Statistical Analysis Plan

Protocol Title:	A Phase 1b/2 Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination With Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination With Systemic Pembrolizumab to Treat Subjects with Advanced Solid Tumors in Phase 2 (MASTERKEY-318)
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	**20AUG2015**	
Amendment 1 (v2.0)	**16FEB2021**	**Aligned the SAP with the changes of protocol amendment 4; clarified the study endpoints for both part 1 and part 2; added details in study design and analyses method; updated the definition of safety analysis set; general typographical, formatting, and editorial changes.**

Amendment 2 (v3.0)	**26JAN2022**	**Aligned the SAP with the changes of protocol amendment 5 and 6; clarified the study safety and efficacy endpoints; updated the definition of BOR, L-ORR and max tumor burden decrease; general typographical, formatting, and editorial changes**

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BC	breast adenocarcinoma
BCC	basal cell carcinoma
BOR	best overall response
BRAF	B-Raf sarcoma viral oncogene homolog
CD	cluster of differentiation
CI	confidence interval
CR	complete response
CRC	colorectal adenocarcinoma
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CSCC	cutaneous squamous cell carcinoma
DCR	disease control rate
DILI	drug-induced liver injury
DLRT	dose level review team
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DRR	durable response rate
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

HCV	hepatitis C virus
[redacted]	[redacted]
irRC-RECIST	immune-related response criteria (irRC) simulating RECIST version 1.1
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MTC	maximum tolerated concentration
mTPI	modified toxicity probability interval
MTV	maximum tolerated volume
non-HCC	metastatic liver tumors (if tumors are present in liver)
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
[redacted]	[redacted]
PR	partial response
PFS	progression-free survival
qPCR	real-time polymerase chain reaction
RP2D	recommended phase 2 dose
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNBC	triple negative breast cancer
T-VEC	talimogene laherparepvec

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20140318, Talimogene Laherparepvec dated **26 Oct 2021**. The scope of this plan includes the interim, primary and the final analyses that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. A separate supplementary SAP may be prepared for the exploratory objectives and these analyses may be reported separately.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• **Part 1:** To evaluate the following, as assessed by the incidence of dose-limiting toxicities (DLTs), in subjects with liver metastases (non-HCC) and subjects with primary hepatocellular carcinoma (HCC) in: **Monotherapy Cohorts:** the maximum tolerated volume and concentration (MTV and MTC) of intrahepatic injection of talimogene laherparepvec into liver tumors in subjects with non-HCC and subjects with primary HCC without active viral hepatitis **Combination Cohorts:** the MTC of intrahepatic injection of talimogene laherparepvec into liver tumors in combination with systemic intravenous (IV) administration of pembrolizumab in subjects with non-HCC, and subjects with primary HCC with or without viral hepatitis	• **Part 1:** **Monotherapy cohorts 1-4:** Subject incidence of DLTs with intrahepatic injection of talimogene laherparepvec into liver tumors in subjects with non-HCC with liver metastases and subjects with HCC without active viral hepatitis. **Combination cohorts 5 and 6:** Subject incidence of DLTs with intrahepatic injection into liver tumors of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab in subjects with non-HCC with liver metastases and subjects with HCC with and without viral hepatitis as assessed by subject incidence of DLTs.
• **Part 2:** To evaluate the efficacy, as assessed by objective response rate (ORR) of intratumoral injection of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab, separately, for each non-HCC tumor type (hormone	• **Part 2:** ORR per modified irRC-RECIST with intralesional injection of talimogene laherparepvec into cutaneous, subcutaneous, lymph node, and liver tumors in combination with systemic IV administration of pembrolizumab separately by tumor type arm

receptor positive breast adenocarcinoma [BC], triple negative breast cancer [TNBC], colorectal adenocarcinoma [CRC], cutaneous squamous cell carcinoma [CSCC], basal cell carcinoma [BCC]) as well as primary HCC with and without viral hepatitis.	(hormone receptor positive BC, TNBC, CRC, CSCC, BCC, and HCC with and without viral hepatitis)
• **Part 2:** To evaluate safety separately for each tumor type as assessed by subject incidence of treatment-emergent and treatment-related adverse events, including DLTs	• **Part 2:** Subject incidence, for each tumor type arm, of treatment-emergent and treatment-related adverse events, including DLTs
Secondary Efficacy	
• **Part 1:** To evaluate the efficacy separately by monotherapy versus combination for non-HCC tumors and HCC with and without viral hepatitis when applicable as assessed by: ORR, best overall response (BOR), durable response rate (DRR), duration of response (DOR), response in injected and uninjected lesions, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)	• **Part 1:** ORR, BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS separately for non- HCC and HCC tumors in monotherapy and combination cohorts
• **Part 2:** To evaluate the efficacy in individual tumor types in the non-HCC group and HCC group with and without viral hepatitis as assessed by: BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS by primary tumor type arm (TNBC, Hormone receptor positive BC, CRC, CSCC, BCC, and HCC with and without viral hepatitis)	• **Part 2:** BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS by primary tumor type (hormone receptor positive BC, TNBC, CSCC, CRC, BCC and HCC with and without viral hepatitis)
Secondary Safety (Parts 1 and 2)	
• To evaluate the safety in each monotherapy and combination cohorts in Part 1 and each arm separately in Part 2, as assessed by subject incidence of treatment-emergent and treatment-related adverse events	• Subject incidence of treatment-related and treatment-emergent adverse events (each monotherapy and combination cohorts in Part 1, and each tumor type separately in Part 2, and

	HCC with and without viral hepatitis)
• To estimate the incidence of detectable talimogene laherparepvec deoxyribonucleic acid (DNA) in blood and urine	• Subject incidence of detectable talimogene laherparepvec DNA in blood and urine
• To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine	• Incidence of clearance of talimogene laherparepvec DNA from blood and urine
• To estimate the rate of detection (per sample) and incidence (per subject) of talimogene laherparepvec DNA and virus at the surface of talimogene laherparepvec injection site, the exterior of the occlusive dressing, and the oral mucosa	• Subject incidence (per subject) and rate of detection (per sample) of talimogene laherparepvec DNA and virus at the surface of injection site, the exterior of the occlusive dressing, and the oral mucosa
• To estimate the incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin	• Subject incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin
Exploratory	
[redacted]	

2.2 Hypotheses and/or Estimations

PART 1:

Monotherapy cohorts 1-4: Talimogene laherparepvec injected intrahepatically into liver tumors will be safe in subjects with non-HCC with liver metastases and subjects with HCC without active viral hepatitis as assessed by subject incidence of DLTs.
Combination cohorts 5 and 6: Talimogene laherparepvec injected intrahepatically into liver tumors in combination with systemically administered pembrolizumab will be safe in subjects with non-HCC with liver metastases and subjects with HCC with and without viral hepatitis as assessed by subject incidence of DLTs.

PART 2:

Talimogene laherparepvec injected intratumorally in combination with systemic IV administration of pembrolizumab will demonstrate at least a 40% ORR in each tumor type and be safe in the individual non-HCC tumor types as well as primary HCC with and without viral hepatitis.

3. Study Overview

3.1 Study Design

This is a phase 1b/2, multicenter, open-label, basket trial to evaluate the safety of talimogene laherparepvec injected intrahepatically into liver tumors alone and in combination with systemic IV administration of pembrolizumab, in subjects with non-HCC liver metastases from BC, CRC, GEC, melanoma, NSCLC, RCC in Part 1 Group A, and subjects with HCC with and without viral hepatitis in Part 1 Group B (viral hepatitis is only applicable in combination setting), and to evaluate the efficacy and safety of intratumoral talimogene laherparepvec in combination with systemic pembrolizumab to treat subjects with advanced TNBC, hormone receptor positive breast cancer, CRC, CSCC, and BCC in Part 2 Group A and subjects with HCC with and without viral hepatitis in Part 2 Group B. The study consists of 2 parts and 2 groups and Part 2 includes 2 stages.

The overall study design is described by a study design and treatment schema at the end of the protocol synopsis section.

3.1.1 Study Design for Part 1

Part 1 is a dose escalation study to evaluate the safety of intrahepatic injection of talimogene laherparepvec into liver tumors alone and in combination with systemic IV administration of pembrolizumab for the non-HCC (Group A) and HCC (Group B) (with and without viral hepatitis; viral hepatitis is only applicable in combination setting) cohorts separately. For talimogene laherparepvec monotherapy cohorts (Cohorts 1-4), safety will be assessed for the non-HCC and HCC groups based on the “3+3” design. The initial concentration in all cohorts will always be 10^6 PFU/mL. Maximum total volumes (up to 4 mL or 8 mL) and subsequent concentrations (10^7 or 10^8 PFU/mL) to be administered will depend on the specific cohort. Combination cohorts (Cohorts 5 and 6) in Part 1 will determine the safety of administering intrahepatic injection of talimogene laherparepvec at 10^7 PFU/mL or 10^8 PFU/mL sequentially (volume up to 4 mL for both doses) in combination with systemic IV administration of pembrolizumab using a modified toxicity probability interval (mTPI) up-and-down design.

3.1.2 Study Design for Part 2 (Non-HCC and HCC Groups)

Part 2 is a 2-stage design to evaluate the efficacy and safety of talimogene laherparepvec in combination with systemic pembrolizumab separately by tumor type. The DLRT will consider prospective guidelines in the DLRT Charter to monitor safety in Part 2 separately by tumor type and, if introduced, talimogene laherparepvec total volumes > 4 mL within Group A and Group B.

