PAREXEL International

Symphogen A/S

Sym013-01

An Open-label, Multicenter, Phase 1a/2a Trial Investigating the Safety, Tolerability and Antitumor Activity of Multiple Doses of Sym013 (Pan-HER), a Monoclonal Antibody Mixture Targeting EGFR, HER2 and HER3, in Patients with Advanced Epithelial Malignancies

Statistical Analysis Plan

Version: Final 1.0

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	28 Oct 2016	New document
Draft 0.2	May 2017	Document Review
Draft 0.3	12 Feb 2019	Document Review and Comments Resolution
Draft 0.4	07 March 2019	Comments Resolution
Draft 0.5	27 March 2019	Comments Resolution
Final 1.0	05 April 2019	Final version for approval

LIST OF ABBREVIATIONS

List and define all acronyms and abbreviations used in the document here. Abbreviations should be spelled out in full and the abbreviation indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation / Acronym	Definition / Expansion
1M FUP	1-Month Follow-up
ADA	Anti-Drug Antibody
ADC	Antibody Drug Conjugate
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{norm, \tau}$	Dose normalized area under the concentration-time curve in a dosing interval, calculated as AUC_{τ} divided by the dose infused
AUC_{τ}	Area under the concentration-time curve in a dosing interval (i.e. from time zero (end of infusion) up to 168 hours).
$AUC_{\tau 0}$	Area under the concentration-time curve from start of infusion up to 168 hours. $AUC_{\tau 0}$ will be calculated similar to AUC_{τ}
BID	Bis in die (twice daily)
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BOR	Best Objective Response
BP	Blood pressure
Bpm	Beats per minute

Abbreviation / Acronym	Definition / Expansion
BUN	Blood Urea Nitrogen
C#/D#	Cycle #/ Day #
C_{avg}	Average concentration at steady state
CDC	Complement-Dependent Cytotoxicity
C_{EOI}	Concentration at End of Infusion
CI	Confidence interval
CL_S	Clearance after first dose
CL_{SS}	Clearance after $3^{rd}/4^{th}$ dose
C_{max}	Maximum concentration
C_{trough}	Trough concentration
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CSP	Clinical Study Protocol
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration in the dosing interval
CS	Clinically significant
$C_{av,ss}$	Average concentration at steady state
$C_{max,ss}$	Maximum observed concentration at steady state
$C_{min,ss}$	Minimum observed concentration at steady state
C_{trough}	Concentration immediately prior to dosing
CT	Computed Tomography
CTCAE v4.03	Common Terminology Criteria for Adverse Events (Version 4.03)
CTR	Clinical Trial Report
CV	Coefficient of variation
CYP	Cytochrome P450
d	decimal places in the original reported value
DBP	Diastolic blood pressure

Abbreviation / Acronym	Definition / Expansion
DCR	Disease Control Rate
CSR	Clinical Study Protocol
DLT	Dose-Limiting Toxicity
DMP	Data Management Plan
d.p.	decimal places
DSUR	Development Safety Update Report
DRM	Data Review Meeting
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion
EOT	End-of-Treatment
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
GnRH	Gonadotropin-Releasing Hormone
HA	Health Authority
HER	Human Epidermal Growth Factor Receptor
HIV	Human Immunodeficiency Virus
HR	Heart rate
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry

Abbreviation / Acronym	Definition / Expansion
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IV	Intravenous
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
L	Linearity index
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MAD	Maximum Administered Dose
MAPK	Mitogen-Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image/Imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
MUGA	Multi-Gated Acquisition
NA	Not available
NE	Not Evaluable
NCS	Not clinically significant
NK	Not known
NOAEL	No Observed Adverse Event Level
NRAS	Neuroblastoma *RAS* Viral Oncogene Homolog
NSAID	Nonsteroidal Anti-Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
OS	Overall Survival

Abbreviation / Acronym	Definition / Expansion
OTC	Over the counter
PD	Pharmacodynamic or Progressive Disease (meaning to be extrapolated by the context)
PDs	Protocol Deviations
PET	Positron Emission Tomography
PI3K	Phosphoinositide 3-Kinase
PK	Pharmacokinetic
PO	Orally, by mouth
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
PT	Prothrombin Time or Preferred Term (meaning to be extrapolated by the context)
PTT	Partial Thromboplastin Time
Q1W	Every week, weekly
Q2W	Every second week
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcB	QT corrected using Bazzett's formula
QTcF	QT corrected using Fridericia's formula
RAS	Rat Sarcoma
RDI	Relative Dose Intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumors (Version 1.1)
RP2D	Recommended Phase 2 Dose
RTK	Receptor Tyrosine Kinase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

Abbreviation / Acronym	Definition / Expansion
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Standard Deviation or Stable Disease (meaning to be extrapolated by the context)
SE	Standard error of the mean
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOI	Start of Infusion
SOP	Standard Operating Procedure(s)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBD	To Be Determined
TEAE	Treatment-emergent adverse event
TKI	Tyrosine Kinase Inhibitor
t_{max}	Time to reach maximum concentration
TTP	Time To Progression
$T_{½}$	Terminal elimination half-life
ULN	Upper Limit of Normal
V_S	Volume of distribution during the terminal phase after first dose
V_{SS}	Volume of distribution during the terminal phase after $3^{rd}/4^{th}$ dose
WHO-DD	World Health Organisation - Drug Dictionary
WT	Wild-Type
λ_z	Terminal rate constant

1 INTRODUCTION

The investigational medicinal product (IMP) tested in this trial is Sym013, referenced as Pan-HER. Pan-HER is a recombinant antibody mixture containing 6 humanized immunoglobulin G1 (IgG1) mAbs, which bind specifically to non-overlapping epitopes on the EGFR (Hu1277 and Hu1565), HER2 (Hu4384 and Hu4517) and HER3 (Hu5038 and Hu5082).

This is the first clinical trial to study Pan-HER.

HER family expression heterogeneity and plasticity in response to therapeutic intervention are important drivers of primary and acquired drug resistance and pose challenges to effective cancer treatment in the clinic. By targeting three receptors of the HER family, Pan-HER effectively inhibits a range of cancers of various tissue origin and genetic background, including cell lines and xenograft models with acquired resistance to therapeutic antibodies. Importantly, by down modulating all three targets simultaneously, Pan-HER prevents compensatory receptor up-regulation and renders the receptors unavailable for ligand binding and activation. Pan-HER represents a novel strategy to deal with primary and acquired resistance and thus may provide a clinically relevant effect in patient populations for which few therapeutic options exist.

Pan-HER is developed for the treatment of patients with resistant or refractory epithelial malignancies. Initially, the safety and efficacy of Pan-HER are investigated in advanced epithelial malignancies. Future development of Pan-HER may include pancreatic, esophageal, gastric, CRC, NSCLC, advanced ovarian, and HER2-postive breast cancer having failed HER2 targeted therapy.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol. This SAP covers the planned analysis of all data collected on paper (source documents /case report forms [CRFs]), captured electronically in DataLabs®, and provided by external vendors. PK/PD and immunogenicity blood samples are analyzed by external laboratory Eurofins Pharma. Tissue samples are analyzed by external laboratory Histogenex. Biomarkers blood samples are analyzed by external laboratory Guardant Health.

The analyses described are based on Clinical Study Protocol (CSP) Final 7.0 incorporating Amendment No.6, dated 14/Jun/2018, Amendment No. 5, dated 23/Jan/2018, Amendment No. 4, dated 04/May/2017, Amendment No. 3, dated 26/Apr/2017, Amendment No. 2, dated 14/Nov/2016, Amendment No. 1, dated 03/Oct/2016 and original CSP Version Final 1.0, dated 13/Jun/2016. The analyses described are based upon electronic Case Report Form (eCRF), version 10.0 dated 18/Oct/2018.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. If this occurs, Symphogen will determine how the revision impacts the study and how the SAP revision should be implemented. The details of the revision will be documented and described in the clinical study report (CSR).

The study was designed to include a Part 1 (Dose-Escalation) followed by a Part 2 (Dose-Expansion).

During Part 1, Symphogen decided to stop the SYM013-01 enrollment. Therefore, no patient is enrolled in Part 2.

All protocol objectives planned data collection and analyses for Part 2 of the study will be omitted hereafter in this SAP.

2 STUDY OBJECTIVES

2.1 Objectives of Part 1, Dose-Escalation

2.1.1 Primary Objective (Part 1)

To assess the safety and tolerability of Pan-HER when administered either Q1W or Q2W by IV infusion to separate dose-escalation cohorts of patients with advanced epithelial malignancies without available therapeutic options.

2.1.2 Secondary Objectives (Part 1)

1. To determine a recommended phase 2 dose (RP2D) and regimen of Pan-HER

2. To evaluate the pharmacokinetic (PK) profile of Pan-HER

3. To evaluate the immunogenicity of Pan-HER

4. To evaluate target engagement in skin biopsy tissue (EGFR and HER3) and tumor biopsy tissue, if available, (EGFR, HER2 and HER3)

5. To evaluate other potential pharmacodynamic biomarkers of Pan-HER action, and estimate, if feasible, the magnitude of biological activity in peripheral blood and in skin biopsy (and tumor biopsy, if available) tissue

6. To make a preliminary evaluation of the antitumor effect of Pan-HER

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label, multicenter trial composed of 2 parts in which Pan-HER will be evaluated when administered by the IV route to patients with advanced epithelial malignancies without available therapeutic options:

- Part 1 is a Phase 1a dose-escalation evaluating Q1W and Q2W schedules of administration in separate dose-escalation cohorts to determine the RP2D and regimen of Pan-HER.

- During Part 1, cohorts of patients will receive increasing doses of Pan-HER on either Q1W or a Q2W schedule until establishment of the following for each schedule:
    - A maximum administered dose (MAD), the highest dose level administered (in mg/kg).
    - A maximum tolerated dose (MTD), the highest dose of SYM013 with <33% patients who have experienced dose limiting toxicity (DLT) as defined by the protocol during cycle 1 of study treatment. Q1W and Q2W regimens may have different MTDs;
    - A RP2D, determined based safety of Q1W and Q2W dose regimens as well as available PK and target engagement results, was to be identified. The RP2D may be equal to or lower than the MTD for the Q1W and/or Q2W dosing regimens.

The Part 1 starting dose of Pan-HER will be 1.0 mg/kg Q1W. The following dose levels of Pan-HER are planned to be evaluated:

Q1W

- Dose Level 1: 1 mg/kg Q1W
- Dose Level 2: 2 mg/kg Q1W
- Dose Level 3: 4 mg/kg Q1W
- *Dose Level 4P: 6 mg/kg Q1W + P (lower doses with prophylaxis may be explored, if indicated)
- *Dose Level 5P: 9 mg/kg Q1W + P
- *Dose Level 6P: 12 mg/kg Q1W + P (no patient enrolled in this dose level)
- *Dose Level 7P: 15 mg/kg Q1W + P (no patient enrolled in this dose level)
- *Dose Level 8P: 18 mg/kg Q1W + P (highest potential dose allowed per protocol) (no patient enrolled in this dose level)

Q2W

- Dose Level 4: 6 mg/kg Q2W
- Dose Level 5: 9 mg/kg Q2W
- *Dose Level 5P: 9 mg/kg Q2W+ P
- *Dose Level 6P: 12 mg/kg Q2W+ P
- *Dose Level 7P: 15 mg/kg Q2W + P
- *Dose Level 8P: 18 mg/kg Q2W + P (highest potential dose allowed per protocol) (no patient enrolled in this dose level)

*Mandatory intensive IRR and oropharyngeal mucositis prophylaxis; 4-hour infusion (designated "P")

Note: Patients entered to Dose Levels 1, 2 and 3 were treated Q1W. As of Amendment 3, the dosing schedule in this trial was changed to Q2W. Patients entered to the trial prior to implementation of this amendment could continue to be treated Q1W.

