
STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated with Talimogene Laherparepvec

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Table of Abbreviations

Abbreviation/Acronym	Definition
AE	Adverse event
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computerized Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Toxicity Criteria for Adverse Events
DMP	Data management plan
DOR	Duration of Response
DRR	Durable Response Rate
DTP	Data transfer plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	Event of Interest
HR	Hazard ratio
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus type 1
IP	Investigational product
IPD	Important protocol deviation
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
ND	Not done
NPV	negative predictive value
OR	Objective response (CR or PR)
ORR	Objective response rate
PD	Progressive disease
PFU	Plaque-forming unit
PPV	positive predictive value
PR	Partial response
PT	Preferred term
qPCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation/Acronym	Definition
SD	Stable disease
SMQ	Standardized MedDRA Queries
SOC	System organ class
SOP	Standard Operating Procedure
TTF	time to treatment failure
UE	Unevaluable for tumor response
ULN	Upper limit of normal
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

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 20120325 entitled “A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated with Talimogene Laherparepvec”.

The scope of this plan includes the primary analysis that is planned and will be executed by the Biostatistics department at Amgen unless otherwise specified. A separate SSAP will be prepared for the exploratory objectives and these analysis may be reported separately.

2. Objectives

Primary Objective:

The primary objective of the statistical analysis is to explore the correlation between a baseline immunoprofile (ie, intratumoral CD8+ cell density) and objective response rate (ORR) in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec.

Secondary Objective(s):

The secondary objectives are as follows:

- to explore the correlation between baseline intratumoral CD8+ cell density and durable response rate (DRR), duration of response (DOR), and changes in tumor burden
- to explore the correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden
- to evaluate ORR, DOR, time to treatment failure (TTF), DRR, OS, and change in tumor burden during treatment
- to evaluate the safety and tolerability of talimogene laherparepvec

Exploratory Objective(s):

The exploratory objectives are as follows:

- to investigate the correlation between the changes in the population of tumor specific cytotoxic T cells and immunoscore during treatment and clinical response

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3. Protocol Overview

3.1 Protocol Design

This is a phase 2, multicenter, open-label, single-arm study CCI

Subjects will be treated with talimogene laherparepvec until the subject has achieved a complete response, all injectable tumors have disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria (WHO handbook for reporting results of cancer treatment, 1979; refer to Appendix D of the protocol), or intolerance of study treatment, whichever occurs first.

Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival every 12 weeks (\pm 28 days) for up to approximately 24 months after the last subject is enrolled. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments (Table 2 of the protocol). Tumor biopsies will be performed on an uninjected lesion on day 1 of week 1, on a different uninjected lesion at week 6 (if available), and at disease progression (PDn or PDr beyond 6 months of treatment) on the lesion responsible for PD as outlined in Section 7.2.2 of the protocol. Blood and tumor tissue samples will be analyzed to explore if an immunoprofile at baseline and its change during treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec. The primary immunoprofile will be tumor cell CD8+ density.

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

3.2 Sample Size

Participants in this clinical investigation shall be referred to as "subjects". Approximately 110 subjects will be enrolled in the study. Refer to Section 10.2 of the protocol for sample size considerations.

4. Protocol Endpoints and Covariates

4.1 Protocol Endpoints

4.1.1 Primary Endpoint

- Correlation between a baseline immunoprofile (ie, intratumoral CD8+ cell density) and objective response rate (ORR)

4.1.2 Secondary Endpoints

- Correlation between a baseline immunoprofile (ie, intratumoral CD8+ cell density) and durable response rate (DRR), and duration of response (DOR), and changes in tumor burden
- Correlation between changes in an immunoprofile during treatment (in injected and uninjected lesions) and ORR, DRR, DOR, and changes in tumor burden
- Efficacy Endpoints: ORR, DOR, time to treatment failure (TTF), DRR, OS, and change in tumor burden during treatment
- Safety Endpoints: subject incidence of treatment-emergent and treatment-related adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, events of interest, adverse events requiring the discontinuation of study drug), clinically significant laboratory changes, and incidence of symptomatic herpetic lesions that are positive for talimogene laherparepvec

4.1.3 Exploratory Endpoints

- Correlation between the changes in the population of tumor specific cytotoxic T cells during treatment and clinical response

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5. Hypotheses

No formal statistical hypothesis will be tested.

6. Definitions

The definitions of primary endpoints are provided in [Section 4](#).

Additional definitions are as follows:

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 ETO system.

Investigational Product

Investigational product (IP) refers to talimogene laherparepvec in this study.

Study Drug

Study drug refers to talimogene laherparepvec in this study.

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 Date 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 the study drug is 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).

Disease Control Rate(also called the **Clinical Benefit Response Rate**)

Disease control rate is the proportion of subjects that have a best overall response in one of the following: CR/ PR/SD.

