CLINICAL TRIAL PROTOCOL

A Phase 1a/2a Cohort Dose Escalation Trial to Determine the Safety, Tolerance, Maximum Tolerated Dose, and Preliminary Antineoplastic Activity of AVID100, an Anti-Human Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody Linked to the Maytansinoid DM1, in Patients with Advanced or Metastatic Solid Tumors of Epithelial Origin

Product:	AVID100
Protocol Number:	AVID100-01
Short Title:	AVID100 in Advanced Epithelial Carcinomas
Phase:	Phase 1a/2a
IND Number:	IND 125294
CTA Number:	e221762
Version/Date:	**v11.0 / 30 May 2020**
Previous:	v10.0 / 16 Nov 2019 v9.0 / 15 May 2019 v8.0 / 14 Nov 2018 v7.0 / 31 Aug 2018 v6.0 / 19 Jun 2018 v5.0 / 26 Sep 2017 v4.0 / 30 May 2017 v3.0 / 12 May 2017 v2.0 / 15 Mar 2017 v1.2 / 09 Dec 2016 v1.1 / 01 Dec 2016 v1.0 / 27 Oct 2016
Sponsor:	Forbius (Formation Biologics) 701Brazos Street, Suite 930 Austin, Texas 78701 USA

REPORTING SERIOUS AND UNEXPECTED ADVERSE EVENTS

Any death or other serious adverse event (SAE), including any suspected unexpected serious adverse reaction (SUSAR) experienced by the patient from signing of informed consent* until 30 days after receiving the final dose of study drug, or any SAE that occurs after 30 days of receiving the final dose of study drug and is believed to be study drug-related, must be promptly reported (within 24 hours of Investigator awareness).

Unless otherwise instructed, SAE Reports are to be submitted electronically or by telefax to the Sponsor's Safety agent, **ProPharma Group**. Where indicated, additional communications may be made by telephone, telefax, or email; however, it is important that the primary route of transmission of SAE data be **ProPharma Group**. This will enable all relevant parties to be made aware of the event in a timely fashion.

Access information and training will be provided to participating study centers prior to or at the time of study initiation.

Please see the Study Operations Manual (or other similar document) for further information on SAE Report submissions.

SAE Submission (Safety Designee):	**ProPharma Group** Fax: +01 (866) 681-1063 **Email: clinicalsafety@propharmagroup.com**
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Forbius Chief Medical Officer:	Paul I. Nadler, MD Email: pnadler@nadlerpharma.com

*Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they are will not be participating in this trial.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Expanded Term
1M FUP	1 month follow-up
Ab	antibody
ACSL	access-controlled secure location
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADCC	antibody dependent cellular cytotoxicity
AE	adverse event
Akt	protein kinase B (PKB)
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
AUC_{last}	area under the plasma concentration curve at the last measurable concentration
AVID100	anti-human EGFR mAb linked to the maytansinoid DM1
BC	breast cancer
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
BID	2 times per day
BSA	body surface area
BUN	blood urea nitrogen
C	Centigrade, Celsius, Cycle
Ca	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIS	carcinoma *in situ*
CK	creatine kinase
Cl	chloride
Cl	clearance
C_{max}	maximum (peak) concentration
C_{min}	minimum (trough) concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRC	colorectal carcinoma
CrCl	creatinine clearance
CRF	case report form
CS	clinically significant
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events (NCI, Version 5.0)
ctDNA	circulating tumor deoxyribonucleic acid
CV	curriculum vitae
CXR	chest X-ray
D, d	day
DCR	disease control rate

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Expanded Term
DEHP	di(2-ethylhexyl)phthalate
dL	deciliter
DL_{CO}	diffusion capacity of carbon monoxide
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
EC	Ethics Committee
ECD	extracellular domain
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EGFRi	epidermal growth factor inhibitors
*EGFR*vIII	*EGFR* mutant type III variant
EMT	epithelial mesenchymal transition
EOI	end of infusion
EOT	end of treatment
ER	estrogen receptor
F	Fahrenheit
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
FVC	forced vital capacity
FWA	Federal-Wide Assurance
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practices
H, h	hour
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HL	Hodgkin's lymphoma
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HNSTD	highest non-severely toxic dose
hpf	high power field
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	Investigational New Drug
INR	international normalized ratio
IP	intraperitoneal
IRB	Institutional Review Board
IRR	infusion-related reaction
IU	international units

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Expanded Term
IV, i.v.	intravenous
K	potassium
kg	kilogram
KO	knock out
KRAS	Kirsten ras oncogene homolog
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
M, m	month, molar, meter
mAb	monoclonal antibody
MAB100	unconjugated monoclonal anti-EGFR antibody precursor of AVID100
MAD	maximum administered dose
MAPK	mitogen activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
mg	milligram
MI	myocardial infarction
min	minute
mL	milliliter
mm	millimeter
MMAE	monomethyl aurostatin E
MRI	magnetic resonance imaging
msec	millisecond
MTD	maximum tolerated dose
mTNBC	metastatic triple-negative breast cancer
MUGA	multiple gated acquisition scan
n	nano
Na	sodium
NaCl	sodium chloride
NCS	not clinically significant
ng	nanogram
NGS	next generation sequencing
nM	nanomolar
NS	normal saline
NSCLC	non-small cell lung carcinoma
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over the counter
P	phosphorus
PA	posterior to anterior
PBS	phosphate buffered saline
PC	pancreatic carcinoma
PD	pharmacodynamic
PD	progressive disease
PE	physical examination
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression free survival
PFT	pulmonary function test
PK	pharmacokinetic
PO, p.o.	per os

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Expanded Term
PR	partial response
PR	progesterone receptor
PS	performance status
PSA	prostate specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	once every 3 weeks
QT	ECG interval between onset of QRS complex to end of the T wave (QT interval)
QTc	QT interval corrected for heart rate
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
RTK	receptor tyrosine kinases
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SAR	suspected adverse reaction
SC	subcutaneous
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SOI	start of infusion
SOP	standard operating procedure
Sq-NSCLC	squamous histology non-small cell lung carcinoma
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TBD	to be determined
TK	toxicokinetic
TKI	tyrosine kinase inhibitor
T_{max}	time to peak plasma concentration
TNBC	triple negative breast cancer
TSC	tumoristatic concentration
TTP	time to progression
ULN	upper limit of normal
µg	micogram
µM	micromolar
V_d	volume of distribution
Vol	volume
VS	vital signs
W, w	week
WBC	white blood cell
WOCBP	women of child-bearing potential
WNL	within normal limits
Y, y	year

1. TRIAL SYNOPSIS

PROTOCOL	
Title	A Phase 1a/2a Cohort Dose Escalation Trial to Determine the Safety, Tolerance, Maximum Tolerated Dose, and Preliminary Antineoplastic Activity of AVID100, an Anti-Human Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody Linked to the Maytansinoid DM1, in Patients with Advanced or Metastatic Solid Tumors of Epithelial Origin
Number	AVID100-01
Date	30 May 2020
Version	10.0
Development Phase	1a/2a
Compound Code	TBD
IP Code	AVID100
IND Number	IND125294
Investigational Drug Description	AVID100, an anti-human EGFR monoclonal antibody linked to the maytansinoid DM1(emtansine)
OBJECTIVES	
Phase 1a **(dose escalation portion of study)**	**Primary** To determine the safety and tolerability, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D)** of sequential escalating doses of AVID100 when administered once every 3 weeks (Q3W) by 2-hour* intravenous (IV) infusions to patient cohorts with locally advanced/unresectable or metastatic solid tumor malignancies of epithelial origin **Protocol v5.0: Extended from 1 hour to 1.5 hours due to Grade 3 IRR observed in Cohort 3 (80 mg/m^2); effective 20Jul2017 and documented in a study Note to File dated 21Jul2017 (see **Section 2.3.2.1**; AVID100-01: Clinical Experience)* **Protocol v6.0: Extended from 1.5 hours to 2 hours due to Grade 2 IRRs observed in Cohort 4(120 mg/m2); effective 21Dec2017 and documented in a study Note to File dated 28Dec2017 (see **Section 2.3.2.1**; AVID100-01: Clinical Experience)* ***Protocol v6.0: The MTD and RP2D has been determined to be 220 mg/m^2* **Secondary** • Characterization of the pharmacokinetic (PK) profile of total antibody (AVID100 plus MAB100), AVID100, and DM1 • Evaluation of the preliminary antineoplastic effects of AVID100 including: o Evidence of objective response (OR) or stable disease (SD)* o Duration of OR or SD* o Time to progression (TTP) of disease* *As assessed by modified Response Evaluation Criteria in Solid Tumors (RECIST, v1.1) **Exploratory** Tests to assess potential biomarkers and response predictors will be conducted and may include: • Evaluation by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) *(or similar assay)* of tumor EGFR-expression in archival, formalin-fixed, paraffin-embedded (FFPE) samples obtained from a previous diagnostic or surgical procedure *(if available)*
Phase 2a **(enrollment of additional patient cohorts at the RP2D)**	**Primary** To further evaluate the safety, tolerability, and preliminary antineoplastic effect of AVID100 when administered at the RP2D in 3 expansion cohorts of patients with locally advanced/unresectable or metastatic solid tumor malignancies of epithelial origin, and expressing the EGFR The tumor types to be evaluated in these expansion cohorts are metastatic triple negative breast cancer (mTNBC), squamous cell carcinoma of the head and neck (SCCHN), and squamous histology non-small cell lung carcinoma (Sq-NSCLC). Note: To be eligible for study enrollment, analytical results documenting EGFR expression positivity by IHC must be documented by a central laboratory in archival FFPE samples obtained from a

	previous diagnostic or surgical procedure. In the mTNBC cohort results must be 3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells. In the SCCHN and Sq-NSCLC cohorts results must be 3+ intensity in ≥ 50% of tumor cells. If tissue is unavailable, patients must have primary or metastatic tumor sites(s) considered safely accessible for biopsy, and must be willing to undergo tumor biopsy. Sufficient FFPE tumor tissue from either a prior procedure or a recent biopsy must also be available for submission to a central laboratory for other study-related evaluations as planned per protocol. **Secondary** Further characterization of the PK profile of total antibody (AVID100 plus MAB100), AVID100, and DM1 **Exploratory** Tests to assess potential biomarkers and response predictors will be conducted and may include but are not limited to: • Evaluation by FISH *(or similar assay)* of tumor EGFR-expression and other potential biomarkers in archival, FFPE samples obtained from a either a previous diagnostic or surgical procedure or a recent biopsy *(required at Screening, optional thereafter)* • Evaluation of circulating tumor DNA (ctDNA) for *EGFR* extracellular domain (*EGFR*-ECD) mutation status and *EGFR* mutant type III variant (*EGFR*vIII) deletions (SCCHN only), as well as evaluation of other potential biomarkers of interest *(required for all indications)*
PATIENT SELECTION	
Investigational Sites	**Phase 1a**: Single center planned (up to 2 centers may participate based on accrual) **Phase 2a**: Approximately 6-12 participating centers; number of sites TBD based on tumor type selection and anticipated accrual
Number of Patients	Approximately 90 patients to be entered during Phase 1a and Phase 2a **Phase 1a:** Approximately 30 patients in escalating dose cohorts • Minimum of 1 to 3 patients per dose cohort; approximately 4 dose cohorts to be evaluated to establish the MTD and/or RP2D • Expansion of any cohort to 6 patients in the event of a Cycle 1 DLT in any of the initial 1 to 3 patients • Minimum of 6 patients to be treated at the MTD (or maximum administered dose [MAD]); expansion of this cohort (or any other) up to 12 patients may be considered to further evaluate tolerability **Phase 2a:** Approximately 60 patients in 3 expansion cohorts (approximately 30 patients in the mTNBC cohort and 15 patients each in the SCCHN and Sq-NSCLC cohorts); more patients may be entered if fewer than 30 patients are required to establish the RP2D in Phase 1a There is potential for entry of additional patients in the Phase 1a portion of the study to: • Assure sufficient evaluable patients per cohort by adding an additional patient to a cohort • Evaluate > 4 dose cohorts should this be necessary to identify the RP2D • Expand a lower dose cohort(s) if an initially identified MTD is expanded and found to exceed tolerability either with single or repeated cycles of therapy • Evaluate a previously unexamined intermediate dose, if indicated There is potential for additional expansion cohorts in the Phase 2a portion of the trial (by amendment only)
Eligibility	**Patients to be Included** *(patients must meet all of the following criteria)* 1. Male or female patients, ≥ 18 years 2. Patients with a documented (histologically- or cytologically-proven) solid tumor epithelial carcinoma that is locally advanced or metastatic 3. Patients with a malignancy that is either refractory to standard therapy, or for which no standard therapy is available 4. Patients with a malignancy that is currently not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor 5. Phase 1a Dose-Escalation Cohorts: Patients with measurable or non-measurable disease according to RECIST, v1.1 criteria. To include patients reasonably likely to express EGFR.

6. Phase 2a Expansion Cohorts ONLY: Patients with mTNBC, SCCHN, or Sq-NSCLC and with:
   - Measurable disease per RECIST, v1.1 criteria
   - An EGFR-expressing solid tumor documented by central laboratory assessment to be positive by immunohistochemistry (IHC)* as follows:
     - mTNBC Cohort**: 3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells (~15 patients each)
     - SCCHN Cohort: 3+ intensity in ≥ 50% of tumor cells (~15 patients)
     - Sq-NSCLC Cohort: 3+ intensity in ≥ 50% of tumor cells (~15 patients)

     *** Recruitment in mTNBC cohort subgroups will be halted after enrollment of 15 patients in order to assess activity.*
   - EGFR assessment to be made using:
     - An archival FFPE tumor specimen (as recent as possible), or
     - Surgical or biopsy specimens if archival tumor tissue results are not available
   - Availability of FFPE tumor tissue from either a prior procedure or a recent biopsy for submission to a central laboratory for other study-related evaluations

   **DAKO EGFRpharmDX™ IHC kit system technology to be utilized. For this study, EGFR-positive staining is defined as 3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells for mTNBC; or 3+ intensity in ≥ 50% of tumor cells for SSCHN and Sq-NSCLC, whether it is complete or incomplete circumferential staining.*
7. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status as follows, and an anticipated life expectancy of ≥ 3 months
   - Phase 1a Dose-Escalation Cohort Patients: 0, 1, or 2
   - Phase 2a Expansion Cohort Patients: 0 or 1
8. Women of childbearing potential (WOCBP) and fertile men with a partner of childbearing potential agreeing to use a highly effective method of contraception during the study and for 3 months after the last dose of study drug; male patients must also agree to refrain from sperm donation during this period.
9. Patients with the ability to understand and give written informed consent for participation in this trial, including all evaluations and procedures as specified by this protocol. ***Informed consent must be obtained prior to patient screening, and before any evaluations or procedures specifically related to this study are performed.***

Patients to be Excluded *(patients must not meet any of the following criteria)*

1. Women who are pregnant or intending to become pregnant during or within 3 months after the last dose of study drug; women who are breastfeeding; WOCBP and fertile men with a WOCBP partner not using and not willing to use a highly effective method of contraception
2. Patients with known central nervous system (CNS) or leptomeningeal metastases, or spinal cord compression not controlled by prior surgery or radiotherapy, or patients with symptoms suggesting CNS involvement for which treatment is required
3. Patients with a malignancy other than that of epithelial origin
4. Phase 2a Expansion Cohorts ONLY: Patients with an active second malignancy or history of another malignancy within the last 2 years with the exception of:
   - Treated non-melanoma skin cancers
   - Treated carcinoma *in situ*
   - Controlled, superficial carcinoma of the bladder
   - T1a carcinoma of the prostate comprising < 5% of resected tissue and prostate specific antigen (PSA) within normal limits (WNL) since resection
5. Patients with any of the following hematologic abnormalities at baseline:
   - Hemoglobin < 9.0 g/dL
   - Absolute neutrophil count (ANC) < 1,500 per mm^3
   - Platelet count < 100,000 per mm^3
6. Patients with any of the following serum chemistry abnormalities at baseline:
   - Total bilirubin ≥ 1.5 × the upper limit of normal (ULN) for the institution
   - AST or ALT ≥ 3 × the ULN for the institution (≥ 5× ULN if due to hepatic involvement by tumor)
   - Serum creatinine ≥ 1.5 × ULN
7. Patients with any of the following coagulation parameter abnormalities at baseline as

	determined by the Investigator: • PT (or INR) ≥ 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated) • PTT (or aPTT) ≥ 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated) 8. Patients with: • Active thrombosis, or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 4 weeks prior to first study drug administration; • Active uncontrolled bleeding or a known bleeding diathesis 9. Patients with a significant cardiovascular disease or condition, including: • Congestive heart failure (CHF) currently requiring therapy • Need for anti-arrhythmic medical therapy for a ventricular arrhythmia or other uncontrolled arrhythmia (patients with controlled atrial fibrillation (heart rate [HR] < 90) for > 30 days prior to study entry are eligible) • Severe conduction disturbances (e.g., 3rd degree heart block) • Angina pectoris requiring therapy • Left ventricular ejection fraction (LVEF) known to be below the lower limit of normal (LLN) for the center, or < 50% by MUGA or echocardiogram if no LLN is defined by the site • QTc interval ≥ 480 msec • Uncontrolled hypertension (per the Investigator's discretion) • Class III or IV cardiovascular disease according to the New York Heart Association's (NYHA) Functional Criteria • History of acute coronary syndromes (including myocardial infarction [MI] and unstable angina), coronary angioplasty, stenting, or bypass grafting within 6 months prior to first study drug administration 10. Patients with a significant ocular disease or condition, including: • History of ocular inflammatory disease • History of disorders of the cornea, including current evidence of keratitis 11. Patients with a significant pulmonary disease or condition, including: • Significant symptomatic chronic obstructive pulmonary disease (COPD), as assessed by the Investigator • History or any current evidence on imaging studies prior to or during study of interstitial lung disease (ILD), pulmonary fibrosis • History of pulmonary inflammatory disease, pneumonitis, acute respiratory distress syndrome (ARDS) 12. Patients with significant gastrointestinal (GI) abnormalities, including but not limited to: • History of inflammatory bowel disease • Diarrhea ≥ Grade 2 within 2 weeks prior to first study drug administration 13. Patients with non-healing wounds on any part of the body 14. Patients with a known or suspected hypersensitivity to any of the excipients of formulated AVID100 15. Patients with any other serious/active/uncontrolled infection, any infection requiring parenteral antibiotics, or unexplained fever >38º C within 2 weeks prior to first study drug administration 16. Patients with unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, peripheral neuropathy, decreased hemoglobin, hypomagnesemia, lymphopenia, and/or end-organ failure being adequately managed by hormone replacement therapy 17. Patients with inadequate recovery from any prior surgical procedure, or patients having undergone any major surgical procedure within 4 weeks prior to first study drug administration 18. Patients with any other serious, life-threatening, or unstable pre-existing medical condition (aside from the underlying malignancy) including significant organ system dysfunction, or clinically significant laboratory abnormality (ies), which, in the opinion of the Investigator, would either compromise the patient's safety or interfere with obtaining informed consent, compliance with study procedures, or evaluation of the

	safety of the study drug 19. Patients with a psychiatric disorder or altered mental status that would preclude understanding of the informed consent process and/or completion of the necessary study-related evaluations 20. Patients with the inability or with foreseeable incapacity, in the opinion of the investigator, to comply with the protocol requirements **Drugs and Other Treatments to be Excluded** *(patients must not be receiving any of the following)* 1. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 2 weeks *(See patients to be excluded for criteria on recovery from prior antineoplastic therapy)* 2. Any other investigational treatments during study. This includes participation in any medical device or other therapeutic intervention clinical trials. 3. Radiotherapy against target lesions within 4 weeks prior to first study drug administration and during study 4. Strong inhibitors and/or inducers of cytochrome P450 (CYP) isoenzyme 3A4 within 2 weeks prior to first study drug administration and during study 5. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone or equivalent) within 2 weeks prior to first study drug administration and during study (*exceptions are provided).* 6. Prophylactic use of hematopoietic growth factors within 1 week prior to first study drug administration and during Cycle 1 of study; thereafter-prophylactic use of growth factors is allowed as clinically indicated. Use of growth factors as treatment is permitted at any time after initiation of study drug as clinically indicated. Transfusions are permitted as needed. *Questions regarding patient eligibility must be addressed and resolved by the Investigator in consultation with the Medical Monitor prior to enrollment.*
INVESTIGATIONAL DRUG	
AVID-100	Labeled supplies will be provided. Each single-use glass vial contains study drug: • as a liquid formulation for intravenous (IV) injection in a total volume of 10 mL • at a concentration of 6 mg/mL for a total vial content of 60 mg.
Formulation Excipients	20 mM sodium succinate, 10% w/v trehalose dihydrate, and 0.02% w/v polysorbate 20, pH 5.5
Storage	Refrigerate (2ºC to 8ºC); store in an access-controlled, secure location
Stability	Once diluted for IV administration (in 0.9 % NaCl solution), AVID100 to be administered within 4 hours
EXPERIMENTAL PLAN	
Design Elements	• Uncontrolled, open-label, non-randomized • Enrollment in the order of confirmation of eligibility • Escalating doses of study drug in sequential patient cohorts (Phase 1a) • Cohort expansion at the MTD or R2PD and in other cohorts based on safety (Phase 1a) • Addition of expansion cohorts of defined patient populations (Phase 2a)
Observation Requirements	Patients will be treated and followed on an outpatient basis. • Phase 1a Dose-Escalation Cohorts: Patients will be observed for a minimum of 4 hours following completion of the first administration of study drug (Day 1) and a minimum of 1 hour following completion of subsequent infusions. • Phase 2a Expansion Cohorts: Patients will be observed for a minimum of 2 hours following completion of the first administration of study drug (Day 1), and a minimum of 1 hour following completion of subsequent infusions. At the end of each infusion, the IV line must remain in place for at least 1 hour to allow administration of IV drugs, if necessary.
Study Start Day / Scheduling and Patient Availability	Initial dose of study drug to be administered on Day 1 of Cycle 1
Combination Agent	None

INVESTIGATIONAL DRUG ADMINISTRATION	
Doses to be Administered	**Doses to be Evaluated During Phase 1a** Dose cohorts will be numbered and entered sequentially. The number of cohorts evaluated will be based upon toxicities experienced during Cycle 1. The initial dose of AVID-100 to be evaluated will be **20 mg/m^2/dose (**with the maximum dose to be administered in this trial not to exceed **330 mg/m^2/dose).** An accelerated titration design (1 patient per cohort) will be used for dose-escalation for up to 2 cohorts or until the occurrence of an event that activates a stopping rule. Thereafter, dose-escalation will follow a standard 3+3 design with a target toxicity level of 33.3% or less as determined by DLTs. Doses will be calculated as follows: • **Dose Part A:** Up to 2 cohorts will receive consecutive 100% increases in dose until: o A study drug-associated* ≥ Grade 2 toxicity or accrual to Cohort 3, whichever occurs first (commence Part B) o A study drug-associated* DLT (commence Part C) • **Dose Part B:** cohorts will receive consecutive 50% increases in dose until: o A study drug-associated* DLT (commence Part C) o > 1 patient with a study drug-associated DLT (stop dose escalation) • **Dose Part C:** cohorts will receive consecutive 25% increases in dose until: o > 1 patient with a study drug-associated DLT (stop dose escalation) **study drug-associated: AEs considered possibly related, probably related, or related to study drug* Note: Based on emerging tolerability data the Sponsor may choose to escalate the dose between cohorts at an increment less than the percent increase allowed above in an effort to protect patient safety. **Dose to be Administered During Phase 2a** Patients entered to the Phase 2a portion of this study will receive study drug at the RP2D established during the Phase 1a portion of the study. **The MTD and RP2D has been determined to be 220 mg/m^2** Ongoing safety evaluations will continue during accrual of patients to the Phase 2a expansion cohorts to determine whether any newly identified AEs necessitate modifications to the protocol or discontinuation of accrual to patients within any cohort. **Changes in Dose to be Administered** Patients will continue to be treated with study drug at that same dose level throughout the duration of their time on study, unless dose reduction is necessary due to the occurrence of a DLT or other toxicity warranting dose reduction at the Investigator's discretion. There will be no intra-patient dose-escalation. *Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institution procedures) at visits that require weight measurement.*
Route of Administration	IV infusion via indwelling venous access catheter, utilizing a controlled infusion device
Dose Preparation	Infusion sets made of DEHP-free material, containing a 0.22 micron in-line filter
Infusion Duration	2 hours (+ 10 minutes)
Infusion Volume	Doses ≤ 180 mg/m^2: 100 mL Doses > 180 mg/m^2: 200 to 250 mL; this may include either: • 100 mL × 2 (dose to be divided between two 100 mL infusion volumes to be administered sequentially) • Up to 250 mL (using a single flexible IV bag)
Diluent	Commercially available sterile 0.9 % NaCl solution for IV infusion
Schedule	Study drug is to be administered once every 3 weeks (Q3W) on Day 1 of each cycle (3 weeks [21 days] equals 1 dosing cycle). End of Cycle 1 (EOC1) assessments are to be performed no sooner than C1/D21 (-2 days). Subsequent cycles may be administered Q3W (± 2 days), unless further delay is required to allow for amelioration of toxicities
STUDY DESIGN	
Cycle 1	A minimum of 1 cycle of AVID100 will be administered, if tolerated. Determinations regarding cohort escalation, DLTs, and MTD will be based on toxicities observed during

	this 3 week (Cycle 1) of treatment. • Patients completing Cycle 1, in the absence of a DLT, will be considered to have tolerated the regimen. • Patients must receive their full planned dose of AVID100 during Cycle 1 in order to be considered evaluable for safety and tolerability, unless dose reduction, interruption, or discontinuation was the result of a DLT. • Dose-Escalation Cohorts: Patients will be replaced, if necessary (e.g., received < 1 full dose of AVID100 plus follow-up through EOC1 [C1/D21 {- 2 days}]) for any reason other than a DLT), to allow for a thorough assessment of the tolerability in any dose cohort. • All enrolled patients will be considered in the assessment of safety and tolerability.
Premedication	Beginning with the first dose, all patients must be premedicated with standard therapies prior to each dose of AVID100 to reduce the risk of infusion-related reactions (IRRs) associated with study drug. The recommended premedication regimen includes administration of dexamethasone 12 hours and 6 hours prior to each dose, as well as administration to begin at minimum 30 minutes prior to each infusion of a glucocorticoid (e.g., dexamethasone) as well as an H1 (e.g., diphenhydramine/hydroxyzine) and an H2-blocker (e.g., ranitidine/famotidine). In the event of other study-drug associated reactions (e.g., nausea, vomiting, diarrhea, etc.), patients may be premedicated with standard therapies in order to reduce the potential for such reactions in the future. Mandatory premedication will be implemented for all patients should a pattern begin to emerge of mild-to-moderate study drug-related reactions that are amenable to prophylaxis with standard agents.
Phase 1a: Rules for Accrual	**Rules for Dose Escalation and Cohort Expansion** Dose escalation of AVID100 is based on demonstrated tolerability during Cycle 1 (i.e., the initial 3 weeks of dosing) and the occurrence of DLTs thought to be associated with (i.e., possibly related, probably related, or related to) study drug. The rules for dose escalation and identification of the MTD(s) in this study are as follows: **Establishment of the MTD** 1. **Dose Part A:** Minimum of 1 patient entered into dose Cohort 1 and 2 ONLY; dose escalation between cohorts will be 100% (until at most Cohort 3). • If during Cycle 1, a patient experiences any ≥ Grade 2 toxicity considered associated with study drug, the cohort will be expanded to 3 patients and Part B will commence. • If during Cycle 1, the patient experiences a DLT considered associated with study drug, the cohort will be expanded to 6 patients and Part C will commence. 2. **Dose Part B:** Minimum of 3 patients entered to each cohort; dose escalation between cohorts will be 50%. • If during Cycle 1, any 1 patient experiences a DLT considered associated with study drug, the cohort will be expanded to 6 patients and Part C will commence. • If during Cycle 1, > 1 patient experiences a DLT dose escalation will STOP. *This will indicate that the MTD has been exceeded.* 3. **Dose Part C:** Minimum of 6 patients entered into any cohort where a DLT is observed in any of the first 3 patients, otherwise a minimum of 3 patients per cohort; dose escalation between cohorts will be 25%. • If during Cycle 1, > 1 patient experiences a DLT, dose escalation will STOP. *This will indicate that the MTD has been exceeded.* 4. If it is determined that a dose level is not tolerated, the previous lower dose cohort will be expanded to 6 patients (if this has not already been accomplished) as a total of 6 patients must be treated before establishing a dose as the MTD. 5. Once the MTD (or maximum dose to be studied) is achieved and the RP2D is identified, that cohort may be expanded up to 12 patients to more fully evaluate safety and tolerability at that dose level at the Sponsor's discretion. 6. Should the DLT rate equal or exceed 33.3% in an expanded MTD cohort, it will be determined that the dose is not tolerated. If this occurs, the previous lower dose cohort may be expanded. Therefore:

	• There is potential for expansion of lower dose cohort(s) if the initially identified MTD is not tolerated (either with single or repeat cycles of therapy), and • There is potential to evaluate and expand a previously unexamined intermediate dose level(s) between 2 established dose levels to more fully characterize tolerability. Note: Based on emerging tolerability data the Sponsor may choose to escalate the dose between cohorts at an increment less than the percent increase allowed above in an effort to protect patient safety. **Rules for Duration of Exposure Prior to Start of Next Patient and Start of Next Cohort** Dose escalation and accrual to the next cohort will occur only after the minimum number of patients required for tolerability assessment in the current cohort have completed Cycle 1, and only after acceptable tolerance has been demonstrated in at least 1 of 1, 3 of 3, or 5 of 6 patients treated in the current cohort (depending on cohort size), and after consultation with the Sponsor's Medical Monitor(s). In cohorts with > 1 patient enrollment will be staggered between the first and second patient by at minimum 24 hours in order to assess for IRRs; thereafter patients within a cohort may be added concurrently. For all patients, EOC1 assessments are to be performed no sooner than C1/D21 (-2 days).
Rules for Establishing the RP2D	The MTD (or a dose lower than the MTD) will be identified as the RP2D, provided a minimum of 6 patients have been treated at that dose, and provided acceptable tolerance has been demonstrated in at least 5 of 6 patients treated. The RP2D choice will be based on the MTD evaluation as well as other toxicities observed in the study, including observations in later cycles of administration of AVID100, as well as on PK and other data.
Phase 2a: Rules for Accrual	Once the RP2D has been identified, approximately 60 patients in 3 expansion will be enrolled to the Phase 2a portion of the study. • Accrual to Phase 2a may begin once the RP2D has been established and a minimum of 6 patients have been treated at that dose. • If the Phase 1a MTD Cohort is to be expanded up to 12 patients to more fully evaluate safety and tolerability at that dose level, accrual to Phase 2a may begin concurrent with accrual of the additional up to 6 patients to that cohort. **Rules for Patient Population to be Treated** Patients will be accrued to 3 expansion cohorts. The tumor types to be evaluated in these expansion cohorts are mTNBC (~30 patients), SCCHN (~15 patients), and Sq-NSCLC (~15 patients). Criteria for eligibility will be as described above with the additional requirement that patient tumors must have been documented to express EGFR by *IHC (3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells in mTNBC; 3+ intensity in ≥ 50% of tumor cells in SCCHN and Sq-NSCLC*) in a central laboratory. Further, FFPE tumor tissue from either a prior procedure or a recent biopsy must be available for submission to a central laboratory for other study-related evaluations. **Rules for Tolerability** The criteria for tolerability during Phase 1a will apply to Phase 2a Expansion Cohorts. Safety will be reviewed on an ongoing basis to determine if the dose and schedule chosen based on the Phase 1a dose escalation is safe and well-tolerated in expanded populations of patients with the tumor types selected for the expansion cohorts (mTNBC, SCCHN, and Sq-NSCLC). Should it be determined that the dose is not well-tolerated (i.e., ≥ 33.3% of patients in an expansion cohort experience a Cycle 1 DLT), the safety of that dose level will be re-evaluated and the next lower dose with established tolerability in Phase 1a will be administered to subsequent patients. An exception will be the occurrence of toxicity suggesting organ damage (e.g., pulmonary fibrosis, drug-induced liver injury) occurring in ≥ 2 patients within an expanded cohort, in which case further accrual to that cohort will be discontinued.
Continued Therapy after Cycle 1	Upon completion of Cycle 1, in the absence of unacceptable toxicity or documented disease progression, patients may continue to be treated with study drug Q3W (± 2 days) unless

	further delay is required to allow for amelioration of toxicities. Administration will be at the same dose and infusion duration established for the patient during Cycle 1, and on the same schedule (unless dose reduction is necessary), provided retreatment guidelines are met. Additional cycles should be initiated within approximately 2 weeks of the completion of the previous cycle, if feasible. **Retreatment Guidelines:** In order to start any new cycle a patient must meet the following criteria: • ANC ≥ 1,000 per mm^3 • Platelets ≥ 75,000 per mm^3 • Ongoing AEs (study drug-associated) should NOT meet the criteria for DLT • Any ongoing AEs should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of Grade 2 alopecia, clinical events that are being adequately controlled with best supportive care (e.g., nausea, vomiting, diarrhea, fatigue), and asymptomatic laboratory abnormalities that are considered clinically insignificant or that are resolving with medical therapy
Duration of Treatment	Additional cycles of AVID100 may continue to be administered if tolerated and in the absence of documented disease progression, at the Investigator's discretion, provided retreatment criteria have been met.
Retreatment Following a Response	Treatment with AVID100 may be restarted in a patient who: • Previously achieved a documented OR or prolonged SD on this study, stopped treatment, and subsequently progresses, or • Discontinued therapy for a reason other than a DLT or PD, and in whom documented OR or prolonged SD is subsequently noted. Such action may be taken at the Investigator's discretion, following discussion with the Medical Monitor, provided retreatment criteria are met, no anti-cancer treatment was administered since the last dose of AVID100, and the trial is still open. This option for retreatment does not apply to patients who previously experienced an unacceptable toxicity that required permanent discontinuation of study drug.
TOXICITY and DLT	
Toxicity Grading	Common Terminology Criteria for Adverse Events [CTCAE Version 5.0] to be used for grading toxicities
Toxicity Management/ Dose Modification	**Management of Dose-Limiting Toxicities** Toxicity that meets the protocol definition of DLT will be managed by either discontinuing the patient from further participation in the study, or the patient may continue on study if there is evidence of response or other clinical benefit, but must do so at a reduced dose of study drug, and ONLY following discussion with the Sponsor's Medical Monitor(s). Patients may not be retreated following the occurrence of a DLT until retreatment criteria have been met. Exceptions to continuing on study at a reduced dose include evidence of pulmonary, neuro-, ocular, nephro-, or hepatotoxicity as detailed in the protocol Criteria for Treatment Discontinuation. In such instances patients must be permanently discontinued from treatment with study drug. **Management of Other Toxicities** Toxicity that does not meet the protocol definition of DLT, but nevertheless warrants dose modification may be managed by either dose reduction or temporary interruption of study drug in order to allow for amelioration of the toxicity.
DLT Definition	Any of the following toxicities, if judged to be associated with study drug (i.e., possibly related, probably related, or related), will be considered a DLT for the purposes of this trial. 1. Evidence of pulmonary fibrosis, any grade (patient must be permanently discontinued) 2. Grade 3 non-hematologic toxicity regardless of duration with the exceptions of: • Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤ 2 days with best supportive care • Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not considered clinically relevant by the Investigator and that resolve with medical therapy 3. AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry as allowed by study eligibility criteria), with total bilirubin > 2 × ULN without initial

	findings of cholestasis (i.e., no elevation in serum alkaline phosphatase [ALP]), that cannot be explained by other factors 4. Any Grade 4 non-hematologic toxicity with the exception of: • Grade 4 asymptomatic electrolyte abnormalities lasting < 7 days that are not considered clinically significant by the Investigator and that are controlled with medical therapy 5. Neutropenia that is: • ≥ Grade 3 and associated with fever (ANC < 1000 per mm^3, temperature > 38.3ºC [101ºF] or a sustained temperature of ≥ 38ºC [100.4ºF] for > 1 hour) (i.e., febrile neutropenia) • Grade 4 and sustained (ANC < 500 per mm^3, duration > 5 days) 6. Thrombocytopenia that is: • Grade 3 with clinically significant hemorrhage or requirement for transfusion • Grade 4 (platelets < 25,000 per mm^3) 7. Inability to complete Cycle 1 at the assigned dose (i.e., receipt of < 1 full planned dose of study drug plus 3 weeks of follow-up due to ≥ Grade 3 toxicity) 8. Treatment delays > 2 weeks from the scheduled "next dose" due to ≥ Grade 3 toxicity *Other toxicities may be considered a DLT as determined by the Investigator in conjunction with the Medical Monitor.* The above criteria will be used to make individual patient determinations regarding dose reductions, interruptions, or discontinuation throughout the course of the trial, but ***only those DLTs occurring during Cycle 1 will be used to make decisions regarding dose escalation and tolerability.*** Events occurring after Cycle 1 will also be evaluated by the Investigator and Medical Monitor and taken into consideration when deciding upon further doses to be assessed as well as to establishment of the RP2D.
MTD Definition	In the Phase 1a portion of this trial, MTD will be defined as the dose below that which produces, during Cycle 1 of treatment, any of the indicated DLTs either in > 1 patient in a 3 to 6 patient cohort, or in > 33.3% of patients in the event of an expanded 7 to 12 patient cohort. The MTD will not be established until all patients entered into the cohort under evaluation have either completed Cycle 1, discontinued further participation in the trial, or had their dose reduced due to the occurrence of a DLT. Previously established tolerability of a dose level will be reevaluated if DLTs thought to be possibly related, probably related, or related to study drug are observed in later cycles.
Safety Monitoring	The Investigator(s) and Sponsor's Medical Representatives will comprise a Study Safety Committee. Clinical and laboratory safety data will be reviewed on an ongoing basis in order to make decisions regarding the advisability of continuing accrual and dose escalation. To do so: 1. The following will be promptly reported to the Sponsor or designee: • SAEs, within 24 hours of Investigator awareness • AEs resulting in permanent discontinuation from study, regardless of seriousness or relationship to study drug • DLTs • Dose modifications (i.e., dose reductions, temporary dose interruptions) 2. AEs will be recorded on the electronic case report form (eCRF) in a timely manner following a patient completing (or being discontinued from) each dosing cycle. 3. The Investigator will make critical laboratory safety data available in a timely manner. 4. Patients will be carefully evaluated for evidence of all AEs, including potential cumulative and/or delayed toxicities, throughout the duration of their time on study. 5. During Phase 1a: Biweekly safety teleconferences will be held between the Investigational Site(s) and the Sponsor and/or designee; frequency may fluctuate based on accrual and study activity. 6. During Phase 2a: Monthly safety teleconferences will be held between the Investigational Site(s) and the Sponsor and/or designee; frequency may fluctuate based on accrual and study activity, as indicated *Availability of these data also will enable the Sponsor (or designee) to notify regulatory*

	authorities, as well as Investigators who may be participating at other sites or in other clinical trials of the study drug, of events occurring during the trial.
PARAMETERS TO BE MEASURED	
Prescreening	• The trial site will prescreen patients for EGFR Tumor Status Determination before entering patients into screening for the treatment portion of the trial. The site should use a separate prescreening informed consent form. Prescreening may be performed outside the 28 (+ 2) day screening period to allow adequate turnaround time for receipt of results, provided separate informed consent has been obtained.
Screening *(Within 14 days prior to 1st dose unless otherwise stipulated)*	• Informed consent • Eligibility assessment • Past medical history • History of the primary malignancy (including data on best response to prior therapy, if available)
Safety Assessment	Patients to be monitored throughout the treatment and follow-up period for occurrence of adverse events (AEs) (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital signs (VS), and laboratory data. **Safety Assessments (1)** *(Within 14 days prior to 1st dose unless otherwise stipulated)* • Medication survey • Adverse events *(collection of data from 1st dose to 30 days after final dose)* • Performance status evaluation (ECOG) • Vital signs (including temperature, pulse, respiratory rate, BP, and O_2 saturation by pulse oximetry) • Physical examination (including weight and pulmonary assessment at each visit) • Hematologic parameters • Serum chemistries • Coagulation parameters • Urinalyses • Anti-drug antibody (ADA) to AVID100 **(Central Lab)** • Pregnancy testing (if applicable) *(serum test within 14 days, urine or serum test repeated within 2 working days prior to 1st dose)* • 12-Lead ECGs **Safety Assessments (2)** *(within 28 days [+2 days] prior to first dose of study drug, provided no antineoplastic therapy has been delivered between safety assessment and first dose of study drug)* • Ophthalmology exam (complete) • MUGA scan or Echocardiogram *(follow-up ONLY in patients with a history of CHF, or in patients developing clinical findings suggestive of cardiac dysfunction at any point during the study or the follow-up period)* • Pulmonary function testing (to include spirometry and DL_{CO}) • Chest X-Ray (PA and lateral)
Disease Assessment *(within 28 days [+ 2 days] prior to 1st dose)*	**Disease Assessments** • EGFR tumor status determination (by local or central evaluation of archival formalin-fixed paraffin-embedded [FFPE] tumor tissue or verification by previous pathology report during Phase 1a and by central evaluation of FFPE tumor tissue [archival or from recent biopsy] during Phase 2a) o Phase 1a Dose-Escalation Cohorts: Optional o Phase 2a Expansion Cohorts: Required; tumor must be EGFR-positive by IHC as specified (*3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells in mTNBC; 3+ intensity in ≥ 50% of tumor cells in SCCHN and Sq-NSCLC*) for patient to be eligible for enrollment • Tumor marker measurement *(as indicated by tumor type) (Phase 1a only)* • Diagnostic imaging for assessment of disease (and pulmonary status) (CT/MRI) o For Phase 2a patients must have documented measurable disease o For safety *(all patients)*, imaging of the chest required at each evaluation • Response assessment (per RECIST 1.1). Data on evidence of and duration of any OR or SD, as well as the TTP to be collected *(all patients)*

