Statistical Analysis Plan

for

INY-P-20-001 – HES™ Hypervascular Tumor Pivotal Study

Instylla

Randomized Multi-Center, Subject and Evaluator Blinded, Parallel-Group Study to Evaluate the Safety and Effectiveness of the Instylla Hydrogel Embolic System (HES) Compared with Standard of Care Transcatheter Arterial Embolization (TAE) / Transcatheter Arterial Chemoembolization (cTACE) for Vascular Occlusion of Hypervascular Tumors; A Pivotal Study

INY-P-20-001

Version 5.0, dated 27 June 2024

SIGNATURE PAGE

The undersigned hereby jointly declare that they have reviewed the Statistical Analysis Plan and agree to its form and content.

Author			
Name	**Function**	**Signature**	**Date**
Elizabeth Kane	**Director, Biostatistics**	DocuSigned by: Elizabeth Kane Signer Name: Elizabeth Kane Signing Reason: I am the author of this document Signing Time: 27-Jun-2024 | 3:05:44 PM EDT F410DEF5F6684C45B1DD943845226FF9	27-Jun-2024 | 3:05:54 PM EDT
Approval by			
Name	**Function**	**Signature**	**Date**
Nicole Rissman	**Sponsor Representative**	DocuSigned by: Nicole Rissman Signer Name: Nicole Rissman Signing Reason: I approve this document Signing Time: 27-Jun-2024 | 12:43:40 PM PDT 1143925B0C1342DE9D0ACBFF135DE25	27-Jun-2024 | 12:44:39 PM PDT
Lynn Morrison	**Sponsor Representative**	DocuSigned by: Lynn Morrison Signer Name: Lynn Morrison Signing Reason: I approve this document Signing Time: 27-Jun-2024 | 12:02:45 PM PDT 3E170364312C45BEB11FD2BCC1872D43	27-Jun-2024 | 12:02:47 PM PDT
Emily E. Zetzer	**Biostatistician**	DocuSigned by: Emily E. Zetzer Signer Name: Emily Zetzer Signing Reason: I approve this document Signing Time: 27-Jun-2024 | 3:03:11 PM EDT BFA0DE4DB786466EA7389BE56E186991	27-Jun-2024 | 3:03:18 PM EDT

TABLE OF CONTENTS

DOCUMENT HISTORY

Version Date	Author	Version	Reason for Change
22OCT2020	Allie Ferreira	1.0	NA – Initial Version
16NOV2020	Allie Ferreira	2.0	Statement that additional safety analyses are not intended for product labeling shifted from section 10.1 to section 10.2.
08JAN2021	Allie Ferreira	3.0	Tipping point sensitivity analysis from protocol added
13NOV2023	Elizabeth Kane	4.0	Updating the number of patients when the interim is performed (originally said 70% of 90 was 56, but 70% of 90 is 63. Clarified analysis populations. Added technical success language when ancillary embolic is used from protocol. Added safety endpoint language clarifying subjects need to complete a follow-up visit at least 30 days post-procedure.
27JUN2024	Elizabeth Kane	5.0	SAP transferred to new template. Specifying that the distribution of the GEE model will be normal for calculating the risk difference. Added sensitivity analysis for primary endpoint. Added Kaplan Meier to assess time to MAE. Added additional wording around CEC review of protocol deviations

1 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AKI	Acute Kidney Injury
CEC	Clinical Events Committee
Control	Standard of Care Transcatheter Arterial Embolization (TAE) / Transcatheter Arterial Chemoembolization (cTACE)
CRF	Case Report Forms
CSR	Clinical Study Report
cTACE	Transcatheter Arterial Chemoembolization
DMC	Data Monitoring Committee
EE	Per-Protocol Effectiveness Evaluable Population
FDA	United States Food and Drug Administration
HES	Hydrogel Embolic System
ITT	Intent-To-Treat Population
MAE	Major Adverse Event
MITT	Modified Intent-To-Treat Population
NTE	Non-target Embolization
PP	Per-Protocol Population
PT	Preferred Term
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SE	Per-Protocol Safety Evaluable Population
SIR	Society for Interventional Radiology
SOC	System Organ Class
TAE	Transcatheter Arterial Embolization

2 SUMMARY

TITLE	Randomized Multi-Center, Subject and Evaluator Blinded, Parallel-Group Study to Evaluate the Safety and Effectiveness of the Instylla Hydrogel Embolic System (HES) Compared with Standard of Care Transcatheter Arterial Embolization (TAE) / Transcatheter Arterial Chemoembolization (cTACE) for Vascular Occlusion of Hypervascular Tumors; A Pivotal Study
PREFACE	This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Instylla protocol INY-P-20-001 (Randomized Multi-Center, Subject and Evaluator Blinded, Parallel-Group Study to Evaluate the Safety and Effectiveness of the Instylla Hydrogel Embolic System (HES) Compared with Standard of Care Transcatheter Arterial Embolization (TAE) / Transcatheter Arterial Chemoembolization (cTACE) for Vascular Occlusion of Hypervascular Tumors; A Pivotal Study). This study is being completed to assess the safety and effectiveness of Instylla HES for the embolization of hypervascular tumors. The following documents were reviewed in preparation of this SAP: • Clinical Research Protocol • Data Monitoring Committee (DMC) Charter • Clinical Events Committee (CEC) Manual of Operations • Case report forms (CRFs)
PURPOSE	The purpose of this SAP is to outline the planned analyses in support of the Clinical Study Report (CSR) for INY-P-20-001. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR.
STUDY OBJECTIVES	To determine whether Instylla HES has the ability to effectively embolize targeted arterial segments of hypervascular tumors as well as (i.e., is non-inferior to) standard of care transarterial embolization/ conventional transarterial chemoembolization, while resulting in an acceptable risk of device and procedure-related serious adverse events.
STUDY DESIGN	This is a subject and evaluator blinded, prospective, randomized, parallel arm, multicenter study to investigate whether Instylla HES is as effective (i.e., non-inferior) as standard of care TAE/cTACE for occluding targeted arterial segments of primary or metastatic hypervascular tumors. It is anticipated that at least 150 men and women with hypervascular tumors will be treated. Randomization to Instylla HES or the Institutional standard of care TAE/cTACE (2:1) will be performed intra-operatively after a satisfactory pre-embolization angiogram and will be stratified by investigational site and tumor location (hepatic or non-hepatic). This study will be conducted at up to 30 sites in the US, plus up to 10 sites outside of the US.

