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SYNOPSIS

Study Title: Phase 1 Safety, Pharmacokinetic And Pharmacodynamic Study Of PF-02341066, A MET/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally To Patients With Advanced Cancer

Study Number: Protocol A8081001

Regulatory Agency or Public Disclosure Identifier Number: 73,544

Study Phase: Phase 1

Name of Study Intervention: Crizotinib (PF-02341066)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Supplemental CSR (sCSR) (Last patient last visit [LPLV] 19 January 2022) Version 1.0	03 June 2022
Final CSR Version 1.0	19 February 2021
Interim CSR (Amended Preliminary Full Clinical Study Report)	12 September 2011

Number of Study Center(s) and Investigator(s):

Refer to Study 1001 final clinical study report (CSR) Synopsis, dated 19 February 2021, for details.

A list of study centers and investigators involved in this study is provided in the final CSR Appendix 16.1.4.1.

Refer to the final CSR Appendix 16.1.11 for a list of publications based on this study.

Study Period:

The first patient first visit (FPFV) was on 19 April 2006, the LPLV was on 19 January 2022.

This study was neither discontinued nor interrupted.

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Rationale:

This sCSR was completed in order to summarize the safety data from the 2 patients (hereafter referred to as the "2 remaining patients") still on crizotinib treatment at the time of database snapshot on 30 July 2020 for the Study 1001 final CSR.

Objectives, Endpoints, and Statistical Methods:

Refer to Study 1001 final CSR Synopsis, dated 19 February 2021, for details.

Methodology:

Study 1001 was a Phase 1, open-label, multicenter study evaluating dose escalation, safety, pharmacokinetics (PK), antitumor activity and pharmacodynamics of crizotinib administered as an oral single agent to patients with advanced cancer (excluding leukemias).

Refer to Study 1001 final CSR Synopsis, dated 19 February 2021, for details.

At the time of the database snapshot date of the final CSR (30 July 2020), 2 patients with MET exon 14-positive non-small cell lung cancer (NSCLC) were still on treatment.

The efficacy data have been fully reported in the previous CSRs including the final CSR, dated 19 February 2021. These efficacy data were not updated in this report.

This CSR Synopsis summarizes the cumulative data from the 2 remaining patients still on treatment at the time of database snapshot (30 July 2020) for the final CSR.

The LPLV for this sCSR was on 19 January 2022 with a database lock on 09 February 2022.

This sCSR presents listings and summary tables for the 2 remaining patients for patient disposition at end of treatment, demographic characteristics, adverse events (AEs) and serious adverse events (SAEs), treatment duration, laboratory test values, and vital signs data.

Number of Patients (planned and analyzed):

Refer to Study 1001 final CSR Synopsis, dated 19 February 2021, for details.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Refer to Study 1001 final CSR Synopsis, dated 19 February 2021, for details.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

For 2 the remaining patients, crizotinib was provided as 50 mg or 100 mg tablets for oral administration (Table S1) once daily (QD) or twice daily (BID) in continuous 28-day cycles.

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Refer to Study 1001 final CSR Synopsis, dated 19 February 2021, for details.

Table S1. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Crizotinib 100mg Oval Tablet	19-DP-00006	19-000503	100 mg	Tablet
Crizotinib 50mg Oval Tablet	19-DP-00005	19-000502	50 mg	Tablet

Duration of Study Intervention:

Treatment was to continue until the occurrence of Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression or clinical deterioration, unacceptable toxicity effects, or withdrawal from the study.

Summary of Results:

Both patients had permanently discontinued from study treatment; 1 patient because the study was terminated by the Sponsor and the second patient due to 'other reasons' (combined use of prohibited medicines, clarithromycin and rifampicin, which were used for the treatment of Mycobacterium avium complex infection). This combined use of the prohibited medicines was assessed as important protocol deviation. No important protocol deviation was reported for the second patient. None of the 2 remaining patients were considered non-compliant.

Demographic and Other Baseline Characteristics:

The remaining 2 Japanese patients were 67 and 69 years old.

Refer to Study 1001 final CSR Synopsis, dated 19 February 2021, for details.

Exposure:

The durations of treatment for the 2 remaining patients were 29.9 and 40.0 months.

Efficacy:

Efficacy analyses for all patients are reported as per protocol in Study 1001 final CSR, dated 19 February 2021. There were no additional efficacy analyses for the 2 remaining patients.

Safety Results:

Both of the 2 remaining patients reported at least 1 treatment-related AE. One all-causality SAE, which was not treatment-related, was reported for 1 (50.0%) patient. This SAE was previously reported in the final CSR, dated 19 February 2021. No new SAEs occurred since the Study 1001 final CSR. No Grade 5 AEs were reported for the 2 remaining patients (Table S2).

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Table S2. Treatment-Emergent Adverse Events For Patients Who Were Ongoing as of Data Snapshot of 30JUL2020 (All-Causality and Treatment-Related) (MET Exon 14 Alterations NSCLC) - Safety Analysis Population

	MET Exon 14 Alterations NSCLC, 250 mg BID (N=2)	
	All-Causality	Treatment-Related
Number of AEs	132	83
Number of patients, n (%)		
With AEs	2 (100)	2 (100)
With SAEs [a]	1 (50.0)	0
With Grade 3 or 4 AEs	2 (100)	1 (50.0)
With Grade 5 AEs	0	0
With AEs associated with		
Dose reduction	2 (100)	2 (100)
Temporary discontinuation	2 (100)	2 (100)

All-causality AEs that occurred in the 2 remaining patients were BRADYCARDIA, Blood creatine phosphokinase increased, Constipation, Diarrhoea, ELEVATED TRANSAMINASES, Nausea, OEDEMA, and Vomiting. Treatment-related AEs that occurred in the 2 remaining patients were BRADYCARDIA, Blood creatine phosphokinase increased, Diarrhoea, ELEVATED TRANSAMINASES, Nausea, OEDEMA, and Vomiting. All other all-causality or treatment-related AEs occurred in 1 patient each, respectively.

Most all-causality AEs in the 2 remaining patients were Grade 1 or Grade 2 in severity. One patient had Grade 3 all-causality AEs of Hyperkalaemia, Hypoxia, and Pneumonia pneumococcal which were not considered to be treatment-related. One patient had a Grade 4 treatment-related AE of Lipase increased.

There were no AEs related to the Coronavirus Disease 2019 (COVID-19) pandemic.

There were no AEs leading to permanent treatment discontinuation for the 2 remaining patients.

There were no dose reductions for either of the 2 remaining patients since the Study 1001 final CSR. Both patients did have a dose reduction prior to the data snapshot date for the Study 1001 final CSR.

There were no temporary treatment discontinuations for either of the 2 remaining patients since the Study 1001 final CSR. Both patients did have temporary treatment discontinuations prior to the data snapshot date for the Study 1001 final CSR.

Neither of the 2 remaining patients had died.

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There were no new SAEs for the 2 remaining patients since the Study 1001 final CSR. One patient had an SAE prior to the data snapshot date for the Study 1001 final CSR.

The review of the clinical laboratory test results from the 2 remaining patients indicated that there were no new safety signals. No additional electrocardiograms (ECGs) were obtained since the data snapshot date for the final CSR for the 2 remaining patients. No other safety data were reported for the 2 remaining patients.

Pharmacokinetic Results: (if applicable):

Not applicable

Pharmacodynamic Results: (if applicable):

Not applicable

Other Results: (if applicable):

Not applicable.

Conclusions:

Review of the safety data from the 2 remaining patients reported in this sCSR did not identify any patterns of AEs indicative of a safety concern with the use of crizotinib. No new safety issues were identified.

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Sponsor: Pfizer Inc.

Investigational Product: Crizotinib (PF-02341066)

Clinical Study Report Synopsis: Protocol A8081001

Protocol Title: Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of PF-02341066, A MET/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients With Advanced Cancer

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: Patients were enrolled at 16 centers in 4 countries; 11 centers in the United States; 3 centers in Japan; and 1 center each in Australia and South Korea (Republic of Korea). Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: Refer to Appendix 16.1.11 for a list of publications based on this study.

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Study Initiation Date: First Patient First Visit (FPFV): 19 April 2006

Study Completion Date: Ongoing

Report Date: 19 February 2021

Previous Report Date: Not applicable

Phase of Development: Phase 1

Primary and Secondary Study Objectives and Endpoints:

Table S1 Study Objectives and Endpoints

Objectives	Endpoints
• Determine the safety profile of crizotinib including identification of dose limiting toxicity (DLT), maximum tolerated dose (MTD). • Determine the recommended Phase 2 doses (RP2D) and regimens of crizotinib.	• Incidence of DLT adverse events (AEs) within the first cycle (28 days) defined and graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. • Number of patients with AEs and serious adverse events (SAEs).

• Determine pharmacokinetics (PK) profile of crizotinib following oral administration including:
  • Effect of food.
  • Initial evaluation of crizotinib-related CYP3A4 inhibition using midazolam (MDZ) as a probe.
	• Plasma PK parameters of crizotinib and its metabolites.
	• PK parameters of MDZ following a single oral 2 mg dose before and after repeated administration of crizotinib.
	• Plasma PK parameters of crizotinib and its metabolite(s) following multiple oral doses of

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• Effect of the coadministration of rifampin or itraconazole on the multiple-dose plasma PK of crizotinib.	crizotinib alone and when coadministered with rifampin or itraconazole.
• Document any evidence of anti-tumor activity of crizotinib.	• Objective response (by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.0 [RECIST version 1.1 for ALK-negative non-small cell lung cancer (NSCLC) cohorts]) for solid tumors and response criteria for lymphomas and multiple myelomas), duration of response, time to response, disease control rate at weeks 8 and 16, progression-free survival (PFS), 6-month PFS, overall survival (OS), probabilities of survival at 6 and 12 months; others as appropriate.
• Evaluate the effect of crizotinib on parameters related to hypogonadism in males.	• Measurements of blood testosterone and other blood parameters associated with detecting hypogonadism in males.

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METHODS

Study Design:

Study A8081001 was a Phase 1, open-label, multicenter study evaluating dose escalation, safety, PK, antitumor activity, and pharmacodynamics of crizotinib administered as an oral single agent to patients with advanced cancer (excluding leukemias).