Pharmacokinetics (Central Lab)	Serum sampling to assess the PK profiles of total antibody (AVID100 plus MAB100), AVID100, and DM1; to be performed throughout the trial *(all patients)*
Biomarker Studies (Central Lab)	• Tumor sample submission: for evaluation of tumor EGFR-expression by FISH and other potential biomarkers; in archival or recently obtained FFPE tumor tissue o Phase 1a Dose-Escalation Cohorts: If available o Phase 2a Expansion Cohorts: ▪ Required at Screening; if not available patient must be willing to undergo tumor biopsy. ▪ Optional Post-Dosing if tumor tissue is available from an interval surgery, in the event of a documented objective response if the patient has accessible tumor or prolonged disease stabilization > 8 weeks, and upon request of the Sponsor based on other study findings (after discussion with the Investigator). • Peripheral blood collection: for evaluation of EGFR ctDNA for *EGFR*-ECD mutation status and *EGFR*vIII deletions (SCCHN patients only), as well as assessment of other potential biomarkers of interest (required for all indications)
STUDY COMPLETION	
Criteria for Treatment Discontinuation	Patients will be discontinued from further treatment with study drug in the event of any of the following: 1. Patient must be permanently discontinued in the event of any major, potentially irreversible organ system DLT , including: • Pulmonary toxicity defined as: o Evidence of pulmonary fibrosis, any grade o Reduction of forced vital capacity (FVC) or DL_{CO} ≥ Grade 3 • Neurotoxicity defined as peripheral neuropathy ≥ Grade 3 • Any ocular toxicity ≥ Grade 3 • Nephrotoxicity defined as: o Acute kidney disease ≥ Grade 3 (i.e., creatinine > 3 × baseline or > 4.0 mg/dL) o Chronic kidney disease ≥ Grade 3 (i.e., estimated glomerular filtration rate [eGFR] or creatinine clearance [CrCl] 29-15 mL/min/1.73 m^2) o Proteinuria ≥ Grade 3 (i.e., ≥ 3.5 g/24 hours) • Hepatotoxicity suggestive of drug-induced liver injury, as characterized by the following 3 criteria: o AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry as allowed by study eligibility criteria) o Total bilirubin > 2 × ULN without initial findings of cholestasis (i.e., no elevation in serum ALP) o No explanation for the above findings, such as: viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury *Adapted from: Hy's Law. Drug–induced liver injury: premarketing clinical evaluation. Guidance for Industry. U.S. Department of HHS, FDA, CDER, CBER, 2009.* 2. Any other DLT considered by the Investigator to require treatment discontinuation. Note: Patients experiencing a DLT not listed in #1 above may continue at a reduced dose if there is evidence of an OR, SD, or other clinical benefit, and ONLY following discussion with the Sponsor's Medical Monitor(s). 3. Another AE not meeting the criteria for a DLT, yet considered by the Investigator to require treatment discontinuation. 4. Documented progressive disease at any time during the study 5. Treatment failure not meeting the criteria for progressive disease, but considered by the Investigator to require treatment discontinuation. 6. Requirement for a significant surgical procedure 7. An intercurrent illness which, in the opinion of the Investigator, would prevent completion of study-related evaluations 8. Significant deviation from the protocol or eligibility criteria. Such patients will be considered protocol violations and will be discontinued from treatment 9. Pregnancy 10. Noncompliance with study or follow-up procedures

	11. Patient withdrawal of consent and election to discontinue treatment with study drug. (Patients may leave the study at any time for any reason if they wish to do so, without any consequence.) 12. Termination of the study by the Sponsor Any other reason which, in the opinion of the Investigator, would justify treatment discontinuation.
Follow-up	• End of Treatment (EOT) evaluations to be conducted within approximately 10 days following the decision to discontinue the patient from further treatment • 1 Month Follow-up (1M FUP) evaluations to be conducted approximately 30 days (+7 days) following the last dose of study drug. • If an observed toxicity thought to be associated with study drug has not resolved by the 1M FUP evaluation, an additional follow-up AE assessment will be conducted approximately 3 months (may be repeated at 6 months if needed) following the last dose of study drug, if feasible, in order to confirm that the event has either resolved, returned to baseline status, or been adequately explained, and that no longer term deleterious effects have become evident. Any patient who develops pulmonary fibrosis will be followed at approximately 3 month intervals for up to 2 years to assess the course of the disease and evaluate potential reversibility of this finding. • In the event of an ongoing OR or SD at the EOT, response assessments based on tumor marker and imaging studies will continue to be performed every 3 months during the first year and every 6 months thereafter, until PD or another therapeutic intervention is initiated, so that data may be collected on the duration of stabilization or response, as well as on the overall TTP.
ANALYSIS PLAN	
Safety/Tolerability	Safety analyses are to be conducted on patients receiving any amount of a dose of AVID100.
Antineoplastic Activity	Patients who complete Cycle 2 (6 weeks) of treatment, receive at least 2 planned doses during that period, and have a follow-up assessment of disease status will be considered evaluable for assessment of antineoplastic activity. Patients who are withdrawn from the study before completion of Cycle 2 because of progressive disease also will be included in assessments of antineoplastic activity.
TRIAL REPORTING	
Final Study Report	Final integrated clinical/statistical study report to be prepared following study completion.

2. SCIENTIFIC BACKGROUND AND RATIONALE

2.1. Background

2.1.1 Overview of the Target: EGFR

Several members of the HER-ERBB family of Type 1 receptor tyrosine kinases (RTK) (including EGFR/HER1/ERBB1, HER2/ERBB2, HER3/ERBB3, and HER4/ERBB4) have been proven to be important targets for cancer therapy (1-5). EGFR has been shown to be highly expressed or in some cases mutated in a variety of human malignancies. Activation of the EGFR pathway results in cell proliferation and inhibition of apoptosis as well as affecting angiogenesis and the metastatic process. EGFR (HER1, ERBB1) has been clinically validated as a target, with marketed products including both tyrosine kinase inhibitors and monoclonal antibodies directed to this cellular receptor shown to be effective therapy for selected human malignancies. EGFR tyrosine kinase inhibitors have been shown to be effective in the treatment of patients with malignancies including non-small cell lung carcinoma (NSCLC) and pancreatic carcinoma (PC), whereas anti-EGFR antibodies have been approved for treatment of colorectal carcinoma (CRC), squamous cell carcinoma of the head and neck (SCCHN), and squamous histology NSCLC (Sq-NSCLC) (6, 7). EGFR inhibitors (EGFRi) have been studied in a wide variety of other indications including but not limited to: ovarian cancer, renal cell cancer, hepatocellular cancer, and breast cancer. In these and other indications limited EGFRi activity was observed either as single agents or in combination with other therapies including chemotherapy, thereby precluding their being developed further.

2.1.2 Overview of EGFR and Breast Cancer

The role of EGFR gene and protein expression as well as activation of EGFR and downstream signaling in patients with subtypes of breast cancer (BC) has been studied intensively but there is no current consensus on the importance of inhibiting this pathway in the treatment of patients with this malignancy. A wide variety of published studies have been performed over nearly three decades evaluating EGFR expression in BC using varied techniques to assess cell surface receptor expression and activation as well as gene amplification (8-16). EGFR expression has been detected in estrogen receptor/progesterone receptor (ER/PR) positive tumors (11) and HER2 amplified and non-amplified tumors (9). The majority of studies suggest that overexpression is most commonly observed in patients with poorly differentiated, inflammatory, basal, and/or triple-negative BC (TNBC) (8, 10-16) although some studies suggested greater expression in HER2+ tumors than in ER-positive BC or TNBC (9, 10, 15). The proportion of patients who are positive varies depending on the patient subset evaluated and the technique(s) used for assessment. Recent studies have been undertaken utilizing a validated modification of the DAKO PharmDx IHC assay to evaluate the proportion of patients with various levels of EGFR expression on several different tumor types. Based on nearly 250 triple TNBC tissue samples it has been determined that: (a) 25% of TNBC cases were either 2+ or 3+ in ≥ 50% of tumor cells; (b) 19% of TNBC cases were 2+ in ≥ 50% of tumor cells; (c) 13% of TNBC cases were 2+ in ≥ 75% of tumor cells and; (d) 6% of TNBC cases were 3+ in ≥ 50% of tumor cells.

EGFR signaling has been shown to play a role in the development and pathogenesis of BC (17) including aspects of bone metastases (18). The role of EGFR on the epithelial-mesenchymal transition (EMT) associated with tumor invasiveness, angiogenesis, and metastasis has also been

documented (19). In addition, hetero-dimerization of EGFR with HER2 and HER3 or with non ERBB family receptors (e.g., MET) may also have a role in either the pathogenesis of subsets of patients with BC or in their resistance to therapy (19).

Very limited activity has been observed in patients with metastatic BC treated with either anti-EGFR monoclonal antibodies (mAbs) or EGFR tyrosine kinase inhibitors (TKI) as single agents (19-23). Some evidence of increased activity of chemotherapy plus the anti-EGFR mAb cetuximab vs. chemotherapy alone has been documented in patients with TNBC but thus far no definitive evidence of efficacy has been presented for any regimen containing an EGFRi (24, 25). These data suggested a need to develop biomarkers to assess potential responses earlier or to select patients with TNBC and other subtypes of BC who may be more responsive to novel therapies (19).

Preclinical data document the potent activity of AVID100 both *in vitro* and *in vivo* in models of BC including TNBC (**Section 2.3.1.1** and **Investigator's Brochure**). In this clinical study one expansion cohort will enroll patients with BC who have not received ado-trastuzumab emtansine (Kadcyla®) and have been prescreened for EGFR overexpression using a validated bioassay. Strong overexpression of EGFR, i.e., ≥ 3+ intensity by immunohistochemistry (IHC) in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells will be utilized as the provisional cut-off for patient entry into this study. Evaluation of EGFR gene expression will also be evaluated in parallel using a validated FISH assay but these results will not be used for selection of patients. The choice of cell surface expression of EGFR and the high cut-off value was based on the primary mechanism of antitumor activity of AVID100 which is dependent on the delivery of the DM1 cytotoxic payload to EGFR-expressing cells. The relatively limited activity of cetuximab, demonstration that cetuximab activity is increased by the addition of chemotherapy, and the strong data that tubulin-targeted agents (e.g. Paclitaxel, docetaxel, ixabepilone, eribulin, and DM1) are active in many patients with BC provide the rationale for testing AVID100 in patients who show a high degree of overexpression of EGFR. Patients with levels of HER2 that are below the level required for treatment with trastuzumab or ado-trastuzumab emtansine and who meet the criteria for EGFR-overexpression may be considered for enrollment.

2.1.3 Overview of EGFR and Squamous Cell Carcinoma of the Head and Neck

The EGFR pathway is a validated target for therapy of patients with SCCHN (26-29). Multiple studies have documented that EGFR is highly expressed in more than 90% of SCCHN tumor samples compared to normal squamous epithelium from non-malignant tissue (26-29) with the majority of specimens being graded 2+ or 3+ by IHC (29). Increased production of transforming growth factor alpha (TGF-α), an EGFR ligand, has also been documented to be increased in SCCHN samples compared to normal mucosa (29). Higher levels of EGFR expression in patients with SCCHN are associated with poor prognosis (26, 27, 29) as well as poor local control of the tumor and reduced responsiveness to cetuximab (29). *EGFR* mutant type III variant (*EGFR*vIII) mutations are present in up to 40% of patients with SCCHN and may contribute to resistance to therapy with anti-EGFR mAbs (28-30) despite documentation that cetuximab binds to, down-modulates, and ultimately inhibits signaling via this mutant receptor (31, 32). *KRAS* mutations occur in less than 5% of patients with SCCHN and their impact on prognosis or response to therapy has not been established (29)

Multiple clinical trials evaluating both anti-EGFR mAbs and EGFR-TKI have been completed over the last two decades. Relatively limited antitumor activity has been observed in patients treated with EGFR-TKI and none of these agents has been approved for treatment of SCCHN (26-28, 33-35). In contrast, activity has been observed with some anti-EGFR mAbs and cetuximab has been approved as a single agent as well as in combination with either chemotherapy or radiotherapy for the treatment of selected patients with SCCHN (33-36). In patients who recently progressed on a platinum-based chemotherapy regimen approximately 13% of recipients of cetuximab achieved a partial response (PR) with a median duration of response of 5.8 months (36, 37). Addition of cetuximab to a regimen of cisplatin or carboplatin plus 5-FU in patients with untreated recurrent or metastatic SCCHN improved OS from 7.4 months in the chemotherapy alone group to 10.1 months in the group receiving chemotherapy and cetuximab (38). Progression-free survival (PFS) was increased by 2.3 months (from 3.3 to 5.6 months) and 36% of the patients treated with cetuximab and chemotherapy experienced objective responses compared to a 20% response rate in recipients of chemotherapy alone (38).

Preliminary data have been presented or published on the clinical activity of other anti-EGFR mAbs as well as on EGFR-TKI. Activity has been observed with many of these agents (33, 34) but thus far the only agent with proven safety and efficacy is cetuximab (36-38). The single agent activity of cetuximab is limited but addition of cetuximab to chemotherapy in a P3 registration study resulted in an incremental improvement in response rate, PFS and OS. Studies of chemotherapy regimens including either paclitaxel or docetaxel plus cetuximab have shown promise (39), both of these approved taxanes have activity in the treatment of SCCHN and docetaxel is approved for this indication (40). These data provide support for treatment of patients with SCCHN with AVID100, an ADC targeting EGFR with a DM1 payload that is a more potent microtubule-targeted agent than available taxanes. AVID100 has shown greater activity that the unconjugated antibody (MAB100) in a variety of in vitro cell lines derived from patients with SCCHN (**Section 2.2.1.1.1** and **Investigator's Brochure**). The preclinical data with AVID100, the documented single agent activity of cetuximab, and the documented role of paclitaxel and docetaxel in patients with SCCHN provides a strong rationale for the evaluation of AVID100 in this patient population.

2.1.4 Overview of EGFR and Non-Small Cell Lung Carcinoma

EGFR has been documented to be a crucial target for specific subsets of patients with NSCLC (4). EGFR tyrosine kinase inhibitors (TKI) (erlotinib, gefitinib, afatinib) have been documented to be active in patients with activating EGFR mutations and superior to first line chemotherapy in this patient population (41). Mutations resistant to the approved EGFR TKIs, including T790M, limit their long term benefits. Recently osimertinib has been approved and shown to be active in patients resistant to first generation inhibitors and more active than available chemotherapy in first line treatment of patients with T790M mutation-positive NSCLC (42).

The evaluation of anti-EGFR mAbs in patients with NSCLC has been more complex with numerous studies and subanalyses required to ultimately delineate a potentially sensitive patient population. Cetuximab, a mouse-human chimeric anti-EGFR mAb, was initially shown to be active in a subset of both EGFR-wild type and EGFR-mutated NSCLC lines *in vitro* and *in vivo* both alone and in combination with chemotherapeutic agents; these data supported subsequent clinical evaluation (43).

Several studies evaluated cetuximab in combination with chemotherapy as a first-line therapy of NSCLC with mixed results (44). Two Phase 3 studies yielded similar efficacy outcomes but disparate results with respect to statistical significance. A modest median OS advantage of 1.2 months (HR 0.87, [95% CI 0.762-0.996], p=0.044) was observed in the FLEX study (1125 patients enrolled) evaluating the addition of cetuximab to cisplatin and vinorelbine versus the chemotherapy combination alone (45). Although the increment in OS was similar, the 1.3 month increase was not statistically significant in the smaller BMS099 study (676 patients enrolled) comparing a taxane and carboplatin regimen with or without the addition of cetuximab (HR 0.89 [95% CI 0.754-1.051], p=0.169) (46). The minor increments in OS and the failure to achieve a statistically significant result in both studies precluded approval of cetuximab in this setting. Subsequent subanalyses of the FLEX trial suggested that patients who received cetuximab in addition to the designated platinum doublet who developed first cycle rash had prolonged OS, PFS and increased responses rates compared to patients who received chemotherapy alone (47). In a separate retrospective subanalysis, the median OS was assessed comparing patients whose EGFR tumor expression denoted by immunohistochemistry H-scores were low (< 200) (69% of patients) compared to those who were high (≥ 200) (31% of patients) (48). Median OS for patients receiving cetuximab plus chemotherapy with high H-scores was 12.0 months [95% CI 10.2-15.2] compared to 9.6 months ([7.6-10.6]; HR 0.73, 0.58-0.93, p=0.011) for patients with high H-Scores who received chemotherapy alone. No effect on OS was observed when comparing the two regimens in patients who had low H-scores (9.8 vs. 10.3 months for the combination vs. the chemotherapy regimen only, respectively, HR 0.99, p=0.88). Many other studies have been completed evaluating the potential efficacy of cetuximab in patients with NSCLC, but none have prospectively confirmed the potential for enrichment based on the EGFR expression criteria delineated by the retrospective analysis of the FLEX trial although some subsequent reviews, meta-analyses and commentaries support the efficacy of cetuximab in the treatment of NSCLC despite the lack of confirmatory evidence (44).

Based on a promising Phase 2 trial, a Phase 3 trial adding cetuximab to either docetaxel or pemetrexed in patients with previously treated NSCLC was undertaken (49). No impact was observed in median PFS in patients treated with cetuximab plus either chemotherapy regimen compared to the single agent chemotherapeutics in this trial of second line therapy. Additional studies have been performed to evaluate the efficacy of cetuximab in treatment-refractory NSCLC. These studies documented that cetuximab as salvage therapy has little or no demonstrable activity in the treatment of previously treated NSCLC patients with or without evidence of EGFR mutations (50, 51).

Two Phase 3 studies have been completed with the second generation recombinant human anti-EGFR monoclonal antibody, necitumumab, resulting in an approval for this agent in combination with chemotherapy for patients with Sq-NSCLC. In the first of two completed Phase 3 trials, INSPIRE, no benefit was observed as a result of the addition of cetuximab to a pemetrexed-cisplatin regimen in patients with Stage IV non-squamous NSCLC (52, 53). In the Phase 3 SQUIRE study, the addition of cetuximab to gemcitabine and cisplatin resulted in an improvement in median OS compared to patients receiving this chemotherapy regimen alone (7, 54). The addition of necitumumab to first-line chemotherapy in this study resulted in a prolongation of the median OS to 11.5 months [95% CI 10.4-12.6] compared to 9.9 months [8.9-11.1] with chemotherapy alone (HR 0.84, [95% CI 0.74-0.96], p=0.01). This survival benefit

was consonant with the observations in FLEX where the best HR for median OS was observed in patients with Sq-NSCLC (47). Although the authors of the SQUIRE study did not find that the cutoff of <200 or >=200 H-scores to be discriminatory, there was a difference in median OS survival between the necitumumab plus chemotherapy-treated and chemotherapy alone groups in patients with high (>= 200) H-score values (12.0 months vs. 9.7 months; HR 0.75 [95% CI 0.60-0.94], p=0.01). For patients with low (<200) H-Scores median OS for patients receiving cetuximab and chemotherapy was 11.1 months compared to 9.7 months for the chemotherapy arm; HR 0.90 [95% CI 0.75-1.07], p=0.23.

The data outlined above along with data on the potent and superior activity of AVID100 compared to cetuximab in *in vitro* and *in vivo* models including models of NSCLC support its evaluation in patients with treatment-refractory NSCLC. The initial study will focus on patients with Sq-NSCLC. This choice based on the known higher EGFR expression in patient with squamous histology compared to patients with non-squamous NSCLC as well as the documented albeit limited activity observed with necitumumab in a Phase 3 trial. If sufficient activity is documented in this patient population additional studies may be conducted in patients with non-squamous NSCLC.

2.1.5 EGFR Extracellular Domain Mutations

Recent studies have documented that one mechanism of resistance to anti-EGFR mAbs in patients with CRC is the emergence of *EGFR* extracellular domain mutations (m*EGFR*-ECD) with reduced binding for the administered mAb and, in some cases, other mAbs targeting EGFR (56, 57). EGFRvIII mutations resulting from a deletion in EGFR exons 2-7 have been observed in multiple tumors and are associated with resistance to cetuximab in patients with SCCHN (58, 28). EGFRvIII expression has been observed in variable numbers of patients with SCCHN with some estimates varying from 0.31% to 42% (28, 58). EGFR tyrosine kinase domain mutations have also been observed in patients with SCCHN but have not been associated with resistance to cetuximab (59, 60). A single documented point mutation in the *EGFR*-ECD has recently been detected in a patient with SCCHN (61). Given the availability of ctDNA and next-generation sequencing (NGS) technology to document the presence of m*EGFR*-ECD these evaluations may be of use in understanding either innate or acquired resistance to AVID100 in patients with SCCHN previously treated with cetuximab.

2.1.6 Overview of the Product: AVID100

Forbius (formerly Formation Biologics, AvidBiologics) has developed AVID100, an antibody-drug conjugate (ADC), consisting of a novel IgG1 anti-EGFR antibody, MAB100, conjugated to the microtubule inhibitory drug DM1, mertansine (a derivative of maytansine), via a stable linker. MAB100 has the same variable region primary sequence as cetuximab. Accordingly, its specificity for EGFR is expected to be identical to this marketed anti-EGFR antibody. MAB100 differs from cetuximab by two amino acid residues in its Fc region. Also, due to its production in CHO cells, the glycosylation of MAB100 is different from that of cetuximab. There are approximately 3.5 DM1 moieties per molecule of antibody (Ab).

Maytansine and its derivatives ("maytansinoids") bind to tubulin and are potent inhibitors of mitosis (62). Maytansine binds to a unique site on ß-tubulin despite evidence of cross-inhibition of binding between vinca alkaloid antineoplastic agents and this agent (62). Synthetic derivatives of maytansine have been developed to facilitate their stable conjugation to mAbs

(63). DM1 is a highly potent maytansine analog that has been conjugated to monoclonal antibodies (63) including an approved agent, ado-trastuzimab emtansine, a HER2-targeted ADC (64). DM1 has been utilized as the cytotoxic moiety conjugated to an anti-EGFR antibody incorporated in the investigational medical product AVID100.

The binding affinity of AVID100 for the recombinant ectodomain of EGFR is approximately 2 nM. AVID100 inhibits ligand binding to EGFR with concomitant inhibition of phosphorylation of this receptor as well as downstream kinases involved in the EGFR pathway (Mitogen Activated Protein Kinase [MAPK] and Akt [Protein Kinase B, PKB]) (Data on File; Forbius/Formation Biologics). AVID100 has also been shown to mediate antibody-dependent cellular cytotoxicity (ADCC) *in vitro*. Upon binding to the extracellular domain III of EGFR, AVID100 is presumed to undergo receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule assembly, which results in cell cycle arrest and apoptotic cell death (65-67). This latter mechanism is presumed to predominate and is responsible for its potent preclinical activity, as demonstrated by its superior activity in *in vitro* and *in vivo* studies compared to unconjugated anti-EGFR antibodies including MAB100 (the AVID100 antibody prior to conjugation to DM1) and cetuximab. AVID100 is being developed as a therapeutic candidate for EGFR-expressing solid tumors.

2.2. Nonclinical Studies

2.2.1 Nonclinical Pharmacology Studies

2.2.1.1. *In Vitro* Pharmacology

2.2.1.1.1. Activity Against Tumor Cell Lines

In vitro studies have been undertaken in a variety of tumor cells lines. AVID100 demonstrated activity in over 30 cell lines. Preliminary studies documented that AVID100 was significantly more active than MAB100 in human cell lines derived from: (a) squamous cell carcinoma of the head and neck; (b) gastric carcinoma; (c) pancreatic carcinoma; (d) squamous cell carcinoma of the lung; and (e) breast carcinoma. In contrast, the colorectal carcinoma cell lines that were tested were resistant to both AVID100 and MAB100.

In many of the cell lines studied AVID100 was more active than MAB100 as denoted by the fold difference in the IC_{50}s. AVID100 was documented to be more active than MAB100 in the head and neck cancer cell lines including: FaDu (pharynx squamous cell carcinoma; 10,000 x); Detroit 562 (pharyngeal cell carcinoma; 1,250 x); Cal 27 (tongue squamous cell carcinoma; 100 x); and SCC9 (tongue squamous cell carcinoma; 100 x). Increased activity was also documented in a variety of pancreatic adenocarcinoma cell lines including: ASPc-1 (100 x); BxPC-2 (2,500 x); Capan-1 (12.5 x); and PANC-02.13 (140 x) as well as a pancreatic epithelioid carcinoma, PANC-1 (50 x). AVID100 also showed increased potency compared to MAB100 in squamous cell lung carcinoma cell lines (H226; 10,000 x and H292; 1000 x), as well as cell lines derived from gastric malignancies (gastric adenocarcinoma, AGS; 50 x or gastric carcinoma, N87; 25 x).

More detailed studies of the *in vitro* antitumor effects of AVID100 were performed in several tumor cell lines and immortalized EGFR-expressing human keratinocytes. More potent growth

inhibition was observed in the MDA-MB-468 (breast) and NCI-H292 (lung) cancer cell lines treated with AVID100 compared to MAB100 or to cetuximab. In contrast, AVID100 cytotoxic potency on HaCaT immortalized normal human keratinocytes was similar to that observed with either MAB100 or cetuximab. These results documented that the DM1-conjugated ADC, AVID100, was more active than the tested unconjugated anti-EGFR antibodies against tumor cell lines *in vitro*, whereas there was no significant increase in its activity on immortalized human keratinocytes suggesting that it may have enhanced activity against certain EGFR-bearing tumors without markedly enhancing cutaneous toxicity.

2.2.1.1.2. Antibody Dependent Cellular Cytotoxicity

The potential of AVID100 to mediate antibody dependent cellular cytotoxicity (ADCC) was evaluated using effector cell lines expressing either high or low affinity FcγRIIIA. No evidence of ADCC was observed in experiments using the low affinity FcR-expressing cells. AVID100 mediated ADCC when using high affinity FcγR-expressing cells as the effector cells.

2.2.1.1.3. Inhibition of EGFR Signal Transduction

In vitro experiments documented that pretreatment with AVID100 inhibited ligand-dependent activation of EGFR. Exposure of three EGFR-expressing cell lines (HaCaT, NCI-H292, and MDA-MB-468) to AVID100 in the presence of an EGFR ligand, epidermal growth factor (EGF), resulted in inhibition of phosphorylation of EGFR *in vitro*. Inhibition was observed in a cell line with evidence of constitutive activation of EGFR presumed to be due to autocrine production of EGFR ligands, MDA-MB-468, as well as cell lines in which EGFR phosphorylation was only observed after exposure to exogenous ligand (HaCaT, NCI-292). In addition to inhibition of EGFR activation, pretreatment of the MDA-MB-468 cell line with AVID100 also resulted in reduction of phosphorylation of MAPK and Akt, two critical downstream signaling targets activated by EGFR.

2.2.1.2. *In Vivo* Pharmacology

Antitumor activity of AVID100 and MAB100 was evaluated *in vivo* in a tumor xenograft model using the EGFR-expressing MDA-MB-468 human breast adenocarcinoma in athymic nude mice. Single doses of MAB100 administered subcutaneously (SC) at 5 and 10 mg/kg resulted in a delay in the rate of tumor growth compared to phosphate buffered saline (PBS) controls, but there was no evidence of tumor regression. In contrast, administration of single doses of either 5 or 10 mg/kg of AVID100 by the SC route resulted in a more marked effect on tumor growth with complete remissions observed in all treated animals (12/12 in each group). No evidence of recurrence in tumors was observed through the end of the study on Day 144. A subsequent experiment evaluated repeated intraperitoneal (IP) doses of AVID100, MAB100, and PBS in the MDA-MB-468 model. Tumor growth inhibition was observed in all animals receiving either AVID100 or MAB100 when compared to control animals receiving PBS. A dose-response relationship was observed with minimal effects being observed with 0.625 mg/kg of AVID100 compared to increasing antitumor effects at doses of 1.25, 2.5, and 5 mg/kg. Ablation of all tumors was observed in animals receiving either 2.5 or 5 mg/kg of AVID100 on this schedule.

A NSCLC model utilizing EGFR-expressing human H292 cells was evaluated using IP doses of 1.5, 3.0,7.5, or 15 mg/kg of AVID100 on Days 0, 7, 11, 15, and 19. Administration of AVID100

was effective in reducing tumor volumes at all doses levels compared to the control group receiving PBS. All dosing levels of AVID100 resulted in complete tumor regression in some of the mice, with a trend toward a greater percentage of complete regression at the higher doses. In an additional H292 xenograft study, serum concentration profiles showed that exposure to AVID100 (total and conjugated Ab) were approximately proportional to dose, and increased with increasing administered dose. In addition, serum concentrations of conjugated antibody were only slightly lower than total antibody. This indicates AVID100 is stable in the circulation and that a relatively small amount of deconjugation occurs *in vivo*. This is consistent with the PK profiles of other ADCs conjugated with a SMCC-DM1 payload (68).

Based on the efficacy (anti-tumor activity)/pharmacodynamics (PD) and PK of AVID100 observed in this H292 xenograft tumor study, a PK/PD model was generated to determine a concentration-effect relationship and a potential target tumoristatic concentration (TSC), which is defined as the predicted concentration at which there is no net tumor growth in this model. Based on this xenograft model, the TSC for AVID100 was estimated to be 1.7 μg/mL with a 95% confidence interval ranging from 0.3 to 3.1 μg/mL.

2.2.2 Nonclinical Pharmacokinetic Studies

The PK profile of AVID100 has been evaluated not only in a non-GLP efficacy study in mice, but also in non-GLP and GLP toxicology studies in cynomolgus monkeys.

2.2.2.1. Non-GLP Pharmacokinetic Study in Mice

The results of the PK and PD study in tumor-bearing mice receiving AVID100 is discussed in **Section 2.2.1.2**.

2.2.2.2. Non-GLP Pharmacokinetic Study in Primates

PK data from the pilot study of administration of 10 mg/kg of AVID100 by one hour IV infusion once every 3 weeks to cynomolgus monkeys revealed that AVID100 exhibited either a bi- or tri-phasic serum elimination profile when using either total antibody or conjugated antibody detection methods. The serum concentration for AVID100 rapidly declined for the first 3 hours after the end of infusion of AVID100, followed by a slower decrease over the subsequent 6 hours post-dose. For AVID100, the terminal half-lives for both total and conjugated antibody were similar, at 34.0 and 37.2 hours, respectively. The average volume of distribution was between 35.1 and 47.8 mL/kg, which suggest that the total and conjugated antibody were distributed primarily within the central compartment. In general, the measured and derived PK parameters between total antibody and conjugated antibody were similar. An additional pilot study evaluating toxicity and PK in cynomolgus monkeys receiving weekly doses of either 10 or 20 mg/kg of AVID100 was performed. In this study the terminal half-life (T½) of conjugated antibody ranged from 30.03 hours to 48.50 hours depending on dose, whereas for the total antibody, the T½ ranged from 34.7 and 62.28 hours depending on dose level and week of dosing. Low to no anti-drug antibody (ADA) responses were detected in either animal, and there was no evidence of increased clearance of AVID100 related to the development of ADA responses. Thus, exposure to AVID100 was maintained throughout the study with once weekly dosing. In addition, serum levels of the catabolite, DM1, were measured and remained low throughout the duration of the study indicating AVID100 remains intact *in vivo*. By correlating the PK results

from this cynomolgus monkey study with the PK/PD model generated from the H292 xenograft tumor study, it can be concluded that the serum concentrations of total and conjugated antibody in this once weekly cynomolgus monkey study exceeded the predicted therapeutic range (as defined by the 95% confidence interval around the TSC derived from the mouse xenograft study).

2.2.2.3. GLP Pharmacokinetic Study in Primates

As part of a 4 week GLP toxicology study the toxicokinetics (TK) of the conjugated and total antibody in male and female Cynomolgus monkey serum was evaluated following IV administration of AVID100 at dose levels of 10 and 25 mg/kg. Peak serum concentrations were observed between 1 and 8 hours and between 1 and 4 hours post start of infusion (SOI) for conjugated and total antibody, respectively. The estimated T½ ranged from 43.7 to 72.5 hours for conjugated antibody and from 55.8 to 68.1 hours for total antibody. The mean estimated clearance (CL) and volume of distribution (Vd) ranged from 0.703 to 1.01 mL/hr/kg and from 69.6 to 86.2 mL/kg across dose levels for the conjugated antibody. For total antibody, the mean estimated CL and Vd ranged from 0.754 to 0.887 mL/hr/kg and from 72.1 to 81.6 mL/kg, respectively. Systemic exposure to the conjugated antibody and total antibody increased with increasing dose in a dose proportional manner between 10 and 25 mg/kg on Day 1. No notable gender differences in exposure were observed for either ADC or total Ab. In general, after repeated administration of AVID100, similar exposure to conjugated and total antibody was observed relative to Day 1, except for some animals where total antibody exposure increased on Day 22 compared to Day 1. The AUC(0-t) ratio of total Ab relative to conjugated antibody ranged from 1.00 to 1.55 and appeared to increase slightly following repeated administration of AVID100. Overall, the antibody generally remained conjugated in the blood.

2.2.3 Nonclinical Toxicology Studies

2.2.3.1. Tissue Cross-Reactivity Studies

AVID100 cross-reactivity on a variety of human tissues was evaluated in detail. AVID100 was used for staining in this study. Since AVID100 has the same variable region primary sequences as cetuximab, its binding affinity and specificity for EGFR is expected to be identical to this marketed anti-EGFR antibody. AVID100 stained a variety of tissue elements including epithelium, mesothelium, spindle cells, perineurium, endoneurium, neural/glial cell processes, pituicytes, arachnoid cap cells, retinal cells, vascular and intrinsic smooth myocytes, mononuclear cells, cells of the glomerular tuft, decidual cells, extracellular proteinaceous material (placenta only), endometrial stromal cells, and testicular interstitial cells. All observed staining with AVID100 was judged expected based on literature reports of broad EGFR expression by a variety of tissue elements. No unexpected AVID100 staining was observed in any of the human tissues.

Cross-reactivity of AVID100 on human, cynomolgus monkey and rat EGFR ectodomain was also evaluated. Human and cynomolgus monkey EGFR share 99% sequence homology, while the sequence homology between human and rat EGFR is only 89% (Protein Blast, ACN#: Human CAA25240.1, Monkey SP005549616.1, and Rat ADT91285.1). The studies documented comparable binding of AVID100 to the human and cynomolgus EGFR but not to rat EGFR.

These data supported the use of cynomolgus monkeys as a relevant species to explore the safety and tolerability of AVID100.

2.2.3.2. Non-GLP Toxicology Studies

2.2.3.2.1. Single Dose Toxicology Study

A single dose non-GLP pilot toxicology study was completed with two cynomolgus monkeys treated with a 10 mg/kg single injection of AVD100. The drug was well-tolerated with no notable toxicities.

