Theriva Biologics, S.L.

CLINICAL STUDY PROTOCOL - CONFIDENTIAL

Protocol Number:	P-VCNA-003
EudraCT/ NCT:	2022-000897-24/ 05673811
Investigational Product:	VCN-01
Title:	A Phase IIb, Open-label, Randomized Study of Nab-Paclitaxel and Gemcitabine plus/minus VCN-01 in Patients with Metastatic Pancreatic Cancer (VIRAGE)
Version and Date:	Amendment V2.1; 10 August 2023
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Confidentiality Statement:
The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Theriva Biologics, S.L. and should not be copied by or distributed to persons not involved in the clinical investigation of VCN-01, unless such persons are bound by a confidentiality agreement with Theriva Biologics, S.L.

SIGNATURE PAGE

Title: A phase IIb, open-label, randomized study of Nab-Paclitaxel and Gemcitabine and plus/minus VCN-01 in Patients with Metastatic Pancreatic Cancer (VIRAGE)

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Signing of this page of the protocol indicates that the protocol format and content has been agreed and approved by signed parties, and that it is agreed that no further changes to the protocol are required at the time of signing.

PROTOCOL AGREEMENT PAGE

I confirm that I have read and that I understand this protocol, the Investigator Brochure, and all other product information provided by Theriva Biologics, S.L. I agree to conduct this study in conformity with this protocol and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the E6 International Council on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), all applicable laws and regulations, including, without limitation, data privacy laws and regulations, and the regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.3.4.7 of this protocol.

Principal Investigator

Title and Name: .....

Position: .....

Signature: .....

Date: .....

SYNOPSIS

Study title:	A phase IIb, open-label, randomized study of Nab-Paclitaxel and Gemcitabine plus/minus VCN-01 in Patients with Metastatic Pancreatic Cancer (VIRAGE)
Protocol number:	P-VCNA-003
Type of study:	Phase IIb
Sponsor:	Theriva Biologics, S.L.
Study medication:	For this study, VCN-01 is considered an Investigational Medicinal Product (IMP) while nab-paclitaxel and gemcitabine are considered non-IMPs to be administrated as standard of care (SoC) under authorized conditions. VCN-01 is an oncolytic replication competent virus vector.
Study centers:	Planned: Approximately 25 sites in North America and EU
Study objectives:	**Primary:** • To evaluate the time from randomization until death in both arms (OS). • To evaluate the safety and tolerability of VCN-01, intravenously (IV) administered at Week 1 and Week 14 in Arm II. **Secondary:** • To evaluate the time to progression (TTP) or progression free survival (PFS). • To determine the Objective Response rate (ORR). • To determine the disease control rate (DCR) (stable disease [SD] + partial response [PR] + complete response [CR]). • To determine the landmark 1-year survival and PFS at the 1-year landmark. • To evaluate the duration of response (DoR). • To assess changes in tumor marker carbohydrate antigen (Ca) 19.9 measured every 4 weeks while on study. **Exploratory:** • To evaluate circulating immune markers in serum, VCN-01 genomes in blood, PH20 levels in serum,

	neutrophil/lymphocyte ratio, and serum levels of neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs). • To evaluate radiomic analysis of computerized tomography (CT) images. • To characterize the Quality of Life (QoL) via the validated European Organization for Research and Treatment Quality of Life Questionnaire (EORTC) QLQ-C30 questionnaire (version 3). • To determine the disease control rate (DCR) (stable disease [SD] + partial response [PR] + complete response [CR]) to the subsequent anti-cancer therapies.
Study design:	This is a multi-center, open label, randomized, 2-parallel arm, phase IIb study of nab-paclitaxel and gemcitabine as SoC plus/minus VCN-01 in patients with metastatic pancreatic cancer. Approximately 92 patients in about 25 sites in North America and European Union (EU) will be recruited and randomized in a 1:1 ratio to one of two treatment arms (i.e., approximately 46 patients per treatment arm): • Arm I: Nab-paclitaxel and gemcitabine as SoC (28-day cycles). Patients in this arm will not receive the IMP (VCN-01). • Arm II: Two (2) doses of VCN-01 administrated in combination with nab-paclitaxel and gemcitabine as SoC (28-day cycles with exception of the IMP dose cycles, which will be 35-day cycles). A Data Monitoring Committee (DMC) will be convened to assess safety and to look at OS to determine if the trial can continue, at regular intervals as mentioned in the DMC charter.
Diagnosis and main criteria for inclusion:	Male/female patients aged 18 years or over with histologically or cytologically confirmed, first line metastatic pancreatic adenocarcinoma stage IV de novo, who never received previous systemic treatment for their pancreatic cancer for which the established therapy is nab-paclitaxel/gemcitabine (clinical SoC). All patients must have at least one measurable tumor lesion that can be imaged for assessments determined by RECIST 1.1.
Dosing regimen:	**Arm I:** Nab-paclitaxel and gemcitabine as SoC (at 28-day cycles). Patients in Arm I will not receive the IMP (VCN-01). Nab-paclitaxel will be administered as an IV infusion at a dose of 125 mg/m^2 and gemcitabine as an IV infusion immediately after the completion of nab-paclitaxel administration at a dose of 1,000 mg/m^2 according to current SoC procedures, on Day 1, Day 8, and Day 15 of each 28-day treatment cycle.

	Arm II: Two (2) doses of VCN-01, each administered as a single IV infusion at dose $1x10^{13}$ vp, in combination with IV nab-paclitaxel and gemcitabine as SoC (28-day cycles with exception of the IMP dose cycles, which will be 35-day cycles). VCN-01 will be administered as a single IV infusion of VCN-01 at a rate of 5 mL/min on Day 1, then 1 week later, 3 cycles of nab-paclitaxel and gemcitabine will be administered. Nab-paclitaxel as an IV infusion at a dose of 125 mg/m^2 and gemcitabine as an IV infusion will be administered immediately after the completion of nab-paclitaxel administration at a dose of 1,000 mg/m^2 according to current SoC procedures during Cycles 1 and 4 on Day 8, Day 15, and Day 22 and during Cycles 2, 3, 5 and subsequent cycles on Day 1, Day 8, and Day 15. On Day 1 of Cycle 4 (+ 1 day to 2 weeks), a second VCN-01 dose will be administered at a rate of 5 mL/min. One week later, subsequent 28-day cycles of nab-paclitaxel and gemcitabine should continue. Patients in both arms will continue study treatment until progressive disease (PD), intolerable/unacceptable toxicity or patient's/investigator's decision. This period will be defined as Treatment period.
Total sample size:	Ninety-two (92) patients, randomized in a 1:1 ratio: • Arm I (SoC): 46 patients • Arm II (SoC + 2 doses of VCN-01): 46 patients
Dose modification:	No dose modifications for VCN-01 are permitted. VCN-01 will be administered at dose $1x10^{13}$ vp. Nab-paclitaxel and gemcitabine interruptions/reductions (if required) will follow the recommendation in the locally approved prescribing information/package insert or summary of product characteristics (SmPC) for metastatic pancreatic cancer.
Number of planned visits:	The trial includes the following periods: • Screening period (approximately 4 weeks prior to first dose): Days -28 to -1 (Week -4 to -1) Note: There is no Day 0 or Week 0 in this study. Study dosing starts on Day 1. • Randomization can occur any time during the 28-day Screening period when all the screening assessments are completed, but dosing (D1) must take place no later than 5 days after randomization. • Treatment period (variable, depending on progression of disease/toxicity and decision of patient/investigator):

	○ Arm I: Cycle 1 (28 days); Cycle 2 (28 days); Cycle 3 (28 days); Cycle 4 (28 days) and subsequent nab-paclitaxel / gemcitabine cycles ○ Arm II: Cycle 1 (35 days); Cycle 2 (28 days); Cycle 3 (28 days); Cycle 4 (35 days) and subsequent nab-paclitaxel / gemcitabine cycles ○ End-of-Treatment (EOT) visit: 1 month after last dose (±1 week) • Follow-up (FU) period: ○ FU without PD (±1 week): every 4 weeks (q4wk) until PD ○ FU due to PD (±1 week): q4wk during the first 6 months; every 2 months (q2mo) until the second year; every 6 months (q6mo) after the second year • End of Study (EOS): Patients will be followed for survival until the EOS regardless of further treatments, or until the sponsor ends the study. Early trial termination of the study by the Sponsor is only anticipated on the basis of safety.
Safety parameters:	Demographics; Medical history; Prior medications and procedures, including standard of care; Concomitant medications and procedures; Physical examinations; Vital signs assessments; Safety laboratory test – biochemistry, hematology, coagulation profile, thyroid stimulating hormone (TSH), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Tuberculosis (TB) test and Human Immunodeficiency Virus (HIV), urinalysis and pregnancy test; 12-Lead electrocardiogram (ECG); COVID-19 testing; Left ventricular ejection fraction (LVEF); Eastern Cooperative Oncology Group (ECOG) score; Fibroscan; adverse event (AE)/serious adverse event (SAE) assessment.
Efficacy parameters:	OS; PFS or TTP; ORR; DCR (SD + PR + CR); Landmark 1-year survival and PFS at 1-year landmark; DoR; Changes in tumor biomarker Ca 19.9; QoL via the validated EORTC QLQ-C30 questionnaire (version 3).
Pharmacodynamic parameters:	VCN-01 genomes in blood; PH20 in serum; circulating immune markers in serum; neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs) in serum; neutrophil/lymphocyte ratio; image biomarkers (radiomics) assessed from the images of CT scans performed during the study.
Statistical methods:	<u>Randomization</u> The randomization will be stratified to take account of the patient's baseline ECOG performance status (0 or 1) and region (North America or EU). <u>Sample Size and Study Power</u>

	Assuming an accrual time of 18 months with (minimum) 12-month FU for all patients, 1-sided alpha = 0.05, beta = 0.2 (80% power), the median OS=10.6 months for Arm I and the median OS=20.8 for Arm II with 1:1 randomization, 46 patients would be needed for each study arm to reach the 57 events needed using the log-rank test. It is therefore planned to randomize a total of 92 adult patients with metastatic pancreatic cancer into the study for final analysis. General Considerations Data will be summarized as follows: Continuous variables by descriptive statistics (number of patients [N], mean, standard deviation, minimum, median and maximum); categorical data by absolute and relative frequencies (n and %). Unless indicated otherwise, summary statistics will be reported for observed data only. Missing data will not be inputed. If a baseline value is missing, no change from baseline will be calculated. Baseline is defined as the last assessment before the start of study treatment. No interim analysis is planned.

TABLE OF CONTENTS

SIGNATURE PAGE **2**

PROTOCOL AGREEMENT PAGE **3**

SYNOPSIS **4**

TABLE OF CONTENTS **9**

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS **16**

1. INTRODUCTION **19**
1.1. GENERAL INFORMATION 19
1.2. MECHANISM OF ACTION 20
1.3. PRE-CLINICAL PHARMACOLOGY 20
1.4. PRE-CLINICAL PHARMACOKINETICS AND BIODISTRIBUTION 22
1.5. PRE-CLINICAL TOXICOLOGY 24
1.5.1. Toxicity Studies Conducted in Combination with Nab-paclitaxel 25
1.6. CLINICAL DATA 26
1.6.1. Ongoing Development Programmes with VCN-01 26
1.6.2. Clinical Safety 27
1.6.3. Clinical Efficacy 29
1.6.4. Clinical Pharmacokinetics 30
1.6.5. Clinical Shedding 30
1.7. DISEASE REVIEW AND RATIONALE FOR THE STUDY 30
1.8. RISK-BENEFIT ASSESSMENT 31
1.8.1. Potential benefits 31
1.8.2. Risks 32
1.8.3. Benefit – Risk Assessment 33

2. OBJECTIVES 35
2.1. PRIMARY OBJECTIVES 35
2.2. SECONDARY OBJECTIVES 35
2.3. EXPLORATORY OBJECTIVES 35

3. ENDPOINTS 36
3.1. PRIMARY ENDPOINTS 36
3.2. SECONDARY ENDPOINTS 36
3.3. EXPLORATORY ENDPOINTS 36

4. INVESTIGATIONAL PLAN 37
4.1. SUMMARY OF STUDY DESIGN 37
4.2. DISCUSSION OF TRIAL DESIGN 39
4.3. TRIAL TIMETABLE (STUDY PERIODS) 39

5. SELECTION AND WITHDRAWAL OF PATIENTS 41
5.1. INFORMED CONSENT 41
5.2. INCLUSION CRITERIA 41
5.3. EXCLUSION CRITERIA 42
5.4. ASSIGNING PATIENTS TO TREATMENT ARMS 44
5.5. PREMATURE WITHDRAWAL OF PATIENTS FROM STUDY AND REPLACEMENT POLICY 44
5.5.1. Discontinuation Criteria 44
5.5.2. Replacement Policy 45

6. STUDY MEDICATION 47
6.1. PRESENTATION, STORAGE, PACKAGING AND LABELLING 47
6.1.1. Presentation, Storage, Packaging and Labelling of Investigational Product 47
6.1.2. Presentation, Storage, Packaging and Labelling of Nab-paclitaxel 49
6.1.3. Presentation, Storage, Packaging and Labelling of Gemcitabine 49
6.2. RECEIPT OF INVESTIGATIONAL PRODUCTS AT THE CENTER/STABILITY DURING SHIPMENT 49
6.3. DOSE, ROUTE AND SCHEDULE OF INVESTIGATIONAL PRODUCT ADMINISTRATION 49
6.4. DOSE JUSTIFICATION 50

6.5. CRITERIA FOR SCHEDULE ADJUSTMENT/DOSE-MODIFICATION OF INVESTIGATIONAL PRODUCT 51
6.6. INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY 51
6.7. VCN-01 PREPARATION 52

7. CONCOMITANT THERAPY/MEDICAL MANAGEMENT OF ADVERSE EVENTS 54
7.1. MEDICATIONS THAT MAY NOT BE ADMINISTERED 54
7.2. MANDATORY CONCOMITANT MEDICATIONS 55
7.3. CONCOMITANT MEDICATIONS RECOMMENDED TO BE USED TO TREAT FLU-LIKE SYMPTOMS 55

8. SCHEDULE OF VISITS 56
8.1. SCREENING EVALUATION 56
8.2. TREATMENT PERIOD(S): DRUG ADMINISTRATION 56
8.2.1. Schedule of Visits for On-treatment Period 56
8.2.2. End of Treatment 57
8.3. FOLLOW-UP PERIOD 57
8.4. WITHDRAWAL 57
8.5. END OF STUDY 57

9. ASSESSMENTS OF EFFICACY 58
9.1. SPECIFICATION OF EFFICACY PARAMETERS 58
9.2. METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING EFFICACY PARAMETERS 58
9.2.1. Overall Survival 58
9.2.2. Landmark 1-year Survival and Progression Free Survival at 1-year Landmark 58
9.2.3. Progression Free Survival or Time to Progression 58
9.2.4. Objective Response Rate 59
9.2.5. Disease Control Rate (DCR) (SD+PR+CR) 59
9.2.6. Duration of Response 59
9.2.7. Changes in Tumor Marker Ca 19.9 59
9.2.8. Quality of Life (QoL) 59

10. ASSESSMENTS OF SAFETY 60
10.1. SPECIFICATION OF SAFETY PARAMETERS 60
10.2. METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING SAFETY PARAMETERS 60
10.2.1. Demographic Data 60
10.2.2. Medical History 60
10.2.3. Prior and Concomitant Medications and Procedures 60
10.2.4. Physical Examination 61
10.2.5. Vital Signs 61
10.2.6. Safety Laboratory Tests 61
10.2.7. 12-Lead Electrocardiogram (ECG) 62
10.2.8. COVID-19 Testing 62
10.2.9. Left Ventricular Ejection Fraction (LVEF) 63
10.2.10. Eastern Cooperative Oncology Group (ECOG) Score 63
10.2.11. Fibroscan 63
10.3. ADVERSE EVENT REPORTING 63
10.3.1. Definition of an Adverse Event 63
10.3.2. Serious Adverse Events 63
10.3.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs 64
10.3.4. Recording and Reporting of Adverse Events 65
10.3.5. Safety Reporting to IECs/IRBs, Competent Authorities, and Investigators 69
10.3.6. Adverse Event Reporting Period 69
10.3.7. Data Monitoring Committee 69

11. ASSESSMENTS OF PHARMACODYNAMICS 71
11.1. SPECIFICATION OF PHARMACODYNAMIC PARAMETERS 71
11.2. METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING PHARMACODYNAMIC PARAMETERS 71
11.2.1. Changes in Biomarkers 71

12. STATISTICS 73
12.1. SAMPLE SIZE AND STUDY POWER 73
12.2. RANDOMIZATION 73

12.3. STATISTICAL METHODS 73
12.3.1. General Considerations 73
12.3.2. Populations for Analysis 73
12.4. BASELINE CHARACTERISTICS 74
12.5. EVALUATION OF EFFICACY 74
12.5.1. Evaluation of Primary Efficacy Endpoint 74
12.5.2. Evaluation of Secondary Efficacy Endpoints 75
12.6. EVALUATION OF SAFETY 75
12.7. EVALUATION OF PHARMACODYNAMICS 76
12.8. INTERIM ANALYSIS 76

13. OBLIGATIONS OF THE PRINCIPAL INVESTIGATOR 77
13.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC) 77
13.2. REGULATORY BODY APPROVAL 77
13.3. GMO (GENETICALLY MODIFIED ORGANISMS) APPROVAL 77
13.4. INFORMED CONSENT 77
13.5. CASE REPORT FORMS AND SOURCE DOCUMENT VERIFICATION 77
13.6. CONFIDENTIALITY 78
13.7. STAFF INFORMATION AND RESPONSIBILITIES 78
13.8. DOCUMENTATION REQUIRED PRIOR TO INITIATION AND DURING THE STUDY 79
13.9. ESSENTIAL DOCUMENT RETENTION 79

14. STUDY MANAGEMENT 80
14.1. MONITORING 80
14.2. QUALITY ASSURANCE AND QUALITY CONTROL 80
14.2.1. Quality Control (QC) 80
14.2.2. Quality Assurance (QA) 80
14.2.3. Audit 80
14.3. DATA QUERY PROCESS 81
14.4. PROTOCOL DEVIATIONS/AMENDMENTS 81
14.5. DISCONTINUATION OF THE STUDY 81

14.6. PUBLICATIONS 81

15. REFERENCES 82

16. APPENDICES 85

LIST OF APPENDICES

APPENDIX 1: HIGHLY EFFECTIVE CONTRACEPTIVE METHODS 85

APPENDIX 2: LABORATORY ASSESSMENTS 86

APPENDIX 3: ECOG PERFORMANCE STATUS 88

APPENDIX 4: RECIST CRITERIA 89

APPENDIX 5: REPRESENTATIVE EXAMPLE OF EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF EORTC QLQ-C30 QUESTIONNAIRE (VERSION 3) 93

APPENDIX 6: GUIDANCE TO ADDRESS COVID-19 PANDEMIC AND THEIR POTENTIAL IMPACT ON THE CLINICAL STUDY 95

APPENDIX 7: STUDY FLOW CHART ARM I 98

APPENDIX 8: STUDY FLOW CHART ARM II 101

LIST OF TABLES

Table 6-1: Quantitative composition of the Investigational Medicinal Product (IMP) 48

Table 6-2: Arm I Treatment Schedule 50

Table 6-3: Arm II Treatment Schedule 50

Table 10-1: Relationship of the Adverse Event to the Study Treatment 67

Table 10-2: Definition of Severity of Adverse Events 67

LIST OF FIGURES

Figure 1-1: Schematic diagram of individual differences between Had5 and VCN-01 19

Figure 4-1: Study Design 38

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

βHCG	Beta human chorionic gonadotropin
Ad5	Adenovirus type 5
ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AR	Adverse reaction
ARM	Adenovirus Reference Material
AST	Aspartate aminotransferase
BP	Blood Pressure
BUN	Blood urea nitrogen
cDNA	Complementary deoxyribonucleic acid
Ca	Carbohydrate antigen
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRP	C-reactive protein
CT	Computerized Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
D	Day (as in treatment day)
DCR	Disease control rate
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EMA	European Medical Agency
EORTC	European Organization for Research and Treatment Quality
EOS	End of Study
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	Fluorescence *In Situ* Hybridization
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase

GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
GMO	Genetically modified organism
HA	Hyaluronan
HAd5	Human adenovirus type 5
HBcAB	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
ICO	Institut Català d'Oncologia
ID	Identification
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International normalized ratio
IP	Interferon gamma-induced protein
IRB	Institutional Review Board
IRT	Interactive Response Technology
IIS	Investigator Initiated Study
ITT	Intent-to-Treat Analysis Set
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LD	Longest diameter
LOQ	Limit of Quantification
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRSD	Maximum Recommended Starting Dose
MTD	Maximum Tolerated Dose
N	Number of patients
NAbs	Neutralizing antibodies
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
ORR	Overall response rate
OS	Overall survival
OV	Oncolytic virus
p.o.	Orally
PAF	Platelet Activating Factor

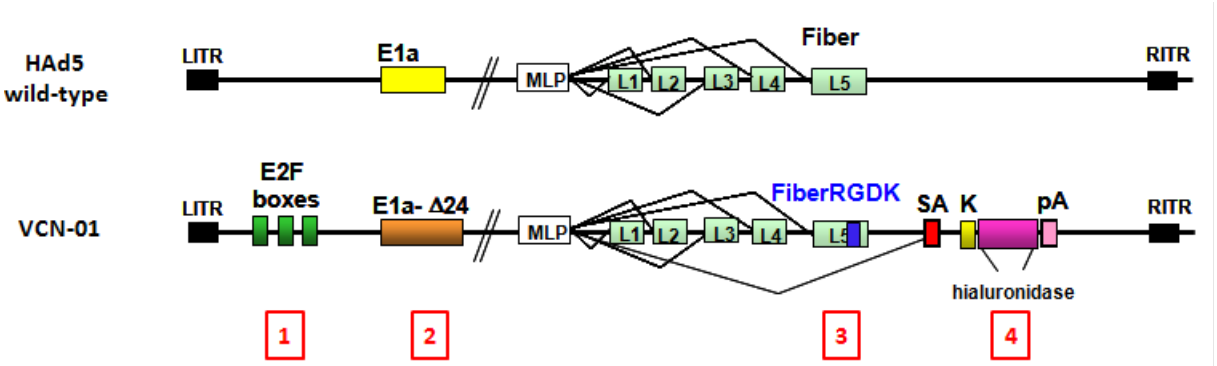
PCR	Polymerase chain reaction
PD	Progressive Disease
PFS	Progression-free survival
pH	potential of Hydrogen
PICD	Patient Informed Consent Document
PK	Pharmacokinetic
PPS	Per-Protocol Set
PR	Partial Response
pRB	Retinoblastoma protein
PT	Preferred term
q2mo	Every 2 months
q4wk	Every 4 weeks
q6mo	Every 6 months
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
RGD	Arginylglycylaspartic acid
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Stable disease
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOC	System organ class
SUSAR	Suspected unexpected SAR
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
US	United States
Vp	Virus Particles
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. GENERAL INFORMATION

VCN-01 is an oncolytic adenovirus. Oncolytic refers to its ability to selectively lyse tumor cells. VCN-01 is a product derived from human adenovirus type 5 (Had5). VCN-01 maintains the ability to replicate in infected tumor cells and to propagate to non-infected cells. Therefore, VCN-01 is considered a replication-competent virus. It is characterized by the presence of four independent genetic modifications in the wild-type Had5 adenoviral backbone that confer tumor selectivity and anti-tumor activity. One of the genetic modifications of VCN-01 is the insertion of an expression unit encoding a human hyaluronidase gene. Viruses that carry exogenous expression units (different from the wild-type viral deoxyribonucleic acid [DNA]) are defined as vectors. Therefore, VCN-01 is defined as a replication -competent virus vector (Rodriguez-Garcia et al, 2015).

