1. TITLE PAGE

Study Title	Cure COVID: A prospective, controlled, randomized study to compare the efficacy of GNS561 versus standard of care in patients with SARS-CoV-2 (COVID-19) infection.
Name of investigational drug	GNS561/ 2-(4-chlorobenzylamino)-4-(4-tert-butylaminopiperidin-1-yl)quinoline
Indication studied	SARS-CoV-2 (COVID-19) infection
Study design	1:1 randomized, multicenter, open-label, placebo-controlled phase 2 trial
Sponsor	Genoscience Pharma
Study Code	GNS561-CL-I-Q-0291
Protocol Number	GNS561-CL-I-Q-0291
EudraCT Number	NA
Development phase of study	Phase I
Study initiation date **Study primary completion date**	18-Nov-2020 (first patient first visit) 06-Feb-2022 (the last patient completed)
Name and affiliation of Coordinating Investigator	Pr Lionel Piroth CHU de Dijon 14 rue Gaffarel 21079 DIJON Cedex
Name of Company/Sponsor signatory	Christelle Ansaldi MD Tel: +33 (0) 4 91 26 99 58 Email: cansaldi@genosciencepharma.com
Date of the report:	17-Feb-2023
Status/version	Final V1.0

STATEMENT

The study investigation was conducted in accordance with the ethical principles of the 18th World Medical Association Declaration (Helsinki, 1964) and all subsequent amendments and guidelines on Good Clinical Practice. Additionally, the clinical trial protocol complies with the laws and legislations of the country in which the study was conducted, all relevant guidelines, as well as those dealing with the protection of personal data. The study sponsor declares that the information provided in this report is an accurate representation of the data captured and analyses performed for this study.

2. SYNOPSIS

Study Title	Cure COVID: A prospective, controlled, randomized study to compare the efficacy of GNS561 versus standard of care in patients with SARS-CoV-2 (COVID-19) infection.
Study code	GNS561-CL-I-Q-0291
Protocol number	GNS561-CL-I-Q-0291
EudraCT number	2020-002249-40
The development phase of the study:	2
Name of Sponsor	Genoscience Pharma
Name and affiliation of Sponsor's responsible medical officer	Christelle Ansaldi MD Tel: +33 (0) 4 91 26 99 58 Email: cansaldi@genosciencepharma.com
Data and Safety Monitoring Board (DSMB) Chairman	Not applicable
Name of test drug/investigational product	GNS561 / 2-(4-chlorobenzylamino)-4-(4-tert-butylaminopiperidin-1-yl)quinoline
Name of active ingredient	Quinoline derivative
Dose and mode of administration of test drug/investigational product	Oral hard gelatin capsules, size 0 elongated, containing 200 mg of GNS561 Patients were instructed to take their assigned oral dose at the same time in the morning on each scheduled day with water after a meal. The dose of GNS561 was 200 mg once a day (QD) orally for 10 consecutive days.
Manufacturing batch number	LC18201A
Reference therapy (placebo or active comparator)	Standard of care
Indication studied	Treatment in moderate to severe SARS-CoV-2 infection
Study centres	Multinational, multicentre trial. Nine study sites in France and three sites in Bulgaria
Publication(s)/references	None
Background	As the Sponsor of the trial with the EudraCT number 2020-002249-40, Genoscience decided to terminate the study as of 23-Dec-2021 due to enrollment and feasibility challenges that made study completion infeasible.

