Phase 1/2, Open-Label, Multi-Center Trial to Assess Safety, Tolerability, Pharmacokinetics , Pharmacodynamics, and Efficacy of CLN-081 in Patients with Locally-Advanced or Metastatic Non-Small Cell Lung Cancer Harboring EGFR Exon 20 Insertion Mutations Who Have Previously Received Platinum-Based Systemic Chemotherapy

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Phase 1Primary ObjectivesTo assess the safety and tolerability of orally administered CLN-081 monotherapy.To define the maximum tolerated dose (MTD) of orally administered CLN-081 monotherapy.Secondary ObjectivesTo assess the anti-tumor activity.To...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON56206

Source
ToetsingOnline

Brief title
CLN-081-001 (REZILIENT1)

Condition

- Respiratory tract neoplasms

Synonym
lung cancer, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Cullinan Oncology Inc.
Source(s) of monetary or material Support: Cullinan Oncology Inc.

Intervention

Keyword: CLN-081, EGFR exon 20 insertion mutations, Non-small cell lung cancer, open-label

Outcome measures

Primary outcome

The rate and severity of treatment emergent AEs, DLTs, SAEs, incidence of

safety laboratory assessment abnormalities

Incidence of abnormalities in vital signs or other clinical safety assessments

ORR based upon both independent central review and local Investigator

assessment by RECIST v1.1

Tumor response characteristics including DOR, DCR, PFS, and time to tumor

response based upon both independent central review and local investigator

assessment and OS

CLN-081 PK

Metabolite identification

Other biomarker data

Diagnostic tumor samples

Please refer to protocol for Primary Objectives of Phase 2a, Module A, Module B part 1 and Module B part 2.

Secondary outcome

To assess the anti-tumor activity of orally administered CLN-081 monotherapy.

To characterize select pharmacokinetics (PK) parameters associated with orally administered CLN-081 monotherapy.

To assess activity of orally administered CLN-081 monotherapy in patients with known central nervous system (CNS) disease.

Please refer to protocol for Secondary Objectives of Phase 2a, Module A, Module B part 1 and Module B part 2.

Study description

Background summary

Among cancer-related deaths, deaths from lung cancer are the most common in the world, and approximately 80% to 85% of lung cancers are classified NSCLC1. Somatic mutation of the EGFR, most of which are concentrated in the region of exon 18 to 21, is a major oncogenic driver and is present in approximately 30% to 50% and 10% to 20% of NSCLC in Asians and in Americans and Western Europeans, respectively2-5. EGFR is a transmembrane glycoprotein and belongs to the ErbB family of tyrosine kinase receptors. Activating mutations in the EGFR kinase domain induce ligand-independent constitutive activation and subsequent downstream molecule phosphorylation, leading to cancer cell growth and survival6,7. Various tyrosine kinase inhibitors (TKIs) targeting EGFR mutations have been developed as anticancer agents: gefitinib, erlotinib, afatinib, for the primary treatment of patients with NSCLC harboring activating mutations, including exon 19 deletions and L858R, and osimertinib has been approved for treating patients with NSCLC harboring T790M acquired resistance mutations8-11. However, the clinical response of NSCLC driven by EGFR ex20ins mutations to EGFR TKIs is much lower8,12-15 because plasma concentrations of these drugs in clinical settings are kept low by dose-limiting toxicities (DLT) caused by wild type (WT) EGFR inhibition16-18.
However, about 4 to 10% of all EGFR mutations consist on insertions in exon 20. Unlike other EGFR mutations, patients with EGFR ex20ins rarely respond to

gefitinib, erlotinib, or afatinib, with response rates of only 8 to 11%.
Overall survival of patients with EGFR ex20ins mutations is similar to that of patients without EGFR mutant NSCLC but inferior to that of patients with EGFR exon 19 deletion or L858R advanced NSCLC. Novel targeted therapies that are safe and effective in patients with EGFR exon 20 insertions are lacking.
3.2 CLN-081
CLN-081 is a novel, orally available EGFR-TKI. Biochemical assays have shown that CLN-081 is selective for EGFR and its mutants over other kinases. In a cell-based assay using genetically engineered cell lines, CLN-081 potently inhibited intracellular phosphorylation of mutant EGFRs, including EGFRs harboring a wide spectrum of ex20ins mutations. Since its inhibitory activity against mutant EGFRs was more potent than that against WT EGFR, CLN-081 exerted a significant antitumor effect in vivo against cancer cells harboring EGFR ex20ins mutations19.

