Janssen Research & Development *

Statistical Analysis Plan

A Phase 3, Multicenter, Randomized, Double-blind Placebo-controlled Study Evaluating the Efficacy and Safety of CNTO 1959 (Guselkumab) Delivered via a SelfDose™ Device in the Treatment of Subjects with Moderate to Severe Plaque-Type Psoriasis

Protocol CNTO1959PSO3006; Phase 3

CNTO 1959 (Guselkumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
DBL	database lock
DC	Discontinuation
ECG	Electrocardiogram
eCRF	electronic case report form
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
FDA	Food and Drug Administration
IGA	Investigator's Global Assessment
IgG1λ	immunoglobulin G1 lambda
IWRS	interactive web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NAbs	neutralizing antibodies
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PK	pharmacokinetic(s)
PQCs	product quality complaints
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SIAQ	Self-Injection Assessment Questionnaire

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analyses of efficacy, safety and pharmacokinetics for the guselkumab (CNTO 1959) clinical study CNTO1959PSO3006. Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that inhibits the biological activity of IL-23 and therefore has the potential for the treatment of psoriasis.

1.1. Trial Objectives

Primary Objectives

The primary objectives are:

- To evaluate the efficacy of guselkumab delivered using the SelfDose device for the treatment of subjects with moderate to severe plaque-type psoriasis.
- To assess the safety and tolerability of guselkumab delivered using the SelfDose device in subjects with moderate to severe plaque-type psoriasis.

Secondary Objectives

The secondary objectives are:

- To assess the PK and immunogenicity of guselkumab following SC administration using the SelfDose device in subjects with moderate to severe plaque-type psoriasis.
- To assess usability and acceptability of the SelfDose device.

1.2. Trial Design

This is a Phase 3, randomized, double-blind, multicenter, placebo-controlled study evaluating the efficacy, safety, PK, immunogenicity, usability, and acceptability of guselkumab delivered using the SelfDose device in subjects with moderate to severe plaque-type psoriasis. The target population is adult men or women, with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis defined by PASI ≥12, IGA ≥3, and involved body surface area (BSA) ≥10%. Subjects must be candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies (Protocol Inclusion Criteria, Exclusion Criteria) or phototherapy for psoriasis. Subjects with nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) are excluded. Subjects who have ever received guselkumab are also excluded.

Approximately 75 subjects who satisfy all inclusion and exclusion criteria will be randomized in a 4:1 ratio to 1 of 2 arms:

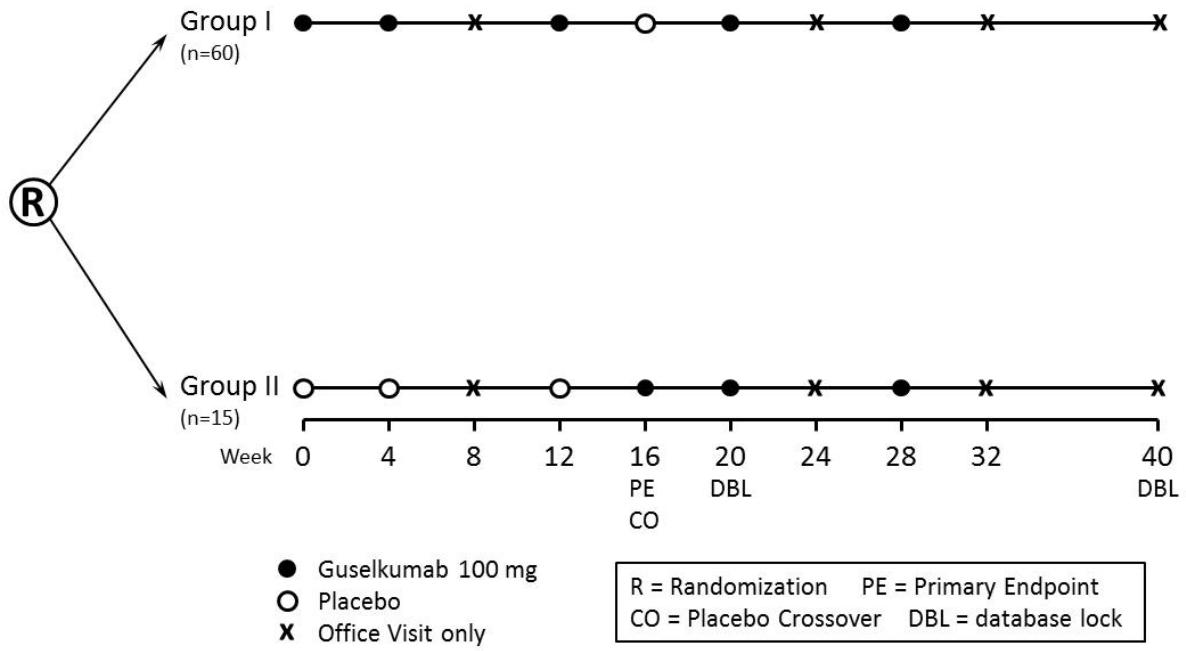
- **Group I** (n=60): guselkumab 100 mg at Weeks 0, 4, 12, 20, and 28; placebo at Week 16 to maintain the study blind.
- **Group II** (n=15): placebo at Weeks 0, 4, and 12; cross over to guselkumab 100 mg at Weeks 16, 20, and 28.

