CLINICAL STUDY REPORT

1 TITLE PAGE

Study Title:	Phase 1/2a Study to Evaluate the Safety, Activity, and Pharmacokinetics of Escalating Doses of GNS561 in Patients with Primary or Secondary Liver Cancer
Investigational Product:	GNS561 Oral Capsules
Indication Studied:	Hepatocellular carcinoma, Intrahepatic cholangiocarcinoma, liver metastatic pancreatic cancer and liver metastatic colorectal cancer
Study Design:	Multicenter, open-label, uncontrolled, repeat-dose Phase 1/2a study
Name of Sponsor:	Genoscience Pharma
Protocol Number:	GNS561-CL-I-Q-0211
Development Phase:	1/2a
Eudract Number	2017-003585-27
Studied Period:	First Patient Enrolled: 20 March 2018 Last Patient Completed*: 09 September 2020 * *Note: Last follow-up visit for Phase 1 of the study, whereafter the relevant patient entered in the survival period.*
Principal Investigator:	Ahmad. H. Awada, MD Institut Jules Bordet, Boulevard de Waterloo 121, 1000 Bruxelles, Belgium
Sponsor Signatory:	Christelle Ansaldi MD Tel: (+33)04 91 26 99 58 (+33)06 63 21 77 51 Email: cansaldi@genosciencepharma.com
GCP Compliance:	This study and the archiving of essential documents were performed in compliance with Good Clinical Practice (GCP).
Version and Date of the Report:	Final, 11 November 2021

2 SYNOPSIS

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Title of Study: Phase 1/2a Study to Evaluate the Safety, Activity, and Pharmacokinetics (PK) of Escalating Doses of GNS561 in Patients with Primary or Secondary Liver Cancer	
Coordinating Investigator: Ahmad H. Awada, MD; Institut Jules Bordet, Boulevard de Waterloo 121, 1000 Bruxelles, Belgium	
Study Centers: 5 centers in 3 countries: France (3 centers); Belgium (1 center), and USA (1 center)	
Publication (Reference): Presentation at American Association for the Study of Liver Diseases 2019 0319: Preliminary safety and pharmacokinetics of a new lysosomotropic oral Agent, GNS561, in a first-in-human study in advanced primary liver cancer patients	
Study Period: The study was expected to take 6 to 12 months to complete Phase 1: dose escalation phase. The Phase 1 part of the study took 2.5 years to complete.	**Phase of Development:** 1/2a

Objectives:

Phase 1 Objectives (Dose escalation phase)

- To characterize the safety and tolerability of GNS561
- To identify the recommended Phase 2 dose (RD)
- To characterize the PK of GNS561

Phase 2a Objectives (all patients in all cycles)

- To characterize the safety and tolerability of GNS561

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- To identify evidence of antitumor activity (tumor control rate: overall response rate (ORR) + stable disease [StD] by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)

Exploratory objectives:

- Pharmacodynamics (PD) biomarker expressions in blood including α-fetoprotein (AFP), carcinoembryonic antigen (CEA) and CA-19-9.
- PD biomarker expressions in liver biopsies including zinc/iron-regulated transporter-like protein 4 (ZIP4), Ki67 expression by immunostaining and an autophagy marker (light chain 3 phosphatidylethanolamine conjugate [LC3-II]).
- To assess the liver/plasma ratio of GNS561 after repeated dosing
- To assess the anti-fibrotic effect of GNS561 on liver after repeated dosing (for Phase 2a only) by a FibroScan® and calculation of a fibrosis score (Fibrotest®/FibroSURE™)

Methodology:

This was a multicenter, open-label, uncontrolled, repeat-dose Phase 1/2a study designed to evaluate the safety profile and to determine the RD of GNS561 in patients with advanced primary or secondary liver cancer. This study planned to enroll approximately 122 patients and consisted of 2 parts: Phase 1 (dose escalation) and Phase 2 (expansion). All patients were treated until the occurrence of an unacceptable toxicity, disease progression, or withdrawal of consent. In this study, a treatment cycle was defined as 4 weeks (28 days). Patients took their assigned dose of GNS561, in the morning and in the evening, at the same time every day, following a meal.