Starting with the FPFV on 19 April 2006, patients with advanced cancers (excluding leukemias) were enrolled in the study. Patients were included in 12 different cohorts or substudies (Figure S1) to study or establish:

- A RP2D for crizotinib;
- Potential for CYP3A inhibition due to crizotinib using MDZ as a CYP3A4 substrate probe;
- Effect of genetic markers of ALK, ROS1, MET (amplification or presence of exon 14) on crizotinib PK, safety and efficacy of crizotinib;
- Crizotinib drug-drug interaction (DDI) with rifampin and itraconazole;
- Crizotinib treatment effect on ophthalmological safety parameters, urinary 6 beta-hydroxycortisol/cortisol (6β-OHC/C), and hypogonadism.

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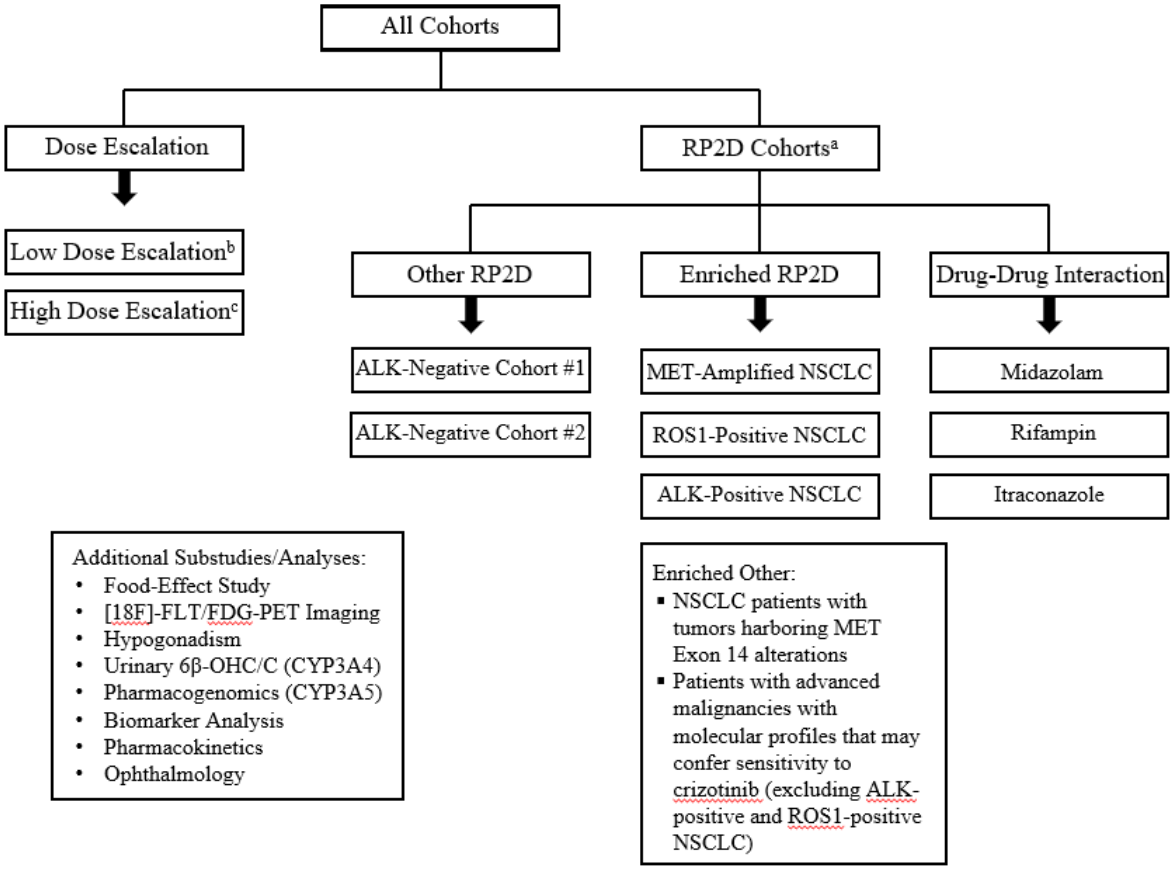
Figure S1. Summary of All Cohorts



a. In the Interim CSR (see below), the RP2D cohorts consisted of cohorts with patients who had ALK-negative NSCLC (referred to as ALK-negative NSCLC cohort #1 in this final Clinical Study Report [CSR]); ALK-positive NSCLC; and ALK-dependent tumors other than NSCLC and MET-dependent tumors and who did not have ALK-positive or ALK-negative NSCLC ("RP2D Other" cohort).
b. Crizotinib dosing of ≤200 mg once a day (QD) or ≤300 mg twice a day (BID).
c. Crizotinib dosing from 300 mg QD to 800 mg once a day (QD).

To further evaluate the antitumor activity of crizotinib associated with MET amplification, patients with MET-amplified NSCLC were further distinguished into categories based on MET/CEP7 ratio: high-level MET gene amplified (MET/CEP7 ratio ≥4.0), medium-level MET gene amplified (MET/CEP7 ratio >2.2 to <4.0), and low-level MET gene amplified (MET/CEP7 ratio ≥1.8 to ≤2.2).

This study was associated with several regulatory submissions and postmarketing requirements/commitments for which individual reports were generated in the past. In this final CSR, results from the previous reports (listed below) are summarized briefly and results of data collected subsequently are presented in detail.

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Previous reports referred to in this final CSR:

- Interim CSR, 12 September 2011
- ALK-Negative Report, 16 February 2015
- Rifampin DDI Report, 16 October 2015
- ROS1-Positive CSR, 01 April 2016
- Ophthalmology Report, 20 December 2016
- Itraconazole DDI Report, 18 April 2017
- ROS1-Positive Technical Report, 20 June 2019

Diagnosis and Main Criteria for Inclusion:
Key inclusion criteria:

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1. Tumor eligibility:

- All cohorts except RP2D enriched population cohort: Histologically confirmed advanced malignancies (except for leukemias) refractory to standard of care therapy, or for whom no standard of care therapy was available.
- RP2D enriched population cohort: Histologically confirmed advanced malignancies that met 1 of the following criteria:
    - Positive for MET amplification by fluorescence in situ hybridization (FISH)
    - Positive for ALK chromosomal translocations or gene amplification
    - Positive for known MET kinase domain activating mutations
    - Chromosomal translocations/fusions that led to altered transcriptional regulation of MET and/or hepatocyte growth factor (HGF)
    - Positive for chromosomal translocations at ROS1 gene
    - Other molecular changes for which there are data to suggest a biologic rationale for crizotinib treatment, eg, TRK1 fusions
- ALK-negative NSCLC cohort #1: Histologically or cytologically proven diagnosis of NSCLC that was locally advanced or metastatic and of the adenocarcinoma subtype (including mixed adenosquamous histology). Patients had to have received only 1 prior chemotherapy treatment and this regimen had to be platinum-based. All patients had either to be non-smokers, ex-smokers or light smokers (≤10 pack-years).
- ALK-negative NSCLC cohort #2: In addition to the criteria for ALK-negative cohort #1, patients had to be ALK-negative by the central laboratory.

2. Solid tumors had to have measurable disease as per RECIST v. 1.0. However, for the enriched population RP2D group, patients whose tumors were not measurable, could have entered the study upon approval by the Sponsor. RECIST v. 1.1 was used to evaluate tumors for patients in the ALK-negative NSCLC cohorts.

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3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. However, patients in the RP2D enriched population cohort or ALK-negative NSCLC cohorts with an ECOG performance status of 2 could have entered the study upon agreement between the investigator and Sponsor.
4. Adequate organ function.

Key exclusion criterion:

1. Major surgery, radiation therapy, or systemic anticancer therapy within 4 weeks of starting study treatment; within 2 weeks of starting study treatment for patients in the RP2D enriched population or ALK-negative cohorts.

2. For MET-dependent tumors, prior therapy specifically directed against MET or HGF; for ALK-dependent tumors, prior therapy specifically directed against ALK; for ROS1 dependent tumors, prior therapy specifically directed against ROS1.

3. Patients with brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease, unless appropriately treated and neurologically stable for at least 4 weeks (2 weeks for the RP2D enriched population cohort and the ALK-negative NSCLC cohorts).

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Study Treatment:

Crizotinib (Table S2) was administered orally QD or BID in continuous 28-day cycles, except for 21-day cycles for patients in the ALK-negative NSCLC cohorts #1 and #2. Treatment was to continue until the occurrence of RECIST-defined disease progression or clinical deterioration, unacceptable toxicity effects, or withdrawal from the study. The various dosing regimens followed are described below.

Dose Escalation Cohorts:

- Low Dose escalation cohort: starting with 50 mg QD and escalating up to ≤300 mg BID

- High Dose escalation cohort: starting with 300 mg QD and escalating up to ≤800 mg QD

Recommended Phase 2 Dose (RP2D) Cohorts

- All cohorts: 250 mg BID

DDI substudy Cohorts:

- MDZ substudy: MDZ 2 mg oral dose alone and coadministered with crizotinib: 100 mg QD, 250 mg BID, or 300 mg BID

- Rifampin DDI: crizotinib 250 mg BID alone and coadministered with rifampin 600 mg QD

- Itraconazole DDI: crizotinib 250 mg QD alone and coadministered with itraconazole 200 mg QD

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Investigational Product Description:
Crizotinib was provided as 50 mg or 100 mg tablets for oral administration (Table S2). Commercially available MDZ, rifampin, and itraconazole (Sporanox®, 100 mg capsules; USA: Janssen Pharmaceuticals, Inc.; Australia: Janssen-Cilag Pty Ltd) were supplied locally by the study sites.