ENDPOINTS	**Primary:** The study's **primary effectiveness endpoint** is delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by an independent radiologist via comparison of the pre and final post procedure angiograms. Subjects may contribute more than one endpoint evaluation, i.e., it is anticipated that on average the number of target vessel embolizations per subject will be 1.5. Target vessels are defined as a single discrete vascular bed. **Safety:** The **primary safety endpoint** is freedom from major adverse events (MAE) through 30 days post-index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG). An **additional safety endpoint** analysis will compare the incidence of device (i.e., embolic agent) and procedure-related events between the Instylla HES and standard of care treatment groups.
INTERIM ANALYSES	Interim review of safety data by the DMC will be performed following accrual of 20 Instylla HES-treated subjects. The formal stopping rule will be considered reached if 4 Instylla HES subjects experience the following specific device or procedure-related events meeting criteria for a Grade ≥3 event per the 2017 SIR adverse event severity classification (as determined by the CEC): non-target injury, target organ ischemia or serious and severe unanticipated adverse device effect. The study will continue uninterrupted if the stopping safety rule is not met. The study will incorporate an adaptive design in which an interim analysis will be performed for purposes of sample size re-estimation in order to maintain adequate power. The ultimate sample size for the trial will be adaptively determined based upon a review performed once 70% of the planned number of target vessels have been evaluated for the primary effectiveness endpoint and 70% of the planned number of evaluable investigational group (HES) subjects have been evaluated for the primary safety endpoint (whichever occurs later). Safety data will be reviewed and adjudicated by a Clinical Events Committee (CEC). The DMC will be responsible for interim review of safety data and will be responsible for reviewing data from the sample size re-estimation analyses.
FINAL ANALYSES	The 90-day visit will be considered the last visit for the purpose of the regulatory phase of the program. The final analysis will occur once all patients are evaluated at 180 days following index procedure (or final HES procedure if applicable.)

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVE

The purpose of this study is to determine whether Instylla HES has the ability to effectively embolize targeted arterial segments of hypervascular tumors as well as (i.e., is non-inferior to) standard of care, transarterial embolization/conventional transarterial chemoembolization, while resulting in an acceptable risk of device and procedure-related serious adverse events.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINTS

The study's **primary effectiveness endpoint** is Technical Success defined as the delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by an independent radiologist via comparison of the pre- and final post- procedure angiograms.

Subjects may contribute more than one endpoint evaluation, i.e., it is anticipated that on average the number of target vessel embolizations per subject will be 1.5. Target vessels are defined as a single discrete vascular bed. If a greater number of embolizations are performed this will increase the power for the endpoint evaluation. Sites must capture a 15 second cine before and after embolization with a minimum frame rate of 2 frames per second to be provided to the Imaging Core Lab for independent assessment.

If technical success of a target vessel cannot be achieved with the assigned therapy, an ancillary (secondary) embolic agent may be used to complete the embolization procedure. If an ancillary (secondary) embolic is required to achieve successful embolization of the target vessel, this will be considered a target vessel technical failure regardless of determination by an independent radiologist.

A target vessel will be considered an effectiveness success upon meeting all of the above criteria.

The study's **primary safety endpoint** is freedom from major adverse events (MAE) through 30 days post-index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG). The following events will be considered MAE if deemed by the CEC to be definitely device and/or procedure-related or probably device and/or procedure related and satisfies the criteria for a Grade ≥ 3 event, classified in accordance with the 2017 Society for Interventional Radiology (SIR) Guidelines.

- Death
- Non-target embolization (NTE) of the index procedure, e.g., severe intractable abdominal pain, gastroduodenal ulceration, intestinal ischemia, pancreatitis, cholecystitis AND angiographic/CT evidence of NTE
- Unintended target tissue ischemia (defined as symptomatic healthy/non-diseased tissue ischemia in the target organ)
- Pulmonary embolism

- Vascular injury requiring surgical/endovascular intervention
- Renal failure defined as increase in serum creatinine of ≥2mg/dL above baseline that persists to the Day 30 visit
- Hepatic failure (Grade 3+ asterixis, encephalopathy) that persists to the Day 30 visit
- Abscess in target organ/tissue: defined as clinical symptoms of infection (fever, leukocytosis, bacteremia), imaging consistent with the diagnosis of abscess, and a positive drainage culture
- Toxic and/or allergic reactions to the HES hydrogel manifested as immediate anaphylaxis or acute kidney injury (AKI - severe azotemia, oliguria and/or anuria) with no other apparent etiology; e.g., contrast sensitivity.

3.2.2 Additional Safety Endpoint

An additional safety analysis will be to compare the incidence of device (i.e., embolic agent) and procedure-related events between the Instylla HES and standard of care treatment groups.

4 Sample Size

It is anticipated that the study will enroll a sample size of 150 randomized and treated subjects with an allocation ratio of 2:1, resulting in approximately 100 subjects in the Investigational Group and approximately 50 subjects in the Control Group. Since both the safety and effectiveness hypotheses must be satisfied for the study to be considered successful, each endpoint is powered at 90% to assure that the overall probability that both null hypotheses are rejected will be at least 80.0%. The overall sample size of 150 randomized and treated subjects also accounts for an approximately 10% attrition and/or missing data rate for effectiveness (anticipated to be primarily due to inadequate or incomplete data) and for an approximately 10% attrition and/or missing data rate for safety (anticipated to be primarily due to subject drop out).
This sample size determination was made based on the following specifications:

Safety Endpoint Assumptions:
The following assumptions were made for estimating sample size for the safety endpoint:

1. Analyzed based on Investigation Group (HES) only with comparison to Performance Goal criterion for Freedom from specific MAE's set to 75.0%
2. True Freedom from Specific MAE's for the Investigational Group is 88.0%
3. Alpha of 0.05 (one-sided)
4. Use of the exact binomial test
5. 90% power

Based on the above assumptions, the minimum sample required for the Investigational Group (HES) for evaluation of safety (unadjusted) is 79 subjects. 100 subjects will be randomized to the HES group; it is anticipated that this will yield the (up to) 90 required evaluable subjects for the primary safety analysis

after accounting for premature dropout before completing follow-up visit and after accounting for missing data.

