [redacted] at selected RP2D of 200 mg and 300 mg once daily, separately, by DCO April 3, 2021) and well tolerated safety profile reported in the ongoing Part A of this study, it was considered resonable to initiate Part B to further assess anti-tumor efficacy and safety of DZD9008 at both 200 mg and 300 mg. The Part B of DZ2019E0001 study is planned as a phase 2, open-label study of DZD9008 to assess its anti-tumor efficacy as primary objective using ORR by IRC in NSCLC patients with EGFR Exon20ins. PK will also be assessed in this Part of the study. The doses of 200 mg once daily and 300 mg once daily were selected as phase 2 dose (s) based on available safety, tolerability, PK and efficacy data from both DZ2019E0001 Part A and DZ2019E0002 studies. In Part B, Dizal plans to enroll NSCLC patients with EGFR Exon20ins which has been confirmed in a local CLIA-certified laboratory (or equivalent) or Sponsor designated central laboratory [redacted]). An adequate amount of archived tumor tissue or fresh biopsy must be available prior to the study entry for EGFR Exon20ins mutation confirmation in Sponsor designated central laboratory using the designated assay and for supporting future companion diagnostics development and approval. If a pre-study written documentation of EGFR Exon20ins in tumor tissue is available from Sponsor designated central laboratory using the designated assay, no additional tumor sample needs to be submitted. In addition, collecting and storing plasma samples for isolation of ctDNA to develop liquid biopsy diagnostic test is also planned.

In addition, Dizal may perform genetic research in the DZD9008 clinical studies to explore if genetic polymorphism/variations may affect the clinical parameters associated with DZD9008. Collection of ctDNA and DNA samples from populations with well described clinical

characteristics may lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guide treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to DZD9008 but also susceptibility to NSCLC for which DZD9008 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

4. PATIENT SELECTION AND RESTRICTIONS

Investigators should keep a record, e.g, patient screening log, of patients who entered pre-study screening. Eligibility should be reviewed and documented by the investigator, or appropriately qualified delegate, prior to enrolment.

Each patient must meet all of the inclusion criteria (core inclusion criteria and cohort specific criteria) and none of the exclusion criteria at the time of starting study treatment. Under no circumstances there can be exceptions to this rule.

4.1 Inclusion criteria

4.1.1 Core inclusion criteria

For inclusion in the study, patients must fulfil all of the following core criteria:

1. Patients must be able to understand the nature of the trial and provide a signed and dated, written informed consent form prior to any study specific procedures, sampling and analyses.

2. Aged at least 18 years old.

3. Histological or cytological confirmed locally advanced or metastatic NSCLC. An adequate amount of tumor tissue (archived tumor tissue, or fresh biopsy if archived tissue is not available) must be available at the time of enrollment for central laboratory confirmation of mutations and/or companion diagnostics development.

4. Patients must exhibit Eastern Cooperative Oncology Group (ECOG) performance status 0 - 1 at ICF signature with no deterioration over the previous 2 weeks.

5. Predicted life expectancy ≥ 12 weeks

6. Patient must have measurable disease according to RECIST 1.1: At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for repeated measurement.

7. Patients with brain metastasis (BM) can only be enrolled under the condition that BM is previously treated and stable e.g., no evidence of progression for at least 2 weeks

after CNS-directed treatment as ascertained by clinical examination and brain imaging (magnetic resonance image [MRI] or computed tomography [CT] scan) during the screening period, neurologically asymptomatic and not require corticosteroid treatment. If BM has been treated with radiation or surgery, there should be a time window of ≥ 2 weeks or ≥ 4 weeks respectively, before the first dosing of DZD9008 to ensure radiation or surgery related AEs have recovered to ≤ grade 1.

8. Adequate organ system functions, as outlined below

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Hemoglobin ≥ 9 g/dL
- Total bilirubin ≤ 1.5 x ULN if no liver metastases or ≤ 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN if no liver involvement or ≤ 5 x ULN with liver involvement
- Creatinine ≤ 1.5 x ULN, or creatinine clearance ≥ 50 mL/min as measured or calculated by the Cockcroft-Gault method or others based on local practice.
- International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (APTT) ≤ 1.5 x ULN; Serum amylase ≤ 1.5 x ULN and serum lipase ≤ 1.5 x ULN

9. For inclusion in the optional genetic research study, patient must provide informed consent for genetic research. If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspect of the study.

4.1.2 Cohort specific inclusion criteria

In addition to meet all of the core inclusion criteria, subjects must meet cohort specific inclusion criteria for their enrolment to specific cohort.

4.1.2.1 Part A

Dose escalation

Patients must have documented histologically or cytologically confirmed locally advanced or metastatic NSCLC with EGFR or HER2 mutations, and have relapsed from, been refractory to or are intolerant to prior standard therapy without preferred alternative therapy.

Dose expansion

Dose expansion cohort 1 and cohort 2: NSCLC patients with EGFR Exon20ins or HER2 Exon20ins, who have relapsed from, been refractory to or are intolerant to at least one line of prior systemic therapy.

Dose expansion cohort 3 and cohort 4: NSCLC patients with EGFR Exon20ins, who have relapsed from, been refractory to or are intolerant to at least one line of prior systemic therapy.

Dose expansion cohort 5: NSCLC patients with EGFR Exon20ins, who have not received prior systemic therapy (treatment naïve).

Dose expansion cohort 6: NSCLC patients with EGFR Exon20ins, who have recevied at least one line of prior systemic therapy, and must have relapsed from, been refractory to or intolerant to Amivantamab treatment.

4.1.2.2 Part B

Patients must have histologically or cytologically confirmed locally advanced or metastatic NSCLC with documented EGFR Exon20ins mutation in tumor tissue from a local CLIA-certified laboratory (or equivalent) or Sponsor designated central laboratory prior to the study entry.

An adequate amount of archived tumor tissue (if a patient has more than one FFPE blocks, the most recent tissue is preferred) or any fresh tumor biopsies (if archived tumor sample is not available) must be available prior to the study entry for EGFR Exon20ins mutation confirmation in Sponsor designated central laboratory using the designated assay and for supporting development of tumor tissue-based companion diagnostics for DZD9008. If a pre-study written documentation of EGFR Exon20ins in tumor tissue is available from Sponsor designated central laboratory using the designated assay, no additional tumor sample needs to be submitted.

Patients should have received at least 1 line, but no more than 3 lines of systemic therapy for metastatic/locally advanced disease (who must have progressed on, or be intolerant of, at least one prior line with platinum-based chemotherapy).

4.2 Exclusion criteria

1. Treatment with any of the followings:

    - For expansion cohorts of Part A and Part B extension cohorts: Patients who have received prior Poziotinib, TAK-788, CLN-081, BDTX-189 or furmonertinib or any other EGFR/HER2 exon20ins small molecule inhibitors treatment should be excluded. Other EGFR TKIs, such as gefitinib, erlotinib, osimertinib, afatinib, dacomitinb are not considered EGFR or HER2 Exon20ins small molecule inhibitors, thus prior treatment with these drugs are allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI, and a minimum wash-out period of 8 days (approximately 5x half-life) prior to the first administration of DZD9008 is needed.

- Treatment with EGFR or HER2 antibodies or other antibodies within 4 weeks before the first administration of DZD9008.
- Any cytotoxic chemotherapy, investigational agents or other anticancer drugs from a previous treatment regimen or clinical study within 14 days before the first administration of DZD9008.
- Major surgery (excluding placement of vascular access) within 4 weeks before the first administration of DZD9008.
- Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation which must be completed within 4 weeks before the first administration of DZD9008.
- Patients currently receiving (or unable to stop using) medications known to be potent inhibitors or inducers of CYP3A within 1 week or 2 weeks, respectively, before the first administration of DZD9008.
- Prior treatment with any onco-immunotherapy (e.g., immune checkpoint inhibitors PD-1, PD-L1, CTLA-4) within 4 weeks before the first administration of DZD9008.
- Treatment with any investigational drug within five half-lives of the compound (or discuss with Dizal Study team).
- Treatment with herbal supplements within 1 week and unable to stop using.

2. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting DZD9008 with the exception of alopecia and grade 2 prior platinum-therapy related neuropathy.
3. Spinal cord compression or leptomeningeal metastasis.
4. As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C, human immunodeficiency virus (HIV) and COVID-19 (per local practice). Screening for chronic condition is not required.
5. Any of the following cardiac criteria

    - Mean resting corrected QT interval (QTc) > 470 msec (if in France and Canada: > 470 msec for women or > 450 msec for men) obtained from 3 electrocardiograms (ECGs) at screening.

- Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG, e.g., complete left bundle branch block, third degree heart block, and second-degree heart block, PR interval > 250 msec.
- Any factors that increase the risk of QTc prolongation, such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval.
- Prior history of atrial fibrillation within 6 months of first administration of DZD9008, except prior drug treatment related and recovered.

6. For Part B, prior malignancy within 2 years requires active treatment, except for adequately treated basal cell skin carcinoma, in situ cervical carcinoma, or other cancer type which has been disease free for > 2 years with life expectancy >2 years.
7. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
8. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of DZD9008.
9. History of hypersensitivity to active or inactive excipients of DZD9008 or drugs with a similar chemical structure or class to DZD9008.
10. Women who are pregnant or breast feeding.
11. Involvement in the planning and conduct of the study (applies to Dizal staff or staff at the study site).
12. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
13. Known history of bleeding diathesis, i.e., hemophilia, Von Willebrand disease.
14. History of stroke or intracranial hemorrhage within 6 months before the first administration of DZD9008.
15. In addition, the following is considered criteria for exclusion from the exploratory genetic research:

- Previous allogenic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

4.3 Restrictions

The following restrictions apply while the patient is receiving study treatment for the specified time before and after:

1. Male patients with female partners of child-bearing potential should be willing to use barrier contraceptives (i.e., by use of condoms), during their participation in this study and for 6 months following the last dose of the study drug. Patients should avoid procreation for 6 months after completion of trial treatment. Male patients must refrain from donating sperm during their participation in the study and at least for 6 months after the last treatment. If male patients wish to father children, they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

2. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuation. Acceptable methods of contraception include total sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera), copper-banded intra-uterine devices and vasectomized partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse. Female patients should not be breast feeding and must have a negative pregnancy test prior to start dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

   - Post-menopausal defined as aged more than 50 years and amenorrhea for at least 12 months following cessation of all exogenous hormonal treatment.
   - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

3. All patients must avoid concomitant use of medications herbal supplements and/or ingestions of foods with known potent inducer/inhibitory effects on CYP3A4 activity whenever feasible. Such drugs must have discontinued for a period of 1 week (CYP3A4 inhibitors) or 2 weeks (CYP3A4 inducers) prior to first administration of DZD9008. Guidance on medications to avoid, medications that require close monitoring and on washout periods is given in Appendix H. Patients may receive any medication that is clinically indicated for treatment of adverse events. All concomitant medications should be captured on the eCRF.

4. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, e.g., grapefruit juice or marmalade) during the study, e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily.

5. Patients should avoid donating blood whilst participating in studies of DZD9008 and for at least 12 weeks after receiving the last dose of the study treatment.

6. Patients who wear contact lens must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤ 2) while receiving treatment with DZD9008 until at least one week after symptoms have resolved. 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 DZD9008 is permanently discontinued. 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 DZD9008 has been permanently discontinued, Patient should consult the clinic promptly if they have any concerns.

7. Patients require anticoagulation and anti-platelet therapy, i.e., with Warfarin, heparin etc. while receiving DZD9008 may be at increased risk of hemorrhage. They should be monitored for any signs of bleeding.

For restrictions relating to concomitant medications, see next Section 4.3.1.

4.3.1 Concomitant treatment

Information about any treatment within 4 weeks prior to starting of DZD9008 and all concomitant treatments given during the study along with reasons for the treatment will be recorded in the Case Report Form (CRF). After permanent discontinuation of DZD9008 and 28 day follow up, only subsequent regimens of anti-cancer therapy will be recorded in CRF. If medically feasible, patients taking regular medication, with the exception of potent inhibitors and inducers of CYP3A4 (see Section 4.2 and Appendix H), should be maintained on it throught the study period.

All patients must avoid concomitant use of medications, herbal supplements and/or ingestions of food with known potent inducer/inhibitory effects on CYP3A activity whenever feasible. Traditional Chinese Medicine should be avoided. Such drugs must have been discontinued for 1 week (CYP3A4 inhibitors) or 2 weeks (CYP3A4 inducers) prior to first administration of DZD9008. Guidance on medications to avoid, medications that require close monitoring and on washout periods is given in Appendix H.

Patients must avoid live vaccines whist receiving study drug and up to 30 days after the last dose of study drug.

Patients may receive any medication that is clinically indicated for treatment of adverse events. All concomitant medications should be captured on the electronic CRF (eCRF).

Other anticancer agents, investigational agents and radiotherapy should not be given while the patient is receiving DZD9008. The patient may be allowed to take localized palliative radiotherapy only if it has been confirmed local lesion is not progressing, and/or after overall response has been evaluated as disease progression. This is to avoid interfering tumor assessment in the event of disease progression. Study drug interruption is not required in the case of local palliative radiotherapy for pain control (excluding chest and brain). For local

palliative radiotherapy to chest and brain, study drug should be interrupted during and up to 7 days post the palliative radiotherapy. Definitive radiotherapy and other anticancer therapy is not allowed.

Blood transfusions and hematopoietic growth factors are allowed as clinically indicated during the study but not during the screening phase (Part A escalation only) to support blood cell count for eligibility and the DLT assessment period (Cycle 1 in Part A) when transfusions should not be administered unless the patient experiences a hematological DLT or require emergency treatment for any condition.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases. Patients may also receive radiotherapy for painful bony metastases.

Supportive care and other medications that are considered necessary for the patient's well-being, may be given at the discretion of the investigator.

5. STUDY TREATMENT AND CONDUCT

5.1 Treatment

Supply, Packaging and Labeling of DZD9008

DZD9008 drug substance and drug product to be used for this clinical study are manufactured in accordance with Good Manufacturing Practice (GMP).

DZD9008 will be supplied by Dizal as 25 mg, 50 mg, 100 mg, 150 mg and 200 mg tablet by IRT system.

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP requirements for labelling. Label text will be translated into local language.

The label will include the Name of the Sponsor, Study Code, for clinical trial use only and /or any other specific requirements.

DZD9008 tablets of 25 mg, 50 mg, and 100 mg strengths are presented as yellow, round shaped, biconvex, and film-coated tablets. Each HDPE bottle contains 25 units of one strength of the above mentioned 3 different tablets, and with 1 g of pre-packed silica-gel. DZD9008 tablets of 150 mg and 200 mg strengths are presented as yellow, caplet shaped ,biconvex ,and film-coated tablets, with debossing of either the "150 mg" or "200 mg" on one side and the company logo on the other side. The tablet core is off-white to pale yellow after removing the coating film. Each HDPE bottle contains 30 units of one strength of the mentioned 150 mg or 200 mg tablets, and with 1 g of pre-packed silica-gel.

DZD9008 tablet must be stored at storage condition of up to 30°C in the original container(s). The stability study of DZD9008 clinical batches is on-going and will be continued to at least cover the whole clinical trial. The shelf life will be evaluated when stability data becomes available.

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label specifies the appropriate storage condition.

Drug administration

DZD9008 will be given orally, once daily except for Cycle 0 in Part A dose escalation and food effect cohort.

In Part A dose escalation cohort and dose expansion cohorts 1 and 2, patients are required to keep a fasted condition for ≥ 1 hour prior to and ≥ 2 hours post dosing. Water is permitted during this fasted period.

In Part A dose expansion cohorts 3 - 6, patients are recommended to take DZD9008 with a low-fat meal. The low-fat meal is defined as approximately 400 to 500 Kcal with about 25% of calories comes from 11 - 14 grams of fat. Meal record will be collected at clinic site on PK sampling days as described in Table 7. Compliance with prandial conditions for non-PK sampling days is to be confirmed by the study personnel during the study visits (e.g., through patient diaries).

In Part B, patients will receive repeat daily dosing of DZD9008 at 200 mg and 300 mg with food to further investigate its anti-tumor efficacy, safety/tolerability and PK.

Following review and approval from IEC/IRB and/or local regulatory authority (as applicable) on the optimal RP2D selection (i.e., dropping the suboptimal dose), patient who is under screening will start treatment at optimal dose level. Patient who has been enrolled in optimal RP2D cohort can stay and maintain the pre-defined treatment course. The ongoing patient who has been randomized to another (suboptimal) Part B dose cohort can maintain the same dose level, or shift to receive the optimal dose if (a) judged by the investigator that it is of the best clinical benefit to patient; (b) patient's re-consent is obtained.

Dose should be taken approximately 24 hours apart at the same time point each day. On PK and plasma ctDNA sampling day, the dose should be instructed to take by site personnel. Doses should not be missed. If a subject misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken and should be recorded, and subjects should be instructed to take the dose at the next scheduled time. If a subject vomits after taking their DZD9008, they should not make up for this dose.

Enrollment of patients into Part A dose expansion cohort 5 will be triggered when emerging data shows DoR reaches 6 months.

5.1.1 Part A, Dose escalation, dose expansion and food effect

5.1.1.1 Starting dose, dose escalation scheme and stopping criteria

Part A, dose escalation

A dose of 50 mg once daily is proposed as the starting dose in this first time in patient study. This is based on international guidance of starting dose selection for agents in cancer patients (ICH S9) which recommends that the starting dose should be either $1/10^{th}$ of the severely toxic dose (STD10) in rodent toxicity studies or $1/6^{th}$ of the highest non-severely toxic dose (HNSTD) in non-rodent studies. From the preclinical GLP toxicity studies, STD10 in rat is defined as 35~50 mg/kg, and HNSTD in dog is defined as 8 mg/kg. HED derived from $1/10^{th}$ of STD10 in rat or $1/6^{th}$ of HNSTD in dog is 35 mg or 43 mg once daily respectively. A dose of 50 mg once

daily which is slightly higher than the ICH S9 recommended starting dose, is proposed in this first time in patient study. The rationales are as follows: 1) The predicted human free AUC and C_{max} at 50 mg once daily are 0.12 μM*hr and 0.006 μM, respectively, which are comparable to or below the drug exposure at NOAEL in preclinical toxicity studies of rat and dog (see below table); 2) The non-clinical GLP tox findings of DZD9008 are similar to that of other EGFR TKIs, such as gefitinib and osimertinib, with dose limiting toxicities related to inhibition of wild type EGFR; 3) The wild type EGFR related toxicities are consistently translatable from non-clinic to clinic across multiple EGFR TKIs; 4) Wild type EGFR related toxicities are generally monitorable, reversible and manageable, and there are extensive clinical knowledge and experience of monitoring and managing these toxicities based on more than 10 years of using EGFR TKIs in clinical practice; 5) From PK/PD modeling, 50 mg once daily is expected to derive biological effect.

Table 1 Exposure of DZD9008 at NOAEL from preclinical toxicity studies and margin to the predicted drug exposure in human at 50 mg once daily

Study	NOAEL (mg/kg)	Mean free AUC (μM*hour)	Mean free C_{max} (μM)	Fold to the predicted drug exposure in human at 50 mg daily (calculated by free AUC)	Fold to the predicted drug exposure in human at 50 mg daily (calculated by free C_{max})
Rat 1 month GLP toxicity study	35 mg/kg	0.64	0.053	5.3X	8.8X
Dog 1 month GLP toxicity study	3 mg/kg (M)	0.086	0.007	0.7X	1.2X
	6 mg/kg (F)	0.122	0.011	1.0X	1.8X

The dose escalation scheme will not exceed doubling of the dose, in principle. However, up to a quadrupling of the dose may be permitted in the first two escalations only, if the drug concentrations from the first or second dose level are not measurable or are below the predicted drug exposure for biological effect. This will ensure the fewest possible cohorts are exposed to DZD9008 below the presumed therapeutic dose. Non-clinical modelling provides only an approximate prediction of human PK, therefore the planned dose escalation scheme has the flexibility to be amended in light of emerging data.

This study will utilize a Bayesian logistic regression model (BLRM) with overdose control (EWOC) similar to that proposed by Babb (18) for dose escalation to improve the efficiency and accuracy of MTD estimation compared to a traditional 3+3 design. The dose-limiting toxicity (DLT) relationship in the dose escalation part of the study is described by the following model:

$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*), \alpha>0, \beta>0$

where $\text{logit}(\pi(d))= \ln(\pi(d)/(1-\pi(d)))$, $\pi(d)$ is the probability of a DLT at dose d.

d* is the reference dose level, setting as 400mg.

A bivariate normal prior for the model parameters (log(α), log(β)) is elicited based on prior guesses from preclinical data and clinical PK/PD modelling:

- The probability for DLT at lowest dose level 50 mg is very low, we assume it as 0.05 ($\pi(d=50) = 0.05$)
- 400 mg may be a reasonable MTD justified for DZD9008.

Using EAST 6.5, setting number of Beta samples as 1000, we will get the parameters of the prior distributions of model parameters as provided as below:

Parameters	Means	Standard deviations	Correlation
log(α), log(β)	(-1.101,0.191)	(1.838, 1.07)	0.488

The target toxicity level is 30%. The following 3 intervals are defined:

1. [0, 20%) under-dosing
2. [20%, 35%) targeted toxicity
3. [35%, 100%] excessive toxicity

Dose recommendation will be based on posterior summaries for each dose, primarily the posterior probabilities for the above three intervals.

Following the principle of escalation with overdose control (EWOC), after each cohort of patients, the recommended dose is the one with the highest posterior probability of the DLT rate falling in the target interval (20%, 35%) among the doses fulfilling EWOC, i.e., it is unlikely (< 25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval.

The operating characteristics will include the accuracy (percentage of correct recommendations) and the safety profile (percentages of subjects experiencing DLTs and subjects exposed to overdosing doses in the trial) under various scenarios.

Patients will be enrolled to ensure approximately minimum of 3 and maximum of 6 evaluable patients per cohort (additional patients may be enrolled to confirm safety and efficacy as agreed by SRC). Dosing will begin at 50 mg once daily. Table 2 shows an example of dose escalation scheme. However, all potential dose escalation or de-escalation levels after the starting dose may be adjusted in light of emerging safety, tolerability and/or PK data.

For the purpose of planning, every 3 week period (21-day repeated dosing) will be called a Cycle (except Cycle 0, a single dosing followed by a 7-day washout period, and Cycle 1 [28-day DLT assessment period]). In the first two patients of each dose cohort, a minimum of 7-day time interval is required between the first dosing of these two patients. Providing that there are no serious or unexplained safety issues, dosing of the remaining patients of the same cohort will continue without requirement in dosing time interval. However, should ambiguous findings occur, the SRC may choose to stagger the start of dosing remaining patients of the same cohort.