Note: As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan- HER over a fixed (at minimum) 4-hour (+10 min) period unless further prolongation is required for an individual patient due to the occurrence of an IRR. For patients entered to the trial prior to Amendment 5, these changes could be implemented at the Investigator's discretion based on the individual patient's prior experience with Pan-HER dosing.

Note: As of Amendment 6, Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5. All patients must receive intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER infusions over a fixed (at minimum) 4-hour (+10 min) period, unless further prolongation is required for an individual patient due to the occurrence of an IRR. Reevaluation of Q1W dosing will begin at the 6 mg/kg dose; however, lower doses may be explored if indicated based on tolerability.

Initially, one patient will be treated at each dose level until the occurrence of a toxicity during Cycle 1 that activates the stopping rule of the single-patient cohort titration design. If such a toxicity has not occurred in the first 3 cohorts (i.e., cohorts of 1 mg/kg, 2 mg/kg, and 4 mg/kg

Q1W), the next cohort to open will be a 3-patient cohort and the design will switch to the 3+3 design.

Further dose-escalation will follow a standard 3+3 design with a target toxicity level of < 33% as determined by the number of cycle 1 DLTs.

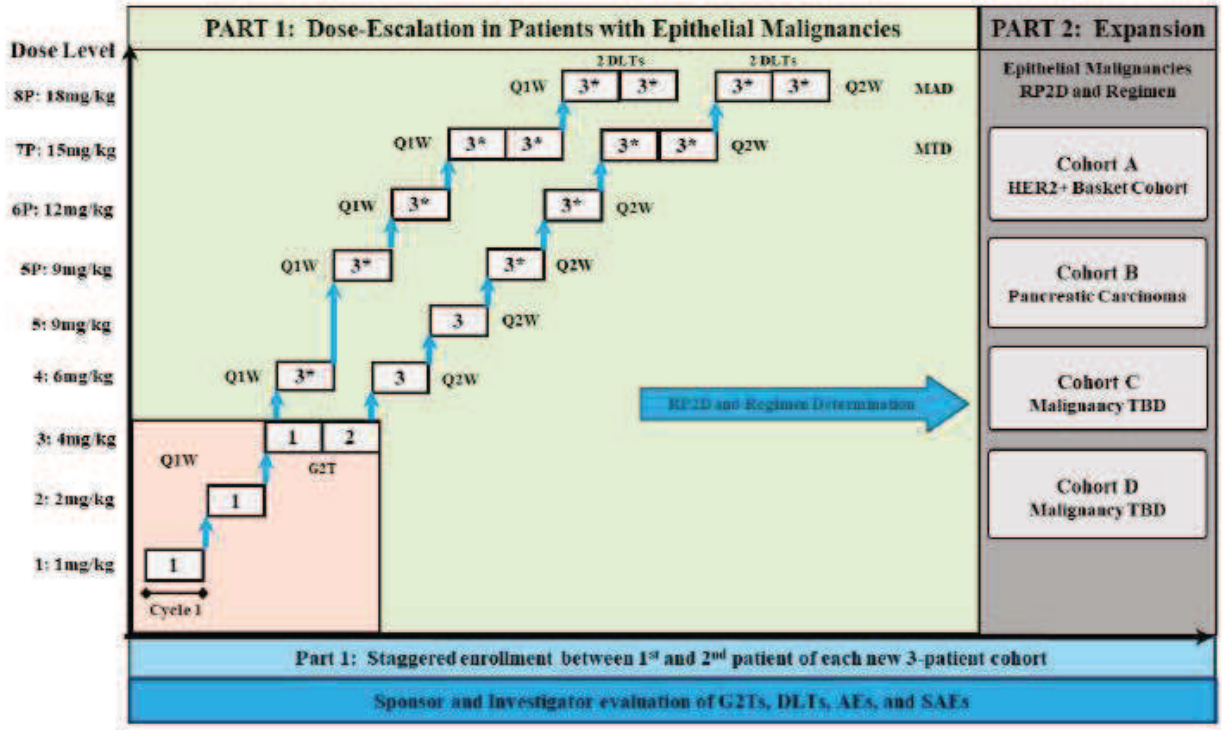
During Part 1, intermediate dose level(s) between 2 planned dose levels may be evaluated to further characterize safety and tolerability of Pan-HER, if indicated based on toxicity observations and/or results from PK and/or target engagement analyses.

A safety monitoring committee (SMC) will be established and will include Investigator(s), Medical Monitor(s) and Sponsor's medical representatives. The SMC will review clinical and laboratory safety data regularly throughout the trial and will select the RP2D and regimen to be used in Part 2 based on safety data, as well as available PK and target engagement results.

The trial design is shown in Figure 1.

The overall Trial Plan is reported in Table - Overall Trial Plan.

Figure 1 Overall Trial Design



Abbreviations: DLT: dose-limiting toxicity; G2T: grade 2 toxicity; MAD: maximum administered dose; MTD: maximum tolerated Dose; P(*): prophylaxis; RP2D: recommended phase 2 dose; Q1W: every week; Q2W: every second week

Table - Overall Trial Plan

Screening Period	
Screening	14 days within first dose of Pan-HER
Treatment Period	
Treatment Allocation	The allocated dose and schedule of Pan-HER will depend upon cohort assignment and will be confirmed by Sponsor or designee on the Screening and Allocation Form.
Pan-HER	Pan-HER will be initiated on C1/D1 and based on cohort assignment, will be administered either Q1W or Q2W to separate dose-escalation cohorts of patients by IV infusion in cycles of treatment: • Q1W: Dosing on Day 1, 8, 15, and 22 of each 28-day cycle (±2 days) • Q2W: Dosing on Day 1and 15 of each 28-day cycle (±2 days) The duration of infusion will be (effective with Amendment 5): • Minimum of 4 hours (+10 min) for all infusions. Titrated rate increases during infusions, and infusion duration reductions after C1/D1, will no longer be allowed. For Part 1 of the trial, Pan-HER will be administered following delivery of intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis.
Discontinuation of Pan-HER	Treatment will continue until unacceptable toxicity or other conditions preventing further treatment, PD, termination of the trial, or patient's decision to withdraw.
End of Treatment	
End of Treatment Visit	Within 10 days after the decision to discontinue Pan-HER, an EOT Visit should be performed.

Follow-up	
One Month Follow-up Visit	Follow-up continues until 1 month (30+7 days) after the last dose of Pan-HER. At that time, a 1M FUP Visit should be performed. This visit constitutes the end of trial participation for the patient.

Abbreviations (in alphabetical order): C1/D1, Cycle1/Day1; CR, complete response; EOT, End of Treatment Visit; IRR, infusion related reaction; IV, intravenous; 1M FUP, 1-Month Follow-up Visit; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

3.2 Endpoints and Associated Variables

Refer to the Schedule of Assessments for timing of assessments.

Primary Endpoint - Part 1, Dose-Escalation

The primary objective of the dose-escalation part is to assess the safety and tolerability of Pan-HER. This will be assessed by the primary endpoint for Part 1: **occurrence of DLTs during Cycle 1 for each of the Pan-HER dose regimens.**

Secondary Efficacy Endpoints

- Documented OR, defined as documented PR or CR, from baseline to end of trial participation (in patients with measurable disease only) (as measured in Part 1)
- Best overall response by RECIST v1.1, categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE)
- Disease Control Rate (DCR)
- Changes in sum of diameters of target lesions from baseline to end of trial participation
- Time to documented PD (Time To Progression [TTP])

Secondary Safety Endpoints

- Nature, incidence and severity of AEs measured from baseline to end of trial participation
- AEs leading to dose-reductions, dose delays and permanent treatment cessation
- Changes in safety laboratory values from baseline to end of trial participation
- Changes in vital signs and physical examinations from baseline to end of trial participation
- Occurrence of ADA to Pan-HER measured in serum at selected timepoints from baseline to end of trial participation

3.2.1 Efficacy Variables

3.2.1.1 Tumor Response according to RECIST v1.1

The anti-tumor activity of Pan-HER will be assessed according to RECIST, v 1.1 using CT or MRI. The use of CT or MRI must be consistent per patient throughout the trial.

Disease Status Evaluation by CT or MRI will occur at:

- Screening

  Note: A CT/MRI performed within 28 days prior to Day 1 may be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the CTP requirements

- End of Cycle 2 and end of every second cycle thereafter, i.e. Cycle 4, 6, 8 etc.

  Note: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle

- After Suspected Progressive Disease (PD) (as soon as possible)
- Confirmation of response, to be performed 28 (+7) days after the first assessment of CR/PR

- EOT (if >3 weeks since previous CT/MRI)
- At 1M FUP (if PD was not documented before or at EOT)

If PD is documented at any time, no further disease assessments will be required. Patients with documented PD will be discontinued from Pan-HER so that alternative management of their malignancy may be considered.

For all imaging time points, the following will be recorded as per RECIST v1.1: Target lesions including size, location, and type (nodal/non-nodal); sum of diameters of target lesions; any new lesions noted during trial, including size, location, and type (nodal/non-nodal); response assessment at each visit (PD, SD, PR, CR or Not Evaluable [NE]), per investigators evaluation.

Tumor evaluation according to RECIST 1.1 will be the basis for the derivation of all efficacy endpoints. To be assigned a status of confirmed PR or CR, changes in disease status must be confirmed by repeat imaging studies performed no less than 28 days (4 weeks) after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after trial entry at a minimal interval in general no less than 6-8 weeks from first dose of Pan-HER; for the scope of derivation of SD as best overall response, a minimal SD duration of 6 week will be required.

The following anti-tumor response endpoints will be derived based on Tumor evaluation according to RECIST 1.1:

- Target and Non Target Response at each timepoint will be derived according to RECIST 1.1 [1].
    - Evaluation of target lesions will be derived based on sum of diameters as follow:
        - *'Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.*

- *Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.*
- *Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: 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 PD, taking as reference the smallest sum of diameters while on study.'*

- Evaluation of non-target lesions: non-target lesions response will be reported in CRF as CR, NON-CR/NON-PD, PD, Not Evaluated; worst response will be taken as the Non-Target Lesion response for the correspondent timepoint; for assessment of worst response the following order will be followed: PD, Not Evaluated, NON-CR/NON-PD, CR.

Target and Non-Target Response at each timepoint, derived as described, will be reviewed by Symphogen and PAREXEL on a patient by patient basis across time.

At each timepoint Overall Responses will be captured in CRF; as well Overall Responses will also be derived according to RECIST 1.1 [1]:

Table 1 of above-mentioned paper [1] is reported below and will be used to derive overall response at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Overall responses derived as described are supposed to coincide with overall responses collected in CRF; cases of mismatch will be queried; any unsolved case of mismatch will be reviewed by Symphogen and PAREXEL on a patient by patient basis across time.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

- Confirmed Best Overall Response (BOR) by RECIST v1.1.

  Per RECIST 1.1[1]:

  'the best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.' 'Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.' 'Best response determination in trials where confirmation of complete or partial response is

required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.'

Table 3 of above-mentioned paper [1] is reported below and will be used to derive confirmed Best Overall Responses. In this study a minimum SD duration of 6 week will be used as criterium to confirm SD as Best Overall Response.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Patients with non-target disease only, may have a time point response of NON-CR/NON-PD, these responses will be included in the count of SD.

Determinations of Best Overall Responses derived as described will be reviewed by Symphogen and PAREXEL on a patient by patient basis across time.

- Unconfirmed BOR by RECIST v1.1:

Per RECIST 1.1 [1]: in cases where confirmation of complete or partial response is not required the Best response is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best unconfirmed response, it must also meet the protocol specified minimum time from baseline.

Patients with non-target disease only, may have a time point response of NON-CR/NON-PD, these responses will be included in the count of SD.

- Documented objective response (OR) confirmed and unconfirmed, based on determination of confirmed and unconfirmed best overall response (BOR) per RECIST v1.1.

  Confirmed OR is defined as the percentage of patients who had confirmed CR or PR.

  Unconfirmed OR is defined as the percentage of patients who had unconfirmed CR or PR.

  'The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).' [1].

