ATTORNEY GENERAL OF THE STATE OF NEW YORK
BUREAU OF CONSUMER FRAUDS AND PROTECTION
HEALTH CARE BUREAU

-x

In the Matter of :

GLAXOSMITHKLINE, plc,
d/b/a GlaxoSmithKline,

and

SMITHKLINE BEECHAM CORPORATION,
d/b/a GlaxoSmithKline.

-x

ASSURANCE OF DISCONTINUANCE
PURSUANT TO EXECUTIVE LAW
SECTION 63, SUBDIVISION 15

WHEREAS, pursuant to the provisions of Executive Law § 63(12) and General Business Law Article 22-A, Eliot Spitzer, the Attorney General of the State of New York ("Attorney General"), caused an inquiry to be made into the business practices of GLAXOSMITHKLINE, plc, d/b/a/ GlaxoSmithKline, and SMITHKLINE BEECHAM CORPORATION, d/b/a/ GlaxoSmithKline (collectively "GSK"), concerning GSK's alleged failure to disclose material information from Clinical Studies that evaluated the safety and efficacy of GSK's antidepressant medication Paxil® in treating Major Depressive Disorder ("MDD") in children and adolescents ("pediatric population"); and

WHEREAS, on June 2, 2004, the People of the State of New York brought an action against GSK in the New York Supreme Court, New York County, Index No. 04401707, alleging that GSK violated N.Y. Executive law § 63(12) by, among other things, failing to disclose certain material Clinical Study information concerning Paxil® in treating MDD in the pediatric population; and

WHEREAS, the parties have agreed to settle said action by entering into a Stipulation and Consent to an Order and Judgment and by moving the Court to enter said Order and Judgment, which provides, among other things, that GSK will provide public access to the Clinical Study Reports of Paxil® as a treatment for MDD in the pediatric population; and

WHEREAS, GSK announced on June 18, 2004, its intention to launch a Clinical Trials Register ("CTR") that would provide information about Clinical Studies involving GSK Drugs; and

WHEREAS, GSK has since developed a protocol and template for its Clinical Trials Register; and

WHEREAS, the Office of the Attorney General has reviewed that protocol and template and finds that it provides useful information to the medical community; and

WHEREAS, GSK is undertaking to Post on the Internet Summaries of Clinical Study Reports,

IT IS HEREBY AGREED by GSK, its assigns, successors, agents, contractors, employees and subsidiaries, without admitting that it has violated any law of the State of New York, that:

DEFINITIONS

1. The Definitions set out in Appendix A, which is attached to and incorporated in this Assurance, shall be used for the purposes of this Assurance, including all Appendices. Any terms that are not defined in Appendix A shall be interpreted to have the same meaning as they have in ICH's *Guidelines for Industry: Structure and Content of Clinical Study Reports* (July 1996), which is annexed as Appendix D.

GSK's CLINICAL TRIAL REGISTER

2. GSK shall Post on the Internet a Summary of every Clinical Study Report for GSK-Sponsored Clinical Studies involving a GSK Drug. Such summaries shall conform to ICH E3 principles and to the template attached hereto as Appendix B and shall relate to:

(a) GSK-Sponsored Clinical Studies completed after December 27, 2000; and

(b) any other GSK-Sponsored Clinical Studies material to a physician's medical judgment, for those prescription drugs that GSK actively promotes.

For studies initiated after the date of this Assurance, GSK will also make reasonable effort to encourage the publication of, or in the alternative, secure the right to publish on the CTR, studies in which GSK had significant participation but did not sponsor.

3. The Summaries of Clinical Study Reports that GSK Posts shall accurately reflect the methodology used to conduct the Clinical Study and the Data obtained during the Clinical Study.

4. GSK shall make all reasonable efforts to Post the Summaries of Clinical Study Reports in accordance with the following time requirements:

(a) Studies completed prior to the Assurance Date: Summaries of Clinical Study Reports with a Study Completion Date that occurred between December 27, 2000, and the Assurance Date, or which occurred prior to December 27, 2000, but are likely to be material to a physician's medical judgment, will be posted by December 31, 2005.

(b) Studies completed after the Assurance Date: (i) With respect to products approved and marketed for any indication prior to the Assurance Date, Summaries of Clinical Study Reports will be Posted no later than ten months after the Study Completion Date, except that the Posting shall occur within eight months of the Study Completion Date if, by that time, either no Peer Reviewed Journal has accepted an original article concerning the Clinical Study or the Peer Reviewed Journal that has accepted such an original article agrees to publish the article irrespective of whether GSK Posts the Summary of the relevant Clinical Study Report; (ii) With respect to products approved for an initial indication after the Assurance Date, Summaries of Clinical Study Reports will be Posted no later than ten months after first marketing.

(c) The parties recognize that, in some instances, there may be a delay in Posting complete Summaries of Clinical Study Reports because GSK must seek intellectual-property protection or comply with policies of Peer Reviewed Journals to which manuscripts have been submitted for publication; and, further, that GSK may be required to withhold certain Summaries of Clinical Study Reports to comply with confidentiality provisions in agreements with other parties. In regard to confidentiality agreements, in all future Clinical Studies GSK will use reasonable efforts to exclude previsions limiting the publication of Summaries of Clinical Study Reports. For all past Clinical Studies with such confidentiality

agreements, GSK will make reasonable efforts to secure the right to publish the Summaries of Clinical Study Reports on the CTR.

5. GSK shall clearly and conspicuously state the location of the Posted information (URL and, where relevant, a link) on the Home Page of the GSK Web Site.

ADDITIONAL GSK OBLIGATIONS

6. Within two weeks of the Assurance Date, GSK shall arrange and pay for the publication of the advertisement annexed hereto as Appendix C to run in the next available print and electronic editions (for at least one month on the electronic editions) of each of the following journals: *Journal of the American Medical Association, New England Journal of Medicine, Pediatrics, Annals of Internal Medicine, Journal of the American Academy of Child and Adolescent Psychiatry, Journal of the American Psychiatric Association, Journal of the American Board of Family Practice*. GSK shall arrange for and pay for the advertisement to be placed between the front cover and the first article in the journal. Letters to the editor do not constitute articles for the purpose of this paragraph. Each advertisement must be at least one-half page in size.

7. GSK shall ensure that all Medical Information Letters and other communications it provides to physicians concerning an Off-Label Use of a GSK Drug shall fairly and accurately reflect the safety and efficacy Data from all Clinical Studies concerning such Off-Label Use.

MONITORING

8. On a random basis, the Office of the Attorney General may request documents, such as Clinical Study Reports, raw Data from such Reports, and annual reports to the FDA, to

confirm that the terms of this Assurance are being complied with and, subject to a reasonable confidentiality agreement, GSK shall cooperate in responding to these requests.

9. For ten years, GSK's Chief Legal Officer will certify to the Office of the Attorney General annually, in a mutually agreeable format, that it has met the terms of this Assurance.

10. Nothing contained in this Assurance shall in any way limit the Attorney's General right to obtain, by subpoena or any other means permitted by law, documents, testimony or other information to determine whether GSK has fully complied with this Assurance.

FUTURE RIGHTS AND OBLIGATIONS

11. Nothing contained in this Assurance herein shall be construed to deprive any individual of any private right of action under the law.

12. This Assurance shall not be admissible in any other case for any purpose.

13. Acceptance of this Assurance by the Attorney General shall not be deemed or construed as an approval by the Attorney General of any of GSK's actions, and GSK shall not make any representation to the contrary.

Acceptance of this Assurance by GSK shall not be deemed or construed to be an admission of liability by GSK or a waiver of any defense which GSK has or may have in any dispute with the Office of the Attorney General or any other person or entity.

15. GSK may apply to the Office of the Attorney General for modification of the obligations imposed by this Assurance in light of changed circumstances, (including, without limitation, the subsequent imposition of different or inconsistent federal or international regulatory requirements).

16. In appropriate circumstances, GSK will, in its sole discretion, make Clinical Study Reports and related Data available to bona fide researchers who are preparing scholarly work for publication in Peer Reviewed Journals.

WHEREFORE, the following signatures are affixed hereto on the specified dates:

AGREED TO by the parties:

Dated: New York, New York
August 26, 2004

ELIOT SPITZER
Attorney General of the
State of New York

By:
BUREAU OF CONSUMER
FRAUDS AND PROTECTION

Thomas G. Conway
Assistant Attorney General in Charge

HEALTH CARE BUREAU

Joseph R. Baker, III
Assistant Attorney in Charge

Rose E. Firestein
Assistant Attorney General

Shirley Stark
Assistant Attorney General

Dated: New York, New York
August 26, 2004

GLAXOSMITHKLINE, plc, d/b/a/
GlaxoSmithKline
SMITHKLINE BEECHAM CORPORATION,
d/b/a/ GlaxoSmithKline

KING & SPALDING, LLP

By:

J. Sedwick Sollers III, Esq.

Dwight J. Davis, Esq.

APPENDIX A

to

Assurance of Discontinuance
In the Matter of GlaxoSmithKline, plc, d/b/a/ GlaxoSmithKline, and
SmithKline Beecham Corporation, d/b/a/ GlaxoSmithKline

DEFINITIONS

"Adverse Events" are unfavorable and undesired effects observed in patients during a Clinical Study. "Serious" Adverse Events are those that, at any dose, are fatal, life-threatening, disabling or incapacitating; result in hospitalization; prolong a hospital stay; or are associated with congenital abnormality, cancer or overdose (whether accidental or intentional). In addition, any event not meeting the above criteria may still be deemed Serious by the Investigator if such an event jeopardizes the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

"Assurance Date" means the date on which the parties sign this Assurance.

"Clinical Study" means a research investigation on human subjects to answer specific questions about a GSK drug. The term "Clinical Study" is not limited to a research study that is randomized, controlled, or blinded.

"Clinical Study Report" of a Clinical Study means a description of the Protocol, all the Data, and the clinically relevant conclusions drawn from the Data, including the answers to the questions posed in the Protocol.

"Data" means all the results and outcome measurements obtained from a Clinical Study. This includes a description and the results of any planned statistical analysis of the Data, as well as a listing of the common Minor Adverse Events and a more detailed listing of Serious Adverse Events.

"GSK Drug" is a prescription pharmaceutical product that is currently sold for human consumption in the United States by GSK, for which GSK has both the clinical development responsibility and the legal right to use or disclose such product's Data.

"GSK-Sponsored Clinical Studies" means Clinical Studies of a GSK Drug where GSK is ultimately responsible for regulatory approvals, site selection, Protocol development, initiation, monitoring, safety reporting, and Data analysis, even if some or all of these activities are transferred to another party (*e.g.*, Clinical Research Organization). "GSK-Sponsored Clinical Studies" excludes studies initiated by a third party for which GSK provides some support, for example by way of a grant or supply of medication, but with sponsor responsibilities for study initiation and management agreed in writing to reside with the third party.

"GSK Web Site" refers only to GSK's main corporate Internet site, currently www.gsk.com.

"Off-Label Use" means the use of a GSK Drug to treat a condition, disease or population not listed as an indication on the U.S. Prescribing Information (labeling) for the GSK Drug.

"Peer Reviewed Journal" refers to a professional periodical that, before accepting an original article for publication, has it reviewed, at minimum for scientific merit, by relevant experts selected by the journal. A "Peer Reviewed Journal" does not include a supplement of a professional periodical that is sponsored or supported in any way by or on behalf of GSK or any other manufacturer, seller or promoter of prescription pharmaceutical products.

"Post" information means to provide access to the information on an Internet site that provides no-cost and unrestricted access to both the site and the information GSK has provided through the site. GSK does not fulfill a requirement to Post information under this Assurance if

it does so on an Internet site, other than the GSK Web Site, that contains any advertising by any pharmaceutical company or for any pharmaceutical product.

"Protocol" means the investigational plan used to conduct the Clinical Study. The Protocol for an acute phase of a Clinical Study is separate from the Protocol for a continuation or extension phase of the Clinical Study.