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Crizotinib 10mg #0 Gray/Gray PIC	CA-1621005	06-033836	10 mg	Capsule
Crizotinib 50mg #0 Gray/Gray PIC	CA-0100107	07-051252	50 mg	Capsule
Crizotinib 100mg #0 Gray/Gray PIC	CA-0260207	07-051590	100 mg	Capsule
Crizotinib 100mg #0 Gray/Gray PIC	080042	08-068605	100 mg	Capsule
Crizotinib 50mg Size 2 Light Gray/Gray PIC	080086	09-072966	50 mg	Capsule
Crizotinib 50mg #0 Gray/Gray PIC	CA-1631005	06-033845	50 mg	Capsule
Crizotinib 50mg #0 Gray/Gray PIC	080041	08-067934	50 mg	Capsule
Crizotinib 100mg Oval Tablet	CM-0260211	11-002370	100 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-0270211	11-002643	100 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-13811	11-009235	100 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-02212	12-001177	100 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-02312	12-001191	100 mg	Tablet
Crizotinib 100mg Oval Tablet	13-106690	13-106690	100 mg	Tablet
Crizotinib 100mg Oval Tablet	GR-SDM	14-005965	100 mg	Tablet
Crizotinib 100mg Oval Tablet	GR-SDM	14-005966	100 mg	Tablet
Crizotinib 100mg Oval Tablet	GR-SDM	16-000476	100 mg	Tablet
Crizotinib 100mg Oval Tablet	GR-SDM	16-000477	100 mg	Tablet
Crizotinib 100mg Oval Tablet	GR-SDM	17-001529	100 mg	Tablet
Crizotinib 100mg Oval Tablet	GR-SDM	17-001530	100 mg	Tablet
Crizotinib 100mg Oval Tablet	19-DP-00006	19-000503	100 mg	Tablet
Crizotinib 100mg #0 Gray/Gray PIC	CA-0270208	08-065179	100 mg	Capsule
Crizotinib 50mg Size 2 Light Gray/Gray PIC	CM-0090209	09-074718	50 mg	Capsule
Crizotinib 100mg #0 Gray/Gray PIC	CM-0100209	09-074818	100 mg	Capsule
Crizotinib 100mg #0 Gray/Gray PIC	CM-0260309	09-075457	100 mg	Capsule
Crizotinib 50mg Size 2 Light Gray/Gray PIC	CM-0250309	09-076000	50 mg	Capsule
Crizotinib 100mg Oval Tablet	CM-0530609	09-076188	100 mg	Tablet
Crizotinib 50mg Tablet	CM-0520609	09-076189	50 mg	Tablet
Crizotinib 50mg Tablet	CM-0970809	09-077722	50 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-1000809	09-077725	100 mg	Tablet
Crizotinib 100mg #0 Gray/Gray PIC	CM-1090809	09-078909	100 mg	Capsule
Crizotinib 100mg #0 Gray/Gray PIC	CM-1080809	09-078997	100 mg	Capsule
Crizotinib 50mg Tablet	CM-1791209	10-080927	50 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-1811209	10-081002	100 mg	Tablet
Crizotinib 50mg Tablet	CM-0210210	10-082078	50 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-0230210	10-082080	100 mg	Tablet
Crizotinib 50mg Tablet	CM-1520910	10-088624	50 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-1510910	10-089144	100 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-1570910	10-089298	100 mg	Tablet
Crizotinib 50mg Tablet	CM-0300211	11-002655	50 mg	Tablet
Crizotinib 50mg Tablet	CM-13511	11-008988	50 mg	Tablet
Crizotinib 50mg Tablet	CM-02012	12-000937	50 mg	Tablet
Crizotinib 50mg Tablet	13-106684	13-106684	50 mg	Tablet

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Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Crizotinib 50mg Tablet	GR-SDM	14-005964	50 mg	Tablet
Crizotinib 50mg Tablet	GR-SDM	16-000475	50 mg	Tablet
Crizotinib 50mg Tablet	GR-SDM	17-001528	50 mg	Tablet
Crizotinib 100mg #0 Gray/Gray PIC	CA-1740707	07-058023	100 mg	Capsule
Crizotinib 50mg #0 Gray/Gray PIC	CA-0260208	08-064662	50 mg	Capsule
Crizotinib 100mg Oval Tablet	CM-1801209	10-081001	100 mg	Tablet
Crizotinib 100mg Oval Tablet	CM-0980809	09-078261	100 mg	Tablet
Crizotinib 25mg/mL Oral Solution in 16 oz HDPE Bottle (475mL)	K040213	13-107843	25 mg/ml	Solution
Crizotinib 25mg/mL Oral Solution in 16 oz HDPE Bottle (475mL)	K091615	15-006040	25 mg/ml	Solution
Crizotinib 25mg/mL Oral Solution in 16 oz HDPE Bottle (475mL)	SW-LDM	16-004754	25 mg/ml	Solution
Crizotinib 50mg Tablet	19-DP-00005	19-000502	50 mg	Tablet

Efficacy Evaluations:
Crizotinib treatment efficacy was evaluated on the basis of disease imaging assessments that included computed tomography (CT) and magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis, as well as brain and bone scans if deemed necessary. The assessments were based on derived investigator tumor assessment and for certain cohorts they were also reviewed by a centralized, independent radiological review for a certain period of time during the study.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations:
Patient blood samples were collected for PK analysis of crizotinib (and its metabolite, if applicable) using standard bioanalytical methods. Series of PK samples were collected starting on Day −7, Cycle 1 Day 1 (C1D1), Cycle 1 Day 15 (C1D15), Cycle 2 Day 1 (C2D1), and predose PK samples were collected on Day 1 of every other cycle up to Cycle 5 (depending on the cohort). PK parameters were determined from plasma concentration-time data using standard noncompartmental methods.

Safety Evaluations:
Safety evaluations included the standard procedures of clinical monitoring, vital signs (heart rate, blood pressure), physical examinations, ECOG performance status, 12-lead electrocardiograms (ECGs), AEs, and safety laboratory tests; and also included determining DLT and MTD of crizotinib treatment during the initial part of the study. In addition, ophthalmologic examinations, urinary 6β-OHC/C measurements, and hypogonadism tests (in male patients) were planned at specific timepoints for certain cohorts for a certain period during the study.

Statistical Methods:
Analysis of objective response rate (ORR), duration of response (DR), time to tumor response (TTR), and disease control rate (DCR) was performed for the response-evaluable

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(RE) population (all patients in the safety analysis population who have an adequate baseline disease assessment). Analysis of PFS, OS, and probabilities of survival at 6 and 12 months was performed on safety analysis (SA) population (all enrolled patients who receive at least one dose of crizotinib on Cycle 1 Day 1).

ORR was defined as the percentage of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST v. 1.0 (or RECIST v. 1.1 for ALK-negative NSCLC cohorts), relative to the RE population. Confirmed responses were those that persisted on repeat imaging study at least 4 weeks after the initial documentation of response. The point estimate of the ORR was provided along with the corresponding 95% confidence interval (CI) using the exact method based on the F-distribution. The best overall response (BOR) was also summarized. The BOR of stable disease could be assigned if stable disease criteria were met at least once after the date of the first dose at a minimum interval of 6 weeks.

DR was defined as the time (in months) from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed, to the first documentation of objective tumor progression or death on-study due to any cause, whichever occurred first. DR was calculated based on the RE population for the subgroup of patients with a confirmed objective tumor response. DR was summarized using the Kaplan-Meier method. The median event time (if appropriate) and 2-sided 95% CI for the median were provided.

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TTR was defined as the time (in weeks) from the date of first dose to first documentation of objective tumor response (CR or PR) that was subsequently confirmed. For patients proceeding from PR to CR, the onset of PR was taken as the onset of response. TTR was summarized using descriptive statistics.

DCR at Weeks 8 and 16 was defined as the percentage of patients with a confirmed CR, confirmed PR or stable disease according to RECIST v. 1.0 based on the response at Weeks 8 and 16, relative to the RE population. DCR at Weeks 8 and 16 was analyzed in a similar way to ORR.

PFS was defined as the time (in months) from the date of first dose to the date of the first documentation of objective tumor progression or death on-study due to any cause, whichever occurred first. PFS in the SA population was summarized using the Kaplan-Meier method. The median event time (and other quartiles) and 2-sided 95% CI for the median were provided. The probability of PFS at 6 months was defined as the probability of being alive and progression-free at 6 months after the date of first dose based on the Kaplan-Meier estimate. A 2-sided 95% CI for the log [-log(6-month PFS probability)] was calculated using a normal approximation and then back-transformed to give a CI for the probability of PFS at 6 months itself.

OS was defined as time from the date of the first dose to the date of death due to any cause. OS in the SA population was summarized using the Kaplan-Meier method. The median event time (and other quartiles) and 2-sided 95% CI for the median were provided. The

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probabilities of survival at 6 and 12 months were defined as the probability of survival at 6 months and 12 months, respectively, after the date of first dose based on the Kaplan-Meier estimate. A 2-sided 95% CI for the log [-log (6-month survival probability)] was calculated using a normal approximation and then back-transformed to give a CI for the probability of survival at 6 months itself. The probability of survival at 12 months was estimated similarly.

PK concentrations of crizotinib are listed, summarized, and plotted for patients in the PK analysis population. For summary statistics and mean/median plots by sampling time, the nominal PK sampling time was used; for individual patient plots by time, the actual PK sampling time was used. Linear and semi-log plots of individual and median crizotinib plasma concentrations were produced for each dose level and/or study days, as appropriate. PK parameters, including but not limited to maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) from time 0 hour to infinity (AUC_{inf}) or from time 0 to time tau (AUC_{τ}), and apparent clearance (CL/F), as appropriate, were estimated using noncompartmental analysis. Descriptive statistics are provided for these PK parameters by dose, including the number of patients (n), arithmetic mean, median, standard deviation, coefficient of variation (CV), minimum, maximum, and geometric mean. Each PK parameter was summarized by dose and included the set of summary statistics.

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Plasma concentrations, predose plasma concentrations (C_{trough}) and steady-state predose concentrations ($C_{trough,ss}$) of crizotinib were listed, summarized and/or plotted for patients in the PK analysis populations. For summary statistics and mean/median plots by sampling time, the nominal PK sampling time was used. C_{trough} was the predose concentration collected on and after C1D15 between 3 hours and 0 hours before the morning dose on the PK collection day (or 9 hours to 15 hours after the evening dose on the prior day in the case of a missing morning dose on the PK collection day). $C_{trough,ss}$ was obtained by using the arithmetic mean of all evaluable C_{trough} on and after C1D15 for each patient in the PKP_$C_{trough,ss}$ population.

Safety data were summarized using the SA population. All AEs reported after initiation of study drug (Cycle 1 Day 1) and pre-existing conditions that worsened during the treatment period were considered as treatment-emergent adverse events. AEs were coded by system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 23.0). AE severity was graded according to NCI CTCAE (version 3.0). Analyses were based on AEs, with the first dose date considered the C1D1 dose, and summarized by MedDRA SOC and PT. Certain PTs were analyzed in aggregate using CLUSTER terms (denoted by capital letters). Descriptive statistics were to be presented for laboratory parameters, vital signs, ECGs, and ophthalmologic examination data.

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RESULTS

Patient Evaluation:

As of the database snapshot date of 30 July 2020, 596 patients were enrolled, 590 patients were assigned to treatment, 578 patients received crizotinib treatment; 576 patients had permanently discontinued treatment; and 2 patients were on treatment (Table S3).