  Duration of Response (weeks) = (Date of PD – Date of first CR/PR [whichever is first recorded] + 1) / 7

- Time to Progression (TTP)

  Time to documented PD (based on radiological assessments) will be derived and expressed in the unit of weeks. TTP is defined as the time from first dose of study drug until objective tumor progression; TTP does not include deaths [3]. Based on this definition, PDs will be counted as outcome; patients with last tumor assessment showing CR or PR or SD will be censored at the time of last available tumor assessment per RECIST v1.1; patients who died for any cause (including deaths of disease but with no documented PD) will as well be censored at the time of last available tumor assessment per RECIST v1.1.

  TTP (weeks) = (Date of PD – Date of first IMP infusion + 1) / 7
  In this study, there is no planned survival status after discontinuation of study treatment, therefore, progression-free survival is not calculated.

- Disease control rate (DCR), based on determination of confirmed BOR per RECIST v1.1.

  The DCR is defined as the percentage of patients who had confirmed BOR of CR, PR or SD of at least 16 weeks. Definition of duration of TTP corresponds to SD duration; thus, these times will be used to determine if a patient was in SD for at least 16 weeks.

- Changes in sum of diameters of target lesions from baseline to end of trial participation

  For patients with measurable disease (i.e., with target lesions), absolute and percent changes in the sum of diameters of target lesions from baseline to end of trial participation will be calculated, the best change will be identified as largest reduction or smallest increase.

3.2.1.2 Tumor Markers

Tumor Markers that are part of the trial site standard practices, as indicated by tumor type, are evaluated at timepoints coinciding with the CT/MRI imaging studies.

3.2.2 Pharmacodynamic, Biomarkers and Immunogenicity

These variables include:

- Archival Tumor Tissue for EGFR, HER2 and HER3 expression level, only applicable to patients included in Part 1

- Biomarkers: Potential biomarkers of interest include genes, gene transcripts, and proteins of the HER family receptors and molecules of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways involved in HER signaling. Peripheral blood samples are taken at Screening (after confirmation of eligibility); end of Cycle 2 (prior to dosing Cycle 3) or upon PD, whichever occurs first; EOT.

- Skin biopsy: All patients enrolled will undergo skin biopsies for evaluation of target-engagement (EGFR and HER3). Skin biopsy will be performed at Screening (after confirmation of eligibility), and end of Cycle 2 (prior to dosing Cycle 3) or upon PD,

whichever comes first. Sampling procedure after amendment 6.0 (protocol version 7.0) was changed to Screening (after confirmation of eligibility) and Cycle 1, day 8 and Cycle 1 day 15.

- Tumor biopsy: Optional for Part 1 and required for Part 2, will be performed after confirmation of eligibility at Screening, and end of Cycle 2 (prior to dosing Cycle 3) or upon PD, whichever occurs first. Analysis of tumor biopsies will include target-engagement (EGFR, HER2 and HER3) and may furthermore include proteins and genes that are unknown or have not been included in the scientific hypotheses at the present time of trial, but that, during the collection of data from this trial, may evolve as new candidate genes and markers related to Pan-HER safety, efficacy, or mechanism of action.

- Immunogenicity (ADA): Analysis of ADA and residual serum levels of Pan-HER will be performed at a central laboratory. ADA will be assessed at C1/D1, C2/D1, Prior to every second cycle thereafter, EOT, 1M FUP.

3.2.3 Pharmacokinetic Variables

Serum concentrations of each of the 6 monoclonal antibodies (mAbs) that comprise Pan-HER will support the PK endpoints of the trial. The serum concentrations may also be used in an exploratory population PK analysis which will be reported separately from the clinical trial report.

PK blood sampling schedules are summarized in below tables (Table 11 and Table 12 from Clinical Study Protocol).

Table 11 Schedule of Pharmacokinetic (PK) Assessments: Q1W Dosing

		Cycle 1				Cycle 2 Onward				EOT	1M FUP
Sampling Time	**Window**	**D1-D3**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Prior to SOI	- 4 h	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
EOI	+ 10 min	X	X[1]	X[1]	X	X[1]	X[1]	X[1]	X[1]		
EOI + 2 h	±30 min	X			X						
EOI + 4 h	±30 min	X			X						
EOI + 8 h[2]	±90 min	X			X						
EOI + 24 h	±6 h	X			X						
EOI + 48 h	-12 h to + 24 h	X			X						
During Visit	NA									X	X

Abbreviations (in alphabetical order): D, day; EOI, End of Infusion, EOT, End of Treatment Visit; NA, Not Applicable; h, hour; min, minutes; 1M FUP, 1-Month Follow-up Visit; SOI, Start of Infusion

1) If Pan-HER dosing is delayed, only one PK sample should be taken during the visit.
2) Effective with Amendment 6, sampling at this timepoint is optional.

Table 12 Schedule of Pharmacokinetic (PK) Assessments: Q2W Dosing

		Cycle 1				Cycle 2		Cycle 3 Onward		EOT	1M FUP
Sampling Time	**Window**	**D1-D3**	**D8**	**D15**	**D22**	**D1-D3**	**D15**	**D1**	**D15**		
Prior to SOI	- 4 h	X		X[1]		X	X[1]	X[1]	X[1]		
EOI	+ 10 min	X		X[1]		X	X[1]	X[1]	X[1]		
EOI + 2 h	±30 min	X				X					
EOI + 4 h	±30 min	X				X					
EOI + 8 h[2]	±90 min	X				X					
EOI + 24 h	±6 h	X				X					
EOI + 48 h	-12 h to + 24 h	X				X					
During Visit	NA		X		X					X	X

Abbreviations (in alphabetical order): D, day; EOI, End of Infusion, EOT, End of Treatment Visit; NA, Not Applicable; h, hour; min, minutes; 1M FUP, 1-Month Follow-up Visit; SOI, Start of Infusion

1) If Pan-HER dosing is delayed, only one PK sample should be taken during the visit.
2) Effective with Amendment 6, sampling at this timepoint is optional.

The PK endpoints with Q1W dosing will be derived based on the concentration time curves of Pan-HER after the first and fourth infusion of Pan-HER.

The PK endpoints with Q2W dosing will be derived based on the serum concentration time curves of Pan-HER after the first and third infusion of Pan-HER.

The planned PK endpoints are listed in Table 13 of Clinical Study Protocol.

The data may not allow for derivation of all endpoints for all mAbs, patients and occasions. C_{max}, C_{EOI}, C_{trough} and T_{max} will be derived from observed data while AUC_{τ}, $AUC_{\tau 0}$, $AUC_{norm,\ \tau}$, CL_S, CL_{SS}, V_S, V_{SS}, and $T_{½}$ will be estimated using non-compartmental methods and actual time points.

Table 13 Pharmacokinetic (PK) Endpoints, Definitions and Derivations

Symbol	Definition and derivation
C_{trough}	Trough concentration (i.e. concentration of Pan-HER measured pre-infusion)
AUC_{τ}	Area under the concentration-time curve in a dosing interval (i.e. from time zero (end of infusion) up to 168 hours). AUC_{τ} will be calculated using the linear trapezoidal method and interpolated in case of measurements after 168 hours, or extrapolated using terminal rate constant and the last quantifiable concentration
$AUC_{\tau 0}$	Area under the concentration-time curve from start of infusion up to 168 hours. $AUC_{\tau 0}$ will be calculated similar to AUC_{τ}
$AUC_{norm,\ \tau}$	Dose normalized area under the concentration-time curve in a dosing interval, calculated as AUC_{τ} divided by the dose infused
C_{max}	Maximum concentration
T_{max}	Time to reach maximum concentration
C_{EOI}	Concentration at End of Infusion
λ_z	Terminal rate constant (negative of the slope of an ln-linear regression of the un-weighted data considering the terminal phase of the concentration-time curve ≥ limit of quantification). λ_z is not an endpoint, but is used for derivation of endpoints

Symbol	Definition and derivation
$T_{½}$	Terminal elimination half-life, calculated as $\ln(2)/ \lambda_z$
CL_S	Clearance after first dose, calculated as Dose/AUC_{inf} for C1/D1, where AUC_{inf} will be calculated as the sum of the area from time zero to time of last quantifiable concentration, t_z, and the area from t_z to infinity. The second area will be estimated using the observed concentration at t_z and the terminal rate constant
CL_{SS}	Clearance after $3^{rd}/4^{th}$ dose, calculated as Dose/AUC_τ
V_S	Volume of distribution during the terminal phase after first dose (CL_S/λ_z)
V_{SS}	Volume of distribution during the terminal phase after $3^{rd}/4^{th}$ dose (CL_{SS}/λ_z)

3.2.4 Safety Variables

The following safety endpoints will be assessed:

- Dose-Limiting Toxicities Evaluation
- (S)AE Survey
- Prior and concomitant medications (medications and/or treatments taken other than Pan-HER)
- Laboratory assessments (biochemistry, hematology, urinalysis, and coagulation)
- Pregnancy test
- 12-lead electrocardiogram (ECG)

- Echocardiogram (ECHO) or Multi-Gated Acquisition (MUGA) Scan
- Vital Signs and Body Measurements
- Physical Examination
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) score

3.2.4.1 Dose Limiting Toxicity

A DLT is defined as any of the following toxicities that occur during the DLT-observation period, if considered related (causality rating of possibly, probably, or related) to Pan-HER:

1. Grade 3 non-hematologic toxicity regardless of duration, with the exception of:
    a. Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤2 days with best supportive care
    b. Grade 3 asymptomatic electrolyte abnormality that is not considered clinically significant by the Investigator and that is controlled with medical therapy
2. Grade 4 non-hematologic toxicity, with the exception of:
    a. Grade 4 asymptomatic electrolyte abnormalities that is not considered clinically significant by the Investigator and that is controlled with medical therapy
3. Neutropenia that is:
    a. Grade 3-4 febrile neutropenia
    b. Grade 4 and sustained (i.e., ANC <0.5 $\times 10^9$/L [500/mm^3], duration >5 days)
4. Thrombocytopenia that is
    a. Grade 3 with clinically significant hemorrhage
    b. Grade 4 (platelets <25 $\times 10^9$/L [25,000/mm^3])
5. AST/ALT elevation >3×ULN with bilirubin elevation >2×ULN without evidence of cholestasis that cannot be explained by factors not related to Pan-HER

6. Evidence of cardiac toxicity as defined by either:

    a. ≥16% absolute decrease in LVEF from baseline, or

    b. LVEF below the institutional lower limit of normal and ≥10% absolute decrease in LVEF from baseline

7. Inability to complete Cycle 1 at the assigned dose due to ≥ Grade 3 toxicity

8. Treatment delays >2 weeks from the scheduled next dose due to ≥ Grade 3 toxicity

DLT events (Yes / No) are collected in CRF as well as date of assessment, DLT description and AE Reference.

The decision to dose-escalate will be based on close monitoring of safety during the observation period for DLTs, defined as the initial 28-day period (±2 days) from first treatment of Pan-HER (i.e. Cycle 1) and including 7 days for Q1W or 14 days for Q2W of follow-up from the last dose of Cycle 1.

A minimum of 4 infusions of Pan-HER (Q1W dosing) or 2 infusions of Pan-HER (Q2W dosing) must have been administered at the assigned dose for a patient to have completed the DLT-observation period.

3.2.4.2 Adverse Events

Definitions

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

Treatment-emergent AEs are events that occur on or after first dose of the study medication or a worsening in severity of a preexisting condition occurring on or after first dose of the study

medication (a pre-existing is a condition that is present before the AE recording period starts and is noted on the medical history/physical examination form).

An IRR is defined as an AE occurring during the Pan-HER infusion and up to 2 hours after the end of infusion (EOI), which is assessed by the Investigator as possibly, probably, or related to Pan-HER; IRRs (Yes/No) will be captured in CRF.

AE duration will be derived as AE duration = (AE end date - AE onset date +1); in case of AE ongoing, the date of last contact with the patient will be used as AE for the scope of derive the AE duration.