Week 28 is the last dosing visit; subjects will be followed for an additional 12 weeks and have a final safety visit at Week 40. The end of the study is defined as the time when last subject completes the Week 40 visit.

There are 2 database locks (DBLs) in this study, 1 at Week 20, and 1 at Week 40.

A diagram of the study design is provided below.

Schematic Overview of the Guselkumab SelfDose Device Study



1.3. Statistical Hypotheses for Trial Objectives

Primary Hypotheses:

The primary hypotheses are that guselkumab treatment delivered using the SelfDose device is superior to placebo as demonstrated by 1) the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 16; and 2) the proportion of subjects achieving a PASI 90 response at Week 16.

Major secondary hypotheses:

- Guselkumab treatment delivered using the SelfDose is superior to placebo as assessed by the proportion of subjects achieving an IGA score of cleared (0) at Week 16.
- Guselkumab treatment delivered using the SelfDose is superior to placebo as assessed by the proportion of subjects achieving a PASI 100 response at Week 16.

1.4. Sample Size Justification

This study is designed to evaluate the efficacy of guselkumab vs placebo using the SelfDose device.

The assumptions for the sample size and power calculations are based on the data from the guselkumab CNTO1959PSO2001 study:

- The proportion of placebo subjects who achieved a PGA score of cleared (0) or minimal (1) and a PASI 90 response was 10% and 5%, respectively. Note PGA was used in CNTO1959PSO2001. PGA is a similar measure to IGA which will be used in this study.
- The proportion of subjects who achieved a PGA score of cleared (0) or minimal (1) response at Week 16 was 86% in the guselkumab 100 mg group.
- The proportion of subjects who achieved a PASI 90 response at Week 16 was 62% in the guselkumab 100 mg group.

As shown in the table below, based on the above assumptions, with a total of approximately 75 subjects randomized in a 4:1 ratio to guselkumab 100 mg (n=60) and placebo (n=15), there will be at least 99% power to detect differences for both co-primary endpoints in the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) and the proportion of subjects who achieve a PASI 90 response between the placebo and guselkumab groups at Week 16, at a significance level of 0.05. This sample size was also chosen to provide adequate power for major secondary endpoints.

Table 1: Power to Detect a Treatment Effect Based on Different Proportions of Subjects Achieving the Co-primary Endpoints

Co-primary Endpoints		Power
IGA cleared (0) or minimal (1) response at Week 16		
Placebo (n=15)	Guselkumab 100 mg q8w (n=60)	
10%	70%	>99%
	75%	>99%
	80%	>99%
PASI 90 response at Week 16		
Placebo (n=15)	Guselkumab 100 mg q8w (n=60)	
5%	55%	99%
	60%	>99%
	65%	>99%

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; q8w=every 8 weeks.

1.5. Randomization and Blinding

1.5.1. Procedures for Randomization and Stratification

Central randomization will be implemented in this study. At Week 0, subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor. Permuted block randomization with stratification by country will be used. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

1.5.2. Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, study drug serum concentrations, antibodies to study drug, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken to subjects, investigators, or site monitors until the Week 40 database is locked and finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date of unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source document; the reason for unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. The decision to continue or discontinue study treatment for these subjects will be based upon consultation of the investigator with the medical monitor.

There are 2 DBLs in this study, 1 at Week 20, and 1 at Week 40. The sponsor, with exception of sponsor site monitors noted below, will be unblinded after the last subject has completed the Week 20 visit and the Week 20 DBL has occurred. The investigators, subjects, and sponsor site monitors will be unblinded after the last subject has completed the Week 40 visit, and the Week 40 DBL has occurred.

2. GENERAL ANALYSIS DEFINITIONS

This analysis plan provides the general analysis definitions and describes the planned subject information, efficacy, safety, pharmacokinetics, and antibody analyses for the two planned DBLs.

2.1. Imputation Rules for Partial or Missing AE Dates

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is the earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is in the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.

Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

Completely missing resolution dates will not be imputed.

2.2. Visit Windows

Nominal visits will be used for all by-visit analyses in the study unless otherwise specified, regardless of the scheduled visit window. The study visits scheduled should occur at the times delineated in the Time and Events Schedule of the protocol. All visits through Week 32 should occur within ±7 days of the scheduled visit. If a study visit occurs outside this window, the

sponsor should be consulted about how the subject should resume his/her normal dosing schedule relative to the baseline visit (Week 0). The Week 40 study visit should occur within +14 days of the scheduled visit.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set

For the efficacy analyses in this study, the full analysis set (FAS) will be used according to subjects' assigned treatment to which they were randomized, regardless of the treatment they actually received. The FAS includes all randomized subjects who received at least 1 injection of study agent. The full analysis set will be used for all primary and secondary efficacy analyses.

For subjects randomized to placebo, only subjects who crossed over to receive guselkumab at Week 16 will be included in the efficacy summaries for the visits after Week 16.

2.3.2. Safety Analysis Set

In contrast to the efficacy analysis set, safety analyses will be performed on the safety analysis set, which is defined as all randomized and treated subjects who received at least 1 injection of study agent (partial or complete) according to the actual treatment received during the study irrespective of the treatment assigned at randomization.