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Table S3 Patient Evaluation Groups - All Enrolled Populations

	Dose Esca-lation	ALK-Negative #1 NSCLC	ALK-Negative #2 NSCLC	MET-Amplified NSCLC	ROS1-Positive NSCLC	ALK-Positive NSCLC	MET Exon 14-Positive NSCLC	Enriched Other – Other Cancers	RP2D MDZ DDI Substudy	Rifampin DDI	Itraco-nazole DDI	Total
Assigned to treatment, N	70 [d]	48 [b]	19 [a,b]	41 [b]	53 [a]	154 [b,c]	85	67 [b]	14 [b,c]	18	21	590
Treated n (%)	65 (92.9)	48 (100)	18 (94.7)	41 (100)	53 (100)	154 (100)	85 (100.0)	66 (98.5)	12 (85.7)	18 (100)	18 (85.7)	578 (98.0)
Discontinued n (%)	65 (92.9)	48 (100)	18 (94.7)	41 (100)	53 (100)	154 (100)	83 (97.6)	66 (98.5)	12 (85.7)	18 (100)	18 (85.7)	576 (97.6)
Ongoing n (%)	0	0	0	0	0	0	2 (2.4)	0	0	0	0	2 (0.3)

a Three (3) patients previously included in the ALK-negative NSCLC cohort #2 were retrospectively found to be ROS1-positive and were included in the ROS1-positive NSCLC cohort instead of the ALK-negative cohort #2 in the final analyses.
b Patients enrolled in the RP2D Other cohort (N=50) of the Interim CSR are now included in the ALK-negative NSCLC cohort #1 (3 patients), ALK-negative NSCLC cohort #2 (2 patients), MET-amplified NSCLC cohort (3 patients), ALK-positive NSCLC cohort (3 patients), Enriched Other – Other Cancers (22 patients), and the MDZ DDI substudy (14 patients); and 3 patients enrolled in the RP2D Other cohort were not treated.
c Fourteen (14) patients under the RP2D MDZ DDI substudy and 1 patient under the ALK-positive NSCLC cohort were all previously included as RP2D Other cohort in the MDZ DDI substudy in the Interim CSR.
d Nine (9) patients from the Dose Escalation cohort (4 at 100 mg QD and 5 at 300 mg BID crizotinib dose) received MDZ oral doses for evaluation of potential crizotinib-related CYP3A4 inhibition.

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Patient Disposition:

Patient disposition at the End of Treatment and based on the database snapshot of this final CSR is presented by-cohort for the Low and High Dose escalation cohorts in Table S4, RP2D cohorts in Table S5, and the DDI cohorts in Table S6. Patient disposition for the remaining cohorts was reported previously as follows:

- MDZ DDI substudy was initially conducted in 9 patients from the Low Dose escalation cohort and later in an additional group of 14 patients from the RP2D Other cohort, as reported in the Interim CSR. Patient disposition was not separately analyzed for this substudy.

- Food Effect substudy was conducted in 13 patients enrolled in the enriched RP2D cohort, as reported in the Interim CSR. Patient disposition was not separately analyzed for this substudy.

- Ophthalmology analysis subgroup patient disposition was reported in the Ophthalmology Report. This included a total of 111 patients who were enrolled variously in the ALK-negative NSCLC cohort #2, the ROS1-positive NSCLC cohort, the MET-amplified NSCLC cohort, Enriched Other cohort, and Rifampin DDI substudy.

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Table S4 Patient Disposition at End of Treatment; Dose Escalation Cohorts – Safety Analysis Populations

Reason for discontinuation	Low Dose Escalation Cohort N=36	High Dose Escalation Cohort N=29
	n (%)	n (%)
Total discontinued	36 (100)	29 (100.0)
Reasons for discontinuation:		
Adverse event	3 (8.3)	4 (13.8)
Progressive disease	23 (63.9)	16 (55.2)
Patient Died	0	2 (6.9)
Patient no longer willing to participate in study	6 (16.7)	4 (13.8)
Other	4 (11.1)	3 (10.3)

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Table S5 Patient Disposition; RP2D Cohorts – Safety Analysis Populations

	ALK-Negative NSCLC Cohort #1 N=48	ALK-Negative NSCLC Cohort #2 N=18	MET-Amplified NSCLC N=41	ROS1-Positive NSCLC N=53	ALK-Positive NSCLC N=154	MET Exon 14-Positive NSCLC [a] N=85	Enriched Other – Other Cancers N=66
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total discontinued	48 (100)	18 (100.0)	41 (100)	53 (100.0)	154 (100%)	83 (97.6)	66 (100)
Reasons for discontinuation:							
Adverse event	4 (8.3)	1 (5.6)	6 (14.6)	0	14 (9.1)	8 (9.4)	9 (13.6)
Progressive disease	21 (43.8)	12 (66.7)	26 (63.4)	25 (47.2)	94 (61.0)	29 (34.1)	42 (63.6)
Patient Died	8 (16.7)	2 (11.1)	2 (4.9)	1 (1.9)	11 (7.1)	7 (8.2)	0
Patient no longer willing to participate in study	3 (6.3)	0	0	8 (15.1)	7 (4.5)	15 (17.6)	1 (1.5)
Lost to follow up	0	0	0	0	0	1 (1.2)	2 (3.0)
Withdrawn Due to Pregnancy	1 (2.1)	0	0	0	0	0	0
Other	11 (22.9)	3 (16.7)	7 (17.1)	19 (35.8)	28 (18.2)	23 (27.1)	12 (18.2)

a In the MET exon 14-positive NSCLC group, 2 (2.4%) patients were on treatment at the database snapshot date.

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Table S6 Patient Disposition; DDI Substudies – Safety Analysis Populations

	Crizotinib 250 mg BID + Rifampin 600 mg QD N=18	Crizotinib 250 mg QD + Itraconazole 200 mg QD [a] N=18
	n (%)	n (%)
Total discontinued	18 (100)	18 (100)
Reasons for discontinuation:		
Adverse event	3 (16.7)	2 (11.1)
Progressive disease	9 (50.0)	4 (22.2)
Patient no longer willing to participate in study	2 (11.1)	2 (11.1)
Other	4 (22.2)	10 (55.6)

a In the Itraconazole DDI substudy, of the 21 enrolled patients, 18 patients were treated and were included in the Safety Analysis population.

Patient Demographics:
Patient demographics were reported previously for the following cohorts/substudies:

- Low Dose escalation cohort, ALK-positive NSCLC cohort, and MDZ DDI substudy in the Interim CSR;
- ALK-negative cohort #2 in the ALK-Negative Report;
- ROS1-positive NSCLC cohort in the ROS1-Positive CSR.

Summary of demographics for the remaining cohorts is presented in Table S7.

Table S7 Patient Demographics – Safety Analysis Populations

Number of Patients	High Dose Escalation Cohort N=29	ALK-Negative NSCLC Cohort #1 N=48	MET-Amplified NSCLC N=41	MET Exon 14-Positive NSCLC N=85	Enriched Other – Other Cancers N=66	Rifampin DDI Substudy N=18	Itraconazole DDI Substudy N=18
Sex, n (%)							
Male	17 (58.6)	24 (50.0)	22 (53.7)	37 (43.5)	41 (62.1)	9 (50.0)	7 (38.9)
Female	12 (41.4)	24 (50.0)	19 (46.3)	48 (56.5)	25 (37.9)	9 (50.0)	11 (61.1)
Age (years)							
Mean	58.6	57.1	64.3	70.4	50.1	61.5	61.3
Median	59.0	58.0	65.0	70.0	53.0	62.5	63.0
Range	38-84	28-82	42-88	34–91	18-88	42-79	40-78
Standard deviation	10.45	14.30	9.93	10.08	19.20	9.40	9.7
Age category							
<65 years	22 (75.9)	30 (62.5)	20 (48.8)	18 (21.2)	51 (77.3)	12 (66.7)	9 (50.0)
≥65 years	7 (24.1)	18 (37.5)	21 (51.2)	67 (78.8)	15 (22.7)	6 (33.3)	9 (50.0)

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Table S7 Patient Demographics – Safety Analysis Populations

Number of Patients	High Dose Escalation Cohort N=29	ALK-Negative NSCLC Cohort #1 N=48	MET-Amplified NSCLC N=41	MET Exon 14-Positive NSCLC N=85	Enriched Other – Other Cancers N=66	Rifampin DDI Substudy N=18	Itraconazole DDI Substudy N=18
Race, n (%)							
White	25 (86.2)	35 (72.9)	38 (92.7)	60 (70.6)	49 (74.2)	16 (88.9)	13 (72.2)
Black	2 (6.9)	1 (2.1)	2 (4.9)	2 (2.4)	4 (6.1)	2 (11.1)	3 (16.7)
Asian	1 (3.4)	9 (18.8)	1 (2.4)	15 (17.6)	9 (13.6)	0	0
Other	1 (3.4)	3 (6.3)	0	8 (9.4)	4 (6.1)	0	2 (11.1)
Body weight (kg)							
Mean	82.26	70.7	80.2	68.2	75.4	74.41	73.7
Median	81.90	68.6	78.8	65.3	76.4	74.72	71.1
Range	46.40-141.10	42.9-116.4	45.4-144.9	41.6-136.2	41.0- 127.1	49.0-129.9	44.2-111.7
Standard deviation	20.37	18.89	20.93	16.93	19.62	18.034	15.3
Smoking classification, n (%)							
Never smoked	18 (62.1)	26 (54.2)	5 (12.2)	31 (36.5)	40 (60.6)	NA	NA
Ex-smoker	10 (34.5)	21 (43.8)	34 (82.9)	53 (62.4)	22 (33.3)	NA	NA
Smoker	1 (3.4)	1 (2.1)	2 (4.9)	1 (1.2)	4 (6.1)	NA	NA
ECOG Performance Status							
0	14 (48.3)	20 (41.7)	13 (31.7)	21 (24.7)	21 (31.8)	2 (11.1)	5 (27.8)
1	15 (51.7)	24 (50.0)	23 (56.1)	62 (72.9)	32 (48.5)	15 (83.3)	13 (72.2)
2	0	4 (8.3)	5 (12.2)	2 (2.4)	13 (19.7)	1 (5.6) [a]	0

NA = Not analyzed
a One patient had an ECOG Performance Status of 1 at screening and 2 at C1D1.