2.2.3.2.2. Multiple Dose Toxicology Study

A repeat dose non-GLP pilot toxicology study was performed with AVID100 in cynomolgus monkeys. Three monkeys received 4 one hour IV infusions of 10 mg/kg of AVID 100 every 3 weeks for a total of 12 weeks (4 doses, days 1, 22, 43, and 64). All of the animals survived until the end of the study although decreased activity, decreased appetite, and dehydration requiring IV fluids were observed. Skin changes considered treatment-related were observed in all animals, and included hyperkeratosis, dryness, and erythema over the bridge of the nose which was noted after the first or second dose and progressed in severity as dosing continued. Other skin changes included hyperpigmentation, facial rash, and in one animal, ulcerative skin lesions were noted after the last dose and required topical treatment and systemic antibiotics. In general, the observed skin changes resolved within 10 days after dosing, indicating that the treatment-related dermal effects were transient and reversible. All skin changes observed in this study were consistent with the known toxicity profile observed with cetuximab or panitumumab in cynomolgus monkeys. Diarrhea and weight loss were observed in one animal. Mild to moderate increases in alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were observed in all animals, however, these increases were transient and ALT and ALP levels returned to or near baseline levels before the next cycle of drug administration or by the end of the study. No changes considered directly related to AVID100 in hematology or urinalysis parameters considered of toxicological relevance were noted in this study. At necropsy, treatment-related findings were limited to dermal changes, such as hyperkeratosis and flaky skin around the nose bridge, hands, feet, and tail base, and dark pigmentation around the mouth, eyes, and penis. Histopathological changes considered treatment-related were observed in the skin of most animals. These dermal changes observed across (but not all) animals included mild, focal acanthosis, hyperkeratosis, fibrosis, and lymphocytic infiltrates. Mild hyperplasia was observed in the colon or jejunum in most animals, with mild lymphoplasmacytic infiltrates in the colon of some animals. These microscopic changes observed in the skin and jejunum/colon are consistent with the toxicity profile of cetuximab, and were considered treatment-related.

An additional pilot repeat dose non-GLP toxicology study evaluated weekly dosing for 4 weeks of either 10 or 20 mg/kg one hour IV infusions of AVID100 in female cynomolgus monkeys. Only two monkeys were included in this preliminary study. Administration of AVID100 once weekly for 4 weeks was clinically well tolerated, and both animals survived to the end of the study. Treatment-related skin changes were observed in both animals, and included mild to moderate erythema, hyperpigmentation, and hyperkeratosis, all of which are consistent with the known toxicity profile of cetuximab. By the last dose fragile skin and skin abrasions were noted in the high-dose animal. A slight decrease in food consumption was observed after the second

dose in the low-dose animal, which was likely secondary to the discomfort associated with the skin effects of AVID100. A mild decrease in body weight was also observed in the high-dose animal. A decrease in platelet counts was observed in both animals, which ranged from 1.5 to 2-fold below baseline; platelet counts, however, recovered between weekly dosing cycles, indicating this change was reversible. The decrease in platelet counts observed in this study is consistent with the effects of DM1, and thus, are likely treatment-related (69). Consistent with the previous studies, mild elevations (in comparison to pre-study values) in ALT and ALP were observed in both animals (72 hours post-dose at each cycle), but despite these elevations, the ALT and ALP levels for both animals were only slightly above the normal range for cynomolgus monkeys. Primary treatment-related changes were observed microscopically in the skin, and characterized as vacuolation of melanocytes in the basal layer of the epidermis with occasional dead cells, mild acanthosis, and orthokeratotic hyperkeratosis, all of which are consistent with the known dermal effects of EGFR inhibitors, such as cetuximab. An increase in mitotic figures in epithelial cells within the collecting ducts of the kidneys and in the crypts of the small intestine was also observed in the 20 mg/kg animal, which is likely treatment-related since this change is consistent with the effects associated with DM1, which is an anti-mitotic microtubule inhibitor (69, 70).

2.2.3.3. GLP Toxicology Studies

2.2.3.3.1. Single Dose Toxicology Study

The objective of this study was to determine the potential toxicity of AVID100 given once by intravenous (IV) infusion to cynomolgus monkeys followed by a 14-day observation period. Three male and three female cynomolgus monkeys received a single IV dose of 25 mg/kg of AVID 100. All animals survived to the end of the study.

AVID100-related findings were generally consistent with the expected pharmacology/toxicology of an antibody-mertansine conjugate targeting the EGF receptor and were similar to those reported for currently approved anti-EGFR antibodies and/or antibody-mertansine conjugates (71, 72).

These findings included adverse skin reactions (reddening, flaking, lesion, scab formation) and microscopic findings of single cell necrosis/increased mitosis predominantly affecting the epithelia of the skin, eyes (cornea), and gastrointestinal (esophagus, stomach, small and large intestines) and urinary tracts (renal pelvic urothelium and bladder). Non-epithelial AVID100-related findings were present in the brain (focal area of minimal glial single cell necrosis/increased mitosis in one female), liver (minimal to mild single cell necrosis/increased mitosis) and spleen (minimal single cell necrosis/increased mitosis within the red pulp stroma). In addition, minimal to mild lymphoid hyperplasia was noted in various lymph nodes and there was minimal to mild lymphoid depletion in the thymus.

Changes in clinical pathology parameters were transient and largely consistent with an inflammatory response or hepatic toxicity.

In conclusion, administration of AVID100 to cynomolgus monkeys by 1-hour IV infusion at a single dose of 25 mg/kg followed by a 14-day observation period resulted primarily in microscopic findings attributable to mitotic arrest in the epithelia of various organs and tissues

consistent with the known pharmacological activity of AVID100 and with the pharmacology/toxicology of approved antibodies targeting EGFR and/or antibody-mertansine conjugates. Since the majority of findings were graded minimal in severity and/or could reasonably be expected to show reversibility and did not result in dose-limiting clinical toxicity, a single dose of 25 mg/kg was considered to represent the highest non-severely-toxic-dose (HNSTD) in this study.

2.2.3.3.2. Multiple Dose Toxicology Study

The objectives of this study were to determine the potential toxicity of AVID100 when given once weekly by IV infusion for a total of 5 weekly doses to cynomolgus monkeys. In addition, the toxicokinetic characteristics of AVID100 were determined.

Two dose levels of AVID100, a mid-dose of 10 mg/kg and a high dose of 25 mg/kg, were compared to a reference control in male and female monkeys.

All animals at 25 mg/kg were euthanized in poor and/or deteriorating condition on Days 13 to 15 (depending on cohort) prior to administration of the third dose. Animals first presented with skin rash (dry, flaking, reddening, lesion with/without discharge) on the limbs, torso and face, and subsequent clinical signs including excessive scratching, reduced activity, reduce appetite, hunched posture, pallor, and suspected dehydration. Similar clinical signs were noted in animals at 10 mg/kg all of which survived to scheduled euthanasia after 5 weekly doses, but in general were later in onset and slower to progress.

In addition to clinical signs, principal AVID100-related findings were generally consistent with the expected pharmacology of an antibody-mertansine conjugate targeting the EGF receptor, and were similar to those reported for currently approved unconjugated anti-EGFR antibodies (cetuximab, panitumumab, necitumumab) or the approved anti-HER2 antibody drug conjugate (ado-trastuzumab emantsine). The most prevalent microscopic findings at 25 mg/kg (2 doses) were epithelial single cell necrosis/increased mitosis predominantly affecting the epithelia of various organs and tissues including the skin, eye (cornea and conjunctiva), digestive tract, trachea, liver, kidney, mammary gland and reproductive tract and was graded as minimal with the exception of the skin where it was graded minimal to mild. Also present in the kidneys were minimal to mild vacuolation of the pelvic epithelium, minimal tubular degeneration and minimal to mild mononuclear cell inflammation in the pelvic region. In the reproductive tract tissues in addition to the single cell necrosis/increased mitosis there was moderate atrophy in the vagina and mild decrease in the corpora lutea and follicles that were considered AVID100-related.

Non-epithelial AVID100-related changes at 25 mg/kg/dose (2 doses) were present in the bone marrow (minimal to moderate reduced cellularity), lymphoid tissues (minimal to marked lymphoid depletion), heart (minimal myocardial degeneration and increased incidence of minimal mononuclear cell infiltration), liver (minimal to mild hepatocellular hypertrophy and minimal hepatocellular vacuolation) and femur (moderate to marked decreased cellularity of the osteoblasts).

AVID100-related findings at 10 mg/kg (5 doses) were similar to those seen at 25 mg/kg (2 doses) with the most prevalent microscopic finding being epithelial single cell necrosis/increased mitosis. However, at 10 mg/kg the findings were generally of a lower severity and involved fewer organs.

Various changes in hematology and clinical chemistry parameters were either consistent with the microscopic findings or considered secondary to the inflammatory response.

There were no AVID100-related effects on any of the other parameters evaluated in this study.

In conclusion, administration of AVID100 to cynomolgus monkeys by weekly 1-hour IV infusion at 10 or 25 mg/kg/dose resulted in adverse clinical signs primarily affecting the skin that necessitated the euthanasia of animals following a second dose of 25 mg/kg. Microscopic examination showed increased cellular mitotic arrest/single cell necrosis in the epithelial of the skin and various other organs and tissues and evidence of potential hepatic, renal, cardiac and lymphoid toxicity. However, none of the findings described, with the exception of those in the skin, were considered to have contributed to the adverse clinical findings that resulted in the decision to euthanize the animals after 2 doses of 25 mg/kg/dose.

All animals at 10 mg/kg/dose survived to scheduled euthanasia after having received 5 weekly doses. Microscopic findings were similar to those described in animals after 2 doses of 25 mg/kg/dose but generally were of a lower severity and/or involved fewer organs and tissues and the majority of observed changes could reasonably be expected to be reversible. Although moderate myocardial degeneration/necrosis was observed in 1 out of 6 animals at 10 mg/kg dose, based on the low incidence of the finding, a weekly dose of 10 mg/kg for 5 doses was considered to represent the highest non-severely-toxic-dose (HNSTD) in this study.

2.2.4 Other Safety Studies

2.2.4.1. Genotoxicity and Mutagenicity

No studies have been performed with AVID100 or MAB100. DM1, the cytotoxic conjugate of AVID100 as well as the prototypical maytansinoid, maytansine, have been shown to be genotoxic.

2.2.4.2. Carcinogenicity

No studies have been performed with AVID100 or MAB100.

2.2.4.3. Immunogenicity

Immunogenicity was not directly monitored in the GLP toxicology studies. However, no effects on AVID100 pharmacokinetics indicative of the presence of anti-drug-antibodies were observed over time in repeat dose studies.

2.2.4.4. Reproductive and Developmental Toxicity

No studies on the potential effects of AVID100 on reproduction function or on embryo-fetal development have been performed. Ovarian weights were decreased in the weekly repeat dose toxicology study and this finding correlated with decreased corpora lutea and decreased follicles. Testicular weight was decreased and reductions in the epididymis and sperm were also observed.

Although directed to ErbB2 (HER2), ado-trastuzumab emtansine is an approved ADC utilizing the same cytotoxic conjugate as AVID100. Exposure to this ADC may result in embryo-fetal death or birth defects. Patients are advised to utilized adequate contraception during treatment and for a period of time after discontinuing this ADC (72).

2.2.4.5. Pharmacologic Toxicity

No formal pharmacologic toxicity studies were performed. As noted above, toxicities expected based on inhibition of EGFR in tissues and organs were observed. Evaluation of electrocardiograms, heart rate, respiratory rate, indirect blood pressure, and neurological examinations including evaluation of behavior was undertaken in the single and multiple dose GLP toxicology studies.

Sinus tachycardia was observed in several animals but there was no clear evidence of a dose-response relationship. Sinus bradycardia was observed in a single animal receiving 10 mg/kg of AVID100. Neither was considered to be test item-related although the single animal experiencing bradycardia also had evidence of minimal myocardial degeneration and minimal mononuclear cell infiltration in the heart. Aside from the instances of sinus tachycardia and sinus bradycardia, all of the electrocardiograms evaluated were qualitatively and quantitatively normal. Heart rate was lower and the RR and QT intervals were shorter in male animals on day 2 following the 10 mg/kg dose. At Day 30, the QTc interval was longer in male and female animals receiving the lower dose (10 mg/kg) than those receiving the reference item by 10.84 and 11.48%, respectively. There were no dose-related changes in the QTc interval and evaluation of within group comparisons from pretreatment to Day 2 showed no clear evidence of changes in the QTc interval in either the low or high dose group animals.

There were no AVID100-related effects on indirect mean arterial blood pressure or respiratory rate. There were no effects on neurological assessment parameters that were considered to be definitively related to treatment with AVID100. Decreased proprioceptive positioning of the left hind limb was observed in 2 out of 3 females in the 10 mg/kg dose group at week 4 but was not observed in the other hind limb or in male animals receiving this dose and was considered of equivocal toxicological significance.

2.2.4.6. Local Tolerance

No abnormalities were observed at the sites of injection.

2.3. Clinical Experience

2.3.1 Clinical Experience with Agents Related to AVID100

2.3.1.1. Safety: Emtansine-DM1

The maytansinoid DM1 is an analog of maytansine, a natural product of ansamycin antibiotic (benzoansamacrolide). Maytansine, the prototypic maytansinoid was found to bind to tubulin, potently inhibit its polymerization at subnanomolar concentrations, and inhibit mitosis. Despite preclinical activity *in vivo* over a wide range of doses in murine models, evaluation in clinical studies was disappointing with very limited evidence of clinical activity as well as documentation of significant toxicities at the defined IV maximal tolerated dose (MTD) of 2 mg/m^2 administered every 3 weeks (66, 67). Gastrointestinal (GI) toxicity including nausea, vomiting, abdominal pain and diarrhea were observed, and depending on the study, GI toxicity along with either central nervous system (CNS) toxicity (e.g., weakness) or liver function abnormalities (primarily ALT elevations) were considered to have been dose-limiting in patients

with cancer receiving this agent. Mild hematological toxicity (primarily thrombocytopenia) was also observed in some but not all clinical studies of maytansine.

2.3.1.2. Safety: Inhibition of EGFR

Numerous preclinical and clinical studies have been performed with inhibitors of EGFR including monoclonal anti-EGFR antibodies, TKIs, and other agents including EGFR-based vaccines and intratumoral injections of antisense to EGFR (1-6, 73-74). EGFR is expressed primarily on normal and tumor cells of ectodermal and mesodermal origin (75). EGFR signaling is involved in the development of epithelial organs and tissues with major abnormalities observed in development in EGFR knock-out (KO) mice (76, 77). The abnormalities observed in the GI tract, skin, eye, lung, kidneys, liver, and brain in KO mice lacking functional EGFR provide insight into the potential for adverse effects observed after administration of agents inhibiting this signaling pathway.

2.3.1.3. Safety: Clinical Adverse Effects of Anti-EGFR Antibodies

The safety and tolerability of unconjugated monoclonal anti-EGFR antibodies has been well-studied and detailed data about the 3 U.S. FDA-approved products (Erbitux-cetuximab, Vectibix-pantitumumab, and Portrazza-necitumuab) are available (71, 78, 79). The most frequent and severe toxicities commonly observed in patients receiving therapy with these 3 antibodies include EGFR inhibitor-induced dermatologic (skin and skin appendage) and mucosal changes, infusion-related reactions (IRR) including fatal reactions, electrolyte depletion (hypomagnesemia > hypocalcemia and hypokalemia), ocular toxicity (keratitis), pulmonary toxicity (pulmonary fibrosis/interstitial lung disease [ILD]), headache, infection, and gastrointestinal disorders including nausea, diarrhea, stomatitis and dyspepsia (71, 78, 79). Certain AEs were observed more frequently with the individual antibodies alone and in combination with other antineoplastic therapies and are detailed in the accompanying prescribing information for these products (71, 78, 79).

2.3.1.4. Safety: Clinical Adverse Effect of Antibody-Drug Conjugates

Several ADCs have been approved for human use and their safety and tolerability have been dependent on both the target of the antibody as well as the drug conjugate used in the construct. Gemtuzumab ozogamicin (Mylotarg®), a conjugate of calicheamicin and an anti-CD33 antibody was approved for treatment of elderly patients with acute myeloid leukemia (AML), was subsequently withdrawn from the market and has recently been approved again for AML patients using a different dose and schedule. Brentuximab vedotin (Adcetris®), an anti-CD30 monoclonal antibody conjugated to a microtubule disrupting agent, monomethyl aurostatin E (MMAE), is approved for the treatment of Hodgkin's lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) (80). Ado-trastuzumab emtansine (Kadcyla®) is a conjugate of DM1, (an analog of maytansine) linked through an SMCC linker with trastuzumab (Herceptin®), an anti-HER2 monoclonal antibody approved for the treatment of patients with breast cancer overexpressing HER2 (72). The safety profile of this latter antibody may provide some relevant background since it and AVID100 are both DM1 conjugates with the SMCC linker. The most common adverse event seen in patients receiving ado-trastuzumab emtansine that is likely to be related to the DM1 moiety (i.e., not commonly observed with trastuzumab

alone) was hepatotoxicity including cases of liver failure. Pulmonary toxicity manifest as interstitial lung disease and infusion-related reactions were also observed in patients receiving this anti-HER2 ADC. Several other toxicities not commonly associated with trastuzumab were observed with ado-trastuzumab emtansine including: fatigue, headache, constipation, thrombocytopenia (the dose-limiting toxicity observed with Kadcyla® administration), hemorrhage, and neurotoxicity manifest as peripheral neuropathy.

2.3.2 Clinical Experience with AVID100

Three antibody-drug conjugates ADC have current approvals by regulatory authorities and a wide variety of ADC with varying specificities, linkers, and cytotoxic components are in clinical development. Several ADCs with antibodies specific for EGFR and different linkers are in clinical development but only limited information is available on these potential products.

2.3.2.1. AVID100-01: Clinical Experience: Phase 1a Dose Escalation

This is the first clinical study of AVID100. A total of 24 patients were entered and treated in the completed Phase 1a dose escalation portion of this trial: 1 patient each at Dose Level 1 and 2 (20 and 40 mg/m^2), after which the protocol transitioned from single-patient cohorts to a 3+3 design and 3 patients each were entered at Dose Level 3, 4, 5, and 6 (80, 120, 180, and 220 mg/m^2, respectively); each dose level was considered to be tolerated according to protocol definitions. Accrual to Dose Level 7 (270 mg/m^2) followed; 7 patients were entered, 2 of whom experienced Cycle 1 dose-limiting toxicities (DLTs) (Grade 4 asymptomatic platelet count decreased and Grade 3 asymptomatic lipase increase), indicating the dose of 270 mg/m^2 was not well tolerated and had exceeded the MTD in this Phase 1 patient population. A trial-drug-related serious adverse event (SAE) also occurred in a patient assigned to the 270 mg/m^2 cohort; a 73 year old female with primary peritoneal carcinoma experienced Grade 3 pneumonitis during Cycle 4 of treatment which improved with glucocorticoid therapy and was considered resolved at the time of most recent follow-up. Three (3) additional patients were entered to the previous Dose Level 6; each tolerated dosing, thus confirming 220 mg/m^2 as the maximum tolerated dose (MTD) of AVID100. This dose level was selected as the recommended Phase 2 dose (R2PD).

All patients were dosed on an every 3 weeks (Q3W) schedule (3 weeks equals 1 cycle). During the dose escalation period, toxicities most frequently observed were Grade 1 to 2 in severity, occurred across all dose levels, and included the following in greater than one patient: rash, including acneiform rash in 16 patients; nausea in 10 patients; fatigue in 7 patients, vomiting in 5 patients with Grade 3 severity reported in 1 patient; diarrhea, dry skin, and headache in 3 patients each; and allergic conjuntivitis, mucositis, and anorexia in 2 patients each.

Laboratory abnormalities observed in greater than one patient were: asymptomatic platelet count decreases in 5 patients during Cycle 1, including a single Grade 4 event (at 270 mg/m^2 and meeting study DLT criteria for the dose cohort, see above), three Grade 3 events (at 120, 220, and 270 mg/m^2), and one Grade 2 event (at 80 mg/m^2); asymptomatic lipase elevations in 4 patients, including a single Grade 4 event during Cycle 8 (at 180 mg/m^2), and three Grade 3 events, one during Cycle 1 (at 270 mg/m^2 and meeting study DLT criteria for the dose cohort, see above), one during Cycle 2 (at 220 mg/m^2), one during Cycle 4 (at 80 mg/m^2); and aspartate aminotransferase (AST) elevations of Grade 3 severity in 2 patients, reported during Cycle 1 for one patient, and Cycles 3, 4, and 5 for the second patient (at 220 and 180 mg/m^2, respectively).

A total of 5 patients experienced infusion-related reactions (IRR), one an SAE of Grade 3 severity during Cycle 4 (at 80 mg/m^2), and four of Grade 2 severity during Cycles 2, 4, 6 and 7 (at doses of 120, 80, 120, and 180 mg/m^2, respectively). The Grade 3 reaction was characterized by dyspnea, bronchospasm, tachycardia, and chest pain; this event was dose-limiting for the patient, the infusion was stopped, and the patient was discontinued from further participation in the trial. The Grade 2 events responded to infusion interruption, symptomatic therapy and were generally restarted at a slower rate and completed. As a result of these events, infusions were lengthened for all patients from 1 hour to 1.5 hours following the Grade 3 event, and then from 1.5 hours to 2 hours following the occurrence of two Grade 2 events within a cohort, as required per protocol*; further, mandatory premedication was implemented (per protocol v5.0).

Other adverse events of note that occurred in single patients included: Grade 3 dyspnea in the patient with pneumonitis, Grade 3 lymphopenia, Grade 3 proteinuria; individual instances of Grade 2 keratitis, watering eyes, abdominal pain, myalgia, weight loss, sinusitis, infections of the oral mucosa and bladder; and Grade 1 dry eyes, pruritus, alopecia, peripheral sensory neuropathy, restless legs/twitching, oral candidiasis, fungal rash, cough, flu-like symptoms, viral upper respriatory infection, dehydration, and hypokalemia in individual patients (**TABLE 1**).

With the MTD and RP2D determined, accrual to the Phase 2a portion began at the RP2D of 220 mg/m^2.

This action to prolong infusions in the event of a Grade 3 IRR in a cohort or a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort is stipulated per protocol (see **Section 6.5.3.3; Duration of Infusion).*

- *In response to the above described Grade 3 event of 19Jul2017 in Cohort 3 (80 mg/m^2), and effective 20Jul 2017, infusions in all future patients were extended from 1 hour to 1.5 hours. Ongoing patients receiving AVID100 over 1 hour were allowed to continue to do so per protocol, or Investigators could opt to extend infusions to 1.5 hours (or longer), at their discretion. Sites were notified of these instructions in writing 20Jul17. The action was documented in a study Note to File dated 21Jul2017, and cited in protocol v5.0.*
- *In response to two Grade 2 events in Cohort 4 (120 mg/m2), and effective 21Dec2017, infusions in all future patients were extended from 1.5 hours to 2 hours. Ongoing patients receiving AVID100 over 1.5 hours were allowed to continue to do so per protocol, or Investigators could opt to extend infusions to 2 hours (or longer), at their discretion. The action was documented in a study Note to File dated 28Dec2017, and cited in protocol v6.0.*

Note: Effective with protocol v5.0, in order to decrease the risk of IRRs all patients will be premedicated with standard therapies prior to each infusion, at minimum through and including Cycle 4. A recommended premedication regimen is provided (see **Section 8.2**; Premedication of Study Drug-Related Toxicities).

TABLE 1: AVID100-01 (PHASE 1A DOSE-ESCALATION) PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS					
Adverse Event Term (in > 1 patient) (N-24*)	**Maximum Grade Per Patient**				
	1	**2**	**3**	**4**	**Total (%)**
Rash (including acneiform, maculopapular, & not specified)	14	2			16 (66.7)
Nausea	6	4			10 (41.7)
Fatigue	5	2			7 (29.2)
Infusion reaction		4	1**		5 (20.8)
Platelet count decreased		1	3	1	5 (20.8)
Vomiting	3	1	1		5 (20.8)
Lipase increased			3	1	4 (16.7)
Diarrhea	2	1			3 (12.5)
Dry skin	2	1			3 (12.5)
Headache	3				3 (12.5)
Allergic conjunctivitis	1	1			2 (8.3)
Mucositis	1	1			2 (8.3)
Anorexia	1	1			2 (8.3)
AST increased			2		2 (8.3)
Also reported, single episodes of:					
Grade 3	dyspnea, lymphocyte count decreased, pneumonitis**, proteinuria				
Grade 2	abdominal pain, bladder infection, keratitis, myalgia, oral mucosal infection, sinusitis, watering eyes, weight loss				
Grade 1	alopecia, cough, dehydration, dry eyes, flu-like symptoms, fungal intertrigo rash, hypokalemia, oral candidiasis, peripheral sensory neuropathy, photophobia, pruritus, restless legs/twitching, viral upper respiratory infection				

*Pts with at least 1 treatment-related AE = 21 of 24
**SAE

2.3.2.2. AVID100-01: Clinical Experience: Phase 2a Dose Expansion

As of **15 Apr 2020** data are available for a total of 18 patients[1] entered and treated in the ongoing Phase 2a dose expansion portion of this trial to cohorts of the 3 tumor types being evaluated: 4 patients to the TNBC cohort; 12 patients to the SCCHN cohort, and 2 patients to the Sq-NSCLC cohort. All patients are being treated at the RP2D of 220 mg/m^2; study drug is being administered by 2-hour IV infusion on the Q3W schedule evaluated in Phase 1a. Three (3)[2] patients in the SCCHN cohort have experienced study drug-related SAEs/DLTs: Grade 4 AST/ALT elevation during Cycle 2 and Grade 4 IRR during Cycle 6 in one patient; Grade 3 mucositis during Cycle 2 in one patient, and Grade 2 subdural hemorrahges during Cycle 1 in a patient with Grade 3 decreased platelets who had a fall hitting his head. The first patient underwent dose reduction to 180 mg/m^2 and continued on study after resolution of the AST/ALT

[1] A total of 22 patients were entered and treated as of this data cutoff date, however data entry was delayed due to coronavirus pandemic mitigations.

[2] Two (2) additional patients, one in the SCCHN cohort and one in the TNBC cohort, experienced study drug-related SAEs/DLTs prior to the data cutoff date, however the events do not appear in the study database due to data entry delays secondary to coronavirus pandemic mitigations: Grade 3 platelet decrease during Cycle 1in one patient and Grade 3 AST increase during Cycle 1 in one patient. The SCCHN patient underwent dose reduction to 180 mg/m^2 and continued on study after resolution of decreased platelets, but was discontinued from study participation as a result of disease progression after 2 cycles at the reduced dose. The TNBC patient was planned to undergo dose reduction to 180 mg/m^2 but discontinued study participation due to disease progression.

elevation, but was discontinued from study participation as a result of the IRR that followed 4 cycles later. The other two patients underwent dose reduction to 180 mg/m^2 and continued on study following resolution of their events per protocol; both patients discontinued from study participation due to disease progression after 3 and 4 additional cycles, respectively, of treatment at the lower dose. One (1) patient in the SCCHN cohort experienced the SAE of Grade 3 pneumonitis considered possibly related to treatment, with onset after study discontinuation due to disease progression (56 days after last dose); at last report the event was was resolving.

Thus far the treatment-related clinical AEs that have been reported for greater than one patient have included: fatigue in 6 patients; rash, including acneiform rash in 5 patients; dry skin and watering eyes in 4 patients each; and mucositis (including the Grade 3 event meeting DLT criteria, mentioned above), keratitis, nausea, and anemia in 2 patients each.

Treatment-related laboratory abnormalities observed in greater than one patient have included: platelet count decreases in 5 patients (including the Grade 3 event that occurred in the patient with subdural hemorrhages, mentioned above); AST elevations in 3 patients (including the Grade 4 event meeting DLT criteria, mentioned above); proteinuria in 3 patients; and alkaline phosphatase increase and hypomagnesemia in 2 patients each. The grades of all events, and other adverse events of note that occurred in single patients are noted in **TABLE 2**.

Accrual to the Phase 2a portion of the study is ongoing.

TABLE 2: AVID100-01 (PHASE 2A DOSE-ESCALATION)
PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS

Adverse Event Term (in > 1 patient) (N-18*)	Maximum Grade Per Patient				
	1	2	3	4	Total (%)
Fatigue	2	3	1		6 (33.3)
Rash (including acneiform and not specified)	5				5 (27.8)
Platelet count decrease	3	1	1^		5 (27.8)
Dry skin	4				4 (22.2)
Watering eyes	3	1			4 (22.2)
AST increase	1	1		1**^	3 (16.7)
Proteinuria	1	2			3 (16.7)
Hypomagnesemia	2				2 (11.1)
Keratitis		2			2 (11.1)
Mucositis		1	1**^		2 (11.1)
Nausea	2				2 (11.1)
Anemia		2			2 (11.1)
Alkaline phosphatase increase		2			2 (11.1)
Also reported, single episodes of:					
Grade 4	ALT increase**^, AST increase**^, IRR**^				
Grade 3	Lipase increase, pneumonitis**				
Grade 2	Anorexia, asthma exacerbation, conjunctival injection, cough, eye pain/irritation, uveitis, hyperhidrosis, malaise, incision site discharge, subdural hemorrhages**^, bilirubin increase, hypoalbuminemia, hypokalemia				
Grade 1	Diarrhea, dry mouth, dysgeusia, epistaxis, pruritus, forced expiratory flow reduced, WBC count decrease, PTT prolonged, amylase increase, hyperuricemia, hyponatremia				

*Pts with at least 1 treatment-related AE = 10 of 13 (data as of 15Apr2020)

**SAE, ^DLT

2.4. Rationale for and Risks of Proposed Clinical Study

2.4.1 Rationale

The clinical utility of a variety of unconjugated anti-EGFR antibodies (cetuximab, panitumumab, necitumumab) has been established in a variety of clinical indications including CRC, SCCHN, and Sq-NSCLC. Despite the documentation of activity of these monoclonal antibodies alone or in combination with standard therapies in these indications, most patients treated with these products do not respond and resistance eventually develops in the majority of patients who derive initial benefit. Conjugation of the anti-EGFR antibody MAB100 to DM1 via a stable linker has resulted in increased antitumor activity *in vitro* and *in vivo* in a variety of tumor models including models using tumor lines that are resistant to cetuximab. Based on prior validation of EGFR as a target as well as the evidence that AVID100 may provide superior antitumor activity based on nonclinical models, this trial aims to evaluate the safety and tolerability of escalating doses of this novel conjugated anti-EGFR antibody followed by a preliminary evaluation of its clinical activity in selected patients with EGFR-overexpressing tumors.

The three indications identified for further study in the Phase 2a segment of the study are patients with mTNBC, SCCHN, and Sq-NSCLC without alternative therapeutic options. The detailed rationale for the choice of each indication is provided (see **Section 2.1.2, Section 2.1.3, Section 2.1.4**). For the purposes of this study the original DAKO PharmDx assay has been revalidated for the assessment of higher levels of EGFR expression to facilitate enrichment of patient populations that may be appropriate targets for AVID100.

Briefly, the EGFR pathway has been documented to play an important role in metastatic BC. EGFR-overexpression is observed in subsets of patients with metastatic BC (most commonly associated with TNBC) and, although limited activity has been observed with single agent therapy with EGFRi, addition of chemotherapy to cetuximab has shown increased activity in Phase 2 studies. The DM1 moiety coupled to trastuzumab has shown activity and is approved for treatment of patients with HER2 over-expressing BC. There is also strong evidence of activity for other tubulin-targeted agents suggesting that AVID100 may be active in the triple-negative subset of patients with metastatic BC who overexpress EGFR (3+ overexpression in ≥ 50% of cells in approximately 6% of patients tested with the validated assay and 2+ overexpression in ≥75% of cells in approximately 13% of cases) (Data on File, Forbius/Formation Biologics).

Cetuximab, an unconjugated chimeric anti-EGFR mAb is approved alone and in combination with radiotherapy and chemotherapy in selected patients with SCCHN. Phase 3 studies of chemotherapy, compared to cetuximab plus chemotherapy, documented increased ORR, PFS, and OS for the combination compared to chemotherapy alone. EGFR overexpression is common in patients with SCCHN (3+ overexpression in ≥ 50% of cells in approximately 22% of patients tested using a validated assay) (Data on File, Forbius/Formation Biologics) . The role of the EGFR pathway in this malignancy has been well-documented. In addition, other microtubule-targeting agents have been shown to be active in the treatment of patients with SCCHN. The documented therapeutic efficacy of anti-EGFR mAbs and taxanes in the treatment of SCCHN, as

well as the significant population of patients whose tumors overexpress EGFR, provides a strong rationale for the evaluation of AVID100 as a potential therapy for patients with this malignancy.

Cetuximab showed variable activity in combination with chemotherapy in the first line treatment of NSCLC. Necitumab, a recombinant human IgG1 monoclonal anti-EGFR antibody, has been shown to be safe and effective in combination with chemotherapy in the treatment of patients with squamous histology but was ineffective in patients with non-squamous histology NSCLC. The incremental activity observed in this setting is modest suggesting that there is room for improved efficacy. The majority of patients with NSCLC overexpress EGFR (3+_ overexpression in ≥ 50% of cells in approximately 22% of patients with NSCLC tested using a validated assay) (Data on File, Forbius/Formation Biologics). Anti-EGFR antibodies have activity in patients with NSCLC including an approved indication in patients with squamous histology NSCLC. Since squamous NSCLC is also sensitive to tubulin-targeted agents in various lines of therapy (paclitaxel, docetaxel, and vinorelbine) there is a strong rationale for targeting patients with this malignancy with an anti-EGFR antibody-DM1 conjugate.

2.4.2 Risks

The potential risks to patients enrolled in this trial have been outlined in sections describing the potential adverse events associated with: (a) maytansine and its analog, DM1; (b) inhibition of EGFR; (c) inhibition of EGFR by anti-EGFR monoclonal antibodies; and (d) antibody-drug conjugates (ADC). Nonclinical toxicology studies have been performed in cynomolgus monkeys to evaluate potential safety issues that may emerge in patients treated with AVID100 and these studies have been utilized to define a starting dose for the first clinical study. A cohort dose escalation plan has been included to rapidly escalate the dose of AVID100 initially, but decrease the incremental increases and increase the patient sample size in subsequent cohorts. Escalation to each subsequent higher dose cohort will require demonstration of safety and tolerability in the preceding cohort until a safe recommended Phase 2 dose (R2PD) and schedule can be established. In the event of certain toxicities the infusions may be slowed, premedications or other supportive measures may be instituted, doses may be decreased, or AVID100 may be discontinued. Premedications for infusion-related reactions are not required, but can be instituted in patients who experience such adverse reactions during any cycle and, premedication for all patients may be instituted if the frequency and/or severity of AEs suggest that this would improve patient safety and the tolerability of AVID100.

Note: Effective with protocol v5.0, in order to decrease the risk of IRRs all patients will be premedicated with standard therapies prior to each infusion, at minimum through and including Cycle 4. A recommended premedication regimen is provided (see **Section 8.2**; Premedication of Study Drug-Related Toxicities).

Because of the risk of pulmonary toxicity that has been observed with ADCs and agents inhibiting EGFR, and because a single patient on the Phase 1a segment of this trial receiving a dose of 270 mg/m^2 developed pneumonitis considered related to AVID100, patients with a history of or evidence of interstitial fibrosis will continue to be excluded from entry into the trial. Patients will be assessed using chest CT every 6 weeks (when disease assessments are scheduled) regardless of whether these imaging studies are required for tumor assessment. Patients will also be evaluated by regular evaluation of oxygen saturation using pulse oximetry, physical exams and queries regarding all adverse events with a detailed assessment of potential

pulmonary adverse events. Pulse oximetry will be conducted prior to and following all infusions of AVID100 throughout the study, and decreases in oxygen saturation will require further evaluation. In the event of patient-reported symptoms of pulmonary toxicity or Investigator-assessed symptoms or signs of potential pulmonary adverse effects, additional studies including interval chest imaging studies will be performed. If pulmonary findings on imaging studies (e.g., evidence of pulmonary fibrosis, interstitial pneumonitis, acute respiratory distress syndrome) or clinical evidence of pulmonary adverse effects are detected, administration of AVID100 will be permanently discontinued and pulmonary consultation will be obtained to consider additional appropriate diagnostic procedures and/or therapeutic interventions.

2.5. Rationale for Starting Dose

The starting dose is based on the observed safety and tolerability of AVID100 in the single dose GLP toxicology study that simulates the intermittent (every 3 week) schedule to be evaluated in this Phase 1a study as well as in the planned Phase 2a expansion cohorts. The 25 mg/kg dose in this study was determined to be the HNSTD. One sixth the HNSTD adjusted for body surface area (BSA) is 1.3 mg/kg. In order to minimize the variability of PK parameters observed when dosing monoclonal antibodies on a mg/kg basis, particularly in obese patients, dosing of AVID100 will be based on a per m^2 basis. The proposed starting dose is **20 mg/m^2**. Data from the multidose GLP study and other pilot toxicology studies were also considered in the determination of the initial dose to be used in this first study in patients. In addition, data on the pharmacokinetic profile of AVID100 as well as studies in tumor models were considered in the choice of the starting dose and escalation scheme. The original maximum dose to be administered in this trial was not to exceed **220 mg/m^2/dose**, based on the initial rate of infusion of AVID100 over 1 hour. Since the infusion rate has been extended the maximum dose to be administered in this trial was adjusted accordingly to **330 mg/m^2**.

2.6. Justification for the Recommended Phase 2 Dose

The R2PD has been determined to be 220 mg/m^2 based on observed DLTs at the highest dose level studied, 270 mg/m^2. Seven patients were treated at a dose of 270 mg/m^2 on an every three week (Q3W) schedule. One patient was not evaluable for safety because of the development of brain metastases secondary to primary breast cancer, diagnosed during Cycle 1. Two Grade 3 toxicities were observed at this dose level during Cycle 1 (asymptomatic Grade 3 lipase elevation without evidence of pancreatitis and Grade 4 thrombocytopenia without sequelae). The occurrence of two DLTs in Cycle 1 determined that this dose level exceeded the MTD. Because of this finding, an additional three patients were added to the previous dose level of 220 mg/m^2, a dose level that had been tolerated without any ≥ Grade 3 AE that met the DLT criteria in the initial 3 patients evaluated (one patient had experienced Grade 3 elevation of AST but this did not meet the protocol-specified criteria for DLT). No DLTs were observed in Cycle 1 in the additional 3 patients treated at this dose level.

Based on safety and tolerability of the 6 patients evaluated, 220 mg/m^2 was determined to be the MTD and has been selected as the R2PD to be evaluated in three expansion cohorts in patients with metastatic TNBC, SCCHN, and Sq-NSCLC, each with high expression of EGFR as determined by standardized immunohistochemistry (IHC) testing.