Objectives	The primary objective was to evaluate the efficacy of GNS561 in patients with COVID-19 infection versus standard care. The secondary objectives in each arm of the study were: • To evaluate the safety of GNS561 in patients with COVID-19 infection. • To evaluate the efficacy of GNS561 in viral replication. • To evaluate the efficacy of GNS561 on the inflammatory reaction induced in patients with COVID-19 infection. The exploratory objectives in each arm of the study were: • To assess Pharmacokinetics of GNS561 in hospitalised patients • To assess the efficacy of GNS561 on pulmonary fibrosis • To evaluate changes in patients microbiota due to COVID-19
Study design	This was a 1:1 randomized, multicenter, open-label, placebo-controlled phase 2 trial on adult patients with moderate to severe COVID-19 infection. The randomization was stratified on patient age (<70 vs. ≥70 years). The randomization plan was generated by the biostatistician.
Number of participants	Planned: 120 patients Screened: 22 patients Randomized: 21 patients (11 on the treatment arm and 10 on the standard of care arm).
Evaluated patients	Efficacy: 21 patients Safety: 21 patients
Diagnosis and main criteria for eligibility	Hospitalized male and female adult patients aged ≥ 18 years with documented moderate to severe COVID-19 infection based on News2 score≥5, and who had adequate bone marrow and end-organ function defined by the following laboratory results in haematology (haemoglobin≥ 7.0 g/dL, Absolute Neutrophils Count (ANC) ≥ 1.0 Gi/L, platelets ≥ 100 Gi/L), hepatic function (Total serum bilirubin ≤ 1.5 x ULN (except patients with Gilbert's syndrome who must have total serum bilirubin ≤ 3.0 x ULN), AST and ALT ≤ 5 ULN), and kidney function (Cr. Cl. ≥ 30ml/min/1.73m² (calculated by MDRD formula). Women of childbearing potential were required to have a negative serum pregnancy test within 72 hours before the trial treatment. Both female and male participants had agreed to use highly effective contraception methods during the trial and up to 6 months after completion of the treatment.
Study endpoints	Due to early termination of the study, the current report is a synopsis-style report. No conclusions on efficacy from the study are provided. The following safety and efficacy criteria were evaluated (except those marked with an asterisk [*]): <u>Primary endpoint</u> The primary endpoint was the loss of one or two grades of NEWS2 score at day 7: from the severe stage at baseline to medium or low stage at day 7 or from the medium stage at baseline, to low stage at day 7. <u>Secondary endpoints were:</u> • Loss of one or two grades of NEWS2 score at day-14: rates of patients with NEWS2 stage "low" at day-14 will be compared between arms • The 28-day survival rate, defined by the crude proportion of patients still alive 28 days after randomization* • The rate of intensive care unit admission to 14-days from randomization • Clinical status at D7, D9, D14, D28, D44 and D60 will be assessed using the WHO-ISARIC seven-category ordinal scale • Mean change in clinical status from baseline to day 28 will be assessed using the WHO-ISARIC seven-category ordinal scale • The rate of oxygenation free at days 14 and 28 • Incidence of non-invasive positive pressure ventilation or heated high flow nasal cannula use from randomization to D28 • The two-month lung fibrosis status will be assessed by Respiratory function

	exploratory and Lung CT scan* • The rate of negative nasopharyngeal swabs at D7, D14 and D28* • The rate of secondary infection by other documented pathogens (bacteria, fungi) at D7, D14, D28, D44 and D60 if available* • The biological parameters changes from baseline* • The safety profile: o Treatment-Emergent Adverse Events, Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions, New Safety Issues described using the NCI-CTC AE classification v5 o The number of participants with discontinuation or temporary suspension of study drugs (for any reason) • In case of hospitalization: o The length of stay in the Intensive Care Unit (from the date of admission in the Unit to the date of discharge) o The duration of mechanical ventilation or high flow oxygen devices (from the date of intubation to the stop date of mechanical ventilation or high flow oxygen)* o The duration of hospitalization (from the date of hospitalization to the date of definitive discharge for live patients) o Time to the first day of recovery from hospitalization until D28* <u>Exploratory endpoints</u> • Pharmacokinetics of GNS561 in hospitalized patients* • Efficacy of GNS561 on pulmonary fibrosis* • Changes in patients microbiota due to COVID-19 infection*
Statistical methods	<u>Efficacy</u> Due to the early termination of the study, the number of participants randomized (21 participants, instead of the planned sample size of 120 participants) was not large enough to perform the planned primary and secondary efficacy analyses (see Appendix 16.1.9 Statistical Analysis Plan). The primary and secondary efficacy analyses performed were based on The Full Analysis Set (FAS population). Safety analyses were performed using the safety population (defined as all randomized participants exposed to the investigational medicinal product, regardless of the amount of treatment administered). Adverse Events (AEs) were tabulated (frequency and percentage) by primary system-organ class (SOC), preferred term (PT) and treatment group. Adverse events reported in the study were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0. Safety analyses are described in Appendix 16.1.9 Statistical Analysis Plan.
Study duration	It was planned that each patient would participate during 2 months: • Treatment duration: 10 days • Active follow-up: 2 weeks • A follow-up period of one month with a report about respiratory symptoms every 2 weeks The overall duration of the trial was 14 months. 18-Nov-2020 (the first patient enrolled) 06-Feb-2022 (the last patient completed)
Early study termination date	The Sponsor had the right to stop the trial including, but not limited to, the reasons mentioned below: - The incidence of severity of adverse event in this or other GNS561 trials indicated a potential health hazard to patients; - Unsatisfactory patients enrolment; - If any information led to doubt as to the benefit/risk ratio of the clinical trial. - After the recommendation of the Data and Safety Monitoring Board and according to stopping rules of the interim analysis Due to unsatisfactory patient enrolment, the trial is prematurely terminated. The last participant's last visit date was 06-Feb-2022.