Part 2 (Group A) of the study will enroll subjects of non-HCC tumors (hormone receptor positive BC, TNBC, CSCC, CRC, BCC). Subjects will be enrolled separately into each tumor type. Stage 1 of Part 2 (Group A) will begin enrolling after MTC has been determined from Cohort 5 and 6 in Part 1.

Part 2 (Group B) of the study will enroll subjects with HCC with and without viral hepatitis. Stage 1 of Part 2 (Group B) will begin enrolling after MTC has been determined from Cohorts 5 and 6 in Part 1.

Subject enrollment and study conduct during Part 2 of the study will progress independently in the non-HCC and HCC groups.

During Stage 1 of Part 2, non-HCC and HCC groups will enroll approximately 10 subjects for each tumor arm (5 tumor arms in Group A and 1 tumor arm in Group B with and without viral hepatitis). Subjects enrolled in Part 2 will initially be administered up to 8 mL of talimogene laherparepvec MTC determined from Cohorts 5 or 6 in Part 1. Administration of up to 8 mL of talimogene laherparepvec was established from Part 1, cohort 3 of either group any newly enrolled subjects in Part 2 can be administered up to 8 mL of talimogene laherparepvec. No intrasubject concentration or volume escalation is allowed. The primary analysis of efficacy will include subjects that receive any volume of talimogene laherparepvec (monotherapy cohorts) and subjects that receive any volume of talimogene laherparepvec and pembrolizumab (combination cohorts). Stage 1 of a 2-stage efficacy assessment will occur once 10 subjects have been enrolled in a tumor type arm. Stage 1 efficacy assessments will occur separately per tumor arm. If efficacy is not futile, Stage 2 will open for that particular tumor arm where approximately an additional 11 treated subjects can be enrolled.

For a full description of the protocol design, please refer to Section 3.1 of the protocol.

3.2 Sample Size

Sample Size Considerations for Part 1

The sample size of approximately 3 to 6 subjects per monotherapy cohort is determined empirically and is consistent with those used in traditional "3+3" phase 1 designs to evaluate safety assuming a true DLT rate of less than 1/3. There are up to 4 monotherapy cohorts in Groups A / B in Part 1. Subjects enrolled in a monotherapy cohort may be replaced if they are not evaluable for DLT (eg, did not receive talimogene laherparepvec or ended the study treatment before completion of the DLT evaluation period for a reason other than experiencing a DLT).

Safety of the combination will be evaluated with the mTPI up-and-down design in Part 1 to determine the talimogene laherparepvec MTC with a target DLT rate of 40%. The maximum sample size in the combination cohorts 5 and 6 or 6a will be 28 (maximum of 12 subjects evaluated at 6b). Unless the cohort 5 is deemed too toxic, patients may be enrolled and assigned to appropriate doses until the maximum sample size is reached or minimum of 12 subjects are enrolled in Cohort 6 provided the mTPI outcome is not at a D or DU in cohort 6. If in Non HCC group, cohort 6b completes prior to cohorts 5 and 6a enrollment, and 6b is deemed safe, then cohorts 5 and 6a will close to enrollment. Full details of the mTPI will be specified in the DLRT Charter.

Part 2 for non-HCC tumor types (Group A) or HCC (Group B) will open if the corresponding group MTC is selected at the end of Part 1.

Sample Size Considerations for Part 2

The recommended phase 2 dose from Part 1 (RP2D) for non-HCC (Group A) and HCC (Group B) will be evaluated in Part 2 independently for each tumor type arm for the combination of talimogene laherparepvec with systemic pembrolizumab. Subjects that initiate treatment at the corresponding RP2D in Part 1 will not be included in the Part 2 efficacy analysis according to their respective tumor type arm.

The primary objective in Part 2 for each tumor type arm will be to evaluate the ORR per modified irRC-RECIST with a minimum potential follow-up of at least 29 weeks. The null hypothesis (H0) for each tumor type is an ORR ≤ 10% which, if true, would not warrant further evaluation in contrast to the alternative hypothesis (H1) of an ORR ≥ 40%.

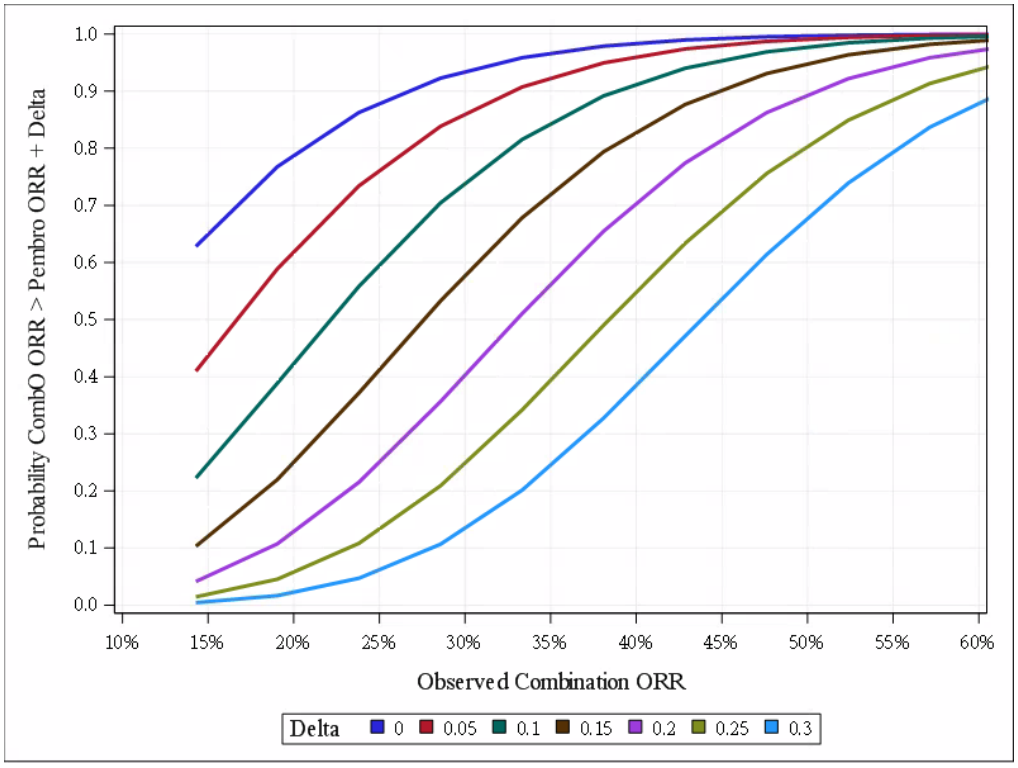
The following 2-stage design will be used to reject H0 at a ≤ 2.5% 1-sided significance level. The efficacy analysis will be based on the Full Analysis Set in part 2 only. A cumulative total of 10 subjects will be treated in Stage 1 and enrollment is planned to stop. If there are 2 or more responders (PR or CR no confirmation is needed), then a total of 11 additional subjects will be treated in Stage 2; otherwise, H0 will be accepted

and enrollment will be permanently discontinued. If the required number of responders to continue to Stage 2 is observed before the end of Stage 1 enrollment, then enrollment will not be suspended.

H0 will be rejected after Stage 2 if there are ≥ 6 responders (with confirmation) in 21 treated subjects, ie, the observed ORR is ≥ 28.6%. In the event precisely 21 subjects are not included in the analysis in total, H0 will be rejected if the lower limit of the 95% exact binomial CI is > 10% (Atkinson and Brown, 1985) (see code fragment in Appendix D.2). If exactly 10 and 11 subjects are included at Stage 1 and 2, respectively, the design achieves a 1-sided 1.3% significance level, 88.4% power, and the probability of stopping at Stage 1 if H0 (H1) is true is 73.6% (4.6%).

For each tumor type that advances to Stage 2, a Bayesian framework may be utilized to assess evidence that the combination ORR exceeds that expected for pembrolizumab alone to aid in decision-making as to whether further evaluation is warranted. Given the observed ORR in the Full Analysis Set, the Bayesian posterior probability will be calculated that the true combination ORR exceeds the expected ORR for pembrolizumab by an absolute amount (delta). Since the data is not available yet, the following is just an illustration how it will work. For example, the expected ORR for pembrolizumab in the study population of one of the tumor arm in part 2 with 9 weeks minimum potential follow-up is approximately 11% and will be represented by a beta(2.2, 17.8) distribution with mean 0.11 and precision 20.0. The ORR for the combination will be represented by a beta(0.2, 1.8) distribution with mean 0.11 and precision 2.0. Figure 1 provides the posterior probability of a delta increase from 0% to 30% in 5% increments for an observed ORR ranging from 14.3% (3/21) to 66.7% (14/21) in the example. It can be updated later once we have more information of pembrolizumab in the study population of one of the tumor arm. The calculation of a 90% credible region for delta are also provided (see Appendix E).

Figure 1. Probability of a Combination Delta Absolute Objective Response Rate Increase Over Pembrolizumab



From 10 to 21 subjects per tumor type are expected to be treated at the RP2D for a total of 60 to 126 subjects.

For Part 2, the DLRT will consider prospective guidelines in the DLRT Charter to monitor safety separately by tumor type arm and, if introduced, talimogene laherparepvec total volumes > 4 mL within Group A and Group B.

The subject incidence of DLT in Part 2 will be based on the DLT Analysis Set with at least 6 weeks minimum potential follow-up.