An SAE is an AE that meets one or more of the following outcome criteria:

- Results in death
- Is life-threatening (patient is at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might cause death if it was more severe)
- Requires in patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is medically important (Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above)

All AEs will be recorded from signing of informed consent for participation in the trial. The recording period ends at the time of the 1M FUP Visit.

All referenced toxicity grading within this protocol will be according to the CTCAE v4.03. If the severity of an AE is not specifically graded by the CTCAE guidance document, the Investigator should use the general definitions of Grades 1 to 5 as per the following, and use his/her best medical judgment to describe the severity of the AE:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death caused by the event

Changes in severity of AEs will be recorded.

AEs will be assessed for causal relationship to the IMP. The causal relationship of an AE to the IMP, Pan-HER, will be rated as follows:

- Not Related (The AE is not related to the IMP)
- Unlikely Related (The AE is considered not related to the IMP)
- Possibly Related (The AE might not be related, but possibility cannot be ruled out with certainty and therefore would be considered related)
- Probably Related (It has been determined with a high degree of certainty that the AE is associated with administration of IMP)
- Related (The AE is related to the IMP)

Outcome of the AE will be assessed utilizing one of the following terms:

- Recovered
- Recovered with sequelae (if recovered with sequelae, specify sequelae)
- Not recovered
- Fatal
- Unknown

Handling of partial AE onset and end date

Any AEs with incomplete start and end dates will be treated as follows:

- Adverse events with completely unknown onset date will be considered as treatment-emergent; for the scope of AE duration derivation, these AE will be considered as occurred the day of first IMP infusion.
- Adverse events with unknown start day and month but with known start year will be considered:
    - as treatment-emergent if the start year coincides or is after the first dosing year; for the scope of AE duration derivation, these AE will be considered as occurred the day of first IMP infusion if the start year coincides with first dosing year, as occurred on 1st January otherwise (i.e. in case the start year is after the first dosing year)
    - as non-treatment emergent if start year is before the first dosing year; for the scope of AE duration derivation, these AE will be considered as occurred on 1st January.
- Adverse events with unknown start day but with known start month and year will be considered:
    - as treatment-emergent if the start month and year coincide or are after the month and year of first dosing; for the scope of AE duration derivation, these AE will be considered as occurred the day of first IMP infusion if the start month and year coincides with first dosing month and year, as occurred on 1st day of the month otherwise (i.e. in case the month and year is after the month and year of first dosing)
    - as non-treatment emergent if start month and year is before the month and year of first dosing; for the scope of AE duration derivation, these AE will be considered as occurred on 1st day of the month.
- Adverse events with completely unknown end date will be considered as ended on the day of last contact with the patient).

- Adverse events with unknown end day and month but with known end year:
    - if the AE end year if before the year of last contact with the patient, AE will be considered as ended on 31th December.
    - if the AE end year coincide with the year of last contact with the patient, AE will be considered as ended on day of last contact with the patient.
    - If AE end year is after the year of last contact with the patient, for the scope of derive the AE duration the date of last contact with the patient will be used as AE end date.
- Adverse events with unknown end day but known end month and end year:
    - if the AE end month and year are before the month and year of last contact with the patient, AE will be considered as ended on last day of the month.
    - if the AE end month and year are coinciding with the month and year of last contact with the patient, AE will be considered as ended on last day of last contact with the patient.
    - If AE end month and year are after the month and year of last contact with the patient, for the scope of derive the AE duration the date of last contact with the patient as AE end date.

Adverse events with completely or partial unknown start and end dates will be shown as not known (NK), for the respective unknown part, in the listings.

3.2.4.3 Clinical Laboratory and Pregnancy Test

- Hematology panel (complete blood count with differential, ANC, and platelet count): at Screening, Cycle 1 (weekly prior to dosing if on dosing day, Day 3. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 and 15 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Biochemistry panel (sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, calcium, magnesium, phosphorus, albumin, total protein, uric acid, amylase, lipase, and creatine kinase): at Screening, Cycle 1 (weekly prior to dosing if on dosing days, Day 3. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 and 15 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Coagulation panel (PT, PTT and INR): at Screening, Cycle 1 (Day 1 and 15 prior to dosing. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Urinalysis (specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen): at Screening, Cycle 1 (Day 1 and 15 prior to dosing. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Pregnancy test (serum human Chorionic Gonadotropin (β-hCG) at screening, urine β-hCG thereafter, in women of childbearing potential): at Screening, EOT and as clinically indicated.

3.2.4.4 Electrocardiogram

A 12-lead ECG will be performed on Screening, EOT, and as clinically indicated.

Parameters measured will include heart rate, PR, R-R, QRS, QT, and QTc intervals (calculated by the Fridericia [QTcF] or Bazzett's [QTcB] correction formula). Clinical assessment (abnormality as clinically significant or not clinically significant) will be performed.

3.2.4.5 Echocardiogram (ECHO) or Multi-Gated Acquisition (MUGA) Scan

Transthoracic echocardiogram (ECHO) or Multi-Gated Acquisition (MUGA) scan will be performed at Screening, EOT, and as clinically indicated.

3.2.4.6 Vital Signs and Body Measurements

Vital signs, including temperature, heart rate, blood pressure, and body weight will be monitored at Screening, prior to each dosing, EOT, 1-month FUP and as clinically indicated.

3.2.4.7 Physical Examination

Full physical examination at Screening to include evaluation of: general appearance, skin, head, ears, eyes, nose, throat, neck/thyroid, chest/breasts, lungs, cardiovascular system, abdomen, musculoskeletal system, pulses, lymph nodes, neurologic status and mental status.

Thereafter, a targeted physical examination may be performed as indicated: at Screening, Day 1 of each cycle prior to dosing, EOT, 1M FUP and as clinically indicated.

3.2.4.8 Eastern Cooperative Oncology Group (ECOG) performance Status (PS) score

ECOG PS will be assessed at Screening, Day 1 of each cycle (prior to dosing), EOT, 1M FUP and as clinically indicated.

ECOG PS Score:

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

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

Baseline

'Baseline' is defined as the last available pre-treatment assessment, considering both scheduled and unscheduled assessments.

Safety assessments at Cycle 1 Day 1 with no time of assessment (i.e. Vital Signs and Body Measurements, ECOG PS, Physical Examination) are assumed to be taken pre-treatment.

End of Treatment (EOT)

'End of Treatment' is defined as the first assessment on or after the last dose of study treatment, considering both scheduled and unscheduled assessments.

Unscheduled assessments

Unscheduled assessments will be presented in listings in chronological order.

Post Baseline unscheduled assessments (for Clinical Laboratory, ECG QTc, etc.) will be used for determination of worst result (i.e. Maximum and Minimum post Baseline result) as well as the maximal laboratory CTCAE grade if applicable; also, all post baseline tumor evaluation assessments will be used to derive BOR.

Except considered as Baseline, EOT or worst result, unscheduled assessments will not be included in summaries.

Treatment Day

'Treatment Day' will be calculated relative to the date of C1/D1 as follow:

- assessments taken before the first infusion of IMP
  Treatment Day = Assessment Date - First IMP infusion Date
- assessments after the first infusion of IMP
  Treatment Day = Assessment Date - First IMP infusion Date + 1.

Missing Data

In case of partially missing date of birth or date of diagnosis, the following rule will be applied: if year and months are known but day is missing, then the day will be imputed as 15th; in case of only year known, the day and month will be imputed as 15th June.

Specific rules for handling for missing efficacy assessments are detailed in section 4.10.1.3.

Methods for handling missing concomitant medication and adverse events dates are detailed in sections 4.8 and 3.2.4.2 respectively.

Imputations will be used to derive parameters, in listings original data will be presented as collected.

Data Listing

All original and derived parameters for all consented patients will be listed.

All listings will include scheduled and unscheduled measurements.

Unless specified otherwise, data in listings will be presented by dose regimen (Q1W or Q2W), dose group, patient, and visit (ordered by date and time within patient).

All listings will display the same number of decimals as in the source data. All raw data will be reported exactly as provided.

Quantitative derived variables (e.g. Duration of Response, Time to Progression, Actual Treatment duration) will be shown with 1 decimal place (d.p.) precision.

The data for the patients who consented but for any reason did not receive any dose of study drug (including screening failures) will be also listed but with a label of '*'and a footnote to flag these.

Efficacy, Exposure and PK/PD Data Listing will be based on Full Analysis Set.

Tables and Descriptive Statistics

Unless specified otherwise all tables and statistics will be presented using the FAS.

Evaluation of DLT will not be based on FAS but on DLT Analysis Set.

Unless specified otherwise summary tables and figures will be presented by dose regimen (Q1W or Q2W), dose group, and visit (where applicable); also, overall summaries will be shown for the two-dosage regimen and for all patients pooled together. In general, summary tables will be structured in three parts: first part will summarize overall results obtained in the two dose regimens Q1W, Q2W and in all patients pooled together; second part will display all dose groups within the dosage regimen Q1W; third part will display all dose groups within the dosage regimen Q2W.

In general, for variables showing multiple possible categories, these will be displayed with following the within variable logic criteria, for example: ECOG categories will be displayed from 0 and going to grow; where such a logic criterium does not exist (example: gender, ethnicity, SOC, PT), categories will be displayed by descending frequencies based on the overall all patients pooled together. In the end, the order used to show categories within variables should be the same in the three parts of each table.

Unless otherwise stated, continuous data will be summarized using descriptive statistics including: number of non-missing observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays. Percentages will be calculated using n as the denominator. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

The following rules will apply to all descriptive statistic displays, except the PK concentrations and parameters that are reported in significant digits described in section 4.10.4.4 below, where d denotes the decimal places in the original reported value:

- n: 0 decimal places (d.p.)
- Mean: d + 1 d.p.
- Confidence Interval: d + 1 d.p.
- SD: d + 2 d.p.
- Median: d + 1 d.p..
- Minimum: d.
- Maximum: d.
- Statistics in percentage: 1 d.p.
- p-value: 4 d.p.
- Except for p-value, a maximum of 3 decimal places will be displayed.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Details for reporting of statistical summaries specific to PK are detailed in section 4.10.1.4.

Figures

If not otherwise specified, each figure will be presented separately for the two dose regimens (Q1W and Q2W) with differentiate legend to discriminate the dose groups within the regimen; moreover, an overall figure will also be presented with differentiate legend to discriminate the two dose regimens. In the end, there will be three panel for each figure: first panel will show all patients, second panel patients in Q1W regimen, third panel patients in Q2W regimen.

All figures will be produced in black and white.

Specification for PK figures will be detailed in section 4.10.4.1.

4.3 Software

The tables, listings, figures and any non-descriptive statistical analysis will be produced using SAS® Software (Version 9.3 or higher). The REPORT procedure (SAS PROC Report) will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures.

All tables, listings, and graphs will be produced to landscape orientation using Courier New 9pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins on standard A4: Margins (top, left, right, and bottom) 2.54 cm.

4.4 Study Patients

4.4.1 Disposition of Patients

The patient disposition including the date the informed consent was signed, date of last infusion of study drug and the primary reason for discontinuation of study treatment will be listed. Moreover, the number of patients who consented to the study, were exposed to study treatment and primary reason for end of treatment will be summarized.

Those patients who did not meet the eligibility criteria or were screen failures will be listed.

A listing of patients included into each of the analysis set will be presented, related summary statistics will be provided.

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

4.4.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. All protocol deviations will be listed by patient. All protocol deviations will be discussed during Data Review Meeting (DRM) and addressed with the “final” classification together their overall effect on a patient, as well, assignment of each patient to the analysis sets will be decided. During DRM, all protocol deviations and their possible impacts will be discussed

between PAREXEL and Symphogen and will be assessed as “minor” or “major”. Major protocol deviations and protocol deviations affecting primary analyses can lead to the exclusion of a patient from the analysis sets. Reasons for excluding patients from any analysis set will be reported and described in the DRM Report that will be finalized before database hard lock and signed off by all relevant scientific experts.