"Study Completion Date" is the date on which the last observation is made either of the last patient who remains enrolled in the Clinical Study or following a decision to terminate the Clinical Study early, whichever happens first.

"Summary of Clinical Study Report" refers to the brief presentations of Clinical Study Reports that are required by this Assurance and that comply with Appendix B.

APPENDIX B

to

Assurance of Discontinuance
In the Matter of
GlaxoSmithKline, plc, d/b/a/ GlaxoSmithKline and
SmithKline Beecham Corporation, d/b/a/ GlaxoSmithKline

The People of the State of New York, by their Attorney General Eliot Spitzer, and GlaxoSmithKline, plc, d/b/a/ GlaxoSmithKline and SmithKline Beecham Corporation, d/b/a/ GlaxoSmithKline (collectively "GSK"), agree that the Summaries of Clinical Study Reports, the Posting of which is the subject of the Assurance of Discontinuance in the above-referenced matter, shall each contain all of the categories of information listed herein (first and second pages of the attached templates for Phase 1 Clinical Studies; third through fifth pages of the attached templates for Phase 2, 3 or 4 Clinical Studies). The following list of categories of information that the parties agree shall be included in the Summaries of Clinical Study Reports does not restrict GSK from including in such Summaries any other information that meets the requirements of the Assurance of Discontinuance:

Use subject not patient throughout (except for the title which should be verbatim from the report)

Study No: study number as in report		
Title : Enter title as in report		
Rationale: Not always available in report. May have to be extracted from introduction		
Phase: Enter phase as in the synopsis of the report		
Study Period: As in the synopsis		
Study design: Enter list of descriptive terms		
Centres: Summarised by region/county		
Indication: Enter indication as in the synopsis of the report, enter none if its not applicable.		
Treatment: # Denotes treatment regimens approved in the US and at least one country in the European Union. Summarised from synopsis		
Objectives: Objectives as written in synopsis/report		
Statistical Methods: : As in the study synopsis. .Add definitions of the populations included in the CTR summary for the assessment of efficacy and safety if not included in the synopsis stats section. Make it clear if the populations for efficacy and safety are not the same		
Study Population: Extracted from synopsis.		
Number of Subjects: Adjust according to study	**Group A**	**Group B**
Planned N	From synopsis or body of the report	
Dosed N		
Completed n (%)		
Total Number Subjects Withdrawn N (%)		
Withdrawn due to Adverse Events n (%)		
Withdrawn due to Lack of Efficacy n (%)		
Withdrawn for Other Reasons n (%)	Add-up ALL other reasons for withdrawal	
Demographics	**Group A**	**Group B**
N (ITT)	From synopsis	
Females: Males		
Mean Age in Years (sd)		
Mean Weight in Kg (sd)		
Race, n (%) Substitute the name of the predominant race(s) studied for the word "Race"		

Pharmacokinetics (PK),pharmacodynamics (PD), PK/PD Endpoints:
Amend heading as necessary eg remove PK or PD if not applicable to the study. Present outcome variable(s) with statistical annotation from synopsis/report. Format and presentation indication/study dependent. Use tables from report if available otherwise use text

Safety results:
Define the period for the collection of 'on therapy' AEs and SAEs as given in the methodology section of the report e.g ., An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

Summarise Adverse events as follows:

30 subjects or less /treatment group: any AE that occurs in more than one patient in any group

More than 30 subjects per treatment group and<= 3 groups: the most frequent 10 events in each group

More than 30 subjects/treatment group and > 3 groups: the most frequent 5 events in each treatment group

The Numerator, denominator and the % will all be given

Adverse Events:	**Group A**	**Group B**
N (ITT)		
No. subjects with AEs n (%)		
Most Frequent AEs		

Serious Adverse Events, n (%) [# considered by the investigator to be related, possibly related, or probably related to study medication]:
Summarise SAEs. Table preferred (if available), otherwise use text/list. In square brackets, indicate the number of specific SAEs considered by the investigator to be related/possibly related/probably related.

Format of presentation is: n (%) [n (%)]

Publications: Add citations

Study No.: As on the report cover		
Title: As on the report cover. Trade name may be used if was included in the report title. All other sections of the CTR summary MUST use the generic name (not the trade name).		
Rationale: From synopsis OR extracted from introduction of report. Do not include information about mode of action. Do not use any trade name(s).		
Phase: As in the synopsis		
Study Period: As in the synopsis		
Study Design: List of descriptive terms taken from appropriate section of synopsis		
Centres: Summarised by region/county		
Indication: As agreed by MDC		
Treatment: # Denotes treatment regimens approved in the US and at least one country in the European Union. Summarised from synopsis (exclude batch numbers) using generic name		
Objectives: Primary objective as written in synopsis		
Primary Outcome/Efficacy Variable: Either from synopsis or body of report		
Secondary Outcome/Efficacy Variable(s): From the body of the report. List only the variables that were prospectively defined in the report not any post hoc analysis. Exclude pharmacoeconomics variables (may need to be taken out of secondary objectives list)		
Statistical Methods: As in the study synopsis. .Add definitions of the populations included in the CTR summary for the assessment of efficacy and safety if not included in the synopsis stats section. Make it clear if the populations for efficacy and safety are not the same.		
Study Population: Extracted from synopsis using key inclusion exclusion criteria		
	A	**B**
Number of Subjects: Adjust layout according to study design		
Planned, N	From body of report	
Randomised, N Note: for non-randomised studies, substitute the number of subjects entered into the study and replace the heading with "Entered, N"	From synopsis	
Completed, n (%)	ditto	
Total Number Subjects Withdrawn, N (%)	ditto	
Withdrawn due to Adverse Events n (%)	From synopsis or body of the report	
Withdrawn due to Lack of Efficacy n (%)	ditto	
Withdrawn for other reasons n (%)	Add-up ALL other reasons for withdrawal	
Demographics	**A**	**B**
N (ITT)	From synopsis	
Females: Males If only one gender was studies, just give information for the one gender and modify the heading accordingly.	ditto	
Mean Age, years (SD)	ditto	
Race, n (%) Substitute the name of the predominant race(s) studied for the word "Race"	ditto	
Include any other relevant demographic criteria, e.g., Children:adolescents	ditto	

Primary Efficacy Results:
Primary outcome variable(s) with statistical annotation must be presented in tabular format. Include p-values, if available. Format and presentation will be indication/study dependent. **No text or contextual statements are to be included.** An example is shown in the instruction text below.

	A	B
Mean Baseline (SE)	From synopsis or report	
Difference between treatments (as appropriate to endpoint)		
95% Confidence Interval		
p-value		

Secondary Outcome Variable(s):

Summarise all variables **in tabular format**. Group similar variables. Use 95% CI when appropriate. **Do not include p-values for secondary endpoints.** The analyses presented should be on the primary of population of interest, as presented in the CSR (for example, ITT or ITT LOCF). Quality of life and population pK endpoints should also be added when included in secondary endpoints. **Do not summarise Pharmacoeconomics or tertiary endpoints.** . No text or contextual statements are to be included.

	A	B
Secondary endpoint	From synopsis or report	
Difference between treatments (as appropriate to endpoint)		
95% CI (if appropriate)		

Safety Results: Define the period for the collection of 'on therapy' AEs and SAEs as given in the methodology section of the report e.g ., An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

Summarise Adverse events as follows:

30 patients or less /treatment group: any AE that occurs in more than one patient in any group

More than 30 patients per treatment group and <= 3 groups: the most frequent 10 events in each group

More than 30 patients/treatment group and > 3 groups: the most frequent 5 events in each treatment group

The Numerator, denominator and the % will all be given

	A	B
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)		
List specific AEs according to guidance above		

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication] Information on **all** on-therapy SAEs by preferred term will be provided. Format will vary, depending on how non-fatal and fatal SAEs were tabulated in the CSR. The table will indicate the number of subjects with specific SAEs, the percentage, and the number considered by the investigator to be related/possibly related/probably related to study medication.

Format of presentation of individual SAEs by preferred term is: n, (%) [n considered "related"]

If the report presents SAEs as "non-fatal SAEs" and "fatal SAEs" (or "deaths") separately, the CTR summary first presents the tabulations of "non-fatal" SAEs and then presents the tabulations of "fatal" SAEs.

If the report presents an all-inclusive SAE (both non-fatal and fatal), then the CTR summary first presents a tabulation of SAEs and then presents a tabulation of fatal SAEs. The heading for the "all SAEs" table should read:

Subjects with any SAEs, n (%)
-Includes both fatal and non-fatal events

	A	B
Subjects with non-fatal SAEs, n (%)		
	n (%) [related]	**n (%) [related]**
Present a table of all on-therapy SAEs using this format: Event A, n (%) [number of subjects who had "related" events]		
Subjects with fatal SAEs, n (%)		
	n (%) [related]	**n (%) [related]**
Event 1, n (%) [number of subjects who had events considered "related"]		

Conclusion:
Within 1 year after study completion this section will either refer you to a publication or contain text interpreting the trial results.

Publications: Add citations

APPENDIX C

to

Assurance of Discontinuance
In the Matter of
GlaxoSmithKline, plc, d/b/a GlaxoSmithKline, and
SmithKline Beecham Corporation, d/b/a GlaxoSmithKline

PUBLIC ACCESS TO SUMMARIES OF GSK CLINICAL STUDIES ON GSK CLINICAL TRIAL REGISTER

GlaxoSmithKline, plc announced that GSK will post on the Internet (www._____) summaries of the clinical study reports conducted on GSK's drugs.

Access to this information is free-of-charge. The content of the summaries will track the categories of information required by the ICH's *Guideline for Industry: Structure and Content of Clinical Study Reports* (ICH's E-3 Guidance).

GSK shall make all reasonable efforts to post before December 31, 2005, the summaries of clinical study reports that were completed before the Assurance/Order date. GSK shall, in general, post the summaries of clinical studies that are completed in the future within 10 months of the study completion date. In some cases, the timing may be affected by the policies of a peer reviewed journal that has accepted an article about the study.

There may be a delay in posting complete trial summaries because GSK may seek intellectual-property protection. Further, GSK may be required to withhold certain trial summaries to comply with confidentiality provisions in agreements with other parties. In regard to confidentiality agreements, in all future Clinical Studies GSK will use reasonable efforts to exclude provisions limiting the publication of Summaries of Clinical Study Reports. For all past Clinical Studies with such confidentiality agreements, GSK will make reasonable efforts to secure the right to publish the Summaries of Clinical Study Reports on the Clinical Trial Register.

Questions concerning GSK's registry should be directed to:

APPENDIX D

to

Assurance of Discontinuance
In the Matter of
GlaxoSmithKline, plc, d/b/a/ GlaxoSmithKline and
SmithKline Beecham Corporation, d/b/a/ GlaxoSmithKline

Guidelines for Industry
Structure and Content of Clinical Study Reports

International Conference on Harmonisation of Technical
Requirements for Registration of Pharmaceuticals for Human Use
(July 1996)
(ICH E-3 Principles)

Guideline for Industry

Structure and Content of Clinical Study Reports

July 1996

ICH E3

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GUIDELINE FOR INDUSTRY[1]

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS
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INTRODUCTION

The objective of this guideline is to facilitate the compilation of a single core clinical study report acceptable to all regulatory authorities of the ICH regions. The regulatory authority-specific additions will consist of modules to be considered as appendices, available upon request according to regional regulatory requirements.

The clinical study report described in this guideline is an "integrated" full report of an individual study of any therapeutic, prophylactic, or diagnostic agent (referred to herein as drug or treatment) conducted in patients. The clinical and statistical description, presentations, and analyses are integrated into a single report, incorporating tables and figures into the main text of the report or at the end of the text, with appendices containing such information as the protocol, sample case report forms, investigator-related information, information related to the test drugs/investigational products including active control/comparators, technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses,and computer output. The integrated full report of a study should not be derived by simply joining a separate clinical and statistical report. Although this guideline is mainly aimed at efficacy and safety trials, the basic principles and structure described can be applied to other kinds of trials, such as clinical pharmacology studies. Depending on the nature and importance of such studies, a less detailed report might be appropriate.