Primary Effectiveness Endpoint Assumptions:
The following assumptions were made for estimating sample size for the primary effectiveness endpoint:

1. The underlying technical success rate is 96% for both treatment groups
2. 10% non-inferiority delta
3. Each subject contributes on average 1.5 endpoints and assuming low correlation of 0.01
4. One-sided alpha of 0.025
5. 90% power
6. Use of the Farrington-Manning test statistic for non-inferiority

The weak correlation (0.01) is justified as follows. Each vascular territory to be embolized will present with its own angioarchitecture and challenges to embolization, and therefore, it is not believed that outcomes will be correlated. This observation is consistent with the opinion of our advising interventional radiologist. Thus, the correlation factor that was selected (0.01 representing a weak correlation) is believed to be conservative. Further, the mechanism of operation of the Instylla HES is not dependent on subject factors such as coagulation status, thus further reducing the potential for any inherent correlation parameter between tumors in a single subject. This provides additional confidence that there will not be a correlation in outcomes for embolization of multiple vascular territories within the same subject. That being said, power is maintained at the desired level if the correlation is as high as 0.10 and power decreases by only approximately 3% if the correlation is as high as 0.25. Thus, power is generally robust even if the correlation assumption of 0.01 is incorrect and the correlation is as high as 0.25.

To support this statement, below is a table containing relevant results from PASS 2020 output, formatted and labeled for ease of interpretation, where PASS 2020 is the software used to determine sample size in this scenario. As can be seen from the first 2 columns in this table, power ranges from 90% to 87% and the within-patient correlation ranges from 0.01 to 0.25.

Power	Within-Patient Correlation	Experimental: Number of Subjects/ Number of Territories Per Patient	Control: Number of Subjects/ Number of Territories Per Patient	Control Success Rate	Experimental Success Rate	Non-Inferiority Margin	One-sided Alpha
90%	0.01	90/1.5	45/1.5	96%	96%	-10%	0.025
90%	0.02	90/1.5	45/1.5	96%	96%	-10%	0.025
90%	0.05	90/1.5	45/1.5	96%	96%	-10%	0.025
89%	0.1	90/1.5	45/1.5	96%	96%	-10%	0.025
87%	0.2	90/1.5	45/1.5	96%	96%	-10%	0.025
87%	0.25	90/1.5	45/1.5	96%	96%	-10%	0.025

Based on the above assumptions, the minimum per- protocol effectiveness evaluable (EE) sample size required for evaluation of effectiveness (unadjusted) is 135 subjects (90 Investigational Group: 45 Control Group). Specification on inclusion criteria for the Per-Protocol Effectiveness Evaluable Population can be found in section 6 below. As noted above, to account for both the safety and effectiveness hypotheses, and to allow for 10% attrition/missing data for effectiveness and 10% attrition missing data for safety, the overall randomized sample size has been increased to 150 patients (100 Investigational Group: 50 Control Group).

Note that power/sample size for the effectiveness endpoint was calculated using the PASS 2020 software as follows: (a) once PASS was opened, the “Proportions” category was clicked; (b) the “Two Proportions (Cluster-Randomized)” option was then clicked; (c) the “Non-Inferiority” option was then clicked; and finally (d) the module “Non-Inferiority Tests for the Difference of Two Proportions in a Cluster-Randomized Design” was chosen. Note that this module assesses power/sample size for non-inferiority using the Farrington-Manning test, accounting for an assumption of the value of the intra-cluster (i.e., within-subject) correlation. However, the application of the Farrington-Manning test to actual study data in the presence of clustering is not well developed. Thus, the GEE approach to assessing non-inferiority will be used to assess non-inferiority for the primary effectiveness endpoint in the presence of clustering.

5 Sequence of Planned Analyses

5.1 Interim Analyses

A Data Monitoring Committee (DMC) will be appointed by Instylla. Members of the DMC will be independent of the investigators and will include a statistician, oncologist, interventional radiologist and gastroenterologist/hepatologist. The DMC will be responsible for interim review of safety data and will be responsible for reviewing data from the sample size re-estimation analysis. The DMC may make formal recommendations for protocol changes to mitigate risk of adverse events. A DMC charter will be prepared prior to the initiation of the study.

The DMC will be responsible for interim review of safety data and will be responsible for reviewing data from the sample size re-estimation analyses. Interim review of safety data by the DMC will be performed following accrual of 20 Instylla HES-treated subjects. The formal stopping rule will be considered reached if 4 Instylla HES subjects experience the following specific device or procedure-related events meeting criteria for a Grade ≥3 event per the 2017 SIR adverse event severity classification (as determined by the CEC):

- non-target injury
- target organ ischemia
- serious and severe unanticipated adverse device effect

Non-target injury and target organ ischemia have been targeted as stopping rule events as they represent events which are of significant concern to interventional radiologists and are those that are most likely to be attributed to the embolic agent and its mode of delivery. Since not all possible adverse events associated with the investigational device may be known at this time, severe and serious (Grade ≥ 3) UADE's will also be considered a stopping rule event. Per the SIR guidelines, the combined acceptable threshold for non-target injury and target organ ischemia for percutaneous transcatheter embolization is approximately 6.5%; however, the combined reported rates reported in the literature for such events approaches 13.5%.

The probability for stopping the trial if 4 subjects experience a stopping rule event once 20 subjects are accrued is dependent on the true (population) event rate as follows:

Accrual (Investigational Group: HES)	**Events Needed to Halt**	**True Event Rate**	**Probability of Halting**
20	4	6.5%	3.7%
		10.0%	13.3%

Therefore, for example, if the true underlying event rate is 6.5%, then it is unlikely (3.7% probability) that 4 subjects will experience an event; so if 4 subjects do experience an event, the true event rate is likely >6.5% and the study should stop. If the true event rate is 10%, the probability of stopping the trial is greater at 13.3%.