2.3.3. Pharmacokinetics Analysis Set

The PK analysis set is defined as subjects who received at least one injection of guselkumab and have at least one valid blood sample drawn for PK analysis.

2.3.4. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all subjects who received at least one injection of guselkumab and have appropriate samples for anti-guselkumab antibody detection.

In both PK and immunogenicity analyses, subjects will be analyzed according to the treatment they actually received, regardless of the treatments they are randomized to.

2.4. Definition of Subgroups

To evaluate the consistency of efficacy based on demographic characteristics, baseline disease characteristics, and psoriasis medication history, subgroup analyses will be performed for the co-primary endpoints. The subgroups for subgroup analyses include the following:

Baseline demographics:

- Sex (male, female)
- Race

- Baseline Age (<45 years, 45 to <65 years, ≥65 years)
- Baseline weight (≤90 kg, >90 kg)
- BMI (Normal [<25], Overweight [25 -<30], Obese [≥30])

Baseline disease characteristics:

- Age at diagnosis (years) (<25, ≥25)
- Psoriasis disease duration (years) (<15, ≥15)
- Baseline PASI (<20, ≥20)
- Baseline IGA (<4, =4)
- Baseline BSA (<20%, ≥20%)
- Psoriatic arthritis (Yes, No)

Psoriasis medication history:

- Phototherapy (ultraviolet B light [UVB] or psoralen and ultraviolet A light therapy [PUVA])
  - Never used
  - Ever used
- Non-biologic systemics (PUVA, MTX, cyclosporine, acitretin, apremilast, or tofacitinib)
  - Never used
  - Ever Used
- Biologics (etanercept, infliximab, alefecept, efalizumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, or adalimumab)
  - Never used
  - Ever Used
- Non-biologic systemics or biologics (as defined above)
  - Never used
  - Ever used

2.5. Statistical Methods

2.5.1. Study Day

Study Day 1 refers to the first study agent administration date. The study day for an event is defined as:

- Event date - (date of Study Day 1) +1, if event date is ≥ date of Day 1
- Event date - date of Day 1, if event date < date of Day 1

2.5.2. Baseline

In general, the baseline measurement is defined as the closest measurement taken prior to or at the time of the first study agent administration date unless otherwise specified.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No formal interim analysis is planned for this study. No data monitoring committee is commissioned for this study.

4. SUBJECT INFORMATION

The full analysis set and the safety analysis set will be used for the subject information analyses unless otherwise noted. The number of subjects in each analysis set will be summarized by treatment group and overall. In addition, the distribution of subjects by country, and site will be presented.

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data and no formal statistical analyses for comparisons of subject information between treatment groups will be performed. In addition, subject listings will also be used to present the data.

4.1. Demographics and Baseline Characteristics

4.1.1. Demographics

Table 2 presents a list of the demographic variables that will be summarized by treatment group, and overall for the full analysis set.

Table 2: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
Categorical Variables:	
Age (<45 years, 45 to <65 years, and ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (Normal [<25], Overweight [25 -<30], Obese [≥30])	

[a]If multiple race categories are indicated, then Race is recorded as "Multiple."

4.1.2. Baseline Characteristics

Psoriasis baseline disease characteristics (i.e., psoriasis disease duration [years], age at diagnosis [years], BSA [%], psoriatic arthritis, baseline IGA score, and baseline PASI score [0-72]) will be summarized by treatment group for the full analysis set.

4.2. Disposition Information

Screened subjects will be summarized overall.

The number of subjects in the following disposition categories will be summarized by treatment group and overall:

- Subjects randomized
- Subjects who received study agent
- Subjects who completed the study
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study

The above categories will include summaries over the period of Week 16, Week 20 and Week 40.

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely
- Subjects who were unblinded during the study period
- Subjects who were randomized yet did not receive study agent

4.3. Treatment Compliance

Study agent compliance will be summarized descriptively through Week 20 and Week 28 for the full analysis set. Number of subjects by randomized treatment versus actual treatment will be presented in a summary table.

4.4. Extent of Exposure

The exposure data will be summarized through Week 20 and through Week 28. The number and percentage of subjects who receive study agent will be summarized by treatment group for the safety analysis set. Descriptive statistics will be presented for the following parameters:

- Number of injections
- Cumulative total dose

In addition, the study agent lots received by treatment, including matching placebo for active treatment will be summarized.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or results of the clinical trial. Subjects with major protocol deviations will be identified prior to database lock and will be summarized by category by treatment group through Week 20 and through Week 40 for the full analysis set.

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received a disallowed concomitant treatment
- Received a wrong treatment or an incorrect dose
- Other

Subjects with major protocol deviations will also be listed by randomized treatment group.

4.6. Prior and Concomitant Medications

Subjects' prior psoriasis medication history with topical agents, phototherapy, non-biologic systemic therapies, and biologic medications will be summarized by treatment group. See Section 2.4 for lists of medications in each category. In addition, reasons for which subjects discontinued previous systemic therapies (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized by randomized treatment group.

The number of subjects who received concomitant treatment with a moisturizer for psoriasis will be summarized by randomized treatment group.

Subjects who received concomitant corticosteroids for indications other than psoriasis and/or psoriatic arthritis will be listed. Subjects with concomitant prophylactic treatments for latent TB infection will also be listed.

5. EFFICACY

In general, efficacy data summaries will be provided by treatment group for the full analysis set.