Efficacy Results:

Efficacy analyses were reported previously as follows:

- Low Dose escalation cohort and ALK-negative NSCLC cohort #1 in the Interim CSR;
- ALK-positive NSCLC cohort in the Interim CSR and updated analyses published by Camidge et al [*Camidge et al. Lancet Oncol. 2012;13(10):1011-9*];
- ALK-negative NSCLC cohort #2 in the ALK-Negative Report;
- ROS1-positive NSCLC cohort in the ROS1-Positive CSR and ROS1-Positive Technical Report.

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Efficacy data collected for the High Dose escalation cohort were not analyzed statistically and are provided as a patient listing in this final CSR. Among the 29 RE patients in the High Dose escalation cohort, the BOR was stable disease for 5 patients.

Summary of efficacy analyses that were planned for the remaining cohorts is presented in Table S8.

Table S8 Efficacy Results Based on Derived Investigator Tumor Assessment - Response-Evaluable Populations

	MET-Amplified NSCLC N = 38	High-Level MET-Amplified NSCLC [a] N = 21	MET Exon 14-Positive NSCLC N = 85	Enriched Other – Other Cancers N = 61
Best overall response, n (%)				
Complete response (CR)	2 (5.3)	2 (9.5)	3 (3.5)	1 (1.6)
Partial response (PR)	10 (26.3)	7 (33.3)	30 (35.3)	4 (6.6)
Stable disease	10 (26.3)	6 (28.6)	35 (41.2)	19 (31.1)
Early death, n (%)	5 (13.2)	1 (4.8)	1 (1.2)	6 (9.8)
Indeterminate response, n (%)	3 (7.9)	2 (9.5)	10 (11.8)	5 (8.2)
Objective response rate (CR+PR), n (%)	12 (31.6)	9 (42.9)	33 (38.8)	5 (8.2)
95% Exact CI	17.5, 48.7	21.8, 66.0	28.4, 50.0	2.7, 18.1
Duration of Response; months; median (95% CI) / n	5.2 (3.8, 12.2) / 10	5.2 (4.9, 12.0) / 8	9.1 (6.5, 12.9) / 23	NA
Time to Tumor Response; weeks; median (range) / n[a]	8.0 (7.1—23.6) / 12	8.0 (7.6—23.6) / 9	7.6 (3.7—47.3) / 33	NA
Progression-Free Survival; months; median (95% CI) / n	4.0 (1.9, 6.9) / 32	6.9 (3.4, 8.3) / 16	7.6 (5.6, 9.1) / 59	NA
Overall Survival; months; median (95% CI) / n	10.1 (7.1, 12.9) / 33	11.0 (9.4, 16.3) / 16	20.0 (13.2, 25.7) / 46	NA
Survival Probability at Month 6, (95% CI)	67.8% (51.1, 79.9)	80.2% (55.4, 92.1)	86.7% (77.3, 92.4)	NA
Survival Probability at	37.1% (22.4, 51.8)	44.1% (22.1, 64.2)	66.0% (54.0, 75.5)	NA

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Month 12, (95% CI)					

n = number of patients with the event
n^a = number of patients with CR or PR
NA = not analyzed.
a Patients with MET Amplification NSCLC, MET/CEP7 ratio cut off ≥4.

Pharmacokinetic Results:

Results from the PK analyses were reported previously as follows:

- Low Dose escalation cohort, the MDZ DDI substudy, and the Food Effect substudy in the Interim CSR;
- ROS1-positive NSCLC cohort in the ROS1-Positive CSR;
- Rifampin and itraconazole DDI substudies in the Rifampin DDI Report and the Itraconazole DDI Report, respectively.

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No PK summary was planned for the ALK-negative NSCLC cohort #1.

A summary of plasma PK parameters of crizotinib in the High Dose escalation cohort is presented in Table S9; summary tables for C_{trough} of crizotinib in the ALK-negative NSCLC cohort #2 and MET-amplified NSCLC cohort in Table S10 and Table S11, respectively; summary tables for C_{trough} and of mean steady-state predose concentrations ($C_{trough, ss, mean}$) of crizotinib in Asian and Non-Asian patients in the ALK-positive NSCLC cohort in Table S12 and Table S13, respectively; summary tables for C_{trough} and $C_{trough, ss}$ of crizotinib in Asian and Non-Asian patients with MET exon 14-positive NSCLC in Table S14 and Table S15, respectively; and a summary table for C_{trough} in the Enriched Other – Other Cancers cohort in Table S16.

Table S9 Descriptive Summary of Plasma Pharmacokinetic Parameters of Crizotinib in the High Dose Escalation Cohort – Study A8081001

Parameters, Units	Parameter Summary Statistics [a] by Crizotinib Treatment				
	300 mg QD	400 mg QD	500 mg QD	650 mg QD	800 mg QD
Day -7 (single dose)					
N, n	6, 5	5, 5	3, 2	6, 6	8, 8
T_{max}, h	4.00 (2.00-6.00)	2.15 (1.00-6.00)	4.00 (2.00-8.00)	4.00 (1.98-6.00)	4.99 (2.15-6.13)
C_{max}, ng/mL	184.7 (65)	115.9 (85)	146.6 (31)	154.3 (30)	270.9 (47)
AUC_{τ}, ng*h/mL	1731 (51)	1377 (114)	1300 (61)	1906 (39)	3423 (57)
AUC_{inf}, ng*h/mL	3457 (42)	3078 (119)	1480, 2990	3979.4 (39)	7547 (76)
CL/F, L/h	86.77 (42)	129.9 (119)	167, 337	163.4 (39)	106.0 (76)

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Table S9 Descriptive Summary of Plasma Pharmacokinetic Parameters of Crizotinib in the High Dose Escalation Cohort – Study A8081001

Parameters, Units	Parameter Summary Statistics [a] by Crizotinib Treatment				
	300 mg QD	400 mg QD	500 mg QD	650 mg QD	800 mg QD
Vz/F, L	5352 (47)	9444 (178)	10400, 24200	9704 (62)	6146 (94)
$t_{1/2}$, h	43.12 (15)	53.56 (39)	43.0, 49.8	41.90 (20)	40.76 (18)
Cycle 1 Day 15 (multiple doses)					
N	6	3	3	5	4
T_{max}, h	5.13 (1.93-7.88)	5.17 (0.933-6.00)	4.00 (4.00-9.00)	5.98 (4.00-6.00)	5.03 (4.00-6.03)
C_{max}, ng/mL	315.2 (50)	215.5 (26)	395.3 (16)	379.2 (28)	671.3 (76)
AUC_{τ}, ng*h/mL	4375 (34)	2860, 4010 [d]	6655 (4)	6362 (37)	10480 (76) [e]
CL/F, L/h	68.57 (34)	99.9, 140 [d]	75.13 (4)	102.2 (37)	76.31 (76) [e]
R_{ac}	2.836 (1.32- 4.02)	2.44, 4.18 [d]	4.159 (3.47-9.30)	3.328 (2.14-7.40)	2.639 (1.83-15.7) [e]
Cycle 2 Day 1 (multiple doses)					
N	6	3	2	4	2
T_{max}, h	3.00 (1.00-5.95)	4.00 (2.08-6.00)	6.18, 9.00	4.30 (4.00-9.00)	4.00, 6.00
C_{max}, ng/mL	275.0 (28)	248.2 (60)	239, 450	419.8 (36)	545, 899
AUC_{τ}, ng*h/mL	4815 (23) [b]	3839 (65)	4170, 9600	7273 (48)	5800, 13100
CL/F, L/h	57.45 (36)	104.2 (65)	52.1, 120	83.70 (59)	60.9, 138
R_{ac}	3.195 (3.04-4.35) [c]	1.650 (1.27-5.63)	2.08, 13.9	2.739 (2.27-3.46) [e]	2.28, 2.88

N is the number of patients; n is the number of patients where terminal $t_{1/2}$ was determined.
Note: individual values presented where N≤2.
a Geometric mean (% geometric CV) for all except: median (range) for T_{max} and R_{ac}, arithmetic mean (%CV) for $t_{1/2}$.
b n=5
c n=4
d n=2
e n=3

Table S10 Predose Plasma Concentrations (C_{trough}) of Crizotinib (ALK-Negative NSCLC Cohort #2) - PKP_C_{trough} Population

	Day 29 (Cycle 2 Day 1)	Day 57 (Cycle 3 Day 1)	Day 113 (Cycle 5 Day 1)
N	9	5	4
C_{trough} [a], ng/mL	208.0 (55)	209.2 (33)	269.0 (46)

Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero.
N is the number of non-missing concentration measurements collected on C1D15 or later.
a Presented as mean (% CV).

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Table S11 Predose Plasma Concentrations (C_{trough}) of Crizotinib (MET-Amplified NSCLC Cohort) - PKP_C_{trough} Population

	Day 15 (Cycle 1 Day 15)	Day 29 (Cycle 2 Day 1)	Day 43 (Cycle 2 Day 15)	Day 57 (Cycle 3 Day 1)	Day 85 (Cycle 4 Day 1)	Day 113 (Cycle 5 Day 1)
N	6	19	7	11	4	15
C_{trough} [a], ng/mL	231.5 (21)	264.9 (90)	245.3 (29)	240.3 (34)	248.5 (26)	221.0 (51)

Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero.
N is the number of non-missing concentration measurements collected on C1D15 or later.
a Presented as mean (% CV).

Table S12 Summary of Predose Concentrations (C_{trough}) of Crizotinib (ALK-Positive NSCLC Cohort) - Study A8081001

Parameter	C_{trough} [a] (ng/mL)				
	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1
N	26	54	51	52	41
Crizotinib	1.9 (44)	270.7 (51)	261.0 (49)	287.8 (43)	286.9 (44)

N is the number of observations for crizotinib.
a Geometric mean (% CV)

Table S13 Summary of Steady-State Mean Predose Concentrations ($C_{trough, ss, mean}$) of Crizotinib in Asian and Non-Asian Patients (ALK-Positive NSCLC Cohort) - Study A8081001

Parameter	$C_{trough, ss, mean}$ [a] (ng/mL)		
	Asian	Non-Asian	All Patients
N	23	88	111
Crizotinib	350 (36.6)	260 (32.3)	276 (36.6)

N is the number of observations for crizotinib.
a Geometric mean (% CV)

Table S14 Predose Plasma Concentrations (C_{trough}) of Crizotinib (MET Exon 14-Positive NSCLC) - PKP_C_{trough} Population

	Day 29 (Cycle 2 Day 1)	Day 57 (Cycle 3 Day 1)	Day 113 (Cycle 5 Day 1)
N	46	43	39
C_{trough} [a], ng/mL	279.9 (54)	250.5 (68)	209.1 (59)

Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero.
N is the number of non-missing concentration measurements collected on C1D15 or later.
a Presented as mean (% CV).

