Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Clinical Trial Results Synopsis

Study title:	An uncontrolled, open-label, multicenter, phase II safety study of BAY 73-4506 in patients with hepatocellular carcinoma (HCC)
Sponsor's study number	14596
NCT number	NCT01003015
EudraCT number:	2009-012570-13
Sponsor	Bayer HealthCare AG
Clinical phase:	II
Study objectives:	The primary objective of this study was to assess the safety profile of regorafenib in subjects with hepatocellular carcinoma (HCC). The secondary objective of the study was to evaluate efficacy, as assessed by: • Time to progression (TTP) • Objective response rate (ORR) • Disease control rate (DCR) (complete response [CR] + partial response [PR] + stable disease [SD]) • Overall survival (OS) Other objectives: • Trough concentrations of regorafenib and its metabolites in European subjects on Cycle 1, Day 15 and Cycle 2, Day 1 • Pharmacokinetics (PK) of regorafenib and its metabolites in Korean subjects on Cycle 1, Day 21
Test drug: **Name of active ingredient(s):** **Dose:** **Route of administration:**	Regorafenib (Stivarga, BAY73-4506) Regorafenib 160 mg (4 x 40-mg tablets) daily 3-weeks-on / 1-week-off Oral

Duration of treatment:	Subjects continued on treatment until one of the following occurred: • Progressive disease (PD) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.0 and Journal of the National Cancer Institute (JNCI) amendments regarding the characterization of HCC lesions • Clinical progression (defined as worsening of the Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≥3) • Death due to any cause • Unacceptable toxicity • Subject withdrew consent • Treating physician determined discontinuation of treatment was in the subject's best interest If, in the Investigator's opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing progression of disease, the subject could have continued treatment following consultation with the Sponsor.
Reference drug:	None
Indication:	Subjects with HCC, liver function status Child-Pugh Class A, who had failed prior systemic treatment with sorafenib
Diagnosis and main criteria for inclusion:	• Male or female patients ≥ 18 years of age • Histologic or cytologic confirmation of HCC or noninvasive diagnosis of HCC as per American Association for the Study of Liver Diseases criteria • Barcelona Clinic Liver Cancer (BCLC) stage Category A, B or C that cannot benefit from treatments of established efficacy with higher priority such as resection, liver transplantation, local ablation, chemoembolization, or systemic sorafenib • Liver function status Child-Pugh Class A. Child-Pugh status was to be calculated based on clinical findings and laboratory results during the screening period. • Failure to prior treatment with sorafenib (defined as radiologic progression under sorafenib therapy) • Local or loco-regional therapy (eg, surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed ≥ 4 weeks before first dose of regorafenib. • ECOG PS of 0 or 1 • Adequate bone marrow, liver, and renal function as assessed by the protocol-specified laboratory tests conducted within 7 days before start of study medication

Diagnosis and main criteria for inclusion, continued:	At least 1 naïve (not previously treated by loco-regional therapy) unidimensional measurable lesion by computed tomography (CT) scan or magnetic resonance imaging (MRI) according to RECIST v 1.0 and JNCI amendments regarding characterization of lesions in HCC.	
Methodology:	This was an uncontrolled, open-label, multicenter, Phase II safety study of regorafenib in subjects with HCC whose liver disease severity was categorized as Class A per Child-Pugh Classification. All subjects who met the entry criteria received regorafenib 160 mg once daily orally on a 3-weeks-on / 1-week-off schedule, in 4-week cycles. During the study period, subjects were to undergo evaluation for safety and efficacy. Drug accountability was performed every cycle. For an individual subject, treatment continued until disease progression, unacceptable toxicity, or another discontinuation criterion was met. If, in the Investigator's opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing progressive disease (PD), the subject could continue treatment following consultation with the Sponsor. Drug safety was monitored and evaluated continuously throughout the study including a 30-day Safety Follow-up Period by obtaining, reviewing, and analyzing data on adverse events (AEs), changes in laboratory values, vital signs, electrocardiograms (ECGs), Child-Pugh Class, and physical examination findings. Blood samples for PK analysis were collected to characterize the PK profile of regorafenib in subjects with mild hepatic impairment (Child-Pugh Class A). Tumors were measured at baseline and 6-week intervals during the active treatment period for the evaluation of TTP, ORR, and DCR. After 6 cycles of treatment, tumor measurements and evaluations were performed every 3 cycles (in Cycle 9, Cycle 12, Cycle 15, etc. [±14 days]).	
Type of control:	Uncontrolled	
Study center(s):	13 sites: Germany and Italy (5 sites each), South Korea (2 sites), Spain (1 site)	
Publication(s) based on the study (references):	Bruix J, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, Mazzaferro V, Wiest R, Reig M, Wagner A, Bolondi L. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. European Journal of Cancer 2013 Nov;49(16):3412-9	
Study period:	**First subject, first visit:** **Primary completion date:** **Study completion date**	22 SEP 2009 03 NOV 2010 13 MAR 2013
Early termination	Not applicable	
Number of subjects per treatment group:	36 subjects (28 from Europe, 8 from South Korea) Analyzed: 36 subjects	

