SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-42756493 Erdafitinib

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Status: Approved

Date: 3 January 2020

Prepared by: Janssen Research & Development, LLC

Protocol No.: 42756493HCC1001

Title of Study: A Phase 1/2a Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of JNJ-42756493, a pan-Fibroblast Growth Factor Receptor (FGFR) Tyrosine Kinase Inhibitor, in Subjects with Advanced Hepatocellular Carcinoma (HCC)

NCT No.: NCT02421185

Clinical Registry No.: CR106971

Principal Investigator: Chia-Jui Yen, MD, National Cheng Kung University Hospital, PPD, China

Study Center(s): Mainland China: 5 sites; Korea: 4 sites; China Taiwan: 4 sites.

Publication (Reference): None

Study Period: 18 June 2015 (Date first subject signed informed consent) to 16 May 2019 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 1/2a

Objectives:

The primary objectives of this study were to determine a safe and tolerable Phase 2 dose (recommended Phase 2 dose [RP2D]) for erdafitinib in subjects with advanced HCC and to evaluate the objective response rate (ORR) of erdafitinib by modified Response Evaluation Criteria in Solid Tumors (mRECIST) at the RP2D in advanced HCC subjects with FGF19 amplification.

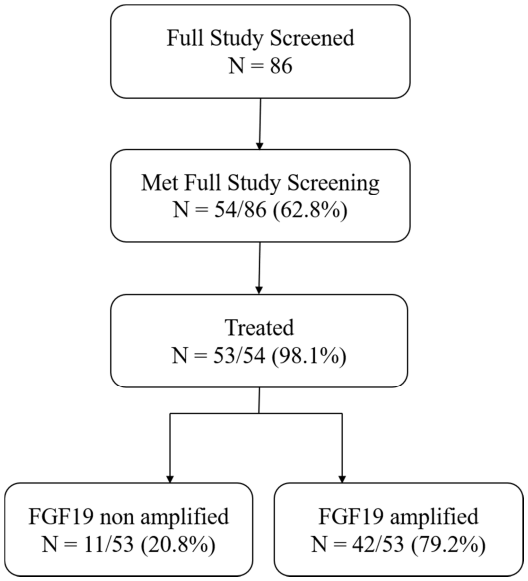
The secondary objectives of this study were to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and predictive biomarkers of erdafitinib, time to progression (TTP), progression-free survival (PFS), disease control rate (DCR, defined as the proportion of subjects with complete response [CR], partial response [PR], or stable disease [SD]), and duration of objective response (DOR).

Methodology:

This was an open-label, multicenter, 2-part, Phase1/2a study conducted at multiple sites in Asia, including South Korea, China Taiwan, and Mainland China, which evaluated erdafitinib in subjects with advanced HCC. The study comprised two parts: Part 1 Dose Escalation and Part 2 Dose Expansion. The Part 1 Dose Escalation Phase was designed to determine the RP2D based on the safety, PK, and PD data of erdafitinib. Part 2 was the Dose Expansion Phase to evaluate the efficacy and safety of the RP2Ds declared in Part 1 for erdafitinib in advanced HCC subjects with FGF19 amplification.

Number of Subjects (planned and analyzed):

Of the 54 subjects meeting full study screening, 53 (98.1%) were treated with erdafitinib. Forty-two treated subjects had FGF19 amplification by fluorescence in situ hybridization (FISH) testing (79.2%).



The actual numbers of subjects enrolled and treated as well as the efficacy and safety analysis population are shown below.

	8.00 mg (7 d on/7 d off)	10.00 mg (7 d on/7 d off)	12.00 mg (7 d on/7 d off)	8.00 mg (QD)	Total
Study population					
Subjects full-study screened					86
Subjects met full-study screening					54
Treated[a]	3	16	4	30	53
Response evaluable (RE)[b]	3	16	4	30	53

[a]The Treated Population was to consist of all subjects who received at least 1 dose of study drug. All safety analyses were to be performed using the Treated Population.
[b]The Response Evaluable (RE) analysis population was to consist of all subjects who were treated by at least 1 dose of study drug and had a baseline and at least 1 adequate post-treatment disease evaluation.