Figure 1-1: Schematic diagram of individual differences between Had5 and VCN-01



These modifications include:

1. Insertion of a tumor-specific synthetic promoter (415 promoter, shown in green) composed of four human E2F-1 transcription factor-binding boxes and one Sp-1-binding box (175 bp fragment) that have been inserted at position 422 in human adenovirus type 5 genome Adenovirus Reference Material (ARM), (GenBank accession no. AY339865), corresponding to the E1A endogenous promoter region.
2. Partial deletion of the E1A gene (Δ24 mutation, shown in orange). This deletion corresponds to a 24 base-pair sequence between positions 923 and 946 in the Had5 ARM genome and codes for amino acids 122 to 129 in the E1A protein sequence.
3. Mutation of bases 31307 – 31319 in the Had5 ARM genome, from AAAAAAACCAAG to CGAGGAGACAAG (shown in blue). This sequence codes for amino acids 90-93 (KKTK) in the adenovirus fiber protein and the presence of the mutation changes these residues to 90RGDK93.
4. Insertion of an expression cassette for the human sperm hyaluronidase (PH20) complementary deoxyribonucleic acid (cDNA). The insert spans 1524 bp and has been included at the position 32826 within the Had5 ARM genome. It contains:

a. A splicing acceptor (SA) signal (IIIa) (identical to the splicing signal present in the IIIa adenovirus gene) that allows the inserted sequence to act as a new viral transcription unit (shown as a red box).
b. A Kozak (K) signal (CCACC) placed immediately before the start codon of the hyaluronidase gene translation (shown as a yellow box).
c. A coding sequence for a truncated form of sperm hyaluronidase enzyme PH20 (shown as a violet box) (1473 bp).
d. Poly-A (pA) sequence to stop gene transcription (shown as a pink box)

1.2. MECHANISM OF ACTION

Considering the naturally lytic replication cycle of adenoviruses together with the genetic modifications inserted in VCN-01 backbone, its biological activity is considered to offer a novel mechanism of action in the field of anti-cancer therapies, and is claimed to be based on two factors:

(1) the selective killing of tumor cells by effect of its replication, which results in a self-amplification of the initial inoculum that is released after cell lysis and spread through the tumor mass.
(2) the expression of hyaluronidase, which degrades partially the extracellular matrix of the tumor facilitating the diffusion of the virus progeny and increasing the accessibility of chemotherapy and other drugs such as therapeutic antibodies.

1.3. PRE-CLINICAL PHARMACOLOGY

The nonclinical pharmacology programme includes *in vitro* characterization studies (replication selectivity, genomic integrity, transgene activity, cytotoxicity in a panel of tumor cells) and *in vivo* studies designed to evaluate the mechanism of action of VCN-01 following single intravenous (IV) administration in the relevant animal models. The *in vivo* studies comprise the administration of VCN-01 alone or in combination with other therapies i.e., the standard of care for the treatment of pancreatic cancer (gemcitabine, nab-paclitaxel plus gemcitabine) or immune checkpoint inhibitors (anti-PD-L1 antibodies such as Durvalumab) for the treatment of recurrent/metastatic squamous cell carcinoma of the head and neck.
VCN-01 is targeted against the retinoblastoma pathway, which is acknowledged to be a hallmark of all cancer cells (Hanahan and Weinberg, 2011). At a molecular level, many if not all anti-proliferative signals are funneled through the retinoblastoma protein (pRB), which blocks cell proliferation by sequestering and altering the function of E2F transcription factors that control the expression of banks of genes essential for progression from quiescent into S phase (Hanahan and Weinberg, 2011). This process ultimately leads to uncontrolled cell growth and cancer. It is generally accepted that the anti-growth circuit converging onto Rb/-E2F complex and the cell division cycle is, one way or another, disrupted in virtually all human cancers (Nevins, 2001). This alteration, however, can occur at multiple points/levels of the pathway among the different cancer cell populations.
The biological feasibility, in terms of selectivity of replication and anti-tumor activity, of the use of VCN-01 in different tumor types was confirmed *in vitro* in several human cancer cell lines studies, including pancreatic carcinoma, head and neck tumor, retinoblastoma, melanoma,

colorectal carcinoma and ovarian cancer (Studies VCNA-B1-05, HSJD-VCN01-01, VCNC-B1-52 and VCNA-B1-101).

Additionally, it was confirmed that VCN-01 cytotoxicity in tumor cells is in the same range as that of a virus without the genetic modifications in its genome. Thus, VCN-01 genetic modifications do not substantially modify the cytotoxic potency of adenovirus, being as potent as the wild-type strain in terms of replication and killing capabilities (Rodriguez-Garcia et al, 2015).
The relevant animal models used in pharmacology *in vivo* studies were the immunodeficient mouse bearing human tumor xenograft model, which has been the standard model to investigate the response to anticancer therapy for the past 25 years (Kelland et al, 2004) and it has the advantage to be the actual human tumor tissue with its genetic complexity and epigenetic abnormalities; and the measurement of the growth rate of the tumor has been reported to often be the most reliable in this model (Richmond and Su, 2008). The other relevant animal model used in proof-of-concept studies following intratumor administration of VCN-01 was the syngeneic tumor-bearing Syrian hamster model (subcutaneous). This animal model is semi-permissive to the replication of adenovirus serotype 5-based oncolytic viruses, and together with the fact that it is an immunocompetent animal species, it has been developed as an alternative to the immunodeficient mice bearing human tumor xenografts (Thomas et al, 2006).
VCN-01 is able to undergo productive replication in tumor cells both *in vitro* (Studies VCNA-A1-01 and VCNA-B1-101) and *in vivo* in different relevant models (Studies VCNA-D2-31_IV and VCNA-D2-59). While not able to efficiently replicate *in vitro* in human non-tumor cultures (Study VCNA-B1-07), VCN-01 replication and secretion of hyaluronidase *in vitro* (Study VCNA-B1-04) correlate with a very robust anti-tumor activity *in vivo* that efficiently controls tumor growth in various models, using different treatment schedules (VCN-01 alone or in combination with chemotherapy) and routes of administration (IV and intratumoral). VCN-01 anti-tumor activity *in vivo* is dose-dependent and maintained for long periods of time after a single administration of the product, validating the self-amplifying nature of VCN-01 (Studies VCNA-B2-10, VCNA-B2-11, VCNA-B2-27, VCNA-B2-13_sgl, VCNA-B2-14, VCNA-B2-16, VCNA-B2-57, VCNA-B2-58, and VCNA-B2-64). The cancer selectivity of the self-amplifying capacity of VCN-01 is also observed in blood, as animals with human tumors show sustained viral levels in blood (up to Day 22 post-administration, study VCNA-B2-70), whereas animals without tumors (even in a semi-permissive model) show a dramatic decrease of virus in blood over the time (Studies VCNA-C2-19 and VCNA-C2-45). It was shown that in studies where VCN-01 elicited a long lasting (up to 80 days) suppression of tumor growth, a significant reduction in the hyaluronan content of the tumors was detected, compared to the sham-treated groups [Studies VCNA-B2-14 and VCNA-B2-27]). This is of relevance as at late time points the tumor models mimic the complex environment of human tumors, in which, not only tumor cells but also high number of fibroblasts are embedded within a dense extracellular matrix.

Hyaluronidase-mediated degradation of the tumor extracellular matrix has been described to facilitate the diffusion of the virus progeny and increase the accessibility for chemotherapy (Nakazawa et al, 2006; Ganesh et al, 2008; Platt and Szoka, 2008 and Guedan et al, 2010). We could clearly confirm this in our *in vivo* studies in mice and hamster models, where VCN-01 in combination with gemcitabine or nab-paclitaxel plus gemcitabine produced a strong

synergic anti-tumor effect, highlighting the chemosensitizing capability of VCN-01 (Studies VCNA-B2-14, VCNA-B2-16, and VCNA-B2-57). Even in a human orthotopic xenograft mouse model with high hyaluronan content, which is considered to be more similar to the clinical situation in patients due to the architecture of the tumor, it was observed that gemcitabine accessibility to the tumor was much higher in some tumors that had been treated with VCN-01 (Study VCNA-B2-58). Tumor extravasation of antibodies with immune check point blockade capability (anti-PD-L1) was also increased in VCN-01 treated animals (subcutaneous human tumor in xenograft mouse model [Study VCNA-B2-70]). These data indicate that VCN-01 is able to increase the accessibility to a variety of treatments into the tumor.

Overall, the conducted pharmacology studies assess the mechanism of action and provide sufficient non-clinical evidence to demonstrate that VCN-01 displays anti-tumor activity alone as well as in combination with chemotherapy. Additionally, the expression of hyaluronidase from VCN-01 replication contributes to degrading the extracellular matrix of the tumor facilitating viral spread, increasing the accessibility of concomitant drugs such as durvalumab (as demonstrated preclinically [Rodriguez-Garcia et al, 2015] and in Study VCNA-B2-70), and potentially easing the infiltration of immune cells due to matrix opening. Considering the potential role of tumor desmoplasia in pancreatic cancer and head and neck carcinomas, associated to highly developed, invasive tumors, metastatic behavior and poor prognosis (Toole, 2004; Bertrand et al, 1992; Karpathiou et al, 2016; Curry et al, 2014), the use of VCN-01 can represent an advantage for patients in the clinical setting.

1.4. PRE-CLINICAL PHARMACOKINETICS AND BIODISTRIBUTION

The pharmacokinetic (PK) profile of VCN-01 has been studied preclinically in immunocompetent mice and has been found to be similar to that described for human wild-type adenovirus (Alemany et al, 2000). The calculated half-time live is below 5 min.

Two Good Laboratory Practice (GLP) biodistribution studies have been conducted in Syrian hamsters, the relevant animal model as it is immunocompetent and semi-permissive to adenoviral infection and replication (Studies VCNA-C2-19 and VCNA-C2-45). Single IV administration of VCN-01 represents the most sensitive approach (first administration) and worst-case scenario (maximal systemic exposure) to study biodistribution, persistence and clearance profile of VCN-01 in non-target tissues.

Additionally, supporting non-GLP biodistribution studies in human tumor-bearing xenograft in immunodeficient mouse (Studies VCNA-D2-31 and VCNA-D2-59) have been conducted to evaluate the effect of viral replication within the tumors and evidenced no differences in VCN-01 biodistribution pattern in non-target organs compared to pivotal GLP.

The two GLP biodistribution studies have tested two viral doses: low dose $2.5x10^{11}$ vp/hamster (Study VCNA-C2-45) and high dose $4x10^{11}$vp/hamster (Study VCNA-C2-19). The high dose (maximum tolerated dose (MTD) in this animal model) was selected to maximize the worst-case scenario and 10 key organs were analyzed (gonads, brain, liver, kidney, lung, heart, spleen, lymph nodes, pancreas, and blood). The low dose represented the pharmacologically active dose used to establish the clinical Maximum Recommended Starting Dose (MRSD) and all organs were analyzed as per European Medical Association (EMA) guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006). Both GLP studies VCNA-C2-19

and VCNA-C2-45 showed consistent results between them. Biodistribution after systemic administration of VCN-01 indicates that at 48 h post IV administration the highest levels are detected in the liver (with ~$4x10^8$ copies per µg of genomic DNA) although the virus is able to reach all tested tissues. VCN-01 was also present in the adrenals, blood, dosing site and gall bladder with similarly high concentrations in both male and female. By Day 8, VCN-01 was detected in all animals albeit at reduced concentrations compared to Day 2, with highest levels at ~10^4 copies/µg DNA showing high heterogeneity for each organ. By Day 28, the levels of VCN-01 target had reduced and ~40% of the tested samples in males and females had cleared to ≤ Limit of Quantification (LOQ). Although VCN-01 viral DNA was still traced in several tissues with high heterogeneity, blood and brain were clear in all animals by Day 28. There was no evidence to suggest that the virus replicated between Days 2 to 28 in any organ.
In non-GLP studies conducted with mice bearing tumors, VCN-01 was able to target human xenograft tumors and replicate within them over the time, reaching a 3-log increase from Day 2 to Day 28. As expected, VCN-01 was highly accumulated in the liver after IV injection. However, in this tissue VCN-01 did not replicate and was eliminated over the time, having up to a 3-log decrease from Day 2 to Day 28 (Studies VCNA-D2-31 and VCNA-D2-59).
This is in line with results from analysis of viral genomes in blood from other studies in tumor-bearing mice. A first peak is observed at 48 h and smaller secondary peaks are observed at longer time points on Days 11 and 22 post-administration (Studies VCNC-D2-09 and VCNA-B2-70), suggestive of adenovirus replication and shedding into the bloodstream. On the contrary, no peak is observed in non-tumor bearing mice (Study VCNA-D2-29).
These results are consistent with the described tissue tropism of human wild-type adenovirus after systemic administration in animal models and with the biodistribution previously reported for similar oncolytic adenoviruses in comparable preclinical models (Page et al, 2007 and Lichtenstein et al, 2009). Specifically the pattern of fully cleared tissues and the levels of remaining genomes at D28 (~10^1 to 10^4 copies/ µg of genomic DNA) are the same in the hamster model with respect to a wild-type adenovirus 5 or other genetically modified oncolytic adenoviruses (Ying et al, 2009; Kim et al, 2016; Tao et al, 2001). The same biodistribution pattern was also confirmed in post-mortem tissue samples of a patient treated with a similar oncolytic adenovirus in a clinical trial (Hamid et al, 2003). This supports the argument that the genetic modifications included in VCN-01 are not expected to modify significantly its biodistribution compared to the wild-type/native capsid or adenovirus expressing arginylglycylaspartic acid (RGD) from fiber knob.

Furthermore, biodistribution data of VCN-01 indicates the lack of integration of VCN-01 in tissues, which is in line with its non-integrative nature and consistent with available data from other replicating adenoviruses. It is of importance that although low levels of VCN-01 were detected at Day 2 in gonads, lack of infection of germ cells by VCN-01 at Day 2 post-administration and disappearance of VCN-01 DNA after Day 8 post-administration was evidenced by a Fluorescence *In Situ* Hybridization (FISH) analysis (Study VCNA-C1-37). These data, supported by other studies in the literature, further supports that the potential risk of germline transmission associated to VCN-01 administration is negligible.

1.5. PRE-CLINICAL TOXICOLOGY

In vitro studies of VCN-01 have demonstrated its selectivity in terms of virus replication and virus-induced cytotoxicity, parameters that characterize the main mechanism of action of VCN-01. The nonclinical toxicology programme includes *in vivo* studies of VCN-01 following single IV administration in the relevant animal models, with VCN-01 administered alone or in combination with other therapies i.e., the standard of care for the treatment of pancreatic cancer (gemcitabine, nab-paclitaxel plus gemcitabine) or immune checkpoint inhibitors (anti-PD-L1 antibodies such as Durvalumab).

Given the species-specific nature of Had5 and VCN-01, it is generally accepted that the Syrian hamster is a relevant animal model in the field of serotype 5-based oncolytic adenoviruses to evaluate the safety and toxicity (Thomas et al, 2006; Lichtenstein et al, 2009; Ying et al, 2009; Kim et al, 2016; Tollefson et al, 2017; Wold and Toth, 2012). Syrian hamster allows to determine the impact of the different factors involved in administration of replicating adenovirus, namely: the presence of high amounts of virus physical particles (capsids eliciting unspecific innate immune cytotoxicity), the early gene expression E1A (that can be highly toxic and immunogenic), the viral replication causing cytotoxicity due to the killing of infected tissues, the virus transgene expression inducing immunogenicity or unwanted pharmacological effects, and the potential for immunotoxicity, i.e. the innate response.

Local, intratumoral administration of VCN-01 induces only minimal toxicity without alterations in biochemical or hematological parameters, which is consistent with a minor systemic exposure of VCN-01 into the bloodstream from injected tumors.

Systemic toxicity after a single administration of VCN-01 has been evaluated in mice at a dose of $5x10^{10}$ vp/mice and in hamsters at doses of $2.5x10^{11}$ and $4x10^{11}$ vp/hamster. Despite differential permissiveness to human adenovirus replication in both species, a similar toxicity profile has been observed in both experimental models.

The liver was the primary target organ for toxicity with secondary effects apparent in the gall bladder, spleen, and bone marrow (results are in line with those observed in biodistribution studies). Mortality due to hepatotoxicity was observed at $4x10^{11}$ vp in hamsters, which corresponds to 4-fold above the highest clinical dose planned in the clinical development of VCN-01. On the contrary, the dose of $2.5x10^{11}$ vp (2.5-fold above the highest clinical dose planned in the clinical development of VCN-01) was better tolerated and mortality was only observed in one animal out of 60. Clinical signs resolved by the end of the first week and were considered to be related to hepatotoxicity. There were dose-related, marked increases in transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and bilirubin levels on Day 2. All these biochemistry parameters were substantially reduced by Day 8 and normalized by Day 28. An increase in leucocyte numbers was apparent on Days 2 and 8 and was considered to reflect an inflammatory response to the injection of viral particles and/or secondary to the damage within the liver. On Day 2, there were also reductions in platelet numbers and increased clotting times that returned to control levels by Day 8. From these pivotal GLP toxicity studies at the dose levels tested in the relevant animal model, a no observed adverse effect level (NOAEL) could not be established; however, this is not considered essential to support clinical use of an anti-cancer pharmaceutical according to International Council on Harmonization (ICH) S9 guideline.

The observed rapid onset of an innate immune response is characterized by elevations in interferon (IFN)-γ, interferon gamma-induced protein (IP)-10 and tumor necrosis factor (TNF)-α after VCN-01 administration in mice with a peak within 6 to 72 h post-administration and are normalized by Day 10 (Study VCNA-C2-32); whereas in the clinical setting there is a dose-dependent peak of interleukin (IL)-6 and IL-10 after 6 h or 24 h, respectively. Platelet Activating Factor (PAF) is immediately increased after VCN-01 administration and was characterized as a potential mediator of toxicity but only in one non-clinical model (the athymic mouse bearing TP-11 orthotopic pancreatic tumors), which has shown to be more sensitive (Studies VCNA-B2-58 and VCNA-B2-64). These elevated cytokines or increased PAF levels in the clinical setting do not correlate to increased toxicity. VCN-01 injection also elicited an immunological response reflected by a sustained increase in specific neutralizing anti-adenovirus antibodies, which were detectable by Day 8 after initial exposure.

1.5.1. Toxicity Studies Conducted in Combination with Nab-paclitaxel

VCN-01 plus --gemcitabine and nab-paclitaxel: no increase in any toxicity parameter such as mortality, clinical signs, body weight, clinical biochemistry and hematology parameters was detected in any of the study when comparing the combination of gemcitabine plus VCN-01 versus VCN-01 alone at the same dose levels of $2.5x10^{11}$ and $4x10^{11}$ vp/hamster (study numbers C2-22 and C2-23). These findings were regardless of the dose level (high or low), the route and the frequency of administration, and include evaluations at late time points after repeated gemcitabine dosing. Gemcitabine/nab-paclitaxel co-administration with IV VCN-01 ($2.5x10^{11}$ vp/hamster) in Syrian hamster was also evaluated at short time points (peak toxicity for VCN-01) and at an intermediate time-point after drug administration (expected peak toxicity for chemotherapy drugs) (study numbers C2-50 and C2-51). Overall, the mortality, body weight variation, clinical signs, biochemical and hematological profile of the animals receiving VCN-01 in combination with gemcitabine/nab-paclitaxel did not differ significantly from those receiving either gemcitabine/nab-paclitaxel or VCN-01 alone.

1.5.2. Repeated Administration Toxicity Studies

The toxicity, after a repeated systemic administration of VCN-01 (Day 1 and Day 92), has been evaluated in hamsters at 2.5E11 vp/animal per dose in a non-clinical toxicity study (VCNAC2- 104). The toxicity of the repeated VCN-01 administration was evaluated when administered alone and in combination with gemcitabine and Nab-paclitaxel.

Neither mortality nor clinically significant adverse events were observed after the first and second VCN-01 administration. Liver histopathology analysis confirmed a subacute viral infection of moderate-severe intensity with the presence of intranuclear viral inclusion corpuscles 48h after the first VCN-01 administration, but not 48h after re-administration of the virus at Day 92 when administered alone or in combination with gemcitabine and nab-paclitaxel. The administration of 3 cycles of chemotherapy did not show a synergy with the toxicity of the viral infection when analyzed at Day 94 (48h after the second VCN-01 administration). These results are consistent with the observed biochemical and hematological alterations observed at Day 3 after first VCN-01 administration. However, the second dose of VCN-01 (three months after the first virus dose) did not show relevant alterations on Day 94 (48h after the second dose), either alone or in combination with gemcitabine and nab-paclitaxel treatment.

Overall, a second dose of VCN-01 when was administered 3 months after the first dose, either alone or in combination with gemcitabine and nab-paclitaxel, showed a tolerable and acceptable toxicity profile in the Syrian hamster model.

1.6. CLINICAL DATA

In June 2011, VCN-01 was granted Orphan Drug designation in the European Union (EU) for the treatment of pancreatic cancer (EU/3/11/880–- EMA/OD/008/11). The development of VCN-01 started in Europe with a programme involving two phase I clinical trials conducted in Spain, both sponsored by VCN Biosciences S.L. (now Theriva Biologics, S.L.):

- **P-VCNA-001:** A Phase I, Open-Label, Dose Escalation Study of IV administration of VCN-01 oncolytic adenovirus with or without gemcitabine and nab-paclitaxel in patients with advanced solid tumors (EudraCT number: 2012-005555-16; NCT02045602). This study is completed (last patient last visit on 23 January 2020) and the clinical study report was submitted to the Spanish Health Authorities in August 2020 and to Food and Drug Administration (FDA; August 2021; IND 27038).
- **P-VCNA-002:** A Phase I, Multicenter, Open-Label, Dose Escalation Study of intratumoral injections of VCN-01 oncolytic adenovirus with or without IV gemcitabine and nab-paclitaxel in advanced pancreatic cancer (EudraCT number: 2012-005556-42; NCT02045589). This study is completed (last patient last visit on 13 September 2018) and the clinical study report was submitted to the Spanish Health Authorities in September 2019 and to FDA (August 2021).

1.6.1. Ongoing Development Programmes with VCN-01

VCN-01 anti-tumor activity is not restricted to any specific tumor type and could hence be a suitable treatment option for a wide range of human solid tumors. Indeed, the expression of hyaluronidase from VCN-01 replication degrades the extracellular matrix of the tumor facilitating viral spread, increasing the accessibility of concomitant drugs, and potentially easing the infiltration of immune cells due to matrix opening. This feature of VCN-01 represents an outstanding characteristic/advantage over current treatments/combination regimens, particularly for tumors with high stroma content.
In line with this rationale, Theriva Biologics is engaged in other clinical development in different indications in collaboration with third parties, mostly early-phase investigator-initiated studies.

- **Head and neck carcinoma**: An investigator-initiated study has been authorized in October 2018 in EU (Spain), sponsored by the public institution Institut Català d'Oncologia (ICO) (L'Hospitalet de Llobregat, Spain), with VCN-01 in combination with an anti-PD-L1 immune checkpoint inhibitor titled "A Phase I Study to Evaluate the Safety, Tolerability, and Efficacy of VCN-01 in Combination With Durvalumab (MEDI4736) in Subjects With Recurrent/ Metastatic Squamous Cell Carcinoma of the Head and Neck" (**ICO-VCN-H&N-2018**; EudraCT number: 2018-001095-38; NCT03799744; dosing completed and follow-up (FU) ongoing).
- **Retinoblastoma:** An investigator-initiated study with VCN-01 following intravitreal injections in pediatric patients is currently ongoing in EU (Spain), sponsored by the Fundació Sant Joan de Déu (Barcelona, Spain), titled "A phase I, unicentre, open-

label, dose escalation study to assess VCN-01 safety and efficacy in refractory retinoblastoma patients" (**FSJD-RTB-2015;** EudraCT number: 2016-001060-11; NCT03284268; recruitment ongoing). This development programme is out of the scope of the present Investigator's Brochure (IB). In February 2022, VCN-01 was granted Orphan Drug designation by the United States (US) FDA for the treatment of retinoblastoma (DRU-2021-8603).