Historically, the efficacy of ADCs is dependent upon multiple factors including the relative expression of the target antigen on tumor and normal tissues as well as the delivery of the ADC to the tumor. The latter parameter depends on the delivery of the highest feasible dose given the relatively low proportion of the ADC that is delivered to the tumor. Given the nature of patients enrolled in the Phase 1a segment (refractory to multiple prior therapy and the requirement that they were epithelial tumors potentially responsive to EGFR inhibitors but were not required to overexpress EGFR) a relatively small number of patients were treated on multiple cycles of AVID100. For this reason, it may be necessary to reevaluate the dose utilized in the Phase 2a expansion cohorts based on observed acute and/or longer term tolerability as more experience with the safety and tolerability of AVID100 is obtained.

FOR ADDITIONAL INFORMATION, PLEASE REFER TO THE INVESTIGATOR'S BROCHURE (IB)

3. TRIAL OBJECTIVES AND DESIGN

3.1. Phase 1a: Dose-Escalation

3.1.1 Primary Objective

To determine the safety and tolerability, dose-limiting toxicities (DLTs), and the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D)** of sequential escalating doses of AVID100 when administered once every 3 weeks (Q3W) by 2-hour* intravenous (IV) infusions to patient cohorts with locally advanced/unresectable or metastatic solid tumor malignancies of epithelial origin

Protocol v5.0: Extended from 1 hour to 1.5 hours due to Grade 3 IRR observed in Cohort 3 (80 mg/m^2); effective 20Jul2017 and documented in a study Note to File dated 21Jul2017 (see **Section 2.3.2.1; AVID100-01: Clinical Experience)*

Protocol v6.0: Extended from 1.5 hours to 2 hours due to Grade 2 IRRs observed in Cohort 4 (120 mg/m2); effective 21Dec2017 and documented in a study Note to File dated 28Dec2017 (see **Section 2.3.2.1; AVID100-01: Clinical Experience)*

***Protocol v6.0: The MTD and RP2D has been determined to be 220 mg/m^2*

3.1.2 Secondary Objectives

- Characterization of the pharmacokinetic (PK) profile of total antibody (AVID100 plus MAB100), AVID100, and DM1 in this patient population *(all patients)*
- Evaluation of the preliminary antineoplastic effects of AVID100 in this patient population *(all patients)*, including:
    - Evidence of objective response (OR) or stable disease (SD)*
    - Duration of OR or SD*
    - Time to progression (TTP) of disease*

*As assessed by standard response criteria (see **Appendix F**; Measurement of Effect; Response Evaluation Criteria for Solid Tumors [RECIST] v1.1)

3.1.3 Exploratory Objective

Tests to assess potential biomarkers and response predictors will be conducted and may include:

- Evaluation by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) *(or similar assay)* of tumor EGFR-expression and other potential biomarkers of pathway activation in archival, formalin-fixed, paraffin-embedded (FFPE) samples obtained from a previous diagnostic or surgical procedure *(if available)*

    Note: *Biopsies for confirmation of EGFR status and performance of biomarker assessments are permissible in Phase 1a patients on a case-by-case basis, if considered safe, following discussion between the Investigator and the Sponsor's Medical Monitor(s).*

3.2. Phase 2a: Dose-Expansion

3.2.1 Primary Objective

To further evaluate the safety, tolerability, and preliminary antineoplastic effect* of AVID100 when administered at the RP2D** and schedule in 3 expansion cohorts of patients with locally advanced/unresectable or metastatic solid tumor malignancies of epithelial origin, that are measurable, and that express the epidermal growth factor receptor (EGFR). The tumor types to be evaluated in these expansion cohorts are metastatic triple-negative breast cancer (mTNBC), squamous cell carcinoma of the head and neck (SCCHN), and squamous histology non-small cell lung carcinoma (Sq-NSCLC).

*As assessed RECIST v1.1
**May be equal to or less than the MTD

Note: To be eligible for study enrollment, analytical results documenting EGFR expression positivity by IHC must be documented by a central laboratory in archival FFPE samples obtained from a previous diagnostic or surgical procedure. In the mTNBC cohort results must be 3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells. In the SCCHN and Sq-NSCLC cohorts results must be 3+ intensity in ≥ 50% of tumor cells. If tissue is unavailable, patients must have primary or metastatic tumor sites(s) considered safely accessible for biopsy, and must be willing to undergo tumor biopsy in order to document EGFR expression positivity to verify study eligibility.

Sufficient FFPE tumor tissue from either a prior procedure or a recent biopsy must also be available for submission to a central laboratory for other study-related evaluations as planned per protocol (see **Section 3.2.3**; Exploratory Objective).

3.2.2 Secondary Objective

Further characterization of the PK profile of total antibody (AVID100 plus MAB100), AVID100, and DM1 in this patient population

3.2.3 Exploratory Objective

Tests to assess potential biomarkers and response predictors will be conducted and may include but are not limited to:

- Evaluation by FISH *(or similar assay)* of tumor EGFR-expression and other potential biomarkers in archival, FFPE samples obtained from either a previous diagnostic or surgical procedure or a recent biopsy *(required at Screening, optional at other indicated timepoints)*
- Evaluation of circulating tumor DNA (ctDNA) for *EGFR* extracellular domain (*EGFR*-ECD) mutation status and *EGFR* mutant type III variant (*EGFR*vIII) deletions (SCCHN only), as well as evaluation of other potential biomarkers of interest *(required for all indications)*

3.3. Trial Design Summary

Patient Population and Objectives

Approximately 90 male and female patients with documented solid tumor malignancies of epithelial origin that are locally advanced or metastatic, and either refractory to standard therapy or for whom no standard therapy is available, will be entered into this Phase 1a/2a, multicenter, open-label, dose-escalation, cohort study of AVID100, an anti-human EGFR monoclonal antibody (mAb) linked to the maytansinoid DM1.

The initial Phase 1a Dose-Escalation portion of the trial (approximately 30 patients) is designed to evaluate the safety and tolerability, as well as identify the DLT(s), MTD, and RP2D of sequential escalating doses of AVID100 (study drug), when administered to patients with tumors reasonably likely to express EGFR; secondary objectives include characterization of the PK profile of total antibody (AVID100 plus MAB100), AVID100, and DM1, as well as preliminary assessment of the antineoplastic activity of AVID100.

Once the MTD and/or RP2D is identified, 3 expansion cohorts of patients (approximately 60 patients total; approximately 30 patients in the mTNBC cohort* distributed equally to enroll 15 patients to each of two cohort subgroups [i.e., either 3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells], and 15 patients to each of the SCCHN and Sq-NSCLC cohorts) with measurable disease and confirmed EGFR-positive tumors will be accrued during the subsequent Phase 2a Dose-Expansion portion of the trial where the goal will be to further evaluate the safety, tolerability, and antineoplastic activity of AVID100 when administered at the RP2D; a secondary objective is to further characterize the PK profile of total antibody, AVID100, and DM1 (PK evaluation will be less extensive in Phase 2a when compared to Phase 1a). The tumor types to be evaluated in these expansion cohorts are mTNBC, SCCHN, and Sq-NSCLC.

An exploratory objective in both the Phase 1a and Phase 2a portions of the trial will be evaluation of the utility of potential biomarkers and response predictors of AVID100 activity in FFPE tumor tissue (optional in Phase 1a patients, required in Phase 2a patients) and peripheral blood (in Phase 2a patients). In addition, SCCHN patients enrolled to Phase 2a will be evaluated for *EGFR*-ECD mutation status and *EGFR*vIII) deletions. Patients will be treated and followed on an outpatient basis throughout the trial, unless hospitalization is required for other reasons, or to assure patient safety.

**Recruitment in mTNBC cohort subgroups will be halted after enrollment of 15 patients in order to assess activity.*

Dosing Schedule and Treatment Duration

- Beginning with the first dose, all patients must be premedicated with standard therapies prior to <u>each</u> dose of AVID100 to reduce the risk of infusion-related reactions (IRRs). Mandatory premedication for other adverse events will be implemented for all patients should a pattern begin to emerge of mild-to-moderate study drug-related reactions that are amenable to prophylaxis with standard agents.
- On Day 1 of study, patients will receive study drug administered by <u>2-hour</u> IV infusion. Patients receiving doses ≤ 180 mg/m^2 will receive study drug in a fixed 100 mL volume;

patients receiving doses > 180 mg/m^2 will receive study drug in a volume of 200 to 250 mL (dose to be divided between two 100 mL infusion volumes [i.e., 100 mL × 2] to be administered sequentially, or delivered in a larger volume up to 250 mL using a single flexible IV bag). AVID100 will be administered once every 3 weeks (Q3W) with administration on Day 1 of the first week, followed by a 3-week recovery period. This 3 week (21 day) period will be considered Cycle 1. In Phase 1a, determinations regarding cohort escalation, DLTs, and MTD will be based on the toxicities observed during this initial cycle. Patients must receive their full planned dose of AVID100, plus complete the designated follow-up period, in order to be considered evaluable for tolerability, unless dose reduction, interruption, or discontinuation was the result of a DLT. End of Cycle 1 (EOC1) assessments are to be performed no sooner than C1/D21 (-2 days).

- In all patients entered, a minimum of at least Cycle 1 of study will be completed, if tolerated, after which, in the absence of documented disease progression or unacceptable toxicity, a patient may continue to receive additional cycles of study drug Q3W (± 2 days), at the same dose and infusion duration established for the patient during Cycle 1, and on the same schedule. These additional 3 week cycles may continue, if tolerated and in the absence of documented disease progression, at the Investigator's discretion, provided specified retreatment criteria have been met. Evidence of progressive disease at any point in the study will necessitate withdrawal of the patient from further participation so that alternative management of their malignancy may be considered.

Doses to be Evaluated

At study entry, patients will be sequentially assigned to fill escalating dose cohorts of AVID100 beginning at the dose of **20 mg/m^2/dose**.

An accelerated titration design (1 patient per cohort) with 100% incremental increases in dose will be used for dose-escalation for up to 2 cohorts (until at most Cohort 3) or until the occurrence of an event that activates a stopping rule. Thereafter, dose-escalation will follow a standard 3+3 design, with 50% and then 25% incremental increases in dose, and with a target toxicity level of 33.3% or less as determined by DLTs. The number of cohorts evaluated and the maximum administered dose (MAD) will depend upon the observed tolerability of AVID100 during Cycle 1 of patient treatment; however, the maximum dose to be administered in this trial is not to exceed **330 mg/m^2/dose.** Doses will be calculated as shown (**Figure 1**).

The Investigator(s) and Sponsor's Medical Monitor(s) will comprise a Study Safety Committee, and will review clinical and laboratory safety data on an ongoing basis throughout the study and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort.

Figure 1: Dose Escalation Schema

Abbreviations (in alphabetical order): DLT, dose-limiting toxicity; Gr, grade; pts, patients

Filling of Cohorts

Phase 1a Dose-escalation: In cohorts with > 1 patient enrollment will be staggered between the first and second patient by at minimum 24 hours in order to assess for IRRs; thereafter patients within a cohort may be added concurrently. Dose escalation and accrual to the next cohort will occur after the minimum number of patients required for tolerability assessment in the current cohort have completed Cycle 1, and only after acceptable tolerance has been demonstrated in at least 1 of 1, 3 of 3, or 5 of 6 patients treated in the current cohort (depending on cohort size), and review of the data with the Sponsor's Medical Monitor(s).

Phase 2a Expansion: Once the MTD (or maximum dose to be studied) is identified, and the RP2D is determined, patients will be enrolled to the Phase 2a portion of the study to receive the RP2D. Patients will be accrued to one of 3 expansion cohorts, by tumor type (**Figure 2**). The tumor types to be evaluated in these expansion cohorts are mTNBC (with 2 subgroups), SCCHN, and Sq-NSCLC. Patients will be identified using the same eligibility criteria except as specified; however, patients must also have measurable disease and documented EGFR-positive tumors as specified, and if patients do not have sufficient archival tumor tissue to submit to a central lab in order to establish EGFR status and be available for completion of biomarker evaluations, they must have primary or metastatic tumor site(s) considered safely accessible for biopsy, and be willing to give consent for biopsy collection of additional tissue.

If the R2PD is not tolerated and a Cycle 1 DLT is experienced in ≥ 33% of patients entered into an expansion cohort, the next lower dose with established tolerability in Phase 1a will be administered to subsequent patients.

**Biopsies for confirmation of EGFR status and performance of biomarker assessments are permissible in Phase 1a patients on a case-by-case basis, if considered safe, following discussion between the Investigator and the Sponsor's Medical Monitor(s).*

Figure 2: Expansion Cohorts

Abbreviations (in alphabetical order): MTD, maximum tolerated dose; mTNBC, metastatic triple-negative breast cancer,; pts, patients; RP2D, recommended phase 2 dose; SCCHN, squamous cell carcinoma of the head and neck, Sq-NSCLC, squamous histology non-small cell lung carcinoma.

Study Assessments

For safety, patients will be monitored throughout the treatment and 1 month follow-up period for evidence of AEs, including changes in clinical status, laboratory data, ECG findings, and either MUGA scans or echocardiograms in patients with a history of CHF. Evaluation of patients for interstitial pulmonary fibrosis or other pulmonary disorders will include evaluation of related signs and symptoms, reported adverse effects, pulse oximetry, pulmonary function tests, and radiographic imaging of the chest (X-ray and CT); evidence of pulmonary fibrosis of any grade at any point in the trial will result in immediate discontinuation from treatment with study drug. Patients will also be evaluated for evidence of antibody formation to AVID100. Patients experiencing a DLT regarded as associated with study drug at any point during treatment will either be discontinued from treatment with study drug, or may continue if there is evidence of an OR, disease stabilization, or other clinical benefit, but must do so at a reduced dose of AVID100 (see **Section 8.3.2**; Dose Reduction), and ONLY following discussion with the Sponsor's Medical Monitor(s). Patients may not be retreated following the occurrence of a DLT until

retreatment criteria have been met. Only DLTs occurring during Cycle 1 will be used to make determinations regarding dose escalation and tolerability. Exceptions to continuing on study at a reduced dose include evidence of pulmonary, neuro-, ocular, nephro-, or hepatotoxicity as detailed in **Section 9.1** (Criteria for Treatment Discontinuation). In such instances patients must be permanently discontinued from treatment with study drug.

4. PATIENT SELECTION

4.1. Number of Patients

4.1.1 Investigational Sites

This is a multicenter trial.

- Phase 1a: Single center planned (up to 2 centers may participate based on accrual)
- Phase 2a: Accrual to be divided between approximately 6-12 participating centers; number of sites TBD based on tumor type selection and anticipated accrual

4.1.2 Number of Patients

Approximately 90 patients to be entered during the combined Phase 1a and Phase 2a portions of the trial.

Considerations for estimating the number of patients to be entered are as follows:

- Phase 1a: Approximately 30 patients in escalating dose cohorts
    - Minimum of 1 to 3 patients per dose cohort; assume approximately 4 dose cohorts to be evaluated to establish the MTD and/or RP2D
    - Expansion of any cohort to 6 patients in the event of a Cycle 1 DLT in any of the initial 1 to 3 patients
    - Minimum of 6 patients to be treated at the MTD (or maximum administered dose [MAD]); expansion of this cohort (or any other) up to 12 patients may be considered to further evaluate tolerability

- Phase 2a: Approximately 60 patients in 3 expansion cohorts (approximately 30 patients in the mTNBC cohort and 15 patients each in the SCCHN and Sq-NSCLC cohorts); more patients may be entered if fewer than 30 patients are required to establish the RP2D in Phase 1a

There is potential for entry of additional patients in the Phase 1a portion of the trial to:

- Assure sufficient evaluable patients per cohort by entering an additional patient to a cohort (e.g., increase a 1 patient cohort to 2 patients, a 3 patient cohort to 4 patients, or a 6 patient cohort to 7 patients)

    Note: Should this action be taken, cohort tolerability assessment and subsequent dose escalation will occur when the minimum number of patients required to evaluate tolerability have completed Cycle 1. However, if any additional patient experiences an event that would, per protocol, result in either cohort expansion or the halting of dose escalation, protocol rules as outlined herein will be followed (see **Section 6.6.2.2**; Rules for Escalation and Cohort Expansion in Phase 1a).

- Evaluate > 4 dose cohorts should this be necessary to identify the RP2D
- Expand a lower dose cohort(s) if an initially identified MTD cohort is expanded and is found to exceed tolerability either with single or repeated cycles of therapy

- Evaluate a previously unexamined intermediate dose level(s) between 2 established dose levels to further characterize safety and tolerability, if indicated

  Note: This action would be taken in the event of an unacceptably high frequency of toxicities observed in patients treated at one dose, considered to be in marked contrast to the tolerability noted in the immediately preceding dose cohort.

There is potential for additional expansion cohorts within the Phase 2a portion of the trial (by amendment only).

Expanded accrual in any cohort will take place at the Sponsor discretion, after discussion with the Investigator(s).

4.2. Criteria for Inclusion

Patients must meet all of the following criteria to be eligible for participation in the trial:

1. Male or female patients, ≥ 18 years of age at the time of obtaining informed consent
2. Patients with a documented (histologically- or cytologically-proven) solid tumor epithelial carcinoma that is locally advanced or metastatic
3. Patients with a malignancy that is either refractory to standard therapy or for which no standard therapy is available
4. Patients with a malignancy that is currently not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor
5. Phase 1a Dose-Escalation Cohorts: Patients with measurable or non-measurable disease according to RECIST, v1.1 (see **Appendix F**; Measurement of Effect). To include patients reasonably likely to express EGFR*

   *Includes patients with breast, ovarian, endometrial, cervical, esophageal, gastric, colorectal, biliary, hepatocellular, pancreatic, prostate, renal cell, bladder carcinoma or gliomas. Patients with squamous cell carcinoma of the head and neck (SCCHN) and NSCLC may only be entered after careful evaluation of their smoking history, pulmonary function, and imaging studies to rule out pulmonary dysfunction, and after discussion with the Medical Monitor.

6. Phase 2a Expansion Cohorts ONLY: Patients with mTNBC, SCCHN, or Sq-NSCLC and with:

   - Measurable disease according to RECIST, v1.1 (determined as 1 or more lesions as assessed by computerized tomography [CT] or magnetic resonance imaging [MRI]).

     Note: Any lesions which have been subjected to locoregional therapies or radiotherapy should not be considered measurable unless the lesion has clearly progressed (per RECIST v1.1) since the procedure.

   - An EGFR-expressing solid tumor documented by central laboratory assessment to be positive by IHC* as follows:

- mTNBC Cohort**: 3+ intensity in ≥ 50% of cells or ≥ 2+ intensity in ≥ 75% of cells (~15 patients in each subgroup)
- SCCHN Cohort: 3+ intensity in ≥ 50% of tumor cells (~15 patients)
- Sq-NSCLC Cohort: 3+ intensity in ≥ 50% of tumor cells (~15 patients)

*** Recruitment in mTNBC cohort subgroups will be halted after enrollment of 15 patients in order to assess activity*

- EGFR assessment to be made using:
  - An archival FFPE tumor specimen *(as recent as possible; sufficient FFPE tissue must be available for submission to a central analytical laboratory in order to confirm EGFR status as well as be available for other study-related evaluations),* or
  - Surgical or biopsy specimens if archival tumor tissue results are not available *(patients must be willing to undergo a pre-dosing biopsy from a primary or metastatic tumor site(s) considered safely accessible for biopsy).*

**DAKO EGFRpharmDX™ IHC kit system technology to be utilized. For this study, EGFR-positive staining is defined as noted above for each cohort.*

7. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) (or equivalent Karnofsky Performance Status; see **Appendix B**; Performance Status Evaluation) as follows, and an anticipated life expectancy of ≥ 3 months:
   - Phase 1a Dose-Escalation Cohort Patients: 0, 1, or 2
   - Phase 2a Expansion Cohort Patients: 0 or 1

8. Women of childbearing potential (WOCBP) and fertile men with a partner of childbearing potential agreeing to use a highly effective method of contraception during the study and for 3 months after the last dose of study drug; male patients must also agree to refrain from sperm donation during this period.

   Note: Women are considered of childbearing potential if they have experienced menarche, and they have not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or are not postmenopausal. Post-menopause is defined as: 1) amenorrhea for > 12 months with no other cause, or 2) irregular menstrual periods, on hormone replacement therapy (HRT), with a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL. In women under 55 years who have not been surgically sterilized, post-menopausal status should be confirmed by evaluation of serum FSH.

   Men are considered fertile unless they have undergone surgical sterilization (bilateral vasectomy or a bilateral orchiectomy).

   A highly effective method of contraception is defined as true abstinence or non-hormonal contraception equivalent to a double-barrier method, or intrauterine device (see **Section 11.1**; Precautions Regarding Procreation).

9. Patients with the ability to understand and give written informed consent for participation in this trial, including all evaluations and procedures as specified by this protocol

Note: Informed consent must be obtained prior to patient screening, and before any evaluations or procedures specifically related to this study are performed.

4.3. Criteria for Exclusion

Patients meeting any of the following criteria are ineligible for participation in the trial.

4.3.1 Patients to be Excluded

1. Women who are pregnant or intending to become pregnant during or within 3 months after the last dose of study drug; women who are breastfeeding; WOCBP and fertile men with a WOCBP partner not using and not willing to use a highly effective method of contraception.

   Note: WOCBP and fertile men will be informed as to the potential risk of procreation while participating in this trial. A pregnancy test must be performed on, and the results reviewed for, each WOCBP prior to first study drug administration (serum at screening, serum or urine thereafter). A negative pregnancy test performed within **≤ 2 working days** prior to first study drug administration must be documented on the patient's electronic case report form (eCRF) (see **Section 11.1**; Precautions Regarding Procreation).

2. Patients with known central nervous system (CNS) or leptomeningeal metastases, or spinal cord compression not controlled by prior surgery or radiotherapy, or patients with symptoms suggesting CNS involvement for which treatment is required

   Note: Patients previously treated for these conditions that have stable CNS disease (verified with 2 consecutive imaging studies performed at least 4 weeks apart with the most recent study performed within 12 weeks prior to first study drug administration), are asymptomatic and are not currently taking corticosteroids, or are on a stable dose of corticosteroids for at least 4 weeks prior to Day 1 of the study, are permitted. Prophylactic anticonvulsant medications are allowed.

   Patients with newly identified CNS disease during study treatment will be considered to have disease progression and will be discontinued from study to allow for appropriate management.

3. Patients with a malignancy other than that of epithelial origin
4. Phase 2a Expansion Cohorts ONLY: Patients with an active second malignancy or history of another malignancy within the last 2 years with the exception of:
   - Treated non-melanoma skin cancers
   - Treated carcinoma *in situ* (CIS) of the breast, cervix, bladder, colon, endometrium, skin (melanoma) provided CR was achieved at least 2 years prior to study and no additional therapy is ongoing or required during study period with the exception of anti-estrogen/androgen therapy or bisphosphonates
   - Controlled, superficial carcinoma of the bladder
   - T1a carcinoma of the prostate comprising < 5% of resected tissue and prostate specific antigen (PSA) within normal limits (WNL) since resection
5. Patients with any of the following hematologic abnormalities at baseline:
   - Hemoglobin < 9.0 g/dL

- Absolute neutrophil count (ANC) < 1,500 per mm^3
- Platelet count < 100,000 per mm^3

Note: Patients may have received a blood/blood product transfusion prior to study, if clinically warranted.

6. Patients with any of the following serum chemistry abnormalities at baseline:
    - Total bilirubin ≥ 1.5 × the upper limit of normal (ULN) for the institution*
    - AST or ALT ≥ 3 × the ULN for the institution (≥ 5 × if due to hepatic involvement by tumor)
    - Serum creatinine ≥ 1.5 × ULN for the institution

    **Patients with evidence of Gilbert's Syndrome as the etiology of elevated total bilirubin will be eligible, provided all other eligibility criteria are met.*

7. Patients with any of the following coagulation parameter abnormalities at baseline (unless on a stable dose of anticoagulant therapy for a prior thrombotic event, as determined by the Investigator):
    - PT (or international normalized ratio [INR]) ≥ 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)
    - PTT (or aPTT) ≥ 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)

8. Patients with:
    - Active thrombosis, or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE), within 4 weeks prior to first study drug administration, unless adequately treated and stable
    - Active uncontrolled bleeding or a known bleeding diathesis

9. Patients with a significant cardiovascular disease or condition, including:
    - Congestive heart failure (CHF) currently requiring therapy
    - Need for antiarrhythmic medical therapy for a ventricular arrhythmia or other uncontrolled arrhythmia (patients with controlled atrial fibrillation (heart rate [HR] < 90) for > 30 days prior to study entry are eligible)
    - Severe conduction disturbance (e.g., 3rd degree heart block)
    - Left ventricular ejection fraction (LVEF) known to be below the lower limit of normal (LLN)* for the center, or < 50% by multi-gated acquisition MUGA scan or echocardiogram (Echo) if no LLN is defined by the site
    - QTc interval ≥ 480 msec
    - Uncontrolled hypertension (per the Investigator's discretion)

- Class III or IV cardiovascular disease according to the New York Heart Association's (NYHA) Functional Criteria (see **Appendix C**)
- History of acute coronary syndromes (including myocardial infarction [MI] and unstable angina), coronary angioplasty, stenting, or bypass grafting within 6 months prior to first study drug administration

*Assessment of LVEF will not be performed routinely in all patients. Patients with a history of CHF will have either a MUGA scan or echocardiogram at Screening. If LLN is not defined for a given institution, then LVEF must be ≥ 50%

10. Patients with a significant ocular disease or condition, including:
    - History of ocular inflammatory disease
    - History of disorders of the cornea, including current evidence of keratitis at screening
11. Patients with a significant pulmonary disease or condition, including:
    - Significant symptomatic chronic obstructive pulmonary disease (COPD), as assessed by the Investigator
    - History or any current evidence on imaging studies prior to or during study of interstitial lung disease (ILD), pulmonary fibrosis
    - History of pulmonary inflammatory disease, pneumonitis, acute respiratory distress syndrome (ARDS)
12. Patients with a significant gastrointestinal (GI) disease or condition, including but not limited to:
    - History of inflammatory bowel disease
    - Diarrhea ≥ Grade 2 within 2 weeks prior to first study drug administration*

    **Patients with recent Grade 2 diarrhea secondary to administration of oral contrast are allowed, provided symptoms have resolved prior to first study drug administration.*
13. Patients with non-healing wounds on any part of the body
14. Patients with a known or suspected hypersensitivity to any of the excipients of AVID100
15. Patients with any other serious/active/uncontrolled infection, any infection requiring parenteral antibiotics, or unexplained fever > 38ºC within 2 weeks prior to first study drug administration
16. Patients with unresolved > Grade 1 toxicity* associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, peripheral neuropathy, decreased hemoglobin, hypomagnesemia, lymphopenia, and/or end-organ failure being adequately managed by hormone replacement therapy

    **AE assessments based on Common Terminology Criteria for Adverse Events [CTCAE Version 5.0]*

17. Patients with inadequate recovery from any prior surgical procedure, or patients having undergone any major surgical procedure within 4 weeks prior to first study drug administration

    Note: Patients having undergone recent placement of a central venous access device will be considered eligible for enrollment.

18. Patients with any other serious, life-threatening, or unstable pre-existing medical condition (aside from the underlying malignancy), including significant organ system dysfunction, or clinically significant laboratory abnormality (ies), which, in the opinion of the Investigator, would either compromise the patient's safety or interfere with obtaining informed consent, compliance with study procedures, or evaluation of the safety of the study drug
19. Patients with a psychiatric disorder or altered mental status that would preclude understanding of the informed consent process and/or completion of the necessary study-related evaluations
20. Patients with the inability or with foreseeable incapacity, in the opinion of the Investigator, to comply with the protocol requirements

4.3.2 Drugs and Other Treatments to be Excluded

1. Any antineoplastic agent for the primary malignancy (standard or investigational), without delayed toxicity, within 2 weeks

   Note: See patients to be excluded for criteria on recovery from prior antineoplastic therapy.

2. Any other investigational treatments during study. This includes participation in any medical device or other therapeutic intervention clinical trials.
3. Radiotherapy
   - For target lesions within 4 weeks prior to first study drug administration and during study
   - For non-target lesions within 1 week prior to C1/D1

     Note: A tumor lesion situated in a previously irradiated area is considered a measurable/target lesion only if subsequent disease progression has been documented in the lesion.

     Radiotherapy for pain control against non-target lesions is allowed, as long as it does not influence bone marrow function (**Section 6.12**)

4. Strong inhibitors and/or inducers of cytochrome P450 (CYP) isoenzyme 3A4 within 2 weeks prior to first study drug administration and during study

   *See <http://medicine.iupui.edu/clinpharm/ddis/>

5. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone or equivalent) within 2 weeks prior to first study drug administration and during study (for exceptions, see **Section 6.12**)

6. Prophylactic use of hematopoietic growth factors within 1 week prior to first study drug administration and during Cycle 1 of study; thereafter prophylactic use of growth factors is allowed as clinically indicated

   Note: Interventional/therapeutic use of growth factors is allowed at any time during study, including during Cycle 1, if deemed necessary by the Investigator. Growth factor use must be consistent with product package insert instructions. Transfusions are permitted as needed.

Questions regarding patient eligibility must be addressed and resolved by the Investigator in consultation with the Sponsor's Medical Monitor(s) prior to enrollment.

5. INVESTIGATIONAL DRUG

In advance of study start the Sponsor (or designee) will provide labeled supplies of AVID100 to the study center Investigational Pharmacy. Instructions for handling, administration, and disposal will be provided in the Study Pharmacy Manual (or other similar document) and are summarized below.

5.1. AVID100

AVID100 injection solution concentrate (AVID100) is formulated as a clear to opalescent, colorless to pale yellow liquid for IV infusion. Formulation excipients include:

- 20 mM sodium succinate
- 10% weight to volume (w/v) trehalose dihydrate
- 0.02% w/v polysorbate 20, pH 5.5

Each single-use, glass vial contains a total volume of 10 mL. Each vial contains AVID100 at a concentration of 6 mg/mL for a total vial content of 60 mg.

AVID100 is to be diluted in commercially available 0.9 % sodium chloride (NaCl, normal saline, NS) solution for IV infusion.

5.2. Storage and Handling of AVID100

Unused vials of AVID100 must be stored refrigerated between 2° C to 8° C in an access-controlled secure location (ACSL). There is no evidence that UV light exposure affects AVID100 but as a precaution, vials should be stored in the shipping box, at temperatures between 2° C to 8° C until use.

The investigational site will be required to maintain a temperature log documenting AVID100 storage conditions. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor (or designee) and the use of drug interrupted until authorization for its continued use has been given.

AVID100 may be accessed only by the Investigator, a member of the Investigator's staff specifically authorized by the Investigator, or a pharmacist, as appropriate. The study center must insure that investigational drug is accessible to authorized personnel only.

Vials of AVID100 are to be allowed to warm to room temperature prior to dilution and use.

5.3. Stability of AVID100

Long term stability of AVID100 is being assessed on an ongoing basis and expiry will be updated as data accrues. The stability of the clinical material will be monitored for at least the duration of the proposed clinical trial.

When diluted in 0.9 % NaCl solution AVID100 has been found to be stable for up to 4 hours at room temperature (therefore, once diluted and prepared for delivery study drug should be administered within 4 hours; see **Section 5.8**, Dose Preparation).

5.4. Labeling of AVID100

Vials of AVID100 will bear the appropriate label text for investigational agents, as required by governing regulatory agencies. This includes but is not limited to the investigational drug name, concentration (6 mg/mL), total withdrawal volume (10 mL/vial), a cautionary statement indicating that the agent is a new drug and restricted to investigational use, storage information, and that it was manufactured for the Sponsor.

5.5. Packaging of AVID100

AVID100 drug product provided as a solution for injection in 10 mL single-use vials will be shipped refrigerated or in insulated packaging maintaining the required temperature of approximately 2°C to 8°C. Temperature range indicators or monitors will accompany each shipping box.

Each shipment of study drug will be accompanied by a shipment inventory document describing the amount of drug shipped to the site. The inventory information must be checked against the actual amount of drug sent and the Sponsor (or designee) notified of any discrepancies. The Investigator (or designee) will then sign the shipment inventory document and maintain it in the study file.

5.6. Administration of AVID100

AVID100 will be administered by IV infusion. An appropriate dose, based on the patient's cohort assignment, is to be diluted to a total volume of:

- 100 mL if ≤ 180 mg/m^2, or to
- 200 to 250 mL if > 180 mg/m^2. This may include either:
    - 100 mL × 2 (to be administered sequentially)
    - Up to 250 mL (using a single flexible IV bag)

AVID100 is to be diluted with 0.9% NaCl and administered over 2 hours (+ 10 minutes), once every 3 weeks (Q3W; 3 weeks [21 days] equals 1 dosing cycle).

5.7. Dose Calculation

The Investigator (or designee) will be responsible for calculating the amount of study drug and the appropriate dose to dispense to the patient as determined by the patient's dose cohort assignment.

The dose level will be multiplied by the patient's body surface area (BSA) in order to arrive at the total dose to be delivered. In situations where this calculation results in a value with an unwieldy number of decimal places, it is permissible to round the value to the nearest "tenth", or according to standard institutional practice. As a convention, values > 5 should be "rounded" to the next higher number.

Please note: The Sponsor reserves the right to "round" the dose to be administered with each cohort in a similar fashion (to the nearest tenth), and will do so at the time a dose cohort is opened for accrual in those situations where deemed practical.

Dosing information will also be recorded on the Drug Dispensing Inventory or other appropriate accountability form in use. This inventory will be maintained throughout the duration of the trial and will be periodically reviewed by a representative of the Sponsor.

5.8. Dose Preparation

The designated dose of study drug must be prepared by the study pharmacist (or designee) and should be administered by the study staff as soon as possible following preparation, within 4 hours and taking into account:

- The total volume of study drug to be delivered will be withdrawn from the study drug vial(s) and added to a prefilled IV bag containing 0.9 % NaCl (following removal of an appropriate volume of saline, such that the final volume to be infused equals 100 mL (doses $\leq$ 180 mg/m^2) or 200 to 250 mL (doses > 180 mg/m^2). Flexible containers should be made of polyvinyl chloride.
- The IV bag containing the diluted study drug solution to be administered should be gently inverted to ensure that the material is well mixed.
- Infusion sets must be made of di(2-ethylhexyl)phthalate (DEHP)-free material and must contain an in-line filter (0.22 micron pore size).

5.9. Accountability

The Investigator acknowledges that the study drug supplies are investigational and, as such, must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator. No study medication will be sent to the study site until all regulatory documents, including Institutional Review Board (IRB) approval, are received by the Sponsor or its designee.

The Investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of investigational drug. Receipt and use of AVID100 will be recorded on the Drug Dispensing Inventory or other appropriate accountability form in use.

5.10. Disposition of Used Supplies

After study drug is prepared for delivery and administered, the health care professional will maintain an inventory of all used vials of study drug, and if authorized by the Sponsor (or designee) such supplies may be destroyed in an appropriate manner according to institutional policy.

Note: **No other use of AVID100 study drug intended for use in this trial is authorized by the Sponsor.** The Investigator (or designee) will be responsible for the appropriate handling and disposition of residual study drug in partially used vials.

5.11. Inventory of Unused Supplies

Unused study materials MUST be returned to the Sponsor or designee, unless otherwise authorized in writing.

5.12. Destruction of Investigational Supplies

No study drug materials may be destroyed or discarded at the site without the written authorization of the Sponsor (or designee). The destruction of study drug materials must be carefully documented per instructions outlined in the Pharmacy Manual (or other similar document). Disposition records must be available for review by a representative of the Sponsor.

5.13. Resupply Requests

Please refer to the Pharmacy Manual (or other similar document) for initial ordering of AVID100 and to request resupply of study drug. Please anticipate resupply needs at least 2 weeks in advance.

6. EXPERIMENTAL PLAN

6.1. Design Elements

- Uncontrolled, open-label, non-randomized
- Enrollment in the order of confirmation of eligibility
- Escalating doses of study drug in sequential patient cohorts (Phase 1a)
- Cohort expansion at the MTD or RP2D and in other cohorts based on safety (Phase 1a)
- Addition of expansion cohorts of defined patient populations TBD (Phase 2a)

6.2. Projected Recruitment Period for this Trial

It is anticipated that enrollment to this study will be completed in approximately 24 months.

- Anticipated date of enrollment of first Phase 1a patient: Q4 2016
- Anticipated date of enrollment of first Phase 2a patient: Q3 2018
- Anticipated date of enrollment of last Phase 2a patient: Q4 2019

Enrollment to the expansion cohorts in Part 2a of the trial will commence upon investigational site approval of a protocol amendment defining the disease indications to be explored.

The end of trial will be reached at the latest 1 month (30 +7 days) after the last patient has been discontinued from study drug. Patients with SD or an ongoing OR at that time will continue to be followed to assess duration of disease stabilization or response.

6.3. Cohort Management

For the purposes of this study, "enrollment" is defined as patient registration to participate in this trial; at this time the patient's study identification code and dose cohort will be assigned.

6.3.1 Prescreening for EGFR

The trial site will prescreen patients, utilizing archival tumor tissue, for EGFR Tumor Status Determination before entering patients into screening for the treatment portion of the trial. The site should use a separate prescreening informed consent form. Prescreening may be performed outside the 28 (+ 2) day screening period to allow adequate turnaround time for receipt of results, provided separate informed consent has been obtained (see **Section 7.4.1**; EGFR Tumor Status Determination).

6.3.2 Patient Screening and Dose Cohort Assignment

Once a patient has given written informed consent, screening assessments will be conducted, and if the patient is identified as meeting the study eligibility criteria the Investigator (or designee) will contact the Sponsor's representative for the purpose of authorizing enrollment of the patient into the trial.

Patients will be enrolled into the study in the order of confirmation of their eligibility, and assigned to a cohort on a "first-come-first-served" basis.

6.3.2.1. Screening of Potential Patients

All screening activities must be performed within 14 days prior to the first day of dosing (Cycle 1/Day 1; [C1/D1]), unless otherwise specified.

The Sponsor (or designee) will be made aware of potential patients for enrollment in order to track such study-related activities.

Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they are will not be participating in this trial.

6.3.2.2. Submission of Patient Enrollment Documentation

Once eligibility has been confirmed in accordance with the protocol-stipulated inclusion and exclusion criteria, patient enrollment information must be submitted to the Sponsor (or designee) via a Patient Enrollment Form. This information will serve to confirm patient eligibility and initiate the enrollment process. The following information must be provided by the study site at this time:

- Patient gender
- Date of birth (or age), as allowed by local regulatory requirements
- Date written informed consent was obtained
- Underlying diagnosis
- Confirmation of compliance with all inclusion/exclusion criteria.