The guideline is intended to assist sponsors in the development of a report that is complete, free from ambiguity, well organized, and easy to review. The report should provide a clear explanation

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[1]This guideline was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 29, 1995. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guideline was published in the *Federal Register* on July 17, 1996 (61 FR 37320) and is applicable to drug and biological products. Although this guideline does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the Agency's current thinking on structure and content of clincial study reports. For additional copies of this guideline, contact the Drug Information Branch, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-827-4573) or the Manufacturers Assistance and Communication Staff (HFM-42), CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the offices in processing your request. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW) (connect to the CDER Home Page at WWW.FDA.GOV/CDER and go to the "Regulatory Guidance" section).

of how the critical design features of the study were chosen and enough information on the plan, methods, and conduct of the study so that there is no ambiguity in how the study was carried out. The report with its appendices should also provide enough individual patient data, including the demographic and baseline data, and details of analytical methods, to allow replication of the critical analyses when authorities wish to do so. It is also particularly important that all analyses, tables, and figures carry, in text or as part of the table, clear identification of the set of patients from which they were generated.

Depending on the regulatory authority's review policy, abbreviated reports using summarized data or with some sections deleted may be acceptable for uncontrolled studies or other studies not designed to establish efficacy, for seriously flawed or aborted studies, or for controlled studies that examine conditions clearly unrelated to those for which a claim is made. A controlled safety study, however, should be reported in full. If an abbreviated report is provided, a full description of safety aspects should be included in all cases. If an abbreviated report is submitted, there should be enough detail of design and results to allow the regulatory authority to determine whether a full report is needed. If there is any question regarding whether the reports are needed, it may be useful to consult the regulatory authority.

In presenting the detailed description of how the study was carried out, it may be possible simply to restate the description in the initial protocol. Often, however, it is possible to present the methodology of the study more concisely in a separate document. In each section describing the design and conduct of the study, it is particularly important to clarify features of the study that are not well-described in the protocol and identify ways in which the study as conducted differed from the protocol, and to discuss the statistical methods and analyses used to account for these deviations from the planned protocol.

The full integrated report of the individual study should include the most detailed discussion of individual adverse events or laboratory abnormalities, but these should usually be reexamined as part of an overall safety analysis of all available data in any application.

The report should describe demographic and other potentially predictive characteristics of the study population and, where the study is large enough to permit this, present data for demographic (e.g., age, sex, race, weight) and other (e.g., renal or hepatic function) subgroups so that possible differences in efficacy or safety can be identified. Usually, however, subgroup responses should be examined in the larger data base used in the overall analysis.

The data listings requested as part of the report (usually in an appendix) are those needed to support critical analyses. Data listings that are part of the report should be readily usable by the reviewer. Thus, although it may be desirable to include many variables in a single listing to limit size, this should not be at the expense of clarity. An excess of data should not be allowed to lead to, for example, overuse of symbols instead of words or easily understood abbreviations, or to too-small displays. In this case, it is preferable to produce several listings.

Data should be presented in the report at different levels of detail: Overall summary figures and tables for important demographic, efficacy, and safety variables may be placed in the text to illustrate important points; other summary figures, tables, and listings for demographic, efficacy, and safety variables should be provided in section 14; individual patient data for specified groups of patients should be provided as listings in Appendix 16.2; and all individual patient data (archival listings requested only in the United States) should be provided in Appendix 16.4.

In any table, figure, or data listing, estimated or derived values, if used, should be identified in a conspicuous fashion. Detailed explanations should be provided as to how such values were estimated or derived and what underlying assumptions were made.

The guidance provided below is detailed and is intended to notify the applicant of virtually all of the information that should routinely be provided so that postsubmission requests for further data clarification and analyses can be reduced as much as possible. Nonetheless, specific requirements for data presentation and/or analysis may depend on specific situations, may evolve over time, may vary from drug class to drug class, may differ among regions, and cannot be described in general terms. It is, therefore, important to refer to specific clinical guidelines and to discuss data presentation and analyses with the reviewing authority, whenever possible. Detailed written guidance on statistical approaches is available from some authorities.

Each report should consider all of the topics described (unless clearly not relevant) although the specific sequence and grouping of topics may be changed if alternatives are more logical for a particular study. Some data in the appendices are specific requirements of individual regulatory authorities and should be submitted as appropriate. The numbering should then be adapted accordingly.

In the case of very large trials, some of the provisions of this guideline may be impractical or inappropriate. When planning and when reporting such trials, contact with regulatory authorities to discuss an appropriate report format is encouraged.

The provisions of this guideline should be used in conjunction with other ICH guidelines.

1. TITLE PAGE

The title page should contain the following information:

- Study title.
- Name of test drug/investigational product.
- Indication studied.
- If not apparent from the title, a brief (one to two sentences) description giving design

(parallel, cross-over, blinding, randomized) comparison (placebo, active, dose/response), duration, dose, and patient population.

- Name of the sponsor.
- Protocol identification (code or number).
- Development phase of study.
- Study initiation date (first patient enrolled, or any other verifiable definition).
- Date of early study termination, if any.
- Study completion date (last patient completed).
- Name and affiliation of principal or coordinating investigator(s) or sponsor's responsible medical officer.
- Name of company/sponsor signatory (the person responsible for the study report within the company/sponsor). The name, telephone number, and fax number of the company/sponsor contact persons for questions arising during review of the study report should be indicated on this page or in the letter of application.
- Statement indicating whether the study was performed in compliance with good clinical practice (GCP), including the archiving of essential documents.
- Date of the report (identify any earlier reports from the same study by title and date).

2. SYNOPSIS

A brief synopsis (usually limited to three pages) that summarizes the study should be provided (see Annex I of the guideline for an example of a synopsis format used in Europe). The synopsis should include numerical data to illustrate results, not just text or p-values.

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

The table of contents should include:

- The page number or other locating information of each section, including summary tables, figures, and graphs.

- A list and the locations of appendices, tabulations, and any case report forms provided.

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A list of the abbreviations, and lists and definitions of specialized or unusual terms or measurement units used in the report should be provided. Abbreviated terms should be spelled out and the abbreviation indicated in parentheses at first appearance in the text.

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

It should be confirmed that the study and any amendments were reviewed by an IEC or IRB. A list of all IEC's or IRB's consulted should be given in Appendix 16.1.3 and, if required by the regulatory authority, thename of the committee Chair should be provided.

5.2 Ethical Conduct of the Study

It should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5.3 Patient Information and Consent

How and when informed consent was obtained in relation to patient enrollment (e.g., at allocation, prescreening) should be described.

Representative written information for the patient (if any) and a sample of the patient consent form used should be provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The administrative structure of the study (e.g., principal investigator, coordinating investigator, steering committee, administration, monitoring and evaluation committees, institutions, statistician, central laboratory facilities, contract research organization (C.R.O.), clinical trial supply management) should be described briefly in the body of the report.

There should be provided in Appendix 16.1.4 a list of the investigators with their affiliations, their role in the study, and their qualifications (curriculum vitae or equivalent). A similar list for other persons whose participation materially affected the conduct of the study should also be provided in Appendix 16.1.4. In the case of large trials with many investigators, the above information may

be abbreviated to consist of general statements of qualifications for persons carrying out particular roles in the study with only the name, degree, and institutional affiliation and roles of each investigator or other participant.

The listing should include:

A. Investigators.

B. Any other person carrying out observations of primary or other major efficacy variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. It is not necessary to include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for any of the above.

C. The author(s) of the report, including the responsible biostatistician(s).

Where signatures of the principal or coordinating investigators are required by regulatory authorities, these should be included in Appendix 16.1.5 (see Annex II for a sample form). Where these are not required, the signature of the sponsor's responsible medical officer should be provided in Appendix 16.1.5.

7. INTRODUCTION

The introduction should contain a brief statement (maximum: one page) placing the study in the context of the development of the test drug/investigational product, relating the critical features of the study (e.g., rationale and aims, target population, treatment, duration, primary endpoints) to that development. Any guidelines that were followed in the development of the protocol or any other agreements/meetings between the sponsor/company and regulatory authorities that are relevant to the particular study should be identified or described.

8. STUDY OBJECTIVES

A statement describing the overall purpose(s) of the study should be provided.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

The overall study plan and design (configuration) of the study (e.g., parallel, cross-over) should be described briefly but clearly, using charts and diagrams as needed. If other

studies used a very similar protocol, it may be useful to note this and describe any important differences. The actual protocol and any changes should be included as Appendix 16.1.1 and a sample case report form (unique pages only; i.e., it is not necessary to include identical pages from forms for different evaluations or visits) as Appendix 16.1.2. If any of the information in this section comes from sources other than the protocol, these should be identified.

The information provided should include:

- Treatments studied (specific drugs, doses, and procedures).
- Patient population studied and the number of patients to be included.
- Level and method of blinding/masking (e.g., open, double-blind, single-blind, blinded evaluators, and unblinded patients and/or investigators).
- Kind of control(s) (e.g., placebo, no treatment, active drug, dose-response, historical) and study configuration (parallel, cross-over).
- Method of assignment to treatment (randomization, stratification).
- Sequence and duration of all study periods, including prerandomization and post-treatment periods, therapy withdrawal periods, and single and double-blind treatment periods. When patients were randomized should be specified. It is usually helpful to display the design graphically with a flow chart that includes timing of assessments (see Annexes IIIa and IIIb for an example).
- Any safety, data monitoring, or special steering or evaluation committees.
- Any interim analyses.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The specific control chosen and the study design used should be discussed, as necessary. Examples of design issues meriting discussion follow.

Generally, the control (comparison) groups that are recognized are placebo concurrent control, no treatment concurrent control, active treatment concurrent control, dose comparison concurrent control, and historical control. In addition to the type of control, other critical design features that may need discussion are use of a cross-over design and selection of patients with particular prior history, such as response or nonresponse to a specific drug or member of a drug class. If randomization was not used, it is important to explain how other techniques, if any, guarded against systematic selection bias.

Known or potential problems associated with the study design or control group chosen should be discussed in light of the specific disease and therapies being studied. For a cross-over design, for example, there should be consideration, among other things, of the likelihood of spontaneous change in the disease and of carry-over effects of treatment during the study.

If efficacy was to be demonstrated by showing equivalence, i.e., the absence of a specified degree of inferiority of the new treatment compared to an established treatment, problems associated with such study designs should be addressed. Specifically, there should be provided a basis for considering the study capable of distinguishing active from inactive therapy. Support may be provided by an analysis of previous studies similar to the present study with respect to important design characteristics (e.g., patient selection, study endpoints, duration, dose of active control, concomitant therapy) showing a consistent ability to demonstrate superiority of the active control to placebo. How to assess the ability of the present study to distinguish effective from ineffective therapy should also be discussed. For example, it may be possible to identify a treatment response (based on past studies) that would clearly distinguish between the treated population and an untreated group. Such a response could be the change of a measure from baseline or some other specified outcome like healing rate or survival rate. Attainment of such a response would support the expectation that the study could have distinguished the active drug from an inactive drug. There should also be a discussion of the degree of inferiority of the therapy (often referred to as the delta value) the study was intended to show was not exceeded. The limitations of historical controls are well known (e.g., difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, change in therapy/disease, difference due to placebo effect) and deserve particular attention.