- **High-grade Brain Tumors**: An investigator-initiated study has been authorized in August 2021 in United Kingdom (UK), sponsored by the University of Leeds (Leeds, UK), with VCN-01 administered IV titled "A clinical study to evaluate the biological effects of preoperative IV administration of VCN-01 in patients prior to surgical resection of high-grade brain tumors" (VCN-01 BRAIN, EudraCT number: 2020-003405-59; recruitment ongoing).
- **Pancreatic/ Serous Epithelial Ovarian Cance**r: An investigator-initiated study has been authorized in September 2021 in US, sponsored by the University of Pennsylvania (Pennsylvania, US), with VCN-01 administered IV titled "Phase 1 Trial of Human Chimeric Antigen Receptor Modified T Cells (huCART-meso) Administered in Combination with VCN-01 in Patients With Pancreatic and Serious Epithelial Ovarian Cancer" (NCT 05057715; recruitment ongoing).

1.6.2. Clinical Safety

Safety data of VCN-01 is available from completed and on-going clinical trials including different routes of administration (IV, intratumoral, intravitreal), different dosing schemes (single dose, multiple intratumoral injections), and different treatment regimens (VCN-01 monotherapy, VCN-01 in combination with gemcitabine, VCN-01 in combination with nab-paclitaxel and gemcitabine in a concomitant or delayed schedule, VCN-01 in combination with durvalumab in a concomitant or delayed schedule).

At the date of the last DSUR, 77 patients have been administered VCN-01, either alone or in combination with other treatments. Within the clinical development programme sponsored by Theriva Biologics S.L. (formerly VCN Biosciences, S.L.), 42 patients have been included and treated with systemic VCN-01 in study P-VCNA-001 and 8 patients intratumorally in study P-VCNA-002. Regarding the Investigator Initiated Study (IIS) in head and neck tumors, 20 patients have been administered VCN-01 systemically, alone or in combination with durvalumab. Regarding the University of Pennsylvania UPCC 03821 huCART-meso+VCN-01 in Pancreatic/Ovarian Cancer clinical trial, one patient has been treated systemically with VCN- 01 in combination with mesothelin-directed huCART. One (1) patient has been treated with intravenous VCN-01 in the VCN-01 BRAIN clinical trial, sponsored by the University of Leeds. Six (6) patients have been treated with VCN-01 intravitreally in the investigator-initiated study in pediatric retinoblastoma. Neither intravitreal nor intratumoral administration are pertinent to the current study.

Available clinical safety data for VCN-01 when administered systemically as a single agent (P-VCNA-001, part I, n=16) show that the highest adverse event (AE) rates observed were pyrexia in 13 out of 16 subjects, asthenia in 11 out of 16 subjects and decreased appetite in 8 out of 16 subjects. Grade 4 treatment-emergent adverse events (TEAEs) related to study drug were only present in the $1x10^{13}$ vp dose group: AST increased, and lipase increased in one subject. There were 3 TEAEs related to VCN-01 in the $1x10^{11}$ vp dose group, 6 related TEAEs

in the $1x10^{12}$ vp dose group, 14 related TEAEs in the $3.3x10^{12}$ vp dose group and 41 related TEAEs in the $1x10^{13}$ vp dose group; being pyrexia (in 13 subjects) the most frequent TEAE related to the study drug. Related TEAEs were dose-dependent.

Regarding the severity of the TEAEs related to study drug, there were 9 Grade 3 TEAEs related to VCN-01: 1 (lipase increased) in the $1x10^{11}$ vp dose group; 3 (AST increased, lymphocyte count decreased and white blood cell count decreased [all in the same subject]) in the $3.3x10^{12}$ vp dose group; and 5 (ALT increased, gammaglutamyl transferase (GGT) increased, amylase increased and platelet count decreased [all in the same subject], and pyrexia [in another subject]) in the $1x10^{13}$ vp dose group. There were 2 related Grade 4 TEAEs, both in the same subject in the $1x10^{13}$ vp dose group (the subject who had 4 related Grade 3 TEAEs): increased AST and lipase.
Regarding the serious TEAEs, there were 14 serious TEAEs, from these serious TEAEs, 5 events in 5 subjects (1 subject in the $3.3x10^{12}$ vp dose group and 4 subjects in the $1x10^{13}$ vp dose group) were assessed as related to the VCN-01: all of them were cases of pyrexia. The safety profile for VCN-01 when administered systemically as a single agent was consistent with the aEs previously reported for other oncolytic adenoviruses. The MTD/recommended phase 2 dose (RP2D) for VCN-01 as a single agent was established at the highest dose ($1x10^{13}$ vp).
Available clinical safety data for VCN-01 when administered one week prior nab-paclitaxel and gemcitabine systemic administration (PVCNA-001, part III, n=14 – although two subjects in the $3.3x10^{12}$ vp dose group did not receive the concomitant chemotherapy with nab-paclitaxel and gemcitabine) show that the most common adverse reactions (aRs) were pyrexia (9 out of 14 subjects, 64.3%), influenza like illness (4 out of 14 subjects, 28.6%) and asthenia (3 out of 14 subjects, 21.4%). Gastrointestinal disorders were also observed, as nausea and vomiting (both events occurring in 3 out of 14 subjects, 21.4%), as well as one event of diarrhea (1 out of 14 subjects, 7.1%) were reported. ALT increased was observed in 3 out of 14 subjects (21.4%) and AST increased was observed only in one subject (7.1%). Two events of platelet count decreased in 2 subjects (14.3%) were reported as aRs. Regarding the severity of the TEAEs related to the study drug, only three from a total of 33 (9.1%) were grade 3 aRs (AST increased and ALT increased, and one diarrhea which was reported as serious). The other events were grade 1 (19 out of 33, 57.6%) or grade 2 (11 out of 33, 33.3%) aRs. It has to be noted that there was not any grade 4 or grade 5 aRs. All the aRs occurred during the first cycle of treatment (35-day cycle).
For hematology and clinical chemistry, only 6 abnormalities were considered a TEAE related to the study drug and were included in the system organ class (SOC) of Investigations: ALT increased (two grade 2 and one grade 3 events), AST increased (one grade 3 event) and platelet count decreased (one grade 1 and one grade 2 events). Moreover, there were no clinically significant abnormalities for any of the coagulation parameters.
Overall, IV VCN-01 in combination with gemcitabine and nab-paclitaxel in a one-week delayed schedule was well tolerated. Reduced toxicity profile has been observed when VCN-01 was administered 7 days before chemotherapy when compared with VCN-01 administered in concomitance with chemotherapy. Of note, the dose $1x10^{13}$ vp/patient was defined as the MTD/RP2D for VCN-01 in combination with gemcitabine and nab-paclitaxel in a delayed treatment schedule. Safety results of a delayed treatment schedule in Part III revealed a reduced number of TEAEs related to the study treatment in comparison with Part II. The

safety profile in the Part III was consistent with the combination of aEs previously reported for other oncolytic adenovirus and in the summary of product characteristics (SmPC) of gemcitabine and nab-paclitaxel.
Other available clinical safety data is included in the IB.

1.6.3. Clinical Efficacy

The results from the phase I clinical trial P-VCNA-001 (EudraCT: 2012-005555-16; NCT02045602) indicate promising VCN-01 anti-tumor activity in patients with advanced pancreatic cancer when it is administered concomitantly with nab-paclitaxel /gemcitabine or when chemotherapy treatment is initiated one week after receiving VCN-01.
Twelve (12) out of 14 patients included in P-VCNA-001 and treated with VCN-01 in combination with gemcitabine and nab-paclitaxel in a one-week delayed schedule, were evaluated for efficacy. One (1) subject in the $3.3x10^{12}$ vp dose group and 5 subjects in the $1x10^{13}$ vp dose group had a partial response (PR). Five (5) subjects (4 in the $3.3x10^{12}$ vp dose group and 1 in the $1x10^{13}$ vp dose group) had stable disease and one subject in the $3.3x10^{12}$ vp dose group had progressive disease (PD) as best response. There was a marked difference between the two dose levels regarding the objective response rate (ORR), which was 83.3% (95% confidence interval [CI], 35.88-99.58) in the $1x10^{13}$ vp dose group and 16.7% (95% CI, 0.42–- 64.12) in the $3.3x10^{12}$ vp dose group. Median progression-free survival (PFS) was 34.9 weeks in the $3.3x10^{12}$ vp dose group and 27.0 weeks in the $1x10^{13}$ vp dose group. Overall, median PFS was 28.9 weeks (ranged from 7.1 to 62.3 weeks), which corresponds to 6.7 months (ranged from 1.6 to 14.4 months) and median overall survival (OS; *post-hoc* analysis reported in Garcia-Carbonero et al, 2022) was 13.5 months (2.6-30.8). Eight (8) patients (66.7%) survived more than 12 months. A subgroup analysis of patients at the RP2D ($1.0x10^{13}$ vp/patient followed by nab-paclitaxel plus gemcitabine one week later, n=6) showed an ORR of 83%, with a median PFS of 6.3 months and median OS of 20.8 months.
Tumor burden at 8 weeks had a median value of -11.5 mm (ranged -36 to 21 mm). Most subjects showed reductions in tumor burden, with increases observed for only one subject of the lowest dose level ($3.3x10^{12}$ vp dose group). Overall, depth of response had a median value of 30.4% and ranged from -31 to 73% and higher depth of response is observed in $1x10^{13}$ vp dose group with respect to $3.3x10^{12}$ vp group.
Significant reductions in carbohydrate antigen (Ca) 19.9 tumor marker were observed in 9 out of 12 subjects (5 in the $3.3x10^{12}$ vp dose group, and 4 in the $1x10^{13}$ vp dose group), and all of them displayed percentage reductions from baseline to nadir higher than 50%. Between those subjects who had PR, 5 out of 6 showed percentage reductions from baseline to nadir, all of them higher than 50% for both carcinoembryonic antigen and CA19.9 tumor markers.
VCN-01 was detected in both primary and metastatic biopsies obtained from patients of the study, indicating that the agent effectively reached the tumor after systemic delivery. PH20 peak serum levels were observed on days 3 and 8 after VCN-01 treatment and similar levels are sustained on day 28 in $3.3x10^{12}$ vp/patient and $1x10^{13}$ vp/patient dose groups. The presence of secondary viremia peaks in blood and PH20 peaks in sera in a dose-dependent manner, together with VCN-01 genome positivity in tumors (all at day 8) was also suggestive of intratumoral viral replication. VCN-01 was able to modulate the tumor environment into a more pro-inflammatory and less immunosuppressive state. The increase of certain immunological markers (IDO expression and CD8+ lymphocyte infiltration) in the tumor

biopsy of some patients, together with the tumor evolution kinetics (existence of delayed responses), suggests the existence of immune-mediated mechanisms of action for VCN-01. After intratumoral administration in clinical trial P-VCNA-002 (EudraCT: 2012-005556-42; NCT02045589), VCN-01 treatment was associated with changes in tumor elastic properties as seen through tumor elastogram: there was a decrease in tumor stiffness including subjects who did not receive nab-paclitaxel. These results, together with pharmacodynamic data suggest that VCN-01 replicates within the tumor leading to hyaluronidase expression with a consequent reduction of tumor stiffness that can potentially increase the extravasation of chemotherapy. Additionally, the presence of VCN-01 in a biopsy prior to the second administration is indicative of viral replication in the tumor cells. Further confirmation of intratumoral replication is supported by secondary peaks of viral genomes in blood samples several days after the intratumoral injection of VCN-01.

1.6.4. Clinical Pharmacokinetics

After a single systemic administration of VCN-01, the PK profile showed an increase of VCN-01 blood levels in some patients administered one of the two highest dose levels ($3.3x10^{12}$ and $1x10^{13}$ vp/patient) from 24 hours post-administration onwards. This increase in blood levels is compatible with the expected blood secondary viremia peaks after replication and with the virus life cycle. VCN-01 presented a relevant exposure at all tested dose levels when administered alone. Dose linearity for VCN-01 was observed in the range of the tested doses of $1x10^{11}$, $1x10^{12}$, $3.3x10^{12}$ and $1x10^{13}$ vp/patient.

Mean blood VCN-01 levels declined after day 1, although there was considerable inter-subject variability. From day 3 to day 28, VCN-01 was not detectable in blood in all subjects in the $1x10^{11}$ vp dose group and in 2-3 subjects in the $1x10^{12}$ vp dose group. The presence of secondary viremia peaks in a dose-dependent manner is suggestive of viral replication.

1.6.5. Clinical Shedding

Available data from study P-VCNA-001 show that the shedding of VCN-01 after systemic administration occurs mainly during the first 8 days post-treatment for all biological fluids analyzed (blood, sputum, feces, and urine). In blood, VCN-01 viral genome peaks are observed in a dose-dependent manner and low levels are maintained in most patients up to Day 28. VCN-01 excretion occurs mainly through sputum and feces, and to a much lesser extent, through urine. Analysis of VCN-01 in sputum using anti-hexon staining found the virus was not functional in this matrix.

1.7. DISEASE REVIEW AND RATIONALE FOR THE STUDY

Despite the existence of authorized treatments and extensive on-going clinical research in the EU and the US, the overall survival of patients with pancreatic cancer remains dismal and there is an urgent need to develop more efficacious treatments. In this context, preclinical and clinical evidence indicates that the addition of VCN-01 to the current standard treatment for metastatic pancreatic cancer patients could potentially provide a significant therapeutic benefit without a relevant increase in toxicity.

Treatment of a range of solid tumors has been limited by a dense, desmoplastic extracellular matrix (stroma) that surrounds the tumor and protects it from therapeutic agents and the patient's immune system. Tumor desmoplasia has been linked to highly developed, invasive tumors, metastatic behavior and poor prognosis (Toole, 2004; Bertrand, P et al, 1992; Karpathiou et al, 2016; Curry et al, 2014) in the target indications of the ongoing clinical trials with VCN-01 (i.e., pancreatic cancer and head and neck carcinoma).
VCN-01 is designed to overcome the tumor stroma barrier. Hyaluronidase expressed during VCN-01 replication degrades a key component of the tumor extracellular matrix. This can facilitate viral spread, increasing the accessibility of concomitant drugs such as chemotherapy agents or anti-PD-L1 antibodies such as durvalumab (as demonstrated preclinically [Rodriguez-Garcia et al, 2015] in Study VCNA-B2-70). Importantly, degrading the tumor matrix can enable a host anti-tumor immune response by exposing tumor neoantigens and easing the infiltration of immune cells into the tumor.
Replication-competent adenoviruses have an inherent ability to sensitize tumor cells to chemotherapy, potentially enabling use of VCN-01 for chemosensitization (Kirn, 2000). A favorable and potentially synergistic interaction between adenoviral therapy and chemotherapy has been shown in multiple clinical trials (with different tumor types and by different routes of administration) with encouraging results (Woller et al, 2014). Current clinical data suggest that combining OVs like VCN-01 with approved chemotherapeutic treatment modalities might be an important key in unlocking the true potential of virotherapeutics while preventing the induction of resistance mechanisms (Binz, 2015).

1.8. RISK-BENEFIT ASSESSMENT

1.8.1. Potential benefits

Taking into account the naturally lytic replication cycle of adenoviruses together with the genetic modifications inserted in VCN-01 backbone, its biological activity is considered to offer a novel mechanism of action in the field of anti-cancer therapies that could potentially overcome some of the current drawbacks facing conventional therapy:
VCN-01 biological activity is claimed to be based on the selective killing of tumor cells by effect of its replication, which results in a self-amplification of the initial inoculum that is released after cell lysis and spread through the tumor mass. This novel mechanism of action is not shared by conventional therapeutic treatments for pancreatic cancer and consequently, the development of cross-resistance with existing treatments that often leads to loss of efficacy is not expected to occur with VCN-01, at least in the short-term.
From a histopathology point of view, many human solid tumors develop extensive fibroses, a result of what is termed the desmoplastic reaction (Whatcott et al, 2011). Desmoplasia leads to the formation of a dense and fibrous connective tissue that is composed of multiple extracellular matrix components. This fibroinflammatory component of tumors (also called stroma) contributes to an increase in tumor interstitial fluid pressure, blocking perfusion of anti-cancer therapies to the tumor cells, and contributes generally to chemoresistance.
Hyaluronan (HA) is a ubiquitous, major component of the extracellular matrix, and often HA levels correlate with invasive and metastatic behavior as high levels have been detected at the invasive front of growing tumors, suggesting that it may be involved not only in cell proliferation but possibly in invasion as well (Bertrand et al, 1992)

and it may also play an important role in acquired resistance to anticancer drugs (Miyamoto et al, 2004; Nakazawa et al, 2006; Boregowda et al, 2006).
VCN-01 biological activity is claimed to be based also on the expression of hyaluronidase, which degrades partially the extracellular matrix of the tumor facilitating the diffusion of the virus progeny; which would circumvent one of the main limitations that might have contributed to limited clinical responses observed in early clinical trials with oncolytic adenovirus. The expression of hyaluronidase has been previously demonstrated to increase the ability of adenovirus to disseminate intratumorally and to enhance antitumor activity in preclinical models (Guedan et al, 2010). Moreover, targeting the components of the stromal compartment, in conjunction with cytotoxic agents directed against tumor cells, is becoming increasingly interesting as a potential approach to treating patients and overcoming chemoresistance as it facilitates the intratumoral accessibility of chemotherapy drugs (Von Hoff et al, 2011; Von Hoff et al, 2013; Borad et al, 2012; Baumgartner et al, 1998). Of importance, the degradation of interstitial matrix induced by PH20 hyaluronidase has been demonstrated in the literature not to result in tumor cell mobilization (Brekken et al, 2000).
Oncolytic cell death per se seems to be an immunogenic phenomenon and can break tumor associated immunotolerance (Alemany, 2007; Woller et al, 2015; Breitbach, 2016). Immune evasion by tumors, which is also one of the hallmarks of cancer, is an important target for new cancer therapeutics. Oncolytic viruses may represent a unique strategy for combining tumor debulking activity, through direct tumor lysis, with potent activation of adaptive and innate immune responses. Targeted infection of the tumor leads to a localized inflammatory response, triggering an immune storm directly within the malignancy and facilitating immune recognition of cancer-specific neoantigens (Melcher et al, 2011; Binz, 2015).
Feasibility of add-on therapy to currently authorized treatments
The inherent ability of replication-competent adenoviruses to sensitize tumor cells to chemotherapy was a discovery that has led to chemosensitization strategies (Kirn, 2000). In line with this synergy, most published preclinical data suggest that virotherapy can be ideally combined with other treatment options, such as chemotherapy (Woller et al, 2014).
Combinatorial treatment regimens exhibit diverse mechanisms of action and thereby more often constitute a successful approach to overcome such resistance mechanisms. Current clinical data suggest that combining OVs with already approved chemotherapeutic treatment modalities might be an important key in unlocking the true potential of virotherapeutics while preventing the induction of resistance mechanisms (Binz, 2015).
Evidence from clinical studies with VCN-01: see Section 1.6.3 for clinical efficacy data and Garcia-Carbonero et al, 2022).

1.8.2. Risks

1.8.2.1. VCN-01 adenovirus monotherapy

According to the clinical data available from study P-VCNA-001, the IV administration of the oncolytic adenovirus VCN-01 has showed no major safety concerns at doses that resulted in the infection of tumors and in antitumoral activity (Garcia-Carbonero et al, 2022).
The evidence seems to indicate that the neutralizing antibodies (NAbs) induced by the injection (which can reach high NAb titers) do not prevent intratumoral infection and

replication. Additionally, there has been no correlation demonstrated between the NAbs titers and viral dose administered, antitumoral activity or viral genome positivity in the blood. Importantly, although a significant increase in NAbs are detected in all patients after the first systemic administration, there has been no correlation established between high titers and increase in AEs or the severity of the flu-like symptoms.

1.8.2.2. VCN-01 virus in combination with chemotherapy (Chemovirotherapy):

VCN-01 plus Nab-paclitaxel/Gemcitabine

Nab-paclitaxel is a microtubule inhibitor which in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. According to the SmPC (EMA), the most common clinically significant adverse reactions associated with the use of nab-paclitaxel have been neutropenia, peripheral neuropathy, arthralgia/myalgia. In addition to the above listed, as included in the FDA Prescribing Information, other most common (≥20%) adverse reactions in adenocarcinoma of the pancreas are fatigue, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash and dehydration (Abraxane - SmPC, 2013; FDA Abraxane Prescribing Information, 2013).

Toxicity interactions between VCN-01 and nab-paclitaxel /Gemcitabine are not expected in the clinical setting, namely lack of additive toxicity is expected as gemcitabine is mainly metabolized intracellularly and its principal target *in vivo* is the spleen and the thymus (Storniolo et al, 1997), which is not coincident with hepatotropism of VCN-01. On the other hand, the metabolism of paclitaxel (nab-paclitaxel) is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (Taniguchi et al, 2005; European Medicines Agency [EMA] 2013). It has been demonstrated that after adenoviral infection, human CYPs are not affected as the hepatic xenobiotic biotransformation activities of many members of the CYP450 family remain unchanged, including CYP3A4 and CYP2C8 (Castell et al, 1997; Jover et al, 2001; Rana, et al, 2010).

The concerns expressed in the past regarding safety and overlapping toxicity profiles of combined chemotherapeutic and virotherapeutic treatment (especially when given concomitantly) have been dampened according to the safety data from P-VCNA-001 Part III protocol. Overall, IV VCN-01 in combination with gemcitabine and nab-paclitaxel in a one-week delayed schedule was well tolerated. Reduced toxicity profile has been observed when VCN-01 was administered 7 days before chemotherapy when compared with VCN-01 administered in concomitance with chemotherapy (as previously reported for Part II of this study). Of note, the dose $1x10^{13}$ vp/patient was defined as the MTD/RP2D for VCN-01 in combination with gemcitabine and nab-paclitaxel in a delayed treatment schedule. Safety results of a delayed treatment schedule in Part III revealed a reduced number of TEAEs related to the study treatment in comparison with Part II. The safety profile in the Part III was consistent with the combination of AEs previously reported for other oncolytic adenovirus and in the SmPC of gemcitabine and nab-paclitaxel.

1.8.3. Benefit – Risk Assessment

The proposed administration of VCN-01 in one-week delayed combination with nab-paclitaxel and gemcitabine is expected to result in a boost of the efficacy of both treatments

and result in a more positive outcome for the patients participating in the study. VCN-01 is anticipated to disrupt tumor organization and result in a more efficient activity of chemotherapy.

The addition of VCN-01 to nab-paclitaxel plus gemcitabine is well justified from prior clinical use in P-VCNA-001 study and is not expected to result in a significant increase of the toxicity. Having assessed the potential benefits and risks of the proposed clinical candidate and taken into account the above considerations, the risk-benefit assessment for the current treatment is judged as positive.

Early clinical analysis shows encouraging activity signals with a response rate of 50% and a median OS of 13.4 months when VCN-01 was combined with nab-paclitaxel plus gemcitabine that deserves to be further explored in a randomized, controlled Phase II clinical trial.

It is argued that there is enough data at the current stage of development to adequately support and justify that the addition of VCN-01 to the current standard treatment for metastatic pancreatic cancer could potentially provide a significant therapeutic benefit in the absence of a substantial increase in toxicity.

2. OBJECTIVES

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- To evaluate the time from randomization until death in both arms (OS).
- To evaluate the safety and tolerability of VCN-01, IV administered at Week 1 and Week 14 in Arm II.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the time to progression (TTP) or PFS.
- To determine the ORR.
- To determine the disease control rate (DCR) (stable disease [SD] + PR + complete response [CR]).
- To determine the landmark 1-year survival and PFS at the 1-year landmark.
- To evaluate the duration of response (DoR).
- To assess changes in tumor marker Ca 19.9 measured every 4 weeks while on study.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate circulating immune markers in serum, VCN-01 genomes in blood, PH20 levels in serum, neutrophil/lymphocyte ratio, and serum levels of neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs).
- To evaluate radiomic analysis of CT images.
- To characterize the Quality of Life (QoL) via the validated European Organization for Research and Treatment Quality of Life Questionnaire (EORTC) QLQ-C30 questionnaire (version 3).
- To determine the disease control rate (DCR) (stable disease [SD] + PR + complete response [CR]) to the subsequent therapies.