Study objective

Phase 1
Primary Objectives
To assess the safety and tolerability of orally administered CLN-081 monotherapy.
To define the maximum tolerated dose (MTD) of orally administered CLN-081 monotherapy.
Secondary Objectives
To assess the anti-tumor activity.
To characterize select pharmacokinetics (PK) parameters.

Phase 2a
Primary Objectives
To evaluate the objective response rate (ORR) of orally administered CLN-081.
To define the recommended phase 2 dose (RP2D) of orally administered CLN-081.
Secondary Objectives
To evaluate duration of response (DOR), disease control rate (DCR), median progression-free survival (PFS) and overall survival (OS), and landmark PFS and OS rates of patients treated with orally administered CLN-081.
To confirm the safety and tolerability of orally administered CLN-081.
To characterize select PK parameters and relationships with various measures of clinical response.

Module A
Primary Objective
To investigate the PK profile of single oral doses of 150 mg of CLN 081 with or without a high fat meal in patients with solid tumors
Secondary Objective
To assess the safety of single oral doses of 150 mg of CLN-081 with or without a high fat meal in patients with solid tumors

Module B, Part 1
Primary Objectives
To define the safety, tolerability and PK profile of CLN-081 administered as repeat doses of 150 mg BID in conjunction with food to patients with locally-advanced or metastatic non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) insertions in EGFR exon 20 (ex20ins) mutations.
To investigate whether administration of CLN-081 in conjunction with food can ameliorate the safety profile, of CLN-081 at a dose of 150 mg BID compared to historical experience with CLN-081 dosed at 150 mg BID in the fasted state.
Secondary Objectives
To evaluate ORR, as assessed by central review (ICR) of CLN-081 administered as repeat doses of 150 mg BID.
Investigate antitumor activity of CLN-081 150 mg BID given with food.
Evaluate concordance between local and central biomarker determination via CDx assay.

Module B, Part 2
Primary Objectives
Evaluate ORR and duration of response (DOR) by ICR of orally administered CLN-081 at RP2D
Secondary Objectives
To evaluate ORR and DOR by Investigator assessment.
To evaluate DCR, median PFS and OS, and landmark PFS and OS rates by ICR and investigator.
To confirm the safety and tolerability.
To further characterize select PK parameters of po-administered CLN-081 monotherapy and relationships with various measures of clinical response.
To evaluate the concordance between local determination of EGFR ex20ins mutational status and central determination via a candidate CDx assay.

Module C
Primary Objectives
To evaluate ORR and DOR by ICR of orally administered CLN-081 100 mg BID in patients whose disease has progressed after prior treatment with an agent for the treatment of EGFR ex20ins mutant NSCLC.
Secondary Objectives
To evaluate ORR and DOR by Investigator assessment of CLN-081 monotherapy among patients treated at 100 mg BID.
To evaluate DCR, median PFS and OS, and landmark PFS and OS rates at 6, 12, and 24 months by ICR among patients treated with CLN-081 monotherapy at 100 mg BID.
To confirm the safety and tolerability of CLN-081 monotherapy at 100 mg BID.
To further characterize select PK parameters of CLN-081 monotherapy and relationships with various measures of clinical response at 100 mg BID.
To evaluate the concordance between local determination of EGFR ex20ins mutational status and central determination via a candidate CDx assay