The DMC may make formal recommendations for protocol changes to mitigate risk of adverse events. The study will continue uninterrupted if the stopping safety rule is not met.

5.1.1 Interim Analyses for Design Adaptation

The study will incorporate an adaptive design in which an interim analysis will be performed for purposes of sample size re-estimation in order to maintain adequate power. The ultimate sample size for the trial will be adaptively determined based upon a review performed once 70% of the planned number of target vessels have been evaluated for the primary effectiveness endpoint and 70% of the planned number of evaluable investigational group (HES) subjects have been evaluated for the primary safety endpoint (whichever occurs later). The maximum enrollment will be set to 270 evaluable subjects (or 405 evaluable vessels). The sample size re-estimation analysis will be performed according to the Mehta & Pocock Promising Zone approach and the DMC may recommend adjusting the sample size upwards (to a maximum of twice the protocol-specified number of evaluable territories and with consideration of the interim observed average number of observations per subject) as indicated by the sample size re-estimation analysis, as long as the conditional power for success using the protocol-specified final number of evaluable territories is in the promising zone (38% - 90%).

An unblinded conditional power calculation and sample size re-estimation will be conducted once approximately 142 total effectiveness evaluable (EE) territories (~70% of the expected 202 [=135*1.5] planned number of evaluable territories) have been evaluated for the primary effectiveness endpoint and approximately 63 HES investigational group subjects (~70% of the 90 expected planned number of safety-evaluable investigational group subjects) have been evaluated for the primary safety endpoint (i.e. experienced the event of interest or completed 30 days of follow-up post-index procedure) (whichever occurs later). The sample size re-estimation will be performed by an independent statistician who is unrelated to the day-to-day conduct of the study and results will be presented to the independent DMC.

The sample size re-estimation will be performed on the basis of the number of subjects and territories (observations), as follows:

1. First, in a blinded manner (i.e., for both treatment groups combined), if the observed attrition rate at the interim effectiveness analysis exceeds the currently expected value of 10%, then the planned final number of randomized subjects for the final effectiveness analysis, prior to performing any sample size-recalculations below, will increase from 150 in order to maintain 135 EE subjects for the effectiveness analysis. For example, if the interim-observed blinded attrition rate is 12%, the planned final number of randomized subjects for the final effectiveness analysis will increase from 150 to 135/0.88 or 154 randomized subjects. Note that if the observed attrition rate at the effectiveness analysis is at or below the expected value of 10%, the final planned randomized sample size will remain at 150.
2. Similarly, in a blinded manner (i.e., for both treatment groups combined), if the observed attrition rate at the interim safety analysis indicates that less than 90 safety-evaluable (SE) patients will be available for the primary safety analysis, then the planned final number of randomized subjects, prior to performing any sample size-recalculations below, will increase from 150 in order to maintain 90 SE HES subjects for the safety analysis. Note that if the observed attrition rate at the safety analysis is at or below the expected value of 10%, the final planned randomized sample size will remain at 150.
3. The number of subjects to be randomized (prior to performing any unblinded sample size recalculations below) will be the maximum of the numbers found in items 1 and 2 above, and the anticipated final number of evaluable subjects/territories for each of effectiveness and safety will be recalculated based on this randomized sample size and based on the safety and effectiveness attrition rates observed in the interim data.

After this point, the following unblinded analysis, for the purposes of sample size recalculation, will proceed for effectiveness:

1. The conditional power to achieve non-inferiority of Instylla HES to standard of care TAE/cTACE (Control) at the final analysis will be calculated, assuming (a) 202 total territories for the final analysis (202 is the protocol-planned expected evaluable number of territories; note that this expected number of evaluable territories for the final analysis may change from 202 based on the

blinded analysis in items 1-3 directly above; if so, the final expected number of evaluable territories will be used in the conditional power calculation in place of 202); (b) the average number of territories per subject in the final analysis is equal to the average observed at the interim; (c) the interim observed effect size (TAE/cTACE primary endpoint rate minus Instylla HES primary endpoint rate) is the true effect size; and (d) non-inferiority margin of 10%.

2. If this conditional power is in the Mehta-Pocock promising zone, then the final number of evaluable territories required to achieve 90% conditional power will be calculated under assumptions (b) through (d) in item 1 directly above.
3. Enrollment will continue until the total number of evaluable territories required to achieve 90% conditional power is reached (regardless of the number of EE subjects it took to reach this total).

As referenced in item 2 above, the sample size re-estimation analysis will be performed according to the Mehta & Pocock Promising Zone approach and the DMC may recommend adjusting the sample size upwards (to a maximum of twice the protocol-specified number of evaluable territories and with consideration of the interim observed average number of observations per EE subject) as indicated by the sample size re-estimation analysis, as long as the conditional power for success using the protocol-specified final number of evaluable territories is in the promising zone (38% - 90%). This analysis will be performed on the Effectiveness Evaluable (EE) analysis population.

For safety, the conditional power to meet the safety performance goal criterion for freedom from specific MAEs at the final analysis will be calculated, assuming (i) 90 Investigation Group (HES) SE subjects for the final analysis (90 is the protocol-planned expected evaluable number of HES patients for the safety analysis; note that this expected number of evaluable patients for the final analysis may change from 90 based on the blinded analysis discussed above; if so, the final expected number of SE patients will be used in the conditional power calculation in place of 90); and (ii) the interim observed rate of freedom from specific MAE for investigation group is the true rate. If this conditional power is in the Mehta-Pocock promising zone, then the number of evaluable subjects required to achieve 90% conditional power will be calculated under assumption (ii). The evaluable sample size can be increased (up to double the planned sample size) in order to maintain 90% conditional power to meet the safety performance goal criterion for freedom from specific MAEs at the final analysis. This analysis will be performed on the safety evaluable (SE) Population.

If an increase in sample size is needed for both the primary effectiveness and safety endpoints according to Mehta & Pocock Promising Zone approach, then the sample size will increase so that at least 90% conditional power for each primary endpoint will be achieved using the evaluable population for that endpoint.