3. ENDPOINTS

3.1. PRIMARY ENDPOINTS

The primary endpoints are:

- OS
- Safety and tolerability

3.2. SECONDARY ENDPOINTS

The secondary endpoints are:

- PFS or TTP
- ORR
- DCR (SD + PR + CR)
- Landmark 1-year survival and PFS at the 1-year landmark
- DoR
- Changes in tumor marker Ca 19.9

3.3. EXPLORATORY ENDPOINTS

The exploratory endpoints are:

- Biomarker levels, such as PH20, VCN-01 genomes, neutrophil/lymphocyte ratio, anti-Ad-NAb, circulating immune markers and/or other markers according to the state of the art, may be determined in blood and serum samples collected at different timepoints during the study.
- Image biomarkers (radiomics) assessed from the images of CT scans performed during the study.
- Change from baseline in values of the QoL via the validated EORTC QLQ-C30 questionnaire (version 3).
- DCR (stable disease [SD] + PR + complete response [CR]) to the subsequent therapies.

4. INVESTIGATIONAL PLAN

4.1. SUMMARY OF STUDY DESIGN

This is a multi-center, open label, randomized, 2-parallel arm, phase IIb study of nab-paclitaxel and gemcitabine as standard of care (SoC) plus/minus VCN-01 in patients with metastatic pancreatic cancer. Ninety-two (92) patients in about 25 sites in the North America and EU will be recruited and randomized in a 1:1 ratio to one of two treatment arms (i.e., 46 patients per treatment arm):

- Arm I: Nab-paclitaxel and gemcitabine as SoC (28-day cycles). Patients in this arm will not receive the Investigational Medicinal Product (IMP; VCN-01).
- Arm II: Two (2) doses of VCN-01 administrated in combination with nab-paclitaxel and gemcitabine as SoC (28-day cycles with exception of the IMP dose cycles, which will be 35-day cycles).

For the purpose of this study, Study **Day 1 (D1)** is defined as the first day of treatment with IMP/SoC. All days thereafter are defined as "Dn" (e.g., D2, D3 etc).

Arm I: Nab-paclitaxel and gemcitabine will be administrated as SoC (at 28-day cycles). Patients in Arm I will not receive the IMP (VCN-01). Nab-paclitaxel will be administered as an IV infusion at a dose of 125 mg/m^2 and gemcitabine will be administered as an IV infusion immediately after the completion of nab-paclitaxel administration at a dose of 1,000 mg/m^2 according to current SoC procedures, both on Day 1, Day 8, and Day 15 of each treatment cycle. See Table 6-2 for Arm I treatment schedule.

Arm II: Two (2) doses of VCN-01, each administered as a single IV infusion at dose 1x10^{13} vp, in combination with IV nab-paclitaxel and gemcitabine as SoC (28-day cycles with exception of the IMP dose cycles, which will be 35-day cycles). VCN-01 will be administered as a single IV infusion of VCN-01 at a rate of 5 mL/min on Day 1 Cycle 1, then 1 week later 3 cycles of nab-paclitaxel and gemcitabine will be administered. Nab-paclitaxel as an IV infusion at a dose of 125 mg/m^2 and gemcitabine as an IV infusion will be administered immediately after the completion of nab-paclitaxel administration at a dose of 1,000 mg/m^2 according to current SoC procedures, during Cycles 1 and 4 on Day 8, Day 15, and Day 22 and during Cycles 2, 3, 5 and subsequent cycles on Day 1, Day 8, and Day 15. On Day 1 of Cycle 4 (+1 day to 2 weeks), a second VCN-01 dose will be administered at a rate of 5 mL/min. One week later, subsequent 28-day cycles of nab-paclitaxel and gemcitabine should continue. See Table 6-3 for Arm II treatment schedule.

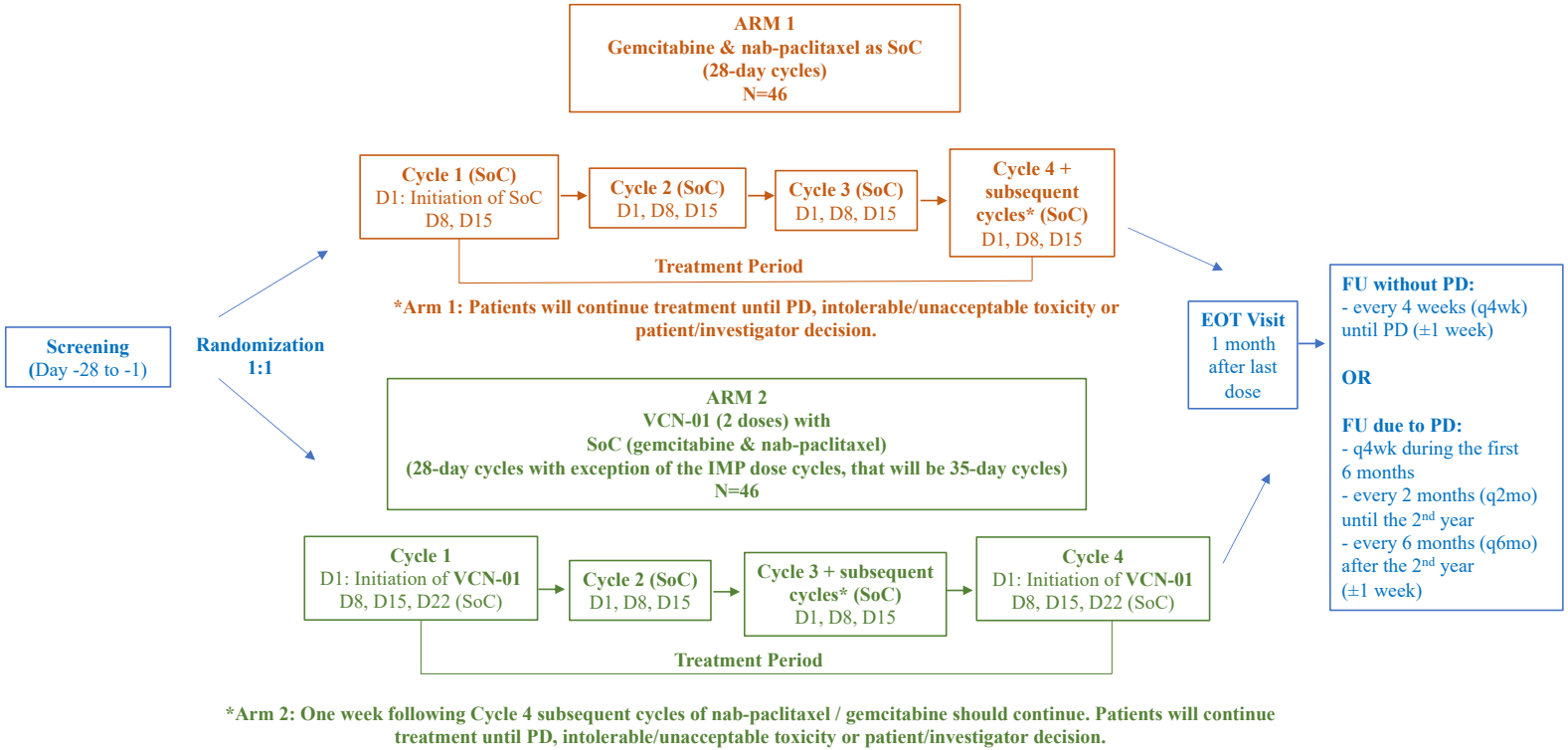
In both treatment arms, patients will continue study treatment until PD (refer to Section 10.3.4.2. for definition of PD), intolerable/unacceptable toxicity or patient's/investigator's decision. This period will be defined as Treatment period.

The primary endpoints will be OS, safety, and tolerability, with secondary endpoints PFS or TTP, ORR, landmark 1-year survival and PFS at the 1-year landmark, DCR, DoR and changes in Ca 19.9 biomarker (refer to Section 3 for all study endpoints).

A Data Monitoring Committee (DMC) will be convened to assess safety and to look at OS to determine if the trial can continue (see Section 10.3.7).

The study design is summarized in Figure 4-1.

Figure 4-1: Study Design



Abbreviations: PD=progressive disease; q2mo=every 2 months; q4wk=every 4 weeks; q6mo=every 6 months, SoC=standard of care

Refer to the schedule of assessments in APPENDIX 7 and APPENDIX 8 for the tests and evaluations to be conducted in Arm I and Arm II, respectively.
For certain dosing days, an acceptable time window of ±3 days will be allowed. For C1D1, certain safety laboratory tests (biochemistry, hematology, and coagulation profile) and non-safety laboratory tests or evaluations (Ca 19.9, full physical exam, body weight, and QLQ-C30) may be performed within 72 hours prior to dosing. EOT and FU visits may take place within a time window of ±1 week. For the second VCN-01 doses at Cycle 4 Day 1 (C4D1) a window of '+1 day up to 2 weeks' is permitted.
The expected duration of the trial is:

- Screening: Up to 28 days
- Treatment period:
  - For patients included in Arm I, the treatment period will be defined as "n" cycles of 28 days of nab-paclitaxel and gemcitabine and an "End of Treatment (EOT)" visit one month later (±1 week) after last treatment dose.
  - For patients included in Arm II, the treatment period will be defined as the two VCN-01 doses plus nab-paclitaxel and gemcitabine, administered on Cycle 1, and Cycle 4 (35-day cycles), "n" cycles of 28 days of nab-paclitaxel and gemcitabine (Cycle 2, Cycle 3, Cycle 5, Cycle 6 and so on [28-day cycles]) and an "EOT" visit one month later (±1 week) after last treatment dose.
- FU period: until death
- Global end of study (EOS) will be either (i) the later of the date of the last patient's last visit or their exitus or (ii) ending of the study by the sponsor. Early termination of the study by the sponsor is only anticipated on the basis of safety.

4.2. DISCUSSION OF TRIAL DESIGN

The design used in this study is a well-established approach for exploration of OS, and safety and tolerability in accordance with health authority guidelines.
Open-label trials are deemed appropriate for comparing two similar treatments to determine which is most effective. Testing the current SoC against the IMP can be used to demonstrate equivalence, non-inferiority, or superiority, and to evaluate comparative safety. This design is most ethical when approved drugs are available for the disease under study. The Declaration of Helsinki mandates the use of standard treatment as controls.
Randomization and stratification (to take account of the patients' baseline Eastern Co-operative Oncology Group (ECOG) performance status [0 or 1] and region [North America or EU]) minimizes the potential for systematic error and balances both the known and unknown confounding factors which leads to wrong conclusions.

4.3. TRIAL TIMETABLE (STUDY PERIODS)

The trial includes the following visits:

- **Screening period (approximately 4 weeks prior to first dose):** Days -28 to -1 (Week -4 to -1)

Note: There is no Day 0 or Week 0 in this study. Study dosing starts on Day 1.

- **Randomization** can occur any time during the 28-day Screening period when all the screening assessments are completed, but dosing (D1) must take place no later than 5 days after randomization.
- **Treatment period (variable, depending on progression of disease/toxicity and decision of patient/ investigator)**:
  - Arm I: Cycle 1 (28 days); Cycle 2 (28 days); Cycle 3 (28 days); Cycle 4 (28 days) and subsequent nab-paclitaxel / gemcitabine cycles
  - Arm II: Cycle 1 (35 days); Cycle 2 (28 days); Cycle 3 (28 days); Cycle 4 (35 days) and subsequent nab-paclitaxel / gemcitabine cycles
  - EOT visit: 1 month after last dose (±1 week)
- **Follow-up period**:
  - FU without PD (±1 week): every 4 weeks (q4wk) until PD
  - FU due to PD (±1 week): q4wk during the first 6 months; every 2 months (q2mo) until the second year; every 6 months (q6mo) after the second year
- End of Study (EOS): EOS for each patient will be the date of his/her exitus. All patients will be followed for OS.

Refer to the schedule of assessments in APPENDIX 7 and APPENDIX 8 for the tests and evaluations to be conducted in Arm I and Arm II, respectively.

5. SELECTION AND WITHDRAWAL OF PATIENTS

Approximately 92 patients with metastatic pancreatic cancer will be recruited and randomized in a 1:1 ratio to one of two treatment arms (i.e., 46 patients per treatment arm). More details are given in the sample size estimation in Section 12.1.

5.1. INFORMED CONSENT

Each potentially eligible patient will be informed of the study's objectives and overall requirements. Prior to conducting any of the study required procedures, the Investigator will explain the study fully to him/her using the patient informed consent document (PICD). The patient will receive all information that is required by local regulations and International Council on Harmonization (ICH) guidelines. If the patient is willing to participate in the study, they will be requested to give written informed consent after being given sufficient time to consider their participation and the opportunity to ask for further details. The PICD (2 originals) will be signed and personally dated by **both** the patient and the Investigator. One original signed form will be provided to the patient, and another will be retained with the source documents at the site. The Investigator or his representative in the study team must participate in discussions with the patient and sign and personally date the PICD, as per the local legislation.

The patient is considered enrolled in the study once they sign the PICD, after which they will be screened to confirm their eligibility. Screening failures are defined as patients who consented to participate in the clinical study but did not subsequently receive SoC or IMP in the study (e.g., a patient is considered as a screening failure when they did not meet the study eligibility criteria at Screening or the patients who met the study eligibility criteria at Screening but not subsequently randomized and treated).

If a protocol amendment is required, the PICD may need to be revised to reflect the changes to the protocol. If the PICD is revised, it must be reviewed and approved by the appropriate Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

A short electronic Case Report Form (eCRF) will be completed for all patients who signed the PICD but who did not subsequently receive SoC or IMP. The patients will be given a patient identifier (unique identification [ID] number). At a minimum, information such as year of birth, gender, and reasons for exclusion from the study will be recorded as per the local regulation.

5.2. INCLUSION CRITERIA

To be eligible for inclusion into this study, each patient must fulfill the following inclusion criteria within 28 days up to and including Study Day 1:

1. Written informed consent obtained prior to any study-specific procedures or assessments.
2. Male/female patients aged 18 years or over.
3. Patients with histologically or cytologically confirmed, first line metastatic pancreatic adenocarcinoma stage IV de novo, who never received previous systemic treatment for their pancreatic cancer for which the established therapy is nab-paclitaxel/gemcitabine (clinical SoC). All patients must have at least one measurable

tumor lesion that can be imaged for assessments determined by RECIST 1.1 (see APPENDIX 4).

4. Patients willing to comply with the study treatment.
5. Patients with a minimum life expectancy of 5 months.
6. ECOG performance status of 0 or 1.
7. Use of a reliable method of contraception in fertile men and women. Female patients of childbearing potential (i.e., female patients who are not postmenopausal or surgically sterile) must agree to use effective contraception. Male patients must agree to use effective contraception or be surgically sterile. All male patients must use a male condom. For details on highly effective contraception refer to APPENDIX 1.
8. Adequate baseline organ function (hematologic, liver, renal and nutritional) verified by laboratory analyses performed within 72 hours prior to dosing*:

Hematology:

- Absolute neutrophil count ≥1.5x10^9 /L
- Hemoglobin ≥9 g/dL
- Platelets ≥100x10^9/L

Coagulation (*except in patients on anticoagulants):

- Prothrombin time or international normalized ratio ≤1x upper limit of normal (ULN)
- Activated partial thromboplastin time ≤1.2xULN

Hepatic:

- Total bilirubin ≤1.5xULN
- ALT and AST ≤2.5xULN (if there are no liver metastases)
- ALT and AST <5xULN, and bilirubin <1.5xULN (if there are liver metastases)

Renal:

- Serum creatinine ≤1.5xULN, and if >1.5xULN: Estimated creatinine clearance >50 mL/min using Cockcroft and Gault formula

Nutritional:

- Serum Albumin ≥30 g/L

Note: If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient.
***Note**: Adequate organ function specified in this criterion must also be met prior to VCN-01 dosing on Cycle 4 Day 1 for ARM II.

5.3. EXCLUSION CRITERIA

Potential participants will be excluded from the study if they meet one or more of the following exclusion criteria within 28 days up to and including Study Day 1:

1. Patients not willing to complete the study procedures for geographic, psychiatric, or social reasons.
2. Active infection or other serious illness or autoimmune disease at the moment of randomization. Active infection includes tuberculosis (TB; clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), Hepatitis B Virus (HBV; positive HBV surface

antigen [HBsAg] result), Hepatitis C Virus (HCV; positive HCV Ribonucleic acid [RNA]), or human immunodeficiency virus (positive HIV 1/2 antibodies). HBV carriers (patients positive for HBsAg) or those patients requiring antiviral therapy treatment for HBV virus or HCV are not eligible to participate.

However, the following patients are eligible to participate in the study:

- Patients with past or resolved TB are eligible;
- Patients with a past or resolved HBV infection (defined as the presence of hepatitis
- B core antibody [HBcAb] and absence of HBsAg) are eligible. Blood HBV DNA must be obtained and must be negative in these patients prior to treatment;
- Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

3. Treatment with live attenuated vaccines in the last 3 weeks and with the adenovirus type-5 (Ad5)-based COVID-vaccine in the last 12 weeks before the administration of study treatment.
4. Known chronic liver disease (liver cirrhosis, chronic hepatitis). If there is a suspicion of hepatic fibrosis, a fibroscan must be performed; patients with a value ≥9.5 kPa will be excluded. Note: Transient elastography (Fibroscan) is a non-invasive method for the assessment of hepatic fibrosis.
5. Treatment with another investigational agent within five of that treatment's half-lives prior to infusion of study treatment.
6. Viral syndrome diagnosed during the 2 weeks before start of study treatment administration.
7. Chronic immunosuppressive and/or disease modifying therapy, except inhaled corticosteroids, and oral or IV corticosteroids with a dose lower than 10 mg prednisone or equivalent/day (exception: dexamethasone 1 mg/day as maximum).
8. Concurrent malignant hematologic or solid disease. Patients with a prior history of cancer can be allowed if complete remission for at least 3 years.
9. Patients in close contact (e.g., living in same house) with immunosuppressed patients (i.e., patients on chronic immunosuppressive therapy including high dose of corticosteroids, patients with acquired immunodeficiency syndrome (AIDS), and other chronic immune system diseases).
10. Patients with Li Fraumeni syndrome or with previously known retinoblastoma protein pathway germline deficiency.
11. A female patient, who is pregnant or lactating.
12. Patients receiving full-dose anticoagulant therapy or in whom these therapies cannot be withdrawn 2 days prior and 2 days after VCN-01 administration. Patients with uncontrolled coagulopathy should be excluded.
13. Untreated brain metastases and/or leptomeningeal carcinomatosis with progressive symptoms despite corticosteroid coverage. Patients with brain metastases with stable symptoms can be included.
14. Any other condition, disease, metabolic dysfunction (e.g., uncontrolled diabetes mellitus), active or uncontrolled infection/inflammation, physical examination finding, mental state or clinical laboratory finding that would contraindicate participation in the clinical study due to safety concerns or compliance with clinical study procedures.
15. Patients with previous pneumonitis or interstitial lung disease.

16. Patients with pre-existing sensory neuropathy >G1.
17. Patients with risk factors for bowel perforation.
18. Patients with QT interval corrected by Fridericia (QTcF) assessment >450 ms for men or >470 ms for women and left ventricular ejection fraction (LVEF) evaluation less than 50% measured by ECHO or multigated acquisition scan.
19. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
20. Subjects, for whom first line treatment options other than the combination Gemcitabine/Nab-Paclitaxel are recommended by the investigator.

5.4. ASSIGNING PATIENTS TO TREATMENT ARMS

Ninety-two (92) patients will be randomized in a 1:1 ratio to either:

- Arm I (SoC): 46 patients
- Arm II (SoC + 2 administrations of VCN-01): 46 patients

The randomization will be stratified to take account of the patients' baseline ECOG performance status (0 or 1) and region (North America or EU). Refer to Section 12.2 for further details on the randomization procedure in the study.
A patient who has signed the PICD will be allocated a patient ID number consisting of the country code, site number and a sequential patient number e.g., 34-01-001. Once the Inclusion and Exclusion criteria assessments have been completed and it is confirmed that the patient is eligible for the study, they will be allocated the next randomization number in the study. Randomization can occur any time during the 28-day Screening period when all the screening assessments are completed, but dosing (D1) must take place no later than 5 days after randomization. The patient number will be automatically generated by the Interactive Response Technology (IRT) upon patients' registration in the study.
The treatment assigned to each patient will be determined according to a computer-generated randomization list.

5.5. PREMATURE WITHDRAWAL OF PATIENTS FROM STUDY AND REPLACEMENT POLICY

5.5.1. Discontinuation Criteria

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. Any withdrawals must be fully documented in the eCRF and should be followed up by the Investigator.
Additionally, the Investigator may withdraw a patient at any time if they consider this to be in the patient's best interest. The study will be terminated if, in the opinion of the investigator and the sponsor, significant safety concerns arise during the conduct of the study.
Patients may be discontinued for any of the following reasons:

- Voluntary discontinuation by the patient, who is free to discontinue their participation in the study at any time without prejudice to further treatment.
- Serious non-compliance with the protocol/study procedures as judged by the investigator and/or the Sponsor.

- Patient lost to FU and not responding after several attempts to contact the patient.
- Changes in medical status of the patient such that the patient no longer meets eligibility requirements for treatment (e.g., recovery), or the Investigator believes that patient's safety will be compromised.
- AE, at the discretion of investigator or Sponsor, or as requested by regulatory authorities.
- Disease progression (see Section10.3.4.2.).
- Other unacceptable toxicity (in the Investigator's opinion).
- Pregnancy.
- Death.
- Initiation of other treatment for metastatic pancreatic adenocarcinoma (i.e., apart from nab-paclitaxel/gemcitabine as SoC).
- Lack of efficacy.
- Investigator decision.
- At the specific request of the sponsor.
- Study terminated by sponsor.

If a patient fails to return for a scheduled visit/FU, attempts should be made to contact the patient to ensure that the reason for not returning is not an AE. Likewise, if a patient declares their wish to discontinue from the study e.g., for personal reasons, an attempt should be made to establish that the true reason is not an AE (bearing in mind the patient is not obliged to state their reasons).

If the IMP therapy is prematurely discontinued (second VCN-01 dose is not administered), the primary reason for discontinuation must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. Discontinuing of IMP administration is not a reason to discontinue from the study SoC treatment. Every effort should be made to collect complete information on patients whether or not they complete the planned treatment. A complete final evaluation following the discontinuation of study treatment should be made, and any AEs should be followed up according to Section 10.3.6. In case of withdrawal for treatment, patients will be asked to continue safety and survival FU, which includes the collection of data on survival, patient-reported outcomes, and subsequent anticancer therapy.

5.5.2. Replacement Policy

Any patient withdrawing from the study before completing the first 28-day cycle (Arm I) or the first 35-day cycle (Arm II) will be replaced. Patients who receive less of the 33% of the nab-paclitaxel and gemcitabine planned dose during the first cycle of treatment, will be replaced.

It is estimated 46 patients would be necessary for each study arm. If necessary, recruitment will be extended until 92 patients have completed the first cycle of the study. Should a patient drop out or be withdrawn from the study, neither their screening number, nor their randomization number will be reallocated. A new patient will be screened and assigned the next screening number and if enrolled will be assigned the next randomization number available.

No rescreening will be allowed in this study (i.e., patients who fail screening may not be rescreened. Patients who drop out or withdraw may also not be rescreened).