Criteria for evaluation	Primary endpoint Safety variables: adverse events (AEs) / National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) toxicity grading, serious adverse events (SAEs); safety laboratory assessments; Child-Pugh score; electrocardiogram (ECG); and vital signs Secondary endpoint Efficacy variables: time to progression (TTP); objective response rate (ORR); disease control rate (DCR); and overall survival (OS) Other Safety Variables: Physical examinations, body weight / height, temperature, vital signs (blood pressure [BP], temperature, respiration, and heart rate), laboratory parameter assessments, 12-lead ECG, and left ventricular ejection fraction were assessed. Transaminases were closely monitored during the study. Laboratory monitoring with weekly checks of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin during the first 2 cycles of regorafenib dosing was required.
Other:	Clinical Pharmacology The following criteria were evaluated: • Trough concentrations of BAY 73-4506 and its metabolites in European subjects on Cycle 1, Day 15, and Cycle 2, Day 1. • PK parameters ($AUC_{(0-24)}$, C_{max}, T_{max}) in Korean subjects on Cycle 1, Day 21
Statistical methods:	As this was a noncomparative study, no inferential testing was performed; all analyses were descriptive only. All analyses were based on the total population. The final analysis for the primary endpoint was performed at primary completion with a data cutoff date of 03 NOV 2010. The primary completion date for this study was the date when each of the subjects assigned to treatment had been observed for at least 2 cycles, unless the subject discontinued earlier. The updated analysis of TTP and OS was performed as of the cutoff date of 01 MAR 2012, when data for the efficacy parameters, TTP, and OS were sufficiently mature such that further data collection would result in only minor changes in the Kaplan-Meier (KM) estimates of these parameters. The updated analysis of TTP and OS with a data cutoff date of 13 MAR 2013, was performed when all patients had discontinued treatment. All demographic and baseline characteristics, as well as subject disposition, were summarized for all treated subjects (intent-to-treat [ITT] population). Safety The Safety Population comprised all subjects who received at least 1 dose of study medication with at least 1 safety assessment after start of study medication. All AEs, treatment-emergent and hematologic/biochemical toxicities based on laboratory measurements, as well as drug-related AEs and SAEs, were summarized according to NCI CTCAE v 3.0 categories and worst