The Fisher's exact test will be used to compare the proportion of subjects responding to treatment if appropriate. Continuous response parameters (i.e. % improvement in PASI) will be compared using Wilcoxon rank-sum test. All statistical testing will be performed 2-sided.

Descriptive statistics, such as mean, median, standard deviation, minimum and maximum, interquartile range for continuous variables, and counts and percentages for categorical variables will be used to summarize the data. Graphical data displays and subject listings may also be used to summarize the data.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical procedures to test superiority hypotheses will be performed at a 2-sided significance level of 0.05. This study is designed to maintain an overall Type I error of 0.05 or less for the primary analysis and major secondary analyses. Nominal p-values will be reported for other secondary analyses.

5.1.1.1. Multiplicity Adjustment for Testing Procedures

There are 2 co-primary endpoints in this study:

- The proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16
- The proportion of subjects who achieve a PASI 90 response at Week 16

Both of the co-primary endpoint analyses will be compared between the guselkumab treatment group and the placebo group and tested at a 2-sided α-level of 0.05. If one of the comparisons is not significant at the 2-sided α-level of 0.05, the co-primary endpoints will be considered not significant.

In addition, there are 2 major secondary endpoints in this study to be compared between the guselkumab 100 mg group and the placebo group:

- The proportion of subjects who achieve an IGA score of cleared (0) at Week 16.
- The proportion of subjects who achieve a PASI 100 response at Week 16.

The analyses of the major secondary endpoints will be performed only if both primary analyses are significant, and will be performed in the fixed sequence testing approach[1], as specified above. If a given comparison is not significant at the 2-sided α-level of 0.05 for superiority hypotheses, the remaining treatment group comparisons in this sequence will be considered not significant and will be considered as supportive analyses.

5.1.2. Definition of the Efficacy Endpoints and Calculation of the Efficacy Instruments

5.1.2.1. Investigator's Global Assessment

The Investigator's Global Assessment (IGA) documents the investigator's assessment of the subject's psoriasis at a given time point. Overall lesions are graded for induration, erythema, and scaling. The patient's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4).

Efficacy endpoints related to the IGA score are defined below:

IGA cleared responder

Subjects who achieve an IGA score of cleared (0) will be considered IGA cleared responders.

IGA cleared or minimal responder

Subjects who achieve an IGA score of cleared (0) or minimal (1) will be considered IGA cleared or minimal responders.

IGA mild or better responder

Subjects who achieve an IGA score of cleared (0), minimal (1), or mild (2) will be considered IGA mild or better responders.

5.1.2.2. Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for the percentage of the area involved, which translates to a numeric score that ranges from 0 (indicates no involvement) to 6 (90%-100% involvement), and for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 (no psoriasis) to 72. A higher score indicates more severe disease.

Efficacy endpoints related to the PASI score are defined below:

PASI 50 Responder

Subjects with ≥50% improvement in PASI from baseline will be considered PASI 50 responders.

PASI 75 Responder

Subjects with ≥75% improvement in PASI from baseline will be considered PASI 75 responders.

PASI 90 Responder

Subjects with ≥90% improvement in PASI from baseline will be considered PASI 90 responders.

PASI 100 Responder

Subjects with 100% improvement in PASI from baseline (PASI score=0) will be considered PASI 100 responders.

5.1.3. Data Handling Rules

The following treatment failure rules and data handling rules will be applied to the PASI and IGA-related efficacy analyses in this study.

5.1.3.1. Treatment Failure Criteria

Subjects who discontinue study agent due to lack of efficacy, an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis are considered as treatment failures.

The particular protocol-prohibited medications/therapies include:

Topical Therapies:

- Any topical therapies used for psoriasis (with the exception of topical moisturizers and shampoos containing tar or salicylic acid only)

Phototherapy or Systemic Therapies:

- Any systemic corticosteroid used for psoriatic arthritis or psoriasis with the exception of intra-articular corticosteroids.
- Any other anti-psoriatic systemic therapy or biologic therapy.
- Phototherapy of UVB or PUVA.
- Any other phototherapy for psoriasis.

5.1.3.2. Treatment Failure Rules

A subject who meets one or more treatment failure criterion specified in Section 5.1.3.1 will be considered a treatment failure from that point onward. The baseline values will be used for all directly measured endpoints regardless of the actual measurements. Zero will be assigned to improvement and percent improvement, and non-responder status will be assigned to binary response variables.

Treatment failure is assumed to have occurred at the earlier of the following dates:

- Date of discontinuation (DC) of study treatment due to lack of efficacy or
- Date of discontinuation of study agent due to an AE of worsening of psoriasis or
- Start date of a protocol-prohibited medication/therapy during the study that could improve psoriasis

5.1.3.3. Missing Data Imputation

After the treatment failure rules are applied, the remaining missing data will be handled as follows for all of the efficacy analyses including the analyses at the key visit (Week 16) and over time:

- Non-responder imputation will be applied for binary endpoints.
- No imputation will be performed for continuous endpoints and the values will remain as missing.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

There are 2 co-primary endpoints in this study: the proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16 and the proportion of subjects who achieve a PASI 90 response at Week 16. Refer to Section 5.1.2.1 and 5.1.2.2 for the definition of IGA score and PASI 90 responder.