6. STUDY MEDICATION

For this study, VCN-01 is considered an IMP while nab-paclitaxel and gemcitabine are considered non-IMPs to be administrated as SoC under authorized conditions.

a) **IV VCN-01**: VCN-01 will be administered only in Arm II as a single IV infusion at dose $1x10^{13}$ vp in a 50 mL prepared solution, at a rate of 5 mL/min on Day 1 of the 1st cycle and then again on Day 1 of the 4th cycle (Day 92) (refer to Table 6-3 below for Arm II treatment schedule).

b) **IV nab-paclitaxel**: Nab-paclitaxel as an IV infusion at a dose of 125 mg/m^2 as part of SoC will be administered in both treatment arms according to current SoC procedures (see Table 6-2 and Table 6-3 for Arm I and Arm II treatment schedules, respectively).

c) **IV gemcitabine**: Gemcitabine will be administered as an IV infusion at a dose of 1,000 mg/m^2 started immediately after the completion of nab-paclitaxel administration as part of SoC in both treatment arms and according to current SoC procdures (see Table 6-2 and Table 6-3 for Arm I and Arm II treatment schedules, respectively). E.g., Patients will visit the hospital for scheduled assessments and study treatment administration as per time points included in the flow chart (see APPENDIX 7 and APPENDIX 8). Patients will only be hospitalized in the instance of a serious adverse event (SAE).

6.1. PRESENTATION, STORAGE, PACKAGING AND LABELLING

6.1.1. Presentation, Storage, Packaging and Labelling of Investigational Product

6.1.1.1. Presentation of VCN-01

VCN-01 will be supplied to the participating sites in a box containing a specific number of 2 mL Type I glass vials, necessary for the preparation of a dose for one patient's infusion.

Composition and Formulation

VCN-01 is classified as a genetically modified organism (GMO; oncolytic replication competent virus vector).

The IMP is a sterile virus suspension in a buffer solution (as described in Table 6-1) and is a concentrate for infusion or injection.

The excipients, Tris, sodium chloride and glycerol comply with the requirements of the relevant Ph. Eur./USP monographs. None of the excipients are of animal or human origin.

Table 6-1: Quantitative composition of the Investigational Medicinal Product (IMP)

Component		*Amount per vial*	*Function*
Active substance	VCN-01 oncolytic adenovirus	1 E+11- 1E+13 vp/ml	Active substance
Excipients	Tris[1]	20 mM	Buffer solution
	Sodium chloride	25 mM	Isotonicity
	Glycerol	2.5%	Stabilizer

[1]Tris(hidroximetil)aminomethane

All of the operations concerning the manufacture, quality control, packaging, labelling, release, warehousing, and distribution of VCN-01 IMP/drug product are carried out in accordance with current Good Manufacturing Practices (GMP).

6.1.1.2. Storage/Stability of VCN-01

VCN-01 IMP is stored frozen below -70 ºC. An on-going GLP/GMP stability study confirms that VCN-01 IMP is stable for at least 108 months under the proposed storage conditions. Any unexpected findings from the ongoing stability studies will be reported to the Investigator, study pharmacist, Simbec-Orion, and the relevant regulatory authority.
VCN-01 IMP vials are to be stored in a deep freezer below -70ºC and should be kept in a secure area with access limited to appropriate pharmacists until dispensed to study personnel for administration to study participants.
Detailed standard operation procedures regarding the preparation and handling of the IMP prior to the administration to the patients is provided in the Pharmacy Manual.

6.1.1.3. Packaging/Labelling of VCN-01

VCN-01 IMP is packaged in 2 mL Type I glass vials, sealed with a flip-off aluminum seal and a bromobutyl rubber stopper. VCN-01 is available as a suspension of virus in 20 mM Tris buffer containing 25 mM NaCl and 2.5% glycerol at pH 8.0.

Biological, physical and chemical characteristics

- Description: Genetically modified HAd5 encoding human PH20 hyaluronidase
- IMP name: VCN-01
- Genomic size: 37607 base-pairs
- Outer capsid: protein (VCN-01 is a non-enveloped virus)
- Shape: icosahedral particle about 80 nm in diameter

VCN-01 will be stored in the freezer below -70 °C until required for treatment.
VCN-01 should be thawed at room temperature and the time between preparation with saline and administration does not exceed 4 hours.
VCN-01 will be labelled and packaged in boxes according to the current legislation.

6.1.2. Presentation, Storage, Packaging and Labelling of Nab-paclitaxel

Nab-paclitaxel is available in sterile lyophilized powder for reconstitution before use. After reconstitution, each mL of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

Re-labelling for clinical trial use will not be required since nab-paclitaxel will be administrated as SoC at site facilities by site staff.

Premedication is generally not needed prior to the administration of nab-paclitaxel.

Refer to the nab-paclitaxel prescribing information/package insert or SmPC for further detail.

6.1.3. Presentation, Storage, Packaging and Labelling of Gemcitabine

Gemcitabine is available as a lyophilized powder in sterile single use vials. Vials with 200 mg and 1 g are available. To reconstitute, add at least 5 mL of sodium chloride 0.9% solution to the 200 mg vial, or at least 25 mL of sodium chloride 0.9% solution to the 1 g vial.
Re-labelling for clinical trial use will not be required because gemcitabine will be administrated as SoC at site facilities by site staff.

Gemcitabine premedication can be scheduled at the site's choice. In case of premedication use, oral and IV corticosteroids are allowed to be administered at a dose according to the information/package insert of the SmPC.

For further details, see the gemcitabine prescribing information/package insert or SmPC.

6.2. RECEIPT OF INVESTIGATIONAL PRODUCTS AT THE CENTER/STABILITY DURING SHIPMENT

After the regulatory green light, VCN-01 will be shipped to the centers on dry ice. If no dry ice is present in the container on arrival at the center, the center pharmacist or designee must inform Simbec-Orion personnel IMMEDIATELY.

A temperature probe and data logger will accompany the drug on shipment. The temperature range reached during shipment should be inspected in the data logger file for any temperature excursion prior to any release of VCN-01 for its use, so that potential stability concerns during shipment can be investigated and appropriate action taken. For further details, see the current Pharmacy Manual.

Blinding

Not applicable as this is an open-label study.

6.3. DOSE, ROUTE AND SCHEDULE OF INVESTIGATIONAL PRODUCT ADMINISTRATION

- Arm I: Patients included in this arm will not receive the IMP. IV nab-paclitaxel and gemcitabine will be administered as SoC (28-day cycles) on Day 1, Day 8, and Day 15 of each 28-day treatment cycle. Nab-paclitaxel will be administered as an IV infusion at a dose of 125 mg/m^2 and gemcitabine as an IV infusion immediately after the

completion of nab-paclitaxel administration at a dose of 1,000 mg/m^2 according to current SoC procedures. See Table 6-2 for Arm I treatment schedule.

- Arm II: Patients included in this arm will receive two (2) doses of VCN-01, each administered as a single IV infusion at dose 1x10^{13} vp in a 50 mL prepared solution, in combination with IV nab-paclitaxel and gemcitabine as SoC (28-day cycles with exception of the IMP dose cycles, which will be 35-day cycles). VCN-01 will be administered as a single IV infusion of VCN-01 at a rate of 5 mL/min on Day 1, then 1 week later, 3 cycles of nab-paclitaxel and gemcitabine will be administered (nab-paclitaxel as an IV infusion at a dose of 125 mg/m^2 and gemcitabine as an IV infusion immediately after the completion of nab-paclitaxel administration at a dose of 1,000 mg/m^2 according to current SoC procedures). On Day 1 of Cycle 4 (+1 day to 2 weeks), a second VCN-01 dose will be administered at a rate of 5 mL/min in the instance the patient is recovered from nab-paclitaxel/gemcitabine hematological and biochemical toxicity. One week later, subsequent 28-day cycles of nab-paclitaxel and gemcitabine should continue. See Table 6-3 for Arm II treatment schedule.

Table 6-2: Arm I Treatment Schedule

Cycle	Screening	C1 (28-day cycle)				C2 (28-day cycle)				C3 (28-day cycle)				C4 + subsequent cycles* (28-day cycle)				Until PD, toxicity, patient withdrawal
Day		1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	
SoC		X	X	X		X	X	X		X	X	X		X	X	X		

SoC=nab-paclitaxel and gemcitabine; C=cycle; PD=progressive disease
*Patients will continue treatment until PD, intolerable/unacceptable toxicity, or patient's/investigator's decision.

Table 6-3: Arm II Treatment Schedule

Cycle	Screening	C1 (35-day cycle)					C2 (28-day cycle)				C3* (28-day cycle)				C4 + subsequent cycles* (35-day cycle)					Until PD, toxicity, patient
Day		1	8	15	22	35	1	8	15	22	1	8	15	22	1	8	15	22	35	
VCN-01		X													X					
SoC			X	X	X		X	X	X		X	X	X			X	X	X		

SoC=nab-paclitaxel and gemcitabine; C=Cycle; PD=progressive disease
* One week following Cycle 4 subsequent 28-day cycles of nab-paclitaxel/ gemcitabine should continue.
Patients will continue treatment until PD, intolerable/unacceptable toxicity, or patient's/investigator's decision.

6.4. DOSE JUSTIFICATION

According to the safety data from phase I clinical trial P-VCNA-001, IV VCN-01 in combination with nab-paclitaxel and gemcitabine in a one-week delayed schedule was well tolerated. Reduced toxicity profile has been observed when VCN-01 was administered 7 days before chemotherapy when compared with VCN-01 administered in concomitance with chemotherapy (as previously reported for Part II of this study). No events qualified as dose limiting toxicities (DLTs) (i.e., no DLTs were reported). Therefore, the dose level 1x10^{13} vp was considered the RP2D of VCN-01 combined with nab-paclitaxel plus gemcitabine when

administered with a 7-day shift (delayed schedule). The safety profile of VCN-01 was consistent with the combination of AEs previously reported for other oncolytic adenovirus and in the SmPC of nab-paclitaxel and gemcitabine.
A second IV administration of VCN-01 was not considered in P-VCNA-001 study as high levels of anti-Ad5 neutralizing antibodies were observed after the first administration. Anti-Ad5 NAbs titers were monitored over longer periods of time in the frame of another clinical trial, ICO-VCN-H&N-2018 "A Phase I Study to Evaluate the Safety, Tolerability, and Efficacy of VCN-01 in Combination With Durvalumab (MEDI4736) in Subjects With Recurrent/ Metastatic Squamous Cell Carcinoma of the Head and Neck", sponsored by Institut Català d'Oncologia. Ad5 NAbs titers were evaluated in P-VCNA-001 study over longer periods of time and it was identified that NAbs anti-Ad5 peaked on Days 15 and 28, then started decreasing over time, reaching a ~15-fold reduction on Day 85-99. Those levels were low enough to allow a second IV administration at approximately 3 months later than the first VCN-01 administration. Regarding toxicity, GLP studies in Syrian hamster (VCNA-C2-19 and VCNA-C2-45) demonstrated that onset of adverse effects starts early after VCN-01 intravenous administration (peak observed at day 2) and animals were recovered by day 28. Results from the part III of the clinical trial in which one single injection of VCN-01 on day 1 followed, seven days later, by nab-paclitaxel plus gemcitabine on days 8, 15 and 22, showed that no virus- associated toxicities were detected after 29 days post virus administration, confirming the non-clinical results in hamster. A second administration of VCN-01 three months after the first one can be considered an independent dose and no accumulated toxicities are expected between both administrations (Garcia-Carbonero et al, 2022).

6.5. CRITERIA FOR SCHEDULE ADJUSTMENT/DOSE-MODIFICATION OF INVESTIGATIONAL PRODUCT

Dose adjustments/dose modifications are not permitted for VCN-01. VCN-01 will be administered at dose $1x10^{13}$ vp. Second VCN-01 dose will be administered at D1 of Cycle 4; however, an acceptable time window of +1 day to 2 weeks will be allowed in the instance the patient is not recovered from nab-paclitaxel/gemcitabine hematological and biochemical toxicity.
Nab-paclitaxel and gemcitabine interruptions/reductions (if required) will follow the recommendation in the locally approved prescribing information/package insert or SmPC for metastatic pancreatic cancer, which will be at the discretion of the PI.
Any dose reductions and/or interruptions (including any missed doses), and the reasons for them must be recorded in the eCRF.

6.6. INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

When IMP is received by the Investigator (or pharmacist), they will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by or on behalf of Simbec-Orion and returning it to Simbec-Orion. A copy will be retained for the Investigator file.
The dispensing of the IMP will be carefully recorded on appropriate drug accountability forms (these will be provided by Simbec-Orion), and an accurate accounting will be available

for verification by the Simbec-Orion Clinical Research Associate (CRA) at each monitoring visit.
IMP accountability records will include:

- confirmation of delivery of the IMP to the trial site,
- the inventory at the site,
- the use by each patient,
- the return to the Sponsor or alternative disposition of unused product(s).

They should include dates, quantities, batch numbers, expiration dates (if applicable), and any unique code numbers assigned to the IMP and/or patients. Investigators should maintain records which document adequately that:

- the patients were provided the doses specified by the protocol/amendment(s),
- all IMP provided by the Sponsor was fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present study.
If appropriate, study personnel responsible for IMP administration should be instructed to return **unused** IMPs to Sponsor, preferably in their original packaging.
As VCN-01 is classified as BSL2 product (Spanish RD 664/1997), the CRA will not perform direct accountability (only review the forms), and after the dilution preparation, the used vials should be accordingly destroyed. Additionally, as VCN-01 is an GMO and ATP product, its traceability from receipt until its administration (or its return of destruction) must be guaranteed (Regulation (EC) 1394/2007 of the European Parliament).
The Simbec-Orion CRA will review the drug accountability forms and check all IMP returns prior to making arrangements for their return to the Sponsor or authorizing their destruction by the study site.

6.7. VCN-01 PREPARATION

Before handling the product, the presence of type III waste containers (biosanitary ware including pungent) and a conventional disinfectant (bleach, soap or similar) in the preparation area will be checked.
VCN-01 should be diluted as close to the administration time as possible, but no longer than 4 hours beforehand. Dilution will be performed in a laminar flow cabinet following biosafety precautions and internal cytotoxic drug handling procedures for a BSL2 biosafety level.
Unopened and undiluted vials of VCN-01 should be thawed at room temperature and the time between preparation with saline and administration does not exceed 4 hours.
The calculation of the clinical dose to be administered to the patients will be made based on the (physical) concentration of the VCN-01 product. The pharmacy site will be responsible of documenting the dilution preparation procedures for the appropriate dose. From the 2 mL Type I glass vials of concentrated solution, the corresponding dilution will be made using physiological saline.
VCN-01 will be administered by IV infusion at a rate of 5 mL/min and the patient will be monitored during administration. The IV tubing will be primed with saline. Following saline priming, 50 mL of prepared VCN-01 will be administered to the patient. Following VCN-01 the administration at the infusion center, an additional volume of saline, that is equal to the dead volume of the tubing, will be used to rinse the infusion bag and tubing and infused to ensure that any remaining product in the infusion set (bag and tubing) reaches the patient. A

complete dose of VCN-01 requires the entire contents of the dosing bag (50 mL prepared solution) to be administered with no VCN-01 remaining in the bag or the infusion lines. Confirm with the clinical site that saline is available for the rinse.

7. CONCOMITANT THERAPY/MEDICAL MANAGEMENT OF ADVERSE EVENTS

Any medications, with the exceptions noted in Section 7.1 below, which are considered necessary for the patient's welfare, and which will not interfere with the study medication, may be given at the discretion of the Investigator. Medications which must be administered as part of the study treatment schedule are listed in Section 7.2. Additionally, medications which may be used with caution are provided in Section 7.3.
All relevant concomitant medications should be recorded in the appropriate section of the eCRF, along with dosage information, dates of administration and reasons for use, according to the following rules:

- Information related to medication that the patient has already been taking before the trial will only be recorded at Screening;
- Starting with the signing of the PICD and ending with withdrawal of the patient from the trial (e.g., progressive disease, unacceptable toxicity, patient/investigator decision) the following information should be recorded:
    - Medication required for the treatment of AEs (serious and non- serious);
    - IMP and SoC premedication (for details see Section 6.1.3);
    - Transfusions, if needed;
    - All treatment that is started on a regular basis during this period;
    - Medications to treat a concurrent illness or concurrent symptoms.

It is not necessary to record information on sporadic treatment that the patient receives during the treatment period (e.g., occasional analgesic or anti-inflammatory agents, antacids).
Additionally, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the appropriate section of the eCRF.
After a patient's withdrawal from the trial, the only medications that should be recorded are (i) medications used to treat an adverse event related to the IMP or SoC; and (ii) subsequent anti-cancer therapies. Medications for the treatment of symptoms of progressive disease or other illnesses will not be recorded.

7.1. MEDICATIONS THAT MAY NOT BE ADMINISTERED

The patient must not take any of the following medications during the course of this study (during the Treatment period, and prior to the start of treatment, as specified below):

- Treatment with live attenuated vaccines 3 weeks before start of study treatment administration and with the adenovirus type-5 (Ad5)-based COVID-vaccine 12 weeks before start of study treatment administration (as per exclusion criteria in Section 5.3);
- Treatment with another investigational agent within five of that treatment's half-lives prior to infusion of study treatment (as per exclusion criteria in Section 5.3);
- Chronic immunosuppressive and/or disease modifying therapy, except inhaled corticosteroids, and oral or IV corticosteroids with a dose lower than 10 mg prednisone or equivalent/day (exception: dexamethasone 1 mg/day as maximum) (as per exclusion criteria in Section 5.3).
  Note: corticosteroids as SoC premedication are allowed according to the SmPC.
- Patients receiving full-dose anticoagulant therapy, including low-dose aspirin (acetylsalicylic acid) at dose 100mg or below, or in whom these therapies cannot be

withdrawn 2 days prior to and 2 days after VCN-01 administration. Patients with uncontrolled coagulopathy should be excluded (as per exclusion criteria in Section 5.3);

- No other chemotherapy, immunotherapy, hormonal therapy, or other novel agent is permitted until completing EOT visit planned 1 month after last dose of study treatment. Patients may continue the use of biphosphonates for bone disease and corticosteroids if the provided dose is stable at least 15 days before and during the study. Also, palliative radiotherapy may be used for treatment of pain at the site of bone metastases that were present at baseline and also if the investigator does not consider that these metastases are indicative of clinical disease progression during the study period.

The use of any herbal/natural products or other "folk remedies" should be discouraged, but use of those products, as well as the use of vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

7.2. MANDATORY CONCOMITANT MEDICATIONS

Nab-paclitaxel and gemcitabine (at 28-day cycles) are not considered IMP but must be given to each patient as SoC and as a part of study treatment. Refer to Section 6 for further detail.

7.3. CONCOMITANT MEDICATIONS RECOMMENDED TO BE USED TO TREAT FLU-LIKE SYMPTOMS

The following medication/therapy can be given to treat flu-like symptoms/pyrexia:

- Antipyretic treatment orally (p.o.) is recommended approximately 30 minutes before the IMP treatment is received. Use of sporadic paracetamol (acetaminophen) is allowed, but the dose must be equal to or less than 3 g/day;
- Anti-inflammatory drug such as ibuprofen or naproxen are not recommended to be used to treat flu-like syndrome during 7-10 days after IMP administration. However, in case of use, a maximum dose allowed is 1200 mg QD for ibuprofen and 1250 mg QD for naproxen.

In case of doubt, contact the Sponsor’s medical contact.

8. SCHEDULE OF VISITS

8.1. SCREENING EVALUATION

A study initiation visit **must** be conducted prior to the commencement of any study activities requiring informed consent. A complete Screening evaluation will be conducted within 28 days prior to each patient starting treatment with either SoC only (nab-paclitaxel and gemcitabine) (in Arm I) or IMP (VCN-01) with SoC (in Arm II). For each patient considered, eligibility criteria will be checked for compliance prior to that patient's inclusion in the study. The Investigator will explain the details of the study to potentially suitable patient. The patient will be given a PICD to read for further information about the study (Refer to Section 5.1 for more details regarding informed consent).
The "screening" log will be provided by Simbec-Orion and completed by the Investigator in order to keep a record of all patients who are considered for entry into the study, whether they subsequently entered the study treatment period or not. The reasons for their exclusion from the study will be recorded, if applicable.
Screen failures are defined as patients who consented to participate in the clinical study but did not subsequently receive SoC or IMP in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs that were considered related to trial participation.
Rescreening of patients who fail the entry criteria (screen failure) will not be allowed in this study.
Repeating laboratory tests within the screening period will not be considered as a rescreen.

8.2. TREATMENT PERIOD(S): DRUG ADMINISTRATION

8.2.1. Schedule of Visits for On-treatment Period

Study treatment (SoC [nab-paclitaxel + gemcitabine] for Arm I and VCN-01 with SoC for Arm II) will be administered from C1D1 if the patient has been confirmed as being eligible for inclusion in the study. Patients will continue study treatment until PD, unacceptable toxicity, or patient/investigator decision. This period will be defined as Treatment period. See Table 6-2 and Table 6-3 for Arm I and Arm II treatment schedules, respectively. All assessments and procedures during the treatment period are outlined in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for the tests and evaluations to be conducted in Arm I and Arm II, respectively).
Patients will visit the hospital for assessments and study treatment administration as per time points included in the schedule of assessments. Patients will only be hospitalized in the instance of an SAE.

8.2.2. End of Treatment

EOT for this study is defined as visit performed 1 month (±1 week) after the last dose of study treatment.
All assessments and procedures for EOT are outlined in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively).

8.3. FOLLOW-UP PERIOD

For FU in this study, there is a distinction between:

- FU of patients without PD, which is scheduled every 4 weeks (±1 week) until PD
- FU of patients due to PD, which is scheduled:
  - q4wk during the first 6 months (±1 week)
  - q2mo until the second year (±1 week)
  - q6mo after the second year (±1 week)

All assessments and procedures during FU are outlined in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively).

8.4. WITHDRAWAL

If the patient withdraws from the study for any of the reasons described in Section 5.5.1, every effort should be made by the site to FU the patient and to complete the Withdrawal visit. All assessments and procedures for EOT as outlined in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively) will be done.
Every effort should also be made to collect complete information on the patients and to be recorded in the eCRF, whether or not they complete the planned treatment. The ongoing AEs will need to be followed up according to Section 10.3.6.
In the case of an ongoing AE, appropriate safety evaluations should be repeated more frequently and/or additional tests performed at any time when clinically indicated or at the discretion of the Investigator, according to Section 10.3.6. If the patient refuses for any of the above assessments to be performed, or if the patient is lost to FU, then this should be noted in the eCRF.

8.5. END OF STUDY

End of Study Definition
EOS for each patient will be the date of his/her exitus. All patients will be followed for OS.

9. ASSESSMENTS OF EFFICACY

9.1. SPECIFICATION OF EFFICACY PARAMETERS

The following efficacy parameters will be assessed at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively):

- OS
- Landmark 1-year survival and PFS
- PFS or TTP
- Objective response rate (ORR).
- DCR (SD + PR + CR)
- Duration of response (DoR)
- Changes in tumor biomarker Ca 19.9
- Quality of life (QoL) via the validated European Organization for Research and Treatment Quality of Life Questionnaire (EORTC) QLQ-C30 questionnaire (version 3)

9.2. METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING EFFICACY PARAMETERS

9.2.1. Overall Survival

OS is defined as the time from randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. For patients who refuse to return for evaluations, survival status will be assessed through phone contact for those who agree to be contacted by phone.

9.2.2. Landmark 1-year Survival and Progression Free Survival at 1-year Landmark

Landmark 1-year survival is defined as survival at 1 year from randomization.
PFS at 1-year landmark is defined as PFS at 1 year from randomization.

9.2.3. Progression Free Survival or Time to Progression

Progression-free survival (PFS) or time to progression (TTP) is defined as the time from randomization until the date of disease progression (as defined in Section 10.3.4.2.) or death (by any cause in the absence of progression).
Disease progression is assessed by CT scan or Magnetic Resonance Imaging (MRI) for assessments determined by RECIST 1.1 (see APPENDIX 4). CT Scan or MRI will be performed every 8 weeks (±1 week) during the study treatment period. In case of equivocal PD, radiological assessments will be performed every 4 weeks (±1 week). CT scan is the preferred imaging modality for this study. In the event MRI will be used, please refer to the Imaging Manual.