Phase 1- Dose Escalation Phase:

Phase 1 used a 3 + 3 design with a dose limiting toxicity (DLT) observation period of 28 days (1 cycle). Each dose level cohort was enrolled sequentially. Up to 7 cohorts were planned with a maximum of 42 evaluable patients enrolled during Phase 1 depending on the dose level at which RD was determined. Dose escalation was carried out as described below.

In the absence of a DLT, and in conjunction with review of the safety, clinical activity, and available PK/PD data from each cohort by the safety monitoring committee (SMC) consisting of enrolling Investigators and Sponsor representatives, dose escalation was planned to occur in the following manner:

- The first dose (Cohort 1) was GNS561 50 mg once a day (QD) either on Monday, Wednesday, and Friday or Tuesday, Thursday and Saturday.
- Doses for each subsequent cohort were escalated by no more than doubling (100% increase) the previous dose until ≥ 1 patient experienced a DLT or ≥ 2 patients in a cohort experienced a drug-related Grade ≥ 2 toxicity. In such instances, and for doses above 400 mg, dose escalation was in increments not greater than 50%.

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- Lesser incremental escalations, and potentially de-escalations (between 10–100%), based on observed toxicities or other pharmacology or preclinical information that became available could have been implemented at the discretion of the SMC.
- Dose change:

  The Cohort 5 dose was GNS561 200 mg twice a day (BID) every day. Doses for each subsequent cohort were escalated by no more than 50% increasing the previous dose until ≥ 1 patient experienced a DLT or ≥ 2 patients in a cohort experienced a drug-related Grade ≥ 2 toxicity.

If a DLT was observed in ≥ 1 patient in a cohort, an additional 3 patients were enrolled in that cohort for a total of 6 patients. The RD was defined as the highest dose level in which DLTs had occurred in ≤ 1/3 or ≤ 2/6 patients in a cohort. Patients were not allowed to be treated in multiple cohorts. Patients in each cohort continued on the dose originally allocated to unless the dose exceeds the maximum tolerated dose (MTD).

In each cohort, the second patient was not allowed to initiate dosing until the first patient had completed a minimum of 7 consecutive days of dosing (sentinel dosing).

PK Sampling in Cycles 1, 2, 3, 4 and 5:

Patients were requested to fast from midnight before their visit on Cycle 1 Day 1. Following initial assessments and collection of the pre-dose PK blood sample, patients were fed a meal 30 to 60 minutes prior to dosing with GNS561. Following dosing, patients were required to remain at the clinic until the 10-hour PK blood sample was collected (PK sampling times: predose, 1, 2, 4, 6, 8, and 10 hours) and then return on Cycle 1 Day 2 for collection of the 24 hour PK sample, and on Cycle 1 Day 3 for the collection of the 48 hour PK sample. The same procedure was applied for Cycle 2 (from D1 to D3 Cycle 2).

Additional PK blood samples were collected predose (if applicable) at each scheduled visit during Cycle 1 and on Day 1 of Cycle 3, 4 and 5 to monitor GNS561 blood levels.

Phase 2a – Expansion Phase:

Once the RD was determined in Phase 1, additional patients were to be enrolled into 4 RD groups; HCC, iCCA, PDAC and CRC, with 20 patients by group in order to obtain up a total of 80 patients in that expansion phase. These additional patients are to have all of the same assessments as the patients enrolled in the dose escalation cohort with the exception of PK sampling, liver biopsy not mandatory and the addition of liver fibrosis assessment every 6 months by a FibroScan® and calculation of a fibrosis score (FibroTest®/FibroSURE™) for HCC and iCCA patients.

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Note: At the time of this report, Phase 2 (expansion phase) has not yet been initiated. Results in this report includes only the data from the Phase 1 (dose escalation) part of the study. Results will be published in separate report by Genoscience Pharma, upon initiation and completion of Phase 2 (expansion phase) part of the study.