The maximum total sample size for Parts 1 and 2 will be approximately 3 to 242 subjects (approximately up to 116 subjects in Part 1; approximately 60 to 126 subjects in Part 2). This estimate includes approximately 126 Full Analysis Set subjects that receive the combination treatment in Parts 1, up to 48 DLT-evaluable subjects from Part 1 monotherapy cohorts. Dose-limiting toxicity non-evaluable subjects will not be replaced in Part 2.

4. Covariates and Subgroups

4.1 Planned Covariates and Subgroups

The following covariates may be used whenever applicable to examine efficacy and safety in subgroups or in multivariate analyses:

• Region, if applicable (USA vs non-USA)

• Age at baseline (< 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years)

• Baseline LDH (≤ ULN vs > ULN)

• Gender (Female vs Male)

• Baseline ECOG (0 vs 1)

• Baseline sum of lengths of measurable lesions

• Baseline sums of lengths of measurable liver lesions

• Prior exposure to chemotherapy (Yes vs No)

• HSV-1 serostatus (Yes vs No)

• Maximum talimogene laherparepvec volume at highest concentration per visit

(≤ 4 mL vs > 4 mL)

• Baseline HBV or HCV status

• Baseline Microsatellite Instability status for CRC subjects

4.2 Subgroups

N/A

5. Definitions

The definition of DLT is provided in Protocol Section 3.1.4.3. Additional definitions are as follows:

DLT evaluation period

- Monotherapy Cohorts: The DLT evaluation period for a given subject will consist of the period between the initial 10^6 PFU/mL dose of talimogene laherparepvec and 3 weeks following the initial 10^7 or 10^8 PFU/mL dose of talimogene laherparepvec.
- Combination Cohorts: The DLT evaluation period for a given subject will consist of the period between the initial 10^6 PFU/mL concentration of talimogene laherparepvec and 3 weeks following the initial 10^7 or 10^8 PFU/mL dose of talimogene laherparepvec. Any subject who has not received at least 2 doses of talimogene laherparepvec (10^6, and 10^7 or 10^8 PFU/mL) and 2 doses of pembrolizumab, will not be considered DLT-evaluable unless they experience a DLT after the first dose.

Maximum Tolerated Dose (MTD)

The MTD is the combination of the maximum tolerated volume (MTV) and the maximum tolerated concentration (MTC) determined from the dose limiting toxicity (DLT) evaluations in Part 1 per group.

Enrollment date

The date subject is enrolled to the study. A subject will be considered enrolled when the investigator confirms that the subject has met all eligibility criteria and the subject is registered as enrolled in the interactive voice response system (IVRS).

Investigational Product

Investigational product (IP) refers to Amgen investigational product talimogene laherparepvec in Part 1 monotherapy cohorts, and refers to Amgen investigational product talimogene laherparepvec and non-Amgen investigational product pembrolizumab in Part 1 combination cohorts and Part 2.

Last IP Dose Date

Last IP Dose Date for each subject is defined as the latest date IP is administered in this study.

End of IP Admin Date

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of IP CRF page in this study.

Screening Phase

The screening phase is the time period after subject signing off the informed consent form and before enrollment when study-specific laboratory tests and procedures are performed, and medical history is reviewed to confirm subject eligibility for the study.

Study Day

Study day is calculated from the first day the study drug is administered to the subject.
Study day = visit date – first dose date +1 if visit date is on or after the first dose date.
Study day = visit date – first dose date, if visit date is before the first dose date.

Study Day 1

Study day 1 is the first day that protocol-specified investigational products are administered to the subject. The day before study day 1 is study day '-1'.

Baseline

Baseline in general refers to study day 1. The baseline value of a parameter (e.g., vital signs, laboratory tests, and tumor measurement) is considered to be the latest value prior to receiving the study drug (i.e., on or prior to the first date of dosing).

Best overall response (BOR) per Modified irRC-RECIST

Best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or un-evaluable (UE) will be derived based on investigator assessment using modified irRC-RECIST as defined in protocol Appendix D.

Overall visit response assessments occurring after the start of the first subsequent anticancer therapy **will not be included. With the exception of a PD observation, the overall visit response** occurring on or after complete or partial removal/reduction of any target lesion which contained cancer on pathology evaluation or pathology results were unknown, will not be included. Consecutive confirmation of CR, PR, and PD is required where the second overall response must be at least 28 days from the first, the only exception being when the investigator reports that an initial PD cannot be confirmed due to rapid clinical deterioration. The following will be considered a confirmed PR: CR followed by PR or PR followed by CR.

BOR is defined as the best visit response in the following order: CR, PR, SD, PD, or UE (see Table 1). BOR is defined as SD if the best overall visit response is an unconfirmed CR or PR, and UE if it is either SD earlier than 77 days after first dose date or an unconfirmed PD when confirmation of PD is required (ie, initial PD without rapid clinical deterioration).

Table 1. Matrix of Determining BOR per Modified irRC-RECIST

Visit Overall Response Sequence	Examples	Best Overall Response	Confirmation specifications
, CR, CR,	PR, CR, CR CR, CR, PD	CR	The confirmatory CR must be at least 4 weeks (28 days) later; a subsequent CR within 28 days will not be valid for

			confirmation and will be ignored; the CR will also not be confirmed if there is a subsequent PR/SD/PD at any time prior to the next CR.
*, PR, PR, * *, PR, CR/PR, non-CR, * *,CR, PR,*	PR, PR, PD PR, CR, PD CR, PR, PD	PR	Criteria for BOR=CR not met. The confirmatory PR/CR must be no less than 4 weeks (28 days) later; a subsequent PR/CR within 28 days will not be valid for confirmation and will be ignored; the PR will also not be confirmed if there is a subsequent SD/PD at any time prior to the next PR/CR.
*, SD, * *,CR, non-PR/CR, * *,PR, non-PR/CR, *	CR PD, CR PR PD, PR, SD SD PD,SD,PD	SD	Criteria for BOR=CR or PR not met. SD must be ≥ 77 days from the date of first dose; however, this is not required for an unconfirmed CR/PR.
*,PD, PD, * *, PDr, * PDr = PD with concurrent or subsequent rapid clinical deterioration as the reason for ending radiographic follow-up.	PD, PD PD, SD, PD, PD PDr	PD	Criteria for BOR= CR, PR, or SD not met. The confirmatory PD must be no less than 4 weeks (28 days) later unless there is rapid clinical deterioration; PDr does not require confirmation; a subsequent PD within 28 days will not be valid for confirmation and will be ignored.
*, SD, * PD	SD UE, SD PD UE, PD	UE	Criteria for BOR=CR, PR, SD, or PD not met. SD must be < 77 days from the date of first dose.

Duration of Response (DOR)

Duration of response is defined as the time from the date of an initial response that is subsequently confirmed to the earlier of PD (see definition of BOR per modified irRC-RECIST) or death. Subjects who have not ended their response at the time of analysis will be censored at the last evaluable tumor assessment before start of the first subsequent anticancer therapy.

Durable Response Rate (DRR)

Durable response rate is defined as the percent of subjects with a CR or PR per modified irRC-RECIST with a DOR ≥ 6 months. One month will be calculated based on 365.25 days per year.

Disease Control Rate (**DCR** also called the **Clinical benefit response rate**)

Disease control rate is the proportion of subjects that have a best overall response of confirmed CR/ PR or SD.

Objective Response Rate (ORR)

The incidence rate of either a confirmed CR or PR per Modified irRC-RECIST. Subjects who do not achieve confirmed CR or PR by the start date of subsequent anticancer therapy or the data cutoff date, whichever occurs earlier, are regarded as non-responders.

Baseline Lesion

Baseline lesion is defined as the lesions identified on or before study day 1 with a positive tumor length. If a baseline lesion has a positive tumor length reported at more than one visit, then the length from the most recent visit will be selected as the baseline length.

New Lesion

New lesion is defined as the lesions that first appear after study day 1 with a positive tumor length. “Baseline” (ie, initial) tumor length of a new lesion will be obtained from the earliest date with a positive tumor length. Lesions that split from other lesions will not be considered as new lesions.

Lesion complete response (L-CR)

Lesion complete response (L-CR) is a response at the lesion level in injected vs uninjected lesions and applies only to target lesions and new measurable lesions. For injected and uninjected lesions, L-CR is defined as complete disappearance of a non-nodal or reduction in short axis to <10 mm for pathological lymph node with confirmation by a repeat consecutive assessment no less than 4 weeks (28 days) after first documented.

Lesion partial response (L-PR)

Lesion partial response (L-PR) is a response at the lesion level in injected vs uninjected lesions and applies only to target lesions and new measurable lesions and is defined as ≥ 30% decrease in lesion length relative to baseline with confirmation by a repeat consecutive assessment no less than 4 weeks (28 days) from the date first documented.

Lesion objective response rate (L-ORR)

Lesion objective response rate (L-ORR) is a response rate at the lesion level in injected vs uninjected lesions and is defined as the incidence among a set of lesions analyzed of L-CR or L-PR.

Response at the lesion-level will be censored at the earliest **after the start of the first subsequent anticancer therapy**, or on or after the event of merging with another lesion, or complete or partial removal/reduction of any target lesion which contained cancer on pathology evaluation or pathology results were unknown. If a lesion splits, the sum of the length of the split lesions will be added together prior to analysis.

Maximum Tumor Burden Decrease

Tumor burden is defined as the sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions and up to 10 (maximum 5 per organ) new measurable lesions. Tumor burden ratio is defined as the ratio of the tumor burden at each assessment divided by the baseline tumor burden. The Maximum tumor burden decrease is defined as smallest tumor burden ratio among all assessments -1.