5.2.2. Estimand

Population: subjects with moderate-to-severe plaque psoriasis who are randomized and treated with guselkumab or placebo using the SelfDose device.

Endpoint: the proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16 and the proportion of subjects who achieve a PASI 90 response at Week 16

Measure of Intervention: the effect of the initially randomized treatment regardless of what treatments are actually received. Non-responder status will be assigned if treatment failure criteria are met or data are missing.

5.2.3. Analysis Methods

These 2 co-primary endpoints will be compared between the guselkumab 100 mg group and the placebo group. In these primary efficacy analyses, data from all randomized and treated subjects will be analyzed according to their assigned treatment group. The number and proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) and PASI 90 response at Week 16 will be summarized for each treatment group respectively. The differences in proportions with exact 95% confidence intervals will also be presented.

To address the primary objective, a 2-sided (α=0.05) Fisher's exact test will be used for the co-primary endpoints.

The study will be considered positive if the guselkumab 100 mg group is significantly different from the placebo group for both co-primary endpoints. Both co-primary endpoints will be tested at a 2-sided α-level of 0.05. If one of the comparisons is not significant, the co-primary endpoints will be considered not significant.

5.2.4. Data Handling

Subjects who meet treatment failure criteria specified in Section 5.1.3.1 prior to Week 16 will be considered not to have achieved an IGA score of cleared (0) or minimal (1) or PASI 90 at Week 16. In addition, subjects with a missing IGA or PASI score at Week 16 or who do not return for evaluation at Week 16 will be considered not to have achieved the respective endpoint at Week 16.

5.2.5. Sensitivity Analysis

To assess the robustness of the co-primary endpoint analysis results, two sensitivity analyses will be conducted in the same manner as the co-primary endpoints. The missing data will be handled as specified below.

Sensitivity Analysis 1

For subjects who do not return for evaluation at Week 16, the missing IGA or PASI score at Week 16 will not be imputed. That is, the analysis will be performed using observed data after applying treatment failure rules (as defined in Section 5.1.3.2).

Sensitivity Analysis 2

The second sensitivity analysis will be performed by using multiple imputations (MI). In this analysis, for subjects who meet one or more treatment failure criterion specified in Section 5.1.3.1, the IGA and PASI score will be treated as missing from that point onward. The missing IGA or PASI score will be imputed using the Markov Chain Monte Carlo (MCMC) algorithm which assumes that all the variables in the imputation model have a joint multivariate normal distribution. The IGA or PASI responses will then be derived based on the imputed score at Week 16.

5.2.6. Subgroup Analysis

For each of the subgroups defined in Section 2.4, the proportion of subjects achieving IGA score of cleared (0) or minimal (1) and the proportion of PASI 90 responders at Week 16 by treatment group will be summarized. Differences in the proportion and the associated exact 95% confidence interval (CI) for the differences will be provided.

In addition, the proportion of subjects achieving IGA score of cleared (0) or minimal (1) and the proportion of PASI 90 responders at Week 16 by country and investigator site will be summarized.

5.3. Major Secondary Endpoints

The analyses for the major secondary endpoints will be performed in the order listed in Section 5.1.1.1.

The sections below outline the major secondary analyses to be performed, as well as the analysis methods and the data imputation rules.

5.3.1. Definition

There are 2 major secondary endpoints in this study to be compared between the guselkumab 100 mg group and the placebo group:

- The proportion of subjects who achieve an IGA score of cleared (0) at Week 16.
- The proportion of subjects who achieve a PASI 100 response at Week 16.

5.3.2. Analysis Methods

For the major secondary analyses, the Fisher's exact test will be used to compare the proportion of subjects responding to treatment. The differences in proportions with exact 95% confidence intervals will be presented. All statistical testing will be performed 2-sided (α=0.05).

5.3.3. Data Handling

Data handling rules specified in Section 5.2.4 will be applied to the major secondary analyses.

5.4. Other Efficacy Variable(s)

Other secondary efficacy endpoints include the endpoints related to

- PASI
- IGA

The analyses of other secondary efficacy analyses outlined in the following sections in general will be carried out for 2 periods

- Analyses through Week 20:
  - Analyses at key endpoints: Week 16
  - Over time summaries: Through Week 20
- Analyses through Week 40

5.4.1. Definition

Refer to Section 5.1.2 for the definitions of the other efficacy endpoints described in the following section.

5.4.2. Analysis Methods

Most of the other secondary efficacy analyses described in this section below will be based on the full analysis set. For subjects randomized to placebo, only subjects who crossed over to receive guselkumab 100 mg at Week 16 will be included in the efficacy summaries for the visits after Week 16. All statistical testing will be performed at the 2-sided 0.05 significance level. Nominal p-values will be presented.

5.4.2.1. Analyses Related to IGA

- The proportion of subjects who achieve an IGA score of mild or better (≤2) at Week 16 will be compared between the guselkumab 100 mg groups and the placebo group using Fisher's exact test. The difference in proportions with exact 95% confidence interval will be presented.
- The proportions of subjects achieve an IGA score of cleared (0); an IGA score of cleared (0) or minimal (1); and an IGA score of mild or better (≤2) will be summarized over time through Week 20 and through Week 40 by treatment group. Line plots will be provided displaying the proportions and exact 95% CIs of subjects achieve an IGA score of cleared (0); and an IGA score of cleared (0) or minimal (1) through Week 20 and Week 40.
- The proportions of subjects achieving an IGA score of cleared (0); an IGA score of cleared (0) or minimal (1); and an IGA score of mild or better (≤2) will also be summarized over time through Week 20 and through Week 40 by treatment group using observed data after applying treatment failure rules.