Dose escalation decision will be made by the Safety Review Committee once the last patient in a cohort has completed Cycle 1. Patients are evaluable if they have completed the first multiple dosing cycles and meet the evaluability criteria (see Section 4.1). Any patient experiencing a DLT is also considered evaluable. SRC will review the overall safety of the last completed cohort and any other safety signals from patients treated at other dose levels, as well as the recommendation provided by the adaptive Bayesian model. The final decision on next dose level will be made by SRC.

Table 2 Indicative dose escalation scheme

Cohort	Dose mg (once daily)
1	50
2	100
3	200
4	300
5	400

Stopping criteria have been set in accordance with traditional oncology phase 1 study methodology.

The overall dose-escalation and de-escalation paradiam is described below:

- If no dose-limiting toxicity (DLT) at any dose has been observed, then dose escalation may occur without further modelling.
- After the first DLT has been observed (at any dose), the Bayesian Logistic Regression model will be run to inform subsequent dose selections. Cumulative data on the evaluable patients will be used to estimate the predicted probability of a DLT and the posterior probabilities of DLT in the under-dosing, target and overdosing toxicity intervals at each study dose level. The recommendation for the next dose will then be based on the following principles, e.g.
  - No dose may be chosen where the predicted probability of a DLT exceeds 50%.
  - The posterior DLT risk in the overdosing toxicity level should not exceed pre-specified tolerated risk level (e.g., 25%).
  - The recommendation for the next dose will be chosen to have the maximum posterior probability of DLT level in the target toxicity interval.
- Dose increases will be permitted after review of data from a minimum of 3 evaluable patients.
- Prior to a dose escalation decision, the SRC will review all available safety and PK data.

- Escalations will not exceed doubling of the dose in principle. However, up to a quadrupling of dosing may be permitted in the first two escalations only, if the drug concentrations of the first or second level are not measurable or are deemed to be far from predicted drug exposure (e.g., greater than 2-fold difference) and there have been no significant safety or tolerability issues.

- Dose escalation and de-escalation will be completed when any of the following occur:

  - The required precision of the estimated MTD is achieved (e.g., the posterior 90% credible interval for the MTD is between 0.05 and 0.6).

  - The maximum absorbable dose is achieved (i.e., when no increase in exposure with increasing dose is observed and a change in scheduling is conducted)

  - Unfeasible number of tablets required to deliver dose.

  - No anticipated improvement in efficacy with increasing dose.

  - Decision made by SRC to stop the dose escalation.

5.1.1.2 Definition of dose limiting toxicity (DLT)

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs from the first dose of study treatment (Day 1, Cycle 0) up to the last day of Cycle 1 (28 days after start of multiple dosing) in dose escalation cohorts and which includes, despite optimal therapeutic intervention:

- Hematological toxicity that is Common Terminology Criteria for Adverse Events (CTCAE 5.0) grade 4

- Non-hematological toxicity ≥ CTCAE grade 3 including:

  - Infection including febrile neutropenia

  - Confirmed QTc prolongation (> 500 msec absolute or > 60 msec above baseline)

  - Grade 3 platelet count decreased associated with clinically significant bleeding

- Grade 4 laboratory abnormalities per CTCAE 5.0 including life-threatening consequences.

- Any other toxicity that is

  - Is greater than that of baseline, is clinically significant, and/or unacceptable, does not respond to supportive care, results in a disruption of dosing schedule of more than 7 days or is judged to be a DLT by the Safety Review Committee (SRC).

- That is a protocol defined stopping criteria

A DLT excludes:

- Alopecia of any grade
- Isolated grade 3 laboratory changes without clinical sequelae or clinical significance

However, the incidence and type of DLT-type toxicity post DLT period and beyond will be taken into consideration by the SRC in determining dose escalation steps.

5.1.1.3 Definition of maximum tolerated dose (MTD)

The MTD is defined as the highest dose at which the frequency of a dose limiting toxicity (DLT) is less than 30%.

5.1.1.4 Definition of maximum feasible dose

A dose will be considered to be the maximum feasible dose and dose escalation will stop if:

- Delivery of the next dose level would require dosing of > 8 tablets per administration, or
- There is evidence in the dose-exposure relationship of saturation of absorption.

5.1.1.5 Definition of evaluable patient

In order to be evaluable for determining dose escalation, an evaluable patient is defined as a patient who has received study treatment as appropriate:

- Received the single dose and at least 80% of planned doses of DZD9008 in Cycle 1 (first 28-day of repeat dosing) of Part A
- Completed minimum required safety evaluations

OR

- Experienced a DLT during the single dose to the end of Cycle 1 of Part A

Any unevaluable patients could be replaced in the dose escalation phase to meet minimum required patient number for dose escalation.

5.1.1.6 Safety Review Committee (SRC)

The SRC will consist of:

- Study Team Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from each investigational site
- Sponsor Safety Physician or delegate

The Chief Medical Officer, Clinical Pharmacology Scientist, Study Statistician, Study Leader, and Tox Project Lead, further internal or external experts may be invited as appropriate.

Once there are at least 3 evaluable patients at a dose level, the SRC will review and assess all available safety data from the cohort together with available PK data to make a decision on the dose for the next cohort. Any dose interruptions and reductions will be taken into consideration.

The decision may be to:

- Proceed with dose escalation – refer to Section 5.1.1.1.
- De-escalate the dose either to a previous lower dose level or to an intermediate lower dose level
- Recommend intermediate dose level, dosing interval and/or schedules prior to declaring the RP2D which will be guided by the evolving safety, preliminary efficacy and PK data
- Further expand the dose cohort to confirm safety and efficacy
- Stop the dose escalation part of the study
- Consider alternative dosing frequencies or intermittent dosing schedules
- Declare MTD
- Declare RP2D
- Approve the treatment ongoing patients in lower dose level cohort to escalate DZD9008 to a higher dose level if it is well tolerated.

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators prior to dosing any new patients.

5.1.2 Part A, dose expansion

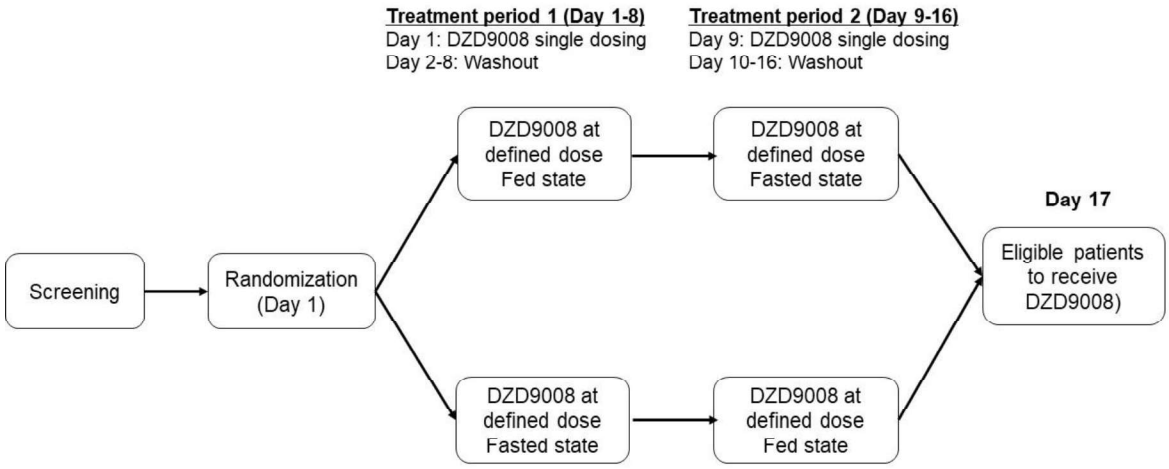
To further evaluate safety, tolearbility, PK and preliminary anti-tumor efficacy of DZD9008 and define RP2D, a total of approximately 90 - 110 additional patients with EGFR or HER2 Exon20ins will be enrolled into 6 different cohorts (Figure 1, study flow chart) at selected doses under fasted or low-fat meal condition. There is no DLT assessment period for patients in Part A expansion cohorts. However, the incidence and DLT-like toxicities will be taken into consideration by the SRC in determining dose escalation steps and RP2D.

Patients will receive repeated dosing of DZD9008 until disease progression, intolerable AEs, discontinuation criteria have met or withdrawal of consent.

5.1.3 The effect of food on PK of DZD9008

An additional cohort (n = ~10) in Part A will be enrolled at the defined dose (i.e. predicted efficacious dose, RP2D, etc) to evaluate food effect on PK of DZD9008.

Figure 2 Study plan of food effect cohort



Note: ~10 patients are planned to be enrolled

* The washout time of each treatment period might be updated in light of emerging human PK data. In general, after single dose, at least 7 days or 5 x half-lives will be allowed for drug elimination.

This is a food effect cohort following cross-over study design. Patients in this cohort will firstly be randomized to receive a single dose of DZD9008 under either fasted or fed condition (a high fat meal), with 5 patients in each condition. After a 7-day washout period or 5 x half-lives (whichever is longer), these patients will be switched to receive a single dose of DZD9008 under cross-over condition. Blood samples will be taken in both conditions at defined time points for the assessment of DZD9008 plasma concentrations.

Fasted condition: Patients must fast for ≥ 1 hours prior to taking a dose and to ≥ 2 hour post dose.

Fed condition: Patients should start ingestion of a recommended meal 30 minutes prior to administration of DZD9008. Patients should finish this meal within 30 minutes or less; however, DZD9008 should be administered at 30 minutes after start of high fat meal. DZD9008 should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 2 hours post-dosing.

Water will be restricted from 1 hour pre-dose until 1 hour post dose, except for the water administered with DZD9008, and any drink provided as part of the meal in the fed portion of the study.

Patients should receive standardized meals. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is

recommended as a test meal. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report. An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

After completion of PK sampling, patients may continue receiving DZD9008 treatment until disease progression, intolerable AEs, discontinuation criteria have met or withdrawal of consent.

5.1.4 Part B, Dose extension of DZD9008

Based on the clinical data from phase 1 study, both 200 mg and 300 mg once daily dosing are selected to further evaluate anti-tumor efficacy, safety and tolerability as well as PK of DZD9008 in EGFR Exon20ins NSCLC in Part B of this study: Following review and approval from IEC/IRB and/or local regulatory authority (as applicable) on the optimal RP2D selection, eligible patients can be enrolled into the optimal RP2D cohort.

Dose and Dosing Regimen

- In the three clinical studies in NSCLC patients (DZ2019E0001, DZ2019E0002 and DZ2020E0001), DZD9008 was well tolerated at doses ranging from 50 mg to 400 mg. Exploratory dose/exposure-safety analysis indicated a positive relationship of DZD9008 exposure with incidence and severity of gastrointestinal (GI) TEAEs. A higher percentage of patients at 400 mg experienced TEAEs which required dose interruption and reduction, compared with patients at other dose levels. Although the incidence of ≥ Grade 3 TEAEs and TEAE related dose interruption and reduction at 400 mg was comparable with that of afatinib (19) and dacomitinib (20), it was not optimal for NSCLC patients with EGFR Exon20ins who require continuous therapy to control this aggressive disease. At the dose level of 200 mg and 300 mg, the incidence of ≥ Grade 3 TEAEs and TEAE related dose interruption and reduction was lower than that of afatinib (19), dacomitinib (20) and mobocertinib (TAK-788) (21).

- Pooled efficacy analysis of the two studies (study DZ2019E0001 [Part A] and DZ2019E0002) showed tumor response at the doses of 100 mg to 400 mg in prior platinum-based chemotherapy treated NSCLC subjects with EGFR Exon20ins. At the dose level of 200 mg and 300 mg, [redacted] In the phase 2, pivotal study DZ2020E0001 in Chinese NSCLC with EGFR Exon20ins, the confirmed ORR at 300 mg QD was [redacted]. This anti-tumor activity was significantly better than current standard therapy, e.g. chemotherapy (12), and comparable to that of mobocertinib (TAK-788) (21) and amivantamab (JNJ-61186372) (22). Noteworthily, tumor response was also observed in patients who relapsed from amivantamab (JNJ-61186372) treatment.

- Higher incidence of dose reduction and interruption occurred at 400 mg cohort was observed as compared to 200 mg and 300 mg cohort, which presumably led to lower clinical efficacy at the 400 mg cohort (ORR 25% at 400 mg).As the doses of 100 mg or above demonstrated clinical activity, and 200 mg or 300 mg is expected to overcome PK variability of DZD9008 to achieve pharmacological relevant exposure required from different subtypes of Exon20ins, thus selecting both 200 mg and 300 mg is appropriate to further evaluate DZD9008 dose optimization for the phase 2 pivotal study.

- DZD9008 elimination half-life is approximately 50 hours following a single dose across the doses investigated, which supports the once daily dosing regimen of DZD9008 in clinical development.

Ethnic sensitivity

- Based on the available data, no obvious difference in safety, PK and anti-tumor efficacy of DZD9008 was observed between Asian and White patients across different regions/countries. Therefore, Dizal believes that the use of same dose and schedule across different regions and countries is appropriate.

Patients enrolled to Part B will receive repeated dosing of DZD9008 at 200 mg or 300 mg once daily. Following review and approval form IEC/IRB and/or local regulatory authority (as applicable) on the optimal RP2D selction, eligible patients can be enrolled into the optimal RP2D cohort. The ongoing patients previously randomized to the suboptimal Part B dose cohort can maintain the same dose level, or shift to receive the optimal RP2D, if judged by the investigator that it is of the best clinical benefit to patients and re-consent is needed (see section 5.1). DZD9008 will be administrated with food as dosing with high fat food in Part A showed limited effect on DZD9008 exposure. Patients with prior therapy may be stratified into sub-cohorts when data is analyzed.

Patients will receive repeated daily dosing of DZD9008 until disease progression, intolerable AEs, discontinuation criteria have met or withdrawal of consent.

5.1.5 Toxicity management and dose modifications

If a patient experiences a CTCAE ≥ grade 3 and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, where the investigator considers the AE of concern to be specifically associated with DZD9008, dosing should be interrupted and supportive therapy will be administered as required in accordance with local practice/guidelines.

If the toxicity does not resolve to ≤ CTCAE grade 2 within 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

If the dose reduction is due to drug related AE, the dose is not allowed to escalate back to the original level after AEs resolve.

On resolution of toxicity within 21 days during treatment, DZD9008 may be restarted at the same dose or a lower dose:

- If a further episode of the same AE subsequently requires dose interruption, patient should restart at one dose level lower (except cohort 1 dose, restart at cohort 1 dose level). (Refer to Table 3). For cohort 2 of Part B, the dose could be reduced to 200 mg and then 150 mg if needed; for cohort 1 of Part B, dose could be reduced to 150 mg).
- If a different AE subsequently requires dose interruption or no prior AE related dose interruption, DZD9008 may restart at same dose level or one dose level lower (unless in Part A Cohort 1, when restart will be at Cohort 1 dose) on improvement of the AE at the discretion of the Investigator.
- Patients who are at the lowest possible dose, and who have demonstrated clinical benefit and an acceptable recovering of AEs to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.
- After a second occurrence of CTCAE grade 4 AE, patient must be permanently withdrawn from study treatment (France and Canada only).

Patients with QTc prolongation fulfilling the following criteria (i.e., confirmed QTc prolongation to > 500 msec absolute or a > 60 msec increase from baseline) should have study treatment interrupted and regular ECGs performed until resolution to baseline. If the toxicity does not resolve to ≤ grade 1 within 3 weeks, the patient will be permanently withdrawn from study treatment. Patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia will permanently discontinue DZD9008.

Patients experiencing corneal ulceration or Interstitial Lung Disease (ILD) will not be permitted to restart study treatment.

Table 3 shows the representative of dose intervention or modification for Part B.

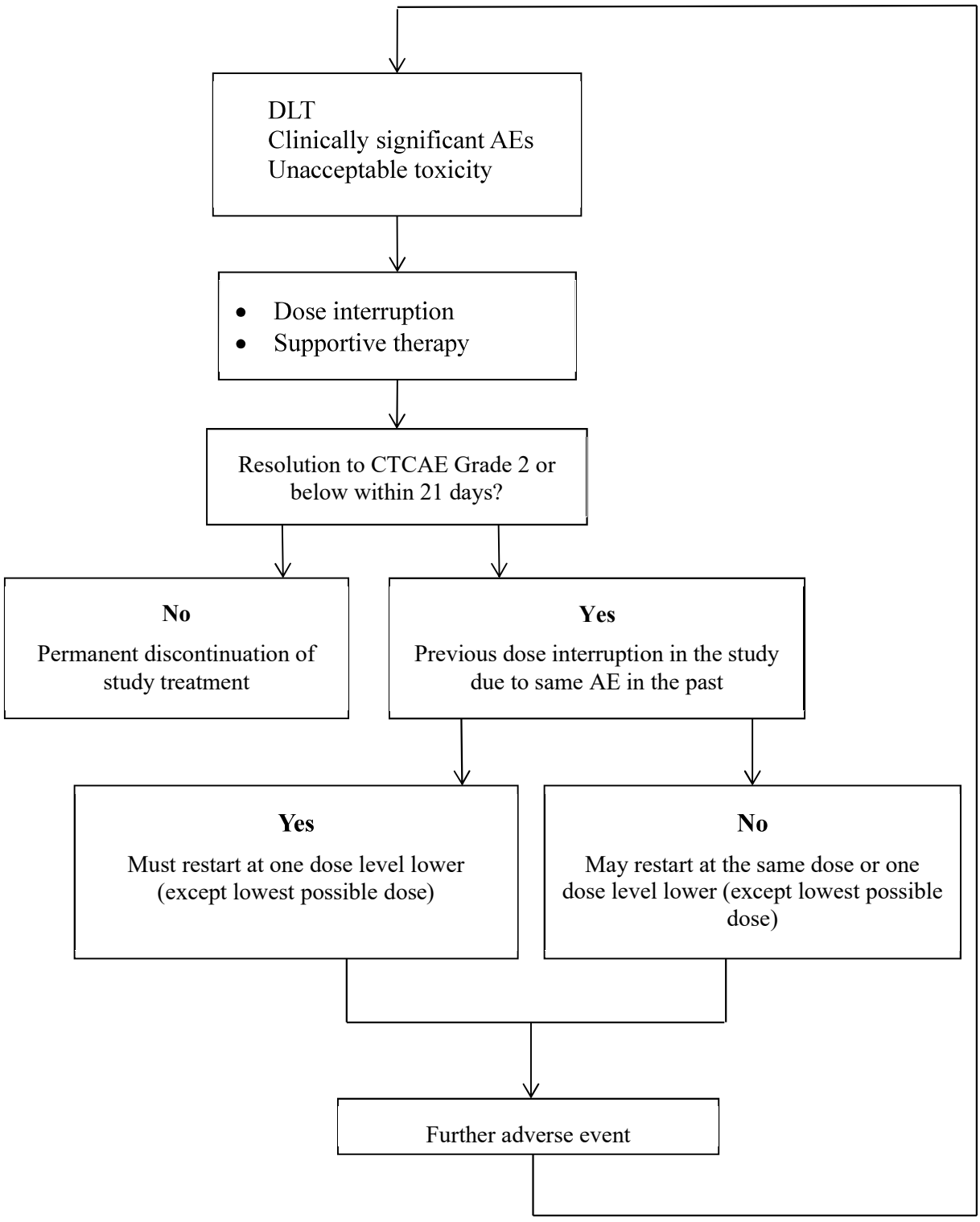
Table 3 Dose interventions

Dose level	DZD9008 dose
Dose level 1 (starting dose for extension cohort 2)	300 mg
Dose level 2 (starting dose for extension cohort 1)	200 mg
Dose level 3	150 mg

5.1.6 Assessment timing if dosing is interrupted

If a patient misses any doses of DZD9008 during the 28-day evaluation period of Cycle 1 of Part A, please contact the Dizal Study Team for advice regarding the evaluability of the patient and appropriate timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to the baseline assessments.

Figure 3 Dose modification for toxicity related to DZD9008



5.1.7 Duration of treatment

Patients may continue on treatment with DZD9008 until RECIST 1.1 defined disease progression or until treatment discontinuation criteria are met or withdrawal of consent, or 2 years post study completion or first indication market available (if patients are still on treatment when study completion).

5.1.8 Treatment compliance and accountability

The investigational product should only be used as directed in this protocol. Details of treatment with investigational product for each patient will be recorded in the CRF.

All patients will be requested to complete a dosing diary, including the date and time that each dose is taken. If a dose is missed, the reason must be noted in the diary. A copy of the dosing diary is provided in the study reference material.

Patients should return all unused medication and empty containers to the investigator. The study personnel at the investigational site will account for all drugs dispensed and returned. Unless otherwise authorized by Sponsor, all investigational product supplies unallocated or unused by the patients must be destroyed by procedures approved by Sponsor or returned to Sponsor or its designee. Certificates of delivery and destruction should be signed.

5.2 Benefit/risk and ethical assessment

5.2.1 Potential benefit

EGFR Exon20ins and HER2 Exon20ins occurred in about 4% patients with NSCLC. The prognosis of these patients is poor as there lacks effective treatment. Chemotherapy is the standard of care, but median PFS and OS were only around 6 months and 24 months, respectively.

In preclinical setting, DZD9008 shows *in vitro* activity in cells expressing EGFR sensitizing mutations, T790M mutation, Exon20ins and uncommon mutations as well as HER2 Exon20ins, with weak activity in cells carrying wild type EGFR. *In vivo*, DZD9008 demonstrates promising anti-tumor efficacy in xenograft models carrying EGFR aberrations.

In the two ongoing phase 1 studies of DZD9008 in NSCLC patients with EGFR and HER2 mutations (by April 3, 2023), DZD9008 demonstrated promising anti-tumor efficacy in patients with EGFR Exon20ins with confirmed ORR of [redacted] and [redacted] selected dose level of 200 mg and 300 mg, separately. In the phase 2, pivotal study DZ2020E0001 in Chinese NSCLC with EGFR Exon20ins, the confirmed ORR at 300 mg QD was [redacted] as assessed by IRC. Anti-tumor activity of DZD9008 was also observed in patients with EGFR sensitizing mutation, T790M, as well as in patients with HER2 Exon20ins. DZD9008 was well tolerated up to 400 mg once daily. The incidences of TEAEs at grade 3 and above, TEAEs leading to dose interruption or reduction were lower than the other EGFR TKIs. The types of TEAEs reported were considered to be related to inhibition of wild type EGFR, and majority of TEAEs were mild or moderate, and could be managed or recover.

These data suggest that DZD9008 has a potential to bring clinical benefit to patients with different types of EGFR or HER2 aberrations, especially in patients with EGFR Exon20ins.

5.2.2 Potential risks identified non-clinically with DZD9008

Section 2.3.4 of this protocol summarizes potential risks based upon non-clinical toxicity studies with DZD9008 in rats and dogs, and in vitro experiments, with further detailed information available in the IB. The monitoring and management of the potential risks based on preclinical findings and clinical EGFR TKIs class effect are discussed below:

5.2.2.1 Gastrointestinal tract effects

Patients with refractory nausea, vomiting and chronic gastrointestinal diseases are excluded from participating in this study. Detailed information on the treatment of gastrointestinal adverse events will be included in the "Guidance for the management of Adverse Events in Studies of DZD9008", which will be provided to the investigators. This guidance is for information sharing only, and investigator can manage these AEs according to their local practice. Investigator will also be advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 5.1.5.