The maximum tumor burden decrease at the subject-level will be censored **at the earliest after the start of the first subsequent anticancer therapy, or on or after the event of** complete or partial removal/reduction of any target lesion which contained cancer on pathology evaluation or pathology results were unknown.

The maximum tumor burden decrease at the lesion-level will be censored at the earliest after the start of **the first subsequent anticancer therapy**, or on or after the event of merging with another lesion, or complete or partial removal/reduction of any target lesion which contained cancer on pathology evaluation or pathology results were unknown. If a lesion splits, the sum of the length of the split lesions will be added together prior to analysis.

Overall Survival (OS)

Overall survival (OS) is defined as the time from the date of first dose date to the date of death from any cause. Death is the event of interest. OS time will be censored at the last date the patient is known to be alive when the confirmation of death is absent or unknown.

Evaluable tumor assessment

An overall visit response other than unevaluable (UE) or not done (ND).

Evaluable lesion

A target lesion or a new measurable lesion with a baseline and at least subsequent non missing dimension.

Progression-free survival (PFS)

PFS is defined as the interval from first dose date to the earlier event of confirmed PD or death from any cause. Subjects without an event will be censored at the latter of their last evaluable tumor assessment if available; otherwise will be censored on Study Day 1.

Treatment Period

Treatment period is defined as the period between the first date of IP administration in the study and 30 days after the last IP administration in the study.

Subject Incidence of Detectable Talimogene Laherparepvec in Blood and Urine

This endpoint is the prevalence of subjects with detectable talimogene laherparepvec DNA per qPCR in the blood /urine after the administration of talimogene laherparepvec within the first 4 cycles and safety follow-up per time point.

Clearance of Talimogene Laherparepvec DNA in Blood and Urine

A subject will be considered to have cleared talimogene laherparepvec DNA in the blood/urine if the qPCR assay for a blood sample is tested as negative following a previous positive qPCR testing. For example, the cycle 2 day 1 prior to injection sample will be used to consider clearance of a positive qPCR post injection from cycle 1.

Rate of Talimogene Laherparepvec DNA Detection and Viral Detection on the Exterior of Occlusive Dressing

The rate of detectable talimogene laherparepvec DNA per qPCR on the exterior of occlusive dressing is defined as the number of cases of detectable talimogene laherparepvec DNA per qPCR divided by all swabs collected on the exterior of occlusive dressing per time point. The rate of viral detection on the exterior of occlusive dressing is defined as the number of cases of detectable talimogene laherparepvec virus (TCID50 positive) divided by the number swabs collected on the exterior of occlusive dressing per time point.

Rate of Talimogene Laherparepvec DNA Detection and Viral Detection at the Skin Surface of Injection

The rate of detectable talimogene laherparepvec DNA per qPCR at the skin surface of injected lesions is defined as the number of cases of detectable talimogene laherparepvec DNA per qPCR divided by all swabs collected at the skin surface of injected lesions per time point. The rate of viral detection in injected lesions is defined as the number of cases of detectable talimogene laherparepvec virus (TCID50 positive) divided by the number of swabs collected at the skin surface of injected lesions per time point.

Rate of Talimogene Laherparepvec DNA Detection and Viral Detection in Oral Mucosa

The rate of detectable talimogene laherparepvec DNA per qPCR in oral mucosa is defined as the number of cases of detectable talimogene laherparepvec DNA per qPCR divided by all swabs collected in oral mucosa per time point. The rate of viral detection in oral mucosa is defined as the number of cases of detectable talimogene laherparepvec virus (TCID50 positive) divided by the number of swabs collected in oral mucosa per time point.

Rate of Detectable Talimogene Laherparepvec DNA per qPCR in Suspicious Lesions to be Herpetic in Origin

The rate of detectable talimogene laherparepvec DNA per qPCR in suspicious lesions is defined as the number of cases of detectable talimogene laherparepvec DNA per qPCR from swabs collected from lesions that are suspected to be herpetic in origin divided by all swabs collected from these lesions per time point.

Treatment-emergent Adverse Events (TEAE)

Treatment-emergent adverse events are defined as any adverse events that occur after the first dose of talimogene laherparepvec or pembrolizumab through 30 days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later. Adverse events that occur on the same day as the first dose date of IP will be treated as treatment-emergent events unless indicated otherwise. (For example, if an event occurs on the same date as the first administration of study therapy and the check box

indicating prior to the first dose of IP is checked, then the event will not be counted as a TEAE).

Treatment-emergent Serious Adverse Events (TESAE)

Treatment-emergent serious adverse events are defined as any serious adverse event occurring after initiation of the first dose of study therapy through 90 days after the last administration of study therapy or 30 days after the last administration of study therapy if the subject initiates new anticancer therapy, whichever is earlier. Serious adverse events that occur on the same day as the first dose date of study therapy will be treated as treatment-emergent serious events unless indicated otherwise. (For example, if an event occurs on the same date as the first administration of study therapy and the check box indicating prior to the first dose of study therapy is checked on eCRF, then the event will not be counted as a TESAE).

On-study Surgery/procedure

On study surgeries or procedures are defined as surgeries or procedures performed from the time of first drug exposure to end of the treatment period or death or end of study, whichever occurs first.

On-study Death

Deaths of all causes that occur any time during the study are defined as on-study deaths. This may include deaths that occur beyond the end of the treatment period. Note that this study has a long-term survival follow-up after the safety follow-up, deaths that occur after the study long-term survival follow-up will be reported in study 20120139, which is the registry study for long-term follow up of clinical trial subjects who have completed talimogene laherparepvec treatment.

6. Analysis Sets

6.1 Full Analysis Set

For efficacy analyses of talimogene laherparepvec monotherapy, the Full Analysis Set will be defined as all subjects who received at least 1 dose of talimogene laherparepvec

and no treatment with systemic pembrolizumab; and for efficacy analyses of talimogene laherparepvec in combination with systemic pembrolizumab, it will be defined as all subjects who received at least 1 dose of talimogene laherparepvec and at least 1 dose of pembrolizumab in combination.

6.2 Safety Analysis Set

The Safety Analysis Set will be defined as all subjects who received study therapy. For monotherapy cohorts, subjects will be included for analysis of safety if they received at least 1 dose of talimogene laherparepvec. For the combination therapy cohorts or part 2, subjects will be included for analysis of safety if they received at least 1 dose of talimogene laherparepvec or at least 1 dose of pembrolizumab.

6.3 DLT Analyses Set(s)

DLT Analysis Set: The DLT analysis set will include DLT-evaluable subjects enrolled in Part 1 and Part 2 defined as follows:

- **Monotherapy Cohorts:** Subjects who have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment and have received at least 1 additional dose of talimogene laherparepvec
- **Combination Cohorts:** Subjects who have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment, and have received at least 2 doses of talimogene laherparepvec and pembrolizumab in combination
- **Subjects experiencing a DLT:** Have a DLT during the DLT-evaluation period after at least 1 dose of talimogene laherparepvec (for monotherapy cohorts) and talimogene laherparepvec and pembrolizumab (for combination cohorts)

[redacted]

6.5 Reactive Swab Analysis Set

Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one swab sample collected from lesions that are suspected to be herpetic in origin. This analysis set is used to examine the number of subjects with a lesion suspected to be herpetic, and detection of talimogene laherparepvec DNA by qPCR in lesions suspected to be herpetic in origin.

6.6 Blood and Urine Evaluable Analysis Sets

Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one post dose blood sample (and urine sample, respectively) collected. The Blood and Urine Analysis Sets will be used for examining the biodistribution of talimogene laherperapvec in the blood and urine, respectively.

6.7 Blood and Urine Clearance Analysis Sets

Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least 2 post dose blood/urine samples collected within the same dosing cycle. In addition, subjects included in the Blood/Urine Clearance Analysis Set must have at least 1 positive talimogene laherparepvec DNA sample and at least 1 subsequent sample at any time during the cycle (including the sample collected prior to the next dose of investigational product, if applicable). A subject will be defined as having cleared talimogene laherparepvec if a negative qPCR in a sample is obtained following a prior positive test and if there are no subsequent positive test results in the same cycle. The Blood/Urine Clearance Analysis Set will be used to evaluate the subject incidence of clearing talimogene laherparepvec DNA in the blood and urine over time in the first three cycles.

6.8 Exterior of Occlusive Dressing Evaluable Analysis Sets

Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one swab collected from the exterior of the occlusive dressing. This analysis set is used to examine the detection of talimogene laherparepvec DNA and virus in the exterior of the occlusive dressing.

6.9 Skin Surface of Injections Evaluable Analysis Sets

Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one swab collected from the skin surface of injections. This analysis set is used to examine the detection of talimogene laherparepvec DNA and virus at the skin surface of in injections.

6.10 Oral Mucosa Evaluable Analysis Sets

Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one swab collected from oral mucosa. This analysis set is used to examine the detection of talimogene laherparepvec DNA.

6.11 Lesion Analysis Sets

The Injected Lesion Analysis Set includes any target lesion and new measurable lesion that was ever injected and the uninjected lesion analysis set includes any target lesion and new measurable lesion that was never injected among subjects in Full Analysis Set. The Injected Lesion Evaluable and Uninjected Lesion Evaluable analysis sets will include the corresponding subset of target lesions and new measurable lesions with at least one post-baseline measurement prior to a censoring event, ie, non-study anticancer therapy, merged with another lesion, or resection (except if it is partial or complete resection and pathology indicates absence of malignant cells). If a lesion splits, the sum of the length of the split lesions will be added together prior to analysis.