5.4.2.2. Analyses Related to PASI

- The proportion of subjects who achieve a PASI 75 response and a PASI 50 response at Week 16 will be compared between the guselkumab 100 mg groups and the placebo group using Fisher's exact test. The differences in proportions with exact 95% confidence intervals will be presented.
- The percent improvement from baseline in PASI score at Week 16 will be compared between the guselkumab 100 mg groups and the placebo group using Wilcoxon rank-sum test.
- The proportions of PASI 100 responders, PASI 90 responders, PASI 75 responders, and PASI 50 responders, and the percent improvement from baseline in PASI will be summarized over time through Week 20 and through Week 40 by treatment group. Line plots will be provided displaying proportions and exact 95% CIs of PASI 100 responders and PASI 90 responders through Week 20 and Week 40.
- The proportions of PASI 100 responders, PASI 90 responders, PASI 75 responders, and PASI 50 responders, and the percent improvement from baseline in PASI will be summarized over time through Week 20 and through Week 40 by treatment group using observed data after applying treatment failure rules.
- The proportion of subjects who achieve 100% improvement, ≥90%, ≥75%, or ≥50% improvement from baseline in PASI component (induration, erythema, and scaling) and region component (head, trunk, upper extremities, and lower extremities) will be summarized at Week 16 by treatment group.

5.4.3. Data Handling

Data handling rules specified in Section 5.2.4 will be applied to all IGA related and PASI related analyses.

6. USABILITY AND ACCEPTABILITY ASSESSMENTS

6.1. Definition

6.1.1. Successful, Problem-Free Injections

Successful, problem-free self-injection (usability) using the SelfDose device will be assessed by the completion of the Observer Injection Checklist at Week 0. Study-site personnel will observe the subject to confirm successful completion of the 3 steps, as described in the instructions for use, required to effectively and safely use the device to deliver the correct dose: (1) remove the cap, (2) position device on the injection site, and (3) inject complete dose. A successful, problem-free self-injection is defined as below:

Observer Injection Checklist	**Required completion for successful, problem-free injection**
(1) Remove cap: Did subject successfully remove cap	Yes
(2) Position device on injection site: Did the subject select the correct injection site?	Yes
(2) Position device on injection site: Did the subject position the device at approximately a 90 degree angle on the injection site	Yes
(3) Inject complete dose: Did the subject push the handle all the way down so the orange dose indicator disappeared completely?	Yes
(3) Inject complete dose: Were there any device-related problems associated with this injection?	No

6.1.2. Self-Injection Assessment Questionnaire

Subjects will be asked to rate the acceptability of their experience using the SelfDose device with the SIAQ which was developed and validated in patients with rheumatoid arthritis (RA). A paper version of the SIAQ will be used in this study.

The SIAQ includes 6 domains: feelings about injections, self-image, self-confidence, pain and skin reactions during or after the injection, ease of use of the self-injection device, and satisfaction with self-injection. Each domain is derived from one or multiple items. The subject rates each item of the SIAQ on a 5-6 point semantic Likert-type scale.

The PRE-self-injection module of the SIAQ includes items assessing domains of feelings about injections, self-confidence, and satisfaction with self-injection, while the POST-self-injection module of the SIAQ includes items assessing all 6 domains. In this study, the subject will complete the PRE-self-injection module before the first self-injection at Week 0, and will complete the POST-self-injection module after self-injection at Weeks 0, 4, 12, and 28.

Scoring

Respondent rates items 1-9 of the PRE SIAQ and 15-21 of the POST SIAQ on a 5-point semantic Likert-type scale, and items 10-14 of the POST SIAQ on a 6-point semantic Likert-type scale. For all items, a score of 1 corresponds to the subject's worst experience and a score of 5 or 6 corresponds to the subject's best experience.

The scoring of domains is performed in 2 steps (Table 3):

- The raw item scores ranging from 1 to 5 (or 1 to 6) are transformed into scores ranging from 0 (worse experience) to 10 (best experience).
- The transformed scores for items contributing to a domain are then averaged into a domain score. Domain scores are calculated only if at least half of the domain items are completed. Domain scores from the PRE module are summarized only with the corresponding domain scores from the POST modules.

Table 3: The calculation of SIAQ scores are as follows:				
	Items	**Transformed item score**	**Domain score calculation**	**Domain score range**
PRE module domain				
Feeling about self-injection	1–3	(raw score-1) x 2.5	Average of transformed item scores	0–10
Self-confidence	4–6	(raw score-1) x 2.5		
Satisfaction with self-injection	7	(raw score-1) x 2.5		
POST module domain				
Feeling about self-injection	1–3	(raw score-1) x 2.5	Average of transformed item scores	0–10
Self-image	4	(raw score-1) x 2.5		
Self-confidence	5–7	(raw score-1) x 2.5		
Pain and reaction during or after the injection	8–9	(raw score-1) x 2.5		
Ease of use of the self-injection device	10–14	(raw score-1) x 2		
Satisfaction with self-injection	15–21	(raw score-1) x 2.5		

6.2. Analysis Methods

The analyses of device usability and acceptability assessments will be performed through Week 20 and through Week 28 by treatment group for the safety analysis set.