All Patients

Blood samples were collected through out treatment period at each scheduled visit for safety laboratory assessments and at each Day 1 visit through Cycles 1, 2, 3, 4 and 5 to monitor GNS561 blood levels. Collection of additional blood samples for PD biomarker testing occurred at screening, on Day 1 of Cycle 2, on Day 1 (± 2 days) of every subsequent cycle, and final follow-up visit. Tumor imaging was performed at screening, the beginning of Cycle 3 (±5 days) and every subsequent odd numbered cycle until disease progression. The target liver tumors were biopsied at the beginning of Cycle 2 (Day 1), if feasible in Phase 2.

All patients remained on their initial assigned dose of study drug. Patients were to be followed for 4 weeks following discontinuation of study drug, and then contacted every 3 months for up to 2 years to assess their status.

Number of Patients (Planned and Analyzed):

Up to 122 patients were planned to be enrolled in this study.

In the dose escalation phase, up to 6 patients were planned to be enrolled in each cohort with a maximum of 7 cohorts.

Additional patients were planned to be enrolled in the RD cohort to obtain a total of 80 patients in 4 groups (20 patients per group, HCC, intrahepatic cholangiocarcinoma [iCCA], pancreatic ductal adenocarcinoma [PDAC] and colorectal cancer [CRC]).

In total, 26 patients were analyzed in the dose escalation phase.

No patients were analyzed in the dose expansion phase at the time of this report.

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Diagnosis and Main Criteria for Inclusion:

The following patients were recruited:

- Patients with locally advanced or metastatic hepatocellular carcinoma (HCC) that is not deemed appropriate for a curative therapy and previously exposed (refractory or intolerant) to sorafenib or another registered therapy and with StD or progressive disease (PDI), or;
- Patients with locally advanced or metastatic iCCA that is not deemed appropriate for a curative therapy and previously exposed (refractory or intolerant) to at least one first line chemotherapy and with StD or PDI, or;
- Patients with PDAC and liver metastasis that is not deemed appropriate for a curative therapy and previously exposed (refractory or intolerant) to at least one first line chemotherapy and with StD or PDI, or;
- Patients with CRC and liver metastasis that is not deemed appropriate for a curative therapy and previously exposed (refractory or intolerant) to prior chemotherapy such as 5-FU, irinotecan, oxaliplatin, and targeted therapies (anti-vascular endothelial growth factor [VEGF] and anti-epidermal growth factor receptor [EGFR]) as deemed active and registered for the treatment of advanced/metastatic CRC and with StD or PDI.

Test Product, Dose and Mode of Administration, Batch Number:

Phase 1- Dose Escalation Phase:

Study drug was provided as oral capsules containing 50 or 200 mg of GNS561. Patients were instructed to take their assigned oral dose at the same time in the morning at each scheduled day with water after a meal. The first cohort received 50 mg QD three times per week (Monday, Wednesday, and Friday or Tuesday, Thursday and Saturday). From Cohort 5, patients were instructed to take their assigned oral dose at the same time in the morning and evening every day with water after a meal. Cohort 5 received 200 mg BID every day.

In the dose escalation phase, on Day 1 of Cycles 1 and 2 only, for collection of PK samples, patients were instructed to fast from midnight before arriving at the clinic and will be fed 30 to 60 minutes prior to dosing. For other collection of PK samples, patients were instructed not to take their dose of GNS561 before blood withdrawal.

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The batch numbers were as follows:

- 50 mg GNS561: LC17086 (bulk), LC17086A (primary packaging);
- 200 mg GNS561 LC17278 (bulk), LC17278A (primary packaging)

Phase 2a Expansion Phase:

Patients are to continue on their originally assigned dose in the expansion phase.