Time to Treatment Failure (TTF)

Time to treatment failure is calculated from first dosing until one or more of the following:

- (1) clinically relevant disease progression(PDr);
- (2) death from any cause;
- (3) non-clinically relevant disease progression (PDn) associated with a requirement for

alternative therapy as the reason for ending treatment or start of new anti-cancer therapy. Subjects without an event will be censored at their last evaluable tumor assessment.

This TTF definition is a modified definition of progression free survival (PFS). We do not penalize stopping treatment for CR or lack of injectable disease. In addition, the confirmation of PD is not required.

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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.

Treatment-emergent Adverse Events

Treatment-emergent adverse events are defined as any adverse event occurring after initiation of the first dose of IP through 30 days after the last administration of IP in the study. 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 talimogene laherparepvec and the check box indicating prior to the first dose of IP is checked, then the event will not be counted as a treatment-emergent AE).

Exposure-adjusted Subject Incidence

Exposure-adjusted subject incidence is defined as the number of subjects experiencing a specific event divided by their total subject-time at risk (summation of the time from first drug exposure to first event for subjects with at least one event or to death/end of study/30 days after last IP dose, whichever occurs first for subjects without the event).

Exposure-adjusted Event Rate

Exposure-adjusted event rates is defined as the number of occurrences that subjects experience of a specific event divided by their total subject-time at risk (summation over all subjects). Multiple occurrences of the same event for a subject are counted as events. For each subject, the time at risk will be defined as the start date of IP to death/end of study/30 days after last IP dose, whichever occurs first.

On-study Surgery/procedure

On study surgeries or procedures are defined as surgeries or procedures performed during the treatment period.

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.

7. Analysis Subsets

Safety Analysis Set: The safety analysis set will include all subjects who have received at least 1 dose of talimogene laherparepvec. The efficacy analysis and safety analysis will be performed on the safety analysis set.

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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.

8. Covariates and Subgroups

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

- Region, if applicable (by countries)
- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Disease stage at baseline: IIIB and IIIC vs IVM1a vs IVM1b vs IVM1c
- Baseline LDH ≤ ULN vs > ULN
- Sex (Female vs Male)
- ECOG (0 vs 1)

9. Interim Analysis

No interim analysis is planned.

10. Data Screening and Acceptance

10.1 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. 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.

10.2 Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management (CDM) department will provide all data to be used in the planned analyses. This protocol will use the RAVE database. In addition, blood and/or tumor tissue samples for CCI, 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. Analysis results of these samples will be transferred to Amgen CDM on a regular basis as per a Data Transfer Plan (DTP) and will be stored on the CDM server.

10.3 Handling of Missing and Incomplete Data

Adverse events with missing severity, seriousness, and/or possible relationship to talimogene laherparepvec should not be imputed for study analyses. Missing data should be queried and resolved. CCI

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

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10.4 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 9.3 or later.

11. Statistical Methods of Analysis

11.1 General Principles

The main goals of this analysis are: (1) to better understand the distribution of intratumoral CD8+ cell density in the overall population and in subgroups; (2) to explore associations among baseline/change in intratumoral CD8+ cell density and efficacy endpoints; and (3) to explore the clinical potential utility of intratumoral CD8+ cell density cut-off values for patient selection.

Changes in intratumoral CD8+ cell density will be analyzed overall and separately for injected and uninjected lesions.

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. P-values will be used mainly as a descriptive measure suggesting comparative strength of association rather than to test hypotheses. Accordingly, nominal p-values will be generated with no adjustment for multiplicity. Analyses will be based on the Safety Analysis Set unless otherwise specified.

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following are some general principles which will be followed to handle such issues for efficacy analyses.

- It is desirable for subgroups to have 10 or more subjects for each dichotomization or categorization scheme, though judgment may be applied.
- Analyses will be more carefully considered for robustness of results (e.g., K-M curves, model building, comparison between subgroups) when some subgroups have a small number of subjects and/or when there are few events for time-to-event endpoints..

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11.3 Efficacy Endpoints

The efficacy analysis will be conducted using the safety analysis set unless otherwise specified. The ORR/ DRR/ Disease control rate will be estimated with the associated exact 95% CI (Clopper and Pearson, 1934). Wilson's score method with continuity correction (Newcombe, 1998) will be used to calculate an approximation of the exact CI for between-group differences in binary rates. Kaplan-Meier (K-M) estimates of landmarks (e.g., 1-, 2-, and 3-year rates) and quartiles for DOR, time to treatment failure and 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). In addition, changes in tumor burden for responders will also be summarized.

11.4 Correlation Between Clinical Response and Baseline/Change in Intratumoral CD8+ Cell Density

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11.6 Important Protocol Deviations

Important Protocol Deviation (IPD) categories are defined by the protocol team before the first subject's visit and updated during the IPD reviews throughout the protocol prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the protocol.

Eligibility deviations are defined in the protocol.