Other than the data handling rules specified in Section 6.1, the analyses for usability and acceptability will be based on observed data without missing data imputation or other data handling rules.

6.2.1. Analyses Related to the Device Usability

- The proportion of subjects with successful, problem-free injections (assessment of usability) at Week 0 will be summarized by treatment group and overall.
- The proportion of subjects who had full delivery of the dose confirmed by inspection of the device at Weeks 4 and 12 will be summarized by treatment group and overall.
- A listing of product quality complaints (PQCs) for Selfdose device will be provided.

6.2.2. Analyses Related to Acceptability Assessments

6.2.2.1. Analyses for Self-Injection Assessment Questionnaire

- Self-Injection Assessment Questionnaire (SIAQ) domain scores on the 3 domains with items common to the SIAQ PRE- (Week 0) and POST- (Week 0 and Week 12) self-injection modules will be summarized by treatment group and overall at Week 0 and Week 12.

- Self-Injection Assessment Questionnaire POST-self-injection domain scores and change from baseline scores for each domain will be summarized by treatment group and overall at Weeks 0, 4, 12, and 28.

6.2.2.2. Analyses for SelfDose Subject Questionnaire

- Ratings for the SelfDose Subject Questionnaire will be summarized at Week 12 by question, by treatment group and overall.

7. SAFETY

Safety will be assessed by summarizing the incidence and type of AEs and examining changes in laboratory parameters (hematology and chemistry), vital signs, and suicidal ideation and behavior.

In all the safety analysis, subjects who were randomized and received at least 1 (partial or complete) dose of study agent administration will be included and analyzed according to the treatment they actually received, regardless of the treatment assigned at randomization. No formal statistical comparison is planned.

Depending on the safety data categories, the cumulative safety data will be analyzed through different study periods which include but are not limited to through Week 16 and through the whole study period as appropriate. Unless otherwise specified, tabular summaries of safety events for key study periods are in general presented as follows:

Summaries through Week 16 (placebo-controlled period):

Safety data through Week 16 will be summarized by treatment groups:

- Placebo
- Guselkumab

This allows between-group comparisons of safety between the guselkumab group and the placebo group based on similar follow-up period in each group.

Summaries through Week 20 or through Week 40

Safety data through Week 20 and through Week 40 will be summarized by treatment group defined as follows:

1. **Placebo → Guselkumab 100 mg:** all subjects who were randomized to placebo at Week 0, started treatment with placebo only, and later crossed over to receive treatment with guselkumab. Only the safety events/measurements from these subjects that occurred on or after their first administration of guselkumab 100 mg will be included in this group.

2. **Guselkumab 100 mg:** all subjects who were randomized to guselkumab 100 mg at Week 0 and received study agent with guselkumab 100 mg. All the safety events/measurements from these subjects that occurred beginning at Week 0 will be included in this group.

3. **Combined Guselkumab 100 mg:** all subjects as described above in the Placebo → Guselkumab 100 mg and the Guselkumab 100 mg groups.

7.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent through the end of the trial is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summary tables will be provided for:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent
- AEs by severity
- AEs by relationship to study agent
- Infections
- Serious infections
- Infections treated with oral or parenteral antimicrobial treatment
- Injection-site reactions
- AEs of psoriasis

In addition to the summary tables, listings will be provided for subjects who:

- Had SAEs
- Had AEs leading to discontinuation of study agent
- AEs of severe intensity
- Serum sickness-like reactions and anaphylactic reactions

In addition, a listing will be provided of all AEs that occurred after Week 16 for subjects who were randomized to placebo at Week 0 and were not crossed over to receive guselkumab.

Any unfavorable or unintended sign that occurs at the injection site is an injection site reaction and will be recorded as an injection site reaction by the investigator on the eCRF. An infection is defined as any AE that was recorded as an infection by the investigator on the eCRF.

The treatment-emergent adverse events of psoriasis include any event of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, inverse psoriasis, palmo-plantar psoriasis and worsening or exacerbation of psoriasis. Frequency of these events will be summarized.

Since safety should be assessed relative to exposure and follow-up, most AE summary tables will include average weeks of follow-up and average number of study agent administrations for each treatment group.

7.2. Clinical Laboratory Tests

All clinical laboratory reports will be displayed for the subjects included in the safety analysis set. The clinical laboratory parameters to be evaluated by the central laboratory include but are not limited to:

- **Hematology**: hemoglobin, hematocrit, lymphocytes, neutrophils, platelets, red blood cell (RBC) count and white blood cell (WBC) count.
- **Chemistry**: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total carbon dioxide (CO2), total bilirubin, blood urea nitrogen/urea, calcium, chloride, creatinine, glucose, potassium, total protein, sodium.

Box plots of laboratory measurements and change from baseline will be provided for selected laboratory analytes.

Applicable laboratory results will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03). The worst NCI-CTCAE will be summarized by treatment group.

For nonfasting glucose, the screening measurement will be used as the baseline measurement. A listing of subjects with 1 or more NCI-CTCAE toxicity grade ≥2 abnormalities in hematology and clinical chemistry laboratory measurements will be provided.