Other specific features of the design may also deserve discussion, including presence or absence of washout periods and the duration of the treatment period, especially for a chronic illness. The rationale for dose and dose-interval selection should be explained, if it is not obvious. For example, once daily dosing with a short half-life drug whose effect is closely related in time to blood level is not usually effective; if the study design uses such dosing, this should be explained, e.g., by pointing to pharmacodynamic evidence that effect is prolonged compared to blood levels. The procedures used to seek evidence of “escape” from drug effect at the end of the dose-interval, such as measurements of effect just before dosing, should be described. Similarly, in a parallel design dose-response study, the choice of doses should be explained.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

The patient population and the selection criteria used to enter the patients into the

study should be described, and the suitability of the population for the purposes of the study discussed. Specific diagnostic criteria used, as well as specific disease(e.g., disease of a particular severity or duration, results of a particular test or rating scale(s) or physical examination, particular features of clinical history, such as failure or success on prior therapy, or other potential prognostic factors and any age, sex, or ethnic factors) should be presented.

Screening criteria and any additional criteria for randomization or entry into the test drug/investigational product treatment part of the trial should be described. If there is reason to believe that there were additional entry criteria, not defined in the protocol, the implications of these should be discussed. For example, some investigators may have excluded or entered into other studies patients who were particularly ill or who had particular baseline characteristics.

9.3.2 Exclusion Criteria

The criteria for exclusion at entry into the study should be specified and the rationale provided (e.g., safety concerns, administrative reasons, or lack of suitability for the trial). The impact of exclusions on the generalizability of the study should be discussed in section 13 of the study report or in an overview of safety and efficacy.

9.3.3 Removal of Patients From Therapy or Assessment

The predetermined reasons for removing patients from therapy or assessment observation, if any, should be described, as should the nature and duration of any planned followup observations in those patients.

9.4 Treatments

9.4.1 Treatments Administered

The precise treatments or diagnostic agents to be administered in each arm of the study, and for each period of the study, should be described including route and mode of administration, dose, and dosage schedule.

9.4.2 Identity of Investigational Products(s)

In the text of the report, a brief description of the test drug(s)/investigational product(s) (formulation, strength, batch number(s)) should be given. If more than one batch of test drug/investigational product was used, patients receiving each batch should be identified in Appendix 16.1.6.

The source of placebos and active control/comparator product(s) should be provided. Any modification of comparator product(s) from their usual commercial state should be noted, and the steps taken to assure that their bioavailability was unaltered should be described.

For long-duration trials of investigational products with limited shelf-lives or incomplete stability data, the logistics of resupply of the materials should be described. Any use of test materials past their expiry date should be noted, and patients receiving them identified. If there were specific storage requirements, these should also be described.

9.4.3 Method of Assigning Patients to Treatment Groups

The specific methods used to assign patients to treatment groups, e.g., centralized allocation, allocation within sites, adaptive allocation (that is, assignment on the basis of earlier assignment or outcome) should be described in the text of the report, including any stratification or blocking procedures. Any unusual features should be explained.

A detailed description of the randomization method, including how it was executed, should be given in Appendix 16.1.7 with references cited if necessary. A table exhibiting the randomization codes, patient identifier, and treatment assigned should also be presented in the Appendix. For a multicenter study, the information should be given by center. The method of generating random numbers should be explained.

For a historically controlled trial, it is important to explain how the particul ar control was selected and what other historical experiences were examined, if any, and how their results compared to the control used.

9.4.4 Selection of Doses in the Study

The doses or dose ranges used in the study should be given for all treatments and the basis for choosing them described (e.g., prior experience in humans, animal data).

9.4.5 Selection and Timing of Dose for Each Patient

Procedures for selecting each patient's dose of test drug/ investigational product and active control/comparator should be described. These procedures can vary from simple random assignment to a selected fixed drug/dose regimen, to use of a specified titration procedure, or to more elaborate response-determined selection procedures, e.g., where dose is titrated upward at intervals until intolerance or

some specified endpoint is achieved. Procedures for back-titration, if any, should also be described.

The timing (time of day, interval) of dosing and the relation of dosing to meals should be described and, if timing was not specified, this should be noted.

Any specific instructions to patients about when or how to take the dose(s) should be described.

9.4.6 Blinding

A description of the specific procedures used to carry out blinding should be provided (e.g., how bottles were labeled, use of labels that reveal blind-breakage, sealed code list/envelopes, double dummy techniques), including the circumstances in which the blind would be broken for an individual or for all patients (e.g., for serious adverse events), the procedures used to do this, and who had access to patient codes. If the study allowed for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Measures taken to ensure that test drug/investigational product and placebo were indistinguishable and evidence that they were indistinguishable should be described, as should the appearance, shape, smell, and taste of the test material. Measures to prevent unblinding by laboratory measurements, if used, should be described. If there was a data monitoring committee with access to unblinded data, procedures to ensure maintenance of overall study blinding should be described. The procedure used to maintain the blinding when interim analyses were performed should also be explained.

If blinding was considered unnecessary to reduce bias for some or all of the observations, this should be explained; e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias. If blinding was considered desirable but not feasible, the reasons and implications should be discussed. Sometimes blinding is attempted but is known to be imperfect because of obvious drug effects in at least some patients (dry mouth, bradycardia, fever, injection site reactions, changes in laboratory data). Such problems or potential problems should be identified and, if there were any attempts to assess the magnitude of the problem or manage it (e.g., by having endpoint measurements carried out by people shielded from information that might reveal treatment assignment), they should be described.

9.4.7 Prior and Concomitant Therapy

Which drugs or procedures were allowed before and during the study, whether and

how their use was recorded, and any other specific rules and procedures related to permitted or prohibited concomitant therapy should be described. How allowed concomitant therapy might affect the outcome due either to drug-drug interaction or to direct effects on the study endpoints should be discussed, and how the independent effects of concomitant and study therapies could be ascertained should be explained.

9.4.8 Treatment Compliance

The measures taken to ensure and document treatment compliance should be described, e.g., drug accountability, diary cards, blood, urine or other body fluid drug level measurements, or medication event monitoring.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The specific efficacy and safety variables to be assessed and laboratory tests to be conducted, their schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to test drug administration, e.g., just prior to next dose, 2 hours after dose), the methods for measuring them, and the persons responsible for the measurements should be described. If there were changes in personnel carrying out critical measurements, these should be reported.

It is usually helpful to display graphically in a flow chart (see Annex III of the guideline) the frequency and timing of efficacy and safety measurements; visit numbers and times should be shown, or, alternatively, times alone can be used (visit numbers alone are more difficult to interpret). Any specific instructions (e.g., guidance or use of a diary) to the patients should also be noted.

Any definitions used to characterize outcome (e.g., criteria for determining occurrence of acute myocardial infarction, designation of the location of the infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between TIA and stroke, assignment of cause of death) should be explained in full. Any techniques used to standardize or compare results of laboratory tests or other clinical measurements (e.g., ECG, chest X-ray) should also be described. This is particularly important in multicenter studies.

If anyone other than the investigator was responsible for evaluation of clinical outcomes (e.g., the sponsor or an external committee to review X-rays or ECG's or to determine whether the patient had a stroke, acute infarction, or sudden death), the person or group should be identified. The procedures used, including means of maintaining blindness and centralizing readings and measurements,

should be described fully.

The means of obtaining adverse event data should be described (volunteered, checklist, or questioning), as should any specific rating scale(s) used and any specifically planned followup procedures for adverse events or any planned rechallenge procedure.

Any rating of adverse events by the investigator, sponsor, or external group (e.g., rating by severity or likelihood of drug causation) should be described. The criteria for such ratings, if any, should be given and the parties responsible for the ratings should be clearly identified. If efficacy or safety was to be assessed in terms of categorical ratings or numerical scores, the criteria used for point assignment should be provided (e.g., definitions of point scores). For multicenter studies, how methods were standardized should be indicated.

9.5.2 Appropriateness of Measurements

If any of the efficacy or safety assessments was not standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents), its reliability, accuracy, and relevance should be documented. It may be helpful to describe alternatives considered but rejected.

If a surrogate endpoint (a laboratory measurement or physical measurement or sign that is not a direct measure of clinical benefit) was used as a study endpoint, this should be justified, e.g., by reference to clinical data, publications, guidelines, or previous actions by regulatory authorities.

9.5.3 Primary Efficacy Variable(s)

The primary measurements and endpoints used to determine efficacy should be clearly specified. Although the critical efficacy measurements may seem obvious, when there are multiple variables or when variables are measured repeatedly, the protocol should identify the primary ones with an explanation of why they were chosen, or designate the pattern of significant findings or other method of combining information that would be interpreted as supporting efficacy.

If the protocol did not identify the primary variables, the study report should explain how these critical variables were selected (e.g., by reference to publications, guidelines, or previous actions by regulatory authorities) and when they were identified (i.e., before or after the study was completed and unblinded). If an efficacy threshold was defined in the protocol, this should be described.

9.5.4 Drug Concentration Measurements

Any drug concentrations to be measured and the sample collection times and periods in relation to the timing of drug administration should be described. Any relation of drug administration and sampling to ingestion of food, posture, and the possible effects of concomitant medication/alcohol/ caffeine/nicotine should also be addressed. The biological sample measured, the handling of samples and the method of measurement used should be described, referring to published and/or internal assay validation documentation for methodological details. Where other factors are believed important in assessing pharmacokinetics (e.g., soluble circulating receptors, renal or hepatic function), the timing and plans to measure these factors should also be specified.

9.6 Data Quality Assurance

The quality assurance and quality control systems implemented to assure the quality of the data should be described in brief. If none were used, this should be stated. Documentation of inter-laboratory standardization methods and quality assurance procedures, if used, should be provided under Appendix 16.1.10.
Any steps taken at the investigation site or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data, such as training sessions, monitoring of investigators by sponsor personnel, instruction manuals, data verification, cross-checking, use of a central laboratory for certain tests, centralized ECG reading, or data audits, should be described. It should be noted whether investigator meetings or other steps were taken to prepare investigators and standardize performance.

If the sponsor used an independent internal or external auditing procedure, it should be mentioned here and described in Appendix 16.1.8; audit certificates, if available, should be provided in the same appendix.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.2 Statistical and Analytical Plans

The statistical analyses planned in the protocol and any changes made before outcome results were available should be described. In this section, emphasis should be on which analyses, comparisons, and statistical tests were planned, not on which ones were actually used. If critical measurements were made more than once, the particular measurements (e.g., average of several measurements over the entire study, values at particular times, values only from study completers, or last on-therapy value) planned as the basis for comparison of test drug/investigational product and control should be specified. Similarly, if more than one analytical

approach is plausible, e.g., changes from baseline response, slope analysis, life-table analysis, the planned approach should be identified. Also, whether the primary analysis is to include adjustment for covariates should be specified.

If there were any planned reasons for excluding from analysis patients for whom data are available, these should be described. If there were any subgroups whose results were to be examined separately, these should be identified. If categorical responses (global scales, severity scores, responses of a certain size) were to be used in analyzing responses, they should be clearly defined.

Planned monitoring of the results of the study should be described. If there was a data monitoring committee, either within or outside the sponsor's control, its composition and operating procedures should be described and procedures to maintain study blinding should be given. The frequency and nature of any planned interim analysis, any specified circumstances in which the study would be terminated, and any statistical adjustments to be employed because of interim analyses should be described.

9.7.2 Determination of Sample Size

The planned sample size and the basis for it, such as statistical considerations or practical limitations, should be provided. Methods for sample size calculation should be given together with their derivations or source of reference. Estimates used in the calculations should be given, and explanations should be provided as to how they were obtained. For a study intended to show a difference between treatments, the difference the study is designed to detect should be specified. For a positive control study intended to show that a new therapy is at least as effective as the standard therapy, the sample size determination should specify the difference between treatments that would be considered unacceptably large and, therefore, the difference the study is designed to be able to exclude.