11.7 Analysis of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or later will be used to code AEs to a system organ class (SOC) and a preferred term (PT) within the SOC. The CTCAE version 3.0 will be used to grade severity of AEs.

A table will be provided with a high-level summary of the subject incidence of any treatment-emergent adverse event and any treatment-emergent, treatment-related adverse event within the following categories: grade 3, grade 4, grades 3 or 4, fatal adverse events; serious; and leading to permanent discontinuation of protocol drug.

Additional subject incidence tables will be presented to describe the treatment-emergent and treatment-related adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events of interest, adverse events requiring permanent discontinuation of protocol drug, and local effects on the tumor[ie, pain, inflammation and ulceration]). Summaries of treatment-emergent and serious AEs occurring in at least 1% of the subjects by preferred term will be provided in descending order of frequency. The subject incidence summaries will be provided in 2 ways: within 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.

Exposure-adjusted subject incidence and exposure-adjusted event rates may be estimated for specific AEs.

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 days from last dose of study drug will be listed.

11.7.1 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 primary analysis. Versions of the PSAP and MedDRA used for the EOI analysis will be documented in clinical study report(s). The subject incidence of treatment-emergent and treatment-emergent, treatment-related events of interest (including all events of interest, serious events of interest, non-serious events of interest) according to the EOI search strategy categories will be summarized.

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

11.7.2 Detectable Talimogene Laherparepvec DNA per qPCR in Suspicious Lesions

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. 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.

11.7.3 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 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.

11.7.4 Laboratory Test Results

Lab-defined lower and upper limits of normal ranges will be used for chemistry and hematology laboratory tests. NCI Common Toxicity Criteria (CTC) version 3.0 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.

11.7.5 Vital Signs

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

11.7.6 Exposure to Talimogene Laherparepvec

Summary statistics for exposure to talimogene laherparepvec, including total doses administered, total volume administered, 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 (concentration of 10^8 PFU/ml). The subject incidence rate and reasons for IP delays, missed treatment, IP volume < 4 ml, and withdrawal will be tabulated.

11.7.7 Concomitant Medication, On-protocol Surgery or Procedure

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 terms as coded by the World Health Organization Drug (WHODRUG) dictionary.

Summary statistics for subjects in the Safety 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.

12. Changes From Protocol-specified Analyses

The following changes from the protocol are made in this document:

1. Remove the term “in injected and uninjected lesions” from the secondary objective: to explore the correlation between changes in an immunoprofile during treatment (in injected and uninjected lesions) and ORR, DRR, DOR, and changes in tumor burden. This revision is to avoid misleading.
2. The TTF definition is a modified definition of progression free survival (PFS). It is anticipated that we will change the endpoint from TTF to PFS in a future protocol amendment.

13. Literature Citations / References

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14. Appendices

Appendix A. Conventions for Clinical Data That Require Imputation for Partial or Missing Date

The following data will be imputed using the following algorithm:

- Adverse Events and Deaths
- Concomitant Medications

Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: yyyyymmdd		Partial: yyyyymm		Partial: yyyy		missing
		< 1 st dose	≥ 1 st dose	< 1 st dose yyyyymm	≥ 1 st dose yyyyymm	< 1 st dose yyyy	≥ 1 st dose yyyy	
Partial: yyyyymm	= 1 st dose yyyyymm	2	1	2	1	n/a	1	1
	≠ 1 st dose yyyyymm		2		2	2	2	2
Partial: YYYY	= 1 st dose YYYY	3	1	3	1	n/a	1	1
	≠ 1 st dose YYYY		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates:

- Initial imputation
 - For partial stop date mmyyyy, impute the last of the month.
 - For partial stop date yyyy, impute December 31 of the year.
 - For completely missing stop date, do not impute.

- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
- If the stop date imputation leads to a stop date that is before the start date, then set the stop date as missing.

Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
 - If mmyyyy for last contact date where subjects are known to be alive = mmyyyy for death date, set death date to the day after the last contact date.
 - If mmyyyy for last contact date where subjects are known to be alive < mmyyyy for death date, set death date to the first day of the death month.
 - If mmyyyy for last contact date where subjects are known to be alive > mmyyyy for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is totally missing, do not impute and censor the subject survival time.

Appendix B. 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

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

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

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

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

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

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

$$\delta = z_{1-\alpha/2} \sqrt{\{l_1(1-l_1)/m + u_2(1-u_2)/n\}}$$

$$\varepsilon = z_{1-\alpha/2} \sqrt{\{u_1(1-u_1)/m + l_2(1-l_2)/n\}}$$

l_1 and u_1 delimit the interval $\{\pi_1 : |\pi_1 - a/m| - 1/(2m) \leq z_{1-\alpha/2} \sqrt{\pi_1(1-\pi_1)/m}\}$ and

l_2 and u_2 delimit the interval $\{\pi_2 : |\pi_2 - b/n| - 1/(2n) \leq z_{1-\alpha/2} \sqrt{\pi_2(1-\pi_2)/n}\}$.