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Diagnosis and Main Criteria for Inclusion:

Asian subjects must have histologically or cytologically confirmed HCC (histology or cytology from prior tumor biopsy specimen was acceptable). HCC subjects with FGF19 amplification were eligible for enrollment in both Part 1 continuous dosing regimen and Part 2 of the study.

Subject must have advanced disease and meet all the following criteria,

a. Disease progression after previous surgical or local-regional therapy, if any

b. Disease ineligible for surgical or local-regional therapy or systemic therapy,

c. Received no more than 1 line of systemic therapy.

Test Product, Dose and Mode of Administration, Batch No.:

Erdafitinib was provided as tablets for oral administration:

- Intermittent dosing: erdafitinib was administered on Days 1 to 7 and Days 15 to 21; not on Days 8 to 14 and Days 22 to 28 of each 28-day cycle, and
- Continuous dosing: erdafitinib was administered once daily for 28 days on a 28-day cycle.

Batch numbers were as follows. Drug substance: HG-15J058, HG-15J059, GCL30, GCL32, HGL2V, HG-15J060, HG-15L073, GCL27, GCL29, HGL2W, HG-15J062, HG-15L074, GCL1W, GCL1Y, and HGL2X. Drug product: 4373470, 4372908, 4374735, 4374339, 4375471, 4372909, 4373471, 4374736, 4374480, 4375472, 4372237, 4372910, 4373472, 4374737, 4374481, and 4375473.

Duration of Treatment:

Subjects were to be treated until disease progression, unacceptable toxicity, or any other protocol-defined reason for treatment discontinuation. After discontinuation of study treatment, subjects were to have follow up for overall survival until the subject died, withdrew consent, was lost to follow-up, or the end of study, whichever was first.

Criteria for Evaluation:

Pharmacokinetic blood samples were collected at selected time points. Plasma concentrations of erdafitinib were measured by a validated analytical method under the direction of the sponsor. The level of α1-acid glycoprotein and the percentage of free fraction of erdafitinib in plasma were determined to calculate the unbound plasma concentration. Pharmacokinetic parameters were derived from plasma concentration versus time for erdafitinib. At the potential pharmacological active plasma level, metabolite profiling was performed and the need for further metabolite assessment in the clinical samples was evaluated.

Pharmacodynamic blood samples were collected at selected time points to assess the modulation of several soluble biomarkers related to the FGFR signaling pathway by erdafitinib. Blood samples were analyzed by enzyme-linked immunosorbent assay (ELISA) for soluble PD biomarkers of FGF19 and FGF23, as well as other potentially relevant biomarkers. Archived or fresh tumor samples from diagnostic biopsies or surgery and serum samples were collected for all subjects in Part 1 and Part 2. Tumor samples were analyzed for FGF19 amplification by FISH assay. Other potential biomarkers, such as FGFR4 were also explored. Tumor tissue was mandatory at predose (fresh biopsy or archived tumor tissue from previous diagnosis); whereas post-treatment tumor biopsies were optional. If applicable (when both pre- and post- treatment tissue samples were available), tumor samples were analyzed by an immunohistochemistry method for phosphorylated extracellular signal-regulated kinase (pErk) as well as other potentially relevant biomarkers.

Response assessment was determined for all subjects in accordance with mRECIST for HCC. During the treatment period, the disease was assessed at baseline and then every 6 weeks during the first 24 weeks on therapy. After 24 weeks, the frequency of radiological assessments was every 12 weeks until disease progression, unacceptable toxicity, or withdrawal from the study. For subjects discontinued study drug prior to disease progression, disease assessment was continued in the follow up period as though they were still under treatment, i.e. every 6-12 weeks as appropriate (at the investigator's discretion) until disease progression, initiation of subsequent anticancer therapy, death, withdrawal of consent, or a maximum of 6 months, whichever occurred first.

Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, electrocardiograms (ECGs), echocardiograms, physical examinations, clinical laboratory tests, and the Eastern Cooperative Oncology Group (ECOG) performance status at specified time points as described in the Time and Events Schedule of the protocol.

Statistical Methods:

The sample size of Part 1 was to be based on the observed toxicity and PK profile of erdafitinib. The total number of subjects to be enrolled in Part 1 depended on the dose level at which DLT of erdafitinib occurred or the RP2D was determined. Efficacy of erdafitinib on RP2Ds was to be evaluated by subjects in Part 2 combined with subjects in Part 1 who were treated at the selected RP2D and with FGF19 amplification. Approximately 40 subjects with FGF19 amplification were to be enrolled in the study on 2 possible RP2Ds declared in Part 1, among which at least 25 subjects were to be treated at the final selected RP2D in Part 2. With FGF19 amplified subjects treated with RP2D in Part 1, at least 28 subjects were to be treated in the final selected RP2D.

With at least 28 subjects who were to be treated at selected RP2D and with FGF19 amplification, an interim analysis was to be conducted after approximately 13 subjects were considered response evaluable. Enrollment was to be terminated for futility according to results of interim analysis

Individual best tumor responses and duration of response were assessed for each cohort in Part 1. The ORR (confirmed CR or PR) was analyzed on the response evaluable population including subjects in Part 2 combined with subjects in Part 1 who were treated at the selected RP2D and with FGF19 amplification. Additionally, the following efficacy analyses were performed to explore the clinical activity of erdafitinib on the treated population, including TTP, PFS, and DOR. The ORR (confirmed CR or PR), DCR, TTP, PFS, and DOR were also explored based on subjects in Part 2 combined with Part 1 who were treated at unselected RP2D and with FGF19 amplification. Safety summaries generated, based on the treated population, included summaries for treatment-emergent adverse events (TEAEs), laboratory results, vital signs and ECG results.

RESULTS:

Of the 54 subjects meeting full study screening, 53 subjects (98.1%) were treated, with 21 subjects for Part 1 and 32 subjects for Part 2. The subjects were treated across the 4 dose regimens, including 30 subjects in the 8-mg continuous dosing regimen, 3 subjects in the 8-mg intermittent dosing regimen, 16 subjects in the 10-mg intermittent dosing regimen and 4 subjects in the 12-mg intermittent dosing regimen. Forty-two treated subjects (79.2%) had FGF19 gene amplification. Two RP2Ds were defined in Part 1 of the study: 10-mg intermittent dose was the first selected and 8-mg continuous dose was the second selected RP2D. Taken together with all the emerging data from other global trials for erdafitinib program, 8-mg continuous dose was selected as the final RP2D for further expansion in HCC indication.

The median age for subjects in all regimens was 56.0 years (range 31 to 74 years) and the majority of subjects were male (44 subjects, 83.0%). All the subjects entered the study with Child Pugh Score of Class A and most with BCLC staging C (48 subjects, 90.6%) as well as ECOG performance status 0 (36

subjects, 67.9%). The median time from progression/relapse since the last line of treatment to first dose of study drug was 49 days and the median time from initial diagnosis to first dose was 683.0 days. All the

subjects had received prior systemic therapy for HCC, with sorafenib (51 subjects, 96.2%) as the most common prior systemic therapy. Results in 8-mg continuous dosing regimen were generally consistent with all regimens combined.

There were 4 subjects (7.5%) with major protocol deviations in the study, including 2 subjects received wrong treatment or incorrect dose, 1 subject developed withdrawal criteria but not withdrawn, and 1 subject entered the study but didn't satisfying all inclusion or exclusion criteria. None of these deviations led to exclusion of data from the safety, efficacy, PK, PD, and biomarker analyses.