The following information may be requested of the study site at this time:

- Patient height and weight or BSA (if required for dose calculation)
- Date of screening
- Stage of disease and current performance status
- Sites of metastases (if applicable)
- Brief description of the prior therapy for the primary diagnosis, including dates of initiation and discontinuation as well as best response
- Planned date of first dosing

The Sponsor (or designee) will review the information provided and by signing the form will authorize eligible patients for start of treatment. A copy of the fully executed Patient Enrollment Form will be returned to the trial site for archiving. This form will document the allocated dose of AVID100, and will serve to assign patients to a dose cohort at the time of enrollment.

6.3.2.3. Patient Identification Code Assignment

Each patient who completes the study screening assessments and is enrolled for study participation will be assigned a unique identification code by the Sponsor (or designee). Identification codes will be assigned in chronological order, and will be concatenated to indicate relevant study information, including: the participating study center, the study phase or cohort, and the patient's order of enrollment to the trial.

6.3.2.4. Screening Failures

A patient found not eligible for the trial after giving informed consent will be considered a screening-failure. A list of patients failing screening and the reason for ineligibility will be maintained by the site on a Patient Screening Log or other similar document.

Re-screening of a patient is allowed, if felt to be justified by the Investigator.

6.3.3 Cohort Closure

The Sponsor (or designee) will be in communication with the sites when the target total enrollment for a cohort has been attained. Once recruitment to a cohort is completed, accrual to the cohort will be closed, and sites will be so notified in writing. Cohorts will remain closed to further accrual, unless a decision is later made by the Sponsor (or designee) to further expand that cohort, based on protocol-defined criteria.

6.4. Requirements for Patient Observation

Patients will be treated on an outpatient basis, and will be evaluated and discharged from the clinic on days of scheduled study visits*, unless hospitalization is required for other reasons or to assure patient safety.

AVID100 must be administered under close supervision in an environment where full resuscitation facilities are immediately available. IV infusions will be carefully monitored to assess safety and tolerability by qualified site medical personnel. Such personnel must be available in order to evaluate and treat any AEs, as well as to evaluate whether continued participation of the patient in the study is warranted or advisable.

- Phase 1a Dose-Escalation Cohorts: Patients will be carefully observed for a minimum of 4 hours following completion of the first administration of study drug (Day 1) for evidence of any treatment-related AE(s), and so that final Day 1 samples for post-dosing PK assessments may be obtained**, and a minimum of 1 hour following completion of subsequent infusions.
- Phase 2a Expansion Cohorts: Patients will be carefully observed for a minimum of 2 hours following completion of the first administration of study drug (Day 1) for evidence of any treatment-related AE(s) **, and a minimum of 1 hour following completion of subsequent infusions. *PK samples will only be collected prior to dosing on Day 1 of each cycle in the Dose Expansion Cohort*s.

At the end of each infusion, the IV line must remain in place for at least 1 hour to allow administration of IV drugs, if necessary.

Patients will be followed on an outpatient basis during the interval between each scheduled study visit.

Clinical and laboratory assessments will occur at the frequencies indicated (see **Section 7; Study Assessments). In the event of an AE, assessment frequencies may be increased, as clinically indicated.*

***Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of 4h samples is logistically difficult due to clinic staff availability, the observation period may be shortened, and an "end of day" sample may be obtained at the latest practical time. Such an option is available ONLY after previous discussion with and approval by the Sponsor.*

6.5. Drug Treatment Regimen

6.5.1 Study Start Day

All patients will receive the initial dose of study drug on Day 1 of Cycle 1 (C1/D1).

On the day of the first scheduled study drug infusion, and prior to the start of infusion (SOI), the Investigator must assess whether any changes have occurred in the clinical state of the patient since Screening, which would exclude the patient from the trial.

6.5.2 Patient Availability During Cycle 1

The site should calculate study assessment days as well as sample collection dates and times in advance of scheduling a patient's first day of study drug administration, so as to plan accordingly to avoid assessment or collection requirements during non-routine times such as weekends, holidays, etc.

Given the schedule of study drug administration outlined herein, and the PK sampling schedule (see **Section 7.5**; Pharmacokinetic Assessments), patients must be available:

- Phase 1a: on Days 1, 2, 4 (± 1 day), and 8 of Cycle 1, therefore, consideration should be given to scheduling Day 1 on a Monday or Tuesday*
- Phase 2a: on Days 1, 4 (± 1 day), and 8 of Cycle 1, therefore consideration should be given to scheduling Day 1 on a Monday, Tuesday, or Friday*

**unless the study site has weekend hours of operation*

6.5.3 Therapy with AVID100

Based on their cohort assignment patients will receive the assigned dose of study drug as described below, by the route and schedule as described below:

6.5.3.1. Doses to be Administered

6.5.3.1.1. Doses to be Evaluated During Phase 1a

Dose cohorts will be numbered sequentially (i.e., Cohort 1, Cohort 2, etc.). The number of cohorts evaluated and the MAD will depend upon toxicities experienced during Cycle 1.

The initial dose of AVID100 to be evaluated is calculated based on the highest non-severely toxic dose (HNSTD) observed in nonclinical toxicology studies, and will be **20 mg/m^2**/dose

(with the maximum dose to be administered in this trial not to exceed **330 mg/m^2/dose).** An accelerated titration design (1 patient per cohort) will be used for dose-escalation for up to 2 cohorts or until the occurrence of an event that activates a stopping rule. Thereafter, dose-escalation will follow a standard 3+3 design with a target toxicity level of 33.3% or less as determined by DLTs. Doses will be calculated as follows:

- **Dose Part A:** Up to 2 cohorts (until at most Cohort 3) will receive consecutive 100% increases in dose (EXAMPLE: Cohort 1 = 20 mg/m^2/dose, Cohort 2 = 40 mg/m^2/dose, etc.) until the occurrence of:
    - A study drug-associated ≥ Grade 2 toxicity or accrual to Cohort 3, whichever occurs first (Part B will commence)
    - A study drug-associated DLT (Part C will commence)
- **Dose Part B:** Cohorts will receive consecutive 50% increases in dose (EXAMPLE: Cohort x = 60 mg/m^2/dose, Cohort x+1 = 90 mg/m^2/dose, etc.) until the occurrence of:
    - A study drug-associated DLT (Part C will commence)
    - > 1 patient with a study drug-associated DLT (dose escalation will stop)
- **Dose Part C:** Cohorts will receive consecutive 25% increases in dose (EXAMPLE: Cohort x = 60 mg/m^2/dose, Cohort x+1 = 75 mg/m^2/dose, etc.) until the occurrence of:
    - > 1 patient with a study drug-associated DLT (dose escalation will stop)

Note: The Investigator(s) and Sponsor's Medical Monitor(s) will review clinical and laboratory safety data on an ongoing basis throughout the study and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort.

Based on emerging tolerability data the Sponsor may choose to escalate the dose between cohorts at an increment less than the percent increase allowed above in an effort to protect patient safety.

6.5.3.1.2. Dose to be Administered During Phase 2a

Patients entered to the Phase 2a portion of this study will receive study drug at the RP2D established during the Phase 1a portion of the study. **The MTD and RP2D has been determined to be 220 mg/m^2.**

Ongoing safety evaluations will continue during accrual of patients to the Phase 2a expansion cohorts to determine whether any newly identified AEs necessitate modifications to the protocol or discontinuation of accrual to patients within any cohort (**Section 6.6.3.3**).

6.5.3.1.3. Changes in Dose to be Administered

In both Phase 1a and Phase 2a, once assigned to a dose cohort each patient will continue to be treated with study drug at that same dose level throughout the duration of their time on study, unless dose reduction is necessary due to the occurrence of a DLT or other toxicity warranting dose reduction at the Investigator's discretion. There will be no intra-patient dose-escalation.

Dose adjustments should be made in the event of noted weight change (± 10%, less at the site's discretion or if required by institution procedures) at visits that require weight measurement.

6.5.3.2. Route of Administration

Study drug will be administered by the IV route, via indwelling venous access catheter, utilizing a controlled infusion device. Infusion sets must be made of DEHP-free material and must contain an in-line filter (0.22 micron pore size). Flexible containers of NS should be made of polyvinyl chloride.

The catheter may be placed into a peripheral vein (if accessible); administration via central venous catheter or port (if in place) is allowed.

In those instances when study drug administration is associated with PK sampling, and administration is via peripheral IV catheter, infusions will be delivered into the arm contralateral to that from which blood samples for PK analysis are being obtained.

6.5.3.3. Duration of Infusion

Study drug will be administered over 2 hours (+ 10 minutes)*

Protocol v5.0: Extended from 1 hour to 1.5 hours due to Grade 3 IRR observed in Cohort 3 (80 mg/m^2); effective 20Jul2017 and documented in a study Note to File dated 21Jul2017 (see **Section 2.3.2.1; AVID100-01: Clinical Experience)*

Protocol v6.0: Extended from 1.5 hours to 2 hours due to Grade 2 IRRs observed in Cohort 4(120 mg/m2); effective 21Dec2017 and documented in a study Note to File dated 28Dec2017 (see **Section 2.3.2.1; AVID100-01: Clinical Experience)*

Administration should be at a constant rate using a programmable volumetric infusion pump in order to assure accuracy of delivery (as well as integrity of PK sampling). The times of infusion initiation and completion must be recorded on the appropriate page of the patient's eCRF.

Note: In the event of an infusion-related reaction (IRR) that does not meet the protocol definition of DLT, the Investigator may elect to prolong the infusion duration to extend longer than the initially assigned duration (for further instructions see **Section 8.3.1**; Prolongation of Infusion Duration).

During Phase 1a, the duration of infusion will be prolonged for all subsequent patients entered to the trial in the following situations:

- In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated).

- In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort

These same criteria will be applied in the event IRRs occur on the extended infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated).

6.5.3.4. Volume of Infusion

All infusions ≤ 180 mg/m^2 will be delivered in a final volume of 100 mL.

All infusions > 180 mg/m^2 will be delivered in a final volume of 200 to 250 mL. This may include either:

- 100 mL × 2 (dose to be divided between two 100 mL infusion volumes to be administered sequentially).
- Up to 250 mL (using a single flexible IV bag)

6.5.3.5. Diluent

Commercially available sterile 0.9% NaCl for IV infusion is to be used as the diluent.

6.5.3.6. Schedule

Study drug is to be administered once every 3 weeks (Q3W) on Day 1 of each cycle (3 weeks [21 days] equals 1 dosing cycle).

End of Cycle 1 (EOC1) assessments are to be performed no sooner than C1/D21 (-2 days). Subsequent cycles may be administered Q3W (± 2 days), unless further delay is required to allow for amelioration of toxicities.

6.6. Cycle 1

A minimum of 1 cycle of AVID100 will be administered, if tolerated. Any interruptions in dosing and the reasons for such interruptions must be documented. If an AE is the cause for dosing interruption, it must be detailed on the Adverse Events page of the eCRF. Determinations regarding cohort escalation, DLTs, and MTD will be based on the toxicities observed during this 3 week period (Cycle 1) of treatment.

- Patients completing Cycle 1, in the absence of a DLT, will be considered to have tolerated the AVID100 regimen.
- Patients must receive their full planned dose of AVID100 during Cycle 1 in order to be considered evaluable for tolerability unless dose reduction, interruption, or discontinuation was the result of a DLT.
- Dose-Escalation Cohorts: Patients will be replaced, if necessary (e.g., received < 1 full dose of AVID100 plus follow-up through EOC1 [C1/D21 {-2 days]}]) for any reason other than a DLT), to allow for a thorough assessment of the tolerability in any dose cohort.
- All enrolled patients will be considered in the assessment of safety and tolerability.

6.6.1 Premedication

6.6.1.1. Premedication for Infusion-Related Reactions

Beginning with the first dose, all patients must be premedicated with standard therapies prior to each dose of AVID100 to reduce the risk of IRRs associated with study drug.

The recommended premedication regimen includes administration of dexamethasone 12 hours and 6 hours prior to each dose, as well as administration to begin at minimum 30 minutes prior to each infusion of a glucocorticoid (e.g., dexamethasone) as well as an H1 (e.g., diphenhydramine/ hydroxyzine) and an H2-blocker (e.g., ranitidine/famotidine) (see **Section 8.2;** Premedication for Study Drug-Related Toxicities).

6.6.1.2. Use of Other Premedications

In the event of other study-drug associated reactions (e.g., nausea, vomiting, diarrhea, etc.), patients may be premedicated with standard therapies in order to reduce the potential for such reactions in the future.

Mandatory premedication will be implemented for all patients should a pattern begin to emerge of mild-to-moderate study drug-related reactions that are amenable to prophylaxis with standard agents.

6.6.2 Phase 1a: Rules for Accrual

6.6.2.1. Filling of Cohorts in Phase 1a

Cohorts will be filled sequentially during the Phase 1a dose escalation portion of the study. Once assigned to a cohort, each patient will continue to be treated at the same dose level and schedule of study drug throughout the course of the study (unless dose reduction is necessary due to the occurrence of a DLT).

6.6.2.2. Rules for Dose Escalation and Cohort Expansion in Phase 1a

Dose escalation of AVID100 is based on demonstrated tolerability during Cycle 1 (i.e., the initial 3 weeks of dosing) and the occurrence of DLTs* thought to be associated with (i.e., possibly related, probably related, or related to) study drug. The rules for dose escalation and identification of the MTD(s)* in this study are as follows:

See **Section 6.8.3; Definition of DLT and **Section 6.9**; Definition of Maximum Tolerated Dose*

6.6.2.2.1. Establishment of the MTD

1. **Dose Part A:** A minimum of 1 patient will be entered into dose Cohort 1 and 2 ONLY; the dose escalation between cohorts (until at most Cohort 3) will be 100%.
    - If during Cycle 1, a patient experiences a ≥ Grade 2 toxicity considered associated with study drug, the cohort will be expanded to 3 patients and Part B will commence.

- If during Cycle 1, a patient experiences a DLT considered associated with study drug, the cohort will be expanded to 6 patients and Part C will commence.

2. **Dose Part B:** A minimum of 3 patients will be entered into each dose cohort; the dose escalation between cohorts will be 50%.
    - If during Cycle 1, any 1 patient experiences a DLT considered associated with study drug, the cohort will be expanded to 6 patients and Part C will commence.
    - If during Cycle 1, > 1 patient experiences a DLT, dose escalation will STOP. *This will indicate that the MTD has been exceeded.*

3. **Dose Part C:** A minimum of 6 patients will be entered into any dose cohort where a DLT is observed in any of the first 3 patients, otherwise a minimum of 3 patients will be entered into each dose cohort; the dose escalation between cohorts will be 25%.
    - If during Cycle 1, > 1 patient experiences a DLT, dose escalation will STOP. *This will indicate that the MTD has been exceeded.*
4. If it is determined that a dose level is not tolerated, the previous lower dose cohort will be expanded to 6 patients (if this has not already been accomplished) as a total of 6 patients must be treated before establishing a dose as the MTD.
5. Once the MTD (or maximum dose to be studied) is achieved and the RP2D is identified, that cohort may be expanded up to 12 patients in order to more fully evaluate safety and tolerability at that dose level at the Sponsor's discretion.
6. Should the DLT rate equal or exceed 33.3%* in an expanded MTD cohort, it will be determined that the dose is not tolerated. If this occurs, the previous lower dose cohort may be expanded as above. Therefore:
    - There is potential for expansion of lower dose cohort(s) if the initially identified MTD is not tolerated (either with single or repeat cycles of therapy), and
    - There is potential to evaluate and expand a previously unexamined intermediate dose level(s) between 2 established dose levels in order to more fully characterize tolerability.

        Note: Such action would be taken by the Sponsor (or designee) in the event of an unacceptably high frequency of toxicities observed in patients treated at one dose level, considered to be in marked contrast to the tolerability noted in the immediately preceding dose cohort.

**i.e., > 2 DLTs when 7 to 9 patients have been treated, > 3 DLTs when 10 to 12 patients have been treated, etc.*

Note: Based on emerging tolerability data the Sponsor may choose to escalate the dose between cohorts at an increment less than the percent increase allowed above in an effort to protect patient safety.

6.6.2.3. Rules for Duration of Exposure Prior to Start of Next Patient and Start of Next Cohort in Phase 1a

Dose escalation and accrual to the next cohort will occur only after the minimum number of patients required for tolerability assessment in the current cohort have completed Cycle 1, and only after acceptable tolerance has been demonstrated in at least 1 of 1, 3 of 3, or 5 of 6 patients treated in the current cohort (depending on cohort size), and after consultation with the Sponsor's Medical Monitor(s).

In cohorts with > 1 patient, enrollment will be staggered between the first and second patient by at minimum 24 hours in order to assess for IRRs; thereafter patients within a cohort may be added concurrently. For all patients, EOC1 assessments are to be performed no sooner than C1/D21 (-2 days).

6.6.2.4. Rules for Establishing the Recommended Phase 2 Dose

The MTD (or a dose lower than the MTD) will be identified as the RP2D, provided a minimum of 6 patients have been treated at that dose, and provided acceptable tolerance has been demonstrated in at least 5 of 6 patients treated.

The RP2D choice will be based on the MTD evaluation as well as other toxicities observed in the study, including observations in later cycles of administration of AVID100, as well as on PK and other data.

6.6.3 Phase 2a: Rules for Accrual

6.6.3.1. Filling of Cohorts in Phase 2a

Once the MTD and/or RP2D have been identified, approximately 60 patients in 3 expansion cohorts will be enrolled to the Phase 2a portion of the study to more fully evaluate safety, tolerability, and the preliminary antineoplastic effect of study drug at that dose level.

Accrual to the Phase 2 Cohort may begin once the RP2D has been established and a minimum of 6 patients have been treated at that dose. If the Phase 1a MTD Cohort is to be expanded up to 12 patients to more fully evaluate safety and tolerability at that dose level, accrual to Phase 2a may begin concurrent with accrual of the additional up to 6 patients to that cohort.

6.6.3.2. Rules for Patient Population to be Treated in Phase 2a

Patients will be accrued to 3 expansion cohorts in the Phase 2a portion of the study. The tumor types to be evaluated in these expansion cohorts are mTNBC (~30 patients), SCCHN (~15 patients), and Sq-NSCLC (~15 patients).

Criteria for eligibility will be as described above with the additional requirement that patient tumors must have been documented to express EGFR by IHC* in a central laboratory. Further, FFPE tumor tissue from either a prior procedure or a recent biopsy must be available for submission to a central laboratory for other study-related evaluations as planned per protocol.

***DAKO EGFRpharmDX™ IHC kit system technology to be utilized. For this study, EGFR-positive staining is defined as 3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells for mTNBC; or 3+ intensity in ≥ 50% of tumor cells for SSCHN and Sq-NSCLC,, whether it is complete or incomplete circumferential staining.*

6.6.3.3. Rules for Tolerability in Phase 2a

The criteria for tolerability during Phase 1a will apply to Phase 2a Expansion Cohorts. Safety will be reviewed on an ongoing basis to determine if the dose and schedule chosen based on the Phase 1a dose escalation is safe and well-tolerated in expanded populations of patients with the tumor types selected for the expansion cohorts (mTNBC, SCCHN, and Sq-NSCLC). Should it be determined that the dose is not well-tolerated (i.e., ≥ 33.3% of patients in an expansion cohort experience a Cycle 1 DLT), the safety of that dose level will be re-evaluated and the next lower dose with established tolerability in Phase 1a will be administered to subsequent patients.

An exception will be the occurrence of toxicity suggesting organ damage (e.g., pulmonary fibrosis, drug-induced liver injury) occurring in ≥ 2 patients within an expanded cohort, in which case further accrual to that cohort will be discontinued.

6.7. Continued Therapy After Cycle 1

Upon completion of Cycle 1, in the absence of unacceptable toxicity or disease progression, patients may continue receive additional cycles of study drug Q3W (± 2 days), unless further delay is required to allow for amelioration of toxicities. Administration of subsequent dosing cycles is allowable at the discretion of the Investigator, provided the patient meets the retreatment criteria listed below. Additional cycles should be initiated as soon as possible, but not longer than 2 weeks after the completion of the previous cycle, if feasible.

6.7.1 Retreatment Guidelines

Clinical judgment will be used when determining whether it is advisable to continue a patient on to the next cycle(s) of dosing. In order to start any new cycle a patient must meet the following criteria:

- ANC ≥ 1,000 per mm^3
- Platelets ≥ 75,000 per mm^3
- Any ongoing AEs should NOT meet the criteria for DLT.
- Any ongoing AEs should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of Grade 2 alopecia, clinical events that are being adequately controlled with best supportive care (e.g., nausea, vomiting, diarrhea, fatigue), and asymptomatic laboratory abnormalities that are considered clinically insignificant or that are resolving with medical therapy.

Should any one of the criteria above not be met, dosing of study drug must be delayed.

6.7.2 Doses and Regimens

For a given patient, subsequent cycles of therapy with AVID100 will be administered at the same dose and infusion duration established for that patient during Cycle 1, and on the same schedule, unless dose reduction is necessary (or a dose adjustment is necessary due to ± 10% [*less at the site's discretion or if required by institution procedures]* fluctuation in patient weight).

6.7.3 Evaluation Schedules

The same evaluations required during Cycle 1 of the study will be conducted during subsequent cycles, at the frequencies indicated (see **Section 7**; Study Assessments).

6.7.4 Duration of Treatment

Additional cycles of AVID100 may continue to be administered if tolerated and in the absence of documented disease progression, at the Investigator's discretion, provided retreatment criteria have been met (see **Section 6.7.1**; Retreatment Guidelines).

Such extended therapy will continue for a period of up to 12 months after achieving the "best response," at which time the Medical Monitor and Investigator will discuss the advisability of continued therapy based upon the patient's ongoing response status and the degree of demonstrated tolerability.

6.7.5 Retreatment Following a Response

Treatment with AVID100 may be restarted in a patient who:

- Previously achieved a documented OR on this study, stopped treatment, and subsequently progresses, or
- Discontinued therapy for a reason other than a DLT or PD, and in whom documented OR or prolonged SD is subsequently noted.

Such action may be taken at the Investigator's discretion, following discussion with the Medical Monitor, provided retreatment criteria are met, no anti-cancer treatment was administered since the last dose of AVID100, and the trial is still open. This option for retreatment does not apply to patients who previously experienced an unacceptable toxicity that required permanent discontinuation of study drug (see **Section 9.1 #1**; Criteria for Treatment Discontinuation).

Retreatment with AVID100 may be initiated at the same dose and infusion duration established for that patient during their previous course of treatment, and on the same schedule, unless dose reduction is necessary.

The same evaluations required during previous treatment will be conducted during subsequent cycles, at the frequencies indicated.

Retreatment cycles of AVID100 may continue to be administered if tolerated and in the absence of further disease progression, at the Investigator's discretion, as long as retreatment criteria continue to be met.

6.8. Toxicity and Dose Limiting Toxicity

6.8.1 Toxicity Grading

The CTCAE Version 5.0*) will be used to grade AEs occurring during this study.

**See < https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm >*

6.8.2 Toxicity Management and Dose Modification

If a significant toxicity thought to be related to study drug is experienced at any point during the patient's participation in the study, the Investigator will determine:

- Whether that toxicity is dose-limiting (see **Section 6.8.3**; Definition of DLT), thus requiring either dose reduction or discontinuation from study; or
- Whether the toxicity does not meet the protocol definition of DLT, but nevertheless warrants dose modification, in which case the Investigator may elect to either reduce the dose of study drug, or temporarily interrupt dosing with study drug, in order to allow for amelioration of the toxicity.

For additional information on toxicity management and dose modification, see **Section 8.1**; Determination of DLT versus Non-DLT, and **Section 8.3**; Dose Modification Options.

6.8.3 Definition of DLT

Any of the following toxicities, if judged to be associated with study drug (i.e., possibly related, probably related, or related), will be considered a DLT for the purposes of this trial.

1. Evidence of pulmonary fibrosis, any grade (patient must be permanently discontinued)
2. Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of:
    - Grade 3 nausea, vomiting, diarrhea, or fatigue lasting $\leq$ 2 days with best supportive care
    - Grade 3 asymptomatic electrolyte abnormalities that are not considered clinically significant by the Investigator and that are controlled with medical therapy
3. AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry as allowed by study eligibility criteria; see **Section 4.3.1 #7**), with total bilirubin > 2 × ULN without initial findings of cholestasis (i.e., no elevation in serum alkaline phosphatase [ALP]), that cannot be explained by other factors
4. Any Grade 4 non-hematologic toxicity with the exception of:
    - Grade 4 asymptomatic electrolyte abnormalities lasting < 7 days that are not considered clinically significant by the Investigator and that are controlled with medical therapy
5. Neutropenia that is:
    - $\geq$ Grade 3 and associated with fever (ANC < 1000 per mm^3; temperature > 38.3ºC [101ºF] or a sustained temperature of $\geq$ 38 ºC [100.4ºF] for > 1 hour) (i.e., febrile neutropenia)
    - Grade 4 and sustained (ANC < 500 per mm^3, duration > 5 days)
6. Thrombocytopenia that is:
    - Grade 3 with clinically significant hemorrhage or requirement for transfusion

- Grade 4 (platelets < 25,000 per mm^3)

7. Inability to complete Cycle 1 at the assigned dose (i.e., receipt of < 1 full planned dose of study drug plus 3 weeks of follow-up due to ≥ Grade 3 toxicity)
8. Treatment delays > 2 weeks from the scheduled "next dose" due to ≥ Grade 3 toxicity

   Other toxicities may be considered a DLT as determined by the Investigator in conjunction with the Medical Monitor.

The above criteria will be used to make individual patient determinations regarding dose reductions, interruptions, or discontinuation throughout the course of the trial, but *only those DLTs occurring during Cycle 1 will be used to make decisions regarding cohort dose escalation and tolerability.*

Events occurring after Cycle 1 will also be evaluated by the Investigator and Medical Monitor and taken into consideration when deciding upon further doses to be assessed as well as to establishment of the RP2D.

6.9. Definition of Maximum Tolerated Dose

The clinical endpoint of the Phase 1a portion of this trial is determination of the MTD of study drug that can be administered by the specified route, infusion duration, and schedule.

MTD will be defined as the dose below that which produces, during Cycle 1 of treatment, any of the indicated DLTs either in > 1 patient in a 3 to 6 patient cohort, or in ≥ 33.3%* of patients in the event of an expanded 7 to 12 patient cohort.

**i.e., > 2 DLTs when 7 to 9 patients have been treated.*

The MTD will not be established until all patients entered into the cohort under evaluation have either completed Cycle 1 or discontinued further participation in the trial (or been dose-reduced) due to the occurrence of a DLT.

Previously established tolerability of a dose level will be reevaluated if DLTs thought to be possibly related, probably related, or related to study drug are observed in later cycles.

6.10. Review of Safety Data During Study

The Investigator(s) and Sponsor's Medical Monitor(s) and Medical Representatives will comprise a Study Safety Committee, and will review clinical and laboratory safety data on an ongoing basis throughout the study and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort. In order to do so:

- The following will be promptly reported to the Sponsor or designee:
  - Serious adverse events (SAEs), within 24 hours of Investigator awareness
  - AEs resulting in permanent discontinuation from study, regardless of seriousness or relationship to study drug
  - DLTs

- Dose modifications (i.e., dose reductions, temporary interruptions)

- AEs will be recorded on the eCRF in a timely manner following a patient completing (or being discontinued from) each dosing cycle.
- The Investigator will make critical laboratory safety data available a timely manner.
- Patients will be carefully evaluated for evidence of all AEs, including potential cumulative and/or delayed toxicities, throughout the duration of their time on study.
- During Phase 1a: Biweekly safety teleconferences will be held between the Investigational Site(s) and the Sponsor and/or designee; frequency may fluctuate based on accrual and study activity, as indicated.
- During Phase 2a: Monthly safety teleconferences will be held between the Investigational Site(s) and the Sponsor and/or designee; frequency may fluctuate based on accrual and study activity, as indicated.

Availability of these data also will enable the Sponsor (or designee) to notify regulatory authorities, as well as Investigators who may be participating at other sites or in other clinical trials of the study drug, of events occurring during the trial.

6.11. Duration of Study Follow-Up

Upon discontinuation of a patient from further treatment with study drug, follow-up assessments will be conducted as detailed below.

- End of Treatment (EOT)* evaluations will be conducted within approximately 10 days following the decision to discontinue the patient from further treatment with study drug.
- 1 Month Follow-up (1M FUP)* evaluations will be conducted approximately 30 days (+7 days) following the last dose of study drug.

  Note: The 1M FUP evaluation should be conducted ≥ 30 days following the last dose of study drug as all patients are to be followed for a minimum of 30 days after study drug discontinuation in order to monitor for the occurrence of suspected AEs that are both serious and unexpected. See **Section 10.3**; Documenting Adverse Events, **Section 10.4**; Reporting SAEs (Including Patient Deaths) and Unexpected AEs, and **Section 10.5**; Required Follow-up of all AEs and SAEs.

  **Given the Q3W dosing frequency, EOT and 1M FUP evaluations may be combined in those situations where scheduling coincides, provided a minimum of 30 days of post-dosing follow-up have been observed.*

- If an observed toxicity thought to be associated with study drug has not resolved by the 1M FUP evaluation, an additional follow-up AE assessment will be conducted approximately 3 months following the last dose of study drug, if feasible, in order to confirm that the event has either resolved, returned to baseline status, or been adequately explained and assessed by the Investigator as chronic and/or stable, and that no longer

term deleterious effects have become evident.* Follow-up may be repeated approximately 6 months following the last dose of study drug, if indicated.

Any patient who develops pulmonary fibrosis will be followed at approximately 3 month intervals for up to 2 years to assess the course of the disease and evaluate potential reversibility of this finding.

In addition, the occurrence of any significant post-therapy event thought to be associated with study drug must be reported to the Sponsor (or designee).

**To confirm that events have resolved, returned to baseline status, or been adequately explained. Investigator discretion may be used with respect to the method of contact for this AE assessment; clinical events may be followed in writing or by telephone (and documented in writing); an in-person visit will not be required.*

- In the event of an ongoing OR or disease stabilization at the EOT, response assessments* based on tumor marker and imaging studies (as indicated by disease type) will continue to be performed every 3 months during the first year and every 6 months thereafter, until disease progression or another therapeutic intervention is initiated, so that data may be collected on the duration of stabilization or response, as well as on the overall time to disease progression.

  **To continue at the intervals specified until disease progression or another therapeutic intervention is initiated; documentation may be submitted in writing; an in-person visit will not be required.*

6.12. Concurrent Treatments and Supportive Care

Therapy for other ongoing medical conditions, as well as palliative and supportive care for the underlying malignancy will be provided prior to and during this trial, as clinically indicated, and in accordance with the standard practices of the institution, except as stipulated by study eligibility criteria (see **Section 4.3.2**; Drugs and Other Treatments to be Excluded).

Other therapies allowed during the conduct of this trial include:

- Prophylaxis for Study Drug-Related Toxicities: Beginning with the first dose, all patients must be premedicated with standard therapies prior to each dose of AVID100 to reduce the risk of IRRs. Patients experiencing other study drug-associated reactions may be premedicated with standard therapies in order to reduce the potential for such reactions in the future.
- Treatment of Study Drug-Related Toxicities: Clinical judgment should be used in the treatment of any AE that occurs during the study and follow-up period.
- Treatment of Concurrent Diseases: Preexisting/concurrent diseases or conditions should be managed and treated as clinically appropriate.
- Blood Products and Growth Factors: Prophylactic hematopoietic growth factors should not be administered during Cycle 1 of study; thereafter prophylactic use of growth factors is allowed as clinically indicated. Interventional/therapeutic use of growth factors is allowed during study, including Cycle 1, if deemed necessary by the Investigator. Growth factor use must be consistent with product package insert instructions. Transfusions are permitted as needed during study.

- Radiotherapy: Radiotherapy for pain control against non-target lesions, as long as it does not influence bone marrow function. Patients requiring radiation therapy during study for pain management of non-target lesions may have their participation temporarily interrupted, at the Investigator's discretion. Such treatment should be discussed with the Sponsor's Medical Monitor(s). Patients with suspected new lesions requiring pain management should be treated and evaluated for potential PD. Patients requiring palliative radiotherapy to target lesions during study will be discontinued.
- Bisphosphonates and denosumab: Bisphosphonates and denosumab for bone metastases and other skeletal conditions are allowed, provided the patient is on a stable dose for at least 4 weeks prior to study start and remains on the stable dose while receiving study treatment.
- Immunosuppressive or systemic hormonal therapy not exceeding 10 mg daily prednisone or equivalent, as well as:
    - Hormonal therapy for appetite stimulation (e.g., Megace)
    - Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
    - Oral replacement glucocorticoid therapy for adrenal insufficiency
    - Stable hormonal therapy for prostate carcinoma*
    - Stable hormonal therapy for ovarian suppression*
    - Steroid therapy for contrast reaction prophylaxis
    - Low-dose maintenance steroid therapy for other conditions (e.g., stable steroid therapy [excluding tapering dose of steroids] for brain edema/metastases/radiation)
    - Hormonal contraceptive therapy (in WOCBP must be combined with non-hormonal contraceptive equivalent to a double-barrier method)
    - Postmenopausal hormone replacement therapy (HRT)
    - Intra-articular steroid injections
    - Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, study drug treatment should be interrupted for the duration of immunosuppressive therapy

  **Prior or concomitant therapies are permitted, however, patients must have been on a stable dose for at least 6 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).*
- Meals and Dietary Requirements: Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.
- Surgical Procedures: Patients requiring a minor surgical procedure (e.g., port placement, stent placement, skin abscess drainage) may undergo such a procedure at the Investigator's discretion following discussion with the Sponsor's Medical Monitor(s) or designee. A brief interruption in therapy may be considered.

Patients requiring a more extensive or major surgical procedure (e.g., resection of hepatic metastases) should have protocol therapy interrupted, but may resume treatment once fully recovered and at a minimum 2 weeks after the procedure. Protocol retreatment criteria must be met.

- Allowed Dosing Delays: Following Cycle 1 and completion of the DLT assessment period, and only if indicated, dosing may be briefly interrupted for situations other than treatment-related AEs such as medical (or surgical events) or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 2 to 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor.

Information on all concomitant therapies administered, as well as other interventions or procedures occurring during the trial period, must be recorded on the appropriate page of the patient's eCRF.

7. STUDY ASSESSMENTS

All patients will be assessed by scheduled clinical, laboratory, and other diagnostic assessments throughout the study.

All efforts should be made to perform assessments as close as possible to the scheduled time points. The projection of visit days within each cycle should be made from Day 1 of the respective cycle. Visit windows are provided below. Study assessments are to be performed as follows:

- Screening evaluations are to be performed within 14 days prior to first study drug dose, unless otherwise specified (for exceptions see Section **7.2.11**; Pregnancy Testing, **Section 7.4**; Disease Assessments).
- The day of first administration of study drug will be considered Day 1 of study.
- Cycle 1/Day 4 evaluations may be conducted ± 1 day
- Dosing and on-study evaluations (including laboratory assessments) are to be performed on or about the indicated study day (i.e., ± 2 working days) (*a slightly longer allowance for routine assessments is permissible in the event of scheduling difficulties associated with weekends, holidays, etc*.).
- End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.
- End of Treatment (EOT)* evaluations are to be performed within approximately 10 days following the decision to discontinue treatment, or before initiation of a new treatment, whichever occurs first.
- 1 Month Follow-up (1M FUP)* evaluations are to be performed approximately 30 days (+7 days) following the last dose of study drug (i.e., as all patients are to be followed for a minimum of 30 days after study drug discontinuation in order to monitor for the occurrence of AEs).

  **Given the Q3W dosing frequency, EOT and 1M FUP evaluations may be combined in those situations where scheduling coincides, provided a minimum of 30 days of post-dosing follow-up have been observed.*

  Note: When a patient discontinues treatment with study drug, for any reason, every effort will be made to collect routine EOT evaluations as well as subsequent 1M FUP evaluations, per protocol, until all protocol-specified assessments have been conducted.

If, during the course of the study, significant changes from baseline are noted, additional monitoring or on-study assessments may be undertaken by the Investigator, or requested by the Sponsor (or designee), in order to determine both the relevance of the finding(s) and the duration of the event(s).

7.1. Consent and Medical History

7.1.1 Signing of Informed Consent/Assessment of Eligibility

- Screening

Note: All patients must sign an IRB-approved informed consent form (ICF) prior to enrollment and prior to submitting to any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient. Disease evaluations [e.g., CT scan, MRI] performed as part of standard of care and obtained prior to patient consent for this trial may be allowed as screening evaluations if conducted within 28 days (+2d) prior to the first study drug dose. A copy of the fully executed ICF will be given to the patient.

7.1.2 Past Medical History

(To include demographic information, prior and ongoing medical illnesses and conditions, prior surgical procedures [not related to the primary diagnosis], smoking history)

- Screening

7.1.3 History of the Primary Malignancy

(To include details of the primary malignancy, including: histological/cytological classification; stage of disease at diagnosis and at entry; prior surgical procedures for the malignancy; prior antineoplastic therapy, prior radiation therapy, as well as dates of treatments, numbers of cycles, and best response to each therapy.)