Study design

This is a Phase 1/2, open-label, multicenter, first-in-human trial to evaluate the safety and tolerability, PK, and antitumour efficacy of CLN-081 in patients with locally advanced or metastatic NSCLC harboring epidermal growth factorEGFR exon 20 insertion mutations, who have previously received platinum-based systemic chemotherapy.
For each patient, the trial will consist of three periods:
• Screening: Up to 28 days prior to the initiation of treatment.
• Treatment: CLN-081 will be dosed BID and/or once daily (QD) during each 21-day cycle (except Module A).
• Follow-Up: Patients will be followed for safety after study drug discontinuation and survival after entering long-term follow-up.
This trial is divided into several components, including the Phase 1 Dose Escalation, Phase 1 Dose Expansion, and Phase 2 Dose Expansion., as well as Module A (Food Effect PK Assessment Module), Module B, Part 1 (assessment of the impact of food on the safety and tolerability of CLN-081 at 150 mg BID), Module B, Part 2 (continued Phase 2 cohort extension at the confirmed RP2D of CLN-081), and Module C (patients with EGFR ex20in NSCLC whose disease has progressed during or after prior treatment with an agent approved by the US FDA for the treatment of EGFR ex20ins mutant NSCLC).

Enrolment to the Phase 1 Dose Escalation Phase 1 Dose Expansion, and the Phase 2 Dose Expansion components of the trial is complete.

Module A and Module B (described below) are the subject of the current amendment of the CLN-081-001 study.

Phase 1 Dose Escalation

Dose escalation in this trial was conducted utilizing an accelerated titration coupled with a Rolling Six design (R6).
• Dose escalation was to initially proceed according to the accelerated titration (AT) design, enrolling one new patient per dose level.
• Upon any instance of a CLN-081 related Grade >= 2 toxicity during Cycle 1, dose escalation was to convert to the R6 design in which a total of 3 to6 patients per dose level be enrolled.
•, In lieu of any CLN-081 related Grade >= 2 AEs, dose levels originally enrolled as accelerated titration cohorts may further be explored by using the R6 design should that dose level demonstrate serum concentration levels associated with efficacy in pre-clinical models

• Accelerated titration cohorts did not restrict prior EGFR tyrosine kinase inhibitors (TKI) exposure.
• R6 cohorts, in addition to their role in dose escalation, were to be assessed to determine whether a dose level meets criteria for expansion and patients

from R6 cohorts were also to be included in the efficacy population. Thus, restrictions on prior EGFR TKI exposure in an R6 cohort were the same as in the Phase 1 and 2a expansion cohorts. However, should an accelerated titration patient fit the R6 eligibility criteria for prior treatment with EGFR TKI, they could also have filled one of the R6 slots.
• In order to further characterize the activity of CLN-081 in patients who had received and were refractory to EGFR ex20ins-targeting drugs, the Safety Review Committee (SRC) may have elected to open cohorts of up to six patients at any dose level already declared safe based upon dose escalation procedures
Enrolment to this component of the CLN-081-001 study is complete.

Phase 1 Dose Expansion
During dose escalation, one or more cohorts may have been selected for expansion, enrolling up to a total of 13 response evaluable patients across a dose level in which >= 1 objective responses (ORs) were observed during dose escalation, and provided that dose was deemed tolerable. The total number of response evaluable patients enrolled in a given expansion cohort depnded upon the number of response evaluable patients enrolled during dose escalation. For instance, if 6 response evaluable patients were enrolled at a particular dose level during escalation, an additional seven would be enrolled in that dose level*s expansion.

Enrolment to this component of the CLN-081-001 study is complete.

Phase 2a Dose Expansion
Further dose expansion in the Phase 2a part of the trial may be explored. Up to an additional 23 response evaluable patients may be enrolled at any dose level in which >= 4 confirmed objective responses have been observed and pre-determined safety criteria have been met in the group of 13 response evaluable patients originally enrolled as part of that dose level*s Phase 1 escalation and expansion. Additionally, one or more cohorts may be added in which patients are dosed QD in addition to the initial BID dosing.

Enrolment to this component of the CLN-081-001 study is complete.

Please refer to protocol for full *Study design*

Intervention

The starting dose for CLN-081 was 30 mg twice a day and increased as per the protocol.