The median treatment duration was 2.3 months and the median dose intensity was 6.0 mg/day in all regimens combined. Fifty-three subjects discontinued study treatment, primarily due to progressive disease (48 subjects, 90.6%). The other causes leading to treatment discontinuation included AEs (3 subjects, 5.7%), death (1 subject, 1.9%) and patient's refusal (1 subject, 1.9%). All the 53 subjects discontinued study, and the reasons were progressive disease (40 subjects, 75.5%), subsequent therapy (8 subjects, 15.1%), death (3 subjects, 5.7%), withdrawal of consent (1 subject, 1.9%) or AE (1 subject, 1.9%).

EFFICACY RESULTS:

Two responders (CR or PR, 3.8%, 95% CI: 0.5%, 13.0%) were observed for all regimens combined (in 10-mg intermittent dosing regimen, with FGF19 amplification) and none for the 8-mg continuous dosing regimen. The DCR were 30.2% (95% CI: 18.3%, 44.3%) and 36.7% (95% CI: 19.9%, 56.1%), respectively. Among the 2 responders (PR) the DOR were 6.93 months and 23.59 months, respectively.

Other time to event outcomes included median PFS (1.58 months [95% CI: 1.38, 2.60] for all regimens combined and 1.58 months [95% CI: 1.38, 2.79] for 8-mg continuous dosing regimen) and median TTP (1.58 months [95% CI: 1.41, 2.60] for all regimens combined and 1.58 months [95% CI: 1.38, 2.79] for 8-mg continuous dosing regimen). No specific finding of interest deserves further investigation for all subgroups of DCR and PFS.

Subjects with FGF19 amplification (n=42) had an ORR of 4.8% (2 subjects) and a DCR of 35.7% (15 subjects). The DCR for those without FGF19 amplification (n=11) was 9.1% (1 subject). For biomarker positive patients in all regimens combined, the median PFS was 1.59 months (95% CI: 1.41, 2.76), while the median PFS of those without FGF19 amplification was 1.31 months (95% CI: 0.95, 2.60).

PHARMACOKINETIC RESULTS:

Erdafitinib has high protein binding, with fraction unbound to plasma proteins on average ranged from 0.267% to 0.528% for all PK evaluable subjects (in both Part 1 and Part 2 of the study) among different cohorts.

After a single dose in the 21 subjects with serial PK sampling in Part 1 of the study, T_{max} values ranged from 1.00 to 6.00 hours post-dose across 8- to 12-mg dose cohorts (1.00-5.90 hours for subjects in the intermittent dosing regimen; 2.20-6.00 for subjects in the continuous dosing regimen), and was not dose-dependent. After C_{max}, the plasma concentration-time profile declined with a long half-life. With limited sample size in this study, C_{max} and AUC_{0-24} did not show clear relationship with change of dose.

In the intermittent dosing regimens after 7 days, median T_{max} times ranged from 2.0 to 5.9 hours post-dose. The accumulation ratios ranged from 2.72-2.82 for C_{max} and were 2.56 to 3.70 for AUC_{TAU}. In the continuous dosing regimen after 8 days, median T_{max} times ranged from 1.9 to 7.0 hours post-dose. The accumulation ratios were 2.32 for C_{max} and 2.73 for AUC_{TAU}.

At steady state (on Cycle 1 Day 21 of continuous dosing regimen), mean accumulation ratios based on C_{max} and AUC_{TAU} were 2.57 and 2.84, respectively. Total apparent clearance (CL/F) ranged from 0.436 to 0.562 L/h and did not show any consistent or relevant dependency on the administered dose. Overall, erdafitinib has slow clearance.

Dose proportional was observed in free erdafitinib C_{max} on Cycle 1 Day1 dosing and both free erdafitinib C_{max} and AUC_{0-24} on Cycle 1 Day 7 across 8-mg, 10-mg and 12-mg intermittent dosing. However, the results for the relationship between dose and PK parameters (both total and free erdafitinib, C_{max}, AUC_{0-24} and AR) should be interpreted with caution due to very small sample size and variability observed for unbound fraction.