7.3. Vital Signs

Vital signs variables including respiratory rate, blood pressure (systolic and diastolic) will be measured at visits as per the time and events schedule in the protocol. Descriptive statistics of the observed value and change from baseline of the vital signs will be summarized by treatment group.

7.4. Other Safety Parameters

7.4.1. Suicidal Ideation and Behavior

The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be used as a screening tool to prospectively evaluate the potential of guselkumab to induce suicidal ideation and

behavior. The eC-SSRS defines five subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent, and is a fully-structured subject self-report questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions. The Screening version of the eC-SSRS will be conducted at Screening followed by the Since Last Visit version of the eC-SSRS at all other visits through Week 40.

The eC-SSRS will be performed during each evaluation visit according to the assessment schedule. The eC-SSRS will be performed at screening after signing informed consent, after the pre-SIAQ at Week 0, and before study agent administration, and as the first assessment for all post-baseline visits. The baseline is defined as the most severe/maximum eC-SSRS score at screening and Week 0.

In addition, potential suicide related adverse events including suicidal ideation, suicidal behavior excluding completed suicide, and completed suicide will be identified by the investigators and collected in the eCRF.

The following are eC-SSRS categories and have binary responses (yes/no). A "yes" response to any eC-SSRS category will be assigned a score as below:

Suicidal Ideation (1-5)

1 = Wish to be Dead

2 = Non-specific Active Suicidal Thoughts

3 = Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

4 = Active Suicidal Ideation with Some Intent to Act, without Specific Plan

5 = Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (6-10)

6 = Preparatory Acts or Behavior

7 = Aborted Attempt

8 = Interrupted Attempt

9 = Actual Attempt (non-fatal)

10 = Completed Suicide

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="Negative result [no suicidal ideation or behavior]"). Higher scores indicate greater severity.

The summary for suicidal ideation and behavior will be based on the safety analysis set. Suicidal ideation and behavior will be summarized based on the most severe/maximum post baseline eC-SSRS outcome or AE of suicidal ideation, suicidal behavior excluding completed suicide or completed suicide through Week 16, Week 20, and Week 40 will be provided. In addition, frequency distribution of the most severe/maximum post baseline eC-SSRS outcome will be tabulated by treatment group through the same 3 time periods.

The maximum score assigned for each subject will also be summarized into one of three broad categories: No suicidal ideation or behavior, suicidal ideation, suicidal behavior. A shift table for change in categories of no suicidal ideation or behavior, suicidal ideation, and suicidal behavior from baseline through Week 16 will be presented, where the baseline category is based on eC-SSRS score and the post baseline is based on eC-SSRS or AE data.

8. PHARMACOKINETICS/PHARMACODYNAMICS

8.1. Pharmacokinetics

Blood samples for measuring serum guselkumab concentrations (pre-injection if it is an injection visit) will be collected from all subjects at scheduled visits as indicated in the time and events schedule in the protocol.

The PK analysis will be based on subjects who received at least 1 administration of guselkumab and had at least one evaluable PK blood sample. No imputation of missing concentration data will be performed, that is, data summaries will be based on the observed data.

All concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration data listings or Statistical Analysis Software™ dataset. Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

For analysis of serum guselkumab concentrations, descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated, where appropriate, by treatment group at each sampling time point. Serum guselkumab concentrations by baseline weight (≤90kg, >90 kg) will also be summarized by treatment group overtime. The PK concentration data may be displayed graphically.

All summaries for serum guselkumab concentration will exclude data collected after subjects (1) did not receive a scheduled guselkumab administration within ± 14 days of the protocol scheduled dosing date, or those subjects who discontinued study agent, (2) received a partial, incorrect, or an additional guselkumab administration, (3) or have invalid sample data if the sample is taken after study agent administration or a concentration value falls outside the predefined range (±10*SD). Of note, serum guselkumab concentrations prior to the first of such events will be included in the summaries.

If needed, a population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of guselkumab in the current study. Data may be combined with those from pivotal Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) to support a relevant structural model. Details will be given in a population PK analysis plan and results of the population PK analysis will be presented in a separate technical report.

The effect of serum guselkumab concentrations on efficacy may be explored.

8.2. Immune Response

Blood samples will be collected for the detection of antibodies to guselkumab at the specified visits as shown in the time and event schedule in the protocol.

The antibodies to guselkumab analysis will be based on subjects who receive at least 1 dose of guselkumab and have appropriate serum samples for antibody detection. No imputation of missing data will be performed, that is, data summaries will be based on the observed data.

The following analyses will be performed by treatment group as appropriate:

- Summary of antibodies to guselkumab status (incidence of positive antibodies to guselkumab and antibody titers)
- List of subjects who are positive for antibodies to guselkumab

In addition, the incidence of neutralizing antibodies (NAbs) to guselkumab will be summarized for subjects who are positive for antibodies to guselkumab and have samples evaluable for NAbs.

The effect of antibodies to guselkumab on PK, efficacy, and safety may be explored.

REFERENCES

1. Maurer, W., Hothorn, L. A., Lehnacher, W. Multiple comparisons in drug clinical trials and preclinical assays: a prior ordered hypotheses. Biometrie in der Chemisch-in-Pharmazeutischen Industrie. 1995, 3-18