9.8 Changes in the Conduct of the Study or Planned Analyses

Any change in the conduct of the study or planned analyses (e.g., dropping a treatment group, changing the entry criteria or drug dosages, adjusting the sample size) instituted after the start of the study should be described. The time(s) and reason(s) for the change(s), the procedure used to decide on the change(s), the person(s) or group(s) responsible for the change(s) and the nature and content of the data available (and to whom they were available) when the change was made should also be described, whether the change was documented as a formal protocol amendment or not. Personnel changes need not be included. Any possible implications of the change(s) for the interpretation of the study should be discussed briefly in this section and more fully in other appropriate sections of the report. In every section of the report, a clear distinction between conditions

(procedures) planned in the protocol and amendments or additions should be made. In general, changes in planned analyses made prior to breaking the blind have limited implications for study interpretation. It is therefore particularly critical that the timing of changes relative to blind breaking and availability of outcome results be well characterized.

10. STUDY PATIENTS

10.1 Disposition of Patients

There should be a clear accounting of all patients who entered the study, using figures or tables in the text of the report. The numbers of patients who were randomized and who entered and completed each phase of the study (or each week/month of the study) should be provided, as well as the reasons for all postrandomization discontinuations, grouped by treatment and by major reason (e.g., lost to followup, adverse event, poor compliance). It may also be relevant to provide the number of patients screened for inclusion and a breakdown of the reasons for excluding patients during screening, if this could help clarify the appropriate patient population for eventual drug use. A flow chart is often helpful (see Annexes IVa and IVb for examples). Whether patients are followed for the duration of the study, even if drug is discontinued, should be made clear.

In Appendix 16.2.1, there should also be a listing of all patients discontinued from the study after enrollment, broken down by center and treatment group, giving a patient identifier, the specific reason for discontinuation, the treatment (drug and dose), cumulative dose (where appropriate), and the duration of treatment before discontinuation. Whether or not the blind for the patient was broken at the time of discontinuation should be noted. It may also be useful to include other information, such as critical demographic data (e.g., age, sex, race), concomitant medication, and the major response variable(s) at termination. See Annex V for an example of such a listing.

10.2 Protocol Deviations

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient managements or patient assessment should be described.

In the body of the text, protocol deviations should be appropriately summarized by center and grouped into different categories, such as:

- Those who entered the study even though they did not satisfy the entry criteria.
- Those who developed withdrawal criteria during the study but were not withdrawn.
- Those who received the wrong treatment or incorrect dose.

- Those who received an excluded concomitant treatment.

In Appendix 16.2.2, individual patients with these protocol deviations should be listed, broken down by center for multicenter studies.

11. EFFICACY EVALUATION

11.1 Data Sets Analyzed

Exactly which patients were included in each efficacy analysis should be precisely defined, e.g., all patients receiving any test drugs/investigational products, all patients with any efficacy observation or with a certain minimum number of observations, only patients completing the trial, all patients with an observation during a particular time window, or only patients with a specified degree of compliance. It should be clear, if not defined in the study protocol, when (relative to study unblinding) and how inclusion/exclusion criteria for the data sets analyzed were developed. Generally, even if the applicant's proposed primary analysis is based on a reduced subset of the patients with data, there should also be, for any trial intended to establish efficacy, an additional analysis using all randomized (or otherwise entered) patients with any on-treatment data.

There should be a tabular listing of all patients, visits, and observations excluded from the efficacy analysis provided in Appendix 16.2.3 (see Annex VI for an example). The reasons for exclusions should also be analyzed for the whole treatment group over time (see Annex VII for an example).

11.2 Demographic and Other Baseline Characteristics

Group data for the critical demographic and baseline characteristics of the patients, as well as other factors arising during the study that could affect response, should be presented in this section and comparability of the treatment groups for all relevant characteristics should be displayed by use of tables or graphs in section 14.1. The data for the patient sample included in the “all patients with data” analysis should be given first. This may be followed by data on other groups used in principal analyses, such as the “per-protocol” analysis or other analyses, e.g., groups defined by compliance, concomitant disease/therapy, or demographic/baseline characteristics. When such groups are used, data for the complementary excluded group should also be shown. In a multicenter study, where appropriate, comparability should be assessed by center, and centers should be compared.

A diagram showing the relationship between the entire sample and any other analysis groups should be provided.

The critical variables will depend on the specific nature of the disease and on the protocol

but will usually include:

- Demographic variables:
  - Age
  - Sex
  - Race

- Disease factors:
  - Specific entry criteria (if not uniform), duration, stage and severity of disease, and other clinical classifications and subgroupings in common usage or of known prognostic significance.
  - Baseline values for critical clinical measurements carried out during the study or identified as important indicators of prognosis or response to therapy.
  - Concomitant illness at trial initiation, such as renal disease, diabetes, heart failure.
  - Relevant previous illness.
  - Relevant previous treatment for illness treated in the study.
  - Concomitant treatment maintained, even if the dose was changed during the study, including oral contraceptive and hormone replacement therapy; treatments stopped at entry into the study period (or changed at study initiation).

- Other factors that might affect response to therapy (e.g., weight, renin status, antibody levels, metabolic status).

- Other possibly relevant variables (e.g., smoking, alcohol intake, special diets) and, for women, menstrual status and date of last menstrual period, if pertinent for the study.

In addition to tables and graphs giving group data for these baseline variables, relevant individual patient demographic and baseline data, including laboratory values, and all concomitant medication for all individual patients randomized (broken down by treatment and by center for multicenter studies) should be presented in by-patient tabular listings in Appendix 16.2.4. Although some regulatory authorities will require all baseline data to be presented elsewhere in tabular listings, the Appendix to the study report should be limited to only the most relevant data, generally the variables listed above.

11.3. Measurements of Treatment Compliance

Any measurements of compliance of individual patients with the treatment regimen under study and drug concentrations in body fluids should be summarized, analyzed by treatment group and time interval, and tabulated in Appendix 16.2.5.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy

Treatment groups should be compared for all critical measures of efficacy (primary and secondary endpoints; any pharmacodynamic endpoints studied), as well as benefit/risk assessment(s) in each patient where these are utilized. In general, the results of all analyses contemplated in the protocol and an analysis including all patients with on-study data should be performed in studies intended to establish efficacy. The analysis should show the size (point estimate) of the difference between the treatments, the associated confidence interval, and, where utilized, the results of hypothesis testing.

Analyses based on continuous variables (e.g., mean blood pressure or depression scale score) and categorical responses (e.g., cure of an infection) can be equally valid; ordinarily both should be presented if both were planned and are available. If categories are newly created (i.e., not in the statistical plan) the basis for them should be explained. Even if one variable receives primary attention (e.g., in a blood pressure study, supine blood pressure at week “x”), other reasonable measures (e.g., standing blood pressure and blood pressures at other particular times) should be assessed, at least briefly. In addition, the time course of response should be described, if possible. For a multicenter study, where appropriate, data display and analysis of individual centers should be included for critical variables to give a clear picture of the results at each site, especially the larger sites.

If any critical measurements or assessments of efficacy or safety outcomes were made by more than one party (e.g., both the investigator and an expert committee may offer an opinion on whether a patient had an acute infarction), overall differences between the ratings should be shown, and each patient having disparate assessments should be identified. The assessments used should be clear in all analyses.

In many cases, efficacy and safety endpoints are difficult to distinguish (e.g., deaths in a fatal disease study). Many of the principles addressed below should be adopted for critical safety measures as well.

11.4.2 Statistical/Analytical Issues

The statistical analysis used should be described for clinical and statistical reviewers in the text of the report, with detailed documentation of statistical methods (see Annex IX) presented in Appendix 16.1.9. Important features of the analysis, including the particular methods used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of dropouts and missing data, adjustments for multiple comparisons, special analyses of multicenter studies, and adjustments for interim analyses, should be discussed. Any changes in

the analysis made after blind-breaking should be identified.

In addition to the general discussion, the following specific issues should be addressed (unless not applicable):

11.4.2.1 Adjustments for Covariates

Selection of, and adjustments for, demographic or baseline measurements, concomitant therapy, or any other covariates or prognostic factors should be explained in the report, and methods of adjustment, results of analyses, and supportive information (e.g., ANCOVA or Cox regression output) should be included in the detailed documentation of statistical methods. If the covariates or methods used in these analyses differed from those planned in the protocol, the differences should be explained and, where possible and relevant, the results of planned analyses should also be presented. Although not part of the individual study report, comparisons of covariate adjustments and prognostic factors across individual studies may be an informative analysis in a summary of clinical efficacy data.

11.4.2.2 Handling of Dropouts or Missing Data

There are several factors that may affect dropout rates. These include the duration of the study, the nature of the disease, the efficacy and toxicity of the drug under study, and other factors that are not therapy-related. Ignoring the patients who dropped out of the study and drawing conclusions based only on patients who completed the study can be misleading. A large number of dropouts, however, even if included in an analysis, may introduce bias, particularly if there are more early dropouts in one treatment group or the reasons for dropping out are treatment or outcome related. Although the effects of early dropouts, and sometimes even the direction of bias, can be difficult to determine, possible effects should be explored as fully as possible. It may be helpful to examine the observed cases at various times or, if dropouts were very frequent, to concentrate on analyses at times when most of the patients were still under observation and when the full effect of the drug was realized. It may also be helpful to examine modeling approaches to the evaluation of such incomplete data sets.

The results of a clinical trial should be assessed not only for the subset of patients who completed the study, but also for the entire patient population as randomized or at least for all those with any on-study measurements.

Several factors should be considered and compared for the treatment groups in analyzing the effects of dropouts: The reasons for the dropouts, the time to dropout, and the proportion of dropouts among treatment groups at various time points.

Procedures for dealing with missing data, e.g., use of estimated or derived data, should be described. Detailed explanation should be provided as to how such estimations or derivations were done and what underlying assumptions were made.

11.4.2.3 Interim Analyses and Data Monitoring

The process of examining and analyzing data accumulating in a clinical trial, either formally or informally, can introduce bias and/or increase type I error. Therefore, all interim analyses, formal or informal, preplanned or ad hoc, by any study participant, sponsor staff member, or data monitoring group should be described in full, even if the treatment groups were not identified. The need for statistical adjustment because of such analyses should be addressed. Any operating instructions or procedures used for such analyses should be described. The minutes of meetings of any data monitoring group and any data reports reviewed at those meetings, particularly a meeting that led to a change in the protocol or early termination of the study, may be helpful and should be provided in Appendix 16.1.9. Data monitoring without code-breaking should also be described, even if this kind of monitoring is considered to cause no increase in type I error.

11.4.2.4 Multicenter Studies

A multicenter study is a single study under a common protocol, involving several centers (e.g., clinics, practices, hospitals) where the data collected are intended to be analyzed as a whole (as opposed to a post-hoc decision to combine data or results from separate studies). Individual center results should be presented, however, where appropriate, e.g., when the centers have sufficient numbers of patients to make such analysis potentially valuable, the possibility of qualitative or quantitative treatment-by-center interaction should be explored. Any extreme or opposite results among centers should be noted and discussed, considering such possibilities as differences in study conduct, patient characteristics, or clinical settings. Treatment comparison should include analyses that allow for center differences with respect to response. If appropriate, demographic, baseline, and postbaseline data, as well as efficacy data, should be presented by center, even though the combined analysis is the primary one.

11.4.2.5 Multiple Comparisons/Multiplicity

False/positive findings increase in number as the number of significance tests (number of comparisons) performed increases. If there was more than one primary endpoint (outcome variable) or more than one analysis of particular endpoint, or if there were multiple treatment groups or subsets of the patient population being examined, the statistical analysis should reflect awareness of this and either explain the statistical adjustment used for type I error criteria or give reasons why it was considered unnecessary.