4.5 Analysis Sets

Two analysis sets will be defined in accordance with the consolidated ICH E9 GCP guidelines.

The Full Analysis Set (FAS) will comprise all enrolled patients who have received at least one dose of Pan-HER. The FAS will be used for evaluation of all endpoints except evaluation of DLTs. The patients in the FAS will contribute to the analyses as allocated to treatment (patients will be reported below the regimen and dosage actually received). For the evaluation of PK endpoints, patients, full profiles, or single measurements can be excluded from the analyses with justification. The decision of excluding patients, full profiles, or part of profiles will be described in the clinical trial report (CTR).

The DLT Analysis Set will comprise all patients in the FAS enrolled in Part 1, except patients who did not complete Cycle 1 for reasons other than drug toxicity. The DLT Analysis Set will be used for evaluation of DLTs and the MTD or lack thereof.

4.6 Demographics and Baseline Characteristics, Disease History and Prior Cancer Therapies

The following demographic and baseline variables will be recorded:

- Date of informed consent
- Date of Birth
- Gender, Race and Ethnicity
- Height
- Weight at screening and baseline

- Stage at initial diagnosis and current stage
- Screening and baseline ECOG PS (categories)
- Disease history and diagnosis (Site of primary tumor, Date of initial diagnosis, Sites of metastases, Date of most recent progression)
- Prior cancer therapies including prior surgical treatment [yes/no], prior radiation therapy [yes/no] and prior systemic therapies, Prior anti-EGFR treatments [yes/no] and Responder to prior anti-EGFR treatments [Positive/Negative], Prior HER2 therapies [yes/no] and Responder to prior HER2 therapies [Positive/Negative]

Age at consent in years will be derived as (Year of informed consent signed – Year of date of birth) + 0 if the month and day of informed consent signed >= the month and day of date of birth, else + 1. The following age classes will be as well derived: < 65 years; 65 - <75 years; 75 - <85 years; 85 years or older.

BMI at baseline will be calculated as Weight [kg] / (Height [m])^2

Time since initial diagnosis will be derived as (Year of informed consent signed – Year of initial diagnosis) + 0 if the month and day of informed consent signed >= the month and day of initial diagnosis, else + 1.

Number of sites with metastases will be derived by counting all sites with metastases.

Prior systemic therapies for cancer will be counted by regimen and summarized as 0, 1, 2, 3, 4+ for each patient.

Regimens containing anti-EGFR or HER2 drugs will be identified.

Demographic and baseline characteristics, Disease History and Prior Cancer Therapies will be listed.

Listing of Systemic Therapies will be reviewed by Symphogen and PAREXEL and regimens with anti-EGFR or HER 2 treatments will be flagged, data should then match with answers collected in CRF for prior anti-EGFR treatments [yes/no] and Prior HER2 therapies [yes/no]; cases of

mismatch will be queried; any unsolved case of mismatch will be reviewed by on a patient by patient basis.

Descriptive continuous statistics will be presented for:

- Demographic and baseline characteristics (including age, height, weight and BMI)
- Disease History information (including Time since initial diagnosis [years]).

The frequency and percentage of patients will be tabulated for:

- Demographic and baseline characteristics categorical variables (including gender, race, and ethnicity);
- Disease History information (including ECOG PS, Site of primary tumor, number and sites of metastases, EGFR and HER2 results [positive/negative])
- Prior Cancer Therapies for current malignancy (including prior surgical treatment [yes/no], prior radiation therapy [yes/no], number of prior systemic therapies [0, 1, 2, 3, More than 3], Prior anti-EGFR treatments [yes/no] and Responder to prior anti-EGFR treatments [yes/no], Prior HER2 therapies [yes/no] and Responder to prior HER2 therapies [yes/no]).

The stage at initial diagnosis and current stage will only be listed.

4.7 Medical History and Concomitant Illnesses

Medical history is assessed at screening and include prior and ongoing medical illnesses and conditions and prior surgical procedures not related to the primary diagnosis.

Medical History terms will be coded using MedDRA, 19.1. Medical History terms will be listed.

4.8 Prior and Concomitant Medications

Medications are all prescription medications, over-the-counter medications, or alternative therapies registered from screening through 30 days after the last dose of study drug. Medications will be listed (excluding those taken prophylactically for Pan-HER reactions).

Medications will be coded using the World Health Organization Drug Dictionary drug (WHODD, September 2016 and will be presented by WHODD Anatomical-Therapeutic-Chemical (ATC) therapeutic classification and preferred term (PT).

Medications and treatments administered prior to the first infusion of study drug which stopped prior to first infusion of study drug will be considered as prior medications and flagged in the listing.

Medications and treatments which started before, on or after the first infusion of study drug and which stopped after first infusion of study drug (including medications and treatments which stopped the day of first infusion) will be considered as concomitant medications.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior.

Prophylactic treatment for Pan-HER related reactions and pre-medication for Pan-HER infusions will be listed separately.

Concomitant procedures performed during the study will be collected and listed.

4.9 Treatment Exposure and Compliance

Data of study drug infusion including dose reduction and interruption information, patient drug administration irregularities (dose reduction and interruption) and infusion related reaction will be listed.

Duration of the Pan-HER exposure, treatment duration, actual number of doses, planned total dose, actual total dose and Relative Dose Intensity (RDI) will be derived as follow:

- Duration of exposure (days) = (last dose date - first dose date +1)
- Actual Treatment duration (weeks) =

(last dose date - first dose date + 7) / 7 for weekly dose (i.e. dose regimen Q1W), or (last dose date - first dose date + 14) / 7 for biweekly dose (i.e. dose regimen Q2W)

- Number of treatment cycles initiated (i.e. at least one infusion for the cycle)
- Number of treatment cycles completed (i.e. all cycle infusions were received by the patient)
- Planned total number of doses for Q1W = (Date of last dose – Date of first dose +1) / 7 rounded up to integer
- Planned total number of doses for Q2W = (Date of last dose – Date of first dose +1) / 14 rounded up to integer
- Planned total dose = Planned dose * Planned total number of doses
- Planned treatment duration (weeks) for Q1W = Planned total number of doses × 1
- Planned treatment duration (weeks) for Q2W = Planned total number of doses × 2
- Relative dose intensity (RDI)

$$RDI\ (\%) = 100\ \times \frac{\text{Sum of all received dose / Duration of exposure (days)}}{\text{Total planned dose / (Planned treatment duration (weeks)x7)}}$$

whereas the total planned dose (mg/kg) and planned dose duration are calculated based on the number of doses of the study medication a patient had received at the initially planned dose (mg/kg) for the cycle according to the planned dosing schedule.

Example, if a patient received 8 bi-weekly (i.e. dose regimen Q2W) doses of a study medication with a loading dose of 12 mg/kg and rest 9 mg/kg, with 1 dose reduction from 9 mg/kg to 6 mg/kg starting at week 14 and 1 week delay and at week 16, then

$$RDI\ (\%) = 100\ \times \frac{(12 + 5 \times 9 + 2 \times 6)\ /\ 119}{(12 + 7 \times 9)\ /\ 112} = 86.6\%$$

The number of initiated and completed cycles of taking Pan-HER will be summarized both as categoric (0, 1, 2, 3, 4, 5, >5) and continuous parameter.

Duration of the Pan-HER exposure will be summarized as actual treatment duration (weeks) and actual number of doses. RDI will be summarized both as categoric (> 100%; 90 % - 100 %; 80 % - < 90%; 70 % - < 80%) and continuous parameter. Swimmer Plot will be presented showing Treatment Duration together with Tumor Response data.

Number of patients who had dose reduction (Any, 1, 2, 3+ times) and dose interruption (Any, 1, 2, 3+ times)) will be summarized.

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

No formal testing of hypotheses has been planned in this study. Therefore, no formal sample size calculations were performed.

Two-sided Confidence Intervals will be presented with α=0.05 (95% CI).

4.10.1.1 Multi-center Studies

There will not be any adjustment for study centers, subgroup analysis based on study centers are not planned.

4.10.1.2 Adjustments for Covariates

No statistical models will be provided for the analysis of Study Endpoints. All study analyses will be descriptive and will be seen from an exploratory perspective. No adjustment for covariates is then expected.

4.10.1.3 Handling of Dropouts or Missing Data

Efficacy data that are reported as missing will be excluded from all descriptive and non-descriptive data analysis. There will be no imputation of missing efficacy data.

For general rules about handling of missing data refer to section 4.2.

4.10.1.4 Multiple Comparisons/Multiplicity

Not Applicable.

4.10.1.5 Interim Analyses

No formal interim analysis is planned.

All relevant safety, PK and toxicity data will be reviewed on an ongoing basis throughout the trial, especially at various decision points for dose escalations and expansion.

4.10.1.6 Examination of Subgroups

Tumor Type will be used as a subgroup to summarize some study endpoints or as stratification factor in certain graphics as appropriately described in the text of this SAP. Tumor type categorization will be based on primary tumor site which may also be combined with tumor histology.

4.10.2 Analysis of Efficacy Variable(s)

All statistical analysis of the efficacy endpoints will be presented using the FAS.

4.10.2.1 Anti-Tumor Response according to RECIST v1.1

The following anti-tumor response endpoints will be measured in Part 1:

- Confirmed and unconfirmed BOR by RECIST v1.1 will be listed and summarized by dose regimen and dose level received using frequency distribution for the categories CR, PR, SD, PD, and Not Evaluable.
- Number and percentage of patients with documented confirmed and unconfirmed OR will be summarized by dose regimen and dose level using frequency distribution with the corresponding 95% exact Clopper-Pearson Confidence Intervals (CI) for binomial proportion. All documented ORs will be listed including duration (weeks) of response.
- Patients in DCR will be listed and summarized by dose regimen and dose level using frequency distribution with the corresponding 95% exact Clopper-Pearson Confidence Intervals (CI) for binomial proportion.
- Time to Progression (TTP)

The median TTP, as well as 26 weeks and 52 weeks TTP rates and the corresponding 95% CIs will be estimated using the product-limit method and presented using a Kaplan-Meier plot. Number and percent of censored patients will be presented, also number and percent of patients censored for death will be presented.

- Changes in sum of diameters of target lesions from baseline to end of trial participation

  Changes in the sum of diameters of target lesions from baseline to end of trial participation will be listed as percentage and absolute value, the best change (i.e., largest reduction or smallest increase) will be identified and presented using summary table and plotted with a waterfall plot. Change in sum of diameters will also be presented by primary tumor type.

- Results of the tumor evaluation by CT/MRI for target lesions, non-target lesions and timepoint tumor response will be listed, as well as derived target and non-target time point responses.

4.10.2.2 Tumor Markers

The date of the tumor evaluation and all test results will be listed.

4.10.3 Pharmacodynamic, Biomarkers and Immunogenicity

4.10.3.1 Pharmacodynamic, Biomarkers, Immunogenicity (ADA) and Archival Tumor

Exploratory analysis may be conducted according to the study exploratory objectives based on the available pharmacodynamic data.

Potential biomarkers of interest include genes, gene transcripts, and proteins of the HER family receptors and molecules of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways involved in HER signaling.

Results of pharmacodynamic biomarkers taken from blood samples will be listed. Blood sample results for anti-drug antibody will be listed. Cancer Gene Mutations will be listed as well.

Exploratory analysis of the biomarker profiles might be performed.

4.10.3.2 Skin Biopsy

The location of the skin biopsy, the date taken, and expression results of EGFR and HER3 and proliferation marker Ki67 will be listed.

EGFR and HER3 receptor down modulation and changes in Ki67 in skin biopsies, measured by percentage and nominal change in target expression from baseline to end of Cycle 2 or PD (whichever comes first) in skin samples will be presented by tumor type using descriptive statistics.

After protocol amendment 6, (version 7.0), EGFR and HER3 receptor down modulation in skin biopsies, measured by percentage and nominal change in target expression from baseline to Cycle 1 day 8 and Cycle 1 day 15 in skin samples will be presented by trial part and tumor type using descriptive statistics, scatter plots of values at Cycle 1 day 8 and Cycle 1 day 15 versus baseline may also be produced.

4.10.3.3 Tumor Biopsy

The date of the tumor biopsy, the tumor site, expression results of EGFR, HER2, and HER3 and Ki67 satining will be listed. EGFR, HER2 and HER3 receptor down modulation and changes in Ki67 in tumor biopsies (may not be available in Part 1), measured by percentage and nominal difference in target expression from baseline to end of Cycle 2 or PD (whichever comes first) in tumor biopsy samples will be presented by tumor type using descriptive statistics including scatter plots of values at end of Cycle 2 versus baseline.

4.10.4 Pharmacokinetics

4.10.4.1 Pharmacokinetic Concentrations

Serum concentrations for each of the six monoclonal antibodies in Pan-HER will be listed by mAb, dose schedule, dose group, patient, actual time relative to dosing, scheduled time and time deviation from scheduled time. The unit for the concentrations will be µg/mL.

Patient profiles serum concentrations vs. time points for each mAb will be plotted by dose schedule and dose group.

The following definitions are used for PK plots and tables:

- First profile for weekly: all PK points from Cycle 1 Day 1 to Cycle 1 Day 8 (pre-dose)
- 2nd profile for weekly (4th dose): all PK points from Cycle 1 Day 22 to Cycle 2 Day 1 (pre-dose)
- First profile for biweekly: all PK points from Cycle 1 Day 1 to Cycle 1 Day 15 (pre-dose)
- 2nd profile for biweekly (3rd dose): all PK points from Cycle 2 Days 1to Cycle 2 Day-15 (pre-dose).
- Dosing/sampling occasions for weekly dosing: Week 1, 2, 3, 4, 5, 6 etc., EOT, 1MFUP
- Dosing/sampling occasions for biweekly dosing: Week 1, 3, 5, 7, 9 etc., EOT, 1MFUP
- Peaks: serum concentration for each mAb assessed at EOI for each dosing occasion
- Troughs: serum concentrations for each mAb assessed prior to SOI for each dosing occasion

Violations of scheduled sampling will be reviewed on a patient by patient basis by Symphogen and PAREXEL. Following data review by Symphogen's pharmacokinetic expert, data points may be excluded from mean calculations and parameter calculation based on the below criteria:

- Individual outlying data points which are markedly deviating from the preceding and following time points
- Data points or PK profiles which are not compatible with known physiological processess underlying the PK properties
- Unexpected events or protocol deviations documented in e.g. laboratory notes or in protocol deviation reviews

Exclusions will be documented in the study files and the PC/PP files.

Following plots will be produced:

- One panel per mAb, Dose Schedule and Dose group combination showing a profile for each patient: Patient Profiles for concentration vs. Actual Time by Dose Schedule and Dose Group (peak and trough for each dosing occasion) – Linear

- One panel per mAb, Dose Schedule and Dose group combination showing a profile for each patient: Patient Profiles for concentration vs. Actual Time by Dose Schedule and Dose Group (peak and trough for each dosing occasion) Semi-log

- One panel per patient with overlaid profiles of all six mAbs: concentration of the six mAbs vs. Actual Time (peak and trough for each dosing occasion) – Semi-log

- One panel per mAb, Dose Schedule and Dose group combination showing a profile for each patient: Patient Profiles for concentration vs. actual time by Dose Schedule and Dose Group (First and 2nd profiles) – Linear

- One panel per mAb, Dose Schedule and Dose group combination showing a profile for each patient: Patient Profiles for concentration vs. actual time by Dose Schedule and Dose Group (First and 2nd profiles) – Semi-log

- One panel per patient with overlaid profiles of all six mAbs vs. actual time (First and 2nd profiles) – Semi-log

Above plots produced per mAb, Dose Schedule and Dose group combination will be composed by one panel for each mAb; moreover, each panel will be composed by the following 7 sub-panels

Sub-panel a) all patients in q1w - 1mg/kg

Sub-panel b) all patients in q1w - 2mg/kg

Sub-panel c) all patients in q1w - 4mg/kg

Sub-panel d) all patients in q1w - 6mg/kg + P

Sub-panel e) all patients in q2w - 6mg/kg

Sub-panel f) all patients in q2w - 9mg/kg and 9mg/kg + P

Sub-panel g) all patients in q2w - 12mg/kg + P

Descriptive summary (n, arithmetic mean, SD, median, minimum, maximum, geometric means, and CV% values) of serum concentrations of each of the six mAbs will be tabulated by dose schedule, dose group and nominal sampling time. Following tables will be produced:

Summary of concentration for each of the six mAbs by Dose Group and Time Point (First and 2nd profiles)

Summary of concentration for each of the six mAbs by Dose Group and Time Point (Peak and trough for each dosing occasion)

The arithmetic and geometric means of the serum concentrations of each of the six mAbs vs. nominal time points will be plotted by dose group with +/-1 standard deviation (for arithmetic means). In figures of geometric means, error bars will be calculated using the following formula: Exp (mean_Ln +/- sd_Ln) where 'sd_Ln' denotes the standard deviation of the concentration values on the log base 10 scale and 'mean_Ln' denotes the arithmetic mean of the concentration values on the log base 10 scale.

The following mean concentration vs. time plots will be produced:

- Arithmetic Mean Concentration for each of the six mAbs vs. Planned Time Point by Dose Group and Dose Schedule (First and 2nd profiles) – Linear
- Geometric Mean Concentration for each of the six mAbs vs. Planned Time Point by Dose Group and Dose Schedule (First and 2nd profiles) – Semi-log
- Arithmetic Mean Peak and Trough Concentrations for each of the six mAbs vs. Planned Time Point by Dose Group and Dose Schedule (peaks and troughs at all dosing occasions) – Linear
- Geometric Mean Peak and Trough Concentrations for each of the six mAbs vs. Planned Time Point by Dose Group and Dose Schedule (peaks and troughs at all dosing occasions) – Semi-log

4.10.4.2 Handling of Values Below the Limit of Quantification (BLQ)

Handling of values below the limit of quantification (BLQ) and missing data in listings and for the calculation of descriptive statistics at each time point**:**

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the ½*lower limit of quantification (LLOQ), and all descriptive statistics will be calculated.
- At a time point where more than 50% of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The max value will be reported from the individual data, and the min and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not Applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, min, median, and max.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

4.10.4.3 Pharmacokinetic Parameters

Pharmacokinetic parameters for the first and second PK profile (as defined in 4.10.4.1) for each patient and each monoclonal antibody will be derived by model-independent, non-compartmental analysis (NCA) according to Symphogen's local procedures.

All derived serum PK parameters will be listed by mAb, dose schedule, dose group, patient, and actual time point (Listing 16.2.6.2.1-2) and summarized descriptively by mAb, dose schedule and group and day (Table 14.2.2.1-2). The following descriptive statistics will be presented for PK parameters: n, arithmetic mean, SD, geometric mean, geometric CV% (calculated as: $gCV\%=SQRT(\exp(s^2)-1)*100$; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

4.10.4.4 Pharmacokinetic Analysis

Descriptive statistics of serum concentrations will be reported with the same precision as the source data and serum concentrations.

In addition to general continuous summary statistics presented in section 4.2, for PK parameters, geometric means with coefficient of variation (CV %) will be also summarized.

For drug concentrations and concentration-dependent pharmacokinetic parameters, the rules of data presentation are described in table below.

Presentation of PK Parameters and Summary Statistics

Typical Variable	N	Digit rule	Minimum /Maximum	Mean Median	SD	Geometric Mean	CV (%)
concentration	X	Significant digits	3	4	4	3	3
C_{max}	X	Significant digits	3	4	4	4	4
t_{max}*	X	Fixed decimal places	as raw data	as raw data	-	-	-
λ_z	X	Significant digits	4	3	5	5	5
$t_{1/2}$	X	Significant digits	3	3	4	4	4
$AUC_{(0-xx)}$	X	Significant digits	3	3	4	4	4
$AUC_{(0-\tau)}$	X	Significant digits	3	3	4	4	4

* Mean and SD, geometric mean and CV will not be calculated for t_{max}.

4.11 Safety Evaluation

All safety summaries will be based upon the FAS as defined in Section 4.5.

4.11.1 The DLT Analysis Set will be used for evaluation of DLTs Dose Limiting Toxicities (DLT)

All DLT events will be listed. Presence and absence of DLTs will be presented by regimen and dose in the order of date of first dose.

4.11.2 Adverse Events

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

TEAEs will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). In all AE summary tables, SOCs and PTs will be presented in the order of descending frequencies as detailed in section 4.2. AE frequency accounts for number and percent of patients who have a specific SOC and PT as well as the worst grade, if there were multiple occurrences at different toxicity grade, which was determined using CTCAE v4.03.

For purposes of the summary tables, AEs will be classified as either being related to study drug or not related. AEs related to study drug will include AEs classified as ‘Related’, 'Probably Related' or ‘Possibly Related’. AEs not related to study drug will include AEs that are ‘Unlikely Related’ or ‘Not Related’.

All AEs will be listed. The AEs will be presented using summary tables including:

- Patient Overall Summary of TEAEs. This table will include following summaries:
    - Any TEAEs
    - Any related TEAEs
    - Any Serious TEAEs
    - Any related Serious TEAEs
    - Grade 3 or higher TEAEs
    - Any Related Grade 3 or higher TEAEs
    - Any TEAEs leading to Permanent Discontinuation of IMP
    - Any Related TEAEs leading to Permanent Discontinuation of IMP
    - Any TEAEs leading to interruption or Stop of study drug
    - Any Related TEAEs leading to interruption or Stop of study drug

  - Any TEAEs with an outcome of reduction or delay of study drug
  - Any Relate TEAEs with an outcome of reduction or delay of study drug
  - Any FATAL TEAEs
    - Fatal TEAEs within 30 days from last IMP infusion
    - Fatal TEAEs beyond 30 days from last IMP infusion

- TEAEs by Dose Group, SOC and PT
- Related TEAEs by Dose Group, SOC and PT
- TEAEs by Dose Group, SOC and PT and Worst CTCAE Grade
- Related TEAEs by Dose Group, SOC and PT and Worst CTCAE Grade
- Serious TEAEs by Dose Group, SOC and PT
- Related Serious TEAEs by Dose Group, SOC and PT
- TEAEs Leading to Withdrawal from Treatment by Dose Group, SOC and PT
- Related TEAEs Leading to Withdrawal from Treatment by Dose Group, SOC and PT
- Serious Adverse Events - Key Patient Information (non TEAEs will be flagged)
- Adverse Events with Outcome of Death - Key Patient Information (non TEAEs will be flagged)
- Adverse Events Leading to Discontinuation of Investigational Product - Key Patient Information
- Adverse Events Leading to Dose Reduction - Key Patient Information
- Adverse Events Leading to Dose Interruption- Key Patient Information
- Adverse Events Leading to Dose Stopped - Key Patient Information

- Listing of Death (Deaths occurring within 30 days from last infusion of IMP will be flagged.) (non TEAEs will be flagged)

4.11.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Reporting of Deaths, Serious Adverse Events and other significant Adverse Events is described in the above section 4.11.2.

4.11.4 Clinical Laboratory Evaluation

All clinical laboratory test results will be presented and summarized using the International System of Units (SI units; Système International d'Unités). The original lab test units will be converted to SI according to *Young, D.S and Huth, E.J; 1998; SI Units for Clinical Measurement; American College of Physicians; Philadelphia* and *Burtis, C.A, Ashwood, E.R and Bruns, D.E; 2008; Fundamentals of Clinical Chemistry; Saunders Elsevier; Missouri* [Laboratory test converted to SI will be stored in SDTM LB domain as LBSTRESU and LBSTRESC]. Additionally, clinical laboratory test results will be converted in Conventional Units, and store in SDTM SUPPLB domain.

All clinical laboratory test results will be graded per NCI CTCAE v4.03 if applicable, as well as high (higher than the normal range), normal (in the normal range) and low (lower than normal range).