5.2.2.2 Dermatological effects

No specific dermatological exclusion criteria are included in this study, however, patients with any unresolved adverse events from prior therapy greater than CTCAE grade 1 will be excluded from participation. Dermatological treatment should be instituted for patients with any CTCAE grade skin reactions, considered by the investigator to be causally related to DZD9008. Detailed information on the treatment of dermatological adverse events will be included in the "Guidance for the Management of Adverse Events in Studies of DZD9008". Investigators will also be advised to follow the general toxicity management guideline regarding dose interruption and reduction as detailed in Section 5.1.5.

5.2.2.3 Ocular surface effects

Full ophthalmic assessment, including slit lamp examination, will be performed at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs may be performed to record any clinically significant findings. Ophthalmology examination results should be collected in the eCRF. Any patient developing corneal ulceration will be permanently discontinued from study treatment and should be followed regularly until resolution of the event.

Patients who wear contact lenses will be advised to discontinue wearing lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤ 2) while receiving treatment with DZD9008 until at least one week after symptoms have resolved. If a patient has recurrence of eye symptoms or experiencing any severe (CTCAE grade ≥ 3) ocular events they should discontinue wearing their contact lenses until at least one week after treatment with DZD9008 is permanently discontinued. Patients should not use any eye drops or ointment for treatment of eye symptoms has been permanently discontinued. Patient will be advised to consult the investigator promptly if they have any concerns.

5.2.2.4 Cardiovascular effects

Patients who have unstable cardiac conditions and risk factors for QT prolongations will be excluded from participation in this study. Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible (See Appendix H), but patients may receive any medication that is clinically indicated for the treatment of AEs. Electrolyte and vital sign assessments, including pulse rate and blood pressure, will be monitored regularly throughout the study. Regular digital ECG assessments will be as described in Section 6.3.4. The investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patient. A paper copy should be filed in the patient's medical records. All digital ECG data will be analyzed. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition.

5.2.2.5 Respiratory effects

Patients with a past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease will be excluded from participation in this study.

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease, an interruption in study treatment dosing is recommended, and the Sponsor 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, hematological parameters, bronchoscopy with biopsy as needed) 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 edema, or pulmonary hemorrhage. 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. In the absence of a diagnosis of interstitial lung disease, study treatment may be restarted following consultation with Sponsor Study Physician.

5.2.2.6 Liver effects

Patients with any evidence of severe or uncontrolled systemic liver disease, including those with known hepatitis B, hepatitis C, human immunodeficiency virus (HIV) or abnormal liver enzymes (defined as AST or ALT > 2.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN if no evidence of liver metastases; AST or ALT > 5 x ULN, total bilirubin > 3 x ULN in the presence of liver metastases) at screening are excluded from participating in the study. During the study, liver function tests will be monitored regularly during the study and recorded at discontinuation. Patients' laboratory results will be assessed against the FDA's Draft Guidance for Drug Induced Liver Injury (FDA Guidance 2005) with the process described in detail in Appendix G.

5.2.2.7 Hematopoietic effects

Patients with inadequate bone marrow reserve as demonstrated by any of the following laboratory values (absolute neutrophil count < 1.5 x 10^9/L; platelet count < 100 x 10^9/L; hemoglobin < 90 g/L)

will be excluded from the study. Hematological parameters will be monitored prior to administration of the first dose, weekly during the first cycle of multiple dosing, at the start of each subsequent cycle, and at discontinuation.

5.2.2.8 Renal effect

Patients with abnormal renal function as defined by creatinine > 1.5 x upper limit of normal (ULN) concurrent with creatinine clearance < 50 mL/min at screening are excluded from participating in the study. During the study, kidney function tests (creatinine and urea nitrogen) will be monitored regularly during the study and recorded at discontinuation. In addition, creatine kinase will be routinely monitored throughout the study.

5.2.2.9 CYP450 induction/inhibition

All patients must try to avoid concomitant use of medications, herbal supplements and/or ingestions of foods with known potent inducer or inhibitors on CYP3A4 activity whenever feasible. Such drugs must have been discontinued for a period of 1 week (CYP3A3 inhibitors) or 2 weeks (CYP3A4 inducers) prior to first administration of DZD9008. Patients taking concomitant medications whose disposition is dependent upon intestinal CYP3A4 and/as or transporter proteins and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result increased exposure of the concomitant medication whilst receiving DZD9008. Guidance on medications to avoid, medications that require close monitoring and on washout periods is given in Appendix H. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4, should be maintained on them throughout the study period. Patients may receive any medication that is clinically indicated for treatment of adverse events.

5.2.2.10 Hemorrhage

DZD9008 was reported to be a potent BTK inhibitor (Investigator's Brochure). Bleeding events, some fatal, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in patients treated with other BTK inhibitors in clinic. Patients receiving antiplatelet or anticoagulant therapies may be at increased risk of hemorrhage. As a precaution, it is suggested per protocol that DZD9008 be withheld for at least 3 days pre- and post-surgery. Patients require anticoagulation or anti-platelet therapy while receiving DZD9008 should be monitored for any signs of bleeding. Patients with hemorrhage should be managed per institutional guidelines or as clinically indicated.

5.2.3 Safety data of DZD9008 in ongoing phase I/II clinical studies

The safety data in the three studies in NSCLC patients (DZ2019E0001, DZ2019E0002 and DZ2020E0001) showed DZD9008 was well tolerated at up to 400 mg once daily, with the majority of adverse events being mild to moderate EGFR-related adverse events (i.e., diarrhea, skin rash, paronychia).

5.2.4 Overall benefit/risk and ethical assessment

For advanced stage NSCLC patients with EGFR or HER2 Exon20ins, there is no effective treatment, and thus prognosis is poor. DZD9008 is a potent, selective and irreversible EGFR TKI which is designed to treat this population of patients with high unmet medical need.

This study is a first-time in-patient study to evaluate DZD9008 in advanced NSCLC with EGFR or HER2 mutation, preferentially focusing on patients with EGFR Exon20ins or HER2 Exon20ins. The starting dose and steps for dose escalation of DZD9008 are defined based on non-clinical toxicity studies. The selected starting dose is predicted to hit the target, in accordance with the ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Section III.A principle of selecting a dose 'that is expected to have pharmacologic effects' (ICH S9). In addition, patients will continue the treatment as long as they are deriving benefit from the treatment according to ICH S9 that 'In Phase I clinical trials, treatment can continue according to the patient's response' (ICH S9). Moreover, predicted human half-life of DZD9008 is ~50 hours, which could potentially achieve continuous inhibition of mutant EGFR pathway and derive clinical activity by once daily dosing. The non-clinical safety profile has not identified any risks that would preclude investigation of DZD9008 in this setting. The study design aims to minimize potential risks, and monitoring is in place for those risks deemed to be most likely or serious.

The selected dose of 200 mg or 300 mg once daily is considered to be appropriate doses with good risk-benefit balance for phase 2. At these two dose levels, by April 3, 2023, the reported incidence of grade 3 and above TEAEs, TEAEs leading to dose interruption and reduction were lower than that of mobocertinib (TAK-788) and other EGFR inhibitors, e.g. afatinib or dacomitinib (19-21); the confirmed ORRs [redacted] of 200 mg and [redacted] of 300 mg dose cohort, respectively) in platinum pretreated patients were superior or comparable to that reported in mobocertinib (TAK-788) (21) and amivantamab (JNJ-61186372) (22) studies. Noteworthily, in patients relapsed from or not responded to amivantamab (JNJ-61186372), DZD9008 also showed tumor response.

The investigation of DZD9008 in this patient population appears acceptable, based upon the emerging safety, PK and anti-tumor efficacy of clinical studies, non-clinical safety profile, the lack of effective alternative treatments available to patients, the limited life expectancy due to malignant disease, and the strength of the specific hypothesis under evaluation. Thus, the benefit/risk assessment for this first-into-human Phase 1 study support the oral administration of DZD9008 to patients with advanced EGFR or HER2 mutant NSCLC. The data generated from phase 1 studies support the evaluation of DZD9008 in phase 2 study, focusing on previously treated EGFR Exon20ins mutant NSCLC, according to the proposed study design.

5.3 Discontinuation of investigational product and withdrawal from the study

Patients may withdraw from the study at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 5.3.2.

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Adverse events

- Severe non-compliance to this protocol as judged by the investigator and/or Study Team
- Confirmed disease progression as per RECIST 1.1, unless, in the opinion of the investigator, the patient is still deriving clinical benefit. **For France and Canada only**: fulfil the following criteria: (a) Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values); (b) Stable ECOG PS; (c) Absence of rapid progression of disease or of progressive tumor at critical anatomical sites that requires urgent alternative medical intervention; (d) Investigators must inform subjects that this practice is not considered standard in the treatment of cancer.
- Patients incorrectly initiated on investigational product (Section 5.3.1)
- Pregnancy

Patients who withdraw from the study but are evaluable for safety assessment in Part A escalation will not be replaced. Any patient that is not evaluable in Part A escalation will be replaced to ensure a minimum number of evaluable patients. Once study medication is permanently discontinued it cannot be restarted.

In Part A expansion and Part B, any patient who discontinues study treatment for reasons other than disease progression should have RECIST assessment performed as scheduled in Table 13 and Table 14 of the protocol until disease progression is documented or death occurs, or consent is withdrawn. Study procedure related SAEs and anti-cancer treatment must be captured until the patient no longer has RECIST 1.1 tumor assessment (disease progression or permanent withdrawal from the study).

After database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive the study treatment, Sponsor will collect information during the treatment period and for 28 days after last dose on SAEs, death (including those due to disease progression), discontinuation due to AEs/SAEs and drug accountability.

5.3.1 Procedures for handling patients incorrectly initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients who do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the Sponsor Study Physician immediately. The decision on when to discontinue the ineligible patient from the study is based on the medical/safety risk for the patient. The Sponsor Study Physician is to ensure all such contacts are appropriately documented.

Any patient who is found to have failed to comply with all of the selection criteria, but has not started treatment, will be removed from the study.

Any patient started on treatment in error, as he/she subsequently been found to have failed to comply with all the eligibility criteria, will undergo a risk/benefit assessment by the SRC: if the patient is judged to be receiving clinical benefit, the investigators may choose to continue to dose them with DZD9008.

5.3.2 Procedures for withdrawal from study

Patients are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment (see Section 6.3.6). Adverse events should be followed up and study drugs should be returned by the patient.

5.3.3 Interim analysis

An interim data analysis will take place when the last evaluable patient in Part A escalation completes the 28-day continuous dosing (DLT phase) with DZD9008 and finishes all the safety evaluation. Data analysis will be performed and a SRC meeting will be held with the decision of RP2D.

To check futility and also inform the dose selection, one interim analysis will be performed in Part B when 39 patients in full analysis set completed at least 2 RECIST assessments in each cohort. If the number of responses is less than or equal to 7 out of 39 patients in the first stage, then the dose cohort will be stopped. A dose cohort passing the first stage is considered as a "competitive" cohort. When both dose cohorts become competitive, the response rate of two cohorts will be compared to identify the more effective dose. The less effective dose may be dropped after the interim analysis.

Dizal may trigger the discussion with regulatory on the optimal RP2D selection upon emerging efficacy and safety data before interim analysis.

5.4 End of study

The earliest data cut-off for the primary analysis of ORR may take place 3 months after the last patient enrolled, to allow all patients to complete two follow-up RECIST assessments. At this time, DoR and safety/tolerability will also be summarized. The CSR of primary analysis may include, but not limited to, ORR, DoR, safety and tolerability data.

The full CSR of Part B will report the analysis of all primary and secondary endpoints (including updated ORR and DoR, DCR, tumor shrinkage, PFS and OS). The data cut-off for this analysis will take place approximately 8 months after the last patient is enrolled to ensure that the last responder could be followed up for at least 6 months after initial documented response. All patients will continue to be followed up for an updated analysis based on cut-off that will occur between 12 - 24 months after the last patient is enrolled. All endpoints will be updated and summarized in an addendum to the CSR.The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. Dizal may also terminate the entire study permaturely if concerns for safety arise within this study or in any other study with DZD9008.

5.5 Post study access to study treatment

Any patients still receiving investigational product at the time of end of the study will be able to continue to receive DZD9008 if in the opinion of investigator they continue deriving clinical benefit with agreement with Dizal study physician. Re-consent is required. Such patients will continue to be monitored for safety assessments until DZD9008 is discontinued. These patients will then be followed up for treatment-related Serious Adverse Events up to 28 days after the last dose of investigational product. A CSR addendum will be prepared to summarize any additional safety data collected.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study plan

Descriptions of the procedures are included in Table 11, Table 12, Table 13 Table 14. The schedule of assessments may change in response to emerging data, updated assessment tables will be provided outside of the protocol. All study visits from Cycle 2 Day 1 onwards may be performed within a visit window of ± 2 days.

6.2 Recording of data

Web Based Data Capture (WBDC) will be used for data collection on the observations, tests and assessments specified in the protocol and query handling. The investigator will ensure that data are recorded on the CRFs as specified in the protocol and in accordance with the instructions provided.

The investigator will ensure the accuracy, completeness, and timeliness of the data recorded and for the provision of answers to data queries according to the Clinical Study Agreement or applicable information.

The investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

For details of data and study management, see Appendix E of this Clinical Study Protocol.

6.3 Safety assessment

6.3.1 Enrolment and screening

At enrollment, each potential patient will provide informed consent prior to starting any study specific procedures (see Appendix D of this Clinical Study Protocol for Ethics and Regulatory Requirements).

IRT system will be used in this study to assign patient enrollment code. Each potential patient will be assigned an unique enrollment number. If a patient withdraws from the study, then the enrollment code cannot be reused.

Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity according to local regulations, and smoking history.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

Each patient will undergo screening (Table 11, Table 12, Table 13, Table 14) during the 28 days prior to first dosing to confirm eligibility. Screen failure reason needs to be recorded in EDC system. Tumor assessment and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of study drug.

All patients should have brain MRI or contrast-enhanced CT within 28 days of first dose to exclude leptomeningeal metastasis or active brain metastasis.

Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available data including vital signs and ECG tracings.

Subjects who have failed previous screening are permitted to be re-screened for once. ICF should be re-signed, and an updated subject code will be assigned. Screening procedures must be repeated (unless the study procedures meet the time window requirement for the second screening). If subjects have provided tumor tissues and/or plasma samples for EGFR Exon20ins mutation confirmation, then no additional tumor tissue and/or plasma samples need to be provided at the re-screening.

6.3.2 Physical examination

A physical examination will be performed and include an assessment of the followings: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems. Performance status will be assessed at the visits as indicated in the Study Plan according to ECOG criteria as follows:

- 0 = Fully active, able to carry out all pre-disease activities without restrictions
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work
- 2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking Hours
- 4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair

6.3.3 Vital sign

Blood pressure and pulse rate

Blood pressure and pulse rate will be measured in supine or siting position after 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (Table 11, Table 12, Table 13, Table 14). Observations will be recorded at the following times:

Part A

- Screening
- First dosing day (Cycle 0 Day 1) for dose escalation: pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing
- On day 1 and day 9 of food effect cohort in Part A: pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing (treatment time might be updated upon emerging human PK data).
- First day of multiple dosing (Cycle 1 Day 1): pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing
- Cycle 1 Day 8 and 15: pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing
- On Day 1 of each subsequent cycles: one assessment at any time during day
- On occurrence of any cardiac AE or clinically indicated at the discretion of the investigator
- Discontinuation visit

Part B

- Screening
- Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 1 Day 15: Pre-dose
- On Day 1 of each subsequent cycles: one assessment at any time during the day
- On occurrence of any cardiac AE or clinically indicated at the discretion of the investigator
- Discontinuation visit
- The timing and frequency of vital signs assessment may be adjusted in response to emerging PK and safety data.

Weight

Weight will be assessed at screening and then Day 1 of each cycle and at the discontinuation visit.

Height

Height will be assessed at screening only.

Any changes in vital signs should be recorded as an AE if applicable.

6.3.4 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis will be taken at the visits as indicated in the Study Plan (see Table 11, Table 12, Table 13, Table 14).Laboratory tests do not need to be repeated at baseline if the baseline visit is within 7 days of the screening sample.

Blood and urine samples for safety assessment will be collected at the following times:

- Screening
- First dosing day (Cycle 0 Day 1) for dose escalation: pre-dose (baseline)
- On day 1 and day 9 of food effect cohort in Part A: pre-dose (treatment time might be updated upon emerging human PK data).
- First day of multiple dosing (Cycle 1 Day 1, both Part A and Part B): pre-dose
- Multiple dosing, day 8 and 15 of Cycle 1 (both Part A and Part B): pre-dose
- On Day 1 of each subsequent cycles: pre-dose
- Discontinuation visit

The date of each collection will be recorded in the appropriate CRF.

Following review of data from a group of patients the timing of blood samples may be adjusted for subsequent groups of patients. Additional sampling times may be added if indicated by the emerging data.

Laboratory values that meet the criteria for CTCAE 5.0 grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables (Table 4) will be measured:

Table 4 Laboratory variables to be measured

Clinical chemistry	Hematology
Serum (S)/Plasma (P)- Albumin	Blood (B)-Hemoglobin
S/P-Alkaline phosphatase	B-Hematocrit
S/P-ALT	B-Platelet count
S/P-AST	B-Reticulocyte
S/P-Bicarbonate	B-Red blood cell count
S/P-Urea nitrogen	B-White blood cell count
S/P-Calcium	B-Absolute leukocyte differential cell count:
S/P-Creatinine	• Basophils
S/P-Glucose	• Eosinophils
S/P-Potassium	• Lymphocytes
S/P-Magnesium	• Monocytes
S/P-Sodium	• Neutrophils
S/P-Total bilirubin	
S/P-Total serum protein	**Coagulation**
S/P-Lipase	APTT
S/P-Amylase	INR
S/P-Creatine phosphokinase	
Urinalysis	
U-Glucose	
U-Protein	
U-Blood	

* Beyond what listed in the table, additional urine/serum samples will be collected from all females of childbearing potential at screening (within 7 days of the first dosing), and at treatment discontinuation for a pregnancy test.
For Italy only, the female subject should only be included or continue receiving study treatment after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test upon local practice.

6.3.5 Other safety assessments

6.3.5.1 Resting 12-lead ECG

Twelve-lead ECGs will be performed at the visit indicated in the Study Plan (see Table 11, Table 12, Table 13, Table 14).

Twelve-lead ECGs will be recorded at the following times:

Part A

- Screening

- First dosing day (Cycle 0 Day 1) for dose escalation: pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing
- On day 1 and day 9 of food effect cohort in Part A: pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing (treatment time might be updated upon emerging human PK data).
- First day of multiple dosing (Cycle 1 Day 1): pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing
- Cycle 1 Day 8 and Day 15: pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dosing
- On Day 1 of each subsequent cycles: one assessment at any time during the day
- On occurrence of any cardiac AE
- Discontinuation visit

Part B

- Screening:
  - For sparse PK group: any time on that day for sparse PK group
  - For intense PK group: pre-dose, 2, 4, 6 and 8 hours post dosing (Since there is no dosing at screening, ECG recording should start at a time that would be consistent with planned dosing times at Cycle 1 Day 1 and Cycle 3 Day1 (for baseline purpose).
- Cycle 1 Day 1 and Cycle 3 Day 1: Pre-dose, 2, 4, 6 and 8 hours post-dosing
- Cycle 1 Day 8 and Cycle 1 Day 15: Pre-dose
- Cycle 2 Day 1: Pre-dose
- On Day 1 of each subsequent cycles after Cycle 3: one assessment at any time during the day
- On occurrence of any cardiac AE
- Discontinuation visit

The timing and number of ECGs may be adjusted depending on the emerging PK and safety data.

A 30 minute window will be allowed for ECGs performed at pre-dose and 15 minute window for 1-10 h, and 1 hour window for ECG performed at 24 hours.

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records if applicable. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

All ECG data will also be collected digitally. Heart rate, PR, R-R, QRS and QT intervals will be determined and reviewed by a cardiologist wherever needed.

For Part B, prior to primary analysis, ECG data will be collected electronically, analyzed and stored by a central ECG vendor as described in the study specific ECG manual. Post primary analysis, ECGs will be collected locally and stored at the site.

6.3.5.2 Echocardiogram/MUGA Scan

Echocardiogram or MUGA scan to assess LVEF will be conducted at baseline (prior to first dose of DZD9008), on Cycle 3 Day 1 (± 7 days), then every 6 weeks (± 1 week) and whenever clinically indicated.

The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator whenever possible, and a quantitative measurement should be taken. Recommendations include having complete high quanlity standardized 2-D with Doppler echocardiographic examinations performed by an experienced sonographer and include evaluation of both systolic and diastolic left ventricular function. Ejection fraction determinations should be determined quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

Any symptomatic decrease in LVEF will prompt the discontinuation of the treatment and a cardiac consultation.

6.3.5.3 Pulmonary function tests (PFTs)

Signs and symptoms (cough, short breath and pyrexia, etc) including auscultation for lung field will be checked at each visit.

PFTs (including spirometry and DLCO) will be performed at baseline (prior to first dose of DZD9008), on Cycle 3 Day 1 (± 7 days), and then every 6 weeks (± 1 week) and whenever clinically indicated.

HRCT scan will be performed at baseline and then when clinically indicated (see below)

- If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease on RECIST scan or decrease in lung function tests (FVC decrease ≥ 10% or DLCO decrease ≥ 15%) is observed, the study treatment dosing should be interrupted and a full diagnostic workup (including chest X-Ray with PA and lateral view, cardiac, infectious and hematological workups) will be performed. A full diagnostic workup is strongly recommended to exclude alternative causes such as disease progression, pleural effusion and cardiac causes. Alternative clinical diagnosis will be managed according to local practice.
- If other causes of respiratory changes have been excluded, an HRCT scan should be performed. If a diagnosis of interstitial lung disease is confirmed study treatment should be permanently discontinued. In the absence of a diagnosis of interstitial lung disease, study treatment may be restarted.

6.3.5.4 Ophthalmologic examination

Full ophthalmologic assessment, including slit lamp examination, should be performed at screening, study drug discontinuation and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE.

Patients experiencing corneal ulceration will not be permitted to restart study treatment.

Ophthalmology examination results should be collected in the eCRF.

6.3.6 Follow up

6.3.6.1 Safety follow up

A post study assessment will be performed at the time investigational product is permanently discontinued.

As a minimum, telephone contact should be made with the patient for 28 days following the discontinuation of DZD9008 to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to Section 6.4.3 for full details on AE recordings during follow-up.

Beyond the 28 day follow up, only ongoing AEs or study procedure-related SAE should be collected. Any SAE will be followed to resolution where possible.