Results	**Population characteristics** Participant Disposition: Between 18-Nov-2020 and 07-Dec-2021, 22 patients were screened, one of whom withdrew his/her consent before randomization. Of the 21 patients randomized, 11 patients were allocated in the GNS561+Standard of Care (SoC) arm (8 from France and 3 from Bulgaria) and 10 patients in the SoC arm (all of them in France) (Appendix 16.2.1 Randomised data [16.2.1.6]. All randomized patients were included in the FAS and the Safety population (Appendix 16.2.3 Analysis Sets [16.2.3.1]). Disposition of screened participants by country and center are provided in Appendix 16.2.1 Subject Disposition [16.2.1.1]. Four randomized patients withdrew prematurely: two patients were lost to follow-up (one in each arm), and two patients died (both in the SoC arm). Premature withdrawals are provided in Appendix 16.2.1 Premature Withdrawals [16.2.1.2]. The median (IQR) between inclusion and withdrawal was 19.0 days for the patient in the GNS561+SoC arm and 7.0 days (6.0; 55.0) for the patients in the SoC arm. Patient visit days are provided in Appendix 16.2.1 Patient Visit Dates [16.2.1.3]. Baseline Demographics: Demographic characteristics and other data at baseline of the FAS population are presented in Appendix 16.2.4). The mean (SD) time from the hospitalization to baseline was 4.86 (3.55) days, from the diagnosis of COVID-19 to baseline it was 7.9 days, and from the start of symptoms to baseline it was 10.52 (3.78) days (Appendix 16.2.3 History of COVID-19, [16.2.4.3]). The mean (standard deviation [SD]) age of subjects in the FAS population was 67.6 (14.2) years, with a similar distribution in both arms. Twelve/21 (57.1%) patients were ≥ 70 years at inclusion (6 patients in each arm). Twelve/21 patients (57.1%) were male, 7/11 (63.6%) and 5/10 (50.0%) in the treatment and standard of care arms, respectively (Appendix 16.2.4 Socio-Demographic Characteristics, [16.2.4.1]). Overall, 6/21 (28.6%) and 11/21 (52.4%) patients were overweight and obese, respectively. In the treatment arm, 2/11 (18.2%) and 7/11 (63.6%) patients were overweight and obese, respectively. In the standard of care arm, 4/10 (40.0%) and 4/10 (40.0%) patients were overweight and obese, respectively. (Appendix 16.2.4 Anthropometric Characteristics, [16.2.4.2]). The values of systolic and diastolic blood pressure, pulse rate, respiratory rate, spo2 and body temperature were all within the normal ranges at baseline. Before the treatment dose, 18/21 (85.7%) of the FAS population performed an ECG in the supine position, 10 patients and 8 patients in the treatment and standard of care arms respectively. Three (3)/18 (16.7%) (1 in the treatment arm and 2 in the standard care arm) were abnormal but not clinically significant as per the investigator's assessment. After the dose administration on baseline, 7/21 (58.3%) of the FAS population performed an ECG in the supine position, all of them in the treatment arm. One (1)/7 (14.3%) ECG in the treatment arm was abnormal but not clinically significant as per the investigator's assessment. For this patient, the ECG was already abnormal but not clinically significant in predose. The medical and surgical history is provided in Appendix 16.2.4 Medical and Surgical History, [16.2.4.4]. Seventeen (81.0%) patients had at least one ongoing concomitant treatment, with a mean (SD) 4.52 (4.87) treatments by subject. Prior and concomitant medications are provided in Appendix 16.2.4 Prior and Concomitant Medications [16.2.4.5]. The median (IQR) NEWS2 score at baseline was 6.00 (6.00; 6.00) in the GNS561 + SoC arm and 6.00 (6.00; 7.00) in the SoC arm (Appendix 16.2.6 NEWS2 [Listing 16.2.6.1])..Ten(10)/11 patients in the GNS561 + SoC arm had a WHO score 4, and one patient had a WHO score 5. All (10) patients in the SoC arm had a WHO score 4 (Appendix 16.2.6 7-Items WHO Ordinal Scale, [Listing 16.2.6.2]).