	grade. In addition, results of physical examination, vital signs, Child-Pugh class status, and ECG were summarized. Efficacy The Efficacy Population comprised the ITT population. For analyses of TTP and OS, the median time to event using the KM method together with its 95% confidence interval (CI) was presented, and survival curves were displayed. Summary statistics were displayed for ORR as well as DCR, and in addition for all best response categories: CR, PR, SD, and PD. Frequency counts and percentages with exact 95% CI were displayed.
Substantial protocol changes:	• Protocol Amendment 1, dated 25 NOV 2009, added 2 centers in South Korea, corrected omissions and errors, and clarified study procedures and data collection. • Protocol Amendment 3, dated 25 MAY 2010, changed the number of sites and the number of subjects to be enrolled, changed the urine analysis assessment categories, provided clarity regarding the timing of radiologic assessments, and incorporated additional but minor changes. • Protocol Amendment 4, dated 26 APR 2011, updated the name of the medical expert, specified the timing of tumor measurements and evaluations after 6 cycles of treatment, specified that an independent radiological review of images could occur in addition to the radiological assessment of the investigator, corrected the schedule of BP assessments, added text to the tumor measurements in the Schedule of Procedures, specified that after 6 cycles of treatment the Day 15 assessments could be performed at the discretion of the investigator, specified the timing of the final statistical analyses of efficacy and safety data, and incorporated minor editorial changes. • Protocol Amendment 5, dated 26 JUL 2011, added text and an in-text table regarding the importance of monitoring transaminases and bilirubin levels during the study in order to detect liver function abnormalities and take appropriate action dependent on the severity of the abnormality, added Investigator's notification to the Sponsor for all AEs of special interest, added reference to CIOMS-IV and an AE of special interest, and incorporated minor editorial changes.

Study subjects

A total of 56 subjects were enrolled, 20 were screen failures, and 36 (100%) were treated, of which none were ongoing as of the data cutoff (13 MAR 2013) and 36 (100%) discontinued treatment. The primary reasons subjects discontinued study treatment were: AEs associated with clinical progression, as well as those not associated with clinical progression, clinical and radiological disease progression, death, withdrawal by subject, and protocol violation.

Of the 36 subjects who entered safety follow-up, 9 (25.0%) did not complete safety follow-up because of death (6 [16.7%]); withdrawal by subject (2 [5.6%]); and lost to follow-up (1 [2.8%]). Twenty-eight (77.8%) of 36 subjects were reported as having entered survival follow-up, of which 26 (72.2%) of 36 subjects discontinued the survival follow-up period. The primary reasons for discontinuation during survival follow-up were death (22 [61.1%]), withdrawal by subject (2 [5.6%]), and lost to follow-up (2 [5.6%]).

More than 85% of the subjects were male; more than two-thirds were White; nearly one-third were Asian; none were Hispanic or Latino; approximately two-thirds were ≤ 65 years of age (median=61.0 years [range 40 to 76 years]), and both the mean and median body mass index (range 16.6 to 33.2 kg/m^2) were <25 kg/m^2.

Per protocol, all subjects had a medical history of HCC. In addition, 24 of 36 subjects had a medical history of liver cirrhosis. Frequent and relevant medical history findings were:

- Hepatitis B virus (HBV) in 18 subjects, 3 of whom had chronic HBV infections
- Hepatitis C virus (HCV) in 13 subjects, 3 of whom had chronic HCV infections
- Esophageal varices in 6 subjects

All enrolled subjects (36 [100%]) received prior diagnostic procedures and prior systemic anticancer therapy. One-half of the subjects (18 [50.0%]) received a prior procedure with therapeutic purposes. None of the subjects received prior systemic anticancer therapy with adjuvant or curative intent. All subjects received sorafenib as a prior systemic anticancer therapy. The median duration of prior treatment with sorafenib was 137 days (range 15 to 993 days).

Efficacy

All 36 (100%) subjects assigned to treatment were valid for the ITT set and the Safety Analysis Set.

Treatment duration

Less than half (44.4%) of the 36 subjects received >24 weeks of study therapy (including interruptions); the median treatment duration was 5.0 cycles. The mean (sd) actual daily dose of study drug was 142.98 (21.72) mg, and the median actual daily dose was 158.11 mg (range: 90.4 to 160.0 mg).

Dose reduction and dose interruption / delay

A total of 17 (47.2%) of 36 subjects required at least 1 dose reduction: 7 (19.4%) of 36 subjects required 1 dose reduction and 8 (22.2%) of 36 subjects required 2 dose reductions. In addition, 1 (2.8%) subject was reported as having 3 dose reductions and 1 (2.8%) subject was reported as having 5 dose reductions. Both of these 2 subjects were reported to have 2 actual dose level reductions; one of the dose reductions was a duplicate report. The other subject was rechallenged twice with the protocol-specified dose and once with a lower-than-protocol dose after dose reduction; these actions represented 5 dose modifications but only 2 dose level reductions. The primary reasons for a dose reduction (by number [%] of events) were: AE per protocol (10 [27.8%]), AE (8 [22.2%]), and other (3 [8.3%]).