7. Planned Analyses

7.1 Interim Analysis

Dose-limiting toxicities interim safety analyses will be performed to support the evaluation of safety and determination of the MTC and MTV of talimogene laherparepvec administered as monotherapy and in combination with systemic pembrolizumab. Interim efficacy analysis for part 1 will be performed as needed. Interim safety and efficacy futility analyses are planned for this study in Part 2 separately for each tumor type arm.

7.1.1 DLT Safety Analysis (Part 1)

The planned interim safety data reviews for monotherapy cohorts in Part 1 to evaluate the subject incidence of DLTs will be conducted according to timing/rules described in Protocol Section 3.1.1. Data will be reviewed by a DLRT. The DLRT will recommend either to declare the cohort dose intolerable, to reassess safety after 3 additional DLT-evaluable subjects, or to declare the cohort dose tolerable and to apply the same evaluation rules to subsequent cohorts. For combination cohorts in Part 1, the DLRT will recommend according to the DLRT Charter whether it is safe to continue enrollment based on the mTPI up-and-down design. The database will be cleaned, and a database snapshot will be used in the analysis.

7.1.2 Interim Safety Analysis (Part 2)

An interim safety data review will occur for each tumor type separately after approximately 10 subjects have been treated in Part 2 with the specific tumor type and have had an opportunity to be followed up for at least 6 weeks.

At the discretion of the DLRT, 2 additional safety analyses may be conducted as warranted during Part 2 after a target of approximately 6 and 16 DLT-evaluable subjects.

A total volume > 4 mL of talimogene laherparepvec may be allowed in Part 2 with systemic pembrolizumab if it is declared safe without pembrolizumab in Part 1. In this event, the DLRT will also monitor safety in Part 2 separately among subjects in non-HCC (Group A) and HCC (Group B) arms that receive at least 1 dose of talimogene laherparepvec with a total volume > 4 mL at the combination MTC with systemic pembrolizumab. Subjects will be included in the safety assessment of > 4 mL with at least 3 weeks follow-up from an initial total volume > 4 mL at the combination MTC.

Safety analyses will be performed at the time of the planned analyses for each tumor type or more frequently at the DLRTs discretion. The database will be cleaned, and a database snapshot will be used in the analysis.

7.1.3 Interim Futility Analysis (Part 2)

One interim efficacy futility analysis will occur after 10 subjects have been treated with the combination in Part 2 by tumor type and have had an opportunity to be followed up for at least 20 weeks. Enrollment will be suspended for the specific tumor type arm pending the outcome of the interim analysis. If there are 2 or more responders (CR or PR confirmation not required), then a total of 11 additional subjects will be treated; otherwise, further enrollment of the tumor type will be permanently discontinued. If at least 2 responders are observed by the enrollment of the 10th treated subject, then enrollment will not be suspended. The database will be cleaned, and a database snapshot will be used in the analysis.

7.1.4 Dose Level Review Team (DLRT)

A DLRT consisting of the Amgen study team, including at least one medical clinician, safety representative and biostatistician, at least one representative of the Merck study team, and at least one participating investigator who has recruited subjects into Part 1, will review the safety data to evaluate possible DLTs. Representative(s) from Merck will participate in DLRT meetings for all cohorts (voting member only for Cohorts 5 and 6 of Part 1 and all cohorts of Part 2). The DLRT will make recommendations in Part 1 and 2 according to a DLRT Charter. The DLRT Charter will include guidelines to monitor safety in Part 2 separately by tumor type arm and, if introduced, talimogene laherparepvec total volumes > 4 mL within Group A and Group

B. In Part 2, the DLRT may consider reducing the RP2D talimogene laherparepvec concentration and/or discontinuation of total volumes > 4 mL, if introduced. The database will be cleaned, and a database snapshot will be used in the analysis.

7.2 Primary Analysis

One clinical study report (CSR) will be written based on the results of the primary analyses across Part 1 and Part 2.

The primary analysis for each combination cohort from Part 2 will occur independently when all subjects in each tumor type arm have a minimum potential follow-up of ≥ 29 weeks. The primary analysis for part 1 will occur after all subjects have a minimum potential follow-up of ≥ 29 weeks. The database will be cleaned, and a locked database will be used in the analysis.

7.3 Final Analysis

The final analysis will occur when all subjects have discontinued the study treatment and have had the opportunity to complete the long-term survival follow-up visit. **One** CSR will be written with the updated results from the final analyses at the completion of the study. The database will be cleaned, and a locked database will be used in the analysis.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

[redacted], HSV antibody serostatus samples, and swab samples collected from lesions suspected to be herpetic in origin, will be processed and analyzed by a vendor of Amgen. [redacted]

8.3 Handling of Missing and Incomplete Data

Adverse events with missing severity, seriousness, and/or possible relationship to talimogene laherparepvec will be included in all AE analyses, except by severity grade and treatment-related analyses.

Partial or missing dates of adverse events and concomitant medications will be imputed.

[redacted] Every effort will be made to obtain complete dates for deaths. [redacted]

8.4 Detection of Bias

NA

8.5 Outliers

The database will be subject to edit checks outlined in the protocol-specific Data Management Plan (DMP). Data with inconsistencies and suspicious values will be queried and resolved before the database lock.

8.6 Distributional Characteristics

NA

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

In Part 1, the efficacy and safety analyses will be conducted separately in monotherapy and combination cohorts. The DLT analysis set will be used to summarize the subject incidence of DLT for the study and the Safety Analysis Set will be used for all other analyses of safety endpoints (including but not limited to all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events requiring discontinuation of study drug, and AEs defined as events of interest). The efficacy analysis will be conducted using the Full Analysis Set unless otherwise specified. All the analysis may be conducted overall or by cohort/ group if appropriate.

In Part 2, the efficacy and safety analyses will be conducted separately by each tumor type arm. The efficacy analysis will be conducted using the Full Analysis Set unless

otherwise specified. The Safety Analysis Set will be used for all other analyses of safety endpoints.

In principle, mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated for continuous variables; frequency count and percent will be calculated for binary and categorical variables. The analysis of response variant endpoints will be based on investigator assessments per modified irRC-RECIST as described in the protocol unless otherwise specified.

9.2 Subject Accountability

The number of subjects enrolled will be tabulated by investigator sites. Subject disposition including screened, enrolled, treated and ended treatment, and completed safety follow-up visit will be summarized for all enrolled subjects in part 1 and part 2 separately. Reasons for discontinuation of study drug, reason for not completing the study, and the reason for not completing safety follow-up will also be summarized overall or by cohort/part/tumor type arm/group if appropriate. Key study dates for the first subject enrolled, last subject enrolled, last subject's end of study, last subject's end of investigational product, and data cut-off date will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. Eligibility deviations that are defined as IPDs will be summarized in both the IPD and Eligibility Deviation table. An IPD and an Eligibility Deviation listing will be provided. The number of subjects with at least one IPD during study will be tabulated.

9.4 Demographic and Baseline Characteristics

Summary statistics of the following demographic, baseline characteristics, and disease characteristics described in 4.1 will be tabulated. These will also be used whenever applicable to examine efficacy and safety in subgroups or in multivariate analyses.

9.5 Efficacy Analyses

The efficacy analysis will be conducted separately for Part 1 and Part 2, using the Full Analysis Set. The efficacy analysis in Part 1 will be conducted overall and by group/cohort. The efficacy analysis in Part 2 will be performed overall and by group/tumor type, unless otherwise specified.

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Part 2: • ORR per modified irRC-RECIST with intratumoralinjection of talimogene laherparepvec into cutaneous, subcutaneous, lymph node, or liver tumors in combination with systemic IV administration of pembrolizumab separately by tumor type.	The 2-stage design will be used to evaluate the ORR per the modified irRC-RECIST. The null hypothesis of a 10% ORR for a given tumor type that continued to Stage 2 will be rejected if an exact binomial 95% CI for the ORR is above 10% (Atkinson and Brown, 1985).	N/A

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Part 1: • ORR, BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS separately for non-HCC and HCC tumors in monotherapy and combination cohorts	• For Part 1, the ORR/DRR/DCR will be estimated with the associated 95% CI (Clopper and Pearson, 1934). • A listing of efficacy endpoints will be provided for whichever combination cohort is not the RP2D, if applicable. • Kaplan-Meier (K-M) estimates of landmarks (e.g., 1-, 2-, and 3-year rates) and quartiles for DOR/PFS/OS will be provided (Kaplan and Meier, 1958). Greenwood's formula (Kalbfleisch and Prentice, 1980) for standard error will be used to calculate CIs for landmark K-M rates. CIs for K-M quartiles will be estimated (Brookmeyer and Crowley, 1982). • Waterfall plots for maximum tumor burden decrease in the lesion diameter at subject-level and lesion-level will also be provided.	N/A
Part 2: • BOR, DRR, DOR, response in injected	• The BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS and OS will be summarized by	N/A

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
and uninjected lesions, DCR, PFS, and OS by primary tumor type.	primary tumor type. The ORR/DRR/DCR will be estimated with the associated 95% CI. Tumor response endpoints may also be evaluated based on modified RECIST v 1.1 for historical comparison for each tumor type that continues to Stage 2 of Part 2. • Kaplan-Meier (K-M) estimates of landmarks (e.g., 1-, 2-, and 3-year rates) and quartiles for DOR/PFS/OS will be provided (Kaplan and Meier, 1958). Greenwood's formula (Kalbfleisch and Prentice, 1980) for standard error will be used to calculate CIs for landmark K-M rates. CIs for K-M quartiles will be estimated (Brookmeyer and Crowley, 1982). • Waterfall plots for maximum tumor burden decrease in the lesion diameter at subject-level and lesion-level will also be provided. • Analysis for response rate in injected vs. uninjected lesions may show the evidence of systemic effect separately in Part 2. Analysis of response at lesion-level will be conducted by lesion type (injected vs. uninjected and liver vs. non-liver), and overall, if appropriate. Wilson's score method with continuity correction (Newcombe, 1998) will be used to calculate an approximate exact CI for between-group differences in binary rates if appropriate.	

