INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

# ICH HARMONISED TRIPARTITE GUIDELINE

# THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

## SAFETY

## NONCLINICAL SUMMARIES AND ORGANISATION OF MODULE 4

Recommended for Adoption

at Step 4 of the ICH Process

on 9 November 2000

by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

# THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE:

# NONCLINICAL SUMMARIES AND ORGANISATION OF MODULE 4

**ICH Harmonised Tripartite Guideline**

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 9 November 2000, this guideline is recommended for adoption to the three regulatory parties to ICH

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# THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE:

## GUIDELINE ON THE NONCLINICAL OVERVIEW AND NONCLINICAL SUMMARIES IN MODULE 2 OF THE COMMON TECHNICAL DOCUMENT

### General Principles

This guideline provides recommendations for the harmonisation of the Nonclinical Overview, Nonclinical Written Summary, and Nonclinical Tabulated Summaries.

The primary purpose of the Nonclinical Written and Tabulated Summaries should be to provide a comprehensive factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e., as applicable to labeling) should be addressed in the Overview.

## NONCLINICAL OVERVIEW

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages.

### General Aspects

The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical. Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidelines should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding its safety should be provided.

Relevant scientific literature and the properties of related products should be taken into account. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidelines. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries, in the following format: (Table X.X, Study/Report Number).

**Content and Structural Format**

The Nonclinical Overview should be presented in the following sequence:

Overview of the nonclinical testing strategy

Pharmacology

Pharmacokinetics

Toxicology

Integrated overview and conclusions

List of literature citations

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, anti-product antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to:

- pharmacodynamics
- toxic signs
- causes of death
- pathologic findings
- genotoxic activity - the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- the carcinogenic risk to humans - if epidemiologic data are available, they should be taken into account
- fertility, embryofetal development, pre-and post-natal toxicity
- studies in juvenile animals
- the consequences of use before and during pregnancy, during lactation, and during pediatric development
- local tolerance
- other toxicity studies/ studies to clarify special problems

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect / phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

- animal species used
- numbers of animals used
- routes of administration employed
- dosages used
- duration of treatment or of the study
- systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarising this information are recommended.
- the effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

## THE NONCLINICAL WRITTEN AND TABULATED SUMMARIES

### Nonclinical Written Summaries

#### *Introduction*

This guideline is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics, and toxicology written summaries in an acceptable format. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Nonclinical Written Summary sections are described below. It should be emphasised that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

### *General Presentation Issues*

Order of Presentation of Information within Sections

When available, in vitro studies should precede in vivo studies.

Where multiple studies of the same type need to be summarised within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

1. Mouse
2. Rat
3. Hamster
4. Other rodent
5. Rabbit
6. Dog
7. Non-human primate
8. Other non-rodent mammal
9. Non-mammals

Routes of administration should be ordered as follows:

1. The intended route for human use
2. Oral
3. Intravenous
4. Intramuscular
5. Intraperitoneal
6. Subcutaneous
7. Inhalation
8. Topical
9. Other

Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures. Examples of formats that might be included in the Written Summaries are shown in Appendix A.

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

Length of Nonclinical Written Summaries

Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100-150 pages.

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

1. Introduction
2. Written Summary of Pharmacology
3. Tabulated Summary of Pharmacology
4. Written Summary of Pharmacokinetics
5. Tabulated Summary of Pharmacokinetics
6. Written Summary of Toxicology
7. Tabulated Summary of Toxicology

***Content of Nonclinical Written Summary***

### 2.3.1 Introduction

The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

1. Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacologic properties.
2. Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.

### 2.3.2 The Pharmacology Written Summary

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

- Brief Summary
- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamic Drug Interactions
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

#### *2.3.2.1 Brief Summary*

The principal findings from the pharmacology studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a brief description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

*2.3.2.2 Primary Pharmacodynamics*

Studies on primary pharmacodynamics* should be summarised and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

*2.3.2.3 Secondary Pharmacodynamics*

Studies on secondary pharmacodynamics* should be summarised by organ system, where appropriate, and* evaluated in this section.

*2.3.2.4 Safety Pharmacology*

Safety pharmacology studies* should be summarised and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in humans. In such cases, these secondary pharmacodynamic studies should be considered along with safety pharmacology studies.