Study burden and risks

As this is a FIH trial, there is no human clinical data for CLN-081.
Preclinically, CLN-081*s toxicity profile is similar to that of other approved

EGFR inhibitors. Additionally, phototoxicity was observed in one in vitro study. A list of potential adverse events based upon CLN-081 preclinical safety profile is outlined in the IB. In animals, all adverse effects were reversible, i.e. they were transient and self-limiting, resolved when dosing stopped or were absent at the end of the recovery period. The same is likely to be true in human subjects, should any of these events occur. Assessment and observations to monitor for and manage these types of toxicities will occur throughout the trial.
Overall, the benefit-risk assessment for this Phase 1/2a study is therefore considered acceptable in light of the nonclinical data to date and design of the current study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

A patient who meets all of the following inclusion criteria will be eligible to participate in this study:
1. Histologically or cytologically confirmed recurrent and/locally advanced or metastatic NSCLC (all patients). For module A only, histologically or cytologically confirmed solid tumor with the exception of esophageal, gastric, pancreatic, hepatobiliary, or small bowel carcinomas, or history of gastric resection.
2. Documented EGFR exon 20 insertionex20ins mutation demonstrated by a validated test routinely used by each institutionlisted in Section 9.7 and performed in a Clinical Laboratory Improvement Amendments (CLIA-)-certified or equivalent laboratory (all patients other than Module A Food Effect PK Assessment Module). Institutions that don*t have access to these tests should contact the sponsor for assistance.
3. Prior treatment in the recurrent/metastatic disease setting including:
a. A platinum-based chemotherapy regiment (or other chemotherapy regimen if platinum-based chemotherapy is contra-indicated)
b. Any other approved standard therapy that is available to the patient, unless this therapy is contraindicated, intolerable to the patient, or is declined by the patient. In the case of a patient declining such therapy, documentation that the patient has been informed and declined should be documented in the medical record.
c. No prior therapy is required for patients enrolled on Module A.
d. Prior therapy with an agent approved by the local regulatory authorities for the treatment of EGFR ex20ins mutant NSCLC (Module C only).
4. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST 1.1.) (except for patients enrolled on Module A).
5. Age >= 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
7. Ability to take pills by mouth.
8. Have the following laboratory values:
a. Serum creatinine < 1.5 × ULNupper limit of normal (ULN) or if higher than normal range, calculated creatinine clearance (CrCl) must be >= 50 mL/min/1.73 m2 (if calculated by Cockroft-Gault formula, the actual body weight must be used for CrCl unless body mass index [BMI] >30 kg/m2 then lean body weight must be used).
b. Total bilirubin <= 1.5 × ULN unless prior history of Gilbert*s syndrome.
c. Aspartate transaminase and alanine transaminaseAST and ALT <= 2.5 × ULN, or <= 5 × ULN if due to liver involvement by tumor.
d. Hemoglobin >= 9.0 g/dL in the absence of transfusion <= 14 days prior to the first dose of study drug on C1D1.
e. Platelets >= 100 × 109 cells/L. in the absence of transfusion <14 days prior to the first dose of study drug on Cycle 1 Day 1 (C1D1).
f. Absolute neutrophil count >= 1.5 ×109 cells/L.
9. For Module A patients only: patients must have a negative coronavirus

disease 2019 (COVID 19) polymerase chain reaction test prior to enrolment.
10. For Module B and Module C patients only: verification of suitable archived tumor tissue available at the participating center for biomarker analysis. A fresh biopsy is required if an archived sample is not available.
11. Ability to understand and the willingness to sign a written informed consent document and comply with study procedures.