11.4.2.6 Use of an "Efficacy Subset" of Patients

Particular attention should be devoted to the effects of dropping patients with available data from analyses because of poor compliance, missed visits, ineligibility, or any other reason. As noted above, an analysis using all available data should be carried out for all studies intended to establish efficacy, even if it is not the analysis proposed as the primary analysis by the applicant. In general, it is advantageous to demonstrate robustness of the principal trial conclusions with respect to alternative choices of patient populations for analysis. Any substantial differences resulting from the choice of patient population for analysis should be the subject of explicit discussion.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

If an active control study is intended to show equivalence (i.e., lack of a difference greater than a specified size) between the test drug/investigational product and the active control/comparator, the analysis should show the confidence interval for the comparison between the two agents for critical endpoints and the relation of that interval to the prespecified degree of inferiority that would be considered unacceptable. (See section 9.2 for important considerations when using the active control equivalence design.)

11.4.2.8 Examination of Subgroups

If the size of the study permits, important demographic or baseline value-defined subgroups should be examined for unusually large or small responses and the results presented, e.g., comparison of effects by age, sex, or race; by severity or prognostic groups; and by history of prior treatment with a drug of the same class. If these analyses were not carried out because the study was too small, it should be noted. These analyses are not intended to "salvage" an otherwise nonsupportive study but may suggest

hypotheses worth examining in other studies or be helpful in refining labeling information, patient selection, or dose selection. Where there is a prior hypothesis of a differential effect in a particular subgroup, this hypothesis and its assessment should be part of the planned statistical analysis.

11.4.3 Tabulation of Individual Response Data

In addition to tables and graphs representing group data, individual response data and other relevant study information should be presented in tables. Some regulatory authorities may require all individual data in archival case report tabulations. What needs to be included in the report will vary from study to study and from one drug class to another, and the applicant must decide, if possible after consultation with the regulatory authority, what to include in an Appendix to the study report. The study report should indicate what material is included as an Appendix, what is in the more extensive archival case report tabulations, if required by the regulatory authority, and what is available on request.

For a controlled study in which critical efficacy measurements or assessments (e.g., blood or urine cultures, pulmonary function tests, angina frequency, or global evaluations) are repeated at intervals, the data listings accompanying the report should include, for each patient, a patient identifier, all measured or observed values of critical measurements, including baseline measurements, with notation of the time during the study (e.g., days on therapy and time of day, if relevant) when the measurements were made, the drug/dose at the time (if useful, given as milligram per kilogram (mg/kg)), any measurements of compliance, and any concomitant medications at the time of, or close to the time of, measurement or assessment. If, aside from repeated assessments, the study included some overall responder versus nonresponder evaluation(s) (bacteriologic cure or failure), it should also be included. In addition to critical measurements, the tabulation should note whether the patient was included in the efficacy evaluation (and which evaluation, if more than one), provide patient compliance information, if collected, and a reference to the location of the case report form, if included. Critical baseline information such as age, sex, and weight; disease being treated (if more than one in study); and disease stage or severity is also helpful. The baseline values for critical measurements would ordinarily be included as zero time values for each efficacy measurement.

The tabulation described should usually be included in Appendix 16.2.6 of the study report, rather than in the more extensive case report tabulations required by some regulatory authorities, because it represents the basic efficacy data supporting summary tables. Such a thorough tabulation can be unwieldy for review purposes, however, and it is expected that more targeted displays will be

developed as well. For example, if there are many measurements reported, tabulations of the most critical measurements for each patient (e.g., the blood pressure value at certain visits might be more important than others) will be useful in providing an overview of each individual's results in a study, with each patient's response summarized on a single line or small number of lines.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

When the dose in each patient can vary, the actual doses received by patients should be shown and individual patient's doses should be tabulated. Although studies not designed as dose-response studies may have limited ability to contribute dose-response information, the available data should be examined for whatever information they can yield. In examining the dose response, it may be helpful to calculate dose as mg/kg body weight or milligram per square meter (mg/m2) body surface.

Drug concentration information, if available, should also be tabulated (Appendix 16.2.5), analyzed in pharmacokinetic terms, and, if possible, related to response.

Further guidance on the design and analysis of studies exploring dose-response or concentration response can be found in the ICH Guideline entitled "Dose-Response Information to Support Drug Registration."

11.4.5 Drug-Drug and Drug-Disease Interactions

Any apparent relationship between response and concomitant therapy and between response and past and/or concurrent illness should be described.

11.4.6 By-Patient Displays

While individual patient data ordinarily can be displayed in tabular listings, it has on occasion been helpful to construct individual patient profiles in other formats, such as graphic displays. These might, for example, show the value of a particular parameter(s) over time, the drug dose over the same period, and the times of particular events (e.g., an adverse event or change in concomitant therapy). Where group mean data represent the principal analyses, this kind of "case report extract" may offer little advantage; it may be helpful, however, if overall evaluation of individual responses is a critical part of the analysis.

11.4.7 Efficacy Conclusions

The important conclusions concerning efficacy should be concisely described, considering primary and secondary endpoints, prespecified and alternative

statistical approaches, and results of exploratory analyses.

12. SAFETY EVALUATION

Analysis of safety-related data can be considered at three levels. First, the extent of exposure (dose, duration, number of patients) should be examined to determine the degree to which safety can be assessed from the study. Second, the more common adverse events and laboratory test changes should be identified, classified in some reasonable way, compared for treatment groups, and analyzed, as appropriate, for factors that may affect the frequency of adverse reactions/events, such as time dependence, relation to demographic characteristics, relation to dose or drug concentration. Finally, serious adverse events and other significant adverse events should be identified, usually by close examination of patients who left the study prematurely because of an adverse event, whether or not identified as drug related, or who died.

The ICH Guideline entitled "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" defines serious adverse events as follows: "A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect."

For the purpose of this guideline, "other significant adverse events" are marked hematological and other laboratory abnormalities and any adverse events that led to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.

In the following sections, three kinds of analysis and display are called for:

1. Summarized data, often using tables and graphical presentations presented in the main body of the report;
2. Listings of individual patient data; and
3. Narrative statements of events of particular interest.

In all tabulations and analyses, events associated with both test drug and control treatment should be displayed.

12.1 Extent of Exposure

The extent of exposure to test drugs/investigational products (and to active control and placebo) should be characterized according to the number of patients exposed, the duration of exposure, and the dose to which they were exposed.

- Duration: Duration of exposure to any dose can be expressed as a median or mean, but it is also helpful to describe the number of patients exposed for specified periods of time, such as for 1 day or less, 2 days to 1 week, more than 1 week to 1

month, more than 1 month to 6 months. The numbers exposed to test drug(s)/investigational product(s) for the various durations should also be broken down into age, sex, and racial subgroups, and any other pertinent subgroups, such as groups defined by disease (if more than one is represented), disease severity, or concurrent illness.

- Dose: The mean or median dose used and the number of patients exposed to specified daily dose levels should be given; the daily dose levels used could be the maximum dose for each patient, the dose with longest exposure for each patient, or the mean daily dose. It is often useful to provide combined dose-duration information, such as the numbers exposed for a given duration (e.g., at least 1 month) to the most common dose, the highest dose, or the maximum recommended dose. In some cases, cumulative dose might be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m<SUP>2 basis, as appropriate. The number of patients exposed to various doses should be broken down into age, sex, racial, and any other pertinent subgroups.

- Drug concentration: If available, drug concentration data (e.g., concentration at the time of an event, maximum plasma concentration, area under curve) may be helpful in individual patients for correlation with adverse events or changes in laboratory variables. (Appendix 16.2.5.)

It is assumed that all patients entered into treatment who received at least one dose of the treatment are included in the safety analysis; if not, an explanation should be provided.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

The overall adverse event experience in the study should be described in a brief narrative, supported by the following more detailed tabulations and analyses. In these tabulations and analyses, events associated with both the test drug and control treatment should be displayed.

12.2.2 Display of Adverse Events

All adverse events occurring after initiation of study treatments (including events likely to be related to the underlying disease or likely to represent concomitant illness, unless there is a prior agreement with the regulatory authority to consider specified events as disease related) should be displayed in summary tables (section 14.3.1). The tables should include changes in vital signs and any laboratory changes that were considered serious adverse events or other significant adverse events.

In most cases, it will also be useful to identify in such tables "treatment emergent signs and symptoms" (TESS: events not seen at baseline and events that worsened even if present at baseline).

The tables should list each adverse event, the number of patients in each treatment group in whom the event occurred, and the rate of occurrence. When treatments are cyclical, e.g., cancer chemotherapy, it may also be helpful to list results separately for each cycle. Adverse events should be grouped by body system. Each event may then be divided into defined severity categories (e.g., mild, moderate, severe) if these were used. The tables may also divide the adverse events into those considered at least possibly related to drug use and those considered not related, or use another causality scheme (e.g., unrelated or possibly, probably, or definitely related). Even when such a causality assessment is used, the tables should include all adverse events, whether or not considered drug related, including events thought to represent intercurrent illnesses. Subsequent analyses of the study or of the overall safety data base may help to distinguish between adverse events that are, or are not, considered drug related. So that it is possible to analyze and evaluate the data in these tables, it is important to identify each patient having each adverse event. An example of such a tabular presentation is shown below.

ADVERSE EVENTS: NUMBER OBSERVED AND RATE, WITH PATIENT IDENTIFICATION

Treatment Group X **N=50**

	Mild		**Moderate**		**Severe**		**Total**		**Total**
	Related[1]	**NR[1]**	**Related**	**NR**	**Related**	**NR**	**Related**	**NR**	**R+NR**
Body System A									
Event 1	6(12%)	2(4%)	3(6%)	1(2%)	3(6%)	1(2%)	12(24%)	4(8%)	
	N11[2]	N21	N31	N41	N51	N61			
	N12	N22	N32		N52				
	N13		N33		N53				
	N14								
	N15								
	N16								
Event 2									

[1]NR = not related; related coud be expanded, e.g., as definite, probable, possible.
[2]Patient identification number.

In addition to these complete tables provided in section 14.3.1, an additional summary table comparing treatment and control groups, without the patient identifying numbers and limited to relatively common adverse events (e.g., those in at least 1 percent of the treated group), should be provided in the body of the report.

In presenting adverse events, it is important both to display the original terms used by the investigator and to attempt to group related events (i.e., events that probably represent the same phenomenon), so that the true occurrence rate is not obscured. One way to do this is with a standard adverse reaction/events dictionary.

12.2.3 Analysis of Adverse Events

The basic display of adverse event rates described in section 12.2.2 (and located in section 14.3.1) of the report should be used to compare rates in treatment and control groups. For this analysis, it may be helpful to combine the event severity categories and the causality categories, leading to a simpler side-by-side comparison of treatment groups. In addition, although this is usually best done in an integrated analysis of safety, if study size and design permit, it may be useful to examine the more common adverse events that seem to be drug related for relationship to dosage and mg/kg or mg/m<SUP>2 dose; dose regimen; duration of treatment; total dose; demographic characteristics such as age, sex, race; other baseline features such as renal status, efficacy outcomes, and drug concentration. It may also be useful to examine time of onset and duration of adverse events. A variety of additional analyses may be suggested by the study results or by the pharmacology of the test drug/investigational product.

It is not intended that every adverse event be subjected to rigorous statistical evaluation. It may be apparent from initial display and inspection of the data that a significant relation to demographic or other baseline features is not present. If the studies are small and if the number of events is relatively small, it may be sufficient to limit analyses to a comparison of treatment and control.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates. When treatments are cyclical, e.g., cancer chemotherapy, it may also be helpful to analyze results separately for each cycle.

12.2.4 Listing of Adverse Events by Patient

All adverse events for each patient, including the same event on several occasions,

should be listed in Appendix 16.2.7, giving both preferred term and the original term used by the investigator. The listing should be by investigator and by treatment group and should include:

- Patient identifier.
- Age, race, sex, weight (height, if relevant).
- Location of case report forms, if provided.
- The adverse event (preferred term, reported term).
- Duration of the adverse event.
- Severity (e.g., mild, moderate, severe).
- Seriousness (serious/nonserious).
- Action taken (none, dose reduced, treatment stopped, specific treatment instituted, and so forth).
- Outcome (e.g., CIOMS format).
- Causality assessment (e.g., related/not related). How this was determined should be described in the table or elsewhere.
- Date of onset or date of clinic visit at which the event was discovered.
- Timing of onset of the adverse event in relation to the last dose of the test drug/investigational product (when applicable).
- Study treatment at the time of event or the most recent study treatment taken.
- Test drug/investigational product dose in absolute amount, mg/kg or mg/m<SUP>2, at time of event.
- Drug concentration (if known).
- Duration of test drug/investigational product treatment.
- Concomitant treatment during study.