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Part 2:

• ORR per modified irRC-RECIST with intrahepatic injection of talimogene laherparepvec into liver tumors in combination with systemic IV administration

of pembrolizumab separately by tumor type (hormone receptor positive BC, TNBC, CRC, CSCC, BCC, without viral hepatitis)

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Part 1:

• ORR, BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS separately for non-HCC and HCC tumors in monotherapy and combination cohorts

Part 2:

• BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS by primary tumor type arm

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Part 1 and Part 2:

Table 9-4. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Part 1: **Monotherapy cohorts 1-4: Subject incidence of DLTs with intrahepatic injection of talimogene laherparepvec into liver tumors in subjects with non-HCC with liver metastases and subjects with HCC without active viral hepatitis.** **Combination cohorts 5 and 6: Subject incidence of DLTs with intrahepatic injection into liver tumors of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab in subjects with non-HCC with liver metastases and subjects with HCC with and without viral hepatitis.**	The subject incidence of DLT will be summarized as a binary variable using the DLT analysis set.	N/A

Part 2: **Subject incidence, for each tumor type arm, of treatment-emergent and treatment-related adverse events, including DLTs.**	The subject incidence of DLT will be summarized as a binary variable using the DLT analysis set.	N/A

9.6.2 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **24.1** or later will be used to code all events categorized as adverse events, disease-related events to a system organ class and a preferred term. The CTCAE version 4.03 will be used to grade severity of AEs. All the safety analysis of adverse events will be evaluated in each monotherapy and combination cohorts in Part 1 (by cohort/group) and each tumor type separately in Part 2 (by tumor type arm/group).

The subject incidence of adverse events will be summarized for all treatment-emergent, treatment-related adverse events within the following categories: grade 3, grade 4, grades 3 or 4, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events.

Additional subject incidence tables will be presented to describe the treatment-emergent and treatment-related adverse events (including all adverse events, grade $\geq$ 3 adverse events, serious adverse events, fatal adverse events, adverse events of interest, adverse events requiring permanent discontinuation of study therapy, and local effects on the tumor[i.e., pain, inflammation and ulceration]). Summaries of treatment-emergent and serious AEs by preferred term will be provided in descending order of frequency. The subject incidence summaries will be provided in 2 ways: within system organ class (SOC) subset by preferred term, and by decreasing order of preferred term frequency. In addition, adverse events and treatment-related adverse events will be tabulated by worst grade within SOC subset by preferred term.

A summary of deaths after initiation of the study through 90 days since the last dose of talimogene laherparepvec or pembrolizumab, whichever is discontinued last will be provided.

Listings will be provided for treatment-emergent and treatment-emergent, treatment-related adverse events (including all adverse events, serious adverse events, fatal adverse events, and adverse events requiring permanent discontinuation of protocol

drug). In addition, screening SAEs prior to study Day 1 and all AEs > 30 (+/-7) days from last dose of study drug will be listed.

Adverse Events of Interest

Adverse events of interest are defined in a version-controlled Product Safety Analysis Plan (PSAP) for talimogene laherparepvec. The search terms of each event of interest (EOI) will be extracted based on the most recent version of the PSAP prior to the database snapshot for the analysis. Versions of the PSAP and MedDRA used for the EOI analysis will be documented in clinical study report(s). All the safety analysis of talimogene laherparepvec adverse events of interest (EOI) and pembrolizumab events of clinical interest (ECI) will be evaluated in each monotherapy and combination cohorts in Part 1 (by cohort/group) and each tumor type separately in Part 2 (by tumor type/group). The subject incidence of treatment-emergent and treatment-emergent, treatment-related EOIs and ECIs (including all events of interest, serious events of interest, non-serious events of interest) according to the EOI search strategy categories and ECI categories will be summarized.

In addition, EOI and ECI may be tabulated by worst grade within EOI category and ECI category by preferred term respectively. A table summarizing the incidence of all treatment-emergent adverse events of interest will also be provided by EOI category and ECI category as a high level summary.

Subject Incidence of Detectable Talimogene Laherparepvec in Blood and Urine

The analysis will be based on the Blood Evaluable Analysis Set in which proportions of subjects that meet the criteria of detectable (defined as positive result by qPCR analysis) DNA in blood will be calculated. The point-wise exact 95% confidence intervals for binomial proportions using the F-distribution (Leemis and Trivedi, et al, 1996) from SAS® PROC FREQ procedure with the binomial option will also be calculated. Similar analysis of incidence of talimogene laherparepvec DNA detected in the urine will be repeated using the Urine Evaluable Analysis Set.

A detailed listing of qPCR results for subjects with detectable talimogene laherparepvec DNA per qPCR timepoints during the first 4 cycles and safety follow-up will be provided.

The analysis will be based on available cases; that is, subjects who do not have blood sample (or urine sample for respective analysis) collected at the respective time points will be excluded from the analysis for that time point.

Incidence of Clearance of Talimogene Laherparepvec DNA in Blood and Urine

The number and proportion of subjects with undetectable talimogene laherparepvec DNA per qPCR in blood among subjects with sample collected in each cycle will be presented. Incidence of clearance of talimogene laherparepvec DNA from Cycle 1, 2 and 3 in blood will be calculated by cycle. The exact 95% CI for the binomial proportions using the F-distribution will be calculated. The analysis of clearance of talimogene laherparepvec in the blood will include subjects in the Blood Clearance Analysis Set. The analysis will be repeated using the Urine Clearance Analysis Set to evaluate clearance in the urine.

In addition, the analysis of incidence of clearance at Day 8 ((± 2 days) of each cycle for cycles 1, 2, and 3 will be repeated by baseline HSV-1 serostatus (i.e., seropositive and seronegative) among subjects with known HSV-1 status at baseline. The difference in clearance rate at Day 8 for cycles 1, 2, and 3 will be provided. The corresponding 95% confidence interval will be based on the Wilson's score method with continuity correction (Newcombe, 1998).

Rate and Subject Incidence of Talimogene Laherparepvec DNA Detection and Viral Detection on the Exterior of Occlusive Dressing

The subject incidence of positive qPCR and subsequent positive plaque testings will be evaluated from swabs of occlusive dressings. The number and proportion of subjects who have at least 1 positive qPCR result from the exterior of occlusive dressing swabs and the number and proportion of subjects exhibiting detectable virus from subsequent plaque testings will be presented. Numeric results of positive qPCR, and separately for positive plaque analysis, will be summarized as a continuous variable.

A detailed listing of qPCR and subsequent plaque results for subjects having a positive qPCR testing will be provided.

The analysis of this endpoint will be based on the Exterior of Occlusive Dressing Evaluable Analysis Set.

Rate and Subject Incidence of Talimogene Laherparepvec DNA Detection and Viral Detection at the Skin Surface of Injections

The subject incidence of positive qPCR and subsequent positive plaque assays will be evaluated from swabs of skin surface of injections. The number and proportion of subjects who have at least 1 positive qPCR result from at the skin surface of the injected

lesions and the number and proportion of subjects exhibiting detectable virus from subsequent plaque testings will be presented. Numeric results of positive qPCR testings, and separately for positive plaque analysis, will be summarized as a continuous variable.

A detailed listing of qPCR and subsequent plaque results for subjects having a positive qPCR testing will be provided.

Analysis of this endpoint will be based on the skin surface of the Injected Lesion Evaluable Analysis Set.

Rate and Subject incidence of Talimogene Laherparepvec DNA Detection and Viral Detection in Oral Mucosa

The subject incidence of positive qPCR and subsequent positive plaque assays will be evaluated from swabs of oral mucosa. The number and proportion of subjects who have at least 1 positive qPCR result from oral mucosa and number and proportion of subjects exhibiting detectable virus from subsequent plaque testings will be presented. Numeric results of positive qPCR, and separately for plaque analysis, will be summarized as a continuous variable.

A detailed listing of qPCR and subsequent plaque results for subjects having a positive qPCR testing will be provided.

Analysis of this endpoint will be based on the Oral Mucosa Evaluable Analysis Set.

Rate and Subject Incidence of Detectable Talimogene Laherparepvec DNA per qPCR in Suspicious Lesions to be Herpetic in Origin

This rate will be calculated based on the Reactive Swab Analysis Set.

The subject incidence will be reported for positive qPCR for talimogene laherparepvec DNA detection in any swab of a lesion suspected to be herpetic in origin. The analysis will be based on the Reactive Swab Analysis Set. A detailed listing of qPCR results for subjects having a positive qPCR testing will be provided. In addition, a listing for all subjects in the Reactive Swab Analysis Set will be provided with reported treatment-emergent adverse events (including preferred term, verbatim term, start and end dates, duration, grade, seriousness, and relationship to IP), and qPCR result (Y/N).