Duration of Treatment:

Patients received GNS561 during the 4-week dose escalation phase and then until disease progression, occurrence of a DLT, or patient discontinuation from the trial.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable

Criteria for Evaluation:

Safety

- Incidence and nature of DLTs during the 4-week dose escalation phase
- Incidence, nature, and severity of adverse events (AEs)
- Change in vital signs, clinical laboratory (chemistry and hematology) values, urinalysis, electrocardiogram (ECGs)

Efficacy

- Response rate (complete response [CR]+partial response [PR])
- Disease control rate (CR+PR+StD)
- Progression free survival

PK

- GNS561 PK over 48 hours following first dose and 1 month dose and minimum plasma concentration (C_{trough}) after 1, 2 and 3 weeks of first dose and at each cycle.

Exploratory

- PD biomarker expressions in blood including AFP for HCC patients, CEA and CA-19-9 for iCCA, CRC, and PDAC patients.
- PD biomarker expression in liver biopsies at Day 1 of Cycle 2 including ZIP4 and Ki67 expression by immunostaining and an autophagy marker (LC3-II).
- To assess the liver/plasma ratio of GNS561 after repeated dosing for one cycle.

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- To assess the anti-fibrotic effect of GNS561 in liver after repeated dosing (for Phase 2a only) by a FibroScan® and calculation of a fibrosis score (Fibrotest®/FibroSURE™) for patients with primary liver cancer (HCC and iCCA).

Statistical Methods:

All statistical analysis will be performed using SAS®, Version 9.4 or higher.

Data were summarized by treatment group. A total column showing all patients was included for baseline and safety summaries. Where appropriate, data were also summarized by visit with summaries for each visit attended as scheduled and an additional summary for final (last scheduled visit or early withdrawal).

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum) are presented. For PK summaries, arithmetic mean (AM), geometric mean (GM) and coefficient of variation (CV%) were used to summarize the data. The minimum and maximum statistics are presented in summary tables to the same number of significant figures as the original data. The mean/AM, median, SD and SE are presented to one more significant than the original data.

Summary – Conclusions:

Safety:

All the patients experienced at least one TEAE. The majority of patients reported at least one severe TEAE (67 events in 22 patients; 84.6%) and one serious TEAE (40 SAEs in 20 patients; 76.9%). A total of 323 TEAEs were reported in 26 patients (100.0%) in the Safety Population in Phase 1. More than half of the patients experienced nausea (57.7%) and vomiting (57.7%) during Phase 1.

Of 67 severe TEAEs, 8 events were drug-related events, all of which were Grade 3 and approximately half of the severe TEAEs were SAEs. All of the drug-related severe events were reported once, except for diarrhea (n=3).

A total of 125 drug-related TEAEs were reported by 21 patients (80.8%) across the dose cohorts. The most common drug-related TEAEs by PT were vomiting (53.8%) and nausea (50.0%).

Overall, 40 serious TEAEs were reported in 20 patients (76.9%). All patients in the 50 mg, 400 mg and 600 mg (300 mg BID) GNS561 cohorts experienced at least one SAE. Of 40 SAEs, 9 events were fatal. The majority (38/40 events; 95.0%) of the SAEs were unrelated to the study drug, except one event each of diarrhea and vomiting. Due to SAEs, study drug was interrupted in 5 patients and withdrawn in 11 patients. None of the patients in the 100 mg GNS561 cohort experienced any SAE.

A total of 8 patients (30.8%) died during Phase 1. Nine (9) TEAEs led to the death of 8 patients with higher incidence in the BID GNS561 dose cohorts (200 mg and 300 mg BID GNS561 cohorts). None of these fatal events were reported as related to GNS561. Fatal events of neoplasm progression, general physical health deterioration and intestinal obstruction were reported in more than one patient. None of the patients in the 100 mg and 200 mg GNS561 cohorts experienced any fatal TEAEs. Of the 26 patients in Phase 1, 25 patients (96.2%) died during the 2-year period following final follow-up visit.

Twelve (12) patients (46.2%) had 15 TEAEs that led to withdrawal from the study.

Most TEAEs were generally recorded in similar proportions of patients across the dose cohorts and there were no apparent dose dependent trends in TEAEs, TEAE severity, treatment related TEAEs and SAEs.

Clinically significant abnormal laboratory values were recorded for the majority of patients in all treatment groups except the 100 mg GNS561 cohort and no dose-dependent trend was noted across the dose cohorts.