Exclusion criteria

R6, Phase 1 Expansion, Phase 2a, Module A and Module B Patients Only
1. Prior treatment with an EGFR ex20ins -targeting drug (eg, including, but not limited to poziotinib, mobocertinib, amivantamab, DZD9008, BDTX-189).
Note: enrolment of patients treated previously with EGFR ex20ins targeting drugs allowed selectively during accelerated titration dose escalation and Module C only.
Module A Food Effect PK Assessment Module patients only
2. Conditions that compromise esophageal or GI function, including esophageal, gastric, hepatobiliary, or small bowel carcinomas or history of gastric resection.
3. Recurrent diarrhea, nausea, or vomiting.
4. Unable to refrain from or anticipates the use of:
a. Any drug, including prescription and non-prescription medications, including drugs that change gastrointestinal motility (eg, loperamide) or gastric pH (eg, antacids, H2 antagonists, proton pump inhibitors), herbal remedies, or vitamin supplements within 14 days prior to the first dosing on Day 1 to follow-up.
b. Any drugs known to be inhibitors or inducers of cytochrome P450 (CYP)3A enzymes and/or p-glycoprotein (P-gp), including St. John*s Wort and grapefruit juice, within 28 days prior to the first dosing and throughout the PK assessment.
5. Any allergies to the composition of the high fat meal.
6. Patients who use tobacco products.
All Patients
7. History of COVID-19-related pneumonitis requiring hospitalization.
8. History of COVID-19 infection within 4 weeks prior to enrolment, have clinically significant pulmonary symptoms related to prior COVID-19 pneumonitis.
9. Treatment with any of the following:
a. An EGFR TKIs <= 8 days or 5 × the terminal phase elimination half-lives, whichever is longer, prior to the first dose of study drug on C1D1
b. Systemic anticancer treatment (excluding EGFR TKIs as described above) <= 14 days prior to the first dose of study drug on C1D1.
c. Radiotherapy < 28 days and palliative radiation <= 14 days prior to the first dose of study drug on C1D1. If irradiated, lesions must have demonstrated clear-cut progression prior to being eligible for evaluation as target lesions.
d. Immunotherapy <= 28 days prior to the first dose of study drug on C1D1.
e. Major surgery (excluding placement of vascular access) <= 28 days of the

first dose of study drug on C1D1.
10. Have any unresolved toxicity of Grade >= 2 from previous anti-cancer treatment, except for alopecia and skin pigmentation. Patients with chronic, but stable Grade 2 toxicities may be allowed to enroll after agreement between the Investigator and Sponsor.
11. Have known or suspected leptomeningeal metastasis. Have known or suspected brain metastases or spinal cord compression, unless the condition has been asymptomatic, treated with surgery and/or radiation (if clinically indicated), and has been stable without requiring escalating corticosteroids or anti-convulsant medications for at least four weeks prior to the first dose of study drug on C1D1.
12. Prior therapy with CLN-081.
13. Known hypersensitivity to CLN-081 or any drugs similar in structure or class.
14. Past medical history of interstitial lung disease, treatment-related pneumonitis, or any evidence of clinically active interstitial lung disease.
15. Cardiac conditions as follows: Patient has a history of congestive heart failure (CHF) Class III/IV according to the New York Heart Association (NYHA) Functional Classification or serious cardiac arrhythmias requiring treatment.
16. Resting corrected QT interval (QTcF) > 470 msec.
17. Patient is unable to take drugs orally due to disorders or diseases that may affect GI function, including but not limited to inflammatory bowel diseases or malabsorption syndrome, or procedures that may affect gastrointestinal function, such as gastrectomy, enterectomy, or colectomy.
18. Have any condition or illness that, in the opinion of the Investigator, might compromise patient safety or interfere with the evaluation of the safety of the drug.
19. Pregnant or lactating females; females of child-bearing potential (FOCBP) must have a negative serum pregnancy test <= 7 days prior to receiving study drug on C1D1. FOCBP and males with partners of child-bearing potential must agree to use adequate birth control (Section 15.3) throughout their participation and for six months following the last dose of study treatment.
20. History of another primary malignancy <= 2 years prior to starting study drug on C1D1, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ.
21. Uncontrolled intercurrent illness including, but not limited to, uncompensated respiratory, cardiac, hepatic, or renal disease, active infection (including human immunodeficiency virus (HIV) and active clinical tuberculosis), or renal transplant; ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirements.
22. For patients with a history of HBV, negative PCR test is required. Patients with active HBV infection. Patients ineligible due to detectable HBV DNA at baseline may be rescreened for enrolment if their HBV DNA levels become undetectable after treatment with antiviral agents, and upon agreement between the Investigator and Sponsor.

23. For patients with a history of hepatitis C, active infection as defined by a reactive hepatitis C virus (HCV) antibody test and detectable HCV ribonucleic acid (RNA).
24. Active bleeding disorders.
25. The patient is, in the Investigator*s opinion, unable or unwilling to comply with the trial procedures.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-06-2020
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not yet known
Generic name:	not yet known

Ethics review

Approved WMO

Date:	14-10-2019
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	27-02-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	28-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	02-05-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-05-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-002409-23-NL
ClinicalTrials.gov	NCT04036682
CCMO	NL70881.031.19