Descriptive statistics (n, mean, standard deviation, median, and range) of the lab parameters and changes from baseline will be presented by regimen and dose group for biochemistry, hematology, and coagulation. Such descriptive statistics will be presented at Baseline and at End of Study, as well, Worst Result post Baseline (i.e. Maximum and Minimum post Baseline including results from unscheduled assessments) will be presented as well.

Shift in biochemistry, hematology, and coagulation result CTCAE grading from baseline will be tabulated at the end of treatment, as well as from baseline to the maximal grade during the study (maximal grade will also include results from unscheduled and repeated assessments).

All clinical laboratory test results will be listed in the original, SI, and Conventional units, for biochemistry, hematology, coagulation, and urinalysis.

Individual patient biochemistry, hematology, and coagulation parameters during the trial can be presented graphically using longitudinal spaghetti plots. Specific lab parameters to be plotted will be decided by Symphogen from clinical meaning perspective after examination of corresponding listings.

Biochemistry, hematology, and coagulation parameters will be presented using box plots by visits and tumor type.

Results from the pregnancy tests will be listed.

4.11.5 Electrocardiogram

ECG parameter data will be listed by part dose group, time point, and patient.

Normal, abnormal, or abnormal clinically significant ECG will be summarized by regimen, dose at Baseline, EOT and Worst Post Baseline; as well, a shift table from baseline to EOT and Worst Post Baseline will be summarized by cohort. Number and percentage of patients with end of treatment and maximum postdose QTcF values of <=450, >450 ms and <=480, >480 ms and <=500, and >500 ms, and maximal change from baseline values of <=30, >30 <=60ms, and >60 ms will be summarized by part and dose group (highest QTcF Prolongations measurement will also include results from unscheduled assessments). Above categories of QTcF are based on ICH E14**[2]**.

4.11.6 Echocardiogram (ECHO) or Multi-Gated (MUGA) Scan

ECHO/MUGA data will be listed.

4.11.7 Vital Signs and Body Measurements

Data for vital signs (body weight, blood pressure, heart rate, temperature) will be listed by part, dose group, patient, at Baseline and EOT.

Descriptive summary statistics (for observed values and changes from baseline) for vital sign parameters (blood pressure and heart rate) will be provided for Baseline, EOT and Worst Result post Baseline (i.e. Maximum and Minimum post Baseline including results from unscheduled assessments) by regimen and dose group.

4.11.8 Physical Examination

All abnormal findings from the physical exam will be listed.

A shift table from baseline to EOT and worst from baseline of normal and abnormal findings in physical examination by regimen and cohort will be produced.

4.11.9 Eastern Cooperative of Oncology Group (ECOG) Performance Status (PS)

ECOG performance status will be listed and summarized by shift table from baseline to EOT and worst from baseline.

4.11.10 Safety Monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

A safety monitoring committee (SMC) was be established and included Investigator(s), Medical Monitor(s) and Sponsor's medical representatives. The SMC reviewed clinical and laboratory safety data regularly throughout the trial and will select the RP2D and regimen to be used in Part 2 based on safety data, as well as available PK and target engagement results. Additionally, the annual Development Safety Update Report (DSUR) was submitted by Symphogen or designee to all appropriate HAs and central IRBs/ECs as per ICH Guidelines. Submission of the DSUR to local IRBs/ECs has been handled as per local regulations and/or requests.

4.12 Other Analyses

No other analyses.

4.13 Determination of Sample Size

No formal testing of hypotheses has been planned in this study. Therefore, no formal sample size calculations were performed.

4.14 Changes in the Conduct of the Study or Planned Analysis

The trial has been stopped during Part 1, no patient is enrolled in Part 2. Part 2 of the trial did not take place.

- Objectives for Part 2 are omitted. Per protocol, the concentration of total Pan-HER (the sum of the serum concentration for all six mAbs) was planned to be used for the PK analysis. However, in an exploratory analysis, the PK of the six mAbs was shown not to be similar, and hence using the sum of concentrations is not justified. Hence, the PK of each mAb is reported;
- Overall Survival was planned as one of the Protocol Endpoints, this analysis will not be performed: patients in this study are not followed up to death so that OS would resulted in a truncated biased estimate;
- Time to documented PD, death, patient withdrawal or end of trial participation, whichever comes first was initially planned in the Protocol Endpoints. Actually, based on FDA guideline as of December 2018 **[3]**, TTP is mentioned as a possible endpoint for oncological studies, '*TTP is defined as the time from randomization until objective tumor progression; TTP does not include deaths.*'. TTP will be used an endpoint in this study instead of the planned time to documented PD, death, patient withdrawal or end of trial participation.
- Duration of SD was initially planned in the Protocol Endpoints, anyway this endpoint is overlapping with TTP being derived in a very similar way; thus, this endpoint will not be part of the data analysis.
- DCR analysis was not included as part of study endpoints in the Protocol, such analysis has been added in this SAP.

Given the early interruption of the trial, Symphogen decided to proceed with an abbreviated Clinical Study Report; from list of Tables, Figures and Listings reported in below section 6, only those flagged with asterisk (*) will be produced for the abbreviated CSR.

5 REFERENCES

[1] E.A. Eisenhauer et Al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). EUROPEAN JOURNAL OF CANCER2009; 45;228-247.

[2] ICH HARMONISED TRIPARTITE GUIDELINE; THE CLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS; E14.

[3] Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, December 2018, U.S. Department of Health and Human Services Food and Drug Administration Oncology Center of Excellence.

[4] SAS® Version 9.3. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

6 TABLES, FIGURES AND LISTINGS

All the Tables, Figures and Listings with asterisk will be included in the CSR.

Table 14.1.1 Patient Enrollment (All Consented Patients) *

Table 14.1.2 Patient Disposition by Treatment Schedule and Dose Group (Full Analysis Set) *

Table 14.1.3 Patient Demographics and Baseline Characteristics (Full Analysis Set) *

Table 14.1.4 Cancer Baseline Characteristics (Full Analysis Set)

Table 14.1.5 Prior Cancer Therapies (Full Analysis Set)

Table 14.2.1.1 Serum Concentration of the six monoclonal antibodies in Pan-HER for single and repeated dose PK profiles (Full Analysis Set) *

Table 14.2.1.2 Peak and Trough Serum Concentration of the six monoclonal antibodies in Pan-HER by Study Day (Full Analysis Set) *

Table 14.2.2 Serum PK Parameters for the six monoclonal antibodies in Pan-HER (Full Analysis Set) *

Table 14.2.3.1 Biomarkers from Skin Biopsy (Full Analysis Set) *

Table 14.2.3.2 Biomarkers from Tumor Biopsy (Full Analysis Set) *

Table 14.2.4.1 Best Overall Response Objective Response and Disease Control Rate (Full Analysis Set) *

Table 14.2.4.2 Time to Progression (Full Analysis Set) *

Table 14.2.4.3 Maximal Reduction in Sum of Diameters of Target Lesion from Baseline (Full Analysis Set)

Table 14.2.4.4 Maximal Reduction in Sum of Diameters of Target Lesion from Baseline by Primary Tumor Type (Full Analysis Set)

Table 14.2.4.5 Number of Treatment Cycles (Full Analysis Set) *

Table 14.2.4.6 Treatment Duration and Dose Intensity (Full Analysis Set) *

Table 14.2.4.7 Dose Reduction, Interruption, and Delay (Full Analysis Set) *

Table 14.2.4.8 Dose-Limiting Toxicity (DLT Set) *

Table 14.3.1.1 Overall Summary of TEAEs (Full Analysis Set) *

Table 14.3.1.2 TEAEs by SOC and PT (Full Analysis Set) *

Table 14.3.1.3 Related TEAEs by SOC and PT (Full Analysis Set) *

Table 14.3.1.4 TEAEs by SOC and PT and Worst CTCAE Grade (Full Analysis Set) *

Table 14.3.1.5 Related TEAEs by SOC and PT and Worst CTCAE Grade (Full Analysis Set) *

Table 14.3.1.6 Serious TEAEs by SOC and PT (Full Analysis Set) *

Table 14.3.1.7 Related Serious TEAEs by SOC and PT (Full Analysis Set) *

Table 14.3.1.8 TEAEs Leading to Permanent Discontinuation of IMP by SOC and PT (Full Analysis Set) *

Table 14.3.1.9 Related TEAEs Leading to Permanent Discontinuation of IMP by SOC and PT (Full Analysis Set) *

Listing 14.3.2.1 Serious Adverse Events - Key Patient Information (Full Analysis Set) *

Listing 14.3.2.2 Adverse Events with Outcome of Death - Key Patient Information Full Analysis Set *

Listing 14.3.2.3 Adverse Events Leading to Permanent Discontinuation of Investigational Product - Key Patient Information Full Analysis Set *

Listing 14.3.2.4 Adverse Events Leading to Dose Reduction - Key Patient Information Full Analysis Set *

Listing 14.3.2.5 Adverse Events Leading to Infusion Interruption or Stop - Key Patient Information Full Analysis Set *

Listing 14.3.2.6 Listing of Death- Key Patient Information (Full Analysis Set) *

Listing 14.3.4.1 Abnormal Hematology Values *

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7 APPENDICES

7.1 Schedule of Assessments Q1W dosing

Pre-Treatment Period		Treatment Period[1]														Post-Treatment Period[2]	
	Screening	Cycle 1					Cycle 2, 4, 6 etc.					Cycle 3, 5, 7 etc.				EOT	1M FUP
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D3	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D8 (±2)	D15 (±2)	D22 (±2)	End of Cycle	D1 (±2)	D8 (±2)	D15 (±2)	D22 (±2)	≤ 10 d from the decision of trial treatment withdrawal	1 month after last dose of trial treatment (30±7d)
Informed Consent[3]	X																
Baseline Characteristics[4]/ Eligibility	X	X															
Safety Assessments																	
Medication/Procedure Survey	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
(S)AE Survey and Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT Evaluation[5] **Part 1 only**		X	X	X	X	X	C2 only										
Vital Signs and Body Measurements	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X
ECOG PS[6]	X	X[6]					X					X				X	X
Physical Examination[7]	X	X[7]					X					X				X	X
ECG[8]	X															X	
ECHO or MUGA scan[9]	X															X	
Safety blood samples[8,9]	X	X[9]	X	X	X	X	X		X			X		X		X	X
Urinalysis[8,9]	X	X[9]			X		X					X				X	X
Pregnancy Test	X															X	
Complement Panel[10] **Part 2 only**		X															
Disease Assessments																	
Disease Status Evaluation by CT/ MRI[11,12]	X										X					X[12]	X[12]
Tumor Marker Evaluation, if applicable[13]	X										X					X	X
Archival Tumor Tissue[14] **Part 1: Submit if available (optional)**	X																
Additional Assessments																	
PK Samples[15]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
ADA Sample		X					C2 only					X				X	X
Skin Biopsy[16]	X			X	X												
Tumor Biopsy[17] **Part 1: Optional** **Part 2: Required**	X										C2 only						
Biomarker Blood Sample[18]	X										C2 only					X	
Trial Treatment																	
Pan-HER Premedication[19]		X		X	X	X	X	X	X	X		X	X	X	X		
Pan-HER Infusion		X		X	X	X	X	X	X	X		X	X	X	X		
Post-Infusion Monitoring		X		X	X	X	X	X	X	X		X	X	X	X		

Abbreviations (in alphabetical order): ADA, anti-drug antibody; C, Cycle; CT, computed tomography; D/d, day(s); DLT, dose-limiting toxicity; EOT, End of Treatment; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition; 1M FUP, 1-Month Follow-up; PK, pharmacokinetic; (S)AE, (serious) adverse event