Efficacy results:

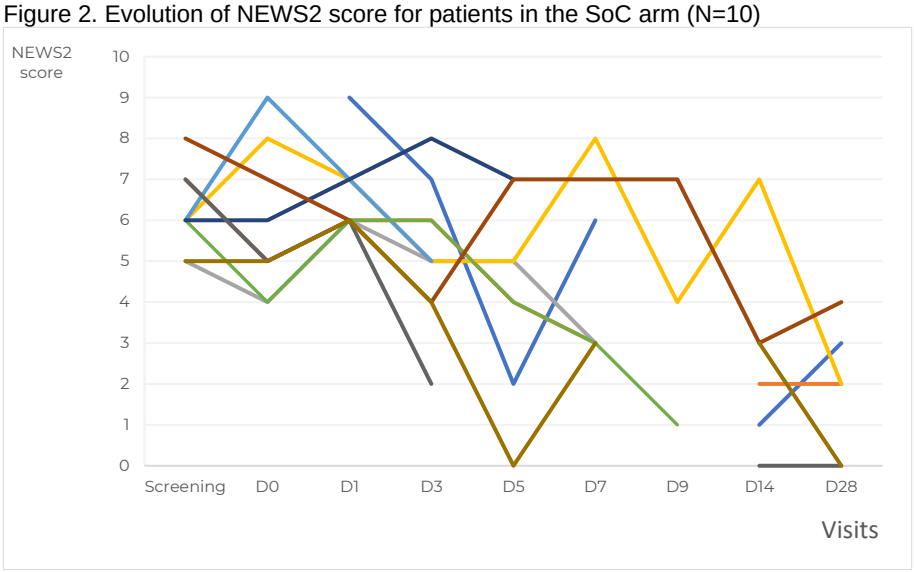
Among the 11 randomized patients in the_GNS561 + SoC arm, 3 patients were compliant to treatment and 8 patients discontinued the study drug permanently (see the safety section) (Appendix 16.2.5 IMP Compliance [Listing 16.2.5.1]).

Efficacy response data are presented in Appendix 16.2.6.

The evolution of the NEWS2 score per patient from screening throughout the follow up is presented in Figure 1 for patients in the GNS561 + SoC arm and in Figure 2 for patients in the SoC arm. Further information is provided in Appendix 16.2.6 NEWS2 [Listing 16.2.6.1].

Figure 1. Evolution of NEWS2 score for patients in the GNS561 + SoC arm (N=11)

Figure 2. Evolution of NEWS2 score for patients in the SoC arm (N=10)



The primary endpoint of the study was the loss of one or two grades of NEWS2 score at day 7: from the severe stage at baseline to medium or low stage at day 7 or from the medium stage at baseline, to low stage at day 7. Table 1 shows the results overall for the FAS population and by arm. Two patients (95% CI: 0.0%;41.0%) in the GNS561 + SoC arm experienced a loss of one or two grades of the NEWS2 score at day 7 versus 3 patients (95% CI: 1.6%;58.4%) in the SoC arm. The difference between the two arms was not statistically significant (p=0.6351).

Table 1. Rate of loss of one or two grades of NEWS2 score at day 7 - FAS population

	GNS561 + SoC arm (N=11)	SoC arm (N=10)	FAS Population (N=21)	P-value
LOSS OF ONE OR TWO GRADES OF NEWS2 SCORE AT D7, N (%)	11	10	21	0.6351 (Fisher exact)
YES	2 (18.2)	3 (30.0)	5 (23.8)	
95% CI	[0.0;41.0]	[1.6;58.4]	[5.6;42.0]	
Missing	0	0	0	

Percentages are based on all subjects from FAS population excluding those with missing values.

The clinical status data at baseline and at day 28 was available for 9 patients in the GNS561 + SoC arm and for 7 patients in the SoC arm. The mean (SD) absolute change of the WHO cardinal scale score was -1.6 (1.9) in the GNS561 + SoC arm and -2.3 (0.5) in the SoC arm (the difference between the two arms was not statistically significant; Wilcoxon p=0.8201).

The evolution of the WHO cardinal scale score at D7, D9, D14, D28, D44 and D60 for each of the arms is shown in Table 2 and in Appendix 16.2.6 7-Items WHO Ordinal Scale, [Listing 16.2.6.2].

Table 2. Evolution of clinical status on the 7-items WHO ordinal scale - FAS population

	EVALUATION OF THE PATIENT STATUS						
	WHO=1	**WHO=2**	**WHO=3**	**WHO=4**	**WHO=5**	**WHO=6**	**WHO=7**
GNS561 + SoC arm							
Screening (N=11)	0			10	1		
D7 (N=9)	1	1	1	4	0	2	0
D9 (N=7)	0	1	0	3	1	2	0
D14 (N=10)	3	3	1	1	0	2	0
D28 (N=9)	4	2	1	0	0	2	0
D44 (N=5)	1	2	0	0	0	2	0
D60 (N=7)	2	3	0	0	2	0	0
SoC arm							
Screening (N=10)	0	0	0	10	0	0	0
D7 (N=9)	1	1	2	4	1	0	0
D9 (N=3)	0	0	1	2	0	0	0
D14 (N=8)	1	6	0	1	0	0	0
D28 (N=7)	2	5	0	0	0	0	0
D44 (N=6)	2	4	0	0	0	0	0
D60 (N=6)	4	2	0	0	0	0	0

The mean (SD) absolute change from the screening of 7-items WHO ordinal scale at D60 was a decrease of -2.1 (1.3), and the decrease was -1.6 (1.5) and -2.7 (0.5) for treatment and standard of care arms respectively.