9.2.4. Objective Response Rate

The percentage of patients with CR or PR to study treatment according to RECIST 1.1 (see APPENDIX 4) at EOT.

9.2.5. Disease Control Rate (DCR) (SD+PR+CR)

The percentage of patients who have achieved CR, PR, and SD to the study treatment according to RECIST 1.1 at EOT as assessed by CT scan or MRI. Refer to APPENDIX 4 for information on tumor response evaluation and definition of CR, PR, and SD. Response will be evaluated throughout the study.

9.2.6. Duration of Response

Duration of response (DoR) will be defined as the time from the date of first documented response until date of documented disease progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.

9.2.7. Changes in Tumor Marker Ca 19.9

Changes in tumor marker Ca 19.9 will be measured every 4 weeks while on study treatment (1st day of each cycle [±1 week]) for both arms, as a potential prognostic biomarker for pancreatic ductal adenocarcinoma, especially with regards, to predicting survival following clinical treatment. Preceding study treatment, a Ca 19. 9 test result available withing 72 hours prior to dosing at C1D1 is acceptable but not mandatory for both arms. Tumor marker Ca 19.9 will be measured at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively). Tumor marker Ca 19.9 will also be tested, according to investigator criteria, when clinically indicated. Refer to Section **10.3.4.2.** for the definition of disease progression.

9.2.8. Quality of Life (QoL)

QoL will be measured via the validated EORTC QLQ-C30 questionnaire (version 3). Patients will be asked to complete a QLQ-C30 questionnaire on Day 1 of Cycle 1 and then once every cycle thereafter. Patients who withdraw will have a QOL assessment at the End of Treatment visit, and any subsequent follow-up visit. Refer to APPENDIX 5 for a representative example of the EORTC QLQ-C30 that will be used in this study.

10. ASSESSMENTS OF SAFETY

10.1. SPECIFICATION OF SAFETY PARAMETERS

The following safety parameters will be assessed at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively):

- Demographics
- Medical history
- Prior medications and procedures, including standard of care
- Concomitant medications and procedures
- Physical examinations
- Vital signs assessments
- Safety laboratory tests – biochemistry, hematology, coagulation profile, thyroid stimulating hormone (TSH), HBV, HCV, TB, HIV, urinalysis and pregnancy tests.
- 12-Lead electrocardiogram (ECG)
- COVID-19 testing (PCR or Antigen test)
- LVEF
- ECOG score
- Fibroscan
- AE/SAE assessment

10.2. METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING SAFETY PARAMETERS

10.2.1. Demographic Data

Patient demographic data will be collected at Screening. These data will include gender, age, race, ethnicity, and toxic habits, according to the local regulation.
Toxic habits (e.g., smoking, alcohol abuse, recreational drug use) should be collected in the patient medical history. The investigator can determine whether the patient's reported Toxic Habits would make them unsuitable for the study. Any Toxic Habit that may adversely impact liver function should be carefully considered as transient increases in liver enzymes are a known AE associated with VCN-01 administration.

10.2.2. Medical History

A complete medical history will be obtained from each patient at Screening. This should include, but are not limited to, metastatic pancreatic cancer history, comorbidities, and medical procedures. Medical history should include all ongoing medical conditions at the time of Screening.

10.2.3. Prior and Concomitant Medications and Procedures

Prior medications/medical procedures are, defined as any medication taken and/or any medical procedures performed within 28 days of the Screening visit, will be recorded

including, start/stop dates, indication, dose, and frequency of the medication. Concomitant medications are defined as per Section 7 above.
Note: Nab-paclitaxel/ gemcitabine to be administered as SoC in this stud, will be recorded as study treatment from the start of administration on D1 and thereafter.
Concomitant procedures (diagnostic, therapeutic or surgical procedures) and concomitant use of herbal/natural products will also be documented for each patient at or after the time of Screening visit at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively).
All therapies documented will be coded using the World Health Organization – Drug dictionary (WHO-DD).
Medications will be recorded using the generic terms in the eCRF.

10.2.4. Physical Examination

Full and abbreviated physical examinations will be performed at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively).
A full physical examination will be performed every cycle and will include an assessment of the following: head, eyes, ears, nose, and throat exam, general appearance, respiratory, cardiovascular, abdomen, skin, lymph nodes, thyroid, musculoskeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height. An abbreviated physical examination will be performed every other visit by the study nurse that includes skin (jaundice, petechiae, bruising, rash), eyes (jaundice), lymphatics (neck, axillary, supraclavicular), respiratory/heart (auscultation, percussion), abdominal (liver, masses, and ascites), neuro (for CNS masses), any previously identified palpable masses.
Information about the physical examinations must be present in the source documentation at the study site. Results of the physical examination prior to the administration of study treatment must be included in the relevant medical history/current medical conditions page of the eCRF. Clinically relevant findings made after the study treatment, which meet the definition of an AE, must be recorded on the AE page of the eCRF.

10.2.5. Vital Signs

Vital signs will be assessed at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively).
Vital signs will include supine systolic and diastolic blood pressure (BP; mmHg), pulse (bpm), body temperature (°C) and respiration rate. Vital signs will be collected prior to administration of the dose, and for patients allocated to Arm II, they also will be collected 4h (±10min) after VCN-01 dose. Body weight (kg) will also be recorded along with vital signs.

10.2.6. Safety Laboratory Tests

Safety laboratory tests will be performed at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively). All laboratory assessments are outlined in APPENDIX 2.
Safety laboratory tests include the following:

- COVID-19 at Screening (PCR or antigen test);
- Hepatitis B/C and HIV at Screening;
- TB test at Screening (Only if active TB infection is suspected or in line with local practice).
- Biochemistry - See APPENDIX 2 for a complete list of biochemistry analyses;
- Hematology - See APPENDIX 2 for a complete list of hematology analyses. Note: The patients receiving gemcitabine will have their neutrophils and platelets assessed prior to dosing;
- Coagulation profile - See APPENDIX 2 for a complete list of coagulation analyses;
- TSH at Screening;

Note: Serum or plasma clinical chemistry, hematology, coagulation profile and TSH may be performed more frequently if clinically indicated.

- Urinalysis (dipstick) will be performed. Microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive (i.e., in case of abnormalities). See APPENDIX 2 for a complete list of analyses;
- Pregnancy test will be performed only in female patients of childbearing potential (i.e., female patients who are not postmenopausal or surgically sterile [refer to APPENDIX 1 for definition). Urine or blood pregnancy test will be performed on the Day 1 of each cycle prior to study treatment dosing. Either serum or urine pregnancy tests will be performed at other time points as provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively).

10.2.7. 12-Lead Electrocardiogram (ECG)

After a 5-minute rest, a 12-lead ECG will be obtained with digital 12-lead ECG machines. At Screening, a single 12-lead ECG will be obtained on which QTcF must be <450 ms for men and <470 ms for women. In case of clinically significant ECG abnormalities, 2 additional ECGs should be obtained over a brief period (e.g., 30 min) to confirm the finding. 12-Lead ECGs will be performed at other timepoints only if clinically indicated.

10.2.8. COVID-19 Testing

The patients will be required to undergo COVID-19 testing using a Polymerase Chain Reaction (PCR) or Antigen test to check for active COVID-19 infection during the study. The PCR or Antigen test will preferably be done with nasal swab, nasopharyngeal swab, oropharyngeal swab, and/or saliva sample, according to the local practice/test guidelines. PCR or Antigen test scheduled during a study visit does not need to be performed if a PCR or Antigen test was performed in the last 72 hours (and lab results/data source shared with the site). If the patient has been tested positive between the study visits, the patients will need to be instructed to inform the Investigator immediately.
Testing to check for active COVID-19 infection to be done at Screening, prior to dosing on C1D1 for Arm I (SoC) and Arm II (VCN-01); prior to dosing on C4D1 for Arm II only and at any time at the discretion of the investigator for all other SoC cycles in both Arms I and II.

10.2.9. Left Ventricular Ejection Fraction (LVEF)

LVEF is the measurement of how much blood is being pumped out of the left ventricle of the heart (the main pumping chamber) with each contraction. LVEF assessments will be performed at Screening and at other timepoints only if clinically indicated. At Screening, LVEF evaluation must not be less than 50% measured by ECHO or multigated acquisition scan.

10.2.10. Eastern Cooperative Oncology Group (ECOG) Score

ECOG score will be assessed at the time points provided in the schedule of assessments (refer to APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively). Patients must have an ECOG Score of 0 or 1 at Screening. Refer to APPENDIX 3 for additional details of ECOG Performance Status, including description of the relevant ECOG grades.

10.2.11. Fibroscan

If there is a suspicion of hepatic fibrosis, a fibroscan must be performed. The fibroscan assessment performed during the Screening period must be <9.5 kPa.

10.3. ADVERSE EVENT REPORTING

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. It is the Investigator's responsibility to ensure compliance with reporting of AEs from their site.
Safety data will be collected as soon as written informed consent has been obtained.

10.3.1. Definition of an Adverse Event

An Adverse Event (AE) is defined as: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.3.2. Serious Adverse Events

10.3.2.1. Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death,

  Death is an outcome of an AE, and not an AE in itself. Event which led to death should be recorded with fatal outcome.

NOTE: Death due (or clearly due) to disease progression should be documented in the eCRF but should not be reported as an SAE. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study treatment and will not be reported as an SAE.

- Is life-threatening (i.e., the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or prolongation of existing hospitalization,

  NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the investigator's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether other events meet the serious criteria, the event is to be considered serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity,

  NOTE: The term "significant disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.
- Results in a congenital anomaly/birth defect,
- Is an important medical event(s) that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in such instances.

10.3.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Laboratory abnormalities or other abnormal assessments (e.g., physical examination, vital signs, ECG) that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event should be reported as AEs.

10.3.4. Recording and Reporting of Adverse Events

All AEs, as defined above, encountered during the clinical study as well as any SAEs (see Section 10.3.2 for SAEs) will be reported in the appropriate section of the eCRF/SAE form. It is important that this includes the duration of the AE (onset/resolution dates), the severity, the relationship to the study treatments and any concomitant treatment dispensed (or other action taken), possible actions that could be taken with the study treatments (dose increased/dose not changed/dose reduced/drug interrupted/drug withdrawn/not applicable/unknown; Note: Dose modifications are only allowed for SoCs). If an AE increases in severity, the highest severity grade attained should be reported. See Section 10.3.4.5. for definition of relationship of AEs to study treatment and Section 10.3.4.6. for definition of severity of AEs.
AE data should be obtained through observation of the patient, from any information volunteered by the patient, or through patient questioning. The patient may be asked “Do you have any health problems?” or “Have you had any health problems since your last clinic visit?”
AEs will be coded using the latest available Medical Dictionary for Regulatory Activities (MedDRA) version.

10.3.4.1. Reporting of Signs and Symptoms versus a Diagnosis

Recording a diagnosis (when possible) is preferred to recording a list of associated signs and symptoms. However, if a diagnosis is known but there are associated signs or symptoms not generally attributed to the diagnosis, the diagnosis and each sign or symptom must be recorded separately.

10.3.4.2. Disease Progression

Progression of Disease (PD) will be defined as having progression of disease according to RECIST 1.1 (as assessed by CT scan or MRI [see APPENDIX 4]). Events due to disease progression should be collected and recorded as AEs.

10.3.4.3. Death

All deaths that occur during the AE Reporting period (refer to Section 10.3.5) must be reported as follows:

- Death due (or clearly due) to disease progression should be documented in the eCRF but should not be reported as an SAE
- Death that is not due (or not clearly due) to disease progression should be documented in the eCRF and as a SAE within 24 hours (see Section 10.3.4.7). The report should detail the main and contributory causes of death. This information should also be accompanied by a death certificate or autopsy report (if available).

10.3.4.4. Pregnancy

Should a pregnancy occur in a female study participant or the partner of a male study participant, it must be reported in accordance with the procedures described in

Section 10.3.4.7. Pregnancy in itself is not regarded as an AE unless there is a suspicion that study treatments may have interfered with the effectiveness of a contraceptive medication. The pregnancy must be followed up on to determine outcome (including spontaneous or voluntary termination), and status of mother and child, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications. Pregnancy itself is not considered to be an AE or SAE.
Consent to report information regarding these pregnancy outcomes should be obtained from the mother. Once consent has been obtained, pregnancy outcomes must be collected for females who took the IMP on the Pregnancy Outcome form and should be sent to Simbec-Orion Pharmacovigilance immediately or within 24 hours of the time the information is known.
If the pregnancy outcome meets the SAE definition, also complete an SAE Form as detailed in Section 10.3.4.7. It is important to monitor the outcome of any pregnancies of patients in order to provide SAE data on congenital anomalies, birth defects or spontaneous abortion.

10.3.4.5. Definition of Relationship of AEs to the Study Treatment

The Investigator must assess the possible relationship between the AE and the study treatments and record that assessment in the eCRF. The Investigator is to make their own assessment of each SAE to be recorded on the eCRF and on the SAE form.
The Investigator should provide a Yes or No assessment as to whether there is a reasonable possibility that the event may have been caused by the study treatments.

The relationship should be assessed according to the criteria in Table 10-1 below:

Table 10-1: Relationship of the Adverse Event to the Study Treatment

Definitely Related	Adverse events that are temporally linked and for which the study product is the most likely explanation, which disappear or decrease when not using study product and reappear when using study product
Probably Related	Adverse events that are temporally linked and for which the study product is more likely to be the explanation than other causes, which may improve when not using study product
Possibly Related	Adverse events that could equally well be explained by study product or other causes, which are usually temporally linked and may improve when not using study product but do not reappear when using study product
Unlikely Related	Adverse events that may be temporally linked, but which are much more likely to be due to other causes than study product and which do not get worse with continuing use of product
Not Related	Adverse events that can be clearly explained by extraneous causes and for which there is no plausible association with study product, or adverse events for which there is no temporal relationship

10.3.4.6. Definition of Severity of Adverse Events

Severity of any AE will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, where applicable.
For each episode, the highest severity grade attained should be reported.
If an AE occurs that is not listed in the CTCAE, the Investigator will evaluate its severity using the definitions in Table 10-2.

Table 10-2: Definition of Severity of Adverse Events

Mild	Grade 1 - Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])
Life Threatening	Grade 4 - Results in risk of death, organ damage, or permanent disability (unacceptable)

Death	Grade 5 – Event has a fatal outcome

Note the distinction between serious and severe AEs. **Severe** is a measure of intensity whereas an event must meet one of the criteria for serious events listed in Section 10.3.2 to be considered **serious**; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 10.3.2. An AE that is assessed as Grade 3 (severe) or Grade 4 (potentially life-threatening) should not be confused with a SAE.

10.3.4.7. SAE Reporting Procedure for Investigators to Simbec-Orion

The Investigator must report all initial and FU reports regarding SAEs, regardless of presumed causal relationship, to the Simbec-Orion's Pharmacovigilance Department, by email, fax, or phone. The completed SAE report form is transmitted via email (preferred method), or fax to Simbec-Orion's Pharmacovigilance Department within 24 hours of awareness of an SAE.

Study Contact for Reporting SAEs.
Simbec-Orion
Preferred method of reporting: Pharmacovigilance@simbecorion.com
SAE Fax: +44 1753 695 101
Back-up SAE fax: +44 1753 695 124

If the SAE is reported by telephone, all points on the SAE form should be covered in the initial telephone report and followed by a completed and signed SAE form to verify the verbal information given previously. In addition, the event must be documented in the eCRF.
The SAE form must be completed as fully as possible with information relevant to the SAE(s) being reported. All fields should be populated or marked accordingly if no information is available.
For all SAEs where important or relevant information is missing, active FU should be undertaken. Investigators or other site personnel should inform Simbec-Orion's Pharmacovigilance Department of any FU information on a previously reported SAE immediately but no later than 24 hours after they become aware of the SAE FU information.
The FU information must be presented on an SAE form marked as FU. It is necessary to provide the new information with the SAE form signed by an Investigator.
Investigators or other site personnel should send relevant eCRF modules by email or fax to Simbec-Orion's Pharmacovigilance Department and any other relevant or requested supporting documentation (e.g., ECG, laboratory results, autopsy report) as above.
The Investigator will ensure that all the necessary information is provided within the timelines stipulated by the Simbec-Orion's Pharmacovigilance Department when the request for information is made.
FU reports (as many as required) should be completed and send via email or fax following the same procedure above.
Investigators are not obligated to actively determine the occurrence of AEs or SAEs in former study participants.

10.3.5. Safety Reporting to IECs/IRBs, Competent Authorities, and Investigators

The Investigator is responsible for informing local IECs/IRBs of the applicable safety reports in compliance with the local regulations. The copies of all correspondence relating to reporting of any safety reports to the local IEC/IRB should be maintained in the Investigator's files and provided to Simbec-Orion.
With respect to suspected unexpected SARs (SUSARs), the reference document for definition of expectedness is the Reference Safety Information section of the IB.
The Sponsor, or its designee, Simbec-Orion, will inform central IECs, regulatory authorities, and local IECs (only when the central IEC is equally the local IEC for a single site in a country) of applicable safety reports, as required.

10.3.6. Adverse Event Reporting Period

All AEs will be collected by the Investigator throughout the study starting from the date of consent until the EOT visit. The following information needs to be recorded: start and end date/time, severity, seriousness, and relationship with the study treatment.
Ongoing events prior to the consent will be recorded in the medical history. If and when such an event resolves, the end date will be recorded in the medical history. If the event worsens, it will be recorded as a new AE in the AE page of the eCRF.
AEs occurring during the Screening period will be recorded on the AE page of the eCRF.
All AEs occurring before the EOT visit will be monitored and recorded as follows:

- AEs that are related to the study treatment will be monitored until they resolve or stabilize at a level acceptable to the Investigator and Medical Monitor;
- AEs that are not related to the study treatment will be monitored until they resolve or stabilize or until the EOT visit, whichever comes first;
- If it is not possible to monitor the AEs as described due to clinical or organizational reasons, or the patient is lost to follow-up, then an outcome assessment must be performed by the Investigator;
- All data pertaining to the AEs will be recorded in the AE page of the eCRF.

If AEs occur after the EOT visit, they will be monitored and recorded as follows:

- AEs that are related to the study treatment will be monitored as AEs i.e., until the event has resolved or stabilized at a level acceptable to the Investigator and the Medical Monitor. The data will be recorded, in the AE page of the eCRF and reported to the Sponsor;
- AEs that are not related to study treatment will neither be monitored nor recorded.

10.3.7. Data Monitoring Committee

An independent DMC was be established to ensure patient safety, to consider patient risks against the potential for meeting trial objectives, and to provide recommendations to the Sponsor with respect to the conduct of the trial.
The DMC will perform the following major functions:

- The DMC will be responsible for the ongoing review of safety data throughout the trial. Primary among the safety data to be reviewed will be SAEs, any adverse drug reactions (ADRs) and all relevant available clinical laboratory data.

- The DMC may review acute and additional safety data, on a patient-by-patient basis, at their discretion. This would be warranted if significant unexpected events are observed.
- The DMC may request additional safety data if, in the view of the committee, these additional data are needed in order to make an informed, responsible decision about the conduct of the trial.
- The DMC will advise the Sponsor regarding safety of patients and continuing validity and scientific merit of the trial. The DMC will also monitor the number of deaths in both arms of the study.

The trial will not be stopped early for a claim due to effectiveness.
All details of the conduct and responsibilities of the study DMC along with the frequency of DMC meetings will be described in the 'DMC Charter', which was finalized on December 12, 2022 prior to the start of patient enrollment.

11. ASSESSMENTS OF PHARMACODYNAMICS

11.1. SPECIFICATION OF PHARMACODYNAMIC PARAMETERS

Exploratory biomarkers may include but are not limited to the following:

- Blood and serum biomarkers including:
  - VCN-01 genomes in blood (Arm II only)
  - PH20 in serum (Arm II only)
  - Circulating immune markers in serum
  - Neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs) in serum (Arm II only)
  - Neutrophil/lymphocyte ratio
- Image biomarkers (radiomics) assessed from the images of CT scans performed during the study.
  Note: Image acquisition guidelines will be provided in the Imaging Manual.

11.2. METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING PHARMACODYNAMIC PARAMETERS

11.2.1. Changes in Biomarkers

Biomarker levels, according to the state of the art, may be determined. Blood and serum samples may include but are not limited to the biomarkers provided below, planned at time points included here (also see the schedule of assessments in APPENDIX 7 and APPENDIX 8 for Arms I and II, respectively).

- In Arm I;
  - serum samples for circulating immune markers will be obtained D1 pre-dose of each treatment cycle; Cycle 1 on D8 and D15 and EOT.
- In Arm II;
  - blood samples for VCN-01 genomes will be obtained C1D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C1D3 (48 h [±3 h] after VCN-01 administration); C1D8; C1D15; C2D1; C3D1; C4D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C4D3 (48 h [±3 h] after VCN-01 administration); C4D8; C4D15; Day 1 of subsequent nab-paclitaxel/gemcitabine cycles; EOT.
  - serum samples for neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs) will be obtained C1D1 pre-dose; C1D8; C1D15; C2D1; C3D1; C4D1 pre-dose; C4D8; C4D15; Day 1 of subsequent nab-paclitaxel/gemcitabine cycles; EOT.
  - serum samples for PH20 will be obtained C1D1 pre-dose; C1D3 (48 h [±3 h] after VCN-01 administration); C1D8; C2D1; C3D1; C4D1 pre-dose; C4D3 (48 h [±3 h] after VCN-01 administration); C4D8; Day 1 of subsequent nab-paclitaxel/gemcitabine cycles; EOT.
  - serum samples for circulating immune markers will be obtained C1D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C1D3 (48 h [±3 h] after VCN-01 administration); C1D8; C2D1; C3D1; C4D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C4D3 (48 h [±3 h] after VCN-01

administration); C4D8; C4D15; Day 1 of subsequent nab-paclitaxel/gemcitabine cycles; EOT.

Sample collection guidelines will be provided in the Lab Samples Manual.

12. STATISTICS

12.1. SAMPLE SIZE AND STUDY POWER

Assuming an accrual time of 18 months with (minimum) 12-month FU for all patients, 1-sided alpha = 0.05, beta= 0.2 (80% power), the median OS=10.6 months for Arm I and the median OS=20.8 for Arm II with 1: 1 randomization, 46 patients would be needed for each study arm to reach the 57 events needed using the log-rank test. It is therefore planned to randomize a total of 92 adult patients with metastatic pancreatic cancer into the study for final analysis.

12.2. RANDOMIZATION

Patients will be randomized in a ratio of 1:1 to receive either SoC or SoC + 2 administrations of VCN-01. Of the 92 patients required, 46 patients will receive SoC, and 46 patients will receive SoC + 2 administrations of VCN-01. The randomization will be stratified to take account of the patient's baseline ECOG performance status (0 or 1) and region (North America or EU).
The randomization list will be prepared by Simbec-Orion according to the current version of the Simbec-Orion Standard Operating Procedure.

12.3. STATISTICAL METHODS

Statistical analyses will be performed by Simbec-Orion. Statistical analyses will be carried out using SAS® Enterprise Guide 8.3, SAS Institute, Cary, North Carolina, USA.
The statistical methods for this study, summarized below, will be described in a detailed statistical analysis plan (SAP) which will be finalized prior to database lock. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report.

12.3.1. General Considerations

Data will be summarized as follows: Continuous variables by descriptive statistics (number of patients [N], mean, standard deviation, minimum, median and maximum); categorical data by absolute and relative frequencies (n and %).
Unless indicated otherwise, summary statistics will be reported for observed data only.
Missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated. Baseline is defined as the last assessment before the start of study treatment.