Thirty-five (97.2%) of 36 subjects required either a dose interruption or dose delay, of which 11 (30.6%) subjects required more than 3 interruptions / delays. The primary reasons for an interruption / delay in dosing (by number [%] of events) were: AE (23 [63.9%]), AE per protocol (18 [50.0%]), subject error (11 [30.6%]), other (13 [36.1%]), and laboratory or test abnormality per protocol (1 [2.8%]).

Response to regorafenib with respect to RECIST criteria

Thirty-six (100%) subjects were evaluable for response per RECIST criteria. Percentages were calculated based on the ITT dataset which comprised 36 subjects. More than two-thirds of the subjects (25 [69.4%]) achieved SD. Less than 15% of the subjects (5 [13.9%]) experienced PD as best response. One (2.8%) subject (95% CI 0.1% – 14.5%) achieved PR after 41 days on treatment.

The duration of best response was a censored observation at 168 days. The maximum reduction of tumor size was -33%. No subjects achieved a CR. Five subjects (13.9%, 95% CI 4.7% – 29.5%) were not evaluable (not applicable) for response per RECIST criteria as they did not have post-baseline tumor assessments.

The DCR was 72.2% (95% CI 54.8% – 85.8%) calculated on the basis of 25 subjects with SD + 1 subject with PR ÷ 36, the number of treated subjects. Based upon the 1 subject who achieved PR and the absence of CR, the ORR was 2.8% (95% CI 0.1% – 14.5%).

Best change from baseline in sum of diameters of target lesions

Two subjects had as best change from baseline an increase above 20%, which is equivalent to PD. Nine (25.0%) subjects had as best change an increase from 1% to 12%, 8 (22.2%) subjects had no change, and one-

third of the subjects (12 [33.3%]) showed a reduction in sum of longest diameters of target lesions. One subject had as best change a decrease above 30%, which is equivalent to PR.

Overall survival

Among the 36 subjects evaluated for OS, 28 (77.8%) subjects died and 8 (22.2%) were censored before or were alive at the cutoff date. Median OS was 419 days (range excluding censored values: 43 to 881 days). The OS rate at 90 days was 0.88 (95% CI 0.72 - 0.95) and at 180 days was 0.79 (95% CI 0.61 - 0.89).

Time to progression

Among the 36 subjects evaluated for TTP, 22 (61.1%) subjects progressed and 14 (38.9%) subjects were censored before the cutoff time. The median KM estimate for TTP was 131 days (approximately 4.3 months).

Efficacy conclusions

The present study was an uncontrolled single-arm study and therefore allowed no statistically supported efficacy conclusions based solely on its results. The analysis of the change in the sum of the longest target lesion diameters suggested that some efficacy of regorafenib was present. This was supported by the finding that the DCR was 72.2% and the median Kaplan Meier estimate for TTP was 131 days (approximately 4.3 months).

Clinical pharmacology

Trough concentrations in European subjects were collected on Cycle 1, Day 15, and Cycle 2, Day 1. Full profile samples for PK analysis were collected on Cycle 1, Day 21 in Korean subjects.

The trough concentrations in European subjects showed high variability and a longer half-life for metabolite M5 (BAY 81-8752) than for BAY 73-4506 or metabolites M2 (BAY 75-7495).

The concentration-time profile in Korean subjects showed multiple peaks following dosing and large intrasubject variability in the PK parameters.

Clinical pharmacology conclusions

The concentrations and PK parameters of BAY 73-4506 and its metabolites M2 (BAY 75-7495) and M5 (BAY 81-8752) show large variability and a significant concentration of M5 remaining in plasma following a 7-day washout.