6.3.6.2 Progression follow up

Patients who discontinue DZD9008 for reasons other than progression will continue RECIST 1.1 assessments on Cycle 3 Day1 (± 7 days), then every 6 weeks (± 1 week) until objective disease progression.

Details of concomitant medications (including any subsequent cancer therapy) should continue to be collected as detailed in the study plan up to the 28-day follow up visit. Beyond the 28-day follow up visit only subsequent cancer therapy and new SAEs due to study procedures should be collected.

6.3.6.3 Survival follow up

In Part B extension cohorts, following disease progression, the patient, patient's family, or the patient's current physician must be contacted every 6 weeks for survival information. Subsequent treatment regimens received following withdrawal and subsequent treatment will also be collected every 6 weeks. Survival data will be collected up to the time of the final OS analysis. Patients should be contacted in the week following the data cut-off for the final survival analyses to provide complete survival data.

6.4 Adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). 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.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an adverse event as far as the deterioration can be anticipated.

The term adverse event is used generally to include any AE whether serious or non-serious.

6.4.2 Definitions of serious adverse events

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B of this Clinical Study Protocol.

For definition of other significant adverse event (OAE), see Section 7.3.

6.4.3 Recording of adverse events

6.4.3.1 Time period for collection of adverse events

AEs will be collected from the first dosing of DZD9008 until the end of the follow-up period. SAEs will be collected from ICF sign. From the phase 1 data, terminal half-life of DZD9008 in human is around 50 hours. The safety follow-up duration would like to cover at least 5 folds of half-life to ensure the safety monitoring until elimination of DZD9008, Thus, the follow-up period is defined as 28 days after study treatment is discontinued.

SAEs occurring in the follow-up period should be reported to Dizal in the usual manner (see Section 6.4.4).

6.4.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

Dizal retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to DZD9008, the investigator should notify Dizal Patient Safety Team or representatives.

Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade, grade change and its associated date
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome

For SAEs other variables will be collected including treatment given for the event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The grading scales found in the current National Cancer Institute CTCAE 5.0 version will be utilized for all events with an assigned CTCAE grading. For those events without assigned

CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Causality collection

The investigator will assess causal relationship between investigational product and each adverse event, and answer 'yes' or 'no' to the question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedure. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B of this Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the Clinical Study Report. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention,

  and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information.

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

Hy's Law

Cases where a patient shows an AST or ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria.

Details of identification of potential Hy's law cases and actions to take are detailed in Appendix G.

Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.

- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to Sponsor representative within the usual timeframes.

6.4.4 Reporting of serious adverse events

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 CRF and paper SAE form (Clinical Safety Event Report).

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate Sponsor representatives (study physician, patient safety, operation manager etc) immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all the necessary information is provided to appropriate patient safety database within one calendar day of initial receipt for fatal and life threatening events and within five calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE immediately, **or no later than 24 hours** of when he or she becomes aware of it.

The Sponsor representative will advise the investigator/study site personnel how to proceed.

The reference documents for definition of expectedness is Investigator's Brochure for DZD9008.

6.5 Pharmacokinetics

6.5.1 Collection of pharmacokinetic samples

For detailed sample collection and processing please refer to lab manual.

A 30 min window is allowed for pre-dose sampling. A 5 min window will be allowed for samples taken at 0.5 hour and 1 hour; a 10 min window for samples taken at 2 - 10 hours; a 1-hour window for samples taken at 12 hours and 24 hours, a 2-hour window at 48 hours, 72 hours, 120 hours and 168 hours.

6.5.1.1 Part A (Dose escalation)

Blood samples

Venous blood samples will be taken at the time points shown Table 5. Discussion with the Clinical Pharmacologist from Dizal Pharmaceuticals is required as to any impact if dose interruption occurs within 3 days of scheduled time points for PK sampling. The date and time of dosing and collection of each sample will be recorded.

Time points on Cycle 0 Day 1 are pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 120 and 168 hours post-dose.

Time points on Cycle 2 Day 1 are pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose. On Cycle 1 Day 1, Day 8, Day 15, and Cycle 3, 4, 5 Day 1, pre-dose samples are collected.

The timing for PK sampling may be adjusted with emerging data during the study, in order to ensure appropriate characterization of the plasma concentration-time profiles of DZD9008 (Table 5).

Hospitalization can be allowed for out of business time PK collection.

Blood samples (approximately 4 mL at each time point) will be collected and put into lavender top (EDTA) Vacutainer® evacuated collection tubes at the time points indicated. After processing, plasma samples will be split, for quantification of DZD9008 and identification and semi-quantification of all possible metabolites. The timing for PK sampling may be adjusted with emerging data during the study, in order to ensure appropriate characterization of the plasma concentration-time profiles of DZD9008.

Urine samples

Urine samples (approximately 5 mL) for the determination of concentrations of DZD9008 and characterization of its metabolites will be taken from the total urine samples provided during 0-24 h at Cycle 2 Day 1. The date and time of collection and the weight of each urine collection will be recorded. Samples will be split into aliquots, for quantification of DZD9008 and for identification and semi-quantification of all possible metabolites.

The interval for urine collection on Cycle 2 Day 1 are 0 - 4, 4 - 12, and 12 - 24 hours. The timing for PK sampling may be adjusted with emerging data during the study, in order to ensure appropriate characterization of urine excretion DZD9008.

In addition, the pharmacokinetic samples may be subjected to further analyze by Dizal Pharmaceuticals or CROs in order to investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

Food effect

Venous blood samples will be taken at the time points shown in Table 6. The date and time of dosing and collection of each sample will be recorded.

A 30 min window is allowed for pre-dose sampling. A 5 min window will be allowed for samples taken at 0.5 hour and 1 hour; a 10 min window for samples taken at 2 - 10 hour; an 1 hour window for samples taken at 12 hour and 24 hour, a 2 hour window at 48 hour, 72 hour, 120 hour and 168 hour (Table 6).

Time points on day1 and 9 are pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 120 and 168 hours post-dose (treatment time might be updated upon emerging human PK data).

Time point on Cycle 2 Day 1: pre-dose.

The timing for PK sampling may be adjusted with emerging data during the study, in order to ensure appropriate characterization of the plasma concentration-time profiles of DZD9008.

Blood samples (approximately 2 mL at each time point) will be collected and put into lavender top (EDTA) Vacutainer® evacuated collection tubes at the time points indicated.

6.5.1.2 Part A expansion

Blood samples

Venous blood samples will be taken at the time points shown in Table 7. Discussion with the Clinical Pharmacologist from Dizal Pharmaceuticals is required as to any impact if dose interruption occurs within 3 days of scheduled time points for PK sampling. The date and time of dosing and collection of each sample will be recorded.

Time points on Cycle 1 Day 1 and Cycle 2 Day 1 are pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hour post-dose. On Cycle 1 Day 8 Day 15, and Cycle 3, 4 Day 1, pre-dose samples are collected (Table 7).

The timing for PK sampling may be adjusted with emerging data during the study, in order to ensure appropriate characterization of the plasma concentration-time profiles of DZD9008.

Blood samples (approximately 2 mL at each time point) will be collected and put into lavender top (EDTA) Vacutainer® evacuated collection tubes at the time points indicated.

6.5.1.3 Part B extension

Patients at selected sites will be invited for intense PK studies (approximately 10% - 30% of patients for each arm) and the remaining for sparse PK to characterize DZD9008 pharmacokinetics as shown in Table 8 and Table 9.

Throughout the treatment, the PK sampling time might be time-matched with the PRO-CTCAE assessments as described in Table 14. Beyond Cycle 3, the PK sampling time might be time-matched with efficacy assessment as described in section 6.8.1. Flexible sampling schedule will be implemented to improve the site feasibility. For example, if the patient already took the study drug before the on-site visit, the patient is still eligible for PK sample collections if the accurate dosing time and sample collection time are recorded accurately.

If there is a dose interruption, dose reduction, or an early termination due to an AE or there is an SAE, the investigator may choose to collect an unplanned blood sample (if possible) within the 24 hour after the last dose, which will be used to explore the exposure-response relationship between study drug exposure and AEs.

Table 5 Blood PK sampling schedule (Part A, dose escalation)

Time relative to dose	Single dosing (Part A, Dose escalation)						Multiple dosing				
							Multiple dosing Cycle 1			Multiple dosing Cycle 2	Multiple dosing Cycle 3, 4, 5
	D1	D2	D3	D4	D6	D8	D1	D8	D15	D1	D1
Pre-dose	X						X	X	X	X	X
0.5 hour	X									X	
1 hour	X									X	
2 hours	X									X	
3 hours	X									X	
4 hours	X									X	
6 hours	X									X	
8 hours	X									X	
10 hours	X									X	
12 hours	X									X	
24 hours		X								X (D2, pre-dose)	
48 hours			X								
72 hours				X							
120 hours					X						
168 hours						X					

Note: The treatment date and sample collection time for each period might change upon emergent human PK data.

a. A 30 min window is allowed for pre-dose sampling.
b. A 5 min window is allowed for samples taken at 0.5 hour and 1 hour;
c. A 10 min window for samples taken at 2-10 hours;
d. A 1 hour window for samples taken at 12 hours and 24 hours,
e. A 2 hour window for samples taken at 48 hours, 72 hours, 120 hours and 168 hours.

Table 6 Blood PK sampling schedule (Part A, food effect)

Time relative to dose	Period 1						Period 2						Cycle2
	D1	D2	D3	D4	D6	D8	D9	D10	D11	D12	D14	D16	D1
Pre-dose	X						X						X

Time relative to dose	Period 1						Period 2						Cycle2
	D1	D2	D3	D4	D6	D8	D9	D10	D11	D12	D14	D16	D1
0.5 hour	X						X						
1 hour	X						X						
2 hours	X						X						
3 hours	X						X						
4 hours	X						X						
6 hours	X						X						
8 hours	X						X						
10 hours	X						X						
12 hours	X						X						
24 hours		X						X					
48 hours			X						X				
72 hours				X						X			
120 hours					X						X		
168 hours						X						X	

Note: The treatment date and sample collection time for each period might change upon emergent human PK data.

a. A 30 min window is allowed for pre-dose sampling.
b. A 5 min window is allowed for samples taken at 0.5 hour and 1 hour;
c. A 10 min window for samples taken at 2-10 hours;
d. A 1 hour window for samples taken at 12 hours and 24 hours,
e. A 2 hour window for samples taken at 48 hours, 72 hours, 120 hours and 168 hours.

Table 7 Blood PK sampling schedule (Part A expansion)

Time relative to dose	Cycle 1			Cycle 2	Cycle 3, 4
	D1	D8	D15	D1	D1
Pre-dose	X	X	X	X	X
0.5 hour	X			X	
1 hour	X			X	
2 hours	X			X	
3 hours	X			X	
4 hours	X			X	
6 hours	X			X	

Time relative to dose	Cycle 1			Cycle 2	Cycle 3, 4
	D1	D8	D15	D1	D1
8 hours	X			X	
10 hours	X			X	
12 hours	X			X	
24 hours	X (prior to next dose)			X (prior to next dose)	

Note: The treatment date and sample collection time for each period might change upon emergent human PK data.

a. A 30 min window is allowed for pre-dose sampling.
b. A 5 min window is allowed for samples taken at 0.5 hour and 1 hour;
c. A 10 min window for samples taken at 2-10 hours;
d. A 1 hour window for samples taken at 12 hours and 24 hours.

Table 8 Blood collection for intense PK (Part B extension)

Time relative to dose	Cycle 1			Cycle 2	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11
	D1	D8	D15	D1	D1	D1	D1	D1	D1
Pre-dose[a]	X	X	X	X	X	X	X	X	X
1 hour[b]	X				X				
2 hours[c]	X				X				
3 hours[c]	X				X				
4 hours[c]	X				X				
6 hours[c]	X				X				
8 hours[c]	X				X				
24 hours[d]	X (prior to next dose)				X (prior to next dose)				

a. A 30 min window is allowed for pre-dose sampling.
b. A ±5 min window is allowed for samples taken at 1 hour;
c. A ±10 min window for samples taken at 2-8 hours;
d. A ±1 hour window for samples taken at 24 hours.

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples.

Table 9 Blood collection for sparse PK (Part B extension)

Time relative to dose	Cycle 1			Cycle 2	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11
	D1	D8	D15	D1	D1	D1	D1	D1	D1
Pre-dose[a]	X	X	X	X	X	X	X	X	X
4 hours[b]	X				X				
8 hours[b]	X				X				

a. A 30 min window is allowed for pre-dose sampling.
b. A ±10 min window for samples taken at 2-8 hours;

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples.

6.5.2 Determination of drug concentration in plasma and urine samples

Samples for determination of DZD9008 and/or metabolite DZ0753 concentrations in plasma will be analyzed using a validated bioanalytical method. All samples within the known stability of the analysts of interest at the time of receipt by the bioanalytical laboratory will be analyzed. Full details of the analytical method used will be described in a separate bioanalytical report.

In addition, the pharmacokinetic samples may be subjected to further analyses by Dizal or CROs in order to investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

6.5.3 Other parameters

A biomarker to determine CYP3A induction, the ratio of 4-β-hydroxy cholesterol / total cholesterol, will be measured at pre-dose of Cycle 0 Day 1, Cycle 1 Day 1, Day 8 and Day 15, Cycle 2 Day 1 (Part A Dose escalation only).

Blood samples (approximately 6 mL at each time point) will be collected and put into lavender top (EDTA) Vacutainer® evacuated collection tubes at the time points indicated.

6.6 Exploratory research

If a patient agrees to participate in the exploratory biomarker research, component of the study biological samples (e.g., blood, plasma, archived and study-obtained tumor, etc.) will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes.

The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies.

6.6.1 Exploratory analyses to support companion diagnostics development

In Part B, all patients will be asked to provide consent to mandatorily donate archived tumor samples (if more than one FFPE blocks from a patient, tissue from the most recent one is preferred) or any fresh tumor biopsies (if archived tumor sample is not available) for confirmation of EGFR Exon20ins status in Sponsor designated central laboratory [redacted] using the designated assay and for the development and approval of tissue-based companion diagnostics for DZD9008. If a pre-study written documentation of EGFR Exon20ins in tumor tissue is available from Sponsor designated central laboratory using the designated assay, no additional tumor sample needs to be submitted. The prior treatment must be clearly indicated for each archival tumor sample provided.

In Part B, the mutation test used in Sponsor designated central laboratory to select EGFR Exon20ins positive patients for this study will be developed for future approval as a companion diagnostics for DZD9008. Some residual tissue and/or DNA will be used for necessary technical studies for future companion diagnostics development and approval.

In addition, all patients in Part B will be asked to provide plasma samples at screening. These samples will be used for the extraction of circulating free tumor DNA (ctDNA) and assessing EGFR Exon20ins status for the development and approval of liquid biopsy companion diagnostics. The plasma samples may also be used for future exploratory research into factors that may influence development of DZD9008 in NSCLC or tumor response to DZD9008.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual. For sampling schedule, see Study Plan (Table 14).

6.6.2 Exploratory biomarker research

6.6.2.1 Archived tumor tissue or fresh biopsy for exploratory biomarker research

All patients will be asked to provide consent to mandatorily donate tumor tissue (archived tumor tissue, or fresh biopsy if archived tissue is not available). In each case the prior treatment must be clearly indicated for each sample provided.

In Part A, the tumor samples will be used for the confirmation of EGFR and HER2 mutations by central lab retrospectively, for the development of diagnostic test for pre-market approval by regulatory authorities and/or potential future exploratory research into factors that may influence development of DZD9008 in NSCLC and/or tumor response to DZD9008 For sampling schedule, see Study Plan (Table 11, Table 12, Table 13).

In Part B, the tumor samples are for potential future exploratory research into factors that may influence development of DZD9008 (Table 14).

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual. For sampling schedule, see Study Plan (Table 11, Table 12, Table 13, Table 14).

6.6.2.2 Paired tumor tissue for proof-of-mechanism (PoM) biomarker study

In Part B, around 10 patients in each dose cohort are requested to provide paired tumor biopsy at pre- and post-dosing to further understand the potential mechanism of DZD9008. For patients

joining the PoM study in Part B, paired tumor biopsy samples will be collected at screening and Cycle 2 Day 1 (± 2 days) (If for any reason the biopsy cannot be collected at Cycle 2 Day 1, it may be taken at any visit within Cycle 2) or discuss with Dizal study team.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual. For sampling schedule, see Study Plan (Table 14).

6.6.2.3 Blood sampling for other exploratory biomarker study

This part of study is optional.

In Part A, if patients consent to donate samples, blood samples will be collected at screening, Cycle 0 Day 1 (pre-dose, Part A dose escalation and food effect cohorts), Cycle 1 Day 1 (pre-dose), Cycle 1 Day 8, Cycle 1 Day 15, Day 1 of each cycle from Cycle 2 to Cycle 6, then Day 1 of each following even Cycle (every 6 weeks) until disease progression, according to RECIST assessment to determine exploratory biomarkers, including EGFR and HER2 (and other genes) mutation status/copy in ctDNA.

In Part B, if patients consent to donate samples, blood samples will be collected on Cycle 1 Day 1 (pre-dose), Cycle 1 Day 8, Cycle 1 Day 15, Day 1 of each cycle from Cycle 2 to Cycle 6, then Day 1 of each following odd Cycle until disease progression, according to RECIST assessment to determine exploratory biomarkers, including EGFR or other gene mutation status/copy in ctDNA.

For Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, a window of ± 2 days will be allowed.

For Day 1 of each cycle from Cycle 3 to Cycle 6, and then Day 1 of each following indicated Cycle (i.e., Cycle 8 Day 1, Cycle 10 Day 1 and so on for Part A; Cycle 7 Day 1, Cycle 9 Day 1 and so on for Part B) until disease progression, according to RECIST assessment, a window of ± 7 days will be allowed.

The blood samples collected prior to dosing may be used to retrospectively confirm EGFR and HER2 mutation by central laboratory.

Patients will also be asked to consent for using these samples to further investigate the relationship between drug exposure and/or disease progression, blood-borne biomarkers and resistant mechanism.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual. For sampling schedule, see Study Plan (Table 11, Table 12, Table 13, Table 14).

6.6.3 Pharmacogenetics

Pharmacogenetic sample evaluation could assist in drug development in NSCLC. If a patient agrees to participate in the host pharmacogenetics research component of the study, a blood sample will be collected.

Dizal intends to perform genetic research in the DZD9008 clinical development program to explore how genetic variations may affect the clinical parameters associated with DZD9008.

The potential benefits of exploring the associations between genes and clinical outcomes in the DZD9008 program include:

- analysis of genes that may affect efficacy, safety and tolerability, and variability (for example, but not limited to, drug metabolizing enzymes and drug transporters).

The single blood sample will be obtained from the subjects prior to the first administration of DZD9008 in the study (pre-dose at Cycle 1 Day 1 in Part B). If for any reason the sample is not drawn prior to dosing, it may be taken at any time visit until the last study visit. Although genotyping is a stable parameter, early sample collection is preferred to avoid introducing bias by excluding patients who may withdraw due to an adverse event. Such patients would be important to be included in any genetic analysis. Only one sample should be collected per subject for pharmacogenetic evaluation during the study.

This part of data will be reported separately and will not form part of the Clinical Study Report.

For information about sample collection, labeling, storage and shipment are detailed in the Laboratory Manual. For sampling schedule, see Study Plan (Table 14).

6.7 Procedures for handling biological samples

6.7.1 Volume of blood

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data becomes available. The estimated total volume of blood that will be drawn from each patient from screening until end of Cycle 6 is around 270 mL in Part A dose escalation, 150 mL in Part A food effect and 170 mL in Part A expansion and Part B extension (Details in Table 15, Table 16, Table 17, Table 18).

6.7.2 Handling, storage and destruction of biological samples

The samples will be used up, or disposed of after analyses or retained for further use as described below.

Biological samples for future research will be retained at Sponsor or it's designee for a maximum of 15 years following the finalization of the Clinical Study Report or per local regulatory requirements, whichever is the earliest. The results from future analysis will not be reported in the Clinical Study Report but separately in a bioanalytical report.

6.7.2.1 Blood Sample for safety and PK

After collection, blood samples will be aliquoted and put into different tubes for safety and PK.

Safety assessment

Safety laboratory assessments will be performed locally at each center's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

Pharmacokinetic assessment

PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

PK samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymized samples will be retained for no more than 5 years after the CSR is finalized.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

Samples for metabolite identification and/or analysis will be shipped to and retained by Sponsor for a maximum of one year following the finalization of CSR. The results from the investigation will not be reported in CSR but in a separate report.

Any PK sample remaining after analysis of DZD9008 and its metabolites may be used for biomarker analyses. These analyses are for Sponsor use only and will not be included in the Clinical Study Report.

6.7.2.2 Blood-borne exploratory biomarker samples

Details of sample collection, processing, shipping and storage are described in the Laboratory Manual. set

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way, exploratory biomarker and genetic data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

Where genetic analysis will be undertaken, the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of sample, the DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the Sponsor genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (Sponsor employee or contract laboratory staff) working with the DNA.

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within Dizal biobank system. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analyzed.

6.7.2.3 Archived tumor tissue or fresh biopsy

In Part A, archived tumor samples or any fresh tumor biopsies (if archived tumor sample is not available) will be used to retrospectively confirm EGFR and HER2 mutations by central laboratory, support the development of diagnostic test for pre-market approval by regulatory authorities and potential future exploratory research into factors that may influence development of DZD9008 in NSCLC and/or tumor response to DZD9008.

In Part B, EGFR Exon20ins will be confirmed by central laboratory testing using analytically validated next generation sequencing-based assay. Archived tumor samples or fresh tumor biopsed tissue will be collected to support companion diagnostics development for approval and potential future exploratory research.

In Part B, around 10 patients of each dose cohort are requested to provide paired pre-and post-treatment tumor biopsies for PoM study. Tumor tissue biopsy should be conducted at screening or post dose on Cycle 2 Day 1, and tissues should be submitted for pEGFR (or other EGFR pathway related biomarkers) IHC testing.

Following biopsy sample taken, tissues should be placed in 10% neutral buffered formalin fixative as quick as possible in order to ensure antigen preservation. Samples should be remained in fixative for 24 to 48 hours at room temperature, then follow a standard overnight processing schedule into paraffin wax. When formalin fixed paraffin embedded (FFPE) block is not possible, unstained sections should be prepared from the FFPE sample block. Tissue sectioning will be cut onto positively-charged glass slides at appropriate time upon Sponsor's request. All blocks or sections must be put into appropriate containers with clear labelling. Finally, the blocks or slides should be shipped in an appropriate condition.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual. For sampling schedule, see Study Plan (Table 11, Table 12, Table 13, Table 14).

6.7.2.4 Samples for pharmacogenetic study

The subject's consent to participate in the pharmacogenetic research components of the study is optional but will be beneficial of drug development in NSCLC.