If the primary safety endpoint requires a sample size increase, but the primary effectiveness endpoint does not, then the sample size will be increased to maintain 90% conditional power for the primary safety endpoint. The final analysis for the primary safety endpoint will be done on the SE population with 30-day data. The primary analysis for the primary effectiveness endpoint will be done on the subset of subjects in the EE population at the time the initial planned EE sample size is achieved (i.e., the first

135 evaluable (EE) subjects enrolled). A sensitivity analysis will be conducted on the entire effectiveness evaluable (EE) population.

Similarly, if the primary effectiveness endpoint requires a sample size increase, but the primary safety endpoint does not, then the sample size will be increased to maintain 90% conditional power for the primary effectiveness endpoint. The final analysis for the primary effectiveness endpoint will be done on the full EE population. The primary analysis for the primary safety endpoint will be done on the subset of subjects in the SE population with 30-day data at the time the initial planned sample size is achieved (i.e., the first 90 evaluable subjects enrolled). A sensitivity analysis will be conducted on the entire safety evaluable (SE) population.

In general, for each endpoint, the primary analysis will be on the initial sample size or, if a sample size increase is required, only on the increased sample size required for that endpoint.

As discussed in Mehta and Pocock (2011) such a sample size increase will not require a penalty to the final significance level. The results of the sample size re-estimation, regardless of outcome, will be summarized and reported to the FDA.

5.1.2 Reports for DMC

Safety updates will be provided to the DMC on a regular basis. The frequency and content of these reports will be outlined in the DMC charter.

5.2 Final Analyses and Reporting

All regulatory phase planned, analyses identified in the protocol and in this SAP will be performed only after the last *subject* has completed the 90-day follow up visit. Key statistics and study results will be made available following database lock. Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented, and reported as necessary. Any results from these unplanned analyses will also be clearly identified as post-hoc analyses. The final analysis will occur once all patients are evaluated at 180 days following index procedure (or final HES procedure if applicable).

6 Analysis Populations

6.1 Intent to Treat Population (ITT)

The ITT population will consist of all enrolled subjects who are randomized.

6.2 Modified Intent to Treat Population (mITT)

The mITT population will consist of all enrolled subjects who are randomized and have a target vessel treated (i.e., embolic agent/chemoembolic agent delivered to target tumor) with data analyzed according to randomized treatment assignment. This population will be utilized as a secondary analysis population for primary effectiveness.

6.3 Per-Protocol Population (PP)

The primary analysis population for the primary effectiveness and primary safety endpoints is identified as the Per Protocol (PP) population in the protocol. However, given the different timing of these endpoints (during procedure for effectiveness and through 30 days for safety), we have further separated out the Per Protocol population into the Effectiveness Evaluable (EE) population and the Safety Evaluable (SE) population, as described in Sections 6.3.1 and 6.3.2, respectively.

The per-protocol population will be comprised of two subgroups: Effectiveness Evaluable Population (EE) and Safety Evaluable Population (SE). Both subgroups will consist of mITT subjects who do not have major protocol deviations that would impact the corresponding endpoint.

6.3.1 Per-Protocol Effectiveness Evaluable Population (EE)

The EE population will consist of mITT subjects who do not have major protocol deviations that would impact the primary effectiveness endpoint. This population will be utilized as the primary analysis population for the primary effectiveness endpoint.

The following are considered major protocol deviations and will exclude a subject from the EE population:

- Inclusionary/exclusionary deviations that may confound technical success
- If subject receives a treatment in the target vessel that is different from what (s)he was randomized to
- Other significant protocol non-compliance that may confound evaluation of the primary effectiveness endpoint including the following:
    - Significant procedural deviations
    - Uninterpretable images

Protocol deviations are reviewed by the CEC on an ongoing basis for major/minor designation. Subjects with such non-compliance to exclude them from the EE analysis population also will be reviewed by the CEC and fully determined prior to database lock.

6.3.2 Per Protocol Safety Evaluable Population (SE)

The SE population will consist of mITT subjects who do not have major protocol deviations that would impact the primary safety endpoint. This population will be utilized as the primary analysis population for the primary safety endpoint.

The following are considered major protocol deviations and will exclude a subject from the SE population:

- If subject receives a treatment in the target vessel that is different from what (s)he was randomized to
- Other significant protocol non-compliance that may confound evaluation of the primary safety endpoint including the following:
    - Significant procedural deviations
    - Withdrawal prior to completing a follow-up visit-unless subject experiences a safety endpoint event prior to withdrawal

Protocol deviations are reviewed by the CEC on an ongoing basis for major/minor designation. Subjects with such non-compliance to exclude them from the SE analysis population also will be reviewed by the CEC and will be fully determined prior to database lock.

6.4 Safety Population

The safety analysis population includes all randomized, treated subjects. Subjects will be analyzed for safety based on the treatment received.

7 General Issues for Statistical Analysis

Descriptive statistics for continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, quartiles, standard deviation [SD], minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of subjects in each category. All results will be presented by treatment and appropriate subject populations. Study days will be calculated relative to the date of initial study treatment (i.e., Day 0 is the date of receipt of study treatment). All statistical tests will be performed as a one-sided 0.025 level of significance unless otherwise specified. Data listings will be presented and sorted by subject number and treatment. All data will be included in the data listings.

7.1 Analysis Software

Analysis data sets, statistical analyses and associated output generated by Avania will be generated using SAS® Software version 9.4 or later and/or R version 3.3.2 or later.

7.2 Disposition of Subjects and Withdrawals

All subjects who provide written informed consent will be accounted for. Primary screen failures would be prior to the procedure. Subjects deemed unsuitable for vascular embolization due to contraindicative findings will be considered intra-operative (secondary) screen failures and the reason for screen failure will be reported.

The number and percent of subjects in each analysis population will be presented, with percentages based on the ITT population. The frequency and percent of subjects who completed each scheduled assessment will be presented in a table. The number and percentage of ITT subjects prematurely withdrawing will be presented overall and by reason of discontinuation.

7.3 Methods for Withdrawals and Missing Data

The primary effectiveness and safety analyses will be performed on observed (available) data. Every attempt will be made to contact subjects who are non-compliant or lost to follow-up, and such attempts will be documented in the subject's study record. All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Since endpoints are assessed acutely (during the

index procedure for effectiveness and at the Day 30 visit for safety), it is anticipated that there will be minimal missing data and therefore no imputation methods are planned for the primary analyses.