12.3.2. Populations for Analysis

The following analysis sets will be analyzed:

Safety Analysis Set (SAF)
The SAF is defined as all patients who are randomized and take any dose of study medication.

Intent-to-Treat Analysis Set (ITT)
The ITT is defined as all patients who are randomized and have received any dose of study medication. The treatment arm is defined as the treatment that is randomized to treat the patient.

Full Analysis Set (FAS)
The FAS is defined as all patients who are randomized and have received at least 1/3 of the planned chemotherapy dose (arm I and II) and a complete dose of VCN-01 (arm II) during the first cycle of the study.

Per-Protocol Set (PPS)
The PPS is defined as patients in the FAS and without any major protocol deviation that could potentially influence a study endpoint.

Pharmacodynamic Set
The Pharmacodynamic Set will consist of all patients in the FAS who had at least 1 pharmacodynamic measurement, had no major protocol deviations affecting pharmacodynamic parameters and no deviation from pharmacodynamic sampling procedures.

12.4. BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized by treatment arm using the FAS.

12.5. EVALUATION OF EFFICACY

12.5.1. Evaluation of Primary Efficacy Endpoint

The primary efficacy endpoint is:

- OS

The primary efficacy endpoint is survival time, defined as time from randomization until death. A Cox Proportional Hazards model will be fitted to the data with the Cox adjustment for tied observations. Model terms will include region, baseline ECOG performance status and treatment.
The log-rank test will be used to test the null hypothesis that there is no difference between the two treatments against the two-sided alternative. An estimate and 95% CI for the hazard ratio will be provided. In addition, Kaplan-Meier curves will be plotted, from which median survival times will be estimated. The assumption of proportional hazards will be checked. Patients who are lost to FU during the trial will be censored at the time of their last visit or contact.
The ITT will be used for demographic and baseline characteristics summary and for all efficacy analyses. The FAS will be used for the efficacy analysis of the primary and secondary endpoints. In addition, the primary efficacy analysis will be repeated using the PPS.

12.5.2. Evaluation of Secondary Efficacy Endpoints

By way of further confirmatory measures of efficacy, the following endpoints will be analyzed:

- PFS or TTP
- ORR
- DCR (SD+PR+CR)
- Landmark 1-year survival and PFS
- DoR
- Changes in tumor marker Ca 19.9

RECIST v1.1 will be followed for the efficacy analysis (see APPENDIX 4).
Objective response rate (ORR) will be defined as the percentage of patients who achieved PRs plus patients who achieved CRs using RECIST version 1.1 criteria.
Progression free survival (PFS) will be defined as the time from randomization to either progression or death from any cause, using the Kaplan-Meier method. PFS will be analyzed in the same way as survival time. Patients who are lost to FU prior to having progression of disease will be censored at the time of their last visit or contact. Patients who die during the trial will be considered to have had progression of disease at the time of death. Time to Progression (TTP) is defined as time from randomization until disease progression or death due to progression and will be analyzed in the same way as survival time.
Two additional, supportive analyses will be presented using Cochran Mantel Haenszel tests [x] adjusting for age group and adjusting for age group and primary infection type.
The survival rates at one year will be presented using Cochran Mantel Haenszel tests adjusting for ECOG status.
The number and percentage of patients will be presented for ORR, DCR, landmark 1-year survival and PFS at 1-year landmark. DoR and changes in tumor marker Ca 19.9 will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum).
Sequential testing will be used to control the overall false positive rate at the 5% (2-sided) significance level for the primary and secondary endpoints, based on the ITT and the data from the central imaging lab. Specifically, the primary variable (OS) will be tested first. If the P-value for OS is < 0.05, then the secondary variables will be tested in the order that is listed above. If at any time the P-value is > 0.05, the testing procedure will stop.
12.5.3. Subgroup Analysis
Subgroup analysis is defined for the primary endpoint (OS) and the main secondary endpoints (PFS, TTP and ORR) using patients who had the first 3 cycles of SoC and started the 4th cycle of SoC chemotherapy in Arm I, and patients who had the first 3 cycles of SoC, started the 4th cycle of SoC chemotherapy and received 2 doses of VCN-01 in Arm II.

12.6. EVALUATION OF SAFETY

The primary safety endpoint is:

- To evaluate the safety and tolerability of VCN-01, IV administered at Week 1 and Week 14 in Arm II.

The incidence of AEs and laboratory abnormalities will be summarized and presented by treatment arm.

All safety data will be analyzed and presented in terms of listings and summary tables. All AEs occurring from the date of consent until the EOT visit will be recorded in the eCRF. AEs and laboratory data will be assessed according to the NCI CTCAE version 5.0. AEs will be presented in listings and summarized as frequency tables. Additional presentations will include summaries by severity and relationship to trial treatment. AEs will be grouped into suitable categories at the body system level (e.g., AEs, SAEs, drug-related AEs, AEs leading to permanent discontinuation of study drug. AEs will also be summarized by SOC and preferred term [PT; these will be coded using MedDRA]).
For laboratory data, summary tables of change from baseline over time will be produced. Abnormal values will be highlighted.

The ECOG Performance score is recorded at baseline and at every visit thereafter. For each level of the ECOG score, the proportion of patients continuing on that or a better score will be estimated for each visit using Kaplan-Meier estimates. At death the patient will be assumed to have risen to the highest ECOG score. This method of presentation will ignore those cases where a patient's ECOG score climbs and then falls again. These proportions will be plotted for each treatment arm across time. For these graphs, missing ECOG scores will be replaced by the closest previous observation. No formal statistical comparison is planned.

Other Assessments: Demographic data, concurrent illnesses, concomitant medication (these will be coded using WHO-DD), physical examination findings, vital signs, 12-Lead ECG, LVEF, fibroscan and QoL will be summarized by treatment arm. Changes in vital signs from baseline will be summarized. Anticancer treatment after discontinuation in trial will be summarized by treatment arms. Changes in weight from baseline will be summarized by treatment arm.

SAF will be used for all safety analyses.

12.7. EVALUATION OF PHARMACODYNAMICS

The following pharmacodynamic endpoints will be analyzed: VCN-01 genomes in blood; PH20 in serum; circulating immune markers in serum; neutrophil/lymphocyte ratio; neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs) in serum; image biomarkers (radiomics) assessed from the images of CT scans performed during the study.

Descriptive statistics will be used to summarize these parameters using the Pharmacodynamic Set.

12.8. INTERIM ANALYSIS

No interim analysis is planned.

13. OBLIGATIONS OF THE PRINCIPAL INVESTIGATOR

The study will be performed in accordance with:

- The study protocol and any amendments
- The most current version of the Declaration of Helsinki
- The most current version of the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP)
- All local regulations and IEC/IRB guidance

13.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The site will not be initiated, and the study will not be started until receipt by Simbec-Orion of approval from the relevant IEC/IRB. Simbec-Orion will provide the Investigator with a copy of the relevant document(s) on behalf of the Sponsor.

13.2. REGULATORY BODY APPROVAL

The site will not be initiated, and the study will not be started until receipt by Simbec-Orion of approval from the relevant regulatory body (or competent authority). Simbec-Orion will provide the Investigator with a copy of the relevant approval document(s) on behalf of the Sponsor, as applicable.

13.3. GMO (GENETICALLY MODIFIED ORGANISMS) APPROVAL

As the IMP is classified as a GMO, the study will not be initiated until a submission to the relevant national competent authority responsible for oversight of GMO approval of the Member States (where it is intended for the study to be undertaken) has been submitted and approved. The study will not be started until receipt of said approval has been received by Simbec-Orion.

13.4. INFORMED CONSENT

The PICDs will normally be based on a master document provided by Simbec-Orion (or the study Sponsor) and are approved by Simbec-Orion and the study Sponsor prior to submission to the IEC/IRB. The content of the PICD will reflect that described in Section 4.8.10 of the ICH Guidelines and any local requirements. A copy of the final, IEC-approved consent form will be provided to the PI prior to initiation of this study. The Investigator should file the signed PICDs for possible review by Simbec-Orion CRAs.
Written informed consent will be obtained from each patient prior to inclusion in the trial, and prior to any study-related assessments are performed, as described in Section 8.1.

13.5. CASE REPORT FORMS AND SOURCE DOCUMENT VERIFICATION

The eCRFs of a design mutually agreed upon by the Sponsor and Simbec-Orion will be supplied by Simbec-Orion. The eCRFs are the sole property of Simbec-Orion (for the Sponsor) and should not be made available in any form to third parties, except for authorized

representatives of appropriate Health/Regulatory Authorities and IECs/IRBs, without written permission from Simbec-Orion. The eCRF will be in compliance with 21 CFR Part 11 and other applicable local regulations.
An eCRF is required and shall be completed for each consented patient. The Investigator will be responsible for the accuracy of the data entered into the eCRF. All data must be entered in **ENGLISH**. The Investigator must sign all eForms electronically by re-entering his username and password, once that eForm is considered clean. If a change is made on any of the eForms after the Investigator has signed that eForm, the Investigator must re-sign the relevant eForm to document that he agrees with the change.
The eCRF will be completed with minimal required information for each screen failed patient.
The relevant completed eForms must be available for review to designated Simbec-Orion representatives at each scheduled monitoring visit.
The Investigator will allow designated Simbec-Orion representatives, Sponsor representatives and regulatory bodies and IECs/IRBs to have direct access to the source documents to verify the data reported in the eCRFs.
Source documents are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial.

13.6. CONFIDENTIALITY

Personal data of the patient shall be processed in a manner that ensures it has appropriate security. This includes protection against unauthorized or unlawful processing and against accidental loss, destruction, or damage and by using appropriate technical or organizational measures. One such measure is for the Investigator to ensure that the patient's' personal information is pseudonymized.
On the eCRFs or other documents submitted to Simbec-Orion, patients will NOT be identified by their names but by an assigned patient number automatically generated by the Interactive Response Technology (IRT) upon patients' registration to ensure confidentiality of the patients' information and that data minimization principles are maintained.
If patient names are included in error on copies of documents submitted to Simbec-Orion, the names will be erased or securely destroyed, and the assigned patient number added to the document.
The Investigator should keep a separate log (Patient Master List) of patient's codes (assigned patient number), names, addresses, telephone numbers and hospital numbers (if applicable).
Documents not intended for submission to Simbec-Orion (e.g., signed consent forms, completed Patient Master List, etc.) should be maintained by the Investigator in strict confidence and not disclosed to any parties outside of this approved agreement. eCRFs should be protected by use of strong encryption.

13.7. STAFF INFORMATION AND RESPONSIBILITIES

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

The Investigator will provide a list of delegated responsibility to Simbec-Orion, detailing the various study tasks to be performed by each member of their study staff. Each staff member should sign in agreement to their performing each of the tasks delegated to them on the list. Simbec-Orion should ensure that the staff have the required knowledge and training for the tasks delegated to them.

13.8. DOCUMENTATION REQUIRED PRIOR TO INITIATION AND DURING THE STUDY

Simbec-Orion will request required documents from the Investigator(s) prior to the submission to the regulatory authorities and IECs/IRBs for study approval.
Simbec-Orion on behalf of the Sponsor undertakes to obtain the necessary approval from the applicable regulatory authority and IEC/IRB prior to initiation of the study by submitting all the relevant documents, as per the local requirement. Any changes to the approved documents will also be submitted for approval to the regulatory authorities and IECs/IRBs during the study, as per the local requirement.

13.9. ESSENTIAL DOCUMENT RETENTION

The Investigator and the Sponsor will retain copies of all the essential documents (as defined by ICH GCP) until at least 25 years after the end of the clinical trial. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements. The Investigator should take measures to prevent accidental or premature destruction of these documents.
The essential documents include: the signed protocol, copies of the completed eCRFs, signed PICDs from all patients who consented, hospital records, diary cards and other source documents, IRB/IEC approvals and all related correspondence, including approved documents, and all other documentation included in the Investigator Site File and Dispensing File.
The Investigator will inform Simbec-Orion and the Sponsor of the storage location of these essential documents and must contact Simbec-Orion and the Sponsor and obtain their approval before disposing of any study-related documents. If the Investigator wishes to assign the files to someone else (e.g., if they retire) or to remove them to another location, the Simbec-Orion and Sponsor Project Manager should be consulted prior to implementing the change.
The Sponsor, or delegate will inform the Investigator in writing when these documents no longer need to be retained.

14. STUDY MANAGEMENT

14.1. MONITORING

Prior to study commencement, the Investigator will be informed of the anticipated frequency of the monitoring visits. They will also receive a notification prior to each monitoring visit during the course of the study. It is expected that the Investigator and/or their sub--Investigator(s) and other appropriate staff will be available on the day of the visit to discuss study conduct. Simbec-Orion is responsible for ensuring the proper conduct of the clinical trial with regards to protocol adherence, validity of the data recorded in the eCRFs, including also remote monitoring if required in the instance CRAs are not allowed to visit sites (e.g., following possible COVID-19 restrictions [See APPENDIX 6).

14.2. QUALITY ASSURANCE AND QUALITY CONTROL

An independent audit of the study may be conducted during the study or after completion. The audit may be conducted by either Simbec-Orion's or the Sponsor's quality assurance (QA) department or an independent auditor or a regulatory authority and IECs/IRBs.

14.2.1. Quality Control (QC)

QC is defined as the operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the trial-related activities have been fulfilled. QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.2.2. Quality Assurance (QA)

QA is defined as the planned and systematic actions that are established to ensure that the trial is performed, and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

14.2.3. Audit

The Investigator will permit an audit mandated by the Sponsor, Simbec-Orion, Sponsor's QA department, an independent auditor acting under instruction from the Sponsor or a regulatory authority and IEC/IRB after reasonable notice. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP and applicable regulatory requirements, that the rights and well-being of patients enrolled have been protected and that all data relevant for the evaluation of the IMP captured, processed, and reported in compliance with the planned arrangements. The Investigator will permit direct access to all study documents, IMP accountability records, medical records, and source data. The Investigator and their study team will also be available for discussion regarding study progress and procedures during the audit (both during the audit and at the end of the audit for an "exit" discussion).

14.3. DATA QUERY PROCESS

Data management of the eCRF will be performed by Simbec-Orion on behalf of the Sponsor. Sites will enter the data from source documents into the eCRF and the data will be verified for missing data, inconsistencies, and for any necessary medical clarifications. Queries arising from these checks will be flagged to the Investigator, within the eCRF. The Investigator will correct data, confirm, or clarify the data as appropriate. All possible attempts should be made by the Investigator to resolve the queries within the requested timeframes. If the Investigator is unsure about the meaning of a query, or what data is required, then they should seek clarification from the Simbec-Orion CRA assigned to their center.
Once all data queries have been resolved, the study will be declared to be "clean", and the eCRF will be locked ready for statistical analysis. After clean-file status has been achieved, Simbec-Orion will provide copies of each patient's eCRF to the Investigator for archiving. Copies of each patient's eCRF will also be archived by the Simbec-Orion.
The data management, data handling, and analysis will be conducted in accordance with good clinical, scientific and data management principles and in compliance with Simbec-Orion's Standard Operating Procedures.

14.4. PROTOCOL DEVIATIONS/AMENDMENTS

Any deviation from the protocol that has not been approved by Sponsor and the IRB/IEC could result in a discontinuation from the study at the center involved. Any amendment(s) to the protocol must be approved by both Sponsor and the IRB/IEC which granted the original approval of the study **prior** to their implementation (unless **only** logistical or administrative aspects of the trial are involved).
However, in the event of any medical emergency, the Investigator is free to institute any medical procedure they deem appropriate. Such events and procedures must be promptly reported to Sponsor representatives.

14.5. DISCONTINUATION OF THE STUDY

Refer to Section 5.5.1 for discontinuation criteria in the instance of premature withdrawal. After a decision to discontinue the study is made, the Investigator must inform all screened patients within 1 week. All delivered study materials must be collected and all eCRFs completed to the extent possible.

14.6. PUBLICATIONS

For any manuscript, abstract or other publication or presentation of results or information arising in connection with the study (including ancillary study involving trial patients), a request must be first submitted to Sponsor. The manuscript will be prepared in conjunction with the study Sponsor and must be submitted to the Sponsor for review and comment prior to submission for publication or presentation.

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16. APPENDICES

APPENDIX 1: HIGHLY EFFECTIVE CONTRACEPTIVE METHODS

Women are considered post-menopausal and of non-childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) and with follicle stimulating hormone (FSH) >40 UI/L, or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before screening. In the case of bilateral oophorectomy alone, female patient is considered of non-childbearing potential only when the reproductive status of the patient has been confirmed by FSH hormone level assessment.
As per the Clinical Trials Facilitation and Coordination Group guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomised partner[1,2]
- sexual abstinence[3]

1. Contraception methods that in the context of this guidance are considered to have low user dependency.
2. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the women of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.
3. In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Source: Clinical Trials Facilitation and Coordination Group guidelines (Version 1.1)
https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

APPENDIX 2: LABORATORY ASSESSMENTS

Hematology (All samples to local laboratory)		
Basophils (absolute and relative)	Monocytes (absolute and relative)	Neutrophils (absolute and relative)
Eosinophils (absolute and relative)	MCH	Platelet count
Hemoglobin	MCV	RBC count
Hematocrit	Mean corpuscular hemoglobin concentration	Lymphocytes (absolute and relative)
D-dimer		White blood cell (WBC) count
Coagulation Panel (All samples to local laboratory)		
aPTT	Prothrombin time	INR
Biochemistry (All samples to local laboratory)		
Albumin	Creatine phosphokinase	Sodium
Alkaline phosphatase	CRP	Total protein
ALT	GGT	Phosphorous
AST	Glucose (fasted)	Transferrin
Bilirubin (total) (Direct bilirubin may also be measured at the investigator's discretion if clinically indicated)	Magnesium	Urea or blood urea nitrogen, depending on local practice
Calcium	Lipase	
Chloride	Amylase	Uric acid
Creatinine	Potassium	Lactate dehydrogenase
Blood Borne Viruses (BBVs) and Infectious Diseases (Samples to local laboratory)		
HB	HCV	HIV
TB	COVID-19	
Serum tumor markers (Samples to local laboratory)		
Ca 19.9 tumor marker		
Hormone levels (Samples to local laboratory)		
TSH		
Pregnancy test in serum and urine (Samples to local laboratory) for women of child-bearing potential		
βHCG (serum)	hCG (urine)	
Urinalysis (All samples to local laboratory)		
Albumin	Creatine	Leukocytes reagent strip result
Bilirubin	Glucose	pH
Blood	Ketones	Sediment
Calcium	Leukocytes per field	Microscopic examination, if needed
Biomarkers (All samples to Central laboratory)		
Circulating immune markers (serum)	VCN-01 genomes (blood)	PH20 (serum)

Neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs) (serum)		

Abbreviations: ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; aPTT=Activated partial thromboplastin time; βHCG=Beta human chorionic gonadotropin; BUN=Blood urea nitrogen; CRP=C-reactive protein; COVID-19=Coronavirus Disease 2019; GGT=Gamma-glutamyl transferase; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=International normalized ratio; MCH=Mean corpuscular hemoglobin; MCV=Mean corpuscular volume; Nabs=Ad-specific neutralizing antibodies; pH=potential of Hydrogen; RBC=Red blood cell; TB=tuberculosis; TSH=thyroid stimulating hormone; WBC=White blood cell

APPENDIX 3: ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

APPENDIX 4: RECIST CRITERIA

The following contains excerpts from the RECIST version 1.1 plus trial specific instructions. A free copy of the revised guidelines is available from https://project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf (Eisenhauer et al 2009).

Measurability of Tumor Lesions at Baseline

Measurable disease is defined by the presence of at least one measurable tumor lesion. At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable) and 20 mm by chest X-ray. For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by a CT scan (at baseline and in FU, only the short axis will be measured and followed).

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to ≥15 mm short axis) and truly non-measurable lesions.

Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Tumor lesions that are situated in a previously irradiated area are not considered measurable.

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation using calipers (or a ruler) if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesions at baseline and during FU. Image-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment. CT is the best currently available and reproducible method for measuring target lesions selected for response assessment. Investigators should utilize the best available CT imaging technique available to them for determining response and PFS of patients participating in the trial.

Tumor Response Evaluation

Baseline Documentation of "Target" and "Non-target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as “target” lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate, reproducible, repeated measurements.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as “non-target” lesions and should also be recorded at baseline. Measurements of these lesions are not required but these lesions should be followed as ‘present’, ‘absent’ or in rare cases ‘unequivocal progression’ and recorded.

Response Criteria

A. Evaluation of Target Lesions

Response Category	**Description**
Complete Response (CR)	Disappearance of all target legions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target legions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD on study. This includes the baseline LD sum if that is the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started

B. Evaluation of Non-target Lesions

Response Category	Description
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [1]

Notes:

1. To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

D. Overall Responses for all Possible Combinations of Tumor Responses in Target and Non-target Lesions With or Without the Appearance of New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response (CR)	CR	No	CR
Complete response (CR)	Non-CR/non-Progressive disease	No	PR
Complete response (CR)	Not evaluated	No	PR
Partial response (PR)	Non-Progressive disease	No	PR
Stable disease (SD)	Non-Progressive disease	No	SD
Not all evaluated	Non-Progressive disease	No	Not evaluable (NE)
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having 'symptomatic deterioration'. Every effort should be made to document the objective disease progression, even after discontinuation of treatment.

CT, MRI

CT is the best currently available and reproducible method to measure lesions selected for response assessment. Guidance (Eisenhauer et al 2009) has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

MRI is also acceptable in certain situations (e.g., for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in Eisenhauer et al 2009.

Source: Eisenhauer *et al*., New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228 – 247.

APPENDIX 5: REPRESENTATIVE EXAMPLE OF EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF EORTC QLQ-C30 QUESTIONNAIRE (VERSION 3)

See below a representative example of the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30) that will be used in this study.

ENGLISH



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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APPENDIX 6: GUIDANCE TO ADDRESS COVID-19 PANDEMIC AND THEIR POTENTIAL IMPACT ON THE CLINICAL STUDY

During the occurrence of COVID-19 pandemic, study conduct may be adjusted due to participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to local lock downs, travel restrictions and the risk of spreading infections, and health care professionals being committed to critical tasks.
Adjustments to this protocol may be made as described below, in line with global regulatory authorities' and IECs/IRBs' guidance in order to ensure the safety of study participants, maintain compliance with GCP, and minimize the risks to study integrity during the COVID-19 pandemic (Medicines and Healthcare products Regulatory Agency, EMA and the US FDA). Other countries may issue their own guidance requiring country specific recommendations to be followed and these guidelines may be amended from time to time.

General Site and Patient Safety Considerations

- COVID-19 screening procedures that may be mandated by the health-care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol, even if done during clinical study visits. The Investigator, in consultation with the Sponsor, will decide whether it is in the best interest of COVID-19–positive participants to remain in the study.
- Regarding COVID-19 status of staff and participants, Investigators should follow their local and institutional guidelines regarding testing, reporting, and management.
- In the event that Investigators are made aware at any time of a participant's COVID-19 status change, Investigators should follow the protocol, including eligibility criteria, individual stopping rules, and good clinical judgement, to assess the participant's ability to safely enroll or continue in the study. Investigator must refer to Section 5.3 for guidance related to COVID-19 vaccine and booter dose administration during the study.

If a site has any participant with suspected or confirmed COVID-19, the site must notify the Sponsor's Medical Monitor (or designee).

Informed Consent

- The PICD will be signed by the patient. If written consent by the study participant is not possible (for example because of physical isolation due to COVID-19), consent could be given orally by the study participant and documented according to regulatory guidance.
- In case a written informed consent cannot be obtained at the clinical site, electronic informed consent can be obtained remotely. Alternatively, the PICD may be sent to the participant by mail, facsimile, or e-mail, and the consent interview may then be conducted by telephone
- If reconsent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to COVID-19 or important safety issues arising in this study), alternative ways of obtaining reconsent may include contacting

the study participant via telephone or video-call to obtain oral consent, which would be documented in the study participant's medical records and supplemented with e-mail confirmation.