The single blood sample for genetic research will be obtained from the subjects prior to the first administration of DZD9008 in the study (pre-dose at Cycle 1 Day 1 in Part B). If for any reason the sample is not drawn prior to dosing, it may be taken at any time visit until the last study visit. Although genotyping is a stable parameter, early sample collection is preferred to avoid introducing bias by excluding patients who may withdraw due to an adverse event. Such patients would be important to be included in any genetic analysis. Only one sample should be collected per subject for pharmacogenetic evaluation during the study.

The processes adopted for the coding and storage of samples for genetic analysis will be strictly adhered to maintain subject confidentiality. Samples will be stored for a maximum of 15 years following the finalization of the Clinical Study Report or per local regulatory requirements, whichever is the earliest, after which they will be destroyed. The results of these optional analyses will be reported either in the Clinical Study Report or as an addendum, or separately

in a scientific report or publication. Samples will be stored and used until depletion, or the maximum storage time has been reached.

For information about sample collection, labelling, storage and shipment are detailed in the Laboratory Manual.

6.7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C of this Clinical Study Protocol 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples taken from the patient unless agreed with Sponsor and appropriate labelling, shipment and containment provisions are approved.

All archival tumor samples should be shipped at ambient temperatures as per the Laboratory Manual to the Dizal or designated Central Contract Research Organization.

6.7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the Sponsor biobank system during the entire life cycle.

6.7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action will be documented. If samples are already analyzed, Sponsor is not obliged to destroy the results of this research.

If collection of the biological samples is an integral part of the study, then the patient may be withdrawn from further participation in the study.

The Principal Investigator:

- Ensures Sponsor is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site.

- Ensures that the patient and Sponsor are informed about the sample disposal

Sponsor ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the document returned to the study site.

Sponsor designated research center will conduct potential exploratory biomarker studies if required. Samples will be stored for a maximum of 15 years following the finalization of the Clinical Study Report or per local regulatory requirements, whichever is the earliest. The results from future analysis will not be reported in the CSR but separately in a CSR Addendum /Scientific Report or Scientific Publication.

At the end of the study, or in the event of a subject withdrawing consent, or as required by law, the Sponsor will return any samples and delete the Study Data in a sensitive way, according to local laws and protocols.

6.8 Anti-tumor efficacy

6.8.1 Tumor assessments

6.8.1.1 Imaging assessment

RECIST 1.1 criteria will be used to assess tumor response to treatment by determining Objective Response rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR) and Progression Free Survival (PFS). The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumor response criteria (complete response, partial response, stable disease or progression of disease) will be used for the assessment of tumors according to Appendix F.

Imaging assessments will be performed using CT scan or MRI to assess extracranial lesions, such as chest, abdomen (including liver and adrenal glands). MRI is the preferred method for analyzing the brain lesion if brain metastasis presents at baseline (within 28 days of treatments start, ideally as close as possible to the start of study treatment), on Cycle 3 Day 1 (± 7 days) and then every 6 weeks ± 7 days until objective disease progression or withdrawal from study. Contrast-enhanced CT can be used if MRI is not feasible. In addition, additional areas should be investigated based on the signs and symptoms of the patient. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Categorization of objective tumor response assessment will be based on the RECIST 1.1: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumor burden is at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline

tumor measurements obtained before starting treatment. For objective response rate (ORR), a visit response of CR or PR must be confirmed by a later scan conducted at the next scheduled visit and no less than 4 weeks after the initial visit response of CR or PR.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan (Table 11, Table 12, Table 13, Table 14).

All images for RECIST 1.1 assessment will be reviewed at site. Duplicates will be collected on an ongoing basis and stored by a Sponsor appointed representative, and sent for Independent Review Committee.

6.9 Other assessments

6.9.1 EQ-5D-5L

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol group in order to proivde a simple, generic measure of health for clinical and economic appraisal (23-25). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

The questionaire assesses 5 dimension: mobility, self-care, usual activities, pain/disconfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The patients will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionaire also includes a visual analogue scale, where the patient will be asked to rate currrent health status on a scale of 0 to 100, with 0 being the worst imaginable health state (Appendix J). EQ-5D-5L will be collected at the timepoints shown in Table 14.

6.9.2 PRO-CTCAE

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Event (PRO-CTCAE) system will be appied to patients in Part A expansion cohorts and Part B. Patients will be asked to complete those items which are considered relevant to TEAEs observed in this study, i.e. Rash, skin dryness, acne, itching, nail loss, nail ridging, decrease appetite,

nausea, vomiting, diarrhea, constipation, abdominal pain, mouth/throat sores, cracking at the corner of the mouth, bloating, fatigue, blurred vision, nosebleed (Appendix J).

PRO-CTCAE will be collected at the timepoint shown Table 13 and Table 14.

6.9.3 FACIT-item GP5

A single PRO questionnaire that can inform the overall tolerability of a dose from Functional Assessment of Cancer Therapy- item GP5 (FACIT- item GP5) will be collected at the timepoint shown in Table 13 and Table 14.

7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

7.1 Definition of study endpoints

In Part A, the primary endpoints for determining the MTD and RP2D are the incidence of dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs) and abnormal laboratory test results. The RP2D definition will be based on integrated analysis of PK, tolerability or anti-tumor efficacy data.

The secondary and exploratory endpoints are as following:

- PK assessment includes concentrations of DZD9008 in plasma and/or urine of individual patient (secondary).
- Preliminary assessment of anti-tumor efficacy includes the objective response rate (ORR), which includes the number of CR and PR based on RECIST 1.1, disease control rate (DCR), and duration of response (DoR) (secondary).
- The effect of food on PK of DZD9008 (secondary).
- To retrospectively assess anti-tumor activity of DZD9008 in patients with EGFR Exon20ins according to RECIST 1.1 by Independent Review Committee (IRC) (secondary).
- Retrospective confirmation of EGFR or HER2 Exon20ins in archived tumor tissue or fresh tumor biopsy or plasma sample (exploratory).
- Metabolite identification (exploratory).
- Other biomarkers (exploratory).
- To explore the relationship between DZD9008 exposure and selected endpoints.

In Part B, the primary endpoints for determining anti-tumor efficacy is ORR according to RECIST 1.1 by Independent Review Committee (IRC).

The secondary and exploratory endpoints are as following:

- Safety and tolerability, including adverse events (AEs), serious adverse events (SAEs) and abnormal laboratory test results (secondary).
- PK assessment includes concentrations of DZD9008 in plasma of individual patient (secondary).
- Additional anti-tumor efficacy endpoints include BOR, DOR, PFS and overall survival (OS) (secondary).
- Collect and store tumor samples for companion diagnostics development and potential future exploratory research that may influence the development of DZD9008 (exploratory).
- To collect and store plasma samples for EGFR Exon20ins mutation testing and necessary technical studies for liquid biopsy companion diagnostic development and approval (exploratory).
- To collect and store blood-based samples for future exploratory research on genes/genetic aberrations that may influence response to DZD9008 treatment and/or susceptibility to DZD9008.
- Other exploratory biomarker data if needed (pEGFR or other pathway biomarker modulation in tumor tissue by DZD9008 (at defined dose[s]) (exploratory).
- To collect and store blood sample for future exploratory research into genes/genetic variation that may influence PK or response to DZD9008 (pharmacogenetics study, exploratory).
- To explore the effect of DZD9008 treatment and disease state on health state utility by using EQ-5D-5L health state utility index based on patient reported data.
- To assess AEs of DZD9008 by using subjects reported specific CTCAE symptoms (PRO-CTCAE) and FACIT GP5 questionnaire (exploratory).

7.2 Determination of sample size

7.2.1 Part A Dose escalation, expansion and food effect cohort

In Part A, all patients dosed with DZD9008 will be included. The total number of patients will depend upon the number of dose escalation necessary. It is anticipated that there will be approximately 5 escalation cohorts, hence approximately 30 evaluable patients will be included for escalation.

To better evaluate the safety and anti-tumor efficacy to help define the RP2D, approximately 90 - 110 patients will be enrolled into 6 different expansion cohorts of Part A to explore safety,

PK and efficacy of DZD9008 under fasted or low-fat meal condition at 200 mg and 300 mg dose level, respectively. In addition, a separated cohort of 10 patients will be recruited to evaluate food effect on the PK.

7.2.2 Part B Dose extension cohort

In Part B, subjects will be randomized into one of the two dose cohorts. Each dose cohort uses a Simon two-stage design.

Considering there are two dose cohorts in the pivotal study and the primary endpoint will be analyzed within each cohort independently, Bonferroni method is employed to control the family-wise type I error (at one-sided 0.025). The analysis in two cohorts will be performed independently, at one-sided significance level of 0.0125.

[redacted]

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, SAEs, laboratory data, vital signs, ECG changes. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 7.8.

ECG Changes

Immediate clinical management of patients will be according to local assessment of the QT interval. For the Clinical Study Report QTc will be calculated using Fridericia's or Bazett's formulae.

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula;

For creatinine values in mol/L

Men: [(140 – age) x weight (kg) x 1.23] / creatinine (μmol/L)

Women: [(140 – age) x weight (kg) x 1.04] / creatinine (μmol/L)

For creatinine values in mg/dL

Men: [(140 – age) x weight (kg)] / (creatinine x 72)

Women: [(140 – age) x weight (kg) x 0.85] / (creatinine x 72)

Or others per local practice.

Other significant adverse events

During the evaluation of the AE data, in addition to CRO medical monitor, a Dizal medically qualified or designated expert or designated will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, adverse events of particular clinical importance may, after consultation with the Study Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events.

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.

7.4 Calculation or derivation of pharmacokinetic variables

The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be determined for DZD9008.

Following the single dose part (or first dose) of the study:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal rate constant (λz), terminal half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$), area under the plasma concentration-time curve from zero to 168 hours ($AUC_{(0-168)}$), from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity ($AUC_{(0-\infty)}$), apparent plasma clearance (CL/F), apparent volume of distribution (V_{ss}/F), mean residence time (MRT) , as well as the regression based diagnostic parameters (λz Interval, λzN, Rsq adj, λz period/$t_{½\lambda z}$, tlast, AUC_{extr}).

For Part A dose expansion and Part B dose extension, maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$).

Following the multiple dose part of the study:

Maximum plasma concentration at steady state ($C_{ss,max}$), time to $C_{ss,max}$ ($t_{ss,max}$), minimum plasma concentration at steady state ($C_{ss,min}$), area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), apparent plasma clearance at steady state (CL_{ss}/F), extent of accumulation on multiple dosing for AUC and C_{max} (RAC(AUC) and RAC (C_{max})), time dependency of the pharmacokinetics, and urinary PK parameters: amount excreted (Ae) [by collection interval and cumulatively over the collection intervals], percentage of the dose excreted unchanged in urine (Fe [%]) [by collection interval and cumulatively over the collection intervals] and urinary clearance (CL_R).

The maximum plasma concentration (C_{max}), the C_{max} at steady state ($C_{ss,max}$), the time of maximum concentration (t_{max}) and the t_{max} at steady state ($t_{ss\ max}$) will be determined by

inspection of the concentration-time profiles. Where possible the λz will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the $t_{½λz}$ will be calculated as ln2/λz. All $AUC_{(0-t)}$ values (($AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-168)}$, AUC_{ss}) will be calculated using the linear up/log down rule. Where appropriate, the $AUC_{(0-t)}$ will be extrapolated to infinity using λz to obtain $AUC_{(0-\infty)}$. The CL/F following the single dose and CL_{ss}/F following multiple dosing will be determined from the ratio of dose/$AUC_{(0-\infty)}$ and dose/AUC_{ss}, respectively. The volume of distribution (V_{ss}/F) will be determined from the mean residence time (MRT) x CL/F. The RAC will be calculated as the ratio of the AUC_{ss} or C_{max} on Cycle 2 Day 1 and $AUC_{(0-24)}$ or C_{max} on Cycle 0 Day 1. The time dependency of the pharmacokinetics on multiple dosing will be assessed by the calculation of the ratio of AUC_{ss} on Cycle 2 Day 1/$AUC_{(0-\infty)}$ on Cycle 0 Day 1.

The equation for calculating the amount excreted in the urine is: Ae (µmol or ng) = urine volume (mL) * concentration (µmol/mL or ng/mL). The weight/volume of urine and the concentration of drug in urine are usually recorded assuming that 1 g corresponds to 1 mL of urine. Urine concentrations below LLOQ will be treated as numerical zero. The percentage of dose excreted unchanged in the urine (e.g. Fe [%]) will be calculated by dividing the corresponding Ae in the collection period by the dose administered and multiplying by 100.

Renal clearance can be calculated by:. CL_R (L/h) = Ae_{0-t} (µmol or ng) / AUC_{0-t} (µmol.h/L or ng.h/L) where the 0-t interval is the same for both Ae and AUC.

Where possible the appropriate pharmacokinetic parameters will also be determined for the metabolites of DZD9008.

Additional PK parameters may be derived where appropriate.

7.5 Calculation or derivation of tumor response variables

Independent Central Review of RECIST based assessments

The Independent Review Committee (IRC) will review all the images collected from Part B of the study and images collected from patients with EGFR Exon20ins in Part A of the study when needed. IRC review of all radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be provided to the IRC. Prior radiotherapy reports for patients (at baseline) and information on biopsied lesions will also be provided to the IRC to allow the selection of appropriate target lesions. The imaging scans will be reviewed by two independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. For each patient, the IRC will define the overall visit response data (CR, PR, SD, PD or NE) and the relevant scan dates for each time point (i.e. for visits where response or progression is/is not identified). If a patient has had a tumor assessment which cannot be evaluated then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD). Endpoints (ORR, DoR, DCR, PFS) will be derived from the scan dates. ORR will only include patients whose response has been confirmed by a second scan at least 4 weeks after the initial response. The endpoint of tumor shrinkage will be assessed from tumor size measurements based on the primary independent radiologist assessment.

Results from the independent review will not be communicated to investigators. The management of patients will be based solely on the results of the RECIST 1.1 assessment conducted by the investigator.

For more detailed information refers to recent IRC charter.

Investigator RECIST based assessments

From the investigators review of the imaging scans, the RECIST tumor response data will be used to determine each subject's visit response according to RECIST version 1.1. At each visit, patients will be assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments.

Progression of TLs will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If a patient has had a tumor assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

- A visit response of CR will not be allowed if any of the TL data is missing

7.5.1 Objective response rate (ORR)

Objective response rate is defined as the percentage of patients who have best overall response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be < 10 mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. A confirmed response of CR/PR means that a response of CR/PR is recorded by two consecutive visits with ≥ 4 weeks' time interval.

When the investigator is in doubt as to whether progression of disease has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Any CR or PR which occur after a further anticancer therapy is received will not be included in numerator of the ORR calculation.

Best overall response (BOR) will be calculated as the best response recorded from study treatment starts until RECIST assessed progression is documented for each patient, prior to any subsequent cancer therapy received and irrespective of whether patients discontinued treatment of DZD9008. When confirmation of CR/PR is required, BOR of CR or PR will only be claimed only if the criterion for confirmed response is met. When SD is believed to be the best response, at least 6 weeks from baseline (with ± 7 day visit window) is required.

7.5.2 Progression Free Survival (PFS)

PFS is defined as the time from date of first dosing until the date of objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the subject withdraws from the study treatments or receives another anticancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. If the patient progresses or dies after two or more consecutively missed RECIST assessments visits, the patient will be censored at the time of latest evaluable RECIST assessment before the missed visit. If the patient has no evaluable visits or does not have baseline data they will be censored on the first dosing date unless they die within two RECIST assessment visits after baseline.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1 and their PFS time will be derived as defined above.

The PFS will always be derived based on scan/assessment dates not visit dates.

Note: Symptomatic deterioration will not be regarded as a progression event.

7.5.3 Duration of Response (DoR)

Duration of response will be defined as the time from the date of first documented response, that is subsequently confirmed until the date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a patient does not progress following a response, then his/her duration of response will use the PFS censoring time.

7.5.4 Disease control rate (DCR)

Disease control rate is defined as the proportion of patients with a best overall response of CR, PR or SD.

7.5.5 Change in tumor size

Tumor size is defined as the sum of the lengths of the longest diameters of the RECIST 1.1 target lesions. Percentage change in tumor size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline.

For further details see Appendix F of this Clinical Study Protocol.

7.5.6 Overall Survival (OS)

Overall survival will be assessed based on the date of first dose and survival status at the time of analysis.

Overall survival is defined as the interval between the date of first dose and the date of patient death due to any cause. Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

7.6 Calculation of patient reported outcome (PRO)

7.6.1 EQ-5D-5L

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondent select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). The score is reported separately.

7.7 Calculation or derivation of exploratory research variables

Results from the exploratory biomarker and pharmacogenetic research etc.may be reported separately from the Clinical Study Report for the main study.

7.8 Analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety result sections, erroneously treated patients (eg, those assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Table 10 Analysis set definition

Analysis Set	Definition
All patients	All patients screened
All randomized patients	All patients who were randomized (applicable for Part B only)
Safety	All patients who received at least 1 dose of DZD9008
Full analysis set (FAS)	All randomized NSCLC patients with documented EGFR Exon20ins mutation in tumor tissue who were previously treated with platinum-based chemotherapy, received at least 1 dose of DZD9008 and have measurable disease at baseline as identified by IRC (applicable for Part B only)
Centrally confirmed EGFR Exon20ins by tumor tissue	All patients in full analysis set with EGFR Exon20ins mutations confirmed in tumor tissue by central laboratory (applicable for Part B only)
Centrally confirmed EGFR Exon20ins by plasma ctDNA	All patients in full analysis set with EGFR Exon20ins mutations confirmed in plasma ctDNA by central laboratory (applicable for Part B only)

Analysis Set	Definition
Pharmacokinetics	All dosed patients who has at least one measurable plasma concentration of DZD9008 post dose with no protocol deviations or AE thought to impact the analysis of the PK data
Food effect	Patients from the food effect cohort for whom a PK profile is available on at least one of the fed and fasted dosing days
Evaluable for response	Dosed patients with measurable disease at baseline and follow up RECIST assessment (Part A)
Exploratory biomarkers	All patients that participate in the exploratory biomarker research
Paired biopsy (PoM cohort)	Dosed patients with a pre-study tumor biopsy and one tumor biopsy on study treatment

7.9 Methods of Statistical analysis

The statistical analyses will be performed by Dizal statistical group or designated third party provider, under the direction of Dizal. Data from Part A and Part B will be provided separately. Summary statistics will be presented by dose group in Part A and by study cohort in Part B.

7.9.1 Demographic data

Characteristics of the patients, including medical history, disease characteristics at baseline, prior and concomitant medications will be listed for each patient and summarized.

Reasons for discontinuation of investigational product will be listed including the day of treatment discontinuation and will be summarized.

7.9.2 Exposure

Dose administration data for the investigational product, including the cycle number, start/end dates, dose (unit), dose modifications will be listed for all patients in the safety analysis set.

Total exposure duration (date of last dose minus date of first dose + 1, regardless of any intermittent interruptions) and the total administered dose, as well as treatment compliance will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption and at least one dose reduction will be presented separately for the initial period defined as 21 days of multiple dosing (cycle 1) and for any time following this initial period of the study.

7.9.3 Safety

All patients who receive at least one dose of DZD9008 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarized by the Medical Dictionary for Regulatory

Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with adverse events in different categories (eg, causally related, CTCAE grade ≥ 3 etc) will be summarized by dose group in Part A and by dose cohort in Part B, and events in each category will be further summarized by MedDRA system organ class and preferred term, by dose group. SAEs will be summarized separately if a sufficient number occur.

Any AE occurring within the defined 28-day follow-up period after discontinuation of investigational product will be included in the AE summaries. Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings. AEs occurring after the 28 day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

Hematology, clinical chemistry, vital signs and ECG data will be listed individually by patient and suitably summarized. For all laboratory variables, which are included in CTCAE 5.0, the CTCAE grade will be calculated. Summary statistics such as mean, median, standard deviation, minimum, maximum and number of observations will be used for continuous variables, frequency and percentages will be used for categorical variables.

Details of any deaths will be listed for all patients.

Any qualitative assessments will be summarized using the number and proportion of patients with results of negative, trace or positive.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

7.9.4 Pharmacokinetics

This will be summarized in the Pharmacokinetics analysis set.

Plasma concentrations of DZD9008 will be summarized by nominal sample time. Plasma concentrations and derived PK parameters will be summarized. Parameters following single and multiple dosing will be summarized separately. Plasma concentrations at each time point will be summarized according to dose by the following summary statistics:

- The geometric mean (G_{mean}, calculated as $\exp[\mu]$, where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as $100\sqrt{[\exp(s^2)-1]}$, where s is the standard deviation of the data on a log scale)
- $G_{mean} \pm$ standard deviation (calculated as $\exp[\mu \pm s]$)
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data

- Median
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, $AUC_{(0-168)}$, $AUC_{(0-t)}$, AUC_{ss}, C_{max}, $C_{ss\ max}$, and $C_{ss\ min}$:

- G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale
- CV, calculated as $100\sqrt{[exp(s^2)-1]}$, where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Median
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for CL/F, CL_{ss}/F, V_{ss}/F, $t_{½\lambda z}$, RAC (AUC) and RAC(C_{max}), time dependency, CL_R, Ae and Fe:

- Arithmetic mean
- Standard deviation
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for t_{max} and $t_{ss\ max}$:

- Median
- Minimum
- Maximum
- Number of observations

Regression based diagnostic parameters (λz Interval, λzN, Rsq adj, λz period/t½λz, tlast, AUCextr) will be listed only and not summarized.

The pharmacokinetic data for DZD9008 after a single-dose and separately, at steady state will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and G_{mean} concentration (+/-standard deviation) versus time, stratified by dose.

Scatter plots of PK parameters versus dose, or log-dose will also be considered following both single (escalation only) and multiple dose administration of DZD9008 to assess dose proportionality in Part A.

In a preliminary assessment of dose proportionality, log-transformed $AUC_{(0-\infty)}$ and/or $AUC_{(0-t)}$ and C_{max} parameter estimates will be examined using the Power Model:

$$\text{parameter} = e^{a} (\text{dose})^{b}$$

$$\text{i.e., } \log(\text{parameter}) = a + (b * \log(\text{dose}))$$

where a is the intercept, depending on patients, and b is the slope, measuring the extent of dose proportionality. Dose proportionality implies that b=1 and will be assessed by estimating b along with its confidence interval.

If there is evidence of departures from dose proportionality, log-transformed dose-normalized AUC and C_{max} of DZD9008 will be analysed separately using a mixed effects model. Dose will be fitted as a fixed effect and patient as a random effect. Point estimates and associated 90% confidence intervals (CIs) for the differences between each dose level and the reference dose (the lowest dose) will be constructed using the residual variance. The estimates will then be back-transformed to provide point estimates and corresponding 90% CIs for the ratios of each dose level to the reference dose on the original scale. No adjustments for pre-planned multiple comparisons will be made. This analysis will only be performed provided there are sufficient data.

If there are more than 20% patients whose $AUC_{(0-\infty)}$ values are not calculable for either treatment due to large extrapolated area (> 20%), Rsq adjusted <0.80 or any other reason, $AUC_{(0-t)}$ will also be analyzed statistically and presented in the same way as $AUC_{(0-\infty)}$. Otherwise, $AUC_{(0-t)}$ will not be statistically analyzed.

The same analysis will be performed on AUC_{ss} and $C_{ss,max}$ from Cycle 2 Day 1 PK data.

7.9.5 The effect of high fat meal

For the assessment of the effect of high fat meal, the primary PK variables $AUC_{(0-\infty)}$ and/or $AUC_{(0-t)}$ and/or $AUC_{(0-72)}$, and C_{max} of plasma DZD9008 will be analyzed in food effect analysis set. These parameters will be natural log-transformed and analyzed using a linear mixed effects model with fixed effects for sequence, period and treatment, and random effect for patient nested within sequence. The difference in treatment means will be determined along with its associated 90% CI and back-transformed to give an estimate of the effect of food on the exposure of DZD9008. The results of this analysis will be presented in terms of geometric means for both treatments, the effect of food on the exposure of DZD9008 (ie, the ratio of the treatment geometric means) and its 90% CI.

In the event of relevant carry-over exposure across periods (predose concentration exceeds 5% of C_{max} for DZD9008 in period 2), the primary analysis will be performed excluding the Period 2 data for patients meeting the carry-over criteria. A secondary statistical analysis may be performed including all patients, irrespective of the degreee of carry-over. If appropiorate, an exploratory analysis on carry-over adjusted concentrations and PK parameters may also be performed.

7.9.6 The effect of low-fat meal

Additional cohorts from Part A investigate PK exposure of DZD9008 at 200 mg and 300 mg, respectively, with low-fat meal. For the assessment of the effect of low-fat meal, the primary PK parameters at steady state (AUC_{ss} and $C_{ss,max}$ at cycle 2 day 1) will be analyzed. These parameters will be natural log-transformed and analyzed using a linear model, with the dose level (200 mg or 300 mg) and food condition (fed or fasted) included as independent variables. The between-food condition difference and 90% confidence intervals (CIs) will be provided.

An evaluable full PK profile between fasted and fed was defined as:

On C2D1 of Part A expansion, the patient took DZD9008 under the originally assigned prandial conditions.

No vomiting occurred within four hours following dose administration on the full PK sampling day.

Additionally, an entire PK profile could be considered non-evaluable as per scientific judgment of clinical pharmacology expert even if the above criteria were fulfilled.

7.9.7 Efficacy

Efficacy endpoints related to RECIST tumor assessment will be analyzed and reported based on the evaluation by IRC and investigators, respectively.

Unless otherwise specified, the efficacy analysis population will be the evaluable for response anlaysis set for Part A and full analysis set for Part B. To support companion diagnostics development, efficacy analysis in centrally confirmed EGFR Exon20ins by tumor tissue and centrally confirmed EGFR Exon20ins by plasma ctDNA analysis sets may be performed for Part B.

7.9.7.1 Tumor response

The analysis population will be the evaluable for response anlaysis set for Part A and FAS for Part B.

Summaries of the number of patients with best overall response in each part will be provided in the following categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE). Objective response rate and disease control rate will be summarized.

For Part B, p value for the test against the null hypothesis of ORR≤17% will reported based on the Simon's two-stage method. ORR and two-sided 97.5% CI will be calculated based on Jung's method (26) to adjust the bias caused by optional sampling in the Simon's two-stage design and provide the uniformly minimum variance unbiased estimator.

Data will be analyzed by subgroup (e.g. taken into consideration of the prior treatment) in Part B.

7.9.7.2 Duration of response

The analysis population for duration of response will be the subset of the evaluable for response population (Part A) or FAS (Part B) with a best overall response of confirmed CR/PR. Duration of response will be summarized and the number (%) of responding patients with a duration of response > 3, > 6, > 9 and > 12 months will be presented. Or if data are appropriate, response ongoing rates at 6, 9 and 12 months will be estimated based on Kaplan-Meier method. A Kaplan Meier plot and median duration of response (calculated from the Kaplan-Meier) will be presented.

7.9.7.3 Change in tumor size

The analysis population for change in tumor size will be the evaluable for response set for Part A and FAS for Part B.

The absolute values and percentage change in target lesion tumor size from baseline will be summarized using descriptive statistics and presented at each time point. The best change will also be summarized.

Tumor size will also be presented graphically using waterfall plots, presenting each patient's percentage change in tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference line at the -30% change in tumor size levels will be added to the plots, which corresponds to the definition of partial response.

7.9.7.4 Progression free survival

The analysis populations for PFS will be the safety analysis set for Part A and FAS for Part B.

PFS will be displayed using a Kaplan-Meier plot. The progression-free survival rates at 6, 9 and 12 months (calculated from the Kaplan-Meier estimator), median and quartiles (if estimable from the Kaplan-Meier estimator) will be summarized.

7.9.7.5 Overall survival

Overall survival will be analyzed and reported in FAS for Part B. The survival status (dead, alive, lost to follow-up, etc) at the end of the study will be summarized. In addition, the number and percentage of patients prematurely censored before data cut-off will be summarized.

Overall survival will be displayed using a Kaplan-Meier plot. The overall survival rates at 6, 9 and 12 months (calculated from the Kaplan-Meier estimator), median and quartiles (if estimable from the Kaplan-Meier estimator) will be summarized.

7.9.8 Patient Report Outcome (PRO)

Descriptive analysis will be perfomed by treatment group and visit for each item and the VAS score in EQ-5D-5L.

7.9.9 PoM biomarker

The pharmacodynamic effect of DZD9008 on pEGFR in tumor tissue from paired biopsies will be evaluated. The technological platform for the pharmacodynamics analysis will be

immunohistochemistry, but may not be limited to this. The biomarker study will include, but not limit to pEGFR. pEGFR expression in tumor tissue with DZD9008 treatment will be summarized and displayed graphically in subset of patient population who have paired tumor tissue biopsies. The baseline and post-treatment pEGFR levels will be compared for individual patient and will be also summarized by dose cohort.

PoM biomarker study result will not constitute the Clinical Study Report.

7.9.10 Exploratory biomarker research and pharmacogenetic study

The number of patients who will agree to participate in the exploratory biomarker and genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. The exploratory biomarker study results will not be included in CSR.

7.10 Publication policy

This policy applies to Spain.

All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

Samples and/or data will be processed centrally, and the results will be sent electronically to the Sponsor or designated CRO. Data that will be processed centrally includes central imaging review data (CT/MRI), central ECG data and centrally analyzed laboratory data including PK and blood/tumor biomarker samples.

The Sponsor has full ownership of the original eCRFs completed as part of the study.

By signing the clinical study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

After conclusion of the clinical trial, an integrated clinical and statistical study report will be prepared by the Sponsor or designee. As soon as possible and no later than one year, the trial results must be entered in European Clinical Trials Database clinicaltrialsregister.eu.

All materials, documents and information supplied by the Sponsor to the Investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the Sponsor. Subject to obligations of confidentiality, the Investigator reserves the right to publish only the results of the work performed pursuant to this protocol, provided, however, that the Investigator provides an authorized representative of the Sponsor with a copy of any proposed publication for review and comment at least 45 days in advance of its submission for publication. In addition, if requested, the Investigator will withhold publication an additional 90 days to allow for filing a

patent application or taking such other measures as Sponsor deems appropriate to establish and preserve its proprietary rights.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

8. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

8.1 Medical emergencies and Sponsor contacts

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 a SAE and is to be reported as such, see Section 6.4.4.**

In the case of a medical emergency the investigator may contact the Study Team Physician. If the Study Team Physician is not available, contact the Study Leader at Dizal Pharmaceuticals.

Name	Role in the study	Address & telephone number
[redacted]	Study Team Physician responsible for the protocol at Dizal	[redacted]
[redacted]	Global Study Leader responsible for the protocol at Dizal	[redacted]
[redacted]	Chief Medical Officer Responsible for the high level strategy	[redacted]

8.2 Overdose

There are no data on overdosing since this is the first study in humans with DZD9008. There is no definition of what constitutes an overdose. There is no known antidote. Investigators will be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.

- An overdose with no associated symptoms is only reported on the overdose CRF module.

If an overdose occurs in the course of the study, then investigators or other site personnel inform appropriate Dizal representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Dizal representative works with the investigator to ensure that all relevant information is provided to the Dizal Patient Safety team or representatives.

For overdoses associated with an SAE, standard reporting timelines apply, see Section 6.4.4.

8.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to Dizal using the appropriate forms.

8.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 28 days after discontinuing investigational product, then investigators or other site personnel inform appropriate Dizal representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Dizal representative works with the investigator to ensure that all relevant information is provided to the Dizal Patient Safety team within 1 or 5 days for SAEs, (see Section 6.4.4) and within 28 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.2 Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 16 weeks after dosing should be reported to Dizal and followed up for its outcome.

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Table 11 Study Plan of Dose Escalation Cohort (Part A, dose escalation)

Assessment	Screen	Cycle 0 Days (cycle 0=8 days)						Cycle 1 (28 days)			Cycle 2 (21 days) onwards	Discontinuation	28 day follow up	Details in section
Day	**-28~ -1**	**1[h]**	**2**	**3**	**4**	**6**	**8**	**1[h]**	**8[a]**	**15[a]**	**1[b]**			
Informed consent	X													4.1.1
Demography & baseline characteristics	X													6.3.1
Medical/surgical history	X													6.3.1
Inclusion/exclusion criteria	X													4.1 & 4.2
Physical examination	X	X						X			X	X		6.3.2
ECOG performance status	X	X						X			X	X		6.3.2
Brain MRI	X													4.1
Pregnancy test (premenopausal females only)[c]	X											X		6.3.4
Ophthalmologic assessment [i]	X											X		6.3.5
Archival tumor tissue or fresh biopsy collection (mutation confirmation)	X													6.6.2
Vital signs	X	X	X					X	X	X	X	X		6.3.3
Height	X													6.3.3
Weight	X	X						X			X	X		6.3.3
ECG	X	X	X					X	X	X	X	X		6.3.5
Clinical chemistry/ Hematology/Urinalysis	X	X						X	X	X	X	X		6.3.4
Echocardiogram/MUGA[e]	X							on Cycle 3 Day1, then every 6 weeks						6.3.5

Assessment	Screen	Cycle 0 Days (cycle 0=8 days)						Cycle 1 (28 days)			Cycle 2 (21 days) onwards	Discontinuation	28 day follow up	Details in section
Day	**-28~ -1**	**1[h]**	**2**	**3**	**4**	**6**	**8**	**1[h]**	**8[a]**	**15[a]**	**1[b]**			
Lung function test (LFT) [e]	X							on Cycle 3 Day1, then every 6 weeks						6.3.5.3
HBV, HCV, HIV, COVID-19[d]	X													4.2
APTT/INR	X	X						X	X	X	X	X		6.3.4
Blood PK samples (including metabolites)		X#	X	X	X	X	X	X	X	X	X#*			6.5.1
PK Urine (including metabolites)											X#			6.5.1
4-β hydroxycholesterol / total cholesterol		X						X	X	X	X (C2 only)			6.5.3
Dose with DZD9008		X						←---------- X (daily dosing) ----------→						5.1
Blood samples for ctDNA & Biomarkers (optional)	X	X						X	X	X	X (C2D1-C6D1 and continuous every even cycle D1 until disease progression)			6.6.2.3
RECIST assessments [f]	X							←--on Cycle 3 Day1, then every 6 weeks until disease progression→						6.8.1
Concomitant medication	←----------→													4.3.1
Adverse events[g]	←----------→													6.4

#: Multiple time point for PK sampling. Hospitalization can be allowed for out of business time PK collection.
*: Day 1 of Cycle 2, 3, 4 and 5

a. ±1 day visit window is allowed for C1D8 & D15.

b. All study visits from Cycle 2 Day 1 onwards may be performed within a visit window of ± 2 days.

c. Pregnancy test needs to be within 3 days of the first dosing.

d. HBV/HCV/HIV/COVID-19 tests can be done based on local practice.

e. Echo/MUGA and LFT at baseline needs to be done within 14 days of the first dosing.

f. CT is preferred. Same scan modality is required to use for tumor scan and RECIST assessment from baseline till follow up for one patient. Please refer to Appendix F of CSP about the details of RECIST assessment.

g. AE will be collected from first dosing of DZD9008; SAE is required to be collected from inform consent

h. For C0D1 and C1D1, -1 day window is allowed for laboratory safety testing and physical examination

i. Eye examination includes: Visual acuity, Pupils, Intraocular pressure, External examination, Slit-lamp examination, and Fundoscopic examination (pupil dilate is not required) and others if clinically indicated.

Table 12 Study Plan of Food Effect Cohort (Part A, food effect)

Assessment	Screen	Cycle 0 * Days (cycle 0=16 days)												Cycle 1 (21 days)			Cycles 2 (21 days) onwards	Disconti nuation	28-day Follow Up	Details in section
Day		**1[h]**	**2**	**3**	**4**	**6**	**8**	**9**	**10**	**11**	**12**	**14**	**16**	**1[h]**	**8[a]**	**15[a]**	**1[b]**			
Informed consent	X																			4.1.1
Demography & baseline characteristics	X																			6.3.1
Medical/surgical history	X																			6.3.1
Inclusion/exclusion criteria	X																			4.1 & 4.2
Physical examination	X	X						X						X			X	X		6.3.2
ECOG performance status	X	X						X						X			X	X		6.3.2
Brain MRI or contrast-enhanced CT	X																			4.1
Pregnancy test (premenopausal females only)[c]	X																	X		6.3.4
Ophthalmologic assessment [i]	X																	X		6.3.5.4
Archival tumor tissue or fresh biopsy (mutation confirmation)	X																			6.6.2
Vital signs	X	X						X						X	X	X	X	X		6.3.3
Height	X																			6.3.3
Weight	X	X												X			X			6.3.3
ECG	X	X						X						X	X	X	X	X		6.3.5
HBV, HCV, HIV, COVID-19[d]	X																			4.2

Assessment	Screen	Cycle 0 * Days (cycle 0=16 days)												Cycle 1 (21 days)			Cycles 2 (21 days) onwards	Discontinuation	28-day Follow Up	Details in section
Day		**1[h]**	**2**	**3**	**4**	**6**	**8**	**9**	**10**	**11**	**12**	**14**	**16**	**1[h]**	**8[a]**	**15[a]**	**1[b]**			
Clinical chemistry/ Hematology/Urinalysis	X	X						X						X	X	X	X	X		6.3.4
APTT/INR	X	X						X						X	X	X	X	X		6.3.4
Echocardiogram/MUGA[e]	X													On Cycle 3 Day1, then every 6 weeks						6.3.5.2
Lung function test (LFT) [e]	X													On Cycle 3 Day 1, then every 6 weeks						6.3.5.3
PK blood samples		X[#]	X	X	X	X	X	X[#]	X	X	X	X	X				X[i]			6.5.1.1
Blood sample for ctDNA & Biomarkers (optional)	X	X												X	X	X	X (C2D1-C6D1 and continuous every even cycle D1 until disease progression)			6.6.2.3
RECIST assessments[f]	X													On Cycle 3 Day 1, then every 6 weeks until progression						6.8.1
Dose with DZD9008		X						X						←---------X (daily dosing) ----------→						5.1.1
Concomitant medication	←----------→																			4.3.1
Adverse events [g]	←----------→																			6.4

#: Multiple time point for PK sampling. Hospitalization can be allowed for out of business time PK collection.
* Treatment date might be update in light of emerging human PK data

a. ±1 day visit window is allowed for C1D8 & D15.

b. All study visits from Cycle 2 Day 1 onwards may be performed within a visit window of ± 2 days.

c. Pregnancy test needs to be within 3 days of the first dosing.

d. HBV/HCV/HIV/COVID-19 tests can be done based on local practice.

e. Echo/MUGA and LFT at baseline needs to be done within 14 days of the first dosing.

f. CT is preferred. Same scan modality is required to use for tumor scan and RECIST assessment from baseline till follow up for one patient. Please refer to Appendix F of CSP about the details of RECIST assessment.

g. AE will be collected from first dosing of DZD9008; SAE is required to be collected from inform consent

h. For C0D1 and C1D1, -1 day window is allowed for laboratory safety testing and physical examination

i. Eye examination includes: Visual acuity, Pupils, Intraocular pressure, External examination, Slit-lamp examination, and Fundoscopic examination (pupil dilate is not required) and others if clinically indicated.

j. Pre-dose on Cycle 2 day 1.

Table 13 Study Plan of Part A Dose Expansion

Assessment	Screen	Cycle 1 (21 days)			Cycle 2 (21 days) onwards	Discontinuation	28-day follow up	Details in section
Day	**-28 to -1**	**1 [h]**	**8[a]**	**15[a]**	**1[b]**			
Informed consent	X							4.1.1
Demography & baseline characteristics	X							6.3.1
Medical/surgical history	X							6.3.1
Inclusion/exclusion criteria	X							4.1 & 4.2
Physical examination	X	X			X	X		6.3.2
ECOG performance status	X	X			X	X		6.3.2
Brain MRI or contrast-enhanced CT	X							4.1
Pregnancy test (premenopausal females only)[c]	X					X		6.3.4
Ophthalmology assessment [i]	X					X		6.3.5.4
Archival tumor tissue or fresh biopsy (mutation confirmation)	X							6.6.2
Vital signs	X	X	X	X	X	X		6.3.3
Height	X							6.3.3
Weight	X	X			X	X		6.3.3
ECG	X	X	X	X	X	X		6.3.5
Clinical chemistry/ Hematology/Urinalysis	X	X	X	X	X	X		6.3.4
HBV/HCV/HIV/COVID-19[d]	X							4.2

Assessment	Screen	Cycle 1 (21 days)			Cycle 2 (21 days) onwards	Discontinuation	28-day follow up	Details in section
Day	**-28 to -1**	**1 [h]**	**8[a]**	**15[a]**	**1[b]**			
APTT/INR	X	X	X	X	X	X		6.3.4
Echocardiogram/MUGA [e]	X	←----------On Cycle 3 Day 1, then every 6 weeks ----------→						6.3.5.2
Lung function test (LFT) [e]	X	←---------- On Cycle 3 Day 1, then every 6 weeks ----------→						6.3.5.3
PRO-CTCAE and FACIT GP5 questions[j]		X	X	X	Weekly until the end of cycle 6, then on day 1 of each cycle	X		6.9.2 & 6.9.3
PK blood samples		X[#]	X	X	X[#*]			6.5.1.2
Blood sample for ctDNA & exploratory Biomarkers (optional)	X	X	X	X	X (C2D1-C6D1 and continuous every even cycle D1 until disease progression)			6.6.2
RECIST assessments [f]	X	←----------On Cycle 3 Day 1, then every 6 weeks ----------→						6.8.1
Dose with DZD9008		←----------X (daily dosing) ----------→						5.1.2
Concomitant medication	←---------- X ----------→							4.3.1
Adverse events [g]	←---------- X ----------→							6.4

#: multiple time point for PK sampling. Hospitalization can be allowed for out of business time PK collection.

*: Day 1 of Cycle 2, 3, 4

a. ±1-day visit window is allowed for C1D8 & D15.

b. All study visits from Cycle 2 Day 1 onwards may be performed within a visit window of ± 2 days.

c. Pregnancy test needs to be within 7 days of the first dosing.

d. HBV/HCV/HIV/COVID-19 test can be done based on local practice.

e. Echo/MUGA and LFT needs to be done within 14 days of the first dosing.

f. CT is preferred. Same scan modality is required to use for tumor scan and RECIST assessment from baseline till follow up for one patient. Please refer to Appendix F of CSP about the details of RECIST assessment.

g. AE will be collected from the first dosing of DZD9008; SAE is required to be collected from inform consent

h. For C1D1, -1 day window is allowed for laboratory safety testing and physical examination

i. Eye examination includes: Visual acuity, Pupils, Intraocular pressure, External examination, Slit-lamp examination, and Fundoscopic examination (pupil dilate is not required) and others if clinically indicated.

j. PRO-CTCAE and FACIT GP5 questionnaire will be collected weekly for the first 18 weeks (to cycle 6), and then on day 1 of each subsequent cycle (expansion cohort 3-6).

Table 14 Study Plan of Part B Dose Extension

Assessment	Screen	Cycle 1 (21 days)			Cycle 2 (21 days) onwards	Discontinuation	28-day follow up	Details in section
Day	**-28 to -1**	**1 [h]**	**8[a]**	**15[a]**	**1[b]**			
Informed consent	X							4.1.1
Demography & baseline characteristics	X							6.3.1
Medical/surgical history	X							6.3.1
Inclusion/exclusion criteria	X							4.1
Physical examination	X	X			X	X		6.3.2
ECOG performance status	X	X			X	X		6.3.2
Brain MRI or contrast enhanced CT	X							4.1
Pregnancy test (premenopausal females only)	X [c]					X		6.3.4
Ophthalmology assessment [i]	X					X		6.3.5.4
Archival tumor tissue or fresh biopsy (mutation confirmation and/or companion diagnostics development)[m]	X							6.6.1
Vital signs	X	X	X	X	X	X		6.3.3
Height	X							6.3.3
Weight	X	X			X	X		6.3.3
ECG	X	X[##]	X	X	X[##]	X		6.3.5
Clinical chemistry/ Hematology/Urinalysis	X	X	X	X	X	X		6.3.4
HBV/HCV/HIV/COVID-19[d]	X							4.2

Assessment	Screen	Cycle 1 (21 days)			Cycle 2 (21 days) onwards	Discontinuation	28-day follow up	Details in section
Day	**-28 to -1**	**1 [h]**	**8[a]**	**15[a]**	**1[b]**			
APTT/INR	X	X	X	X	X	X		6.3.4
Echocardiogram/MUGA [e]	X	←----------On Cycle 3 Day 1, then every 6 weeks ----------→						6.3.5.2
Lung function test (LFT) [e]	X	←---------- On Cycle 3 Day 1, then every 6 weeks ----------→						6.3.5.3
EQ-5D-5L		X	Every 6 weeks relative to first dose ↔			X		6.9.1
PRO-CTCAE and FACIT GP5 questions		X	X	X	Weekly until the end of cycle 6, than on day 1 of each cycle ↔	X		6.9.2 & 6.9.3
PK blood samples [l]		X	X	X	X			6.5.1.3
Paired tumor biopsy (Subject joins PoM study only)	X				X (C2D1)			6.6.2.2
Plasma sample for the development of liquid biopsy companion diagnostic	X							6.6.1
Blood sample for ctDNA & exploratory Biomarkers (optional)		X	X	X	X (C2D1-C6D1 and continuous every odd cycle D1 until disease progression)			6.6.2.3
Blood sample for pharmacogenetics (optional)		X[j]						6.6.3
RECIST assessments [f]	X	←----------On Cycle 3 Day 1, then every 6 weeks ----------→						6.8.1
Dose with DZD9008		←----------X (daily dosing) ----------→						5.1.4
Concomitant medication	←---------- X ----------→							4.3.1
Adverse events [g]	←---------- X ----------→							6.4
Survival status [k]	←---------- X ----------→							6.3.6.3

##: multiple time points for ECG. Refer to section 6.3.5.1 for details.