- Screening

7.2. Safety Assessments (1)

(To be performed within 14 days prior to first dose of study drug unless otherwise specified)

7.2.1 Medication Survey

(To include indication for use; corresponding illness or condition must appear on the Medical History pages of the eCRF)

- Prior Medication Survey
  - Screening (to assess eligibility)
  - For a period of 14 days prior to first study drug dose
- Concomitant Medication Survey (excluding study drug)
  - Throughout the study
  - For a period of 30 days following last study drug dose

7.2.2 Adverse Event Assessment

- Prior to first study drug dose*
- Throughout the study
- For the period of 30 days following last study drug dose
- For the period of 3 to 6 months following last study drug dose, if events associated with study drug persist**
- For the period of up to 2 years in the event of pulmonary fibrosis***
- As clinically indicated

**To detail any symptoms that may be present prior to first study drug dose beginning from date of enrollment*

***To confirm that events have resolved, returned to baseline status, or been adequately explained. Investigator discretion may be used with respect to the method of contact for this AE assessment; clinical events may be followed in writing or by telephone (and documented in writing); an in-person visit will not be required.*

****Any patient who develops pulmonary fibrosis will be followed at approximately 3 month intervals for up to 2 years to assess the course of the disease and evaluate potential reversibility of this finding.*

7.2.3 Performance Status Evaluation

*(To be assessed by ECOG score; see **Appendix B**; Performance Status Evaluation)*

- Screening
- Cycle 1
  - Day 1*
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be assessed prior to Cycle 1 if ≤ 7 days since screening*

7.2.4 Vital Signs

(Vital signs [VS] to include temperature, pulse, respiratory rate, blood pressure[BP], and oxygen saturation by pulse oximetry)

Phase 1a Dose-Escalation Cohorts

- Screening
- Cycle 1
  - Day 1
    - Prior to SOI
    - EOI (± 5 min)

        - 2 and 4 hours after EOI (± 15 min)
    - Day 2
    - Day 4 (± 1 day)
- Each cycle thereafter
    - Day 1
- EOT
- 1M FUP
- As clinically indicated

Phase 2a Expansion Cohorts

- Screening
- Cycle 1
    - Day 1
        - Prior to SOI
        - EOI (± 5 min)
- Each cycle thereafter
    - Day 1
- EOT
- 1M FUP
- As clinically indicated

**SOI-Start of Infusion; EOI-End of Infusion*

***Comprehensive assessment of vital signs is critical to the conduct of this study. In situations where an assessment at 4h after EOI is logistically difficult due to clinic staff availability, the observation period may be shortened, and an "end of day" assessment may be obtained at the latest practical time. Such an option is available ONLY after previous discussion with and approval by the Sponsor.*

7.2.5 Physical Examination

*(Complete at screening including height, weight, general appearance, skin, ears, eyes, nose, throat, neck/thyroid, chest, heart, abdomen, musculoskeletal system, peripheral pulses, lymph nodes, neurologic and mental status; directed thereafter, must include weight** and pulmonary assessment*** at each visit)*

- Screening
- Cycle 1
    - Day 1*
- Each cycle thereafter
    - Day 1 (prior to dosing)
- EOT

- 1M FUP
- As clinically indicated

** Need not be assessed prior to Cycle 1 if ≤ 7 days since screening*

*** Dose adjustments may be made in the event of noted weight change (± 10% [less at the site's discretion or if required by institution procedures]).*

**** Pulmonary findings will be evaluated in detail at each visit by the PI (or physician designee); evaluation to include review of pulmonary symptoms including but not limited to: cough, sputum production, hemoptysis, wheezing, dyspnea, dyspnea on exertion, chest pain, and/or chest pain associated with respirations.*

Note: See Appendix H (Recommendations for Management of Keratitis and Rash) for dose modification instructions for rash

7.2.6 Hematology Panel

(To include complete blood count [CBC] with differential, ANC, and platelet count)

- Screening
- Cycle 1
  - Day 1*
  - Day 4 (± 1 day)
  - Day 8
- Each cycle thereafter
  - Day 1 (prior to dosing)
  - Day 8
- EOT
- 1M FUP
- As clinically indicated**

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

***In the event of hematologic toxicity, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated.*

7.2.7 Serum Chemistry Panel

*(To include Na, K, Cl, bicarbonate or carbon dioxide, BUN, creatinine, glucose, bilirubin [total and direct], AST, ALT, alkaline phosphatase, Ca, Mg, phosphorus, albumin, total protein, uric acid, amylase, lipase, and creatine kinase[CK]***)*

- Screening
- Cycle 1
  - Day 1*
  - Day 4 (± 1 day)

  - Day 8
- Each cycle thereafter
  - Day 1 (prior to dosing)
  - Day 8
- EOT
- 1M FUP
- As clinically indicated**

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

***In the event of significant serum chemistry abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. Clinically significant electrolyte abnormalities should be corrected prior to dosing.*

****In the event of CK abnormalities while on study, please perform isoenzyme analysis*

7.2.8 Coagulation Panel

(To include PTT [or aPTT], PT and/or INR)

- Screening
- Cycle 1
  - Day 1*
  - Day 4 (± 1 day)
  - Day 8
- Each cycle thereafter
  - Day 1 (prior to dosing)
  - Day 8
- EOT
- 1M FUP
- As clinically indicated

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.9 Urinalysis

(Multipanel chemical test strips are acceptable and should include assessment of: specific gravity, pH, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and occult blood; include microscopic sediment evaluation if clinically indicated if gross findings are abnormal, including white blood cells [WBC] per high power field [hpf] and RBC per /hpf)

- Screening
- Cycle 1
  - Day 1*
  - Day 4 (± 1 day)

- Day 8

- Each cycle thereafter
  - Day 1 (prior to dosing)
  - Day 8
- EOT
- 1M FUP
- As clinically indicated

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.10 Anti-Drug Antibody (ADA) to AVID100 (Central Lab)

(To assess the potential immunogenicity of AVID100; serum to be isolated; r*esidual sample material may be used for biomarker assessments (**Section 7.6.2**))*

- Cycle 1
  - Day 1 (prior to SOI)
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated in the event of an IRR

Note: Whole blood (~ 5 mL) to be collected in serum acquisition tubes at each of the indicated timepoints (see also **Appendix A**; Schedules of Events). In the event that a collected serum sample is inadequate or insufficient for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same time point, if available.

Detailed procedures for collection, handling, and shipment of samples will be provided by the Sponsor (or designee) in the study Laboratory Manual (or other similar document).

7.2.11 Pregnancy Testing

(beta-human chorionic gonadotropin [β-hCG] in WOCBP; serum at screening, urine or serum thereafter; negative test must be confirmed within 2 working days prior to first dose of study drug)

- Screening
- Cycle 1
  - Day 1 (within ≤ 2 working days of dosing)
- EOT
- As clinically indicated

7.2.12 Electrocardiogram

(To include standard 12-lead ECG with measurement of PR interval, QRS duration, QT interval, and QTc interval [msec], as well as heart rate [BPM])

(To be evaluated locally; to be performed after patient has been supine for ≥ 10 minutes) (Repeat subsequent time points in triplicate separated by 5 minutes for 4 cycles in patients with a QTc that is either: a) > 500 msec; b) increased by 60 msec over baseline; or c) decreased by 20 msec under baseline*)*

- Screening
- Cycle 1
  - Day 1
    - Prior to SOI
    - EOI (± 5 min)
    - 30 minutes after EOI (± 5 min)
- Subsequent 4 cycles, if QTc abnormalities are observed during Cycle 1
  - Day 1
    - Prior to SOI (in triplicate)
    - EOI (± 5 min) (in triplicate)
- EOT
- As clinically indicated**

**When evaluating QTc, baseline should be considered the ECG immediate preceding the start of study drug infusion on the day of assessment.*

***In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated.*

7.3. Safety Assessments (2)

(To be performed within 28 days [+2 days] prior to first dose of study drug, provided no antineoplastic therapy has been delivered between safety assessment and first dose of study drug)

7.3.1 Ophthalmology Examination

(To include slit lamp evaluation, tests to evaluate corneal integrity and visual acuity assessment)

- Screening
- End of Cycle 2*,**
- EOT**
- As clinically indicated

**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle.*

***May be combined if patient discontinues treatment at End of Cycle 2*

Note: See Appendix H (Recommendations for Management of Keratitis and Rash) for dose modification instructions for keratitis (corneal inflammation/ulceration)

7.3.2 MUGA Scan or Echocardiogram

(For measurement of LVEF; to be performed ONLY in patients with a history of CHF; individual patients should be followed with the same testing procedure throughout the study)

- Screening
- EOT
- As clinically indicated

Note: Assessment of LVEF will not be performed routinely in all patients. Patients with a history of CHF will have either a MUGA scan or echocardiogram at Screening.

7.3.3 Pulmonary Function Testing

(PTF to include spirometry and diffusing capacity [DL_{CO}] to assess for evidence of pulmonary fibrosis. Spirometry assessments are to include but are not limited to: forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], forced expiratory flow 25% to 75% [FEF25-75], functional residual capacity [FRC], residual volume [RV], and total lung capacity [TLC].)

- Screening
- EOT
- As clinically indicated

7.3.4 Chest Radiography

(To include posterior to anterior[PA] and lateral views of the chest to assess for evidence of pulmonary fibrosis)

- Screening
- EOT
- As clinically indicated

Note: Diagnostic imaging (CT/MRI) being conducted to for Assessment of Disease will be utilized to assess for evidence of pulmonary fibrosis while patients are on (see **Section 7.4.3**; Diagnostic Imaging for Assessment of Disease (and Pulmonary Status).

7.4. Disease Assessments

(Screening assessments to be performed within 28 days (+ 2 days) prior to first study drug dose)

7.4.1 EGFR Tumor Status Determination

(To include assessment of FFPE tumor tissue; by local or central evaluation of archival tissue or verification by previous pathology report during Phase 1a and by central evaluation of tumor tissue [archival or from a recent biopsy] during Phase 2a)

Phase 1a Dose-Escalation Cohorts: Optional (**Local or Central Lab**)

Phase 2a Expansion Cohorts: Required (**Central Lab**); tumor must be EGFR-positive by IHC as specified* for patient to be eligible for enrollment. If archival tissue is not available patient must be willing to undergo pre-dosing biopsy from a primary or metastatic tumor site**

- Screening***
- Post-dosing: Upon request of the Sponsor based on other study findings, after discussion with the Investigator; if available a request may be made for collection of additional archival tissue for exploratory biomarker assessments (**Section 7.6.1**): Optional

** DAKO EGFRpharmDX™ IHC kit system technology to be utilized. For this study, EGFR-positive staining is defined as ≥ 3+ intensity in ≥ 50% of tumor cells or ≥ 2+ intensity in ≥ 75% of tumor cells for mTNBC; or 3+ intensity in ≥ 50% of tumor cells for SSCHN and Sq-NSCLC, whether it is complete or incomplete circumferential staining.*

***Sufficient FFPE tissue must also be available for submission to a central analytical laboratory for other study-related evaluations (see **Section7.6.1**; Exploratory EGFR Studies in Tumor Tissue).*

****The trial will prescreen patients for EGFR Tumor Status Determination before entering patients into screening for the treatment portion of the trial. The site should use a separate prescreening informed consent form. Prescreening may be performed outside the 28 (+ 2) day screening period to allow adequate turnaround time for receipt of results, provided separate informed consent has been obtained.*

7.4.2 Tumor Marker Measurement (Phase 1a only)

(As indicated by tumor type)

- Screening
- End of Cycle 2 (and every even-numbered cycle thereafter)*
- At least 4 weeks following documentation of an OR
- EOT (if > 6 weeks since previous assessment)
- 1M FUP (if PD was not documented before or at EOT)
- Extended Follow-up** *(in the event of an ongoing OR or SD at EOT)*
  - Every 3 months during the first year of follow-up
  - Every 6 months thereafter

**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle.*

***To continue at the intervals specified until disease progression or another therapeutic intervention is initiated; documentation may be submitted in writing, an in-person visit will not be required.*

7.4.3 Diagnostic Imaging for Assessment of Disease (and Pulmonary Status)

(To include diagnostic imaging by computerized tomography [CT] or magnetic resonance imaging [MRI] of the chest with each evaluation (for disease evaluation where indicated, and to assess for evidence of pulmonary fibrosis) plus abdomen and pelvis, and other sites as indicated based on tumor type and clinical judgment in order to assess the status of the underlying malignancy. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated.

*The same method(s) of disease evaluation and the same technique should be used throughout the study. The location and dimensions of "marker" lesions, where such information is available, will be documented on the patient's eCRF. Standard response criteria will be applied for disease assessments and response evaluations [see **Appendix F**; Measurement of Effect]).*

- Screening
- End of Cycle 2 (and every even-numbered cycle thereafter)*
- At least 4 weeks following documentation of an OR
- EOT (if > 6 weeks since previous assessment)
- 1M FUP (if PD was not documented before or at EOT)
- Extended Follow-up** *(in the event of an ongoing OR or SD at EOT)*
  - Every 3 months during the first year of follow-up
  - Every 6 months thereafter

**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle.*

***To continue at the intervals specified until disease progression or another therapeutic intervention is initiated; documentation may be submitted in writing, an in-person visit will not be required.*

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

To be assigned a status of partial response (PR) or complete response (CR), changes in disease status must be confirmed by repeat studies performed 4 weeks (+ 7 days) 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 study entry at for a minimum duration in general not less than 8 weeks.

In the event of an ongoing OR or SD at the EOT, data will continue to be collected on the duration of OR or SD, as well as on the overall time to PD.

Imaging data (imaging studies and derived assessments) will be stored according to usual practice by the sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer.

7.4.4 Response Assessment

(The anti-tumor activity of study drug will be assessed by the Investigator or qualified designee according to RECIST v1.1 at the intervals specified)

- End of Cycle 2 (and every even-numbered cycle thereafter)*
- At least 4 weeks following documentation of an OR
- EOT (if > 6 weeks since previous assessment)
- Extended Follow-up** *(in the event of an ongoing OR or SD at EOT)*
  - Every 3 months during the first year of follow-up
  - Every 6 months thereafter

**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle.*

***Continue at the intervals specified until disease progression or another therapeutic intervention is initiated.*

7.5. Pharmacokinetic Assessments

Every effort will be made to collect PK samples at the timepoints specified. Sampling times may be adjusted according to early trial results in order to optimize evaluation. No additional samples will be collected without formal amendment to this protocol. Residual sample material may be used for biomarker assessments (**Section 7.6.2**). Detailed procedures for collection, handling, and shipment of samples will be provided by the Sponsor (or designee) in the study Laboratory Manual (or other similar document). (see also **Appendix A**; Schedules of Events).

7.5.1 Peripheral Blood Collection (Central Lab)

(Samples will be evaluated for concentrations of total antibody [AVID100 plus MAB100], AVID100, and DM1; to include assessment of PK parameters such as C_{max}, T_{max}, AUC, etc.; serum to be isolated)

Phase 1a Dose-Escalation Cohorts

- Cycle 1
  - Day 1
    - Prior to SOI
    - EOI (± 5 min)
    - 2 and 4 hours after EOI (± 15 min)
  - Day 2
    - 24 hours after EOI (± 1 h)

  - Day 4 (± 1 day)
    - At time of visit
  - Day 8
    - At time of visit

- Cycle 2
  - Day 1
    - Prior to SOI
    - EOI (± 5 min)
  - Day 8
    - At time of visit
- Each cycle thereafter
  - Day 1
    - Prior to SOI
- EOI (± 5 min)EOT
- 1M FUP
- As clinically indicated in the event of an IRR

Phase 2a Expansion Cohorts

- Cycle 1 and Cycle 5
  - Day 1
    - Prior to SOI
    - EOI (± 5 min)
  - Day 8
    - At time of visit
- Each other cycle
  - Day 1
    - Prior to SOI
- EOT
- 1M FUP
- As clinically indicated in the event of an IRR

**Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of a 4h after EOI sample is logistically difficult due to clinic staff availability, the observation period may be shortened, and an "end of day" sample may be obtained at the latest practical time. Such an option is available ONLY after previous discussion with and approval by the Sponsor.*

Note: Whole blood (~ 5 mL) to be collected in serum acquisition tubes at each of the indicated timepoints. In the event that a collected serum sample is inadequate or insufficient for PK analysis, the analysis of PK can be done using an anti-drug antibody (ADA) serum sample from the same time point, if available.

7.6. Biomarker Assessments

To assess potential biomarkers and response predictors; every effort will be made to collect samples as specified. Detailed procedures for collection, handling, and shipment of samples will be provided by the Sponsor (or designee) in the study Laboratory Manual (or other similar document) (see also **Appendix A**; Schedules of Events).

All analyses will be related to and used only in connection with the data collected in the present trial and the identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient or their relatives

7.6.1 Exploratory Studies in Tumor Tissue (Central Lab)

(For assessment of tumor EGFR-expression by FISH (or similar assay) and other potential biomarkers in submitted FFPE tumor tissue

Phase 1a Dose-Escalation Cohorts: Optional

Phase 2a Expansion Cohorts:

- Screening: Required*; if archival tissue is not available patient must be willing to undergo pre-dosing biopsy from a primary or metastatic tumor site
- Post-dosing: If tumor tissue is available from an interval surgery performed during study participation : Optional
- Post-dosing: In the event of a documented objective response if the patient has accessible residual tumor; in the event of prolonged disease stabilization > 8 weeks: Optional
- Post-dosing: Upon request of the Sponsor based on other study findings, after discussion with the Investigator: Optional

To be performed in tumor tissue submitted for eligibility (see **Section 7.4.1; EGFR Tumor Status Determination by IHC). It must be ensured that the archived tissue is sufficient and can be made available to the central analytical laboratory prior to deciding to omit a tumor biopsy procedure at the time of screening. If available a request may be made for collection of additional archival tissue for exploratory biomarker assessments; such a request would be made post-dosing based on other study findings, after discussion with the Investigator.*

Biopsies are permissible in Phase 1a cohorts in consenting patients, on a case-by-case basis, if considered safe and following discussion between the Investigator and the Sponsor's Medical Monitor.

Note: Archival FFPE material, either block tissue samples of the patient's primary tumor, or slides cut from the paraffin block(s) will be submitted. Unused portions of paraffin blocks will be returned to the referring institution. Tumor specimens should be identified only by the patient's study identifier, surgical pathology and/or histology

accession numbers. Identifiers, such as patient names, and government-issued identifiers, such as social security numbers, should not be recorded in order to ensure confidentiality. Samples will be kept until used up, or stored for up to 15 years after completion of the trial where after all remaining samples will be destroyed. Samples will be used for Forbius research purposes only.

If required, pre-dosing biopsy is to be performed on a primary, recurrent, or metastatic lesion after eligibility has otherwise been confirmed and prior to the first AVID100 administration. The tumor biopsy must be conducted with minimal morbidity to the patient by a percutaneous core needle biopsy either with or without the aid of an imaging modality chosen at the discretion of the physician performing the biopsy. Specimens should be obtained using standard sterile surgical techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. All tumor tissue samples should be reviewed by a pathologist to confirm the presence of tumor cells before the tissue sample (block or slides) is sent to the central laboratory for analysis.

7.6.2 Exploratory Studies in Peripheral Blood (Central Lab)

(For, but not limited to, assessment of EGFR ctDNA for EGFR-ECD mutation status and EGFRvIII deletions (SCCHN only), as well as assessment of other potential biomarkers of interest (required for all indications); may be obtained for submission any time after confirmation of eligibility and study enrollment but prior to dosing on C1/D1)

- Screening
- EOT
- As indicated (ONLY if using residual material available from ADA and PK samplings; no additional blood to be drawn)

Note: Whole blood (~ 20 mL) to be collected;

8. MANAGEMENT OF TOXICITY

Comprehensive assessments of any toxicity experienced by the patient will be performed throughout the course of this study. The Principal Investigator, Subinvestigator, or designated health professional must be available throughout the course of the study in order to evaluate and treat any AE(s), as well as to evaluate whether continued participation in the trial is warranted or advisable.

Anticipated toxicities are detailed in this protocol (see **Section 2.4**; Rationale for and Risks of Proposed Clinical Study, and **Section 11**; Precautions when Dosing with AVID100), as well as in the IB. Patients will be evaluated throughout the trial for evidence of acute as well as delayed and/or cumulative toxicities. Significant changes in a patient's clinical status or laboratory assessments will be followed until the abnormality either resolves, returns to baseline status, or is adequately explained and assessed by the Investigator as chronic and/or stable, and that no longer term deleterious effects have become evident.

Grades of toxicity (CTCAE v5.0), as well as clinical judgment, will be used to determine appropriate management of the patient experiencing any AE while participating in this study, including determining whether the toxicity warrants premedication (**Section 8.2.2, Section 8.2.3**) or a dose modification option such as infusion prolongation (in the event of an IRR) (**Section 8.3.1**), temporary dose delay (**Section 8.3.2**), or dose reduction (**Section 8.3.3**). AEs requiring discontinuation from study treatment are detailed in **Section 9.1**.

8.1. Determination of DLT versus Non-DLT

When an AE occurs, the Investigator will also determine whether the protocol definition of a DLT is met (**Section 6.8.3**). If so, the patient will be either discontinued from treatment or may continue treatment if there is evidence of an OR, SD, or other clinical benefit, but must do so at a reduced dose of study drug, and ONLY following discussion with the Sponsor's Medical Monitor(s). Patients may not be retreated following the occurrence of a DLT until retreatment criteria have been met (**Section 6.7.1**).

Alternatively, the Investigator may determine that the toxicity does not meet the protocol definition for DLT, but nevertheless warrants dose modification, because it is:

- Not controlled by optimal supportive care, or
- Not tolerated due to symptomatology or interference with normal daily activities

For toxicity that does not meet the protocol definition of DLT, the Investigator may, as described below, elect to prolong the infusion duration (for IRRs), reduce the dose of study drug, and/or temporarily delay dosing with study drug in order to allow for amelioration of the toxicity.

8.2. Premedication for Study Drug-Related Toxicities

8.2.1 Infusion-Related Reactions

An IRR is defined as an AE occurring during the study drug infusion and up to 24 hours after the end of infusion (EOI), which is assessed by the Investigator to be related to the infusion. Signs of

IRRs may include but are not limited to facial flushing and swelling, headache, nausea, dizziness, anxiety, diaphoresis, tachycardia, hypotension, fever, chills/rigors, chest and throat tightness, shortness of breath, wheezing, bronchospasm, as well as chest, back and/or abdominal pain or discomfort.

If an IRR occurs, it should be classified according to the CTCAE (v5.0). Recommended management guidelines are provided (see **Appendix G:** Grading and Management of Infusion Reactions).

8.2.2 Premedication for IRRs

Beginning with the first dose, all patients must be premedicated with standard therapies prior to each dose of AVID100 to reduce the risk of infusion-related reactions (IRRs).

The recommended premedication regimen to be administered prior to each study drug infusion, beginning with the dose to be delivered on Day 1 of study, is as follows **(TABLE 3)**:

TABLE 3: RECOMMENDED PREMEDICATION REGIMEN

	Medication	Dose and Route	Alternative Medication	Dose and Route
1	dexamethasone*	10 mg p.o. (12h prior ± 2h)		
		10 mg p.o. (6 h prior ± 2h)		
		10 mg, i.v.		
2	diphenhydramine	50 mg, i.v.	hydroxyzine	25 mg, p.o.
3	ranitidine	50 mg, i.v.	famotidine	20 mg, i.v.

Note: Medications to be delivered at minimum 30 minutes prior to the start of study drug infusion.

*Use of other IV glucocorticoids is allowed, per institutional practice

8.2.3 Other Study Drug-Related Toxicities

Following the first dose, should a patient experience symptoms suggestive of other mild to moderate study drug-related reactions (e.g., nausea, vomiting, diarrhea, etc.), that patient may be premedicated with standard therapies in order to reduce the potential for such reactions in the future.

Mandatory premedication will be implemented for all patients treated on this study should a pattern begin to emerge of other mild-to-moderate study drug-related reactions that are amenable to prophylaxis with standard agents. Such action will occur following discussions between the Investigator(s) and the Sponsor's Medical Monitor(s).

Any medications administered for either prophylaxis or therapy of symptoms considered to be associated with study drug will be documented on the appropriate page of the eCRF.

8.3. Dose Modification Options

8.3.1 Prolongation of Infusion Duration

All IRRs that result in infusion prolongation must be reported promptly to the Sponsor (or designee).

For IRRs the following infusion prolongation instructions are provided:.

- For Grade 1 reactions, consider slowing the infusion to 50% of the prior rate. If the infusion is slowed, deliver subsequent infusions at the prolonged rate.
- For Grade 2 reactions, interrupt the infusion for a minimum of 30 minutes, and at least until there is either amelioration to ≤ Grade 1 severity or return to baseline status. Administer supportive care as medically indicated. Restart the infusion at 50% of the prior rate. Subsequent infusions must be administered at the prolonged rate.
- For Grade 3 reactions, STOP the infusion. Administer supportive care. The occurrence will be considered a DLT and the patient will be either discontinued from treatment, or will receive subsequent treatments at a reduced dose and at 50% of the prior rate or longer.
- For Grade 4 reactions, STOP the infusion. Administer supportive care. The patient will be permanently discontinued from treatment.

Guidelines for the grading and management of IRRs of all severities are provided (see Appendix G: Grading and Management of Infusion Reactions).In all cases the Investigator should use best clinical judgment in managing such reactions.

Should an increased incidence begin to occur of mild-to-moderate IRRs that are managed by prolongation of infusion, consideration will be given to extending the infusion duration in this study. Such action will occur following discussions between the Investigator(s) and the Sponsor's Medical Monitor(s).

All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the patient's eCRF.

Note: Any assessments to be performed or samples to be collected (e.g., vital signs, PK) at the end of or following the EOI will still be performed or collected beginning at the delayed EOI timepoint. In situations where collection of late day samples, in particular the 4h sample, is logistically difficult due to clinic staff availability, an "end of day" sample may be obtained at the latest practical time on the day of the reaction.

To enhance patient safety following an infusion prolongation, subsequent infusions will be administered at the prolonged rate. Rechallenge with a shorter duration of infusion (no less than 2 hours) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity.

8.3.2 Temporary Dose Interruption (Delay)

All dose interruptions of AVID100 must be reported promptly to the Sponsor (or designee).

8.3.2.1. Delay Between Dosing

If indicated, the period between any 2 scheduled doses may be extended to allow for amelioration of the toxicity. However, if any observed Grade 3 or Grade 4 toxicity thought to be associated with study drug results in delay of dosing beyond 2 weeks of the next scheduled dose, regardless of whether the criteria for DLT are met, the event will be considered a DLT, necessitating that the patient either have their dose of study drug reduced or be discontinued from further treatment with study drug.

For toxicities not meeting the protocol definition of DLT that are to be managed by dose interruption, dosing may be restarted at the same or a reduced dose(s), as clinically indicated. However, for a DLT that is managed by dose interruption, administration of study drug MUST be restarted at a reduced dose once retreatment criteria have been met (see **Section 6.7.1**; Retreatment Guidelines).

8.3.3 Dose Reduction

All dose reductions of AVID100 must be reported promptly to the Sponsor (or designee).

In the event that toxicity is to be managed by dose reduction, the study drug dose will be decreased as indicated in the following table **(TABLE 4)**.

TABLE 4: DOSE REDUCTION SCHEDULE FOR AVID100

Starting Dose	First Reduction	Second Reduction
Dose Level 1	½ of Dose Level 1	¼ of Dose Level 1
Dose Level 2	Dose Level 1	½ of Dose Level 1
Dose Level 3	Dose Level 2	Dose Level 1
Dose Level 4	Dose Level 3	Dose Level 2
Continue as above	next lower tolerated dose	next lower tolerated dose

Note: In the event that an intermediate dose is explored in this study, dose reductions in such cases will be to the next lower established tolerated dose level(s).

Patients may have a maximum of 2 dose reductions for study drug-related toxicity, after which they will be generally be discontinued from further treatment with study drug. If indicated, further dose reduction in patients with an ongoing OR or SD may be considered after discussion with the Sponsor's Medical Monitor(s).

Once a patient has undergone a dose reduction, the patient will continue to be treated at the reduced dose throughout the remainder of their time on study treatment. There is no provision in this study for either re-escalation or rechallenge with a higher dose of AVID100.

8.3.4 Schedule Alterations

Altered schedules of study drug (i.e., reduced number of treatment days, longer interval between treatment days) may be explored as a means of dose reduction, only after discussion with the Sponsor (or designee), and only during subsequent cycles of treatment (Cycle 2 and beyond).

Patients requiring such schedule alterations during Cycle 1 of the study will be considered to have met the criteria for DLT due to the inability to complete Cycle 1 of study drug treatment.

Note: Any modification of AVID100 administration, and the reason for such action, must be clearly noted on the patient's eCRF. If such a modification impacts upon a PK sampling interval, the details of such action must also be documented on the appropriate page of the eCRF (to aid in the interpretation of PK findings).

9. REMOVING PATIENTS FROM STUDY TREATMENT

Every reasonable effort will be made to keep patients in the study; however, in the event that a patient is discontinued from study treatment, every effort will be made by the Investigator to complete and report the reasons for treatment discontinuation as thoroughly as possible. This evaluation should include EOT observations, as required by the protocol at the time of treatment discontinuation (see **Section 7**; Study Assessments), as well as 1M FUP evaluations. The reason(s) for treatment discontinuation must be clearly documented on the appropriate page of the eCRF. An eCRF must be completed for any patient who receives any amount of study drug.

9.1. Criteria for Treatment Discontinuation

Patients will be discontinued from further treatment with study drug in the event of any of the following:

1. Patient must be permanently discontinued in the event of any major, potentially irreversible organ system DLT , including:
    - Pulmonary toxicity defined as:
        - Evidence of pulmonary fibrosis, any grade
        - Reduction of forced vital capacity (FVC) or DL_{CO} ≥ Grade 3
    - Neurotoxicity defined as peripheral neuropathy ≥ Grade 3
    - Any ocular toxicity ≥ Grade 3
    - Nephrotoxicity defined as:
        - Acute kidney disease ≥ Grade 3 (i.e., creatinine > 3 × baseline or > 4.0 mg/dL)
        - Chronic kidney disease ≥ Grade 3 (i.e., estimated glomerular filtration rate [eGFR] or creatinine clearance [CrCl] 29-15 mL/min/1.73 m^2)
        - Proteinuria ≥ Grade 3 (i.e., ≥ 3.5 g/24 hours)
    - Hepatotoxicity suggestive of drug-induced liver injury, as characterized by the following 3 criteria:
        - AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry as allowed by study eligibility criteria; see **Section 4.3.1 #7**)
        - Total bilirubin > 2 × ULN without initial findings of cholestasis (i.e., no elevation in serum ALP)
        - No explanation for the above findings, such as: viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

      Adapted from: Hy's Law. Drug–induced liver injury: premarketing clinical evaluation. Guidance for Industry. U.S. Department of HHS, FDA, CDER, CBER, 2009.

2. Any other DLT (see **Section 6.8.3**; Definition of DLT) considered by the Investigator to require treatment discontinuation.

   Note: Patients experiencing a DLT not listed in #1 above may continue at a reduced dose if there is evidence of an OR, SD, or other clinical benefit, provided protocol stipulated retreatment criteria delineated in **Section 6.7.1** (Retreatment Guidelines) have been met, and ONLY following discussion with the Sponsor's Medical Monitor(s)).

3. Another AE not meeting the criteria for a DLT, yet considered by the Investigator to require treatment discontinuation.

   Note: AEs resulting in a patient's permanent discontinuation from study treatment, regardless of seriousness or relationship to study drug, MUST be reported promptly to the Sponsor (or designee).

4. Documented progressive disease at any time during the study
5. Treatment failure not meeting the criteria for progressive disease, but considered by the Investigator to require treatment discontinuation.
6. Requirement for a significant surgical procedure

   Note: Patients requiring a minor surgical procedure (e.g., port placement, skin abscess drainage) may continue at the Investigator's discretion following discussion with the Sponsor's Medical Monitor(s). A brief interruption in therapy may be considered.

7. An intercurrent illness which, in the opinion of the Investigator, would prevent completion of study-related evaluations
8. Significant deviation from the protocol or eligibility criteria. Such patients will be considered protocol violations and will be discontinued from treatment
9. Pregnancy
10. Noncompliance with study or follow-up procedures
11. Patient withdrawal of consent and election to discontinue treatment with study drug. (Patients may leave the study at any time for any reason if they wish to do so, without any consequence.)
12. Termination of the study by the Sponsor
13. Any other reason which, in the opinion of the Investigator, would justify treatment discontinuation. In such a case, the Investigator's reason for treatment discontinuation must be recorded on the appropriate page of the eCRF.

9.2. Replacements

Phase 1a: Dose-Escalation: Should a patient discontinue treatment with study drug for reasons other than the occurrence of a study drug-induced toxicity prior to completing Cycle 1 a replacement patient will be obtained using the original eligibility criteria. Patients discontinued due to study drug-associated toxicity will not be replaced.

Note: Patients must receive their full planned dose of AVID100 during Cycle 1 in order to be considered evaluable for tolerability, unless dose reduction, interruption, or discontinuation is the result of a DLT. Patients receiving < 1 full planned study drug dose plus 3 weeks of follow-up during Cycle 1 for reasons other than toxicity will be replaced.

Phase 2a Dose-Expansion: It is not planned to replace any patients in the 3 dose-expansion cohorts.

10. ADVERSE EVENTS

10.1. Definitions

10.1.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

This includes any unintended or undesirable, noxious, or pathological change, compared to pre-existing conditions, experienced by a patient during a clinical study or the follow-up period, regardless of relationship to study drug.

AEs include:

- Suspected adverse drug reactions
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug.
- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptoms, or apparently unrelated illnesses.

10.1.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Note: By definition, all SARs, are AEs, however the converse is not the case as all AEs are not SARs.

10.2. Evaluating Adverse Events

The Investigator will determine the seriousness, intensity, and causality of an AE based on the following definitions:

10.2.1 "Serious" Adverse Events and Suspected Adverse Reactions

(Notify Sponsor or designee within 24 hours of Investigator awareness; document on eCRF)

An AE or SAR is considered "serious" if, in the view of either the Investigator or Sponsor (or designee), it results in any of the following outcomes:

1. **Death:** This includes any death that occurs while the patient is "on study" as well as any death that occurs within 30 days after study drug administration. If an autopsy is performed, results may be requested by the Sponsor (or designee). Possible evidence of

organ toxicity (e.g., radiation damage) and the potential relationship of the toxicity to the study treatment will be of particular interest.

2. **A life-threatening AE:** This includes any occurrence that places the patient at immediate risk of death from the reaction as it occurred. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. **Inpatient hospitalization or prolongation of existing hospitalization**
4. **A persistent or significant disability/ incapacity:** A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.
5. **A congenital anomaly/birth defect**
6. **Requirement for intervention to prevent permanent impairment or damage:** Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Planned or elective hospitalizations, or hospitalizations for the administration of protocol therapy, should not be considered SAEs.

10.2.2 "Unexpected" Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

(Notify Sponsor or designee within 24 hours of Investigator awareness; document on eCRF)

All AEs or SARs that are both unexpected and serious (i.e., suspected unexpected serious adverse reactions; SUSARs) are subject to expedited reporting. An AE or SAR is considered "unexpected" if it is not listed in the IB or protocol (see **Section 2.4**; Rationale for and Risks of Proposed Clinical Study, and **Section 11**; Precautions when Dosing with AVID100) , or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.2.3 Non-Serious Adverse Events

(Document on eCRF)

All other AEs not fulfilling the previous definitions are classified as non-serious.

10.2.4 Protocol-Related Adverse Events

AEs that are not study drug-related may nevertheless be considered by the Investigator or the Sponsor (or designee) to be related to the conduct of the clinical study. That is, the event may be related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an event that occurs during a washout period or that is related to a procedure required by the protocol.

10.3. Documenting Adverse Events

Information regarding the occurrence of AEs should be elicited through open-ended questioning of the patient, review of physical examination findings, and review of laboratory results.

All AEs (**including SAEs**) are to be detailed in the source documents and accurately recorded on the Adverse Event page of the patient's eCRF. All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur from signing of informed consent* through the period of protocol-specified follow-up, must be captured. AEs occurring within 30 days after the last dose of study drug must be reported. SAEs, thought by the Investigator to be related to study drug, however, must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 30 days after the last dose of study drug.

AE terms should be recorded concisely, using acceptable medical terms, and, when possible, a diagnosis (i.e., disease or syndrome) rather than the component signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated or atypical to encountered syndromes or diseases are to be recorded as individual AEs on the eCRF (e.g., if congestive heart failure and severe headache are observed at the same time, each event is to be recorded as an individual AE). The AE should not be recorded as a procedure or clinical measurement (i.e., a laboratory or vital sign), but should reflect the reason for the procedure or diagnosis. For fatal AEs, death is considered to be an outcome of the AE. The cause of death (rather than the term "death") should be recorded as the AE in the eCRFs. AEs terms will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system.

*Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they are will not be participating in this trial.

10.3.1 Information to be Provided for each AE

The following information will be provided for each AE term reported:

- Each event will be graded according to the CTCAE (v5.0) as to severity. For events not listed in the CTCAE, severity will be graded on a 5-point scale as mild, moderate, severe, life threatening, or fatal, which correspond to Grades 1, 2, 3, 4, and 5, respectively on the CTCAE (see **Appendix D**; Adverse Event Grading Scale).

- The date of onset as well as the duration of the event will be recorded (i.e., date of resolution).
- The method used to treat the AE, specifically, the action taken regarding the study drug will be provided (e.g., none, infusion temporarily interrupted, infusion prolonged, infusion stopped, dose reduced, dose schedule altered, dosing permanently discontinued).
- The outcome of the AE (e.g., ongoing, resolved, resolved with sequelae, fatal) will also be noted.
- The Investigator will attempt to assess the relationship of the event to study drug. Investigators are required to assess whether there is a reasonable possibility that the investigational drug caused or contributed to an AE. Determination of whether there is a reasonable possibility includes assessing temporal relationships, biologic plausibility, dechallenge/rechallenge information (if available), association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause. The Investigator must attempt to determine if an AE is in some way related to the use of the study drug using a 5-point causality scale (i.e., unrelated, unlikely-related, possibly related, probably related, related) (see **Appendix E**; Clinical Adverse Events: Determining Relationship to Study Drug).

Preexisting condition (i.e., disorders present before the AE reporting period started and noted during the Screening period) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be noted as the intervention for the AE.

Abnormal laboratory values or abnormalities in other physiological testing (such as ECGs) per se need not be reported as AEs unless the Investigator feels they are clinically significant (CS), they are an SAE, they require an intervention, they result in a change to protocol therapy, or they result in a patient discontinuing protocol therapy. Laboratory abnormalities associated with a diagnosis (e.g., elevated hepatic enzymes in a patient with hepatitis) need not be listed as a separate AE. If a patient with elevated hepatic enzymes has jaundice but no clinical diagnosis or syndrome has been established, then both jaundice and elevated hepatic enzymes should be reported as AEs.

AEs of CTCAE Grade 4 or 5 generally qualify for SAE reporting to the Sponsor or designee, however the definition of CTCAE Grade 4 does not necessarily always meet the regulatory definition of "life-threatening". As example, a laboratory abnormality of CTCAE Grade 4 does not need to be reported as an SAE, unless it meets one of the seriousness criteria.

Progressive neoplastic disease should not be reported as an AE, as this will be recorded as part of the patient's efficacy evaluation. Progressive disease may be reported as an AE in the case of patient death, with death being the outcome of the event.

10.3.2 Timeframe for Recording AEs

The AEs pages of the eCRF will be completed in a timely manner following a patient completing (or being discontinued from) each dosing cycle.

This will enable the Sponsor (or designee) to tabulate the occurrence of AEs, and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort. Availability of these data will also enable the Sponsor (or designee) to notify any other Investigator participating in clinical studies of the study drug of events occurring during the trial, where indicated.