Safety evaluation

All 36 (100%) subjects experienced at least 1 TEAE. For 24 (66.7%) subjects, the worst CTCAE Grade was 3 or 4. Eight (22.2%) subjects died, and the cause of death (hematoma) for 1 of these subjects was determined by the Investigator to be drug-related.

Although nearly all subjects (35 [97.2%]) experienced at least 1 drug-related TEAE, few subjects (5 [13.9%]) experienced an SAE determined by the Investigator to be drug-related.

For 27 (75.0%) of 36 subjects, 1 or more TEAEs led to dose modifications. The most frequent TEAEs leading to dose modification were hand-foot skin reaction (HFSR), fatigue, and diarrhea. For 21 (58.3%) of these 36 subjects, at least 1 of the TEAEs leading to dose modification was assessed as a drug-related TEAE. For approximately one-half (19 [52.8%]) of the subjects, at least 1 TEAE led to permanent discontinuation of study drug. The most frequent TEAE resulting in permanent discontinuation of study drug was fatigue. For 7 (19.4%) of 36 subjects, at least 1 of the TEAEs leading to permanent discontinuation was assessed as a drug-related TEAE.

The most frequently experienced TEAEs (reported in ≥25.0% subjects) were: fatigue in 28 (77.8%) subjects; diarrhea in 20 (55.6%) subjects; HFSR in 19 (52.8%) subjects; anorexia in 18 (50.0%) subjects; hypothyroidism in 17 (47.2%) subjects; nausea and pain abdomen not otherwise specified (NOS), each in 15 (41.7%) subjects; voice changes in 14 (38.9%) subjects; hypertension, fever, hemoglobin and constipation, each in 13 (36.1%) subjects; bilirubin (hyperbilirubinemia) in 11 (30.6%) subjects; weight loss and ascites, each in 10 (27.8%) subjects; and pain, head/headache in 9 (25.0%) subjects.

Eight (22.2%) subjects experienced at least 1 TEAE of worst Grade 5 by CTCAE term: hematoma (1 subject); CNS hemorrhage (2 subjects); death not associated with CTCAE term, disease progression NOS (2 subjects); liver dysfunction (2 subjects); and metabolic / lab, other (1 subject).

Six (16.7%) subjects experienced at least 1 TEAE of worst Grade 4 by CTCAE term as follows: one experienced hyperuricemia and hemoglobin; one experienced cardiac ischemia / infarction; one experienced hyperbilirubinemia, two experienced fatigue; one experienced conduction abnormality, AV block - third-degree (complete AV block); and one experienced CNS hemorrhage, hyperbilirubinemia and AST.

The most frequent Grade 3 TEAEs overall were fatigue and bilirubin (hyperbilirubinemia) (each 6 [16.7%]), followed by HFSR and abdominal pain (each 5 [13.9%]).

The most frequent drug-related TEAEs (reported by ≥25% of subjects) were: fatigue in 20 (55.6%) subjects; HFSR and diarrhea, each in 19 (52.8%) subjects; hypothyroidism in 15 (41.7%) subjects; hypertension and anorexia, each in 13 (36.1%) subjects; nausea in 12 (33.3%) subjects; and voice changes and constipation, each in 10 (27.8%) subjects. Hematoma (1 [2.8%] subject) was the only Grade 5 drug-related TEAE, and fatigue (1 [2.8%] subject) was the only Grade 4 drug-related TEAE. The most frequent Grade 3 drug-related TEAEs overall were fatigue and HFSR, each in 5 (13.9%) subjects, followed by bilirubin (hyperbilirubinemia), diarrhea, and hypophosphatemia, each in 2 (5.6%) subjects.

Nineteen (52.8%) subjects experienced at least 1 TEAE that led to permanent discontinuation of study drug treatment. For 7 (19.4%) subjects, these TEAEs were determined by the Investigator to be drug-related; in 1 subject, 4 of 5 TEAEs leading to discontinuation of study drug were assessed as drug-related.

Twenty-eight subjects (77.8%) died as of the database cutoff on 13 MAR 2013. Twenty deaths occurred during survival follow-up with the cause of death reported as disease progression NOS. Eight (22.2%) deaths were flagged as treatment-emergent. The cause of death for 2 subjects was attributed to CTCAE term "Death not associated with CTCAE term, disease progression NOS". One (2.8%) treatment-emergent death was judged to be related to study drug.