For the primary effectiveness endpoint, a tipping point sensitivity analysis will be used to assess the effect of missing data on the primary effectiveness endpoint results. i.e., if the null hypothesis is rejected on the EE population, then the EE population with missing data (e.g., uninterpretable imaging for core lab review) will be imputed as a technical failure, one at a time cumulatively, and the null hypothesis will be tested after each cumulative imputation until the "tipping point" is reached (i.e., until the null hypothesis is no longer rejected). There will be no imputation of missing data for any other endpoints.

7.4 Protocol Deviations

Protocol deviations will be summarized in the CSR for the ITT population. This summary will include the number and percent of subjects with each deviation type. The protocol deviations for this protocol consist of, but are not limited to the following:

- Inclusionary/exclusionary deviations that may confound technical success
- If subject receives a treatment in the target vessel that is different from what (s)he was randomized to
- Other significant protocol non-compliance that may confound evaluation of technical success for the effectiveness endpoint (i.e., significant procedural deviations or uninterpretable cineangiograms).

Subjects with such non-compliance will be determined prior to database lock.

7.5 Multiple Comparisons and Multiplicity

There will be no adjustment for multiple comparisons.

7.6 Assessment of Homogeneity

A test of homogeneity across sites will be done to determine if the study sites within a location have reasonably homogeneous responses. This analysis will be done by assessing treatment-by-site interaction assessment in a GEE regression model utilizing a normal distribution with an identity link for the primary effectiveness dichotomous outcome using a 0.15 level of significance. If the responses are not homogenous, the appropriate regression analysis will be done to determine if the lack of homogeneity is due to the site or due to a possible imbalance in baseline characteristics of the subjects [or tumor type] across study sites. If the site effect is no longer significant at $P<0.15$ after adding the potentially unbalanced baseline covariates, then site will not be considered a source of lack of homogeneity. A similar analysis will be conducted to assess homogeneity between US and OUS sites.

8 Baseline Characteristics

8.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics for the ITT, mITT, EE and SE populations will be summarized in a table. Sex, race, and ethnicity will be summarized with frequency and percent. Age, height, weight, BMI, SBP, DBP and, respiratory rate, heart rate, and temperature will be summarized with number of observations, mean, median, minimum, maximum and standard deviation.

8.2 Prior and Concurrent Medications

All relevant prior and concomitant medications will be presented in a listing for the mITT population, with a column indicating if the subject is in the EE and/or SE populations.

8.3 Baseline and Screening Conditions

Smoking history (current/past/never), treatment for metastatic disease (yes/no), ECOG Performance, NYHA classification, and Child-Pugh Classification, and indication for vascular embolization will be summarized by presenting the frequency and percent of subjects in each category for the mITT population. A listing will also be generated with a column indicating if the subject is in the EE and/or SE populations.

8.4 Baseline Medical History & Disease Description

A summary of baseline medical history including primary diagnosis, carcinoma staging, Barcelona Clinic Liver Cancer Staging System, and prior cancer therapies will be provided in a table for the mITT population. The summary will report the frequency and percentage of subjects with a history of each condition. A listing of medical history data will be presented and will include medical condition and status (occurred/ongoing), with a column indicating if the subject is in the EE and/or SE populations.

8.5 Baseline Surgical History

A listing of baseline surgical history data will be presented for the mITT population, with a column indicating if the subject is in the EE and/or SE populations.

8.6 Baseline Physical Exam

A summary of baseline examination findings will be presented by body system and status (abnormal/normal/not done) by the frequency and percentage of subjects by system for the mITT population, with a column indicating if the subject is in the EE and/or SE populations.

8.7 Baseline Labs

A summary of baseline laboratory exams will be provided in a table including AFP, alkaline, RBC, WBC, Hematocrit, Hemoglobin, Platelets, INR, Albumin, Serum Creatinine, Total Bilirubin, ALT, AST, and Glucose. Baseline labs will be summarized using sample size, mean, SD, median, minimum, and maximum for the mITT population. A listing will also be generated with a column indicating if the subject is in the EE and/or SE populations.

9 EFFECTIVENESS ANALYSES

9.1 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint for this study is the proportion of target vessels in which Technical Success is achieved defined as delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by a central independent radiologist (Core Laboratory) via comparison of the pre and final post procedure angiograms. Note, pre-specified vessels where delivery of the embolic agent to the index tumor feeding vessel was attempted and subsequently assessed by the Core Laboratory will be included in the primary effectiveness endpoint.

If technical success of a target vessel cannot be achieved with the assigned therapy, an ancillary (secondary) embolic agent may be used to complete the embolization procedure. If an ancillary (secondary) embolic is required to achieve successful embolization of the target vessel, this will be considered a target vessel technical failure regardless of determination by an independent radiologist.

Subjects may contribute more than one endpoint evaluation, i.e., it is anticipated that on average the number of target vessel embolizations per subject will be 1.5. Only those vessels targeted for embolization **prior to randomization** will be included in the primary effectiveness analysis.

The primary study hypothesis is that Instylla HES is non-inferior to standard of care TAE/cTACE (Control) for successfully embolizing hypervascular tumors. Therefore, the statistical hypotheses are as follows:

$$H_0: \pi_2 - \pi_1 \geq 0.1$$
$$H_1: \pi_2 - \pi_1 < 0.1$$

where π_1 and π_2 is the true incidence for tumors achieving primary effectiveness endpoint success for Instylla HES and Control respectively. The non-inferiority margin of 10% was developed based upon consensus from Instylla's interventional radiologist advisors. This value takes into account that some vascular territories may be more difficult to embolize and therefore there may be some variability in achieving primary endpoint success.

Non-inferiority will be assessed using a generalized estimating equation (GEE) model with robust estimation where (a) the dependent variable is the binomial primary effectiveness endpoint of success, the independent variable is treatment group (Instylla HES and control); (b) the exchangeable correlation structure will be the assumed within-subject correlation structure; (c) the identity link will be used for the GEE model in order to obtain an estimate of the risk difference between treatments and its two-sided 95% confidence interval.