Any abbreviations and codes should be clearly explained at the beginning of the listing or, preferably, on each page.

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths, other serious adverse events, and other significant adverse events deserve special attention.

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Listings, containing the same information as called for in section 12.2.4, should be provided for the following events.

12.3.1.1 Deaths

All deaths during the study, including the post-treatment followup period, and deaths that resulted from a process that began during the study, should be listed by patient in section 14.3.2.

12.3.1.2 Other Serious Adverse Events

All serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be listed in section 14.3.2. The listing should include laboratory abnormalities, abnormal vital signs, and abnormal physical observations that were considered serious adverse events.

12.3.1.3 Other Significant Adverse Events

Marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events, should be listed in section 14.3.2.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

There should be a brief narrative describing each death, other serious adverse event, and other significant adverse event that is judged to be of special interest because of clinical importance. These narratives can be placed either in the text of the report or in section 14.3.3, depending on their number. Events that were

clearly unrelated to the test drug/investigational product may be omitted or described very briefly. In general, the narrative should describe the following: The nature and intensity of event; the clinical course leading up to event, with an indication of timing relevant to test drug/investigational product administration; relevant laboratory measurements; whether the drug was stopped, and when; countermeasures; post-mortem findings; investigator's opinion on causality and sponsor's opinion on causality, if appropriate.

In addition, the following information should be included:

- Patient identifier.
- Age and sex of patient; general clinical condition of patient, if appropriate.
- Disease being treated (this is not required if it is the same for all patients) with duration (of current episode) of illness.
- Relevant concomitant/previous illnesses with details of occurrence/ duration.
- Relevant concomitant/previous medication with details of dosage.
- Test drug/investigational product administered; drug dose, if this varied among patients; and length of time administered.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The significance of the deaths, other serious adverse events, and other significant adverse events leading to withdrawal, dose reduction, or institution of concomitant therapy should be assessed with respect to the safety of the test drug/investigational product. Particular attention should be paid to whether any of these events may represent a previously unsuspected important adverse effect of the test drug/investigational product. For serious adverse events that appear of particular importance, it maybe useful to use life table or similar analyses to show their relation to time on test drug/investigational product and to assess their risk over time.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Patient (Appendix 16.2.8) and Each Abnormal Laboratory Value (see section 14.3.4)

When required by regulatory authorities, the results of all safety-related laboratory tests should be available in tabular listings, using a display similar to the following, where each row represents a patient visit at which a laboratory study was done, with patients grouped by investigator (if more than one) and treatment group, and columns include critical demographic data, drug dose data, and the results of the laboratory tests. Because not all tests can be displayed in a single table, they should be grouped logically (e.g., hematological tests, liver chemistries, electrolytes, urinalysis). Abnormal values should be identified, e.g., by underlining or bracketing. These listings should be submitted as part of the registration/marketing application, when this is required, or may be available on request.

List of Laboratory Measurement

							Laboratory Tests			
Patient	Time	Age	Sex	Race	Weight	Dose	SGOT	SGPT	AP	X
#1	T0	70			70 kg	400 mg	V1†	V5	V9	
	T1						V2	V6	V10	
	T2						V3	V7	V11	
	T3						V4	V8	V12	
#2	T10	65	F	B	50 kg	300 mg	V13	V16	V19	
	T21						V14	V17	V20	
	T32						V15	V18	V21	

†Vn = value of particular test

For all regulatory authorities, there should be a by-patient listing of all abnormal laboratory values in section 14.3.4, using the format described above. For laboratory abnormalities of special interest (abnormal laboratory values of potential clinical importance), it may also be useful to provide additional data, such as normal values before and after the abnormal value, and values of related laboratory tests. In some cases, it may be desirable to exclude certain abnormal values from further analysis. For example, single, nonreplicated, small abnormalities of some tests (e.g., uric acid or electrolytes) or occasional low values of some tests (e.g., transaminase, alkaline phosphatase, or BUN) can probably be defined as clinically insignificant and excluded. Any such decisions should be clearly explained, however, and the complete list of values provided (or available to authorities on request) should identify every abnormal value.

12.4.2 Evaluation of Each Laboratory Parameter

The necessary evaluation of laboratory values will in part be determined by the results seen, but, in general, the following analyses should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and compatible with study size. In addition, normal laboratory ranges should be given for each analysis.

12.4.2.1 Laboratory Values Over Time

For each parameter at each time over the course of the study (e.g., at each visit) the following should be described: The group mean or median values, the range of values, and the number of patients with abnormal values or with abnormal values that are of a certain size (e.g., twice the upper limit of normal or five times the upper limit; choices should be explained). Graphs may be used.

12.4.2.2 Individual Patient Changes

An analysis of individual patient changes by treatment group should be given. A variety of approaches may be used, including:

i) "Shift tables" - These tables show the number of patients who are low, normal, or high at baseline and at selected time intervals.

ii) Tables showing the number or fraction of patients who had a change in parameter of a predetermined size at selected time intervals. For example, for BUN, it might be decided that a change of more than 10 mg/dL BUN should be noted. For this parameter, the number of patients having a smaller or greater change would be shown for one or more visits, usually grouping patients separately depending on baseline BUN (normal or elevated). The possible advantage of this display, compared to the usual shift table, is that changes of a certain size are noted, even if the final value is not abnormal.

iii) A graph comparing the initial value and the on-treatment values of a laboratory measurement for each patient by locating the point defined by the initial value on the abscissa and a subsequent value on the ordinate. If no changes occur, the point representing each patient will be located on the 45 deg. line. A general shift to higher values will show a clustering of points above the 45 deg. line. As this display usually shows only a single time point for a single treatment, interpretation requires a time series of these plots

for treatment and control groups. Alternatively, the display could show baseline and most extreme on-treatment value. These displays identify outliersreadily (it is useful to include patient identifiers for the outliers).

12.4.2.3. Individual Clinically Significant Abnormalities

Clinically significant changes (defined by the applicant) should be discussed. A narrative of each patient whose laboratory abnormality was considered a serious adverse event and, in certain cases, considered an "other significant adverse event," should be provided under section 12.3.2 or 14.3.3. When toxicity grading scales are used (e.g., WHO, NCI), changes graded as severe should be discussed regardless of seriousness. An analysis of the clinically significant changes, together with a recapitulation of discontinuations due to laboratory measurements, should be provided for each parameter. The significance of the changes and likely relation to the treatment should be assessed, e.g., by analysis of such features as relationship to dose, relationship to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs, other physical findings, and other observations related to safety should be analyzed and presented in a way similar to laboratory variables. If there is evidence of a drug effect, any dose-response or drug-concentration-response relationship or relationship to patient variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events.

12.6 Safety Conclusions

The overall safety evaluation of the test drug(s)/investigational product(s) should be reviewed, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk should be identified and particular attention should be paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of drug metabolism or excretion. The implication of the safety evaluation for the possible uses of the drug should be described.

13. DISCUSSION AND OVERALL CONCLUSIONS

The efficacy and safety results of the study and the relationship of risks and benefits should be briefly summarized and discussed, referring to the tables, figures, and sections above as needed. The presentation should not simply repeat the description of results nor introduce new results.

The discussion and conclusions should clearly identify any new or unexpected findings, comment on their significance, and discuss any potential problems such as inconsistencies between related measures. The clinical relevance and importance of the results should also be discussed in the light of other existing data. Any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies should be identified. Alternatively, such discussions may be reserved for summaries of safety and efficacy referring to the entire dossier (integrated summaries).

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Figures should be used to visually summarize the important results, or to clarify results that are not easily understood from tables.

Important demographic, efficacy, and safety data should be presented in summary figures or tables in the text of the report. However, if these become obtrusive because of size or number they should be presented here, cross-referenced to the text, along with supportive, or additional, figures, tables, or listings.

The following information may be presented in this section of the core clinical study report:

14.1 Demographic Data Summary figures and tables.

14.2 Efficacy Data Summary figures and tables.

14.3 Safety Data Summary figures and tables.

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each patient)

15. REFERENCE LIST

A list of articles from the literature pertinent to the evaluation of the study should be provided.

Copies of important publications should be attached in an Appendix (Appendices 16.1.11 and 16.1.12). References should be given in accordance with the internationally accepted standards of the 1979 Vancouver Declaration on “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” or the system used in “Chemical Abstracts.”

16. APPENDICES

This section should be prefaced by a full list of all Appendices available for the study report. Where permitted by the regulatory authority, some of the following Appendices need not be submitted with the report but need to be provided only on request.

The applicant should therefore clearly indicate those Appendices that are submitted with the report.

N.B.: In order to have Appendices available on request, they should be finalized by the time of filing of the submission.

16.1 Study Information

16.1.1 Protocol and protocol amendments.

16.1.2 Sample case report form (unique pages only).

16.1.3 List of IEC's or IRB's (plus the name of the committee chair if required by the regulatory authority) and representative written information for patient and sample consent forms.

16.1.4 List and description of investigators and other important participants in the study, including brief (one page) CV's or equivalent summaries of training and experience relevant to the performance of the clinical study.

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement.

16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.

16.1.7 Randomization scheme and codes (patient identification and treatment assigned).

16.1.8 Audit certificates (if available).

16.1.9 Documentation of statistical methods.

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used.

16.1.11. Publications based on the study.

16.1.12 Important publications referenced in the report.

16.2 Patient Data Listings

16.2.1 Discontinued patients.

16.2.2 Protocol deviations.

16.2.3 Patients excluded from the efficacy analysis.

16.2.4 Demographic data.

16.2.5 Compliance and/or drug concentration data (if available).

16.2.6 Individual efficacy response data.

16.2.7 Adverse event listings (each patient).

16.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities.

16.3. Case Report Forms (CRF's)

16.3.1 CRF's for deaths, other serious adverse events, and withdrawals for adverse events.

16.3.2 Other CRF's submitted.

16.4 Individual Patient Data Listings

ANNEX I

SYNOPSIS

Name of Sponsor/Company:	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product:		
Name of Active Ingredient:		

Title of Study:	
Investigators:	
Study centre(s):	
Publication (reference)	
Studied period (years): (date of first enrolment) (date of last completed)	Phase of development:
Objectives:	
Methodology:	
Number of patients (planned and analyzed):	
Diagnosis and main criteria for inclusion:	
Test product, dose and mode of administration, batch number:	
Duration of treatment:	
Reference therapy, dose and mode of administration, batch number	

Name of Sponsor/Company:	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:		

Criteria for evaluation:
Efficacy:

Safety:

Statistical methods:

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

SAFETY RESULTS:

CONCLUSION:

Date of the report:

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S)

OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

_____

STUDY TITLE: .....

STUDY AUTHOR(S): .....