There was 1 Grade 1 SAE (constitutional symptoms – other [specify]). This SAE was experienced by 1 subject who also experienced a Grade 5 SAE hematoma. There was 1 Grade 2 SAE (hearing [without monitoring program]) experienced by 1 subject who also experienced a Grade 4 SAE of cardiac ischemia / infarction. Both of these Grade 1 and Grade 2 SAEs were not counted in the overall total number of subjects with ≥1 SAE. There was 1 Grade 2 SAE of fever, 1 Grade 2 SAE of GI – other (specify), and 1 Grade 2 SAE of pleural effusion.

A total of 8 (22.2%) subjects experienced SAEs that were Grade 5 (death), resulting in a fatal outcome. Five of the 8 subjects who died did so due to fatal liver dysfunction (2 subjects), fatal hematoma (1 subject), fatal intracranial hemorrhage (1 subject), and fatal intracerebral hemorrhage (1 subject).

Grade 3 SAEs occurring in only 1 (2.8%) subject were: liver dysfunction; hemoglobin; bilirubin (hyperbilirubinemia); allergic reaction; supraventricular arrhythmia, atrial fibrillation; diarrhea; hemorrhage, GI, duodenum; hemorrhage, GI, rectum; infection-other (specify); ataxia; encephalopathy; pain, abdomen NOS; pain, other (specify); and intraoperative injury – other (specify).

Serious adverse events assessed as Grade 4 included hemoglobin (1 [2.8%] subject); fatigue (2 [5.6%] subjects); bilirubin (hyperbilirubinemia) (1 [2.8%] subject); conduction abnormality, AV block – 3rd degree (complete AV block) (1 [2.8%] subject); and cardiac ischemia / infarction (1 [2.8%] subject).

Five subjects (13.9%) were determined by the Investigator to have experienced at least 1 treatment-emergent SAE that was causally related to study drug. Six subjects underwent dose modification as a result of a treatment-emergent SAE. Eleven subjects experienced an SAE leading to permanent discontinuation.

The most frequently experienced Grade 3 hematological and biochemical toxicity overall was gamma-glutamyl transferase (GGT) in 13 (36.1%) subjects, followed by hypophosphatemia in 10 (27.8%) subjects, hyponatremia in 9 (25.0%) subjects, and lymphopenia in 6 (16.7%) subjects. Most toxicities were Grade 1 or Grade 2 in intensity; only events of bilirubin, amylase, and hypoglycemia (1 subject each) were Grade 4. The hematological and biochemical toxicities reported in more than three-fourths of the subjects were AST in 33

(91.7%) subjects, hemoglobin in 31 (86.1%) subjects, and alkaline phosphatase and GGT, each in 30 (83.3%) subjects.

The median (95% CI) time to ECOG worsening was 148 (95% CI 61 - 289) days. Eighteen (50.0%) subjects showed a change in Child-Pugh Classification from A to either B or C post-baseline.

Overall conclusions

Regorafenib showed activity in the treatment of subjects with HCC, liver function status Child-Pugh Class A, who failed prior systemic treatment with sorafenib. The following conclusions can be made:

- Regorafenib can be administered safely to patients with HCC who have progressed on prior sorafenib treatment, and has an AE profile that is manageable and not unusual for this patient population.
- The KM estimate for TTP was 131 days (approximately 4.3 months) and the DCR was 72.2%.
- Median OS was 419 days (range: 18 to 981 days); the OS rate was 0.88 (95% CI 0.72 - 0.95) at 90 days and 0.79 (95% CI 0.61 - 0.89) at 180 days.

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
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Sponsor in Germany (if applicable)	
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Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Stivarga
Brand/Trade Name(s) ex-US	
Generic Name	Regorafenib
Main Product Company Code	BAY73-4506
Other Company Code(s)	
Chemical Description	IUPAC Name: 4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide
Other Product Aliases	

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