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Table S15 Mean Steady-State Predose Concentrations ($C_{trough,ss}$) of Crizotinib (Asian, Non-Asian and Overall) (MET Exon 14-Positive NSCLC) Following 250 mg BID Crizotinib - PKP_$C_{trough,ss}$ Population

	Asian (N=5)	Non-Asian (N=46)	Total (N=51)
$C_{trough,ss}$ [a], ng/mL	408.2 (53)	234.4 (48)	247.5 (51)

Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero.
N is the number of observations for crizotinib.
a Presented as geometric mean (geometric % CV).

Table S16 Predose Plasma Concentrations (C_{trough}) of Crizotinib (Enriched Other – Other Cancers) - PKP_C_{trough} Population

	Day 15 (Cycle 1 Day 15)	Day 29 (Cycle 2 Day 1)	Day 43 (Cycle 2 Day 15)	Day 57 (Cycle 3 Day 1)	Day 85 (Cycle 4 Day 1)	Day 113 (Cycle 5 Day 1)
N	31	39	19	17	9	11
C_{trough} [a], ng/mL	296.1 (51)	279.2 (62)	268.9 (44)	302.7 (59)	321.2 (44)	265.4 (63)

Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero.
N is the number of non-missing concentration measurements collected on C1D15 or later.
a Presented as mean (% CV).

Safety Results:

Safety analyses were reported previously as follows:

- Low Dose escalation cohort, ALK-negative NSCLC cohort #1, and ALK-positive NSCLC cohort in the Interim CSR;
- ALK-negative NSCLC cohort #2 in the ALK-Negative Report;
- ROS1-positive NSCLC cohort in the ROS1-Positive CSR and ROS1-Positive Technical Report.

Summary of safety analyses is presented by-cohort for the High Dose escalation cohort and ALK-negative NSCLC cohorts #1 and #2 in Table S17; for the MET-amplified NSCLC, ROS1-positive NSCLC, ALK-positive NSCLC, MET exon 14-positive NSCLC, and Enriched Other – Other Cancers cohorts in Table S18; and for the rifampin and itraconazole DDI substudy cohorts in Table S19.

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For the Low Dose escalation cohort, the MTD and RP2D of crizotinib were determined to be 250 mg BID; and for the High Dose escalation cohort, the QD MTD was determined to be 650 mg QD based on discussions with the investigators as both 650 mg QD and 800 mg QD had 1 DLT each.

Table S17 Safety Results for Dose Escalation Cohorts and Other RP2D Cohorts – Safety Analysis Populations

	High Dose escalation cohort N = 29	ALK-negative NSCLC cohort #1 N = 48	ALK-negative NSCLC cohort #2 N = 18
Treatment duration, months; median (range)	1.12 (0—5.6)	1.8 (0.1—49.0)	1.3 (0.4—48.4)
All-Causality AEs, n (%)			
AEs	28 (96.6)	47 (97.9)	18 (100)
SAEs [a]	11 (37.9)	22 (45.8)	9 (50.0)
Grade 3 or 4 AEs	17 (58.6)	31 (64.6)	14 (77.8)
Grade 5 AEs	4 (13.8)	14 (29.2)	3 (16.7)
AEs associated with n (%)			
Permanent discontinuation	6 (20.7)	12 (25.0)	3 (16.7)
Dose reductions	2 (6.9)	4 (8.3)	3 (16.7)
Temporary discontinuation	8 (27.6)	11 (22.9)	9 (50.0)
Treatment-Related, n (%):			
AEs	25 (86.2)	43 (89.6)	16 (88.9)
SAEs [a]	0	1 (2.1)	2 (11.1)
Grade 3 or 4 AEs	4 (13.8)	13 (27.1)	5 (27.8)
Grade 5 AEs	0	1 (2.1)	0
AEs associated with: n (%)			
Permanent discontinuation	1 (3.4)	4 (8.3)	0
Dose reductions	2 (6.9)	4 (8.3)	3 (16.7)
Temporary discontinuation	3 (10.3)	5 (10.4)	5 (27.8)
Most Frequent (≥30%) All-causality AEs (PT/CLUSTER Term)	Constipation, Nausea, VISION DISORDER, Vomiting, and Fatigue	VISION DISORDER, Vomiting, Fatigue, Constipation, Nausea, Diarrhoea, OEDEMA, and DYSPNOEA	VISION DISORDER, Constipation, Nausea, Vomiting, and Fatigue

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Table S17 Safety Results for Dose Escalation Cohorts and Other RP2D Cohorts – Safety Analysis Populations

	High Dose escalation cohort N = 29	ALK-negative NSCLC cohort #1 N = 48	ALK-negative NSCLC cohort #2 N = 18
Most Frequent (≥30%) Treatment-related AEs (PT/CLUSTER Term)	VISION DISORDER, Nausea, and Vomiting	VISION DISORDER, Vomiting, Fatigue, Nausea, and Diarrhoea	VISION DISORDER, Nausea, and Vomiting
Most Frequent (≥5%) All-Causality Grade 3 AEs (PT/CLUSTER Term)	Vomiting, Nausea, OEDEMA, CHEST PAIN, and Fatigue	Vomiting, Fatigue, Nausea, Decreased appetite, DYSPNOEA, and Hypophosphataemia	Hypophosphataemia [b]
Most Frequent (≥5%) Treatment-related Grade 3 AEs (PT/CLUSTER Term)	0	Fatigue, Hypophosphataemia, Nausea, and Vomiting	Hypophosphataemia [b]
Most Frequent (≥2 patients) All-Causality Grade 4 AEs (PT/CLUSTER Term)	Cardiac arrest	PULMONARY EMBOLISM	PULMONARY EMBOLISM
Most Frequent (≥2 patients) Treatment-related Grade 4 AEs (PT/CLUSTER Term)	0	0	0
Grade 5 All-Causality AEs (PT/CLUSTER Term)	Disease progression, Hypoxic-ischaemic encephalopathy	Disease progression, Pneumonia, Cardio-respiratory arrest, Death, Myocardial infarction, Pneumothorax, and Small cell lung cancer	Disease progression, Acute respiratory failure, and Respiratory failure
Grade 5 Treatment-Related AEs (PT/CLUSTER Term)	0	Death	0
Most Frequent (≥2 patients) Clinical Laboratory Evaluation shifts from Grade ≤2 at baseline to maximum Grade 3 postbaseline	Hypoalbuminemia, and alkaline phosphatase	Absolute lymphocytes, absolute neutrophils, hemoglobin; hypophosphatemia, alkaline phosphatase, hyponatremia, ALT and hypoalbuminemia	Absolute lymphocytes and hypophosphatemia
Most Frequent (≥2 patients) Clinical Laboratory Evaluation shifts from Grade ≤2 at	0	0	0

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Table S17 Safety Results for Dose Escalation Cohorts and Other RP2D Cohorts – Safety Analysis Populations

	High Dose escalation cohort N = 29	ALK-negative NSCLC cohort #1 N = 48	ALK-negative NSCLC cohort #2 N = 18
baseline to maximum Grade 4 postbaseline			
QTcF ≥500 msec; n (%) / NE	2 (6.9) / 29	1 (2.2) / 45	0
Increase from baseline in QTcF ≥60 msec; n (%) / NE	2 (6.9) / 29	2 (4.5) / 44	0

NA = Not analyzed
NE = number of evaluable patients
a Seriousness was according to the investigator's assessment.
b For this cohort, the frequency cutoff applied for this parameter was changed from "≥5%" (1 patient) to "≥2 patients".

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Table S18 Safety Results for Enriched RP2D Cohorts – Safety Analysis Populations

	MET-Amplified NSCLC N = 41	ROS1-Positive NSCLC N = 53	ALK-Positive NSCLC N = 154	MET Exon 14-Positive NSCLC N = 85	Enriched Other – Other Cancers N = 66
Treatment duration, months; median (range)	3.3 (0.1—94.1)	20.6 (0.5—97.9)	13.1 (0.2—124.0)	7.4 (0.4—51.1)	1.8 (0.4—50.4)
All-Causality AEs, n (%):					
AEs	41 (100)	53 (100)	154 (100.0)	85 (100.0)	66 (100)
SAEs [a]	25 (61.0)	24 (45.3)	75 (48.7)	54 (63.5)	29 (43.9)
Grade 3 or 4 AEs	33 (80.5)	36 (67.9)	104 (67.5)	65 (76.5)	40 (60.6)
Grade 5 AEs	10 (24.4)	10 (18.9)	27 (17.5)	15 (17.6)	14 (21.2)
AEs associated with: n (%)					
Permanent discontinuation	9 (22.0)	1 (1.9)	26 (16.9)	16 (18.8)	10 (15.2)
Dose reductions	10 (24.4)	11 (20.8)	19 (12.3)	37 (43.5)	8 (12.1)
Temporary discontinuation	24 (58.5)	27 (50.9)	76 (49.4)	48 (56.5)	23 (34.8)
Treatment-Related AEs, n (%):					
AEs	38 (92.7)	53 (100)	152 (98.7)	82 (96.5)	63 (95.5)
SAEs [a]	4 (9.8)	2 (3.8)	12 (7.8)	14 (16.5)	8 (12.1)
Grade 3 or 4 AEs	20 (48.8)	19 (35.8)	52 (33.8)	26 (30.6)	17 (25.8)
Grade 5 AEs	1 (2.4)	0	1 (0.6)	1 (1.2)	0
AEs associated with: n (%)					
Permanent discontinuation	4 (9.8)	0	6 (3.9)	7 (8.2)	4 (6.1)
Dose reductions	9 (22.0)	11 (20.8)	19 (12.3)	34 (40.0)	8 (12.1)
Temporary discontinuation	12 (29.3)	14 (26.4)	38 (24.7)	24 (28.2)	13 (19.7)

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Table S18 Safety Results for Enriched RP2D Cohorts – Safety Analysis Populations