A sensitivity analysis will be conducted using all embolized vessels from the index procedure. Pending sufficient data from additional procedures, a second sensitivity analysis may be conducted using all

embolized vessels from the index procedure and additional procedures. The sensitivity analyses will be summarized based on treatment received.

10 Safety Analyses

The primary safety endpoint will be analyzed in the SE population and will include subjects who have completed a follow-up visit at least 30 days post-procedure prior to study exit or have a primary safety endpoint event prior to day 30 or study exit (whichever comes first). The additional safety endpoints and all adverse event analyses will be shown for the safety population. There will be no adjustment for multiple comparisons due to the exploratory nature of the additional safety analyses.

10.1 Primary Safety Endpoint

The primary safety endpoint will be freedom from specific MAE through 30 days post-index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG). The following events will be considered MAE if deemed by the CEC to be definitely device and/or procedure-related or probably device and/or procedure related and satisfies the criteria for a Grade ≥ 3 event in accordance with the SIR recommendations.

- Death
- Non-target embolization (NTE) of the index procedure, e.g., severe intractable abdominal pain, gastroduodenal ulceration, intestinal ischemia, pancreatitis, cholecystitis AND angiographic/CT evidence of NTE
- Unintended target tissue ischemia (defined as symptomatic healthy/non-diseased tissue ischemia in the target organ)
- Pulmonary embolism
- Vascular injury requiring surgical/endovascular intervention
- Renal failure defined as increase in serum creatinine of ≥2mg/dL above baseline that persists to the Day 30 visit
- Hepatic failure (Grade 3+ asterixis, encephalopathy) that persists to the Day 30 visit
- Abscess in target organ/tissue: defined as clinical symptoms of infection (fever, leukocytosis, bacteremia), imaging consistent with the diagnosis of abscess, and a positive drainage culture
- Toxic and/or allergic reactions to the HES hydrogel manifested as immediate anaphylaxis or acute kidney injury (AKI - severe azotemia, oliguria and/or anuria) with no other apparent etiology; e.g., contrast sensitivity.

The safety hypotheses to be evaluated in this study are as follows:

$$H_0: \delta \leq PG$$
$$H_1: \delta > PG$$

Where δ is the proportion of subjects who are free from CEC adjudicated MAE for Instylla HES and PG represents the literature-derived performance goal which has been set to 75.0%. A one-sided p-value will be derived based on an exact binomial test and the study device will be considered to have achieved the safety objective if the one-sided p-value is less than 0.05 (or equivalently, the lower limit of the one-sided 95% confidence limit based on the exact method is greater than the pre-specified performance goal.)

The literature-derived performance goal is based on a review of the literatures which has established that the cumulative threshold values for incidence of the safety endpoint events identified is 25%. Thus, the PG for Freedom from MAE has been set to 75%.

10.1.1 Kaplan-Meier Analysis –Time to MAE

Kaplan-Meier curves will be presented by treatment group displaying the time to MAE. MAE will be defined as above in Section 10.1, using the first known adverse event date at which a subject has reported an MAE.

Subjects will be considered censored at the time of last contact and censoring will be displayed on curve. Additionally, a table below the figure will display number of subjects at risk for MAEs to occur.

10.2 Additional Safety Endpoint

An additional safety analysis will be to compare the incidence of device (i.e., embolic agent) and procedure-related events between the Instylla HES and standard of care treatment groups. 95% exact (Clopper-Pearson) confidence intervals for the true proportions and an exact 95% confidence interval based on a score statistic for the difference in proportions between treatments will be presented. The true proportions will be compared using a two-sided Fisher's Exact Test at the 0.05 significance level.

Further, all adverse events experienced by subjects occurring from the time of the Index Procedure and up through and including the Day 90 visit will be reported and listed. The incidence of adverse events will be summarized by term, by term and primary attribution, and by term and severity. The true proportions of adverse events by SOC term using MedDRA will be compared using a two-sided Fisher's Exact Test at the 0.05 significance level.

There will be no adjustment for multiple comparisons due to the exploratory nature of these analyses. The results from the additional safety analyses are informative only and not intended for product labeling.

11 Adverse Events

All adverse events (AEs) will be coded using the standardized Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 23.1 or greater. Adverse Events will be evaluated per NCI

CTCAE Version 5.0 and all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity Classification. Note if a subject is experiencing pain, the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represents the worst-possible pain.

Adverse events (AEs) and/or serious adverse events (SAEs) may have additional summaries and/or listings subset by time period if deemed appropriate.

11.1 All Adverse Events

The occurrence of all adverse event (AEs) will be documented in all study subjects from the index procedure throughout the study follow-up period. CEC adjudicated summaries of incidence rates of individual AEs overall and by SOC and PT will be prepared. Because a subject may experience more than one AE, summaries will provide both the number of subjects experiencing at least one event and the number of events. Percentages provided will be the percent of subjects experiencing one or more adverse events. In addition, incidence of AEs will be presented by severity (mild, moderate, severe, life-threatening or disabling event, subject death or unexpected pregnancy abortion), and by causality (investigational device related, study procedure related, procedure occurring after Index Procedure (surgery or local therapy), other concomitant treatment, pre-existing or underlying condition, or other). Subjects experiencing an event within a given PT and SOC more than once will be counted under the maximum severity/relationship experienced.

A listing of all AEs will include the subject number, AE number, days since index procedure, the AE SOC and PT, the severity of AE, whether or not the AE is classified as serious (SAE), the relationship of the AE to the investigational procedure, the action taken, the outcome, and the adjudication status. An additional listing will be provided that includes both site reported and adjudicated information for AEs that are adjudicated.

11.2 Serious Adverse Events

CEC adjudicated summaries of incidence rates and relationship to the investigational device/procedure of individual SAEs by System Organ Class (SOC) and Preferred Term (PT) will be prepared. Summaries will provide both the number of subjects and the number of events. Percentages provided will be the percent of subjects experiencing one or more serious adverse events. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF. Whether an AE meets the definition for serious adverse event will be initially determined by the study investigator followed by CEC adjudication.