There were no notable trends in vital signs, physical examination, ECG, echocardiogram or ECOG status values recorded over time or by dose.

There was no clear pattern or discernible trend in prior or concomitant medication following treatment with GNS561 between the dose cohorts.

Efficacy

Tumor Response

No CR, nor PR was reported for any patients included in the Efficacy Population. There was a 23% decrease in one patient with iCCA.

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There were cases of stable disease during Phase 1, but these were low (15.0% at Final Assessment [Final Assessment was the last evaluation for tumor imaging during treatment period]; 25.0% at Cycle 3, Day 1, 10.0% at Cycle 5 Day 1 and 5.0% at Follow-up).

There were no meaningful differences noted in tumor response across the dose cohorts investigated.

Survival

Progression-free survival was highest in the 200 mg GNS561 cohort when compared to the other dose cohorts, with a median of 15.6 weeks.

At Follow-up, no patients in the Efficacy Population were free of disease progression. There were 3 deaths in this population during the study caused by disease progression. The additional 17 patients in the Efficacy Population all died during the survival period, most cases due to disease progression, with the exception of 3 unknown causes for death and 1 report of malignant neoplasm progression.

There were no meaningful differences noted in survival between dose cohorts.

Pharmacodynamics

Variations in AFP, CEA or CA-19-9 were observed across the dose cohorts; however, no trends were seen across the dose cohorts investigated. It is important to note that PD results are available for a low number of patients, which renders results for these parameters inconclusive. Pharmacodynamics (PD) will be further explored in Phase 2.

Pharmacokinetics

Pharmacokinetic (PK) data were analyzed by Eurofins Amatsi Analytics and results are presented in a separate PK report.

After the first once every three days administration on Day 1 of Cycle 1 and Cycle 2, an increase in plasma exposure with the increasing dose was observed.

It was observed that on Cycle 2 after once every three days administration, the kinetic profile was relatively flat with concentrations remaining at approximately the same level from 0 to 48 hours.

Accumulation was observed after 2 cycles of once every three days administration, with a higher accumulation of 3.9-fold for C_{max} and 9.3-fold for AUC_{24}. After 2 cycles of BID administration at 200 mg, C_{max} and AUC_{24} increased by 5.5-fold and 15-fold respectively, showing that GNS561 increased substantially after repeated administration.

Plasma exposure was higher after BID administration.

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Discussion and Overall Conclusions:

Phase 1 study was a first-in-human trial to evaluate the safety of GNS561 in patients with primary or secondary liver cancer and to evaluate the safety and the tolerability of the drug and determine the RD for further evaluation.

GNS561, administered as an oral dose of thrice weekly 50 mg QD, 100 mg QD, 200 mg QD, 400 mg QD, 200 mg BID or 300 mg BID, was considered generally safe. Though all the patients experienced at least one TEAE, there was no visible trend to suggest a dose-related increase in any of the safety parameters recorded. A total of 8 patients (30.8%) died due to TEAEs during Phase 1 and the majority of the patients (76.9%) experienced at least one SAE, however, the majority of these events were not related to GNS561. Overall, the safety profile of the dose cohorts was comparable and there appeared to be no discernible differences in safety profile across these dose cohorts.

For efficacy, there were no meaningful differences noted in either tumor response or survival between dose cohorts in Phase 1. It is important to note that efficacy results are available for a low number of patients, which renders results for these parameters inconclusive for Phase 1. Efficacy of the study drug will be further explored in Phase 2 as the main objectives of Phase 1 were safety and PK.

Similarly, PD will be further explored in Phase 2. Although no trends were seen in AFP, CEA or CA-19-9 variations across the dose cohorts investigated, it is important to note that PD results are available for a low number of patients, which renders results for these parameters inconclusive.

During the meeting on 30 September 2020, the SMC suggested 200 mg BID GNS561 as the RD for further clinical investigation.

Date of the Report:

11 November 2021

Clinical Project Manager: Christelle Ansaldi Date: 25 April 2022 Signature: