0319 : PRELIMINARY SAFETY AND PHARMACOKINETICS OF A NEW LYSOSOMOTROPIC ORAL AGENT, GNS561, IN A FIRST-IN-HUMAN STUDY IN ADVANCED PRIMARY LIVER CANCER PATIENTS

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Background

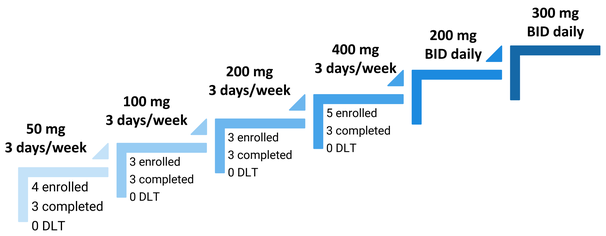
Lysosome has been described as target of interest for cancer therapy. GNS561 is a new oral lysosomotropic small molecule which displays meaningful activity against several tumor types, specifically in hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). Herein, we report preliminary results of the Phase 1b/2a study of GNS561 in advanced primary liver cancer patients (NCT003316222).

Methods

The Phase 1b portion is a non-randomized, single arm (3+3 design) clinical trial with a maximum enrolment of 36 patients. GNS561 was administered orally to histologically confirmed HCC or iCCA adult patients not eligible for curative therapy in 4 week cycles.
Other inclusion criteria are: measurable tumor per RECIST v1.1 criteria, Child-Pugh A and ECOG PS ≤ 1.

The objectives are to assess the safety and pharmacokinetics (PK) of GNS561 and to determine the recommended Phase 2 dose. Early safety, Pharmacodynamic and PK data from patients of the 4 first dose levels are reported.

Figure 1. Study Flowchart



enrolled : patient who has taken at least one dose of GNS561
Completed: patient who has taken GNS561 during at least one cycle.
BID: twice a day

A maximum of 7 cohorts are planned in the current phase 1b. The recommended dose of GNS561 is expected, based on preclinical pharmacokinetics, to occur in 5th or 6th cohort.

Results

As of October 2019, 15 patients were enrolled with 12 patients having completed the study with at least one cycle of treatment. Median patient age was 66 years (range 31 - 80), 3 (20%) were female, 7 (47%) had HCC; median number of prior systemic therapies was 1 (range 1-5).

Table 1. Baseline patients demographic characteristics

	50 mg (N=4)	100 mg (N=3)	200 mg (N=3)	400 mg (N=5)	Total (N= 15)
Median Age (years)	54 (48-67)	70 (69-80)	66 (60-67)	54 (31-80)	66 (31-80)
Male, n (%)	3 (75%)	2 (66%)	3 (100%)	4 (80%)	12 (80%)
Pathology					
HCC, n (%)	1 (25%)	2 (66%)	1 (33%)	3 (60%)	7 (47%)
iCCA, n (%)	3 (75%)	1 (33%)	2 (66%)	2 (40%)	8 (53%)
ECOG PS					
0, n (%)	2 (50%)	1 (33%)	1 (33%)	3 (60%)	7 (47%)
1, n (%)	2 (50%)	2(66%)	2 (66%)	2 (40%)	8 (53%)
Cirrhosis					
yes, n (%)	2 (50%)	1 (33%)	1 (33%)	2 (40%)	6 (40%)
no, n (%)	2 (50%)	2 (66%)	2 (66%)	3 (60%)	9 (60%)
Median number of prior systemic therapies	1 (1-3)	2 (1-5)	1 (1-4)	1 (1-5)	1 (1-5)
Median tumor size (mm) - RECIST 1.1	107 (58-127)	67 (30-96)	89 (36-164)	150 (69-200)	106 (30-200)

Eight patients were evaluable for tumor imaging assessment according to RECIST 1.1: 38% of them (n=3) were stable at the beginning of Cycle 3, among which 2 patients had stable disease at the beginning of Cycle 5 (Figure 2).

Figure 2a. Duration of treatment (days) per patient

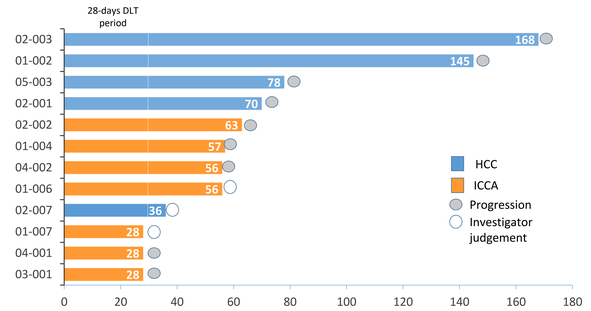
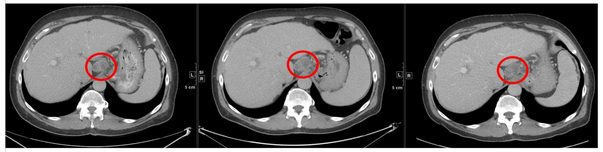


Figure 2b. Patient 02-003 Tumor imaging during GNS561 treatment



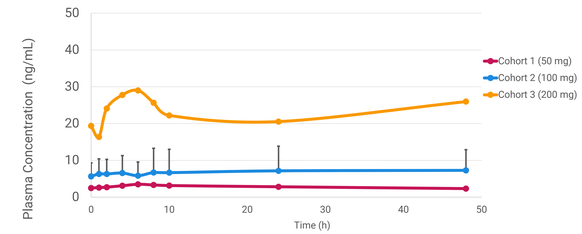
Nine (60%) patients interrupted treatment because of tumor progression, 3 (20%) for serious adverse events and 3 (20%) for investigator decision (due to no benefit on clinical symptoms).

Table 2. Adverse events related to GNS561

Adverse event (AE)	Number of AEs	Number of grade 3 and 4 AEs
Nausea	12 (80%)	0
Vomiting	9 (60%)	0
Diarrhea	4 (26%)	2 (13%)
Fatigue	6 (40%)	2 (13%)
Anemia	1 (7%)	0
Zinc deficit	2 (13%)	0
Blurred Vision	1 (7%)	0
Abdominal Pain	1 (7%)	0
High Blood Pressure	1 (7%)	0
Hemorroids	1 (7%)	0
Dyspnea	1 (7%)	0
Anorexia	1 (7%)	0
AST increased	2 (13%)	1 (7%)
Bilirubin increased	1 (7%)	0
ALT increased	1 (7%)	1 (7%)
Renal Colic	1 (7%)	0

Thus far, no dose-limiting toxicity (DLT) have been observed. Most of related-AEs are digestive toxicities (grade 1-2 nausea, vomiting and diarrhea), fatigue and blood parameters abnormalities. There were no treatment-related deaths or grade 5 adverse events. Grade 3 and 4 adverse events related to GNS561, among which one (diarrhea) was reported as serious adverse event, are summarized in Table 2. These AEs were observed in 4 patients in cohorts 2, 3 and 4. Fifteen Serious AEs were reported among which only one (diarrhea) has been related to GNS561.

Figure 3. Plasma exposure after 1 month of treatment



Conclusion

Current data show that oral GNS561 displays a favorable safety profile, and exposure in blood and liver throughout the dosing interval.

Enrollment in Phase 1b is continuing before extension to Phase 2a, at the recommended dose.

References & Contacts

We thank the patients and their families.
Conflict of interests: CA, MR, CS, SB, PH and ER are employed by Genoscience Pharma, that is the sponsor of the study. CA, CS, SB, ER and PH are shareholders of Genoscience Pharma.
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