Reporting of Suspected or Known Unintended Exposure to Talimogene Laherparepvec and Herpetic Illness in Close Contacts and Healthcare Providers

Potential or known unintended exposure to talimogene laherparepvec, and any related suspected signs or symptoms in a subject's close physical contact, household member, caregiver, or healthcare provider will be reported. If consent of a close contact or healthcare provider is provided, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec in suspicious lesions. The positive qPCR for talimogene laherparepvec DNA detection from suspicious lesions will be reported. These individual cases in secondary contacts will be reported with separate ID numbers to distinguish them from subjects' data. More details will be provided in a program-level SSAP for unintended exposure to talimogene laherparepvec.

Disease-related Events

A sensitivity analysis of treatment-emergent adverse events will be conducted that considers any disease-related events as an adverse event if the disease-related event was reported in the study for any subject as a treatment-emergent adverse event. Subject incidence of disease-related events will be summarized for all treatment-emergent disease-related events, fatal disease-related events, serious disease-related events, disease-related events leading to withdrawal from study drug, and significant disease-related events will be provided separately as a sensitivity analysis.

9.6.3 Laboratory Test Results

Lab-defined lower and upper limits of normal ranges will be used for chemistry, hematology, coagulation, immunology, and toxicology laboratory tests. NCI Common Toxicity Criteria (CTC) version 4.03 grading will be used. Laboratory results will be summarized with descriptive statistics at baseline and selected time points. Grade shifts in important laboratory results from baseline to worst on-protocol value will be presented. The incidence of post-baseline laboratory abnormalities will be provided.

9.6.4 Vital Signs

Descriptive analyses of temperature, blood pressure**,** respiratory rate, and heart rate will be conducted at baseline and selected time points.

9.6.5 Physical Measurements

Descriptive analyses of temperature, blood pressure**,** respiratory rate, and heart rate will be conducted at baseline and selected time points.

9.6.6 Exposure to Investigational Product

In Part 1, descriptive statistics will be produced to describe the exposure to Amgen investigational product talimogene laherparepvec and non-Amgen investigational product pembrolizumab by cohort/group (non-HCC vs HCC vs overall). Subjects in **cohort 1** to cohort 4 will be exposure to monotherapy treatment.

In Part 2, descriptive statistics will be produced to describe the exposure to Amgen investigational product talimogene laherparepvec and non-Amgen investigational product pembrolizumab by tumor type/group (non-HCC vs HCC vs overall).

Summary statistics for exposure to talimogene laherparepvec or/and pembrolizumab, including total doses administered, total volume administered, treatment visits with IP MTV <= 4ml, treatment visits with MTV volume > 4ml, duration from the first to the last administration of talimogene laherparepvec, and the average volume received by subject per visit will be provided and will be separated by the first (concentration of 10^6 PFU/ml) and subsequent doses. The subject incidence rate and reasons for IP delays, missed treatment, and withdrawal will be tabulated.

9.6.7 Exposure to Other Protocol-required Therapy

Summary statistics for subjects in the Full Analysis Set who undergo on-protocol surgery including any surgery/procedure performed, type of procedure, and intent of surgery (e.g., palliative) will be provided.

9.6.8 Exposure to Concomitant Medication

Concomitant medications include all medications received during the treatment period other than the protocol drug. The number and proportion of subjects receiving any concomitant medications during the treatment period will be summarized by preferred term as coded by the World Health Organization Drug (WHO DRUG) dictionary. A list of selected medications and their groupings are provided.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

A separate SSAP will be prepared for the exploratory endpoints and this analysis may be reported separately.

Enter Analyses of Health Economic Endpoints

[redacted]

10. Changes From Protocol-specified Analyses

N/A

11. Literature Citations / References

Clopper, C.; Pearson, E. S. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika.* 1934:26:404–413.

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Brookmeyer, R. and Crowley, J. A Confidence Interval for the Median Survival Time. *Biometrics.* 1982:38:29–41.

Kalbfleisch, J.D. and Prentice, R.L. The Statistical Analysis of Failure Time Data, *New York: John Wiley & Sons*. 1980

Leemis LM, Trivedi, KS. A comparison of approximate interval estimates for the Bernoulli parameter. *The American Statistician.* 1996;50:63-68.

Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998:17:873-890.

Atkinson AN and Brown BW. Confidence Limits for Probability of Response in Multistage Phase II Clinical Trials. Biometrics. 1985;41 : 741-744.

12. Prioritization of Analyses

N/A

13. Data Not Covered by This Plan

N/A

14. Appendices

Appendix A. Reference Values/Toxicity Grades

CTCAE v. 4 grading scale will be used for adverse event coding:

1 – Mild

2 – Moderate

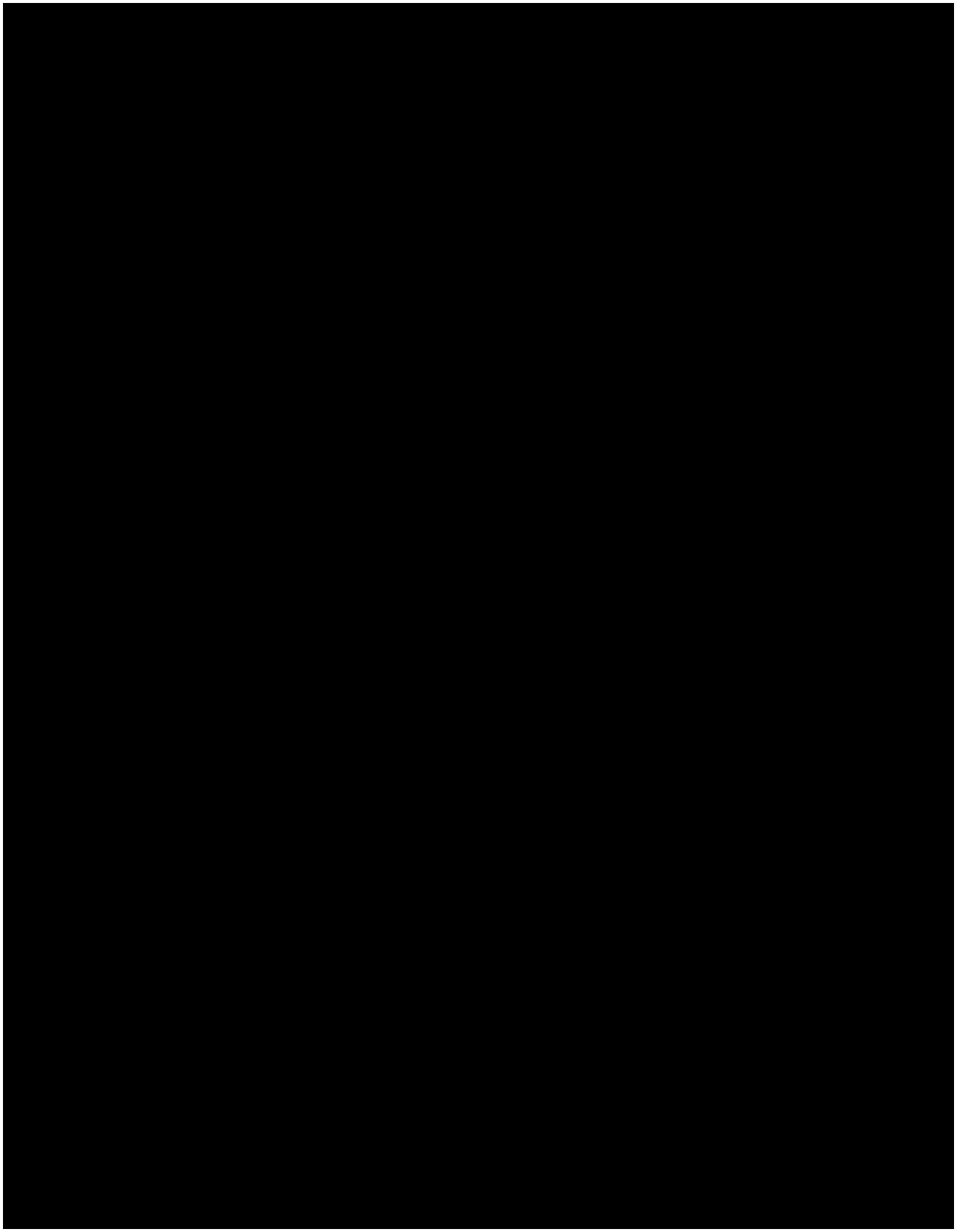
3 – Severe

4 – Life-threatening

5 – Death

Enter Appendix Concomitant Medications

[redacted]



Appendix C. Wilson's Score Method with Continuity Correction in Calculating the 95% Confidence Intervals for Difference in 2 Independent Proportions

The following formula of interval estimation is extracted from Newcombe 1998 paper:

Assuming

$$X_i \overset{i.i.d.}{\sim} Bernoulli\ (\pi_1), where\ i = 1, 2, ..., m.$$

$$Y_j \overset{i.i.d.}{\sim} Bernoulli\ (\pi_2), where\ j = 1, 2, ..., n.$$

$$\theta = \pi_1 - \pi_2$$

$$\hat{\pi}_1 = \sum_{i=1}^{m} x_i / m = a / m\ .$$

$$\hat{\pi}_2 = \sum_{j=1}^{n} y_j / n = b / n\ .$$

Then the 100(1- α)% confidence interval for $\hat{\theta} = \hat{\pi}_1 - \hat{\pi}_2 = a/m - b/n$, with continuity correction is

$$\delta = \sqrt{\{(a/m - l_1)^2 + (u_2 - b/n)^2\}}$$

$$\varepsilon = \sqrt{\{(u_1 - a/m)^2 + (b/n - l_2)^2\}}$$

l_1 and u_1 delimit the interval $\{\pi_1 : |\pi_1 - a/m| - 1/(2m) \le z_{1-\alpha/2}\sqrt{\pi_1(1-\pi_1)/m}\}$ and l_2 and u_2 delimit the interval $\{\pi_2 : |\pi_2 - b/n| - 1/(2n) \le z_{1-\alpha/2}\sqrt{\pi_2(1-\pi_2)/n}\}$.