11.3 Device or Procedure Related Adverse Events

CEC adjudicated summaries of incidence rates of device and procedure related AEs by System Organ Class and Preferred Term will be prepared. Summaries will provide both the number of subjects and the number of events within a reporting period. Percentages provided will be the percent of subjects experiencing one or more device or procedure related adverse events. Data listings of device and procedure related AEs will also be provided, displaying details of the event(s) captured on the CRF. Relationship of the AE to the device placement procedure or the HES will be initially judged by the

investigator by adverse event relatedness categories (unrelated, unlikely, possible probable, definitely) followed by CEC adjudication.

11.4 Deaths

Should any subjects die during the course of the trial, relevant information will be supplied in a data listing.

12 Other Planned Analyses

12.1 Planned Subgroup Analyses

For informational purposes, the primary safety and effectiveness endpoints will be presented by strata (i.e., hepatic and non-hepatic) and by gender. While the study is not powered to detect a difference between subgroups, an analysis to check homogeneity across subgroups will be conducted as outlined in Section 7.6 of the SAP.

12.2 Other Data Collected

12.2.1 Procedural Characteristics

- Embolization Procedure Time (minutes), time elapsed from time of insertion of the outer microcatheter to completion of final arteriography will be summarized separately by radial vs. femoral access.
- Embolization Time (minute): time elapsed from initiation of embolic agent injection through final embolic agent injection (per vessel and per patient).
- Cumulative procedural fluoroscopy time and cumulative fluoroscopy dose (mGy).
- Overall Procedure Time: from placement to removal of the arterial sheath
- Volume of Embolization Material delivered (excluding priming volume) per vessel and per patient.
- Instances when the catheter is repositioned due to non-embolization per vessel and per patient.
- Number of “assisted embolization” successes per vessel (i.e. multiple embolics used during single procedure).
- Embolization Agent Preparation Time (start time, end time).
- Number of times HES/Embolic Agent syringes are filled.
- Ease of Embolic Delivery:(5-point Likert scale from easy to difficult where 1= Very difficult, 2=Difficult, 3=Neither easy nor hard, 4=Easy, 5=Very easy).

12.2.2 Quality of Life

- QoL (e.g., EORTC QLQ-C30 and EORTC QLQ-HCC 18 as appropriate) will be summarized by follow up visit.

12.2.3 Tumor Response

- Objective Tumor Response at all follow up visits by index tumor response assessment schema and outcome, and evidence of revascularization.
- Time to Progression/survival will be summarized by evidence of local tumor progression (i.e., foci of disease encompassed within area previously treated).

12.2.4 Device Observations

- Device observations in both treatment groups as appropriate will presented in a listing.

12.2.5 Other Evaluations

- EGOG and Child-Pugh scores will be summarized across follow-up time points. Other evaluations may be summarized as appropriate.

13 Reporting Conventions

All reporting will meet the standards of SOP-68 AS Data Analysis Reporting and SOP-83 AS Programming Standards.

DocuSign

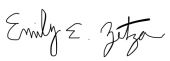
Certificate Of Completion

Envelope Id: A415B304B68D43B8B00BCC171A6281F3
Status: Completed
Subject: Complete with Docusign: 20240627_Instylla_HVT_SAP_Rev_5.0.docx
Source Envelope:
Document Pages: 26
Signatures: 4
Certificate Pages: 6
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Envelope Originator:
Emily Zetzer
100 Crowley Drive Suite 216
Marlborough, MA 01752
Emily.Zetzer@avaniaclinical.com
IP Address: 73.225.213.216

Record Tracking

Status: Original
6/27/2024 2:58:16 PM
Holder: Emily Zetzer
Emily.Zetzer@avaniaclinical.com
Location: DocuSign

Signer Events	Signature	Timestamp
Elizabeth Kane elizabeth.kane@avaniaclinical.com Director, BS Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: F410DEF5-F668-4C45-B1DD-943845226FF9 Using IP Address: 104.28.39.30 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 6/27/2024 3:01:59 PM Viewed: 6/27/2024 3:04:42 PM Signed: 6/27/2024 3:05:54 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Emily Zetzer emily.zetzer@avaniaclinical.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: BFA0DE4D-B786-466E-A738-9BE56E186991 Using IP Address: 73.225.213.216 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/27/2024 3:02:00 PM Viewed: 6/27/2024 3:02:50 PM Signed: 6/27/2024 3:03:18 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
Lynn Morrison lynnm@instylla.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Lynn Morrison Signer Name: Lynn Morrison Signing Reason: I approve this document Signing Time: 27-Jun-2024 | 12:02:45 PM PDT 3E170364312C45BEB11FD2BCC1872D43 Signature Adoption: Pre-selected Style Signature ID: 3E170364-312C-45BE-B11F-D2BCC1872D43 Using IP Address: 98.58.104.21 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/27/2024 3:01:59 PM Viewed: 6/27/2024 3:02:31 PM Signed: 6/27/2024 3:02:47 PM
Electronic Record and Signature Disclosure: Accepted: 6/27/2024 3:02:31 PM ID: 607ab3b7-06a5-4ccb-9eeb-6bcc5c637a68		
Nicole Rissman nicoler@instylla.com Security Level: Email, Account Authentication (Required)	Nicole Rissman Signature Adoption: Pre-selected Style Signature ID: 1143925B-0C13-42DE-9D0A-CBFF1356DE25 Using IP Address: 72.197.221.221 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/27/2024 3:02:00 PM Viewed: 6/27/2024 3:43:25 PM Signed: 6/27/2024 3:44:39 PM
Electronic Record and Signature Disclosure: Accepted: 6/27/2024 3:43:25 PM ID: 7033af20-ab88-450a-a5ee-ef80e7095c4d		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	6/27/2024 3:02:00 PM
Certified Delivered	Security Checked	6/27/2024 3:43:25 PM
Signing Complete	Security Checked	6/27/2024 3:44:39 PM
Completed	Security Checked	6/27/2024 3:44:39 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Avania (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Avania:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: thomas.mouraviev@avaniaclinical.com

To advise Avania of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at thomas.mouraviev@avaniaclinical.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Avania

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to thomas.mouraviev@avaniaclinical.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Avania

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to thomas.mouraviev@avaniaclinical.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Avania as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Avania during the course of your relationship with Avania.