*: Day 1 of Cycle 2, 3, 4

a. ±1-day visit window is allowed for C1D8 & D15.

b. All study visits from Cycle 2 Day 1 onwards may be performed within a visit window of ± 2 days. Survival follow up may be performed within a visit window of ± 7 days.

c. Pregnancy test needs to be within 7 days of the first dosing. For Italy only: additional tests at pre-dose on Day 1 of Cycle 2 and each subsequent cycle, as clinically indicated, and during the safety follow-up period (2 weeks ± 3 days after the last dosing).

d. HBV/HCV/HIV/COVID-19 test can be done based on local practice.

e. Echo/MUGA and LFT needs to be done within 14 days of the first dosing.

f. It is suggested that site to conduct the first tumor assessment no earlier than C3D1 (±7days). CT is preferred for extracranial tumor. Same scan modality is required to use for tumor scan and RECIST assessment from baseline till follow up for one patient. Please refer to Appendix F of CSP about the details of RECIST assessment.

g. AE will be collected from the first dosing of DZD9008 and SAE is required to be collected from inform consent

h. For C1D1, -1 day window is allowed for laboratory safety testing and physical examination

i. Eye examination includes: Visual acuity, Pupils, Intraocular pressure, External examination, Slit-lamp examination, and Fundoscopic examination (pupil dilate is not required) and others if clinically indicated.

j. If for any reason the sample is not drawn prior to first dose (pre-dose at C1D1) it may be taken at any visit until the last study visit.

k. Survival status including anti-cancer therapy will be collected every 6 weeks following disease progression or withdrawal from treatment.

l. Multiple time point for PK sampling on C1D1 and C3D1, details refer to Table 8 and Table 9. Hospitalization can be allowed for out of business time PK collection. If there is a dose interruption, dose reduction, or an early termination due to an AE, or there is an SAE, the investigator may choose to collect an unplanned blood sample (if possible) within the 24 hour after the last dose.

m. Adequate amounts of archived tumor tissue or fresh biopsy (if archived tissue is not available) will be collected for Sponsor designated central laboratory confirmation of EGFR Exon20ins mutations. If a pre-study written documentation of EGFR Exon20ins in tumor tissue is available from Sponsor designated central laboratory using the designated assay, no additional tumor sample needs to be submitted. Requirements of tumor tissue sample collection can be referred to the Laboratory Manual.

Table 15 Lab visits and clinical monitoring (Part A, dose escalation)

Measurement	Screening		C0D1		C1D1		C1D8		C1D15		C2D1		C2D8		C2D15		C3D1		C4 & C5 onwards D1		End of treatment	
		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.
Hematology	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml					x	4ml	x	4ml	x	4ml
Clinical chemistry	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml					x	4ml	x	4ml	x	4ml
APTT/INR	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml					x	4ml	x	4ml	x	4ml
HBV, HCV, HIV screening	x	6ml																				
Urinalysis	x		x		x		x		x		x		x		x		x		x		x	
Pregnancy Test (Urine)	x																				x	
Plasma PK Pre			x	4ml	x	2ml	x	2ml	x	2ml	x	4ml					x	2ml	x	2ml		
Plasma PK 0.5h post			x	4ml							x	4ml										
Plasma PK 1h post			x	4ml							x	4ml										
Plasma PK 2hr post			x	4ml							x	4ml										
Plasma PK 3hr post			x	4ml							x	4ml										
Plasma PK 4hr post			x	4ml							x	4ml										
Plasma PK 6hr post			x	4ml							x	4ml										
Plasma PK 8hr post			x	4ml							x	4ml										
Plasma PK 10hr post			x	4ml							x	4ml										
Plasma PK 12hr post			x	4ml							x	4ml										
Plasma PK 24hr post			x	4ml							x	4ml[c]										
Plasma PK 48hr post			x	4ml																		
Plasma PK 72hr post			x	4ml																		
Plasma PK120hr post			x	4ml																		

Measurement	Screening		C0D1		C1D1		C1D8		C1D15		C2D1		C2D8		C2D15		C3D1		C4 & C5 onwards D1		End of treatment	
		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.
Plasma PK168hr post			x	4ml																		
Urine PK											x [d]											
4-β-hydroxycholesterol / total cholesterol			x	6ml	x	6ml	x	6ml	x	6ml	x	6ml										
Blood sample for ctDNA & Exploratory Biomarker	x	10ml	x	10ml	x	10ml	x	10ml	x	10ml	x	10ml					x 10ml (C3-C6 D1 and continuous every even cycle D1 afterwards)[b]					
BP/HR	x		x [a]		x [a]		x [a]		x [a]		x						x		x		x	
ECG	x		x [a]		x [a]		x [a]		x [a]		x						x		x		x	

a: time point: pre-dose, 1, 2, 4, 6, 10, 24 hours post dose. The 24 hours' time point falls on the 2nd day.
b: detailed time points see Section 6.6
c: 24hr post dosing should be collected before dosing on C2D2
d: The interval for urine collection on cycle 2 day 1 are 0-4, 4-12, and 12-24 hours. Next dosing on C2D2 should be given after the urine collection.

Table 16 Lab visits and clinical monitoring (Part A dose expansion)

Parameters	Screening		C1D1		C1D8		C1D15		C2D1		C3D1		C4 onwards D1		End of treatment	
		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.
Hematology	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml
Clinical chemistry,	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml
APTT/INR	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml
HBV, HCV, HIV screening	x	6ml														
Urinalysis	x		x		x		x		x		x		x		x	
Pregnancy Test (Urine)	x														x	
Plasma PK Pre			x	2ml	x	2ml	x	2ml	x	2ml	x	2ml	x	2ml (only C4)		
Plasma PK 0.5hr Post			x	2ml					x	2ml						
Plasma PK 1hr Post			x	2ml					x	2ml						
Plasma PK 2hr Post			x	2ml					x	2ml						
Plasma PK 3hr Post			x	2ml					x	2ml						
Plasma PK 4hr Post			x	2ml					x	2ml						
Plasma PK 6hr Post			x	2ml					x	2ml						
Plasma PK 8hr Post			x	2ml					x	2ml						
Plasma PK 10hr Post			x	2ml					x	2ml						
Plasma PK 12hr Post			x	2ml					x	2ml						
Plasma PK 24hr Post			x	2ml[b]					x	2ml[c]						
Blood sample for ctDNA & Exploratory Biomarker	x	10ml	x pre-dose	10ml	x	10ml	x	10ml	x	10ml	x 10ml (C3-C6 D1 and continuous every even cycle D1 afterwards)[a]					
BP/HR	x		x [d]		x [d]		x [d]		x		x		x		x	
ECG	x		x [d]		x [d]		x [d]		x		x		x		x	

[a]: detailed time points see Section 6.6
[b]: 24hr post dosing should be collected before dosing on C1D2
[c]: 24hr post dosing should be collected before dosing on C2D2
[d]: time points: pre-dose, 1, 2, 4, 6, 10, 24 hours post dose. The 24 hours' time point falls on the 2nd day.

Table 17 Lab visits and clinical monitoring (Part A, food effect)

		Cycle 0												Cycle 1			Cycle 2 & onward		
	Screening	D1	D2	D3	D4	D6	D8	D9	D10	D11	D12	D14	D16	C1D1	C1D8	C1D15	C2D1	C3D1 and onward	End of study
Plasma PK Pre		2 ml						2 ml									2 ml		
Plasma PK 0.5hr post		2 ml						2 ml											
Plasma PK 1hr post		2 ml						2 ml											
Plasma PK 2hr post		2 ml						2 ml											
Plasma PK 3hr post		2 ml						2 ml											
Plasma PK 4hr post		2 ml						2 ml											
Plasma PK 6hr post		2 ml						2 ml											
Plasma PK 8hr post		2 ml						2 ml											
Plasma PK 10hr post		2 ml						2 ml											
Plasma PK 12hr post		2 ml						2 ml											
Plasma PK 24hr post			2 ml						2 ml										
Plasma PK 48hr post				2 ml						2 ml									
Plasma PK 72hr post					2ml						2 ml								
Plasma PK 120hr post						2 ml						2 ml							
Plasma PK 168hr post							2 ml						2 ml						
Pregnancy test	x																		
Hematology	4 ml	4 ml												4 ml			4 ml	4 ml	4 ml
Clinical chemistry	4 ml	4 ml												4 ml			4 ml	4 ml	4 ml
Blood sample for ctDNA & Exploratory Biomarker	10ml	10ml												10ml	10ml	10ml	× 10ml (C2-C6 D1 and continuous every even cycle D1 afterwards)[b]		
BP/HR		x[a]	x[a]					x[a]	x[a]					x[a]	x[a]	x[a]	x	x	x
ECG		x[a]	x[a]					x[a]	x[a]					x[a]	x[a]	x[a]	x	x	x
HBV/HCV/HIV	6 mL																		

		Cycle 0												Cycle 1			Cycle 2 & onward		
	Screening	**D1**	**D2**	**D3**	**D4**	**D6**	**D8**	**D9**	**D10**	**D11**	**D12**	**D14**	**D16**	**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C3D1 and onward**	**End of study**
APTT/INR	4 ml	4 ml												4 ml			4 ml	4 ml	4 ml

a: time point: pre-dose, 1, 2, 4, 6, 10, 24 hours post dose. The 24hour time point falls on the 2nd day.
b. detailed time points see Section 6.6

Table 18 Lab visits and clinical monitoring (Part B dose extension)

Parameters	Screening		C1D1		C1D8		C1D15		C2D1		C3 D1		C4 onwards D1		End of treatment	
		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.		Blood Vol.
Hematology	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml
Clinical chemistry,	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml
APTT/INR	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml	x	4ml
HBV, HCV, HIV, COVID-19 screening	x	6ml														
Urinalysis	x		x		x		x		x		x		x		x	
Pregnancy Test (Serum/ Urine)	x [d]														x	
Plasma PK Pre			x	2ml#	x	2ml#	x	2ml#	x	2ml#	x	2ml#	**x**	2ml# (C5, C7, C9 and C11)		
Plasma PK 1hr Post			x	2ml*							x	2ml*				
Plasma PK 2hr Post			x	2ml*							x	2ml*				
Plasma PK 3hr Post			x	2ml*							x	2ml*				
Plasma PK 4hr Post			x	2ml#							x	2ml#				
Plasma PK 6hr Post			x	2ml*							x	2ml*				
Plasma PK 8hr Post			x	2ml#							x	2ml#				
Plasma PK 24hr Post			x	2ml*							x	2ml*				
Blood sample for the development of liquid biopsy companion diagnostic	x	20ml														
Blood sample for pharmacogenetics (optional)			x (pre-dose)	5ml												
Blood sample for ctDNA & Exploratory Biomarker (optional)			x (pre-dose)	10ml	x	10ml	x	10ml	x	10ml	x 10ml (C3-C6 D1 and continuous every odd cycle D1 afterwards)[a]					
BP/HR	x		x		x		x		x		x		x		x	
ECG	x[c]		x[b]		x		x		x		x [b]		x		x	

#: PK sample collection for both sparse and intense PK group* PK sample collection for intense PK group only.
a. detailed time points see section 6.6
b. multiple time for ECG. Details refer to section 6.3.5
c: multiple time point (pre- and 2, 4, 6, 8 hr post) for ECG of intense PK cohort. pre-dose ECG for sparse PK cohort. Details description refer to section 6.3.5.
d: pregnancy testing needs to be performed within 7 days of the first dosing, For Italy only: additional tests at pre-dose on Day 1 of Cycle 2 and each subsequent cycle, as clinically indicated, and during the safety follow-up period (2 weeks ± 3 days after the last dosing).

Appendix A SIGNATURE

INVESTIGATOR STATEMENT

Principal investigator Signature

Protocol Number: DZ2019E0001

Protocol title: A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 mutation.

I understand that all information concerning DZD9008 in connection with this study and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Study Protocol, Case Report Form, clinical methodology, and basic scientific data.

I will not initiate this study without approval from the Institutional Review Board/Ethics Committee and I understand that any changes in the protocol must be approved in writing by Dizal (Jiangsu) Pharmaceutical Co., Ltd and the Institutional Review Board/Ethics Committee before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

By my signature below, I attest that I have read, understand, and agree to abide by all the conditions, instructions, and restrictions contained in Protocol Number DZ2019E0001, and will conduct the trial in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

_____

Principal investigator/Printed Name

_____ _____

Principal investigator/Signature Date

Appendix B FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement should be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

A guide to interpreting the causality QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped?

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix C INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION (IATA) 6.2 GUIDANCE DOCUMENT

Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories**.** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D ETHICAL AND REGULATORY REQUIREMENTS

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 the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements and the Dizal policy on Bioethics and Human Biological Samples.

Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. This will include approval of the exploratory biomarker and pharmacogenetic research and associated consent(s) forms. The investigator/The Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff. In Japan, the head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to Dizal before enrolment of any patient into the study. In Japan, the Head of the study site should submit a notification of direction/determination as well as the Institutional Review Board (IRB) written approval to Dizal. If applicable this approval should clearly state that the exploratory biomarker and pharmacogenetic research is approved.

The Ethics Committee should approve all advertising used to recruit patients for the study.

Dizal should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

In Japan, the Head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the Head of the study site at the time of the protocol re-approval.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

Dizal will handle the distribution of any of these documents to the national regulatory authorities.

Dizal will provide Regulatory Authorities, Ethics Committees and Principal Investigators (in Japan, also the Head of the study site) with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. Dizal will provide this information to the Principal Investigator so that he/she can meet these reporting requirements. In Japan, the Head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by Dizal.

Informed consent

Any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation should be described in the informed consent form that is approved by an Ethics Committee.

The Principal Investigator at each center will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the optional exploratory biomarker and genetic research component(s)
- Ensure that each patient is notified that they are free to withdraw from the study or the research components at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed Informed Consent Form is stored in the Investigator's Study File/medical records
- Ensure a copy of each signed Informed Consent Form is given to the patient

The exploratory biomarker and genetic research component(s) of this study are voluntary, and the patient may participate in the main study without participating in the exploratory biomarker and/or genetic research part(s) of the study. To participate in the exploratory biomarker and/or genetic component of the study the patient should sign and date the consent form for the main study and as applicable separate consent forms for the exploratory biomarker and/or the genetic components of the study.

Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and Dizal Pharmaceuticals.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a Clinical Study Protocol Amendment and where required in a new version of the protocol (Revised Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

Dizal will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to Ethics Committee see Section 2.2.

If a protocol amendment requires a change to a center's Informed Consent Form, Dizal and the center's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

In Japan, study procedures will not be changed without the mutual agreement of the Principal Investigator and Dizal. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the study site and be approved by its IRB. If applicable, Dizal should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a study site's Informed Consent Form, then Dizal and the center's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by Dizal and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

Audits and inspections

Authorized representatives of Dizal, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an 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 Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact Dizal immediately if contacted by a regulatory agency about an inspection at the center.

Appendix E PATIENT DATA PROTECTION

The 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.

Due to the exploratory nature of the biomarker and genetic research, there will be no routine communication of these results to patients. Dizal will not provide individual results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a Dizal physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of Dizal to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of Dizal or its representatives. This will be documented in a Clinical Study Agreement between Dizal and the investigator

Training of study site personnel

Before the first patient is entered into the study, a Dizal representative will visit the study site to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also to train them in any study specific procedures including collection of samples and the WBDC system utilized. The additional requirements for the collection of the patients' samples for the exploratory biomarker and genetic research will also be clarified.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all staff members involved in the study (medical, nursing and other staff).

Source data

Refer to the Clinical Study Agreement for location of source data.

Monitoring of the study

During the study, a Dizal representative will have regular contacts with the study sites, 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 including the specific requirements of the biomarker and genetic research, that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of the Informed Consent Form(s)of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- If applicable, ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

The Dizal representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

Data management by Dizal /delegate

Data management will be performed by the CRO Data Management team.

Data entered in the WBDC system or data captured electronically will be immediately saved to the applicable database and changes tracked to provide an audit trail.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the latest version of WHODrug. All coding will be performed by the Medical Coding Team at the CRO Data Management team.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment-revealing data may thereafter be added, and the final database will be locked.

Genotype data generated in this study will be stored in the appropriate secure system, separate from the database used for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, 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 with respect to the conduct of the study and the treatment of patients and in all other respects, the terms of the Clinical study Agreement shall prevail.

Specific reference to requirements relating to this optional biomarker and genetic research will be included in the study agreement(s).

Agreements between Dizal and the Principal Investigator should be in place before any study-related procedures can take place, or patients be enrolled.

Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement.

End of study

The end of the study is defined as the last visit of the last patient undergoing the study.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. Dizal may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with DZD9008.

Appendix F GUIDELINE FOR EVALUATION OF OBJECTIVE TUMOR RESPONSE USING RECIST 1.1 (RESPONSE EVALUATION CRITERIA IN SOLID TUMORS)

Introduction

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines (Eisenhauer et al 2009) for the study with regards to investigator assessment of tumor burden including protocol-specific requirements for this study.

Definition of measurable, non-measurable, target and non-target lesions

Patients with at least one lesion measurable that can be accurately assessed at baseline by computerized tomography (CT), magnetic resonance imaging (MRI) or plain X-ray should be included in this study.

Measurable lesions

At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short access ≥ 15mm) with computered tomograpghy (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI

- Previously irradiated lesions as localized post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment

- Skin lesions assessed by clinical examination

- Brain metastasis

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these non-cystic lesions should be selected as the target lesions (TLs).

Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

The methods to be used for RECIST assessment are summarized in Table 19 and those excluded for tumor assessments in this study are discussed below, with the rationale provided.

Table 19 Summary of Methods of Assessment

Target Lesions	Non target lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, chest X-ray	X-ray, chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In this study it is recommended that CT examinations of the chest and abdomen will be used to assess tumor burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible, or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used

to assess NTLs in patients that also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

X-rays

Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor measurements.

Tumor markers

Tumor markers will not be used for tumor response assessments per RECIST 1.1.

Cytology and histology

Histology will not be used as part of the tumor response assessment per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that

was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Tumor response evaluation

Schedule of evaluation

CT examinations of the chest and abdomen (including liver adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. CT examination with intravenous contract media administration is the preferred method. MRI should be used where CT is no feasible or it is medically contra-indicated.

Baseline tumor assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments should be performed every 6 weeks (± 7 days) after the start of treatment until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up. Following the 24 month DCO, tumor assessment will be performed in accordance with clinical practice with the exception of those in the Phase I first line expansion cohort. For the Phase I first line expansion cohort RECIST 1.1 assessments will continue every 12 weeks (± 7 days) until disease progression.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments as their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at different frequency than other patients.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible

repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion
- When a TL has had any intervention e.g., radiotherapy, embolization, surgery etc., during the study, the size of the TL should still be provided where possible

Evaluation of target lesions

Table 20 provides the definitions of the criteria used to determine objective tumor visit response for TLs.

Table 20 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.

Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

Non-Target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 21 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 21 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of study treatment without objective evidence of disease progression at that time should continue to undergo RECIST 1.1 assessments according to the clinical study protocol until objective disease progression is observed.

Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 22.

Table 22 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/non PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs at baseline)

Specifications for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT Scan

CT scans of chest and abdomen (including liver and adrenal glands) should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most solid tumors is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without

intravenous contrast is an option for the thorax, abdomen and pelvic examinations. For assessment of brain lesions MRI is the preferred method.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5mm contiguous slice thickness, and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

REFERENCES

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.

Appendix G ACTIONS REQUIRED IN CASE OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN-HY'S LAW

Introduction

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Dizal clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2 x ULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 x ULN **and** TBL ≥ 2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

Identification of potential Hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3x ULN
- AST ≥ 3x ULN
- TBL ≥ 2x ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Dizal representative

- Determine whether the patient meets PHL criteria (see Section Definitions of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the Dizal representative or delegate that subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section Actions required when potential Hy's law criteria are met before and after starting study treatment)
- Notify the Dizal representative who will then inform the central Study Team
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of potential Hy's law cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Dizal Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the standard processes
- If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:
- Report an SAE (report term 'Hy's Law') according to Dizal standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions required when potential Hy's law criteria are met before and after starting study treatment

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being, even if there has been no significant change the patient's condition[#] compared with pre-study treatment visits, the Investigator will:

- Notify the Dizal representative who will inform the central Study Team.

- Follow the subsequent process described is Section Potential Hy's Law Criteria met of this Appendix.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

Actions required for repeat episodes of potential Hy's law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section Actions required when potential Hy's law criteria are met before and after starting study treatment?

If No: follow the process described in Section Potential Hy's Law Criteria met of this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Appendix H GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products (e.g., herbal supplement), as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

DZD9008 is an investigational drug for which no data on *in vivo* drug-drug interactions (DDI) are currently available. *In vitro* data have shown that the principal CYP enzymes responsible for the Phase I metabolism of DZD9008 are CYP 3A4/5, and glutathione conjugation may be alternative pathway for DZD9008 metabolism.

In vitro DZD9008 showed either no inhibition or a low level reversible inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 activity. DDI risk is considered low with these CYP enzymes, although the risk of a clinical interaction via inhibition CYP2D6 and intestinal CYP3A4 cannot be excluded at clinically relevant exposure.

There was not time dependent inhibition observed for DZD9008 *in vitro* with CYPs 1A2, 2C9 and 2C19. Time dependent inhibition was observed for CYP2D6 only at 50 μM and CYP3A4/5 at both 10 and 50 μM, however at clinically relevant exposure of DZD9008 the risk of a clinically meaningful drug interaction arising from CYP3A4/5 inhibition is minimal.

DZD9008 was shown to be an inhibitor of the active efflux transport protein P-gp and BCRP. It has also been determined to be an inhibitor of the active uptake transport mediated by OATP1B1. A clinical meaningful interaction with both intestinal P-gp, BCRP and OATP1B1 transporter cannot be excluded.

Restrictions regarding drug affecting CYP3A4 metabolism

CYP3A4/5 is considered to be the predominant metabolic pathway, thus modulation of CYP3A4/5 activity may increase or decrease exposure to DZD9008, respectively. In clinical DDI study, when co-administered with multiple doses of strong CYP3A4 inhibitor itraconazole, DZD9008 C_{max} and AUC increase by 32% and 51%, respectively. DZD9008 C_{max} and AUC decrease by 38% and 48%, respectively, when co-administered with multiple doses of strong CYP3A4 inducer carbamazepine.