SAFETY RESULTS:

Overall Summary of Treatment-emergent Adverse Events; Treated Subjects (Study JNJ42756493-HCC1001)

	8.00 mg (7 d on/7 d off)	10.00 mg (7 d on/7 d off)	12.00 mg (7 d on/7 d off)	8.00 mg (QD)	Total
Number of subjects in treated population	3	16	4	30	53
TEAE					
Any grade	3 (100.0%)	16 (100.0%)	4 (100.0%)	30 (100.0%)	53 (100.0%)
Grade ≥3	2 (66.7%)	7 (43.8%)	1 (25.0%)	14 (46.7%)	24 (45.3%)
Treatment-emergent serious adverse Events					
Any grade	2 (66.7%)	5 (31.3%)	1 (25.0%)	4 (13.3%)	12 (22.6%)
Grade ≥3	1 (33.3%)	4 (25.0%)	1 (25.0%)	4 (13.3%)	10 (18.9%)
Treatment-emergent drug-related adverse Events					
Any grade	2 (66.7%)	15 (93.8%)	4 (100.0%)	30 (100.0%)	51 (96.2%)
Grade ≥3	0	3 (18.8%)	0	11 (36.7%)	14 (26.4%)
Treatment-emergent drug-related serious adverse events	0	3 (18.8%)	0	0	3 (5.7%)
Treatment-emergent adverse events leading to dose reduction	0	1 (6.3%)	1 (25.0%)	13 (43.3%)	15 (28.3%)
Treatment-emergent adverse events leading to dose interruption	2 (66.7%)	6 (37.5%)	1 (25.0%)	22 (73.3%)	31 (58.5%)
Treatment-emergent adverse events leading to treatment discontinuation	0	1 (6.3%)	0	2 (6.7%)	3 (5.7%)
Treatment-emergent serious adverse events leading to hospitalization	2 (66.7%)	5 (31.3%)	1 (25.0%)	4 (13.3%)	12 (22.6%)
Treatment-emergent adverse events leading to death	0	1 (6.3%)	0	0	1 (1.9%)

Note: Treatment-emergent adverse events are defined as adverse events with onset or worsening on or after date of first dose of study treatment up to and including 30 days after date of last dose of study medication. Note: Percentages are calculated with the number of subjects in treated population of each treatment group as the denominator.

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Safety analyses from HCC1001 study were based on the total number of subjects treated with at least one dose of study drug, across all dosing regimens (n=53).

All treated subjects in all regimens (n=53) experienced at least one TEAE. The most commonly reported TEAEs (incidence greater than 30%) were hyperphosphatemia (47 subjects, 88.7%), paronychia (17 subjects, 32.1%) and dry mouth (16 subjects, 30.2%). These events are largely non-systemic and non-life threatening. The most frequent (>5%) Grade 3 or above TEAEs in all regimens were onycholysis (7 subjects, 13.2%), AST increased (6 subjects, 11.3%) and ALT increased (4 subjects, 7.5%).

Serious TEAEs were experienced by 22% (12/53) in all regimens, and 5.7% (3/53) of subjects had serious TEAEs that were considered to be related to erdafitinib. Individual terms were reported with low

frequency with none reported to be >6.0% (pyrexia [n=3, 5.7%]; general disorders; oesophageal varices haemorrhage [n=2, 3.8%] and aspartate aminotransferase increased [n=2, 3.8%]).

Treatment-emergent adverse events leading to dose reduction and interruption were reported for 28.3% (15/53) and 58.5% (31/53) of subjects respectively. For both interruption and reduction, the most

common TEAEs were hyperphosphatemia (30.2% [16 subjects] and 7.5% [4 subjects]), and onycholysis (11.3% [6 subjects] and 9.4% [5 subjects]). Three subjects (5.7%) permanently discontinued erdafitinib due to TEAEs (including cataract, onycholysis and paronychia; one subject for each event; all drug-related).

Three subjects (5.7%) in all regimens died as of the clinical cut-off, and 2 of these subjects (3.8%) died within 30 days of last dose. One subject died due to progressive disease, while the rest due to AEs (oesophageal varices haemorrhage and gastrointestinal haemorrhage, respectively), which were considered not related to erdafitinib.