Appendix D. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

D.1 Sample Posterior Probability Calculation

```
%macro bayb1s (as    = ,    /* Standard beta a                */
               bs    = ,    /* Standard beta b                */
               ce    =,   /* Exp beta precision             */
               delta =,   /* Exp mean - std mean            */
               n     =,  /* 1-arm study sample size        */
               x     =,   /* # responders                   */
               dmin  = 0,   /* Plot delta min                 */
               dmax  = 30,  /* Plot delta max                 */
               dby   = 5,   /* Plot delta increment           */
               alpha =0.10 /* 100-alpha credible intervals    */);

*** Prior distributions for standard and experimental ***;
data _null_;
  * Prior for standard (s) ;
  as    = &as;
  bs    = &bs;
  ms    = as/(as+bs);    * mean of single agent ;
  Bsc   = beta(as,bs);

  * Prior for experimental (e) ;
  ce    = &ce;           * Concentration parameter (sample size) ;
  delta = &delta;        * Absolute rate increase over standard ;
  ae    = ce*(ms + delta/2);
  be    = ce*(1 - (ms + delta/2));
  me    = ae/(ae+be);    * Mean of experimental ;

  call symput('ms',trim(left(put(ms,6.4))));
  call symput('Bsc',Bsc);
  call symput('ae',trim(left(put(ae,6.4))));
  call symput('be',trim(left(put(be,6.4))));
  call symput('me',trim(left(put(me,6.4))));
run;


*** Experimental posterior distribution ***;
data combo_post;
  ae_p=&ae+&x;
  be_p=&be+&n-&x;
  me_p=ae_p/(ae_p+be_p);

  * 95% credible interval for experimental ORR ;
  cr_ll=betainv(0.025,ae_p,be_p);
  cr_ul=betainv(0.975,ae_p,be_p);

  call symput('ae_p',trim(left(put(ae_p,6.2))));
  call symput('be_p',trim(left(put(be_p,6.2))));
  call symput('me_p',trim(left(put(me_p,6.4))));
run;

proc print data=combo_post noobs;
  var ae_p be_p me_p cr_ll cr_ul;
  title1 "Prior standard Beta(&as,&bs), mean=&ms; Prior experimental
Beta(&ae,&be), mean=&me";
  title1 "Experimental posterior ORR 95% Credible Region";
  title2 "N=&n, X=&x";
run;
```

```
*** Plot of experimental prior and posterior ***;
data plot;
  * Prior ;
  lab='Prior    ';
  Bec = beta(&ae,&be);
  do x=0 to 1 by .001;
    if x le 1 then f=(x**(&ae-1)) * ((1-x)**(&be-1))/Bec;
    output;
  end;
  * Posterior ;
  lab='Posterior';
  Bec_p = beta(&ae_p,&be_p);
  do x=0 to 1 by .001;
    if x le 1 then f=(x**(&ae_p-1)) * ((1-x)**(&be_p-1))/Bec_p;
    output;
  end;
run;

axis1 minor=none value=(h=2.25) length=65
  label=(a=90 h=2.5 'Beta Density');
axis2 label=(h=2.5 'Objective Response Rate') minor=none value=(h=2.25)
  order=(0 to 1 by .1);
symbol1 v=none w=2 i=spline line=1 c=blue;
symbol2 v=none w=2 i=spline line=2 c=black;
legend1 label=none value=(h=2.25 j=l) down=2 mode=share
  position=(inside top middle);
title; footnote;

data _null_;
  set combo_post;
  call symput('cr_ll',trim(left(put(cr_ll,6.2))));
  call symput('cr_ul',trim(left(put(cr_ul,6.2))));
run;

filename gf   "&prefix.Exp_prior_post.emf";
proc gplot data=plot;
  plot f * x = lab
    / vaxis=axis1
      haxis=axis2 noframe
      legend=legend1;
  note h=2.25
    move=(70,73) 'Prior'
    move=(70,70) "Beta (&ae, &be)"
    move=(70,67) "Mean = &me"
    move=(70,61) 'Posterior'
    move=(70,58) "Beta (&ae_p, &be_p)"
    move=(70,55) "Mean = &me_p"
    move=(70,52) "95% CR: &cr_ll, &cr_ul";
run; quit;


*** Calculate posterior prob. exp ORR >= std ORR + delta ***;
%macro suba;
data inc;
  retain rec 0;
  do c=&dmin to &dmax by &dby;
    d=c/100;
    rec+1;
    output;
  end;
run;
%macro n_obs(ds    =, /* Dataset                 */
             whr   =, /* Where clause            */
             n_var =  /* Name of output variable */ );
```

```
%global &n_var;
data n_obs_;
  set &ds
    %if &whr ne %then %do;
     (where=(&whr))
      %end; ;
data _null_;
  dsid=open("n_obs_");
  nobs=attrn(dsid,"nobs");
  call symput("&n_var",trim(left(put(nobs,8.0))));
run;
%mend n_obs;
%n_obs(ds=inc,whr=,n_var=n_obs);

%do i=1 %to &n_obs;
  data _null_;
    set inc (where=(rec=&i));
    call symput('d',trim(left(put(d,6.4))));
    call symput('ul',trim(left(put(1-d,6.4))));
  run;

  proc iml;
    start fun(x);
      v = (1-probbeta(x+&d,&ae_p,&be_p)) * (x**(&as-1)) * ((1-x)**(&bs-
1))/&Bsc;
      return(v); finish;

    * Prob. Exp ORR >= Std + delta ;
    lim = {0 &ul};
    call quad(pr,"fun",lim);

    create p1 from pr  [colname='pr_d']; append from pr; close p1;
  quit;
  data t; set p1; d=&d+0; n=&n+0; x=&x+0; rate=x/n; run;

  %if &i=1 %then %do;
    data prs; set t; run;
  %end;
  %else %do;
      data prs; set prs t; run;
  %end;
%end;

proc print data=prs noobs label split='\';
  var d pr_d;
  title 'Posterior probability Exp ORR >= Std ORR + delta';
  label d='Delta' pr_d='Prob\Exp-Std ORR\>=Delta';
  format pr_d 8.3;
run;
%mend suba;
%suba;


*** Posterior mean and equal-tail credible interval for delta ***;
data dat;
  arm=2; n=&n+0; y=&x+0;
run;

ods output PostIntervals=PostInt PostSummaries=PostSum;
*ods listing gpath="&gpath" image_dpi=150;
*ods graphics on / imagefmt=wmf imagename="Post" reset=index width=4.5in
height=3in;
proc mcmc data=dat outpost=post
    seed=11810 nbi=1000 mintune=4 maxtune=24 ntu=2000
    nmc=50000 thin=1
```

```
    monitor=(_parms_ pe_pc) diagnostics=all
    stats(alpha=&alpha)=all
    /*plots=(trace autocorr density)*/;

  parms pc pe;
  prior pc ~ beta(&as, &bs);
  prior pe ~ beta(&ae, &be);

  pe_pc = pe - pc;

  if arm=1 then llike=lpdfbin(y,n,pc);        * logL of standard *;
  else if arm=2 then llike=lpdfbin(y,n,pe);   * logL of experimental *;

  model general(llike);
run;
*ods graphics off;

data post;
  merge postint (where= (parameter='pe_pc') keep=parameter alpha CredibleLower
CredibleUpper)
        postsum (where= (parameter='pe_pc') keep=parameter mean);
  by parameter;
  n=&n+0; x=&x+0; rate=x/n;
data _null_;
  call symput('cr',trim(left(put(100-&alpha*100,8.0) )));
run;
proc print data=post noobs label;
  var parameter mean alpha CredibleLower CredibleUpper;
  title "Delta &cr% Credible Interval";
run;
%mend baybls;
```

D.2 Two Stage Confidence Interval by Atkinson and Brown

```
%macro cal (n1=10, /*first stage sample size*/
            n=, /*total number of subjects enrolled*/
                    c1=2, /*critical value for rejection in the first stage */
                    c=, /*the total number of responses observed */
                    alpha=0.05 /*100-alpha credible intervals*/);

data m1;
n1=&n1;
n2=&n-n1;
c1=&c1;
do theta =0 to 1 by 0.0001;
   do j= c1 to &c;
     if j=c1 then do; y1=cdf('BINOM', c1, theta, n1);
        output;
        end;
      else   do;
      do i=c1+1 to j;
          y1=pdf('BINOM', i, theta, n1)*pdf('BINOM', j-i, theta, n2);
            output;
        end;
        end;
   end;
  end;
run;

proc sql ;
create table sum as
select distinct n1, n2, c1, theta, sum(y1) as sum1
from m1
```

```
group by theta
having calculated sum1 >= &alpha/2
order by  theta desc
;
create table sum2 as
select distinct n1, n2, c1, theta, sum(y1) as sum2
from m1
where j ne 5
group by theta
having  calculated sum2 <= (1-&alpha/2)
;

data _null_;
set sum ;
if _n_=1 then call symput ("Upper_Limit", theta);
run;

data _null_;
set sum2 ;
if _n_=1 then call symput ('Low_Limit', theta);
run;

%put &Low_Limit &Upper_Limit;
%mend;
```