	MET-Amplified NSCLC N = 41	ROS1-Positive NSCLC N = 53	ALK-Positive NSCLC N = 154	MET Exon 14-Positive NSCLC N = 85	Enriched Other – Other Cancers N = 66
Most Frequent (≥30%) All-causality AEs (PT/CLUSTER Term)	OEDEMA, Diarrhoea, Vomiting, Nausea, and VISION DISORDER	VISION DISORDER, Nausea, OEDEMA, Vomiting, Diarrhoea, Constipation, DIZZINESS, ELEVATED TRANSAMINASES, Fatigue, NEUROPATHY, UPPER RESPIRATORY INFECTION, DYSPNOEA, and Decreased appetite	VISION DISORDER, Nausea, Diarrhoea, OEDEMA, Vomiting, Constipation, DIZZINESS, UPPER RESPIRATORY INFECTION, Fatigue, NEUROPATHY, and Decreased appetite	OEDEMA, Diarrhoea, Nausea, Constipation, VISION DISORDER, Fatigue, Vomiting, NEUROPATHY, DYSPNOEA, and DIZZINESS	Nausea, Vomiting, Diarrhoea, VISION DISORDER, Fatigue, OEDEMA, and Decreased appetite
Most Frequent (≥30%) Treatment-related AEs (PT/CLUSTER Term)	Diarrhoea, Vomiting, and OEDEMA	VISION DISORDER, Nausea, OEDEMA, Diarrhoea, Vomiting, ELEVATED TRANSAMINASES, and Constipation	VISION DISORDER, Nausea, Diarrhoea, OEDEMA, Vomiting, and Constipation	OEDEMA, Diarrhoea, Nausea, VISION DISORDER, and Vomiting	Nausea, VISION DISORDER, Diarrhoea, and Vomiting

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Table S18 Safety Results for Enriched RP2D Cohorts – Safety Analysis Populations

	MET-Amplified NSCLC N = 41	ROS1-Positive NSCLC N = 53	ALK-Positive NSCLC N = 154	MET Exon 14-Positive NSCLC N = 85	Enriched Other – Other Cancers N = 66
Most Frequent (≥5%) All-Causality Grade 3 AEs (PT/CLUSTER Term)	Hyponatraemia, ANAEMIA, DYSPNOEA, Pneumonia, ELEVATED TRANSAMINASES, Hypophosphataemia, Hypoxia, and LYMPHOPENIA	Hypophosphataemia, NEUTROPENIA, DYSPNOEA, Headache, Vomiting, ELEVATED TRANSAMINASES, and Syncope	ELEVATED TRANSAMINASES, Hypophosphataemia, NEUTROPENIA, Pneumonia, ANAEMIA, Syncope; DYSPNOEA, LYMPHOPENIA, and Hyponatraemia	DYSPNOEA, Pneumonia, Hyponatraemia, Syncope, ELEVATED TRANSAMINASES, Hypoxia, and Pleural effusion	Hyponatraemia, ANAEMIA, ELEVATED TRANSAMINASES, Hypophosphataemia, and NEUTROPENIA
Most Frequent (≥5%) Treatment-related Grade 3 AEs (PT/CLUSTER Term)	ELEVATED TRANSAMINASES and LYMPHOPENIA	Hypophosphataemia and NEUTROPENIA	NEUTROPENIA, ELEVATED TRANSAMINASES, and Hypophosphatemia	DYSPNOEA, ELEVATED TRANSAMINASES, and INTERSTITIAL LUNG DISEASE	ELEVATED TRANSAMINASES
Most Frequent (≥2 patients) All-Causality Grade 4 AEs (PT/CLUSTER Term)	PULMONARY EMBOLISM	PULMONARY EMBOLISM	PULMONARY EMBOLISM, ELEVATED TRANSAMINASES, NEUTROPENIA, Deep vein thrombosis, Haemoptysis, Hypoxia, INTERSTITIAL LUNG DISEASE, Pneumonia, Respiratory failure, and THROMBOCYTOPENIA	PULMONARY EMBOLISM, Embolism, Respiratory failure, Brain oedema, and Cerebrovascular accident	ANAEMIA

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Table S18 Safety Results for Enriched RP2D Cohorts – Safety Analysis Populations

	MET-Amplified NSCLC N = 41	ROS1-Positive NSCLC N = 53	ALK-Positive NSCLC N = 154	MET Exon 14-Positive NSCLC N = 85	Enriched Other – Other Cancers N = 66
Most Frequent (≥2 patients) Treatment-related Grade 4 AEs (PT/CLUSTER Term)	0	0	NEUTROPENIA	0	ANAEMIA
All-causality Grade 5 AEs (PT/CLUSTER Term)	Disease progression, Pneumonia, Encephalopathy, INTERSTITIAL LUNG DISEASE, and Respiratory failure	Disease progression	Disease progression, Pneumonia, Respiratory failure, Aspergillus infection, Disseminated intravascular coagulation, Pulmonary haemorrhage, and Subcutaneous emphysema	Disease progression, INTERSTITIAL LUNG DISEASE, Respiratory failure, Cardiac arrest, Cardio-respiratory arrest, Large intestinal obstruction, Respiratory arrest, and Subdural haematoma	Disease progression, Pneumonia, and Septic shock
Treatment-Related Grade 5 AEs (PT/CLUSTER Term)	INTERSTITIAL LUNG DISEASE	0	Disseminated intravascular coagulation	INTERSTITIAL LUNG DISEASE	0

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Table S18 Safety Results for Enriched RP2D Cohorts – Safety Analysis Populations

	MET-Amplified NSCLC N = 41	ROS1-Positive NSCLC N = 53	ALK-Positive NSCLC N = 154	MET Exon 14-Positive NSCLC N = 85	Enriched Other – Other Cancers N = 66
Most Frequent (≥2 patients) Clinical Laboratory Evaluation shifts from Grade ≤2 at baseline to maximum Grade 3 postbaseline [b]	Absolute lymphocytes, hemoglobin; hypophosphatemia, hyponatremia, ALT, and hypoalbuminemia	Absolute lymphocytes, absolute neutrophils, WBCs; hypophosphatemia, hyponatremia, ALT, AST, hyperkalemia, and hypoalbuminemia	Absolute lymphocytes, absolute neutrophils, WBCs, hemoglobin, platelets; hypophosphatemia, ALT, hyponatremia, hyperglycemia, AST, hypocalcemia, hypoalbuminemia, hypokalemia, and alkaline phosphatase	Absolute lymphocytes, hemoglobin, hyponatremia, hypophosphatemia, hyperkalemia, ALT, AST and hyperglycemia, alkaline phosphatase, and hypokalemia	Absolute lymphocytes, absolute neutrophils, platelets, hyponatremia, hypophosphatemia, ALT, alkaline phosphatase, AST, hypoalbuminemia, and hypocalcemia
Most Frequent (≥2 patients) Clinical Laboratory Evaluation shifts from Grade ≤2 at baseline to maximum Grade 4 postbaseline	0	Absolute lymphocytes	Absolute lymphocytes, absolute neutrophils, and ALT	Absolute lymphocytes	Hemoglobin
QTcF ≥500 msec; n (%) / NE	1 (2.6) / 39	2 (3.8) / 53	2 (1.3) / 154	0	2 (3.2) / 63
Increase from baseline in QTcF ≥60 msec; n (%) / NE	1 (2.6) / 39	2 (3.8) / 53	7 (4.5) / 154	0	5 (7.9) / 63

NE = number of evaluable patients
a Seriousness was according to investigator's assessment.
b Hy's Law criteria were met by 1 patient each in the ROS1-positive NSCLC and ALK-positive NSCLC cohort.

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Table S19 Safety Results for Drug-Drug Interaction Cohorts - Safety Analysis Populations

	Crizotinib 250 mg BID + Rifampin 600 mg QD N = 18	Crizotinib 250 mg QD + Itraconazole 200 mg QD N = 18
Treatment exposure; median (range)	2.0 (1—13) cycles started	47.0 (7—331) days
All-Causality AEs, n (%):		
AEs	18 (100)	18 (100)
SAEs [a]	6 (33.3)	7 (38.9)
Grade 3 or 4 AEs	9 (50.0)	12 (66.7)
Grade 5 AEs	0	0
AEs associated with: n (%)		
Permanent discontinuation	4 (22.2)	3 (16.7)
Dose reductions	0	1 (5.6)
Temporary discontinuation	7 (38.9)	9 (50.0)
Treatment-related AEs [b], n (%):		
AEs	16 (88.9)	17 (94.4)
SAEs [a]	2 (11.1)	4 (22.2)
Grade 3 or 4 AEs	2 (11.1)	5 (27.8)
Grade 5 AEs	0	0
AEs associated with: n (%)		
Permanent discontinuation	1 (5.6)	1 (5.6)
Dose reductions	0	1 (5.6)
Temporary discontinuation	3 (16.7)	4 (22.2)
Most Frequent (≥30%) All-Causality AEs (PT/CLUSTER Term)	VISION DISORDER, Nausea, Vomiting, Constipation, Diarrhoea, Decreased appetite, and Fatigue	Constipation, Nausea, VISION DISORDER, DYSPNOEA, Fatigue, Vomiting, Diarrhoea, and OEDEMA
Most Frequent (≥30%) Treatment-Related AEs (PT/CLUSTER Term)	VISION DISORDER, Nausea, and Vomiting	Nausea, VISION DISORDER, Vomiting, Constipation, Diarrhoea, OEDEMA
Most Frequent (≥2 patients) All-Causality Grade 3 AEs (PT/CLUSTER Term)	Hypokalaemia	ANAEMIA, Ascites, Blood alkaline phosphatase increased, Deep vein thrombosis, and Vomiting
Most Frequent (≥2 patients) Crizotinib-Related Grade 3 AEs (PT/CLUSTER Term)	Hypokalaemia	0
Most Frequent (≥2 patients) All-Causality Grade 4 AEs (PT/CLUSTER Term)	0	Hyperuricaemia

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Most Frequent (≥2 patients) Crizotinib-Related Grade 4 AEs (PT/CLUSTER Term)	0	0
Grade 5 AEs (PT/CLUSTER Term)	0	0
Most Frequent (≥2 patients) Clinical Laboratory Evaluation shifts from Grade ≤2 at baseline to maximum Grade 3 postbaseline	Hyponatremia	Alkaline phosphatase
Most Frequent (≥2 patients) Clinical Laboratory Evaluation shifts from Grade ≤2 at baseline to maximum Grade 4 postbaseline	0	0
QTcF ≥500 msec; n (%) / NE	0	0
Increase from baseline in QTcF ≥60 msec; n (%) / NE	0	0

NE = number of evaluable patients
a Seriousness was according to the investigator's assessment.
b AEs related to crizotinib treatment only.