The median (IQR) duration of hospitalization was 13.5 (11.0;19.0) days for 8 patients with data in the GNS561+SoC arm and 10.5 (10.0;16.5) days for 8 patients in the SoC arm.

The median (IQR) length of stay in ICU was 49.5 (9.0; 125.0) days for 4 patients with data in the GNS561+SoC arm and 5.0 (3.0; 16.0) days for 3 patients in the SoC arm (Appendix 16.2.3 Admission to ICU and Length of Stay [16.2.6.3]).

The number of patients free of oxygenation on D14 and D28 in the GNS561+SoC arm were 7/10 and 6/9 (1 missing data), respectively, and in the SoC arm they were 7/8 and 6/7 (1 missing data) (Appendix 16.2.6 Oxygenation rate [16.2.6.4]).

The rate of patients with a recovery status (negative result on nasopharyngeal Swab test for SARS-CoV2) at D28 was 72.7% (8/11 patients) in the GNS561+SoC arm and 80.0% (8/10 patients) in the SoC arm (Appendix 16.2.6.6 Nasopharyngeal Swab Negativation [Listing 16.2.6.6]).

The incidence of Non-invasive Positive Pressure Ventilation or Heated High Flow Nasal Canula is presented in Appendix 16.2.6.5 Incidence of Non-invasive Positive Pressure Ventilation or Heated High Flow Nasal Canula [Listing 16.2.6.5].

Safety results:
Fourteen(14)/21patients of the safety population reported at least one adverse event (AE) (8 in the GNS561 + SoC arm and 6 in the SoC arm). All AEs were TEAEs (Appendix 16.2.7 Adverse Events [16.2.7.1]). The two most frequently reported AEs were coded with the PT “Diarrhoea” and “Vomiting” with 5/21 patients from the GNS561 + SoC arm each. All “Vomiting” events and 4/5 “Diarrhea” events were related or possibly related to the study drug.

Eight (8)/21 patients reported at least one SAE (4 in each arm), 3/21patients reported a fatal AE (grade 5) (1 in the GNS561 + SoC arm and 2 in the SoC arm). None of SAE was related or possibly related to the study drug during the treatment period.

Seven (7)/21patients reported an AE possibly related or related to the study drug (6 in the GNS561 + SoC arm and 1 in the SoC arm) (Table 3).
Eight patients reported at least one AE that led to drug withdrawal, all of them in the GNS561 + SoC arm.

Table 3. Summary of AEs possibly related or related to study drugs by patient according to SOC and PT - Safety population

	GNS561 + SoC arm (N=11)	**SoC arm (N=10)**
GASTROINTESTINAL DISORDERS[a], N (%)	6 (54.5)	0
Vomiting	5 (45.5)	0
Diarrhoea	4 (36.4)	0
Nausea	2 (18.2)	0
Abdominal pain upper	1 (9.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS[a], N (%)	0	1 (10.0)
Injection site haematoma	0	1 (10.0)
METABOLISM AND NUTRITION DISORDERS[a], N (%)	1 (9.1)	0
Cell death	1 (9.1)	0
NERVOUS SYSTEM DISORDERS[a], N (%)	1 (9.1)	0
Headache	1 (9.1)	0

[a]If a subject experienced more than one event in a category, the subject was counted only once in that category.
Percentages are based on all subjects from Safety population excluding those with missing values

A listing of all AEs is provided in Appendix 16.2.7 Adverse event data.

Conclusion

Trial EudraCT number 2020-002249-40 was prematurely terminated due to enrolment and feasibility challenges. At study termination, 21 adult outpatients newly diagnosed with COVID-19 had been randomized in the study; 11 participants were randomized to the GNS561 arm (8 from France and 3 from Bulgaria) and 10 participants into the standard care arm (all of them from France).
GNS561 was well tolerated in the exposed participants and no emerging safety concerns were observed. No conclusions on efficacy from the study are available.

Date of the report	17-Feb-2023