10.3.3 Required Follow-up for AEs

Appropriate consultation and follow-up evaluations should be carried out until the event either resolves, returns to baseline status, or has been adequately explained and assessed by the Investigator as chronic and/or stable, and that no longer term deleterious effects have become evident. This follow-up may extend up to 6 months after the end of study if indicated, if the event has not resolved or been adequately explained.

10.4. Reporting SAEs (Including Patient Deaths) and Unexpected SAEs

10.4.1 24-Hour Requirement for Reporting to the Sponsor

All SAEs, including SUSARs and patient deaths, experienced by the patient from signing of informed consent until 30 days after receiving the final dose of study drug, or any SAE that occurs after 30 days of receiving the final dose of study drug and is believed to be study drug-related, must be promptly reported (within 24 hours of Investigator awareness) even if the experience does not appear to be associated with the study drug or the protocol. Reports will be made by telephone, telefax, or e-mail transmission to the Sponsor or the Sponsor's designee.

Where SAE submissions are made to the Sponsor's Safety Designee, such submissions must then be transmitted by to the Sponsor's Medical Monitor(s). The SAE Form must be transmitted to the Medical Monitor(s) whether full information regarding the event is known or not.

*Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they are will not be participating in this trial.

10.4.2 Governing Regulatory Requirements Regarding Sponsor Review

Under ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, and per Food and Drug Association (FDA) ruling (U.S. Code of Federal Regulations, Title 21 CFR Part 312.32), the Sponsor (or designee) must promptly review all information relevant to the safety of the study drug obtained or otherwise received by the Sponsor (or designee) from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or *in vitro* studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

Prompt reporting by the Investigator to the Sponsor (or designee) facilitates the Sponsor's ability to remain compliant with this ruling.

10.4.3 Governing Regulatory Requirements Regarding Sponsor Reporting

Compliance with this requirement for prompt reporting to the Sponsor (or designee) is essential also in that the Sponsor is obligated to, and will be responsible for subsequently informing the FDA and local governing Health Authorities, as well as all other participating Clinical Investigators (i.e., all Investigators to whom the Sponsor or designee is providing drug under its INDs or under any Investigator's IND) of potential serious risks from clinical trials or any other source, of events that meet reporting criteria.

10.4.3.1. Reporting Criteria

Under ICH Guidelines and FDA ruling the Sponsor (or designee) is required to submit written documentation detailing:

- **Any SAR that is both serious and unexpected.** Reporting is required only if there is evidence to suggest a causal relationship between the drug and the AE, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
    - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
    - An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the Sponsor, that suggest a significant risk in humans exposed to the drug.
- Any findings from laboratory animals or *in vitro* testing, whether or not conducted by the Sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure dose.
- Any clinically important increase in the rate of a serious SAR over that listed in the protocol or IB.

10.4.3.2. Reporting Format

Written submission of such reactions or findings, from the Sponsor (or designee) to FDA must be in the form of an **IND Safety Report** presented in a narrative format, or on FDA Form 3500A (MedWatch form). For international trials a Council for International Organizations of Medical

Sciences (CIOMS) I form may be used for U.S. FDA reporting as well as ex-U.S. reporting to relevant local governing Health Authorities.

10.4.3.3. Reporting Timeframes

Written submission must be made by the Sponsor (or designee) to FDA and other relevant local governing Health Authorities and Investigators as soon as possible, but in no case later than **15 calendar days** after the Sponsor (or designee) determines that the information qualifies for reporting (i.e., usually after initial notification of the reaction or finding).

In addition, the Sponsor (or designee) is further required to report, by either telephone or facsimile transmission or in writing to the FDA, the occurrence of any unexpected fatal or life-threatening SAR as soon as possible, but in no case later than **7 calendar days** after the Sponsor (or designee's) initial receipt of the information.

10.4.4 Information to be Provided by the Investigator to the Sponsor

10.4.4.1. Initial Information on an SAE

At the time of the initial contact(s), the Investigator must transmit information to the Sponsor (or designee) sufficient for completion of an IND Safety Report or similar document. The Sponsor (or designee) will request the following information about the patient and the event:

- Patient identification number, gender, date of birth (or age)
- Height, weight or body surface area (only where required for dose calculation)
- Primary disease under treatment
- Lot number and expiration date of study drug (if available)
- Dose, schedule, and route of study drug administered
- Date of most recent study drug administration
- Date of event onset (Start Date) and duration (Stop Date) indicating the period during which the event met the serious criteria.
- Description of event
- Date of death (if applicable)
- Action take regarding study drug (e.g., none, infusion temporarily interrupted, infusion prolonged, infusion stopped, dose reduced, dose schedule altered, dosing permanently discontinued)
- Intervention(s) required (e.g., none, drug treatment required, non-drug treatment or procedure required)
- Concomitant therapy (including regimen(s) and indication)
- Pertinent laboratory data/diagnostic study (including dates)
- Pertinent medical history

- Did event abate after interruption of study drug administration (if applicable)?
- Did event recur after study drug was reintroduced (if applicable)?

In addition to the above information, the Sponsor (or designee) will require the Investigator's assessment of the following:

- Severity of the AE
- Relationship of the AE to study treatment
- Outcome of the AE (e.g., resolved, recovery with sequelae, event ongoing, patient died)

10.4.4.2. Follow-up Information on an SAE

Information not available at the time of the initial report (e.g., resolution date for the SAE, laboratory and diagnostic test reports, physician's summaries, etc.) must be submitted to the Sponsor (or designee), as it becomes available, in the form of a follow-up SAE report. The same timelines governing initial reports apply to follow-up reporting.

10.4.4.3. SAE Review and Potential Impact On Trial Conduct

The Investigator will review each SAE report and evaluate further the relationship of the AE to study drug and to the patient's underlying disease.

Based on the Investigator's assessment of causality of the AE and discussions with the Medical Monitor(s), a decision will be made by the Sponsor (or designee) concerning the need for further action with respect to the future conduct of this trial. The primary consideration governing further action is whether new findings affect the safety of other patients participating in the clinical study. If the discovery of a new AE related to study drug raises concern over the safety of its continued administration to patients, the Sponsor (or designee) will take immediate steps to notify FDA, other local governing Health Authorities, and all Investigators participating in clinical studies of the study drug.

Further action required may include any of the following:

- Alteration of the existing research program by modification of the protocol
- Discontinuation or suspension of the study
- Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings
- Modification of previously identified expected AE lists, including those included in the IB, to include AEs newly identified as study drug-related

10.5. Required Follow-up for All AEs and SAEs

Appropriate consultation and follow-up evaluations should be carried out until the event has resolved, returned to baseline, or is otherwise explained by the Investigator.

All SAEs should be promptly reported by the Investigator to his/her Institutional Review Board (IRB) or Ethics Committee (EC) according to their IRB/EC submission requirements. Should the FDA or other governing Health Authorities require that the Sponsor submit additional data on the event, the Investigator will be asked to provide those data to the Sponsor (or designee) in a timely fashion.

Note: All patients are to be followed for a minimum of 30 days after study drug discontinuation in order to monitor for the occurrence of SARs that are both serious and unexpected. A longer period of time may be specified by the Sponsor (or designee) if required to assure the safety of the patient.

11. PRECAUTIONS WHEN DOSING WITH AVID100

11.1. Precautions Regarding Procreation

11.1.1 Reproduction

No studies specifically evaluating the effects of AVID100 on reproductive function in animals are available. Thus, patients receiving study drug must be informed that there could be potential risks relating to reproductive outcomes as a result its administration.

11.1.2 Contraception

AVID100 has not been evaluated in human studies of embryo fetal development. For this reason women of childbearing potential (WOCBP), and fertile men with a partner of childbearing potential, should only be administered study drug when highly effective contraceptive measures have been taken, and in potential women participants when predosing pregnancy tests are negative.

- Women are considered of childbearing potential if they have experienced menarche, and they have not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or are not post-menopausal. Post-menopause is defined as: 1) amenorrhea for > 12 months with no other cause, or 2) irregular menstrual periods, on HRT, with a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL. In women under 55 years of age who have not been surgically sterilized, post-menopausal status should be confirmed by evaluation of serum FSH.

  Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, transdermal patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence, or where their partner is surgically sterile (e.g., vasectomy), should be still be considered of childbearing potential and must agree to true abstinence or to use a highly effective method of contraception during the study and for 3 months after the last dose of study drug.

- Men are considered fertile unless they have undergone surgical sterilization (bilateral vasectomy or a bilateral orchiectomy), and must with their partner of childbearing potential agree true abstinence or to to use a highly effective method of contraception during the study and for 3 months after the last dose of study drug, and refrain from sperm donation during this period.

- A highly effective method of contraception is defined as true abstinence or non-hormonal contraception equivalent to a double-barrier method (includes a single-barrier method in combination with a spermicide) or intrauterine device.

11.1.3 Pregnancy

Female subjects cannot be pregnant at the time of study entry, must be removed from study therapy if they do become pregnant during treatment, and should not become pregnant within 3 months following the last dose of study drug. Male subjects must avoid procreating during study or within 3 months following the last dose of study drug.

A pregnancy test must be performed on, and the results reviewed for, on each WOCBP prior to first study drug administration. A negative pregnancy test performed within ≤ 2 working days prior to first study drug administration must be documented on the patient's CRF.

If it is confirmed that a study participant has become pregnant while participating in this trial, study drug administration will be discontinued immediately. Any pregnancy occurring during this study will be reported immediately to the Sponsor (or designee). The Investigator will then report follow-up information to the Sponsor (or designee) regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of the fact that the patient has discontinued treatment with study drug. Once the newborn is determined to be healthy, as defined by and agreed upon by the Sponsor (or designee) and Investigator, additional follow-up will no longer be required. A female partner of a male patient on the trial who becomes pregnant will be approached for permission to have the pregnancy followed until term and reported upon to the Sponsor (or designee).

11.1.4 Breastfeeding

There is no information regarding presence or absence of study drug in breastmilk. There is also no information regarding the effects of study drug on maternal milk production or on suckling neonates. For these reasons, women who are nursing are not eligible to participate in this study. Lactating women who do participate in this study must discontinue nursing during study and until 3 months after the last dose of study drug.

11.2. Additional Precautions

There are no known contraindications to the administration of AVID100, however the following additional precautions are provided.

In studies of other monoclonal antibodies and ADCs:

- IRRs have been observed, therefore safety in patients with previous presumed formulation-related infusion reactions should be carefully evaluated prior to administration of AVID100. Premedication to prevent infusion reactions should be administered to all patients with a history of such reactions, and facilities and personnel to treat such reactions, if they occur, should be available. In the event of an IRR, the infusion should be slowed/interrupted so that appropriate measures may be taken.

In nonclinical toxicology studies of AVID100:

- Changes in the skin that were related to AVID100 were observed including: hyperkeratosis, dryness, flaking, erythema, hyperpigmentation, lesions, fragile skin, scab formation, abrasions and ulcerations. Skin findings worsened over time with continued dosing and resolved over a period of 10 days in a recovery study. Skin findings led to

excessive scratching in severely affected animals. Severe skin rash accompanied by other findings led to early sacrifice of animals treated at the highest dose (25 mg/kg) on a weekly schedule. Histopathological changes in the skin considered to be related to AVID100 included single cell necrosis, fibrosis, and lymphocytic infiltrates. These findings were consistent with those observed with other anti-EGFR antibodies (i.e., cetuximab, panitumumab).

- Diarrhea, dehydration, decreases in food consumption and weight loss were observed in some animals. Mild hyperplasia was observed in the colon and jejunum of some animals. Mild lymphocytosis was observed in the colon of some animals. As with the skin toxicity detailed above, these findings were treatment-related and believed to be consistent with the toxicity profile of cetuximab.
- Mild to moderate increases of ALT and ALP were observed in all studies. Levels of both of these enzymes returned to near baseline levels before the next dose on a weekly schedule or by the end of the study. Minimal to mild hepatocellular hypertrophy and minimal hepatocellular vacuolation as well as hepatic single cell necrosis and increased mitosis were observed microscopically. Hepatoxicity has been identified as a major toxicity of an approved ADC conjugated to DM1, ado-trastuzumab emtansine.
- Decreases in platelet counts which were reversible were observed and considered to be treatment related. Platelet counts recovered between weekly doses suggesting that this toxicity is reversible. Similar effects on platelets have been observed with ado-trastuzumab emtansine and are consistent with the effects of the cytotoxic moiety DM1. Slight reductions in red cell parameters were also observed. Minimal to moderated bone marrow reduced cellularity has been observed.
- Minimal to marked lymphoid depletion was observed in lymphoid organs in repeat dose studies although enlarged lymph nodes and lymphoid hyperplasia has also been observed in the single dose GLP study in 5 of 6 animals. In this same study thymic atrophy and lymphoid hypoplasia were observed.
- Cardiac effects were not prominent in these studies, although sinus tachycardia and sinus bradycardia were observed in some animals but these findings were not considered to be related to AVID100 administration. All of the electrocardiograms were qualitatively and quantitatively within normal limits. The QTc interval was longer in animals treated with 10 mg/kg AVID100 but these changes were minor and there was no evidence of a dose response effect. In the heart there was AVID100-related minimal to moderate myocardial degeneration and increased incidence of minimal mononuclear cell inflammation. This finding was only observed in 1 of 6 animals receiving 10 mg/kg and this dose level was declared the HNSTD in the 4 week study.
- There were no AVID100-related ocular changes during the course of the 4 week GLP study in animals receiving 10 mg/kg. AVID100-related epithelial changes in the eye consisted of single cell necrosis/increased mitosis in the cornea and conjunctiva.
- Increased single cell necrosis/increased mitosis was observed in a wide variety of organs and tissues, although only the findings in the skin were considered to have contributed to the toxicity seen in animals receiving 25 mg/kg in the GLP weekly dosing study. In

addition to these changes seen in skin, similar findings were observed in the kidney, reproductive tract, mammary gland, trachea, and other tissues.

- Toxicity to the ovaries, including degradation of corpora lutea, was observed in nonclinical toxicology studies. Severe sperm depletion was also noted in repeat dose studies.

In addition to findings in toxicology studies a number of other potential risks of AVID100 administration have been identified.

- The use of AVID100 in lactating women or in children has not been evaluated. These patients will be excluded from study entry.
- No formal drug interaction studies have been performed, therefore no specific guidance can be provided about use of concomitant medications. Use of strong inhibitors or inducers of CYP3A4 is not permitted in patients treated with AVID100.
- There is no experience with clinical overdose of AVID100. Higher doses of AVID100 in animals have resulted in skin and other toxicities including lethality in animals receiving repeated doses of 25 mg/kg. If severe reactions occur in patients receiving AVID100 it should be discontinued and all appropriate supportive medical care should be instituted to ameliorate these potential adverse effects.

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Conditions of Testing

In sponsoring this study, it is the intention of the Sponsor to obtain patient safety data for submission to regulatory authorities. In agreeing to conduct this investigation, the investigative facility agrees to follow all requirements stipulated in this protocol as well as regulations described in the U.S. Code of Federal Regulations (CFR) and by local governing Health Authorities concerning:

- Responsibilities of Investigators (in the U.S. Title 21CFR, Part 312)
- Informed Consent of Human Subjects (in the U.S. Title 21 CFR, Part 50)
- Institutional Review Boards (in the U.S. Title 21 CFR, Part 56)

In addition, , this trial will be conducted in compliance with, and the Investigator agrees to perform the study in accordance with, the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH E6(R2) GCP) (EMA/CHMP/ICH/135/1995) Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulations.

12.2. Institutional Review

The Investigator will submit this protocol, any protocol modifications, and the patient consent form to be utilized in this study, to the appropriate Institutional Review Board or Ethics Committee for review and approval. This committee must operate in accordance with ICH E6(R2) GCP, the U.S. Code of Federal Regulations, Title 21 CFR Part 56, and/or local governing Health Authorities, as appropriate. A letter confirming approval of the protocol, and the informed consent document, must be forwarded to the Sponsor (or designee) prior to initiation of this study. The Investigator will not start the study, nor will study drug be shipped to the investigational site, before providing the Sponsor (or designee) with evidence of this approval.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to his/her IRB or EC. The Investigator will not make any changes in the protocol without IRB or EC approval, except where necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB or EC as required by the IRB or EC. If the study remains in progress for more than one year, the Investigator must obtain annual renewal and re-approval from the IRB or EC where appropriate. Documentation of renewal must be submitted to the Sponsor (or designee). The Investigator will provide notice to the IRB or EC of completion of participation in the study.

12.3. Informed Consent

The Investigator agrees to protect the rights, safety, and welfare of the patients entered into the study, including obtaining written informed consent prior to performing any study-related procedures, and informing each patient that the study drugs are being used for investigational purposes.

Prior to study start, the Sponsor will provide a sample informed consent form (ICF) for modification, as appropriate, by each Investigator. The sample ICF must include all elements required by ICH Good Clinical Practices and must adhere to the IRB/EC requirements and ethical principles that have their origin in the Declaration of Helsinki.

The Investigator's revision to the Sponsor's sample ICF, along with any other written study information to be provided to the patient, must then be reviewed and approved by the investigational site's IRB or EC. A copy of the investigational site's IRB-approved or EC-approved consent form document to be utilized during the study then must be submitted to the Sponsor (or designee) for review prior to study initiation.

Prior to each patient's entry to the study, the Investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, its expected duration, and the potential risks associated with participation. All questions about the trial will be answered to the satisfaction of the patient or the patient's legal representative. The patient will be informed of the right to withdraw from the study at any time without consequence, and without having to provide a reason for this decision. Following the discussion, the patient will be asked if they are willing to personally sign and date the statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study.

It is the responsibility of the Investigator to obtain written informed consent from each patient, thereby attesting that consent was freely given freely, in accordance with ICH E6(R2) GCP, the U.S. Code of Federal Regulations, Title 21 CFR Part 50, or local governing Health Authorities, as appropriate. An Investigator listed on Form FDA 1572 (or similar document for ex-U.S sites) will then co-sign the informed consent document. A copy of the signed and dated informed consent document will be provided to the patient. The original executed version must remain in the Investigator's file, per local requirements, and must be available for verification by a representative of the Sponsor (or designee).

12.4. Conditions for Modifying or Terminating the Study

12.4.1 Modification of the Study Protocol

In the event that modifications in the experimental design, dosages, assessments, patient selection, etc., of the protocol are indicated or required, such changes will only be instituted following consultation between the Sponsor (or designee) and Investigator and will be accomplished through formal amendment(s) to this protocol and approval by the appropriate review committees, except where necessary to immediately eliminate apparent hazards to patients. Protocol changes to eliminate an apparent hazard to a trial patient may be implemented by the Investigator immediately. The Investigator must then, without delay, inform the local IRB and the Sponsor (or designee), who will immediately notify local governing Health Authorities.

A modification to the protocol will not be made without the express written approval of the Sponsor (or designee). Any amendment prepared by the Sponsor (or designee) will be implemented according to the Sponsor (or designee's) standard operation procedures (SOPs) and will be reported to the appropriate regulatory body, the appropriate IRB(s) or EC(s), and made a formal component of the protocol document.

12.4.2 Modification of the Informed Consent Document

In the event that modifications in the experimental design, dosages, assessments, patient selection, etc., of the protocol are indicated or required, and in the event that such modifications substantially alter the study design or increase the potential risk to patients, the Investigator will prepare a revision to the existing Informed Consent document. Such a revision will be reviewed and approved by the appropriate IRB(s) or EC(s), and documentation of this approval will be forwarded to the Sponsor (or designee) for submission to the appropriate regulatory body.

In addition, all current study participants, as well as subsequent study candidates, will be informed of the study design modification or increase in potential risk, and written informed consent for the modification/risk will be obtained as outlined above (see **Section 12.3**; Informed Consent).

12.4.3 Conditions for Termination of the Study

The Sponsor reserves the right to terminate the study, or terminate a clinical trial site's participation in the study, at any time. Should the Sponsor, the Sponsor's designee, and/or the Investigator(s) discover conditions, during the course of the study, that indicate that it should be discontinued, an appropriate procedure for termination will be instituted. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP, or regulatory requirements
- Unsatisfactory enrollment with respect to quantity or quality
- Incomplete data collection; inaccurate or knowingly false data submission
- Safety concerns; incidence and/or severity of AEs in the study that indicate a potential health hazard or unexpected, serious, or unacceptable risk caused by the study treatment
- Drug supply or manufacturing issues
- The Sponsor's decision to modify or discontinue development of the study drug
- A request to discontinue the study by a regulatory or health authority

If terminating the study, the Sponsor and Investigator(s) will assure that adequate consideration is given to the protection of patients' interests.

12.5. Deviation from the Protocol

The study is to be conducted as described in this protocol. Under no circumstances should the protocol be modified for any patient without the prior consent of the Sponsor, and, if necessary the IRB or Ethics Committee responsible for patients at the investigative site.

Departures from either the protocol eligibility criteria or the experimental plan, as outlined herein, will be determined as allowable only in extremely rare instances, and only on a case-by-case basis. The Investigator, or other health professional in attendance, must prospectively contact the Sponsor's Medical Monitor(s) to discuss the associated circumstances. Based on the information provided, a decision will be made as to the patient's continued eligibility status.

Authorization granted for any departure from the protocol applies only to the specific individual patient being discussed.

12.6. Documents to be Submitted to the Sponsor

The following documents must be submitted to the Sponsor (or designee) prior to study initiation:

1. Local health authority permission to conduct the study and local import licenses (copy) (ex-U.S. sites, where applicable)
2. Signed and dated Form FDA 1572* (original) (or similar document confirming trial responsibility for ex-U.S. sites)

   **In conducting this study the Investigator agrees to comply with commitments listed under Section 9 of Form FDA 1572.*
3. Signed and dated curriculum vitae (CV) of the Principal Investigator and each Subinvestigator* named on Form FDA 1572 (copies). Physician CVs should be current (updated within 2 years) and accompanied by a copy of the current medical license.

   **A Subinvestigator is defined as a clinician responsible for study-related medical decisions, diagnoses, and treatment.*
4. Written, signed notification of IRB or EC approval of the study protocol (copy)
5. Written, signed notification of IRB or EC approval of the informed consent document to be used during the study (copy)
6. Written, signed notification of IRB or EC approval of any other material provided to potential trial participants with information about the trial (e.g., advertisements) (copy)
7. IRB-approved or EC-approved informed consent document to be used during the study (copy)
8. A current IRB or EC membership list for the reviewing committee, or the multiple project assurance number from the Federal-Wide Assurance (FWA) program (www.ohrp.osophs.dhhs.gov)
9. Laboratory normal ranges for the reference laboratories to be utilized (protocol-specific analytes only)
10. Name, location, and current laboratory certification (with date), for the reference laboratories to be utilized; curriculum vitae of the laboratory director
11. Signed and dated Investigator Protocol Agreement Statement; statement is included as part of this protocol (original)

12. Fully executed clinical trial agreement
13. Financial disclosure information for the Investigator and each Subinvestigator(s)

12.7. Data Review During this Study

Data obtained as a result of the study will be reviewed in a timely manner throughout by the Sponsor (or designee) and Sponsor's Medical Monitor(s) in order to assess safety and the progress of the project.

12.8. Trial Registration

The trial will be registered in one or more public trial registries (e.g., ClinicalTrials.gov). The trial results will be posted in the same clinical trial registries as the initial registration in accordance with the latest International Committee of Medical Journal Editors (ICMJE) recommendations (URL: www.icmje.org).

13. INVESTIGATOR RESPONSIBILITIES

13.1. Medical Supervision

An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in U.S. Code of Federal Regulations, Title 21 CFR Part 312 and ICH Good Clinical Practices.

Medical supervision for the conduct of this protocol is the responsibility of the Principal Investigator. The Principal Investigator must name all Subinvestigators and may delegate certain day-to-day activities to such Subinvestigators, but, retains overall responsibility for ensuring that the study is conducted properly and in accordance with the design and intent herein. A memorandum outlining the specifics of the delegation will be maintained at the investigational site, in the study files, and will be updated as appropriate.

The Principal Investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies. The Principal Investigator is required to ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the protocol. The Principal Investigator is responsible for ensuring that the study is conducted according to sound medical practices.

13.2. Confidentiality

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigator (or any company acting on their behalf), inclusive of this protocol, the patient electronic Case Report Forms and the IB are the exclusive property of the Sponsor. Documents and information provided to the Investigator by the Sponsor may not be given or disclosed by the Investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

It is specified that the submission of this protocol and other necessary documentation to the IRB or Ethics Committee is expressly permitted, the IRB or Ethics Committee members having the same obligation of confidentiality.

The Investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed to a third party mandated by applicable law.

Note: Any language relating to these issues appearing in the clinical trial agreement will supersede that which is outlined in this section.

13.3. Use of Information and Publication

Publication of a summary of the results of the study is permissible according to the Sponsor and is not inconsistent with the preceding affirmation. Scientific dissemination of the results of this study is encouraged. Any formal publication of data collected as a result of the study will be considered a joint publication by the Investigator and the appropriate personnel of Forbius or their designees. Authorship will be determined by mutual agreement.

In the event of a publication describing multicenter trial results, the Investigator with the largest number of evaluable patients enrolled into the study will be named as first author. The second highest enroller will be named as second author, and so forth. However, the Sponsor retains the right to designate one of the authors or someone else involved to be named as the primary author. In such an event, the Sponsor will strive to ensure that all Investigators who actively participated in the study are given appropriate credit in the publication.

For any publication or presentation, a manuscript of the paper or abstract must be received and approved by the Sponsor prior to outside submission. Whether or not there is a Forbius author of the publications or presentations, a manuscript will be forwarded to Forbius for review and approval at least 30 days prior to submission of a journal publication, or at least 10 days prior to submission of an abstract.

Note: Any language relating to these issues appearing in the clinical trial agreement will supersede that which is outlined in this section.

13.4. Patient Screening Log

A record listing all patients entered into the study, as well as those considered for entry into the study and subsequently excluded, must be maintained by the Investigator. Patients excluded from the study will have the reason for exclusion recorded on the Patient Screening Log (or other similar document).

13.5. Drug Dispensing Inventory

Study center personnel will maintain adequate records of the receipt, dispensing, and disposition of all study drug that the Sponsor ships to the site. Records will be maintained, either on a form to be provided by the Sponsor or on a reasonable facsimile authorized for use by the Sponsor, and should include appropriate dates, quantities received, quantities dispensed, lot number (or kit number), disposition details, and the identification code of the patient who received the study drug.

The Investigator agrees to administer study drug only to patients under his/her personal supervision. The Investigator will not supply study drug to any person not authorized to receive it.

13.6. Handling and Disposal of Investigational Drug

Study drug should be stored in a secure location, under the indicated conditions (see **Section 5**; Investigational Drug). After study drug is prepared for delivery and administered, the health care professional will maintain an inventory of all used vials of study drug, after which, with authorization from the Sponsor, all such supplies may be destroyed in an appropriate manner according to institutional policy. Destruction of such supplies will be documented. Information regarding the number of vials utilized for each patient, as well as the dose of study drug administered to the patient, will be recorded on the appropriate drug inventory form.

Periodically throughout and at the conclusion of the study, unused vials of study drug will be inventoried by a representative of the Sponsor (or designee). At the completion of this trial, all

unused study materials MUST be returned to the Sponsor (or designee), unless otherwise authorized in writing.

13.7. Recording and Processing of Data

Clinical trial data for this study will be captured in an electronic format. Electronic data capture (EDC) services will be provided by a vendor to be determined by the Sponsor. The Investigator agrees to provide all information requested on the electronic case report forms (eCRF) in an accurate manner according to instructions provided. Electronic CRFs are designed for computer processing and analysis. All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be tracked within the EDC system. Data must be entered onto eCRFs in a timely fashion.

An eCRF is required to be submitted for every patient who receives any amount of study drug. This includes submission of retrievable data on patients who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where indicated, by either the Principal Investigator or a physician Subinvestigator whose name is listed on Form FDA 1572 for this study.

13.8. Source Document Requirements

The Investigator will maintain adequate and accurate records for each patient treated with study drug. Source documents such as hospital, clinic or office charts, laboratory reports, radiology and pathology reports, pharmacy records, study worksheets, and signed informed consent documents, must completely reflect the nature and extent of the patient's medical care, must be included in the Investigator's files along with patient study records, and must be available for source document verification against entries in the eCRF.

The Sponsor (or designee) will check eCRF entries against source documents according to the guidelines of Good Clinical Practice. The consent form will include a statement by which patients allow the Sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data on the eCRF (e.g., patient medical files, appointment books, original laboratory records, etc.). The Sponsor (or designee), bound by confidentiality and privacy regulations, will not disclose patient identities or personal medical information.

13.9. Laboratory Reports

Prior to initiation of this study, the Investigator must supply the Sponsor (or designee) with the normal laboratory values for the laboratories to be utilized; specifically, the normal laboratory values for analytes required to be measured, per protocol, are to be supplied. The corresponding laboratory certification number must also be noted, and a copy of the Director's curriculum vitae provided.

Laboratory safety evaluations must be performed at the intervals specified. If unexplained laboratory abnormalities occur, corroborative tests will be performed until the laboratory abnormality has resolved, returned to baseline status, and/or adequate explanation of the abnormality has been provided.

Copies of any additional records pertinent to the study (e.g., laboratory data, radiological reports, patient chart summaries, autopsy reports) must be made available to the Sponsor (or designee) or governing Health Authorities, if requested, with due precaution taken to ensure patient confidentiality.

13.10. Record Retention

Regulatory authorities require that the Investigator retain copies of all files pertaining to the study (i.e., records of study article disposition, signed informed consent documents, electronic case report forms, all correspondence, dates of monitoring visits, and records which support them) for a period of 2 years following the date of marketing application approval of the drug, for the indication that is the subject of the study. If no application is filed, or the application is not approved for the indication under study, all files pertaining to the study are to be maintained for 2 years after the investigation is discontinued and governing regulatory agencies have been so notified. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary. The Investigator must obtain written permission from the Sponsor prior to disposing of any records.

If the Investigator relocates, retires, or withdraws for any reason from the study, trial records may be transferred to an acceptable designee, such as another Investigator within the institution. The Sponsor (or designee), as well as the responsible IRB or Ethics Committee, must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage.

13.11. Monitoring of the Study

The Sponsor has responsibility to governing regulatory authorities to take all reasonable steps to ensure the proper conduct of the study with respect to trial ethics, protocol adherence, and data integrity and validity.

This study will be closely monitored by representatives of the Sponsor (and/or designee) throughout its duration. Monitoring will be in the form of personal visits with the Investigator and his/her staff as well as any appropriate communications by telephone, telefax, mail, or e-mail transmission. The purpose of these contacts is to review study progress, Investigator and patient adherence to protocol requirements, and any emergent problems associated with the conduct of the study. The following points will be usually assessed during monitoring visits at the site:

- Required regulatory documentation
- Signed informed consent documents
- Patient accrual and follow up
- Study drug inventory records
- Investigator and patient compliance to the study protocol
- Concomitant therapy use
- AE documentation
- Data as accurate, complete, and verifiable when compared to source documents

The Investigator and study staff are expected to cooperate with monitors during such visits and provide them with all relevant study documents.

In addition, the study may be evaluated by Sponsor auditors (and/or designees) and government inspectors who must be allowed access to eCRFs, source documents and other study files. Sponsor reports will be kept confidential. The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, patient authorization to use personally identifiable health information may be required from each patient before research activities. This Authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose, and for how long.

13.12. Patient Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of patients during this clinical study. Coded patient identifiers will be utilized at all times (including in any publications) when referring to a particular patient. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, or their designee, as well as authorized representatives of the governing regulatory agency, to inspect the facilities used in this study and to inspect, for purposes of verification, the hospital or clinic records of all patients enrolled into this study. A statement to this effect should be included in the informed consent document.

13.13. Financing and Insurance

The study will be supported by the Sponsor. Specifics of the financing and insurance coverage will be addressed in the clinical study agreement between the Sponsor and the Investigator or Institution.

14. STATISTICAL ANALYSIS AND REPORTING OF DATA

14.1. Statistical Considerations

The primary objectives of the Phase 1a portion of this trial are to assess the safety, tolerability, DLTs, and, if feasible, the MTD of AVID100 when administered by 2-hour* IV infusion to patients with a histologically-documented, measurable or non-measurable, locally advanced or metastatic solid tumor malignancy of epithelial origin that is refractory to standard therapy or for which no standard therapy is available. These effects will be assessed by treating patient cohorts with sequentially escalating doses of AVID100. Other studies to be conducted during this trial include characterization of the pharmacokinetic profile of AVID100, and description of the preliminary antineoplastic activity of AVID100 in these same patient cohorts.

In addition, once the MTD is identified, the Phase 2a portion of the trial will enroll patients to 3 expansion cohorts of patients (approximately 60 patients total) with advanced (unresectable or metastatic) malignancies of epithelial origin (tumor types mTNBC, SCCHN, and Sq-NSCLC), and confirmed as expressing the EGFR and with measurable disease, will be entered to further evaluate tolerability and assess the preliminary antineoplastic activity of AVID100 in this patient population.

Data on safety and preliminary activity collected from additional patients added to the Phase 2a expansion cohorts will be summarized with patients treated at that same dose level in the Phase 1a portion of the trial. No tests of statistical inference will be performed.

Protocol v5.0: Extended from 1 hour to 1.5 hours due to Grade 3 IRR observed in Cohort 3 (80 mg/m^2); effective 20Jul2017 and documented in a study Note to File dated 21Jul2017 (see **Section 2.3.2.1; AVID100-01: Clinical Experience)*

Protocol v6.0: Extended from 1.5 hours to 2 hours due to Grade 2 IRRs observed in Cohort 4(120 mg/m2); effective 21Dec2017 and documented in a study Note to File dated 28Dec2017 (see **Section 2.3.2.1; AVID100-01: Clinical Experience)*

14.2. Sample Size Considerations

Sample size for the Phase 1a dose escalation portion of the study will be determined by safety observations, occurrence of DLTs, and the number of cohorts required to evaluate safety and choose an RP2D. It is assumed that approximately 4 cohorts will be required to determine the MTD, thereby enrolling approximately 14-30 patients during the dose escalation phase of the study. However, the protocol allows for enrollment of > 4 cohorts, should this be necessary to identify the MTD.

Sample size for the Phase 2a Expansion Cohorts will be approximately 60 patients treated at the RP2D, with accrual to be divided among up to 3 cohorts (tumor types mTNBC, N=30; SCCHN, N=15; and Sq-NSCLC, N=15; all approximations); additional patients may be entered to the Phase 2a Expansion Cohorts if fewer than 30 patients are required to establish the RP2D in Phase 1a.

The current planned initial enrollment of 15 patients per cohort (or cohort subgroup in the case of mTNBC) may be expanded based on initial observation of > 2 objective responses (13% ORR) in any of the three indications to be studied. This sample size has a 35.2% power to detect a 40% ORR compared to a potential control response of 20% at a two-sided 0.05 level of significance (**TABLE 5**). In addition, the power is between 45-54% to detect objective response rates between 20 to 40% in a 15 patient cohort at a two-sided 0.05 level of significance (**TABLE 7**).

After evaluation of the initial ORR in each cohort a decision will be made to either continue to include patients with treatment-refractory advanced/metastatic malignancies without other therapeutic options on an open-label trial(e.g., if the objective response rate is ≥ 20% and responses are durable), consider alternative trial designs for further exploration of efficacy in any of the indications, or discontinue development if fewer than two (0 or 1) responses are observed in any of the three initial fifteen patient cohorts. The durability of objective responses and disease stabilization > 8 weeks will also be considered in the decision to expand cohorts or pursue other options for further development in any of the three indications (**TABLE 4**). See also **Appendix I**.

TABLE 5: TEST OF NULL AT 0.05 LEVEL (TWO SIDED) USING NORMAL APPROXIMATION
Power (%) for specified N (Computed using EAST 6.4)

Null (π_0)	True (π)	N=15	N=20	N=34	N=40
0.20	0.30	13.2	16.3	24.6	28.1
	0.40	35.2	44.7	66.3	73.3
	0.50	64.2	76.5	93.8	96.7
	0.60	88.5	95.5	99.7	99.9

TABLE 6: SMALLEST VALUE OF P (%) FOR STATISTICAL SIGNIFICANCE
(Level 0.05, 2-Sided)

π_0	N=15	N=20	N=34	N=40
0.20	45.2	41.7	36.2	35.0
0.25	50.4	46.9	41.6	40.2
0.30	55.2	51.9	46.8	45.5
0.35	59.9	56.8	51.8	50.5
0.40	64.3	61.4	56.7	55.5
0.45	68.6	65.8	61.4	60.2
0.50	72.6	70.1	66.0	64.9

14.3. Statistical Analysis

Statistical analyses will be carried out using SAS Version 9.3 or higher. The statistical methods for this study will be described in a detailed statistical analysis plan (SAP) which will be finalized prior to database lock. Any deviations from the planned analysis will be justified in the final study report.

Patient characteristics including race, ECOG PS, and age will be described using descriptive statistics. Frequency tables will summarize the incidence and type of treatment-related AEs by severity, experienced by patients who received at least 1 dose of study drug (Safety population).

Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. Time-to-event data will be summarized using the Kaplan-Meier method. Withdrawals of patients from study medication and causes of death will also be reported as listings and summary tables.

Unless indicated otherwise, summary statistics will be reported for observed data only. Missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated. Baseline is defined as the last available observation prior to the first administration of study drug on Cycle 1/Week 1/Day 1.

14.3.1 Analysis Sets

- Safety analyses will be conducted on patients receiving any amount of a AVID100 dose (partial or complete). Patients completing Cycle 1 in the absence of a DLT, will be considered to have tolerated the AVID100 regimen. Patients must receive their planned dose of AVID100 during Cycle 1 plus 2 weeks of follow-up in order to be considered evaluable for tolerability, unless dose reduction, interruption, or discontinuation was the result of a DLT.
- PK analyses will be performed in Dose Escalation Cohorts and Expansion Cohorts on patients who receive any amount of their assigned dose of AVID100 and have an adequate number of concentration determinations to allow for PK calculation.
- All enrolled* patients will be evaluated for antineoplastic activity. In addition, patients who complete Cycle 2 (6 weeks) of treatment, receive at least 2 planned doses during that period, and have a follow-up assessment of disease status will be considered evaluable for assessment of antineoplastic activity. Patients who are withdrawn from the study before completion of Cycle 2 because of progressive disease also will be included in assessments of antineoplastic activity.

  ** For the purposes of this study, "enrollment" is defined as patient registration to participate in this trial; at this time the patient's study identification code and dose cohort will be assigned.*

14.3.2 Safety Analysis

14.3.2.1. Adverse Events

AEs will be coded by system-organ-class and preferred term using the most current MedDRA. Events will be recorded starting at study enrollment through 30 days following the last dose of AVID100, and will be tabulated by maximum severity according to the CTCAE (v5.0).