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR:_____ SIGNATURE(S)_____
OR SPONSOR'S RESPONSIBLE
MEDICAL OFFICER

AFFILIATION:_____ _____

_____

DATE:_____

ANNEX IIIa

STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

TREATMENT PERIOD	A	B		C	
		B1	B2	C1	C2
	Run-in	**TEST DRUG/ INVESTIGATIONAL PRODUCT A**		**TEST DRUG/ INVESTIGATIONAL PRODUCT A**	
		5 mg	**10 mg**	**5 mg**	**10 mg**
		TEST DRUG/ INVESTIGATIONAL PRODUCT B		**TEST DRUG/ INVESTIGATIONAL PRODUCT B**	
		5 mg	**10 mg**	**5 mg**	**10 mg**

Weeks	-2(-3)	0	3	6	9	12
Visit	1	2	3	4	5	6
Exercise test 24 h	x[1]	x[2]	x	x	x	x
Medical history	x					
Physical examination	x					x
ECG	x					x
Lab. invest.	x					x
Adverse events		x	x	x	x	x

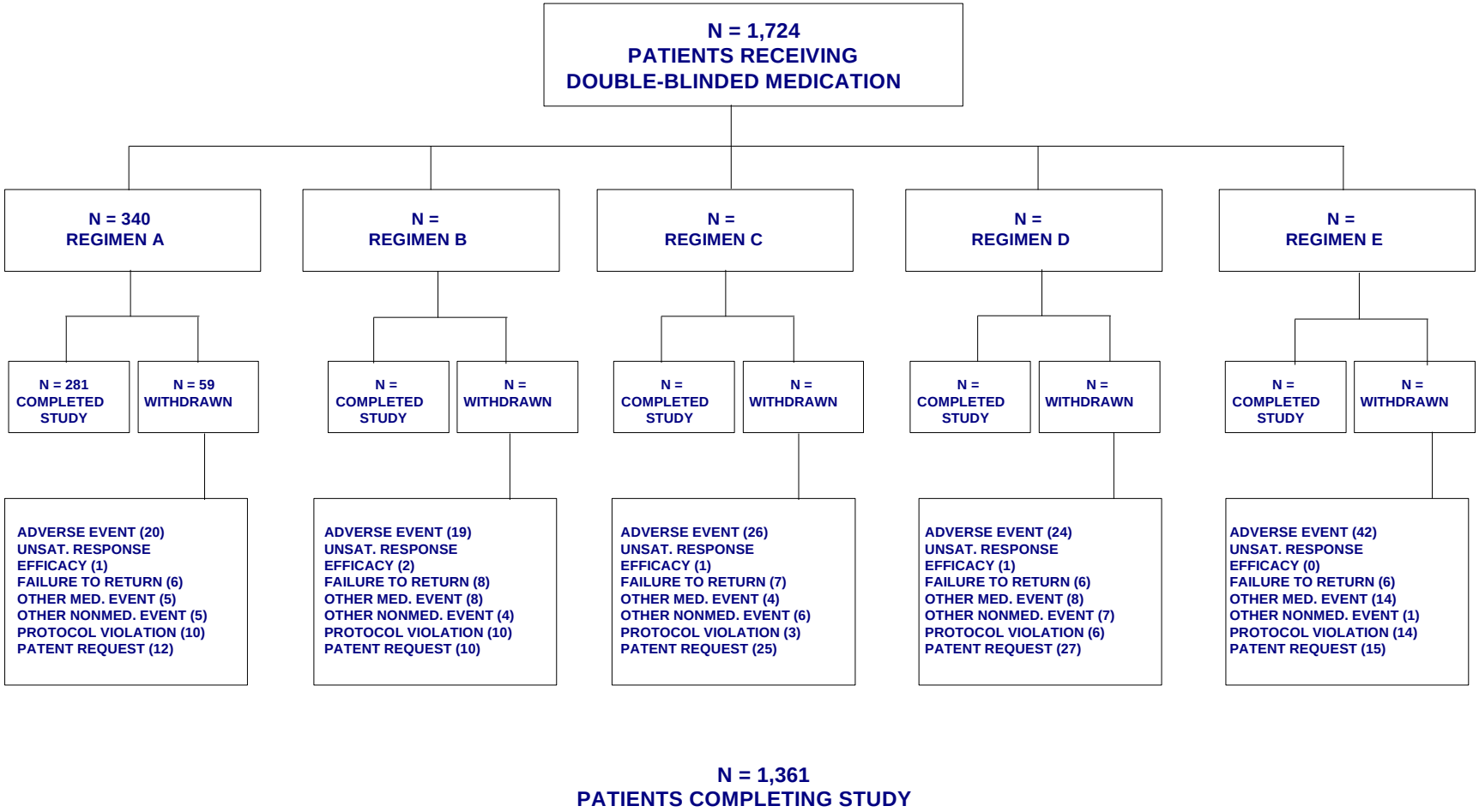
1 = 14-20 days after visit 1
2 = 1-7 days after the first exercise test

ANNEX IIIb

STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

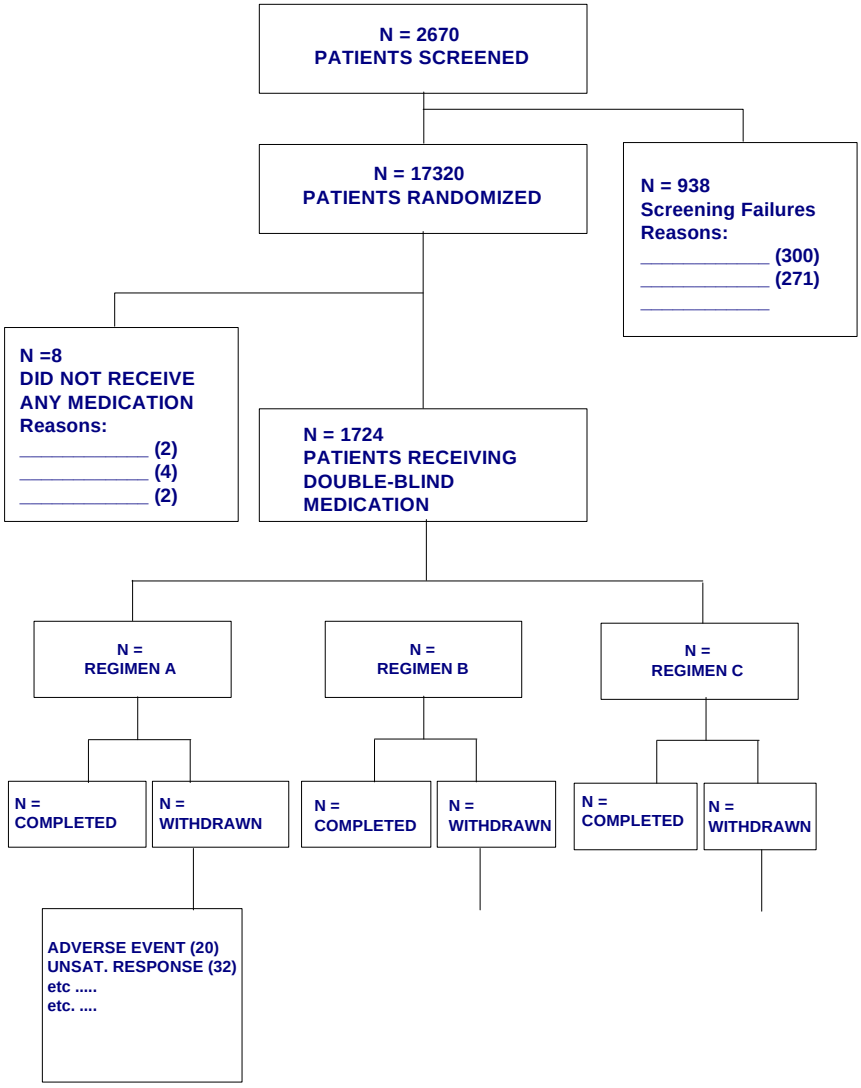
Assessment	**Screening**	**Run-in**	**Baseline**	**Treatment**				**Follow-up**		
Study Week	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**
Informed Consent	x									
History	x									
Physical Exam.	x									x
<u>Effectiveness</u>										
primary variable	x	x	x	x	x	x	x	x	x	x
secondary variable	x	x	x	x		x			x	x
<u>Safety</u>										
Adverse events	x	x	x	x	x	x	x	x	x	x
Lab. tests	x		x	x			x		x	x
Body weight	x		x						x	x

Disposition of Patients



N = 1,361
PATIENTS COMPLETING STUDY

DISPOSITION OF PATIENTS



ANNEX V

STUDY #
(Data Set Identification)

LISTING OF PATIENTS WHO DISCONTINUED THERAPY

Centre.:

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason for Discontin.
Test Drug/ investigational product								Adverse reaction* • • • Therapy failure

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason for Discontin.
Active Control/ Comparator								

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason for Discontin.
Placebo								

* The specific reaction leading to discontinuation

(Repeat for other centers)

ANNEX VI

STUDY #
(Data Set Identification)

Listing of Patients and Observations Excluded from Efficacy Analysis

Center.:

Treatment Patient # Sex Age Observation Excluded Reason(s)

Test Drug/Investigational Product

Treatment Patient # Sex Age Observation Excluded Reason(s)

Active Control/Comparator

Treatment Patient # Sex Age Observation Excluded Reason(s)

Placebo

(Repeat for other centres)

Reference Tables

Summary:

ANNEX VII

STUDY #
(Data Set Identification)

Number of Patients Excluded from Efficacy Analysis

Test Drug/Investigational Product N =

	Week			
Reason	1	2	4	8
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
Total	_____	_____	_____	_____

Similar tables should be prepared for the other treatment groups.

ANNEX VIII

GUIDANCE FOR SECTION 11.4.2 -- STATISTICAL/ANALYTICAL ISSUES AND APPENDIX 16.1.9

A. Statistical Considerations

Details of the statistical analysis performed on each primary efficacy variable should be presented in Appendix 16.1.9. Details reported should include at least the following information:

(a) The statistical model underlying the analysis. This should be presented precisely and completely, using references if necessary.

(b) A statement of the clinical claim tested in precise statistical terms, e.g., in terms of null and alternative hypotheses.

(c) The statistical methods applied to estimate effects, construct confidence intervals, etc. Literature references should be included where appropriate.

(d) The assumptions underlying the statistical methods. It should be shown, insofar as statistically reasonable, that the data satisfy crucial assumptions, especially when necessary to confirm the validity of an inference. When extensive statistical analyses have been performed by the applicant, it is essential to consider the extent to which the analyses were planned prior to the availability of data and, if they were not, how bias was avoided in choosing the particular analysis used as a basis for conclusions. This is particularly important in the case of any subgroup analyses, because if such analyses are not preplanned they will ordinarily not provide an adequate basis for definitive conclusions.

(i) In the event data transformation was performed, a rationale for the choice of data transformation along with interpretation of the estimates of treatment effects based on transformed data should be provided.

(ii) A discussion of the appropriateness of the choice of statistical procedure and the validity of statistical conclusions will guide the regulatory authority's statistical reviewer in determining whether reanalysis of data is needed.

(e) The test statistic, the sampling distribution of the test statistic under the null hypothesis, the value of the test statistic, significance level (i.e., p-value), and intermediate summary data, in a format that enables the regulatory authority's statistical reviewer to verify the results of the analysis quickly and easily. The p-values should be designated as one or two tailed. The rationale for using a one-tailed test should be provided.

For example, the documentation of a two-sample t-test should consist of the value of the t-statistic, the associated degrees of freedom, the p-value, the two sample sizes, mean and variance for each of the samples, and the pooled estimate of variance. The documentation of multicenter studies analyzed by analysis of variance techniques should include, at a minimum, an analysis of variance table with terms for centers, treatments, their interaction, error, and total. For crossover designs, the documentation should include information regarding sequences, patients within sequences, baselines at the start of each period, washouts and length of washouts, dropouts during each period, treatments, periods, treatment by period interaction, error, and total. For each source of variation, aside from the total, the table should contain the degrees of freedom, the sum of squares, the mean square, the appropriate F-test, the p-value, and the expected mean square.

Intermediate summary data should display the demographic data and response data, averaged or otherwise summarized, for each center-by-treatment combination (or other design characteristic such as sequence) at each observation time.

B. Format and Specifications for Submission of Data Requested by Regulatory Authority's Statistical Reviewers

In the report of each controlled clinical study, there should be data listings (tabulations) of patient data utilized by the sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the regulatory authority's statistical review, and the sponsor may be asked to supply these patient data listings in a computer-readable form.