Strong inhibitors and strong inducers of CYP3A4/5 should not be combined with DZD9008. Moderate inhibitors and inducers of CYP3A4/5 are permitted but caution should be exercised, and patients monitored closely for possibly drug interactions. Strong inhibitors or inducers of CYP3A4 should be stopped at least 1 week for inhibitors or 2 weeks for inducers before the first dose of DZD9008 (Table 23 & Table 24).

These lists are not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact Dizal with any queries you have on this issue.

If the investigator feels that concomitant administration of medications or herbal supplements that strongly modulate CYP3A4/5 is essential during the trial, DZD9008 treatment should be discontinued.

Table 23 Drugs that are strong inhibitors of CYP3A4

Contraindicated drugs	Withdrawal period prior to DZD9008 start
Boceprevir, clarithromycin, conivaptan, grapefruit juice*, indinavir, itraconazole, ketoconazole, lopinavir/RIT, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, Voriconazole, elvitegravir/RIT, fluconazole	1 week

* Double-strength grapefruit juice
* Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g., grapefruit juices or marmalade) during the study

Table 24 Drugs that are strong inducers of CYP3A4

Contraindicated drugs	Withdrawal period prior to DZD9008 start
Avasimibe, Carbamazepine, phenobarbital, phenytoin, Rifampicin, rifabutin, rifapentin St John's Wort, Phenobarbitone	2 weeks

Drugs whose exposure may be affected by DZD9008 that Dizal considers may be allowed with caution, see Table 25.

In vitro data shows that DZD9008 is a weak inhibitor of CYP3A4/5, DZD9008 has the potential to increase the exposure of CYP3A4/5 substrate whose absorptive process is restricted by CYP3A4/5 metabolism in the intestine which includes some of the statins.

DZD9008 induces CYP3A4 and 2C8 but not CYP1A2, 2B6, 2C9 and 2C19 isoforms *in vitro* in human primary hepatocytes. The exposure of co-medications where disposition is dependent on CYP3A4, or CYP2C8 isoforms and P-gp which may also be induced, may be reduced when co-administrated with DZD9008.

CYP2C8 and P-gp substrate

Sensitive CYP2C8 and P-gp substrate with narrow therapeutic range are permitted but caution should be exercised, and patients monitored closely for possible drug interactions.

CYP3A4 substrate and P-gp and/or BCRP substrates

In vitro data suggests DZD9008 has the potential to cause drug interactions at the intestinal level through CYP3A4. It has also been shown that there is a potential for a DDI when dosed with sensitive substrates of P-gp, BCRP or OATP1B1. DDI was predicted following more conservative approaches recommended by EMA and PMDA. Although a potential interaction with DZD9008 and OATP1B3, MATE1 and MATE2 K substrates cannot be ruled out, the

predicted values are close to cut-off and therefore DDI risks with these transporter substrates are considered to be low. Table 25 outlines some of the drugs that are sensitive substrates of CYP3A4, CYP2C8, P-gp, BCRP, OATP1B1/3, MATE1 and MATE2 K. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to depend on CYP3A4 and/or transporter proteins for disposition and/or metabolism. Appropriate medical judgement is required. Please contact Dizal with any queries you have on this issue.

Patients taking concomitant medications such as statins whose disposition is dependent upon Breast Cancer Resistance Protein (BCRP) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving DZD9008. If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever, statins must be stopped, and any appropriate further management should be taken.

Table 25 Exposure, pharmacological action and toxicity may be increased or decreased by DZD9008

Warning of possible interaction	Advice
CYP3A4 substrate: alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus **CYP2D6 substrate**: Pimozide, thioridazine **CYP2C8 substrate**: Repaglinide	Drugs are permitted but caution should be exercised, and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with DZD9008.
P-gp substrate: Digoxin	Monitor for increased digoxin concentrations if increase in intolerability is observed due to increased systemic exposure. Monitor for adverse reactions if concomitant use of DZD9008 with other P-gp substrates with a narrow therapeutic index cannot be avoided
BCRP substrate: Methotrexate, topotecan, or irinotecan, rosuvastatin, sulfasalazine **MATE1 and MATE2-K substrate**: metformin **OATP1B1/3**: atorvastatin, pitavastatin, pravastatin, simvastatin acid	Drugs are permitted but caution should be exercised, and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with DZD9008.

Drugs that may prolong QT interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: https://crediblemeds.org/.

Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with DZD9008. Recommended withdrawal periods following cessation of treatment with these agents are provided in Table 26 & Table 27.

Table 26 Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to DZD9008 start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 27 Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to DZD9008 start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprim-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks

Drug	Minimum treatment period on medication prior to DZD9008 start
Tamoxifen	8 weeks

Restriction regarding drugs may affect DZD9008 absorption

DZD9008 exhibited pH-dependent solubility, thus the absorption may be affected by altered intragastric pH. When intragastric pH is elevated, DZD9008 GI solubility, bioavailability and eventually treatment efficacy may be influenced. To avoid reduced oral absorption of DZD9008 and safeguard optimal DZD9008 therapy, intake of gastric acid suppressive agents relative to DZD9008 treatment is suggested to be managed (Table 28).

Table 28 Gastric acid suppressive agents that may affect DZD9008 exposure

Type of gastric acid suppressive agents	Dosage management relative to DZD9008 administration
Proton pump inhibitors	PPIs should be avoided.
H2- antagonists	DZD9008 should be taken at least 2 h before or 10 h after the H2- antagonist intake.
Antacids	DZD9008 should be administrated at least 2 h before or 2 h after antacid intake.

Appendix I GUIDANCE FOR THE SAFETY MONITORING AND MANAGEMENT OF ADVERSE EVENTS

Introduction

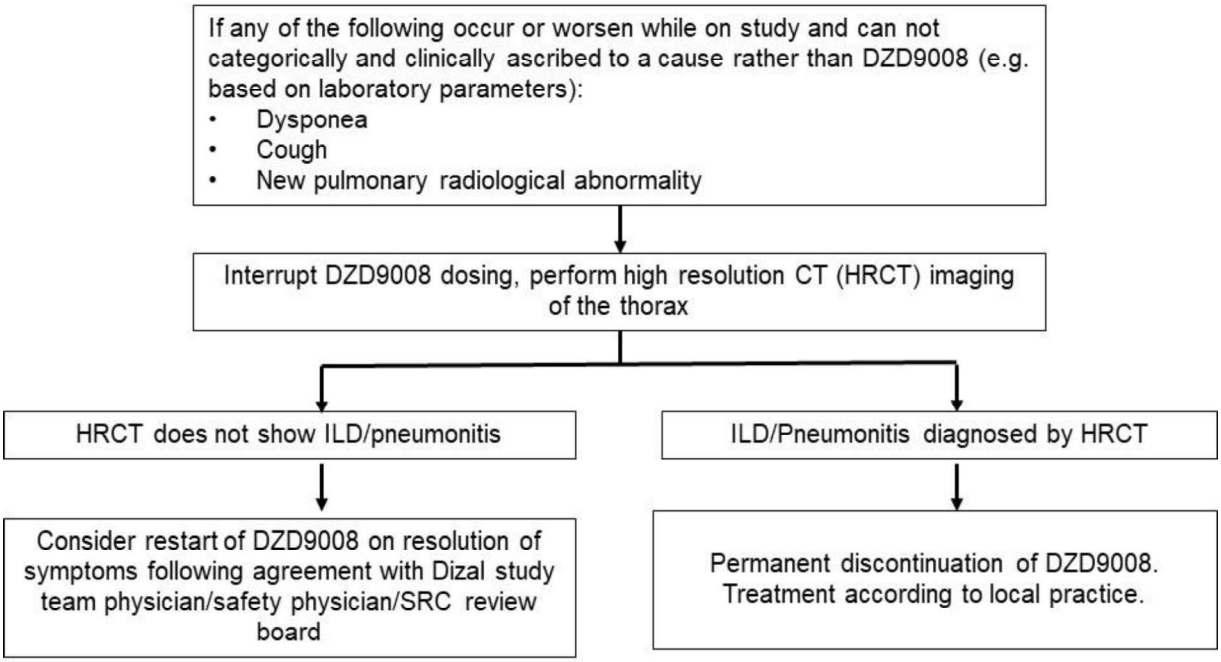
DZD9008 is an oral, potent, selective and irreversible EGFR tyrosine kinase inhibitor (TKI) targeting EGFR sensitizing mutations, T790M resistance mutation, EGFR Exon20ins and uncommon mutations as well as HER2 Exon20ins. It is intended for the treatment of advanced non-small cell lung cancer (NSCLC) patients with EGFR or HER2 mutation as monotherapy.

Whilst there is no clinical experience with DZD9008, preclinical studies suggest a potential association between the use of DZD9008 and adverse events of skin, gastro-intestinal tract, liver, lung, eyes etc. been observed. When the appropriate treatment of these events is instituted, they can be tolerable, allowing patients to continue receiving treatment.

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 monitoring and treatment for specific adverse events across DZD9008 clinical development program.

ILD/Pneumonitis Assessments Flow Chart



Diarrhea Treatment Guidance

An association between the use of EGFR inhibitor and the occurrence of diarrhea has been observed, as a result, Dizal has chosen to include the following in the clinical study during using with DZD9008.

Uncomplicated CTCAE (V5) Grade ≤2 diarrhea:

- 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 4 mg, followed by 2 mg every 4 hours or after every unformed stool.
    - Grade 1 intermittent diarrhea may not require treatment
    - Consider continuous of loperamide until diarrhea-free for 12 hours
    - Consider electrolyte replacement, as appropriate

CTCAE (V5) Grade ≥ 3 or any Grade with complications (dehydration, fever and/or Grade ≥3 neutropenia):

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

Skin effects- Rashes & Acnes

An association between the use of EGFR inhibitor and the occurrence of skin adverse events has been observed. As a result, Dizal has chosen to include the following in the clinical study when DZD9008 is used:

- Patients should be informed that skin reactions are not contagious or not result from allergy to treatment.
- Patients should be encouraged to report any instance of skin reaction 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 is spreads or becomes painful).

- Any occurrence of a skin event should be recorded as an Adverse Event b completing the AE CRF, and the severity captured using the CTCAE (v5) grading system.
- Sponsor will be reviewing dermatological adverse events on an ongoing basis and may ask for additional information to be provided.
- Treatment administered should be recorded.
- It may be beneficial to avoid irritating skin products (e.g., irritating soaps, products containing retinol or retinoic acid). Use of topical benzoyl peroxides and other irritating anti-acne agents should be avoided.
- Camouflage make-up (non-comedogenic or non-pore blocking) can be used during study treatment.
- Patients may consider applying over-the-counter moisturizing cream to face, hands and feet twice daily 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.
- 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.

Skin effects- Rash Treatment Guidance

CTCAE (v5) 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

CTCAE (v5) 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 (v5) Grade 3

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

Topical steroid moderate strength bid

and

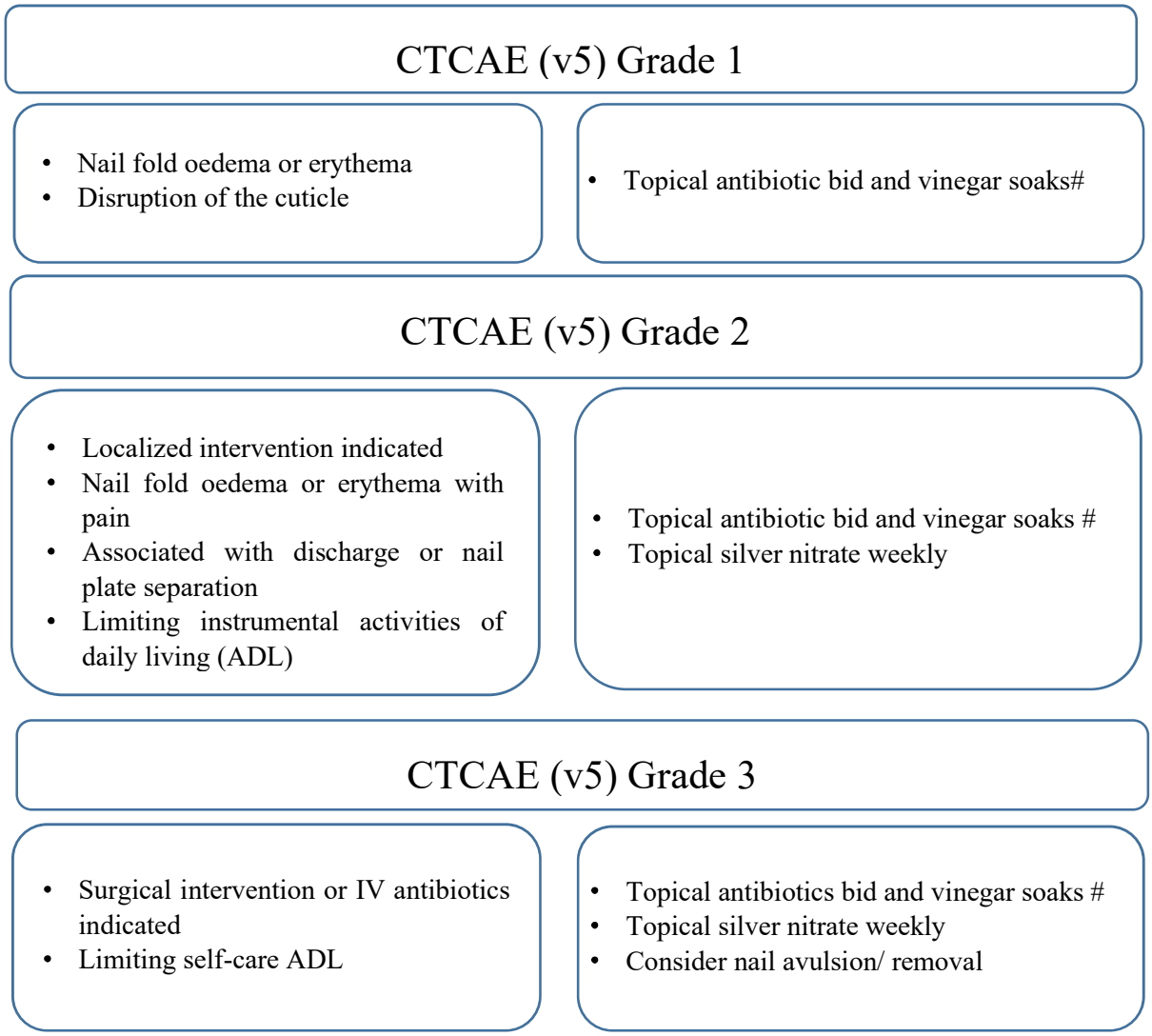
Oral antibiotics for 6 weeks

Switch to broad spectrum/gram negative cover if infection suspected (yellow crusts, purulent discharge, painful skin/nares)

Skin effect-- Dry Skin/ Xerosis Treatment Guidance

CTCAE (v5) Grade 1	
• Mild or localized • Topical intervention indicated	• Topical steroid moderate strength bid or topical antipruritic bid
CTCAE (v5) Grade 2	
• Intense or widespread • Intermittent • Skin changes from scratching (e.g., oedema, papulation, excoriation, lichenification, oozing/crusts) • Oral intervention indicated • Limited instrumental ADL	• Topical steroid moderate strength bid or topical antipruritic bid • Oral antihistamine
CTCAE (v5) Grade 3	
• Intense or widespread • Limiting self-care ADL or sleep • Oral corticosteroid or immunosuppressive therapy indicated	• Oral antihistamine • GABA agonist (gabapentin 300mg or pregabalin 50-75 mg every 8 hours)

Skin effect-- Paronychia Treatment Guidance



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

Ophthalmic assessments

The ophthalmic adverse events were observed in the preclinical safety assessment of DZD9008. As a result, Dizal has chosen to include the following in the clinical study when DZD9008.

- Full ophthalmological assessments at baseline 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.

Some key points for Ophthalmic Guidance

- It is important that patients are fully informed that ophthalmic event may occur during treatment with DZD9008.
- DZD9008 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 instance 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 been resolved.
- Only after agreement with the investigator, patients may use eye drops or ointment for treatment of eye symptoms.
- 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 DZD9008 is permanently discontinued.
- Ulcerative events must result in permanent discontinuation from study.
- Patients with ophthalmic AEs of CTCAE grade≥ 3 (For France and Canada only: CTCAE grade ≥ 2) 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 activity 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 Dizal team if required.

Baseline assessment

- Full ophthalmological assessment, including slit lamp examination performed by an ophthalmologist (or appropriately qualified individual)
- Date of assessment should be recorded on the CRF
- Results should be recorded in the patients' notes

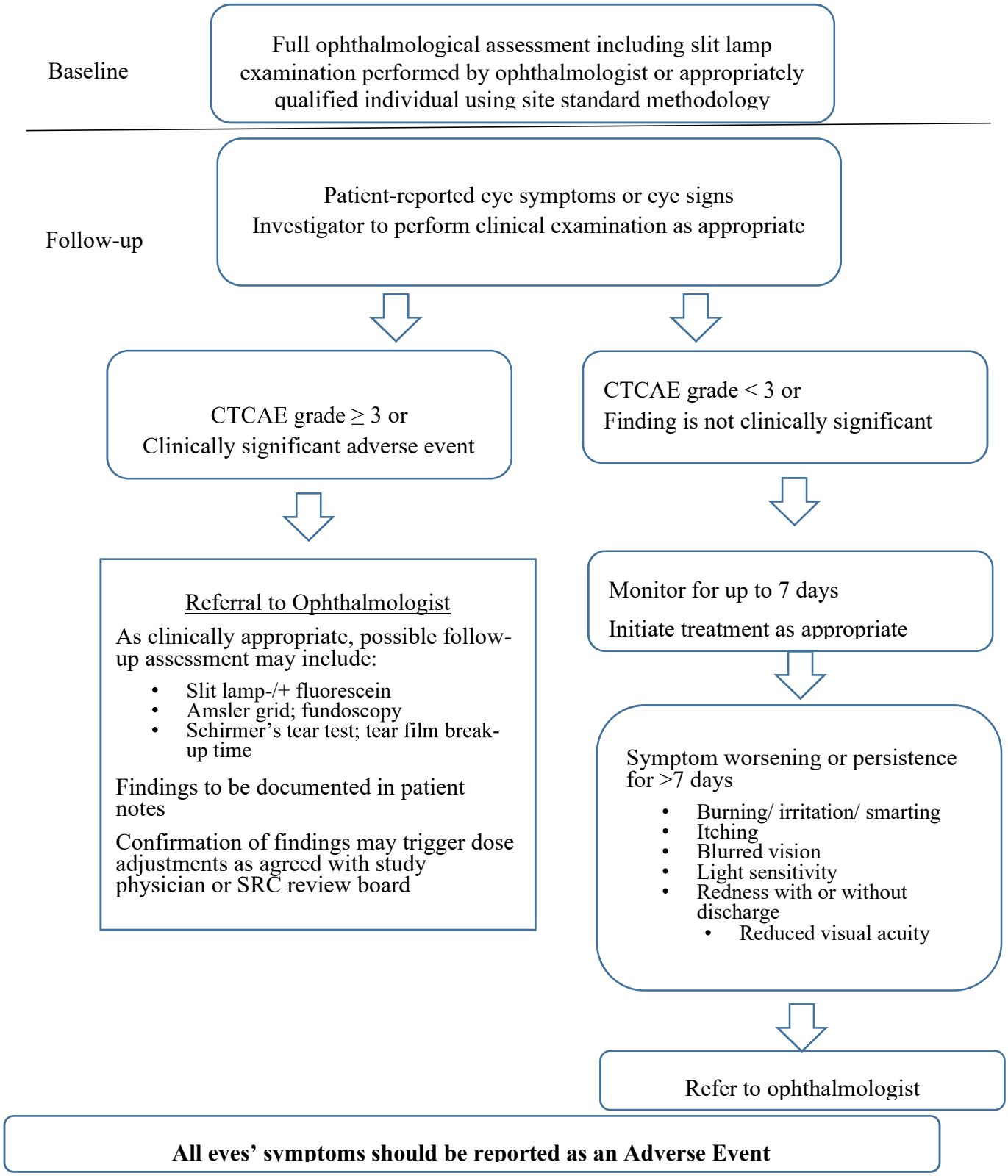
Follow-up assessment

- If the patient reports any eye symptoms during treatment with DZD9008 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
- Eye drops or ointment for treatment of eye symptoms may be used, **ONLY** after it is agreed with a study doctor.
- Findings and treatment should be documented in the patient's notes.

Post-baseline Ophthalmic assessment

- Any clinically significant post-baseline ophthalmic findings, including those confirmed by the ophthalmologist, must be recorded as an Adverse Events by completing the AE module, and the severity captured using CTCAE 5.0 grading system.
- In addition, a report should be provided to Dizal detailing:
    - Ophthalmic examination performed
    - Findings
- Treatment administered should be captured on the CRF.

Ophthalmic Assessment Flow Chart



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 DZD9008

Initiate ophthalmic treatment as appropriate and withhold DZD9008 dose for up to 3 weeks

- If adverse event improves to CTCAE Grade ≤ 1 within 3 weeks reinstate DZD9008 at the current dose maintaining treatment as appropriate
- If adverse event improves to CTCAE Grade 2 within 3 weeks reinstate DZD9008 at a reduced dose, 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 DZD9008 interruption, DZD9008 should be permanently discontinued.

Appendix J Patient Reported Outcomes (Selected PRO-CTCAE items, FACIT item GP5 and 5Q-5D-5L)

Selected PRO-CTCAE items

As individuals go through treatment for their cancer, they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days.

Rash	
a. In the last 7 days, did you have any RASH?	
○ Yes	○ No

Skin dryness				
a. In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Acne				
a. In the last 7 days, what was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Itching

a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Nail loss	
a. In the last 7 days, did you LOSE ANY FINGERNAILS OR TOENAILS?	
○ Yes	○ No

Nail ridging	
a. In the last 7 days, did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS?	
○ Yes	○ No

Nail discoloration	
a. In the last 7 days, did you have any CHANGE IN THE COLOR OF YOUR FINGERNAILS OR TOENAILS?	
○ Yes	○ No

Decreased appetite

a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Nausea				
a. In the last 7 days, how OFTEN did you have NAUSEA?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Vomiting				
a. In the last 7 days, how OFTEN did you have VOMITING?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Diarrhea				
a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

Constipation				
a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Abdominal pain				
a. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
b. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
c. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Mouth/throat sores				
a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Cracking at the corners of the mouth (cheilosis/cheilitis)				
a. In the last 7 days, what was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Bloating				
a. In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
b. In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Fatigue				
a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
b. In the last 7 days, how much did FATIGUE INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Blurred vision				
a. In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
b. In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Nosebleed				
a. In the last 7 days, how OFTEN did you have NOSEBLEEDS				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
b. In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				

○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

FACIT-Item GP5 (Version 4)

Functional Assessment of Cancer Therapy - Item GP5

Item GP5 from the FACIT Measurement System

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

GP5 I am bothered by side effects of treatment…….

Not at all	A little bit	Somewhat	Quite a bit	Very much
0	1	2	3	4

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