- The informed consent procedure is to remain compliant with the study protocol, as well as local regulatory requirements. All relevant records should be archived in the Investigator's site master file. A signed and dated PICD should be obtained from the study participant as soon as possible.

Study Visits and Procedures

- Local guidance may require a mandatory quarantine period for anyone traveling across cities/local zones. Investigators should ensure that their study participants are aware of these travel mandates and the potential impact on study visits and assessments.
- In the case of missed visits due to COVID-19 related reasons:
    - The site should make every effort to contact the study participant to confirm and document the reason for the missed hospital visit, and at minimum evaluate AEs/SAEs, and concomitant medications in order to assess participant safety.
- In order to maintain the integrity of the study, alternative methods of collecting study procedures may be considered where possible:
    - In cases where COVID-19-related circumstances preclude a visit to the investigative site, remote visits (*e.g.,* by telemedicine or phone contact) will be allowed for relevant study procedures.
    - If a subject suffers from COVID and is unable to return to the site for a visit, a subset of assessments can be performed/documented remotely. The following assessments (if applicable for that visit) may be performed:
        - Concomitant medication.
        - Subsequent cancer therapies.
        - ECOG, if possible.
        - Follow-up survival status.
    - In certain situations, with Sponsor approval, and according to site business continuity plans, home visits may be used, *e.g.,* to collect laboratory samples and assessments as required by the protocol.
    - Study assessments will only be conducted in a remote manner if they can be done without affecting the wellbeing of the participant during the study and with the same level of scientific integrity as assessments conducted in a physical study center.
    - Remote study assessments can be completed via online technology. The participant may interact with study personnel using online communication tools which incorporate telemedicine.

- In certain situations, with Sponsor approval, a local laboratory may be used to collect laboratory samples as required by the protocol. Local analysis can be used for safety decisions. Normal ranges will be collected from the lab by the Sponsor. Timeline to receive results will be mutually agreed between the Sponsor and the lab.
- Missed assessments for primary and secondary endpoints should be discussed with the Sponsor for approval. In certain situations, with prior approval, other options or delayed visits can be considered.
- For assessments deemed to put participant and/or site safety at potential risk during a public health emergency, Investigators are encouraged to identify and use, with prior Sponsor approval, alternative options to assess baseline patient health status for inclusion or continued participation in the study.

Monitoring and Audits

- Certain Sponsor oversight responsibilities, such as monitoring and QA activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required. On-site audits will be avoided or postponed, and if permitted under local regulations, social distancing restrictions should apply.
- Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits will be allowed.
- To the extent on-site monitoring remains feasible, it should take into account national, local and/or organizational social distancing restrictions.
- Centralized monitoring can be considered for data acquired by electronic data capture (EDC) systems (*e.g.,* eCRFs, central laboratory or ECG data, electronic patient-reported outcomes, etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.
- Off-site monitoring can be conducted and will include phone calls, video visits, e-mails, or other online tools in order to discuss the study with the Investigator and site staff. Remote monitoring should be focused on review of critical study site documentation and source data. These activities could be used to get information on the clinical study progress, to exchange information on the resolution of problems, review of procedures, study participant status as well as to facilitate remote site selection and Investigator training for critical study procedures.

Risk Mitigation

The Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to study participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures

APPENDIX 7: STUDY FLOW CHART ARM I

Cycle	**Screening**	**C1 (28 days)**			**C2 (28 days)**			**C3 (28 days) and subsequent cycles**			**EOT visit/ Withdrawal**	**FU without PD**	**FU due to PD[20]**
Week	**-4 to -1**	**1 to 4**			**5 to 7**			**9 to 12**			**1 month after last treatment dose (±1 week)**	**q4wk until PD (±1 week)**	**q4wk→6mo q2mo→2yr q6mo→ >2yr (±1 week)**
Day of cycle	**-28 to -1**	**D1**	**D8 (±3)**	**D15 (±3)**	**D1 (±3)**	**D8 (±3)**	**D15 (±3)**	**D1 (±3)**	**D8 (±3)**	**D15 (±3)**			
Informed Consent[1]	X												
Medical history	X												
Prior medication	X												
Physical Examination (F=Full)[2]	XF	XF	X	X	XF	X	X	XF	X	X	XF	XF	X
Vital signs and body weight[3]	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[4]	X	If clinically indicated											
LVEF[5]	X	If clinically indicated											
Randomization[23]	X												
Concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography[7]	X												
ECOG[8]	X	X	X	X	X	X	X	X	X	X	X	X	
Eligibility criteria[9]	X	X (review)											
COVID-19 testing[21]	X	X[21]											
QLQ-C30 questionnaire[22]		X			X			X			X	X	X
Fibroscan[10]	if clinically indicated												
Biochemistry[11]	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[11]	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation profile[11]	X	X			X						X		
Thyroid stimulating hormone[11]	X												
HBV, HCV, TB and HIV[24]	X[24]												
Urinalysis	X												
Pregnancy test[12]	X	X			X			X					
Ca 19.9[13]	X	X			X			X			X	X	
AE/ SAE assessment[14]	X	X	X	X	X	X	X	X	X	X	X		
Nab-paclitaxel /Gemcitabine[15]		X	X	X	X	X	X	X	X	X			

Cycle	Screening	C1 (28 days)			C2 (28 days)			C3 (28 days) and subsequent cycles			EOT visit/ Withdrawal	FU without PD	FU due to PD[20]
Week	-4 to -1	1 to 4			5 to 7			9 to 12			1 month after last treatment dose (±1 week)	q4wk until PD (±1 week)	q4wk→6mo q2mo→2yr q6mo→ >2yr (±1 week)
Day of cycle	-28 to -1	D1	D8 (±3)	D15 (±3)	D1 (±3)	D8 (±3)	D15 (±3)	D1 (±3)	D8 (±3)	D15 (±3)			
Serum collection[16]		X	X	X	X			X			X		
Radiology (CT Scan, MRI)[17]	X	Every 8 weeks (±1w) (Every 4 weeks if there is a suspicion of PD not radiologically confirmed)											
Subsequent cancer therapies[18]												X	X
FU Survival status[19]												X	X

Abbreviations: AE=adverse event; C=cycle; Ca=carbohydrate antigen; CT=computerized tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Co-operative Oncology Group; EOT=End of Treatment; FU=follow-up; HBV=Hepatitis B Virus; HCV=Hepatitis C Virus; HIV= Human Immunodeficiency Virus; LVEF=left ventricular ejection fraction; MRI=Magnetic Resonance Imaging; PD=progressive disease; q2mo=every 2 months; q4wk=every 4 weeks; q6mo=every 6 months; SAE=serious adverse event, TB=tuberculosis

1. The signature of the Patient Informed Consent Document (PICD) must be obtained before performing any study-specific procedures. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of treatment administration.
2. Full physical examination will be performed every cycle and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, lymph nodes, thyroid, musculoskeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height. An abbreviated physical examination will be performed every visit by the study nurse that includes skin (jaundice, petechiae, bruising, rash), eyes (jaundice), lymphatics (neck, axillary, supraclavicular), respiratory/heart (auscultation, percussion), abdominal (liver, masses, and ascites), neuro (for CNS masses), any previously identified palpable masses. A full physical examination performed within 72 h prior to dosing at C1D1 will be considered acceptable.
3. Vital signs will include supine systolic and diastolic blood pressure (BP; mmHg), pulse (bpm), body temperature (°C) and respiration rate. Vital signs will be collected pre-dose. Body weight (kg) will also be recorded along with vital signs. Body weight recorded within 72 h prior to dosing at C1D1 will be considered acceptable.
4. At Screening, a single 12-lead ECG will be obtained on which QT interval corrected by Fridericia (QTcF) must be <450 ms for men and <470 ms for women. In case of clinically significant ECG abnormalities, 2 additional ECGs should be obtained over a brief period (e.g., 30 min) to confirm the finding. 12-Lead ECGs will be performed at other timepoints only if clinically indicated.
5. At Screening, LVEF evaluation must not be less than 50% measured by ECHO or multigated acquisition scan.
6. Medications taken after signing of the PICD(medications for the treatment of AEs, IMP or standard of care [SoC] premedication, transfusions, medications started on a regular basis, medications for treatment of concurrent illness or concurrent symptoms) until the EOT visit are to be recorded as concomitant medications. It is not necessary to record information on sporadic treatments (e.g., occasional analgesic or anti-inflammatory agents, antacids). From the EOT visit to the End of Study (EOS) visit, only those concomitant medications to treat AEs related to IMP or SoC should be recorded.
7. Toxic habits must be collected.
8. Patients must have an ECOG Score of 0 or 1 at screening.

9. All patients must fulfill ALL inclusion criteria and none of the exclusion criteria at Screening visit. Review of inclusion and exclusion criteria to ensure that the patient meets all inclusion criteria and none of the exclusion criteria within 72 hours prior to dosing.
10. If indicated, the fibroscan assessment performed during the screening period must be <9.5 kPa.
11. As per Inclusion Criterion #8, local lab samples for biochemistry, hematology and coagulation profile for C1D1 may be obtained within 72 hours prior dosing. Serum or plasma clinical chemistry, hematology, coagulation profile and TSH may be performed more frequently if clinically indicated. Note: Patients receiving gemcitabine will have their neutrophils and platelets assessed prior to dosing.
12. Only women of childbearing potential (i.e., female patients who are not postmenopausal or surgically sterile). Urine or blood pregnancy test will be performed on the Day 1 of each cycle prior to study treatment dosing. Either serum or urine pregnancy tests will be performed at other time points.
13. Biomarker Ca 19.9 must be tested at screening and the first day of each cycle (±1 week) at study visits and at follow-up visits without PD assessment. It will also be tested, according to investigator criteria, when clinically indicated. A Ca 19.9 test result available within 72h prior to dosing at C1D1 is acceptable but not mandatory.
14. AEs will be recorded from the time the PICD is signed until the EOT visit. The following information is to be recorded: start and end date/time, severity, and relationship with the treatment. All SAEs must be reported within 24 h. If AEs occur after the EOT visit and they are related to the study treatment, they will be monitored as AEs i.e., until the event has resolved or stabilized at a level acceptable to the Investigator and Medical Monitor. AEs that are not related to study treatment, occurring after the EOT visit, will neither be monitored nor recorded.
15. Nab-paclitaxel/Gemcitabine will be administered until disease progression, intolerable/unacceptable toxicity, consent withdrawal or investigator's decision.
16. Serum samples for circulating immune markers will be obtained D1 pre-dose of each treatment cycle; Cycle 1 on D8 and D15 and EOT.
17. CT Scan or MRI will be performed every 8 weeks (±1 week) during the study treatment period. If there is a suspicion of PD, radiological assessments will be performed every 4 weeks (±1 week). CT scan is the preferred imaging modality for this study. In the event MRI will be used, please refer to the Imaging Manual.
18. Subsequent anticancer therapies should be collected, if possible, as well as tumor response to these therapies
19. Survival: For patients who refuse to return for evaluations, survival status will be assessed through phone if they have agreed to be contacted by phone.
20. q4wk during the first 6 months; q2mo until the second year; q6mo after the second year (±1 week)
21. Testing to check for active COVID-19 infection (PCR or Antigen test) to be done at Screening, prior to dosing on C1D1 (SoC). COVID-19 testing after C1D1 will be done at any time at the discretion of the Investigator for all other SoC cycles.
22. Patients will be asked to complete a QLQ-C30 questionnaire on Day 1 of Cycle 1 (within 72 h prior to dosing at C1D1 is acceptable) and then once every cycle thereafter. Patients who withdraw the trial will have a QOL assessment at End of Treatment visit and any subsequent follow-up visit.
23. Randomization can occur at any time during the 28-day Screening period when all the screening assessments are completed, but dosing (D1) must take place no later than 5 days after randomization.
24. TB screening will be performed only if active infection is suspected and/or if in line with local practice. Patients with past or resolved TB are eligible to participate in the study. Patients will be screened for HBV, HCV, and HIV according to standard test practices for screening. Patients with active HBV (positive HBsAg), HCV (positive HCV RNA), or HIV (positive HIV 1/2 antibodies) are ineligible to participate in the study. Patients with a past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) may participate in the study but must be negative for blood HBV DNA prior to treatment. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

APPENDIX 8: STUDY FLOW CHART ARM II

Cycle	**Screening**	**C1 (35 days)**					**C2 (28 days)**			**C3 (28 days) and subsequent cycles[22]**			**C4 (35 days)**					**EOT visit/ With-drawal**	**FU without PD**	**FU due to PD[21]**
Week	**-4 to -1**	**1**		**2 to 5**			**6 to 9**			**10 to 13**			**14 (+1 day to 2 weeks)**		**15 to 18**			**1 month after last dose (±1 week)**	**q4wk until PD (±1 week)**	**q4wk→6mo q2mo→2yr q6mo→>2yr (±1 week)**
Day of cycle	**-28 to -1**	**D1**	**D3**	**D8 (±3)**	**D15 (±3)**	**D22 (±3)**	**D1 (±3)**	**D8 (±3)**	**D15 (±3)**	**D1 (±3)**	**D8 (±3)**	**D15 (±3)**	**D1 (+14)**	**D3**	**D8 (±3)**	**D15 (±3)**	**D22 (±3)**			
Informed Consent[1]	X																			
Medical history	X																			
Prior medication	X																			
Physical Examination (F=full)[2]	X[F]	X[F]	X	X	X	X	X[F]	X	X	X[F]	X	X	X[F]	X	X	X	X	X[F]	X[F]	X
Vital signs and body weight[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[4]	X	If clinically indicated																		
LVEF[5]	X	If clinically indicated																		
Randomization[25]	X[25]																			
Concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography[7]	X																			
ECOG[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Eligibility criteria[9]	X	X (review)																		
COVID-19 testing[23]	X	X[23]											X[23]							
QLQ-C30 questionnaire[24]		X					X			X			X					X	X	X
Fibroscan[10]	if clinically indicated																			
Biochemistry[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation profile[11]	X	X	X	X			X						X					X		
Thyroid Stimulating	X																			

Cycle	Screening	C1 (35 days)					C2 (28 days)			C3 (28 days) and subsequent cycles[22]			C4 (35 days)					EOT visit/ With-drawal	FU without PD	FU due to PD[21]
Week	**-4 to -1**	**1**		**2 to 5**			**6 to 9**			**10 to 13**			**14 (+1 day to 2 weeks)**		**15 to 18**			**1 month after last dose (±1 week)**	**q4wk until PD (±1 week)**	**q4wk→6mo q2mo→2yr q6mo→>2yr (±1 week)**
Day of cycle	**-28 to -1**	**D1**	**D3**	**D8 (±3)**	**D15 (±3)**	**D22 (±3)**	**D1 (±3)**	**D8 (±3)**	**D15 (±3)**	**D1 (±3)**	**D8 (±3)**	**D15 (±3)**	**D1 (+14)**	**D3**	**D8 (±3)**	**D15 (±3)**	**D22 (±3)**			
Hormone[11]																				
HBV, HCV, TB and HIV[26]	X[26]																			
Urinalysis	X																			
Pregnancy test[12]	X	X					X			X			X							
Ca 19.9[13]	X	X					X			X			X					X	X	
AE/ SAE assessment[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
VCN-01administration[15]		X											X							
Nab-paclitaxel /Gemcitabine administration[16]				X	X	X	X	X	X	X	X	X			X	X	X			
Blood/Serum collection[17]		X	X	X	X		X			X			X	X	X	X		X		
Radiology (CT Scan, MRI)[18]	X	Every 8 weeks (±1w) (4 weeks if there is a suspicion of PD not radiologically confirmed)																		
Subsequent cancer therapies[19]																			X	X
FU Survival status[20]																			X	X

Abbreviations: AE=adverse event; C=cycle; Ca=carbohydrate antigen; CT=computerized tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Co-operative Oncology Group; EOT=End of Treatment; FU=follow-up; HBV=Hepatitis B Virus; HCV=Hepatitis C Virus; HIV= Human Immunodeficiency Virus; IMP=Investigational Medicinal Product; LVEF=left ventricular ejection fraction; MRI=Magnetic Resonance Imaging; PD=progressive disease; q2mo=every 2 months; q4wk=every 4 weeks; q6mo=every 6 months; SAE=serious adverse event; TB=tuberculosis

1. The signature of the Patient Informed Consent Document (PICD) must be obtained before performing any study-specific procedures. The informed consent donation for future investigations will also be offered to the patient. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of treatment administration.
2. Full physical examination will be performed every cycle and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, lymph nodes, thyroid, musculoskeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height. An abbreviated physical examination will be performed every visit by the study nurse that includes: skin (jaundice, petechiae, bruising, rash), eyes (jaundice), lymphatics (neck, axillary,

supraclavicular), respiratory/heart (auscultation, percussion), abdominal (liver, masses, and ascites), neuro (for CNS masses), any previously identified palpable masses. A full physical examination performed within 72 h prior to dosing at C1D1 will be considered acceptable.

3. Vital signs will include supine systolic and diastolic blood pressure (BP; mmHg), pulse (bpm), body temperature (°C) and respiration rate. Vital signs will be collected pre-dose and 4h (±10min) post-VCN-01-dose. Body weight (kg) will also be recorded along with vital signs (pre-dose only). Body weight recorded within 72 h prior to dosing at C1D1 will be considered acceptable.
4. At Screening, a single 12-lead ECG will be obtained on which QT interval corrected by Fridericia (QTcF) must be <450 ms for men and <470 ms for women. In case of clinically significant ECG abnormalities, 2 additional ECGs should be obtained over a brief period (e.g., 30 min) to confirm the finding. 12-Lead ECGs will be performed at other timepoints only if clinically indicated.
5. At Screening, LVEF evaluation must not be less than 50% measured by ECHO or multigated acquisition scan.
6. Medications taken after signing of the PICD (medications for the treatment of AEs, IMP or standard of care [SoC] premedication, transfusions, medications started on a regular basis, medications for treatment of concurrent illness or concurrent symptoms) until the EOT visit are to be recorded as concomitant medications. It is not necessary to record information on sporadic treatments (e.g., occasional analgesic or anti-inflammatory agents, antacids). From the EOT visit to the End of Study (EOS) visit, only those concomitant medications to treat AEs related to IMP or SoC should be recorded..
7. Toxic habits must be collected.
8. Patients must have an ECOG Score of 0 or 1 at screening.
9. All patients must fulfil ALL inclusion criteria and none of the exclusion criteria at Screening visit. Review of inclusion and exclusion criteria to ensure that the patient meets all inclusion criteria and none of the exclusion criteria within 72 hours prior to dosing. Adequate organ function must be met prior to VCN-01 dosing on Cycle 4 Day 1.
10. If indicated, the fibroscan assessment performed during the screening period must be <9.5 kPa.
11. As per Inclusion Criterion #8 local lab samples for biochemistry, hematology and coagulation profile for C1D1 may be obtained within 72 h prior to dosing. All local lab samples for biochemistry, hematology and coagulation profile may be obtained within 72 h prior to dosing at C4D1. Serum or plasma clinical chemistry, hematology, coagulation profile and TSH may be performed more frequently if clinically indicated. Note: Patients receiving gemcitabine will have their neutrophils and platelets assessed prior to dosing.
12. Only women of childbearing potential (i.e., female patients who are not postmenopausal or surgically sterile). Urine or blood pregnancy test will be performed on the Day 1 of each cycle prior to study treatment dosing. Either serum or urine pregnancy tests will be performed at other time points.
13. Biomarker Ca 19.9 must be tested at screening and the 1st day of each cycle (±1 week) at study visits, and at follow-up visits without PD assessment. It will also be tested, according to investigator criteria, when clinically indicated. A Ca 19.9 test result available within 72 h prior to dosing at C1D1 will be considered acceptable but is not mandatory.
14. Adverse events will be recorded since the ICF signature till the EOS visit. AEs will be recorded from the time the PICD is signed until the EOT visit. The following information is to be recorded: start and end date/time, severity, and relationship with the treatment. All SAEs must be reported within 24 h. If AEs occur after the EOT visit and they are related to the study treatment, they will be monitored as AEs i.e., until the event has resolved or stabilized at a level acceptable to the Investigator and Medical Monitor. AEs that are not related to study treatment, occurring after the EOT visit, will neither be monitored nor recorded.
15. On Day 1 of Cycle 1 and Cycle 4 (Arm II), a dose of 1 x10^{13} vp 50 mL VCN-01 will be administered as a 50 mL solution in saline (NaCl 0.9%). Antipyretic treatment p.o. will be recommended before the IMP treatment is received.
16. Nab-paclitaxel/Gemcitabine will be administered until disease progression, intolerable/unacceptable toxicity, consent withdrawal or investigator's decision.
17. Blood samples for VCN-01 genomes will be obtained C1D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C1D3 (48 h [±3 h] after VCN-01 administration); C1D8; C1D15; C2D1; C3D1; C4D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C4D3 (48 h [±3 h] after VCN-01 administration); C4D8; C4D15; Day 1

of subsequent nab-paclitaxel/gemcitabine cycles; EOT. Serum samples for neutralizing anti-VCN-01 antibodies (Anti-Ad-Nabs) will be obtained C1D1 pre-dose; C1D8; C1D15; C2D1; C3D1; C4D1 pre-dose; C4D8; C4D15; Day 1 of subsequent nab-paclitaxel/gemcitabine cycles; EOT. Serum samples for PH20 will be obtained C1D1 pre-dose; C1D3 (48 h [±3 h] after VCN-01 administration); C1D8; C2D1; C3D1; C4D1 pre-dose; C4D3 (48 h [±3 h] after VCN-01 administration); C4D8; Day 1 of subsequent nab-paclitaxel/gemcitabine cycles; EOT. Serum samples for circulating immune markers will be obtained C1D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C1D3 (48 h [±3 h]) after VCN-01 administration; C1D8; C2D1; C3D1; C4D1 pre-dose and 4 h (±10 min) after VCN-01 administration; C4D3 (48 h [±3 h] after VCN-01 administration); C4D8; C4D15; Day 1 of subsequent nab-paclitaxel/gemcitabine cycles; EOT.

18. CT Scan or MRI will be performed every 8 weeks (±1 week) during the study treatment period. If there is a suspicion of PD, radiological assessments will be performed every 4 weeks (±1 week). CT scan is the preferred imaging modality for this study. In the event MRI will be used, please refer to the Imaging Manual.
19. Subsequent anticancer therapies should be collected, if possible, as well as tumor response to these therapies, if available.
20. Survival: For patients who refuse to return for evaluations, survival status will be assessed through phone if they have agreed to be contacted by phone.
21. q4wk during the first 6 months; q2mo until the second year; q6mo after the second year (±1 week)
22. One week following Cycle 4 IMP dosing, subsequent 28-day cycles of nab-paclitaxel / gemcitabine can continue.
23. Testing to check for active COVID-19 infection (PCR or Antigen test) to be done at Screening, prior to dosing on C1D1 (VCN-01); prior to dosing on C4D1 (for Arm II only) and at any time at the discretion of the investigator for all other SoC cycles.
24. Patients will be asked to complete a QLQ-C30 questionnaire on Day 1 of Cycle 1 (within 72 h prior to dosing at C1D1 is acceptable) and then once every cycle thereafter. Patients who withdraw the trial will have a QOL assessment at End of Treatment visit and any subsequent follow-up visit.
25. Randomization can occur any time during the 28-day Screening period when all the screening assessments are completed, but dosing (D1) must take place no later than 5 days after randomization.
26. TB screening will be performed only if active infection is suspected and/or if in line with local practice. Patients with past or resolved TB are eligible to participate in the study. Patients will be screened for HBV, HCV, and HIV according to standard test practices for screening. Patients with active HBV (positive HBsAg), HCV (positive HCV RNA), or HIV (positive HIV 1/2 antibodies) are ineligible to participate in the study. Patients with a past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) may participate in the study but must be negative for blood HBV DNA prior to treatment. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.