Central serous retinopathy is a known class effect of FGFR inhibitors and has been identified as an adverse event of special interest (AESI). Other known class effects include hyperphosphatemia (47 subjects, 88.7%), nail toxicity (25 subjects, 47.2%), and skin toxicity (14 subjects, 26.4%), which are adverse events of clinical importance.

Ocular Adverse Events

Overall, 2 subjects (3.8%) experienced TEAEs of central serous retinopathy (which included PTs of chorioretinopathy and detachment of retinal pigment epithelium). All events were Grade 1. Central serous retinopathy was managed with dose interruptions for 1 subject in the 8-mg continuous dosing regimen; the other one in the 10-mg intermittent dosing regimen did not require dose modification. Neither subject permanently discontinued drug due to central serous retinopathy.

Twenty-one subjects (39.6%) in all regimens were reported to have eye toxicities of clinical importance (other than central serous retinopathy). Serious events were reported for 1 subject, dose reduction for 2 subjects, and dose interruption for 6 subjects. One subject discontinued erdafitinib due to the event of cataract.

Hyperphosphatemia

Hyperphosphatemia was the most frequently reported TEAE (47 of 53 subjects, 88.7%), but nearly all were Grade 1 or Grade 2 (45 subjects, 84.9%) and none were serious. Two subjects (3.8%) were reported to have Grade 3 hyperphosphatemia. Hyperphosphatemia was self-limiting, and started returning to baseline levels after 3 to 4 months even with continued erdafitinib administration. Phosphate elevations were managed primarily by dose modification and treatment with phosphate binders. Dose interruption was reported for 16 subjects and dose reduction for 4 subjects. No erdafitinib discontinuation due to hyperphosphatemia was reported.

Other Adverse Events of Clinical Importance

For all regimens combined, nail toxicity (25 of 53 subjects, 47.2%) and skin toxicity (14 of 53 subjects, 26.4%) were common with erdafitinib treatment, and were primarily Grade 1 or 2. Most subjects with nail or skin toxicities continued erdafitinib treatment, with 2 subjects discontinuing erdafitinib (onycholysis and paronychia, single occurrence).

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

The conclusions of the study are:

- A total of 53 subjects with HCC were treated. Two RP2Ds were defined in Part 1 of the study: 10-mg intermittent dose was the first selected and 8-mg continuous dose was the second selected RP2D. Taken together with all the emerging data from other global trials for erdafitinib program, 8-mg continuous dose was selected as the final RP2D for further expansion in HCC indication. Maximum tolerated dose was not determined.
- The ORR (CR and PR) was 3.8% based on the treated population, and the DCR (CR+PR+SD) was 30.2%. There were two responders overall observed from 10-mg intermittent dosing regimen, with DOR of 6.93 months and 23.59 months, respectively. Median PFS and median TTP for all regimens combined were both 1.58 months.
- The subjects having FGF19 amplification (42 out of 53 treated subjects) had an ORR of 4.8% (2 subjects). The FGF19 amplification rate in HCC was 33.7% and 29.7% respectively if excluding and including result failure. Aside from the 2 responders, little activity was observed in advanced HCC patients harboring FGF19 gene amplification.
- Erdafitinib, with dose modifications, was well tolerated as a single agent in HCC subjects. The safety profile shows that primarily FGFRi-specific, non-systemic toxicities were generally reversible, usually not dose limiting, and could be managed by supportive care and dose modification.
- Systemic exposure of erdafitinib generally increased with increasing doses. However, no clear trend was observed based on the limited sample size. Median T_{max} was observed at 2.30-4.10 hours post-dose after single dosing and 3.00-4.46 hours post-dose after repeated dosing. The accumulation ratios at steady state were 2.57 and 2.84 based on C_{max} and AUC_{TAU}, respectively. Erdafitinib was characterized by a low total apparent plasma clearance (on average 0.436-0.562 L/h).

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