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For the 8 hypogonadism parameters measured in this study, there was a reduction from baseline in the levels of most parameters and the geometric mean of the ratio of C2D1/C1D1 calculated for evaluable patients was statistically significant (p values <0.05) for testosterone (0.47; p<0.0001), sex hormone-binding globulin (SHBG9 (0.24, p<0.0001), serum luteinizing hormone (0.42; 0.0019), dihydroepiandosterone sulfate (0.85; p=0.0120), and estradiol (0.72; p=0.0133), but was not statistically significant for free testosterone (1.31; p=0.0776), prolactin (0.89; p=0.3111), and follicle stimulating hormone (0.69; p=0.0508). As there was no adjustment for multiple testing, these values should be viewed descriptively.

Abnormalities in clinical laboratory results or assessments of vital signs, ECGs, and physical examinations reported on crizotinib treatment were generally manageable by dosing interruption, dose reduction, and/or standard medical therapy.

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CONCLUSIONS

In the following subsections, conclusions drawn in previous reports that remained unchanged are presented verbatim in *italics* and any updates made for the respective cohort as well as conclusions for cohorts not previously reported, based on the database snapshot date for this final CSR, are presented in regular font.

Safety and Efficacy:

Dose Escalation Cohorts

- For the Low Dose escalation cohort, the MTD and RP2D of crizotinib were determined to be 250 mg BID (Interim CSR).
- For the High Dose escalation cohort, the QD MTD was determined to be 650 mg QD based on discussions with the investigators as both 650 mg QD and 800 mg QD had 1 DLT each.
- In the Low Dose escalation cohort, the best overall response was PR for 1 patient and was stable disease for 11 patients (Interim CSR).
- Efficacy data for the High Dose escalation cohort were listed but were not analyzed in this final CSR.

ALK-Negative NSCLC Cohort #1

- The AE profile for the ALK-negative NSCLC patients treated with crizotinib in the ALK-negative NSCLC cohort #1 in this study was consistent with the established safety profile of crizotinib.
- Efficacy data for the ALK-negative NSCLC cohort #1 were listed but were not analyzed in this final CSR.

ALK-Negative NSCLC Cohort #2

The following conclusions were drawn for the 21 patients included in the ALK-negative NSCLC cohort #2, based on a data cutoff date of 24 June 2014, as reported in the ALK-Negative Report, with updates made based on the database snapshot date for this final CSR:

- The AE profile for the ALK-negative NSCLC patients treated with crizotinib in this study was consistent with the established safety profile of crizotinib.
- *As expected, based on the mechanism of action of crizotinib, antitumor activity was much lower in ALK-negative NSCLC patients than in ALK-positive NSCLC patients.*

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- *No ALK-negative NSCLC patients achieved a CR, and 4 of 21 ALK-negative NSCLC patients had a PR, for an ORR of 19.0% (95% CI: 5.4%, 41.9%). These 4 patients included 1 patient with ROS1-positive NSCLC and 2 patients with unknown ROS1 and/or MET status*.

- *Eleven patients were known to have NSCLC that was negative for the 3 identified genetic alterations targeted by crizotinib that were tested (ie, ALK fusion, ROS1 fusion, and MET amplification).*

  - *In these 11 patients, 1 patient achieved a PR for an ORR of 9.1% (95% CI: 0.23%, 41.3%). Given the low response rate in a small sample size, this could potentially represent a patient with a false-negative ALK, ROS1, or MET test result or a patient with yet another genetic alteration sensitive to inhibition by crizotinib that was not tested.*

- There did not appear to be any relationship between percent ALK positivity and best overall response.

- The ORR in ALK-negative NSCLC patients treated with a multi-targeted agent such as crizotinib may reflect inadequate testing of all relevant genetic alterations rather than inadequacy of a specific test for a single gene alteration or its cutoff.

MET-Amplified NSCLC Cohort

- The safety profile of crizotinib in patients with MET-amplified NSCLC was generally consistent with the established safety profile of crizotinib.

- Crizotinib provided meaningful clinical benefit in the high-level MET gene amplified category as evidenced by objective responses that were rapid and durable, with complete responses in some cases.

  - The ORR in the total MET-amplified NSCLC cohort (N=38) was 31.6%; 2 (5.3%) patients had a CR, 10 (26.3%) patients had a PR, and a further 10 (26.3%) patients had stable disease as their BOR. Median TTR was 8.0 weeks, median DR was 5.2 months, and median PFS was 4.0 months.

  - The highest ORR among the 3 MET amplification categories was observed in the high-level MET gene amplified category (N=21), which was 42.9% with 2 patients who had a CR and 7 patients who had PR as their BOR; the median TTR was 8.0 weeks, median DR was 5.2 months, and median PFS was 6.9 months.

ROS1-Positive NSCLC Cohort

- *Crizotinib was generally well-tolerated and manageable by dosing interruption, dose reduction, and/or standard medical therapy* (ROS1-Positive CSR).

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- *Crizotinib provided meaningful clinical benefit as evidenced by a high rate of objective responses that were rapid, substantial, and durable, with complete response in some cases* (ROS1-Positive CSR).

    - The ORR was 71.7% (N=53); 6 (11.3%) patients had a CR, 32 (60.4%) patients had a PR, and a further 10 (18.9%) patients had stable disease as their BOR. Median TTR was 7.9 weeks, and median PFS was 19.3 months (ROS1-Positive Technical Report).

    - *The median DR was estimated to be approximately 25 months* (ROS1-Positive Technical Report).

    - *The median OS was more than 4 years* (ROS1-Positive Technical Report).

ALK-Positive NSCLC Cohort

The safety conclusions for the ALK-positive NSCLC cohort were initially drawn, based on the database snapshot date of 01 November 2010, in the Interim CSR; minor updates were made based on the database snapshot date for this final CSR.

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- The AE profile of crizotinib 250 mg BID orally was generally safe and well-tolerated, with the most frequent AEs in ALK-positive NSCLC patients of Grade 1 VISION DISORDER, gastrointestinal events, including Nausea, Diarrhoea, Vomiting, and Constipation, and OEDEMA, which were all Grade 1 to Grade 3 in severity.

- The incidence of severe and serious AEs and laboratory abnormalities reported on crizotinib treatment was relatively low and generally manageable in this patient population by dosing interruption, dose reduction, and/or standard medical therapy, with the most frequently reported treatment-related SAEs in ALK-positive NSCLC patients of ELEVATED TRANSAMINASES in 3 (1.9%) patients and RENAL CYST in 2 (1.3%) patients.

- The efficacy of crizotinib 250 mg BID in the ALK-positive advanced NSCLC cohort was robust with an investigator-assessed ORR of 60.8%, durable with a median DR estimate of 49.1 weeks, and clinically meaningful with a median PFS estimate of 9.7 months (updates reported in Camidge et al [Camidge et al. Lancet Oncol. 2012;13(10):1011-9]).

Enriched Other Cohort

MET Exon 14-Positive NSCLC Patients

- The safety profile of crizotinib in patients with MET exon 14-positive NSCLC was generally consistent with the established safety profile of crizotinib.

- Crizotinib provided meaningful clinical benefit as evidenced by objective responses that were rapid and durable, with complete responses in some cases.

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- The ORR based on derived investigator tumor assessment was 38.8% (N=85); 3 (3.5%) patients had a CR, 30 (35.3%) patients had a PR, and a further 35 (41.2%) patients had stable disease as their BOR. Median TTR was 7.6 weeks, median DR was 9.1 months, median PFS was 7.6 months and median OS was 20.0 months.

Enriched Other – Other Cancers

- The safety profile of crizotinib in other cancer patients (with molecular markers other than ALK-positive NSCLC and ROS1-positive NSCLC, that could confer sensitivity to crizotinib), was generally consistent with the established safety profile of crizotinib.

- The antitumor activity was lower than that observed for patients with ALK-positive and ROS1-positive NSCLC.

  - The ORR was 8.2% (N=61); 1 (1.6%) patient had a CR, 4 (6.6%) patients had a PR, and a further 19 (31.1%) patients had stable disease as their BOR.

Drug-Drug Interaction Cohorts

- There were no new crizotinib safety signals when coadministered with rifampin during the Rifampin DDI substudy (Rifampin DDI Report).

- There were no new crizotinib safety signals when coadministered with itraconazole during the Itraconazole DDI substudy.

- Efficacy was not evaluated in the DDI cohorts.

Pharmacokinetics:

Dose Escalation and RP2D Cohorts

The following conclusions were drawn from crizotinib PK data that were available for:

i) A total of 204 patients, 37 of whom were receiving crizotinib 50 to 200 mg QD or 200 to 300 mg BID in the Low Dose escalation cohort and 167 of whom were from the RP2D cohorts, as reported in the Interim CSR, with updates made based on the database snapshot date for this final CSR, and

ii) A total of 28 patients receiving crizotinib 300 to 800 mg QD in the High Dose escalation cohort, which were combined with data from patients on QD dosing schedule in the Low Dose escalation cohort, and other patients with different tumor types receiving crizotinib 250 mg BID, as reported in this final CSR:

- *After single oral doses of crizotinib, peak plasma concentrations were achieved approximately 4 hours postdose, and the terminal elimination half-life was 42.4 hours; food did not markedly change crizotinib systemic exposure* (Interim CSR).

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- After multiple oral BID and QD doses of crizotinib, steady state was reached within 15 days (Interim CSR).

- After multiple dosing, dose-proportional increases in crizotinib exposure were observed over the dosing range of 200 to 300 mg BID and 100 to 800 mg QD.

- There was no overt difference in crizotinib PK in patients with NSCLC with various gene abnormalities and other tumor types tested in this study.

Drug-Drug Interaction Cohorts

- *Crizotinib 250 mg BID increased the AUC of MDZ by 3.65-fold after repeated administration, indicating that crizotinib is a moderate CYP3A inhibitor* (Interim CSR).

- *Coadministration of multiple doses of crizotinib 250 mg BID with rifampin (600 mg QD), a strong CYP3A inducer, decreased steady-state AUC_{tau} and C_{max} of crizotinib by 84% and 79%, respectively, compared to crizotinib treatment alone* (Rifampin DDI Report).

- *Coadministration of crizotinib (250 mg QD) with itraconazole (200 mg QD), a strong CYP3A inhibitor, increased steady-state AUC_{tau} and C_{max} of crizotinib by 57% and 33%, respectively, compared to crizotinib administered alone* (Itraconazole DDI Report).

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