The calculation of AE incidence will be based on the number of patients per AE category. For each patient who has multiple AEs classified to the same category, that patient will be tabulated

under the highest toxicity grade for that AE category. Summary tables will be presented by dose level, seriousness, severity, and relatedness.

During Phase 1a, first-cycle DLTs, AEs leading to death or to discontinuation of study treatment, and SAEs will be evaluated with special attention.

14.3.2.2. Laboratory Determinations

Actual values and change-from-baseline values for continuous data from laboratory determinations (serum chemistry, hematology, coagulation studies, and urinalysis) will be presented in listings. Categorical data measurements will be similarly summarized for the actual values. Laboratory measurements will be graded according to CTCAE, when applicable. The frequencies of the highest CTCAE grade observed will be displayed for each AE and for each starting dose level. Laboratory determinations categorized as in or out of normal range will be summarized in some cases using worst-case shift tables. Clinically significant (CS) or not clinically significant (NCS) criteria may be applied for out-of-range values.

14.3.2.3. Vital Signs, Body Weight, Physical Exam Findings

Actual values and change-from-baseline values for vital signs and body weights, as well as physical examination findings, will be summarized descriptively.

14.3.2.4. ECG Findings

Descriptive statistics of ECG observations will be presented. The frequency and percentage of ECG results will be summarized for the following ECG measurements: heart rate, PR interval, QRS duration, QT interval and QTc interval. The heart rate-corrected QT interval (QTc), indicating repolarization time, will be calculated. T-wave and ST-segment ECG abnormalities will be graded based on definitions in the NCI Common Toxicity Criteria (CTC). Additional details regarding the ECG analyses will be provided in the SAP.

14.3.2.5. Other Safety Data

Concomitant medications and findings in physical examinations, pulmonary function tests, and anti-drug antibody analyses (ADA) will be summarized in text as recorded in the eCRF, and as made available from an independent central assay laboratory, in the case of ADA data.

14.3.2.6. Maximum Tolerated Dose

For Phase 1a, a table will be presented showing the MTD as well as a summary of the dose escalation and any subsequent dose reductions.

14.3.3 Other Analyses

14.3.3.1. Antineoplastic Activity

<u>Phase 1a</u>

As the primary objective in the Phase 1a portion of the study is to determine the MTD and to evaluate the safety of the study treatment, all antineoplastic activity analyses will be descriptive and exploratory in nature. Disease status will be summarized by cycle and dose group,

including changes from baseline. As a secondary objective, OR, duration of OR, SD, and TTP will be assessed and calculated, wherever possible, according to standard response criteria (see **Appendix F**; Measurement of Effect**).**

Phase 2a

As a primary objective of the Phase 2 portion of the trial, OR, duration of OR and SD, as well as TTP will be assessed and calculated, wherever possible, according to standard response criteria (see **Appendix F**; Measurement of Effect). Frequency counts and percentages will be presented for an objective response rate (ORR) and disease control rate (DCR). For analysis of TTP, the median time to event and 95% confidence intervals will be calculated using the Kaplan-Meier method.

Response Calculations

In the event of an OR (CR or PR) the duration of the OR will be determined from the day the initial response is observed (using screening/baseline images for comparison) to the day that progression is observed. Duration of SD (minimum duration of not less than 8 weeks) will also be assessed using the time from the first dose of AVID100 to the day that PD is documented.

The ORR will be calculated as the proportion of patients who achieve either a complete response or a partial response (CR+PR). ORR, time to OR, and duration of OR will be determined.

DCR will be calculated as the proportion of patients who achieve either a complete response, partial response, or disease stabilization for a minimum of 8 weeks (CR+PR+SD).

TTP will be measured from the treatment start date (date of first dose) to either the date the patient is first recorded as having disease progression (even if the patient went off treatment because of toxicities), or the date of death if the patient dies due to any cause before progression. If a patient is lost to follow-up, the patient will be censored as of the date of last contact. Patients who start a new treatment before they progress will be censored as of the date of start of the new treatment. If a patient has not progressed nor died, time to progression is censored at the date of last follow-up. TTP will be analyzed using the method of Kaplan and Meier.

Imaging Data

Imaging data (imaging studies and derived assessments) will be stored by the sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer. If an independent radiology review is conducted, a charter will be prepared and finalized by the Sponsor (or designee) prior to initiating the radiology reviews.

14.3.3.2. Pharmacokinetic Parameters

The PK profile of total antibody (AVID100 plus MAB100), AVID100, and DM1 will be determined by noncompartmental analysis using standard PK software (e.g., Phoenix WinNonlin). Parameters to be determined will include time of maximum observed concentration (T_{max}), maximum (peak) concentration (C_{max}), minimum (trough) concentration (C_{min}), and area under the concentration curve for the last measurable concentration (AUC_{last}). When the terminal elimination phase can be identified, additional parameters such as elimination half-life ($T½$), clearance (Cl), and volume of distribution (V_d) will be determined.

Evaluations to delineate dose-response and PK parameter-response relationships will be undertaken.

14.3.3.3. Biomarker Parameters

Biomarker assessments, to include collection of archival or recent biopsy tissue for assessment of EGFR-expression and other potential biomarkers, will be conducted in on an optional basis in consenting patients in Phase 1a, and in all patients in Phase 2a.

A summary of the changes in potential biomarker(s) will be presented.

Biomarker analyses will be performed according to standard methodologies and will examine relationships between the biomarker assessments and clinical toxicities observed during the study. These analyses will be described in the SAP.

14.4. Clinical Study Report

Following study completion a final integrated clinical/statistical study report will be prepared. Further studies may be planned depending on a review of the data

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APPENDIX A
Study Assessments

TABLE 7: STUDY ASSESSMENTS SCHEDULE

STUDY ASSESSMENTS	Screen	CYCLE 1				CYCLE 2			SUBSEQUENT CYCLES			EOT ≤10d after decision to dis-continue	1M FUP* 30 d (+7) after last dose	Extended Follow Up* if OR or SD at EOT	As Clinically Indicated
		D1	D2	D4 +/- 1d	D8	D1	D8	End of Cycle 2	D1	D8	End of Even Number Cycles[d]				
CONSENT AND MEDICAL HISTORY															
Informed Consent[1]/ Eligibility Assessment	x														
Past Medical History	x														
History of Primary Malignancy[2]	x														
SAFETY ASSESSMENTS (1) ***(screening assessments within 14 days prior to first study drug dose unless specified)***															
Medication Survey[3]	x	from 14 days prior to 1st dose through 30 days after last dose													
AE Assessments[4]		from enrollment through 30 days after last dose; through 3 months (or 6 months to 2 years) follow-up if associated AEs persist													
ECOG PS Evaluation	x	x[a]				x			x			x	x		x
Phase 1a: Vital Signs[5]	x	SOI; EOI; 2, 4h after EOI	x	x		x			x			x	x		x
Phase 2a: Vital Signs[5]	x	SOI, EOI				x			x			x	x		x
Physical Exam/to include weight and pulmonary assessment[6]	x	x[a]				x			x			x	x		x
Hematology Panel[7]	x	x[a]		x	x	x	x		x	x		x	x		x
Serum Chemistry Panel[8]	x	x[a]		x	x	x	x		x	x		x	x		x
Coagulation Panel[9]	x	x[a]		x	x	x	x		x	x		x	x		x
Urinalysis[10]	x	x[a]		x	x	x	x		x	x		x	x		x
ADA to AVID100[11]		x				x			x			x	x		x[e]
Pregnancy Testing[12] *(w/in 2 days of 1st dose)*	x	x										x			x
ECG (12-lead)[13]	x	SOI, EOI, 30 min after EOI										x			x
SAFETY ASSESSMENTS (2) ***(screening assessments within 28days (+/- 2) prior to first study drug dose provided no antineoplastic therapy has been delivered between assessment and first dose of study drug)***															
Ophthalmology Exam[14]	x										End of C2 only	x			x
MUGA Scan or Echo[15]	x											x			x
Pulmonary function tests[16]	x											x			x
Chest radiography (PA and lateral)	x											x			x
DISEASE ASSESSMENTS ***(screening assessments within 28 days (+2d) prior to first study drug dose)***															
Phase 1a only: Document EGFR positivity[17]	optional														
Phase 2a only: Document EGFR positivity[17]	required														
Phase 1a only: Tumor Marker Measurement[18]	x							x			x	x[b]		q3m for 1y, q6m after[c]	
Imaging for Disease (and Pulmonary Status)[19]	x							x			x	x[b]		q3m for 1y, q6m after[c]	
Response Assessment[20]								x			x	x[b]		q3m for 1y, q6m after[c]	
ADDITIONAL ASSESSMENTS															
Phase 1a: PK Sampling[21]		SOI; EOI; 2, 4h after EOI	24h after EOI	x	x	SOI EOI	x		SOI EOI			x	x		x[e]
Phase 2a: PK Sampling[22]		SOI EOI			x	SOI			SOI, EOI-C5 only	C5 only		x	x		x[e]
Phase 1a: Archival Tumor for EGFR confirmation and biomarker studies[22]		optional; submit any time after study enrollment; if available													
Phase 2a: Tumor for exploratory studies[22]	required														

Phase 2a: Blood for Exploratory Studies [23]	x										x			
TRIAL TREATMENT														
AVID100 Infusion (2-h)		x				x			x						
Phase 1a: Post-Infusion Monitoring		4h				x			x						
Phase 2a: Post-Infusion Monitoring		2h				x			x						

**Given the Q3W dosing frequency, EOT and 1M FUP evaluations may be combined in those situations where scheduling coincides, provided a minimum of 30 days of post-dosing follow-up have been observed.*

Abbreviations: SOI-start of infusion; EOI-end of infusion; EOT-end of treatment; 1M FUP-1 month follow-up

[a] Need not be assessed prior to Cycle 1 if ≤ 7 days since screening;
[b] Conduct only if > 6 weeks since the previous assessment;
[c] To be conducted in the event of ongoing objective response (OR) or stable disease (SD) at the end of treatment; continue until progressive disease (PD) or another therapeutic intervention is initiated
[d] End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle.
[e] Additional ADA and PK sampling to be performed in the event of an IRR, as close as possible to the onset of the event

1. Informed Consent: To be signed prior to enrollment and prior to performing any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient.
2. History of Primary Malignancy: To include details of the primary malignancy, including: histological/cytological classification; stage of disease at diagnosis and at entry; prior surgical procedures for the malignancy; prior antineoplastic therapy, prior radiation therapy, as well as dates of treatments, numbers of cycles, and best response to each therapy.
3. Medication Survey: To include period within 14 days prior to first study drug dose and throughout study for a period of 30 days following last study drug dose.
4. AE Assessments: To detail symptoms that may be present prior to/at the time of first administration. AEs to be assessed from enrollment, throughout study and for the 1 month period (30 days) following last study drug dose; AEs to continue to be assessed for the 3 month (and if necessary 6 month) period following last study drug dose if events associated with study drug persist (to confirm that events have resolved, returned to baseline status, or been adequately explained. Investigator discretion may be used with respect to the method of contact for this AE assessment; clinical events may be followed in writing or by telephone (and documented), an in-person visit will not be required). Any patient who develops pulmonary fibrosis will be followed at approximately 3 month intervals for up to 2 years to assess the course of the disease and evaluate potential reversibility of this finding.
5. Vital Signs: To include temperature, pulse, respiratory rate, blood pressure, and pulse oximetry.
6. Physical Examination: Complete at screening including height, weight, general appearance, skin, ears, eyes, nose, throat, neck/thyroid, chest/breasts, lungs, heart, abdomen, musculoskeletal system, pulse, lymph nodes, neurologic and mental status; directed thereafter, must include weight and pulmonary assessment. Dose adjustments may be made in the event of noted weight change (± 10% [less at the site's discretion or if required by institution procedures]). Pulmonary findings will be evaluated in detail at each visit by the PI (or physician designee); evaluation to include review of pulmonary symptoms including but not limited to: cough, sputum production, hemoptysis, wheezing, dyspnea, dyspnea on exertion, chest pain, and/or chest pain associated with respirations.
7. Hematology Panel: To include CBC with differential, ANC, and platelet count. Evaluation frequency should be increased in the event of hematologic toxicity.
8. Serum Chemistry Panel: To include Na, K, Cl, bicarbonate or carbon dioxide, BUN, creatinine, glucose, bilirubin [total and direct], AST, ALT, alkaline phosphatase, Ca, Mg, phosphorous, albumin, total protein, uric acid, amylase, lipase, and CK (in the event of abnormalities while on study, please perform isoenzyme analysis). Evaluation frequency should be increased in the event of significant serum chemistry abnormalities. Clinically significant electrolyte abnormalities should be corrected prior to dosing.
9. Coagulation Panel: To include PTT (or aPTT), PT and/or INR
10. Urinalysis: Multipanel chemical test strips are acceptable and should include assessment of: specific gravity, pH, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and occult blood; include microscopic sediment evaluation if clinically indicated if gross findings are abnormal, including WBC/high power field [hpf] and RBC/hpf.
11. ADA to AVID100 **(Central Lab)**: To assess immunogenicity; whole blood (~5 mL at each timepoint) will be collected for serum acquisition. In the event that a collected serum sample is inadequate or insufficient for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same time point, if available. Residual sample material may be used for biomarker assessments. See Laboratory Manual (or other similar document) for details regarding collection, handling, and shipping.
12. Pregnancy Testing: β-hCG in WOCBP; serum at Screening, urine or serum thereafter; negative test must be confirmed within 2 working days prior to first dose of study drug
13. ECG (12-Lead): To include measurement of PR interval, QRS duration, QT interval, and QTc interval [msec], as well as heart rate [BPM]; to be performed after patient has been supine for ≥ 10 minutes; repeat subsequent time points in triplicate separated by 5 minutes for 4 cycles (Day 1 at SOI and EOI) in patients with a QTc that is either: a) > 500 msec; b), increased by 60 msec over

baseline; or c) decreased by 20 msec under baseline.

14. Ophthalmology Examination: To include slit lamp evaluation, tests to evaluate corneal integrity, and visual acuity assessment. End of C2 and EOT may be combined if patient discontinues treatment at End of C2
15. MUGA Scan or Echocardiogram: For measurement of LVEF; to be performed ONLY in patients with a history of CHF, individual patients should be followed with the same testing procedure throughout the study.
16. Pulmonary Function Tests: To include spirometry and diffusing capacity (DL_{CO}) to assess for evidence of pulmonary fibrosis (spirometry assessments are to include but are not limited to: forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], forced expiratory flow 25% to 75% [FEF25-75], functional residual capacity [FRC], residual volume [RV], and total lung capacity [TLC])
17. EGFR status determination/documentation of EGFR positivity by IHC:
    - Phase 1a: Optional (**Local or Central***)
    - Phase 2a: Required (**Central Lab***); tumor must be EGFR-positive for patient to be eligible for enrollment

    ****The trial site will prescreen patients for EGFR Tumor Status Determination before entering patients into screening for the treatment portion of the trial. The site should use a separate prescreening informed consent form. Prescreening may be performed outside the 28 (+ 2) day screening period to allow adequate turnaround time for receipt of results, provided separate informed consent has been obtained.***
18. Tumor Marker Measurement (Phase 1a only): As indicated by tumor type.
19. Imaging for Assessment of Disease (and Pulmonary Status) (e.g., diagnostic imaging / marker lesion measurements, etc.; as indicated by tumor type, imaging of the chest imaging required with each evaluation (for disease evaluation where indicated, and to assess for evidence of pulmonary fibrosis): Follow with the same procedure(s) throughout; no further disease assessments required after documented PD and/or initiation of another therapeutic intervention; duration of OR to be measured from date initial response is observed to date PD is observed; for PR or CR, tumor measurement changes must be confirmed no less than 4 weeks after criteria for response are met; for SD, follow-up measurements must meet the SD criteria at least once after study entry at a minimal interval of not less than 8 weeks. Imaging studies documenting response must be available for review by the Sponsor (or designee).
20. Response Assessment: To be assessed by the Investigator according to RECIST v1.1
21. PK Sampling **(Central Lab)**: Whole blood (~5 mL at each timepoint) will be collected for serum acquisition. In the event that a collected serum sample is inadequate or insufficient for PK analysis, the analysis of PK can be done using an anti-drug antibody (ADA) serum sample from the same time point, if available. Residual sample material may be used for biomarker assessments. See Laboratory Manual (or other similar document) for details regarding collection, handling, and shipping. PK sampling times may be adjusted according to early trial results in order to optimize evaluation.
22. Tumor for Exploratory Studies **(Central Lab):** *For assessment of tumor EGFR-expression by FISH (or similar assay) and other potential biomarkers*. Directions for submitting blocks or pre-cut slides to be provided by the Sponsor (or designee) in the Laboratory Manual or other similar document.
    - Phase 1a: To be submitted if available.
    - Phase 2a: Required; to be performed in tumor tissue submitted for eligibility; if archival tissue is not available the patient must have primary or metastatic tumor sites(s) considered safely accessible for biopsy, and must be willing to undergo tumor biopsy
23. Blood for Exploratory Studies **(Central Lab)**: Phase 2a; may be obtained for submission any time after confirmation of eligibility and study enrollment but prior to dosing on C1/D1

TABLE 8: PHARMACOKINETIC SAMPLING SCHEDULE See also TABLE 4				
Study Day	**Phase 1a**	**Phase 2a**	**Allowance** (+/-)	**Reference**
CYCLE 1				
Day 1	SOI	SOI		*Prior to SOI*
	EOI	EOI	*5 min*	*EOI*
	2h		*15 min*	
	4h		*15 min*	
Day 2	24h		*1h*	
Day 4	At time of visit		*1 day*	
Day 8	At time of visit	At time of visit		
CYCLE 2				
Day 1	SOI	SOI		*Prior to SOI*
	EOI		*5 min*	*EOI*
Day 8	At time of visit			
POST-TREATMENT				
EOT	At time of visit	At time of visit		
1M FUP	At time of visit	At time of visit		
In the event of an IRR	At time of event	At time of event		
TOTAL SAMPLES	**12**	**5**		

SOI = Start of Infusion
EOI = End of Infusion

PK samples for each additional cycle:

- Phase 1a: Day 1 (SOI, EOI)
- Phase 2a: Day 1 (SOI)

  Day 1 (SOI, EOI) *Cycle 5 only*
  Day 8 (at time of visit) *Cycle 5 only*

Actual collection times are to be recorded on the patient's eCRF or other equivalent sample collection log as authorized by the Sponsor (or designee).

Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of the 4h sample is logistically difficult due to clinic staff availability, an "end of day" sample may be obtained at the latest practical time. Such an option is available ONLY after previous discussion with and approval by the Sponsor.

TABLE 9: MAXIMUM TOTAL BLOOD COLLECTION VOLUMES

STUDY ASSESSMENTS	Vol./ sample (mL)	Screening		Cycle 1		Cycle 2		EOT		1M FUP		TOTAL VOLUME
		# of Samples	Vol. (mL)	*# of Samples*	Vol. (mL)	*# of Samples*	Vol. (mL)	*# of Samples*	Vol. (mL)	*# of Samples*	Vol. (mL)	
Phase 1a												
Hematology	5	*1*	5	*3*	15	*2*	10	*1*	5	*1*	5	40
Chemistries	10	*1*	10	*3*	30	*2*	20	*1*	10	*1*	10	80
Coagulation	5	*1*	5	*3*	15	*2*	10	*1*	5	*1*	5	40
Pregnancy Test	5	*1*	5	*0*		*0*		*0*		*0*		5
ADA Testing	5	*0*		*1*	5	*1*	5	*1*	5	*1*	5	20
Tumor Markers	5	*1*	5	*0*		*1 (end)*	5	*1*	5	*1*	5	20
PK Studies	5	*0*		*7*	35	*3*	15	*1*	5	*1*	5	60
Total Volume			30		100		65		35		35	**265**
Phase 2a												
Hematology	5	*1*	5	*3*	15	*2*	10	*1*	5	*1*	5	40
Chemistries	10	*1*	10	*3*	30	*2*	20	*1*	10	*1*	10	80
Coagulation	5	*1*	5	*3*	15	*2*	10	*1*	5	*1*	5	40
Pregnancy Test	5	*1*	5	*0*		*0*		*0*		*0*		5
ADA Testing	5	*0*		*1*	5	*1*	5	*1*	5	*1*	5	20
PK Studies	5	*0*		*3*	15	*1*	5	*1*	5	*1*	5	30
Exploratory Studies	20	*1*	20	*0*		*0*		*1*	*20*	*0*		**40**
Total Volume			45		80		50		50		30	**255**

Along with Screening, single days not detailed with maximum blood volume requirements > 20 mL:

- Phase 1a: Cycle 1/Day 1= 50mL, Day 4=25mL
- Phase 2a: Cycle 1/Day 1=35mL (55 mL if biomarker sample is drawn prior to dosing on C1/D1)

Blood volumes for each additional cycle: 50 mL, 60 mL for Cycle 5

If sites are able to perform hematology, serum chemistry, and coagulation studies with smaller volumes of blood per sample, they are encouraged to do so. Required PK, and ADA volumes are fixed and should not be reduced.

For the purpose of estimating a patient's total blood collection volume during study participation, maximum estimates are used. During a patient's study participation, the maximum amounts of venous blood that will be collected are listed above. Study duration is based on 6 weeks estimated average patient participation, i.e., an average of Cycle 1 (3 weeks) plus Cycle 2 (3 weeks).

An indwelling venous access device is required for PK blood sample collections on Day 1 of Cycle 1. When an indwelling catheter (or equivalent venous access) is utilized, a blood flush discard of up to 3 mL is to be done before drawing the first blood tube collected on the scheduled day/time for routine laboratory tests and PK samples. **Blood flush discard volumes ARE NOT included in volume calculations in table above and should be considered when summarizing actual blood collection volumes.**

Given the Q3W dosing frequency, EOT and 1M FUP evaluations may be combined in those situations where scheduling coincides, provided a minimum of 30 days of post-dosing follow-up have been observed.

In the event of an IRR:
If a patient should have an IRR associated with AVID100 administration, all attempts will be made to obtain blood samples as close to the onset of the event as possible for assessment of the presence of ADA and PK (to provide information on the nature of the infusion reaction). Blood volume for such collections is not included on this table; however, it is anticipated that a total of approximately 10 mL would be required; ADA (5 mL), PK (5 mL).

APPENDIX B

Performance Status Evaluation

TABLE 10: MEASURES OF PERFORMANCE STATUS				
Percent	**KARNOFSKY[1] Performance Status Description**		**Level**	**ECOG[2]**
100	Normal; no complaints, no evidence of disease		0	Normal activity
90	Able to carry on normal activity; minor signs or symptoms of disease			
80	Normal activity with effort; some signs or symptoms of disease		1	Symptoms but ambulatory
70	Cares for self; unable to carry on normal activity or do active work			
60	Requires occasional assistance but is able to care for most needs		2	In bed < 50% of time
50	Requires considerable assistance and frequent medical care			
40	Disabled; requires special care and assistance		3	In bed > 50 % of time
30	Severely disabled; hospitalization is indicated although death is not imminent			
20	Very sick; hospitalization is necessary		4	100 % bedridden
10	Moribund; fatal processes progressing rapidly			
0	Death		5	

[1]Karnofsky DA, Abelman WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer*. 1948;1:634-656.
[2]Oken M, Creech RH, Tormey DC, Horton J, Davis TE, McFadden E, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. (CCT) 1982; 5:649-655.

APPENDIX C

New York Heart Association's Functional Criteria

TABLE 11: NEW YORK HEART ASSOCIATION FUNCTIONAL CRITERIA	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest. If any physical activity is undertaken discomfort increases.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

APPENDIX D

Adverse Event Grading Scale

TABLE 12: CLINICAL ADVERSE EVENT GRADING		
Severity	**CTCAE* Grade**	**Definition**
Mild	1	Awareness of symptom, but easily tolerated. Event is usually transient requiring no special treatment; does not interfere with usual status or activities
Moderate	2	Event may be ameliorated by simple therapeutic measures; may interfere with usual activities
Severe	3	Event results in temporary disability or incapacity; inability to perform usual activities; requires intervention
Life-threatening	4	Event requires immediate intervention; need for emergency treatment; patients is at risk of death at the time of the event
Fatal	5	Event resulting in the subsequent death of the patient

Note: In those cases where further definition of an event is provided by the NCI Common Terminology Criteria for Adverse Events (CTCAE, v5.0), please refer to that document for grading and severity information.

*< *https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm* >

APPENDIX E

Clinical Adverse Events: Determining Relationship to Study Drug

TABLE 13: CLINICAL ADVERSE EVENTS: DETERMINING RELATIONSHIP TO STUDY DRUG
UNRELATED
This category applies to those AEs which, after careful medical consideration, are clearly felt to be due to extraneous causes (disease, environment, etc) that are unrelated to the administration of study drug.
UNLIKELY RELATED (must have first 2)
This category applies to those AEs which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered unlikely if: • It does not follow a reasonable temporal sequence from administration of the drug. • It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known response pattern to the suspected drug. • It does not reappear or worsen when the drug is readministered.
POSSIBLY RELATED *(must have first 2)*
This category applies to those AEs which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug, but the possibility cannot be ruled out with certainty. The relationship of an AE to the study drug can be considered possible if: • It follows a reasonable temporal sequence from administration of the drug. • It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It follows a known response pattern to the suspected drug.
PROBABLY RELATED *(must have first 3)*
This category applies to those AEs which, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered probable if: • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient. • It disappears or decreases upon cessation of drug or reduction in dose.* • It follows a known response pattern to the suspected drug.
RELATED *(must have first 3)*
This category applies to those AEs, which, after careful medical consideration, are felt to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered related if: • It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues. • It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient. • It disappears or decreases upon cessation of drug or reduction on dose and appears upon rechallenge.* • It follows a known response pattern to the suspected drug.

Adapted from: Karch FE and Lasagna L. Adverse drug reactions: a critical review. *JAMA*. 1975 Dec 22; 234 (12):1236-1241.

**There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists, e.g., 1) tardive dyskinesia, 2) fixed drug eruptions.*

APPENDIX F

Measurement of Effect

TABLE 14: RESPONSE CRITERIA FOR SOLID TUMORS
Summary of RECIST v1.1 Guidelines

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of objective response (OR).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

A. DEFINITIONS

Evaluable for Toxicity: All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

B. DISEASE PARAMETERS

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥10 mm with CT scan, or as ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest

lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

C. METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Note: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline defines measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal

limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. *Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.*
b. *No FDG-PET at baseline and a positive FDG-PET at follow-up:*
   - *If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.*
   - *If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).*
   - *If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.*
c. *FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.*

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

D. RESPONSE CRITERIA

1. Evaluation of Target Lesions

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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 diameters while on study.

2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* *See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.*
** *Only for non-randomized trials with response as primary endpoint.*
*** *In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.*

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

E. DURATION OF RESPONSE

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR or 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 since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

F. PROGRESSION-FREE SURVIVAL

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Adapted from: Eisenhauer EA, Therasse P, Bogaerts J, et. al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer. 2009; 45:229-247.

<http://www.eortc.be/recist/documents/RECISTGuidelines.pdf >

APPENDIX G

Grading and Management of Infusion Reactions

Grading of Infusion Reactions

The CTCAE v5.0* definition of infusion-related reactions (General Disorders and Administration Site Conditions) is shown below. Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "Infusion-related Reaction" and any additional terms (including those not listed here) that best describe the event. Those described should be graded as follows:

TABLE 15: GRADING OF INFUSION REACTIONS

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia is caused by the release of cytokines from the cells.					

**See < https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm >*

Guidelines for Management of Infusion Reactions

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade ≥ 2 allergic/hypersensitivity reactions. The Sponsor should be contracted immediately if questions arise concerning the grade of the reaction. The following are recommended management guidelines for infusion reactions associated with AVID100 administration. In all cases the Investigator should use best clinical judgment in managing such reactions.

TABLE 16: MANAGEMENT OF INFUSION REACTIONS	
Grade 1	• Consider slowing the infusion to 50% of the prior rate • Monitor the patient for worsening condition • If the infusion is extended, administer subsequent infusions at the prolonged rate
Grade 2	• Interrupt the infusion for a minimum of 30 minutes • Administer additional pharmacologic therapy (e.g., diphenhydramine, acetaminophen) and appropriate supportive care (e.g., oxygen), as medically indicated • Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1 • Monitor the patient for worsening condition • Administer subsequent infusions at the prolonged rate
≥ Grade 3	• Stop the infusion • Administer additional pharmacologic therapy (diphenhydramine, dexamethasone) and appropriate supportive care (e.g., oxygen) for the infusion reaction, as medically indicated • Administer epinephrine or bronchodilators as medically indicated • Hospital admission for observation may be indicated • Do not resume infusion after a ≥ Grade 3 reaction • Patients who have a Grade 3 infusion reaction will be considered to have had a DLT and will be either discontinued from treatment, or receive subsequent treatments with a reduced dose of AVID100 (see **Section 8.3.2**; Dose Reduction) • Patients who have a > Grade 3 infusion-related reaction will be considered to have had a DLT and will be discontinued from treatment • Administer subsequent infusions at the prolonged rate

In the Event of Infusion Prolongation

Any assessments to be performed or samples to be collected (e.g., vital signs, PK) at the end of or following EOI will still be performed or collected beginning at the delayed EOI timepoint. In situations where collection of late day samples, in particular the 4h sample, is logistically difficult due to clinic staff availability, an "end of day" sample may be obtained at the latest practical time on the day of the reaction.

Rechallenge with a shorter duration of infusion (no less than 2 hours) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity.

All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the patient's eCRF.

Modification of Infusion Duration for the Trial

During Phase 1a, the duration of infusion will be prolonged for all subsequent patients entered to the trial in the following situations:

- In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated).
- In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort

These same criteria will be applied in the event IRRs occur on the extended infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated).

APPENDIX H

Recommendations for Management of Keratitis and Rash

Management of Keratitis

Any symptoms of keratitis (corneal inflammation/corneal ulceration) should prompt a follow-up ophthalmologic evaluation as soon as possible.

- Grade 1 Keratitis
  Will result in treatment with preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks.
- Grade 2 Keratitis
  Will be managed as described above, with continuation of study drug dosing at the discretion of the investigator. Persistence of Grade 2 keratitis (> 2 weeks), while on therapy will result in immediate interruption of dosing with study drug. Patients may be retreated at the discretion of the investigator, at a reduced dose, after resolution or amelioration of findings to ≤ Grade 1 severity.
- Grade 3 Keratitis
  Will result in immediate interruption of study drug dosing. Patients may be retreated at the discretion of the investigator, at a reduced dose, after resolution or amelioration of findings to ≤ Grade 1 severity.

  Patients with persistent ≥ Grade 2 keratitis after 7 days of interrupted dosing will be discontinued from further participation in the trial, with scheduled follow-up ophthalmologic assessments at a frequency deemed medically appropriate.

Management of Rash

Several different treatment options have been utilized in order to relieve symptoms and improve the rash associated with study drug therapy. **When possible, topical therapy is preferred.** Although no single approach has emerged as superior, recommendations for management are as follows:

- Grade 1Rash
  Mild, grade 1 rash has been observed to resolve without intervention.
- Grade 2 Rash
  May be treated according to current standard of care
- Grade 3 (or greater) Rash (or intolerable Grade 2 Rash)
  Will result in dose reduction of study drug and treatment.

APPENDIX I

Sample Size Considerations

The sample size considerations are presented for estimation and testing with respect to the response rate for efficacy, i.e., inference regarding the true probability of response. The normal approximation to the binomial distribution is used, unless otherwise specified.

Let π denote the true unknown probability of interest. The goal is to conclude that this probability exceeds a specified value ($\pi 0$).

Testing the null hypothesis H0: $\pi = \pi 0$ against the one-sided alternative hypothesis H1: $\pi > \pi 0$ can be used to achieve this goal. This test is performed at the 2.5% level, which is equivalent to testing the two-sided alternative at the 5% level.
The test procedure is to conclude that the observed result is statistically significant if:

$$n1/2\ (p- \pi 0)/(p(1-p))1/2 > 1.96,$$

where p is the observed proportion of responses from n subjects.

The smallest value of p required to have statistical significance for specified values of $\pi 0$ and n is the solution to this inequality, but a "closed expression" is not possible. This value of p is determined by evaluating $n1/2\ (p- \pi 0)/(p(1-p))1/2$ and then comparing this value to 1.96, and is given in the following table.

SMALLEST VALUE OF P (%) FOR STATISTICAL SIGNIFICANCE (Level 0.05, 2-Sided)				
π_0	N=15	N=20	N=34	N=40
0.20	45.2	41.7	36.2	35.0
0.25	50.4	46.9	41.6	40.2
0.30	55.2	51.9	46.8	45.5
0.35	59.9	56.8	51.8	50.5
0.40	64.3	61.4	56.7	55.5
0.45	68.6	65.8	61.4	60.2
0.50	72.6	70.1	66.0	64.9

Other alternatives for this examination are power considerations: (1) determination of power for specified n and assumed true value of π, (2) determination of n required to have power 80% or 90% for assumed true value of π, and (3) determination of π for specified n and power. The latter is related to a confidence interval (CI) because it is estimation of π, so the 95% CI is presented for specified values of the observed proportion of responses from n subjects (p); this is also related to the values given in the first Table. In addition to the 95% CI using the normal approximation, the 95% CI using the exact binomial method is also presented as these are presented in the protocol for p=15% and 25%.

Power (%) for specified n and sample size (n) required for power 80% or 90% for assumed true value of the true probability of response (π) are given in the following table.

		POWER (%) FOR SPECIFIED N				SAMPLE SIZE REQUIRED FOR SPECIFIED POWER	
Null (π_0)	**True (π)**	**N=15**	**N=20**	**N= 34**	**N=40**	**Power=80%**	**Power=90%**
0.20	**0.30**	**13.2**	**16.3**	**24.6**	**28.1**	**165**	**221**
	0.35	22.9	29.0	45.0	51.2	80	107
	0.40	35.2	44.7	66.3	73.3	48	64
	0.45	49.5	61.3	83.4	88.8	32	42
	0.50	64.2	76.5	93.8	96.7	22	30
	0.55	77.8	88.2	98.4	99.4	16	22
	0.60	88.5	95.5	99.7	99.9	12	16
0.25	0.45	34.3	43.6	65.0	72.0	49	66
	0.50	0.491	60.9	83.0	88.5	32	43
	0.55	0.646	76.9	94.0	96.8	22	29
	0.60	0.790	89.2	98.6	99.5	16	21
0.30	0.50	0.341	43.2	64.5	71.6	50	66
	0.55	0.495	61.3	83.4	88.8	32	42
	0.60	0.660	78.2	94.6	97.2	21	29
	0.65	0.811	90.7	99.0	99.6	15	20
0.35	0.55	0.343	43.6	65.0	72.0	49	66
	0.60	0.507	62.6	84.5	89.8	31	41
	0.65	0.683	80.3	95.6	97.8	20	27
0.40	0.60	0.352	44.7	66.3	73.3	48	64
	0.65	0.528	65.0	86.4	91.2	29	39

* Computed using EAST 6.4

95% CI FOR PROBABILITY OF RESPONSE (Π;%)							
	Normal Approximation to Binomial				Exact Binomial		
p	**N=15****	**N=20**	**N=34****	**N=40**	**N=15**	**N=20**	**N=40**
10%	(0, 25.2)*	(0, 23.1)*	(0, 20.1)*	(0.7, 19.3)		(1.2, 31.7)	(2.8, 23.7)
15%	(0, 33.1)*	(0, 30.6)*	(3.0, 27.0)	(3.9, 26.1)		(3.2, 37.9)	(5.7, 29.8)
20%	(0, 40.2)*	(2.5, 37.5)	(6.6, 33.4)	(7.6, 32.4)	(4.3, 48.1)	(5.7, 43.7)	(9.1, 35.6)
25%	(3.1, 46.9)	(6.0, 44.0)	(10.4, 39.6)	(11.6, 38.4)		(8.7, 49.1)	(12.7, 41.2)
30%	(6.8, 53.2)	(9.9, 50.1)	(14.6, 45.4)	(15.8, 44.2)		(11.9, 54.3)	(16.6, 46.5)
35%	(10.9, 59.1)	(14.1, 55.9)	(19.0, 51.0)	(20.2, 49.8)		(15.4, 59.2)	(20.6, 51.7)
40%	(15.2, 64.8)	(18.5, 61.5)	(23.5, 56.5)	(24.8, 55.2)	(16.3, 67.7)	(19.1, 63.9)	(24.9, 56.7)

p= Observed Proportion From epitools.ausvet.com.au

* Computed lower limit is negative.

** Not all observed proportions given above are possible for n=15 and n=34

The overall sample size for the Phase 2a Expansion Cohorts will be approximately 60 patients treated at the RP2D, with accrual to be divided among up to 3 cohorts (tumor types mTNBC, SCCHN, and Sq-NSCLC); additional patients may be entered to the Phase 2a Expansion Cohorts if fewer than 30 patients are required to establish the RP2D in Phase 1a.

The current planned initial enrollment of 15 patients per cohort (or in each subcohort in the case of TNBC) may be expanded based on initial observation of > 2 objective responses (13% ORR) in any of the three indications (two separate cohorts in TNBC) to be studied. This sample size has a 35.2% power to detect a 40% ORR compared to a potential control response of 20% at a two-sided 0.05 level of significance. In addition, the power is between 45-54% to detect objective response rates between 20 to 40% in a 15 patient cohort at a two-sided 0.05 level of significance. After evaluation of the initial ORR in each cohort a decision will be made to either continue to include patients with treatment-refractory advanced/metastatic malignancies without other therapeutic options on an open-label trial (e.g., if the objective response rate $\geq$ 20% and responses are durable), consider alternative trial designs for further exploration of efficacy in any of the indications, or discontinue development if fewer than two (0 or 1) responses are observed in any of the three initial fifteen patient cohorts. The durability of objective responses

and disease stabilization > 8 weeks will also be considered in the decision to expand cohorts or pursue other options for further development in any of the three indications.

TEST OF NULL AT 0.05 LEVEL (TWO SIDED) USING NORMAL APPROXIMATION Power (%) for specified N (Computed using EAST 6.4)					
Null (π_0)	**True (π)**	**N=15**	**N=20**	**N=34**	**N=40**
0.20	0.30	13.2	16.3	24.6	28.1
	0.40	35.2	44.7	66.3	73.3
	0.50	64.2	76.5	93.8	96.7
	0.60	88.5	95.5	99.7	99.9

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