1) The treatment period continues until the patient is withdrawn from Pan-HER.
2) **Applicable for Part 2 only**: After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.
3) Informed consent may be obtained outside the 14-day screening period prior to C1/D1, but is recommended to be obtained no earlier than 4 weeks prior to the planned C1/D1.
4) Screening assessments/baseline characteristics include demographics, medical history, tumor histology, mutation status, extent of disease, prior anti-cancer treatment etc.
5) DLT evaluation. **Applicable for Part 1 only**: DLTs are reported during Cycle 1 with final assessment 7 days after the last dose of Cycle 1 or prior to dosing on C2/D1.
6) Does not need to be performed on C1/D1 if performed during screening ≤ 7 days from C1/D1.
7) In addition to the scheduled timepoints, an ECG should be performed in the event of cardiac symptoms.
8) In addition to the scheduled timepoints, an ECHO/MUGA should be performed in the event of cardiac symptoms.
9) Local laboratory results must be available and assessed prior to each Pan-HER infusion for all infusions during Cycle 1, and for every second infusion from Cycle 2 onwards. Refer to **Section 8.2.9** for further details
10) Complement sampling, **Applicable for Part 2 only**, will be done C1/D1and in the event of an IRR. Refer to **Section 8.2.10** for further details.
11) CT or MRI imaging schedule and conditions, applying to all cohorts:
    - A CT/MRI performed within 28 days prior to C1/D1 can be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the clinical trial protocol requirements.
    - The first CT/MRI assessment for response is done at the end of Cycle 2 and thereafter repeated at the end of every second cycle (in the week prior to Day 1 of the next cycle).
    - In the event of suspected PD, a CT/MRI is to be performed as soon as possible.
    - In the event of CR/PR, a confirmatory CT/MRI is to be performed 28 (+7) days after the first assessment of CR/PR.
12) A CT/MRI at EOT should only be performed if the previous CT/MRI has been performed >3 weeks before; a CT/MRI scan at 1M FUP should only be performed if no CT/MRI documents disease progression before or at EOT.
13) Tumor marker evaluation to include tumor markers that are part of the trial site standard practices as indicated by tumor type, if applicable.
14) Archival tumor tissue, **applicable for patients in Part 1 only if tissue is available**: To be assessed locally, preferably by immunohistochemistry (IHC). Does not need to be repeated if EGFR and HER2 status have been assessed previously and the pathology report is available to document findings.
15) Extended PK sampling for PK profiling will be done starting C1/D1 and C1/D22. Refer to **Table 11** for further details.
16) Skin biopsy: All patients enrolled will undergo skin biopsies. Sample is to be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated Cycle 1/Day 8 (prior to dosing) and Cycle 1/Day 15 (prior to dosing).
17) Tumor biopsy, **Optional for patients in Part 1. Required for all patients in Part 2**: To be assessed centrally. Tumor biopsy is to be performed after patient eligibility has been confirmed. Archival tissue may be accepted at screening if suitable for central analysis. Sampling is repeated at the end of Cycle 2 or upon PD, whichever occurs first. Refer to **Section 8.7** for further details.
18) Biomarker blood sample: To be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated at the end of Cycle 2 or upon PD, whichever occurs first, and at EOT.
19) Premedication. For Part 1, premedication is mandatory prior to each dose of Pan-HER. For Part 2, premedication is mandatory prior to each dose of Pan-HER during Cycle 1. In Part 2, premedication may be withdrawn after Cycle 2 on a patient-by-patient basis, if the patient is without evidence of IRRs. Refer to **Section 7.2.1** for details.

7.2 Schedule of Assessments Q2W dosing

Pre-Treatment Period		Treatment Period[1]										Post-Treatment Period[2]	
	Screening	Cycle 1					Cycle 2, 4, 6 etc.			Cycle 3, 5, 7 etc.		EOT	1M FUP
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D3	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	End of Cycle	D1 (±2)	D15 (±2)	≤ 10 d from the decision of trial treatment withdrawal	1 month after last dose of trial treatment (30+7d)
Informed Consent[3]	X												
Baseline Characteristics[4]/Eligibility	X	X											
Safety Assessments													
Medication/Procedure Survey	X	X	X	X	X	X	X	X	X	X	X	X	X
(S)AE Survey and Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT Evaluation[5] **Part 1 only**		X	X	X	X	X	C2 only						
Vital Signs and Body Measurements	X	X		X	X	X	X	X		X	X	X	X
ECOG PS[6]	X	X[6]					X			X		X	X
Physical Examination[7]	X	X[6]					X			X		X	X
ECG[7]	X											X	
ECHO or MUGA scan[8]	X											X	
Safety blood samples[6,9]	X	X[6]	X	X	X	X	X	X		X	X	X	X
Urinalysis[6,9]	X	X[6]			X		X			X		X	X
Pregnancy Test	X											X	
Complement Panel[10] **Part 2 only**		X											
Disease Assessments													
Disease Status Evaluation by CT/ MRI[11,12]	X								X			X[12]	X[12]
Tumor Marker Evaluation, if applicable[13]	X								X			X	X
Archival Tumor Tissue[14] **Part 1: Submit if available (optional)**	X												
Additional Assessments													
PK Samples[15]		X	X	X	X	X	X	X		X	X	X	X
ADA Sample		X					C2 only			X		X	X
Skin Biopsy[16]	X			X	X								
Tumor Biopsy[17] **Part 1: Optional / Part 2: Required**	X								C2 only				
Biomarker Blood Sample[18]	X								C2 only			X	
Trial Treatment													
Pan-HER Premedication[19]		X			X		X	X		X	X		
Pan-HER Infusion		X			X		X	X		X	X		
Post-Infusion Monitoring		X			X		X	X		X	X		

Abbreviations (in alphabetical order): ADA, anti-drug antibody; C, Cycle; CT, computed tomography; D/d, day(s); DLT, dose-limiting toxicity; EOT, End of Treatment Visit; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition; 1M FUP, 1-Month Follow-up Visit; PK, pharmacokinetic; (S)AE, (serious) adverse event

1) The treatment period continues until the patient is withdrawn from Pan-HER
2) **Applicable for Part 2 only**: After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation
3) Informed consent may be obtained outside the 14-day screening period prior to C1/D1, but is recommended to be obtained no earlier than 4 weeks prior to the planned C1/D1
4) Screening assessments/baseline characteristics include demographics, medical history, tumor histology, mutation status, extent of disease, prior anti-cancer treatment etc.
5) DLT evaluation. **Applicable for Part 1 only**: DLTs are reported during Cycle 1 with final assessment 7 days after the last dose of Cycle 1 or prior to dosing on C2/D1
6) Does not need to be performed on C1/D1 if performed during screening ≤ 7 days from C1/D1
7) In addition to the scheduled timepoints, an ECG should be performed in the event of cardiac symptoms
8) In addition to the scheduled timepoints, an ECHO/MUGA should be performed in the event of cardiac symptoms
9) Local laboratory results must be available and assessed prior to each Pan-HER infusion for all infusions during Cycle 1, and for every second infusion from Cycle 2 onwards. Refer to **Section 8.2.9** for further details
10) Complement sampling. **Applicable for Part 2 only**, will be done C1/D1and in the event of an IRR. Refer to **Section 8.2.10** for further details
11) CT or MRI imaging schedule and conditions, applying to all cohorts:
    - A CT/MRI performed within 28 days prior to C1/D1 can be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the clinical trial protocol requirements
    - The first CT/MRI assessment for response is done at the end of Cycle 2 and thereafter repeated at the end of every second cycle (in the week prior to Day 1 of the next cycle)
    - In the event of suspected PD, a CT/MRI is to be performed as soon as possible
    - In the event of CR/PR, a confirmatory CT/MRI is to be performed 28 (+7) days after the first assessment of CR/PR
12) A CT/MRI at EOT should only be performed if the previous CT/MRI has been performed >3 weeks before; a CT/MRI scan at 1M FUP should only be performed if no CT/MRI documents disease progression before or at EOT
13) Tumor marker evaluation to include tumor markers that are part of the trial site standard practices as indicated by tumor type, if applicable
14) Archival tumor tissue, **applicable for patients in Part 1 only if tissue is available**: To be assessed locally, preferably by immunohistochemistry (IHC). Does not need to be repeated if EGFR and HER2 status have been assessed previously and the pathology report is available to document findings
15) Extended PK sampling for PK profiling will be done starting C1/D1 and C2/D1. Refer to **Table 11** for further details
16) Skin biopsy: All patients enrolled will undergo skin biopsies. Sample is to be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated Cycle 1/Day 8 and Cycle 1/Day 15 (prior to dosing)
17) Tumor biopsy, **Optional for patients in Part 1. Required for all patients in Part 2**: To be assessed centrally. Tumor biopsy is to be performed after patient eligibility has been confirmed. Archival tissue may be accepted at screening if suitable for central analysis. Sampling is repeated at the end of Cycle 2 or upon PD, whichever occurs first. Refer to **Section 8.7** for further details
18) Biomarker blood sample: To be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated at the end of Cycle 2 or upon PD, whichever occurs first, and at EOT. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, blood sample to be collected first.
19) Premedication: For Part 1, intensive prophylaxis, as defined herein, on a mandatory basis is required to reduce the risk of IRRs and oropharyngeal mucositis. For Part 2, prophylaxis is mandatory during Cycle 1 and Cycle 2. Thereafter, if the patient is without evidence of IRRs or mucositis, the Investigator may choose to withdraw related medications with subsequent dosing. Refer to **Sections 7.2.1** and **7.2.2** for details

7.3 Derivation of CTCAE Grade – Hematological Tests

Tests	Direction	Grade			
		1	2	3	4
Hemoglobin (g/dl, mmol/L or g/L)	↓	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN -100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L;	Life-threatening consequences;
Platelet (/mm3 or /L)	↓	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 -50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Neutrophils (/mm3 or /L)	↓	<LLN - 1500/mm3; <LLN - 1.5 x109 /L	<1500 - 1000/mm3; <1.5 - 1.0 x10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocyte (/mm3 or /L)	↓	<LLN - 800/mm3; <LLN - 0.8 x10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x10e9 /L	<200/mm3; <0.2 x 10e9 /L
Note: 10e9 = 10^9; LLN = Lower Limit of Normal; ULN = Upper Limit of Normal					

7.4 Derivation of CTCAE Grade – Clinical Chemistry Tests

Tests	Direction	Grade			
		1	2	3	4
Sodium (mmol/L)	↓	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Sodium (mmol/L)	↑	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Potassium (mmol/L)	↓	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Potassium (mmol/L)	↑	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>5.5 - 6.0 mmol/L	>7.0 mmol/L
Glucose	↓	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Glucose	↑	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8mmol/L	>500 mg/dL; >27.8 mmol/L
Creatinine	↑	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Bilirubin	↑	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Alkaline phosphatase (AKP)	↑	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST (SGOT)	↑	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT (SGPT)	↑	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Uric Acid	↑	>ULN - 10 mg/dL (0.59 mmol/L)	-	-	>10 mg/dL; >0.59 mmol/L
Calcium	↑	Corrected serum	Corrected serum	Corrected serum	Corrected serum

Tests	Direction	Grade			
		1	2	3	4
		calcium of Hypercalcemia >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1mmol/L; Ionized calcium >1.5 -1.6 mmol/L	calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L	calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L
Calcium	↓	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN -1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L;	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L;
Phosphate	↓	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L
Note: 10e9 = 10^9; **LLN** = Lower Limit of Normal; **ULN** = Upper Limit of Normal					

7.5 Derivation of CTCAE Grade – Coagulation Tests

Tests	Direction	Grade			
		1	2	3	4
Activated partial thromboplastin time prolonged	↑	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-
Fibrinogen decreased	↓	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL

Sym013-01

Symphogen A/S

Sym013-01

An Open-label, Multicenter, Phase 1a/2a Trial Investigating the Safety, Tolerability and Antitumor Activity of Multiple Doses of Sym013 (Pan-HER), a Monoclonal Antibody Mixture Targeting EGFR, HER2 and HER3, in Patients with Advanced Epithelial Malignancies

Statistical Analysis Plan

Symphogen A/S SIGNATURE PAGE

Approved by:

Cliff L. Ding, Ph.D.

April 5, 2019

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