*2.3.2.5 Pharmacodynamic Drug Interactions*

If they have been performed, pharmacodynamic drug interaction studies should be briefly summarised in this section.

*2.3.2.6 Discussion and Conclusions*

This section provides an opportunity to discuss the pharmacologic evaluation and to consider the significance of any issues that arise.

*2.3.2.7 Tables and Figures*

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

### 2.3.3 The Pharmacology Tabulated Summary (see Appendix B)

### 2.3.4 The Pharmacokinetics Written Summary

The sequence of the Pharmacokinetics Written Summary should be as follows:

- Brief Summary
- Methods of Analysis
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions
- Other Pharmacokinetic Studies
- Discussion and Conclusions

* See ICH Guideline S7, *Safety Pharmacology Studies for Human Pharmaceuticals*, Note 2. p. 8, for definitions.

- Tables and Figures (either here or included in text)

*2.3.4.1 Brief Summary*

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasising, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

*2.3.4.2 Methods of Analysis*

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

*2.3.4.3 Absorption*

The following data should be summarised in this section:

- Absorption (extent and rate of absorption, in vivo and in situ studies)
- Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/blood PK studies)

*2.3.4.4 Distribution*

The following data should be summarised in this section:

- Tissue distribution studies
- Protein binding and distribution in blood cells
- Placental transfer studies

*2.3.4.5 Metabolism (inter-species comparison)*

The following data should be summarised in this section:

- Chemical structures and quantities of metabolites in biological samples
- Possible metabolic pathways
- Pre-systemic metabolism (GI/hepatic first-pass effects)
- In vitro metabolism including P450 studies
- Enzyme induction and inhibition

*2.3.4.6 Excretion*

The following data should be summarised in this section:

- Routes and extent of excretion
- Excretion in milk

*2.3.4.7 Pharmacokinetic Drug Interactions*

If they have been performed, nonclinical pharmacokinetic drug-interaction studies (in vitro and/or in vivo) should be briefly summarised in this section.

*2.3.4.8 Other Pharmacokinetic Studies*

If studies have been performed in nonclinical models of disease (e.g., renally impaired animals), they should be summarised in this section.

*2.3.4.9 Discussion and Conclusions*

This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise.

*2.3.4.10 Tables and Figures*

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

### 2.3.5 The Pharmacokinetic Tabulated Summary (see Appendix B)

### 2.3.6 The Toxicology Written Summary

The sequence of the Toxicology Written Summary should be as follows:

- Brief Summary
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Studies in Juvenile Animals
- Local Tolerance
- Other Toxicity Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

*2.3.6.1 Brief Summary*

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than 6). In this section, the extent of the toxicologic evaluation can be indicated by the use of a table listing the principal toxicologic studies (results should not be presented in this table), for example:

TOXICOLOGY PROGRAMME

| Study type and duration | Route of administration | Species | Compound administered* |
|---|---|---|---|
| Single-dose | po and iv | Rat and mouse | Parent drug |
| toxicity | po and iv | Rat and mouse | Metabolite X |
| Single-dose toxicity | | | |
| Repeat-dose | po | Rat and dog | Parent drug |
| toxicity | po | Rat | " " |
| 1 month | po | Dog | " " |
| 6 months | | | |
| 9 months, etc. | | | |

* This column required only if metabolite(s) are investigated.

The scope of the toxicologic evaluation should be described in relation to the proposed clinical use. A comment on the GLP status of the studies should be included.

*2.3.6.2 Single-Dose Toxicity*

The single-dose data should be very briefly summarised, in order by species, by route. In some instances, it may be helpful to provide the data in the form of a table.

*2.3.6.3 Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)*

Studies should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g., nature and severity of target organ toxicity, dose (exposure)/response relationships, no observed adverse effect levels, etc.). Non-pivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH Guideline M3).

*2.3.6.4 Genotoxicity*

Studies should be briefly summarised in the following order:

- *in vitro* non-mammalian cell system
- *in vitro* mammalian cell system
- *in vivo* mammalian system (including supportive toxicokinetics evaluation)
- other systems

*2.3.6.5 Carcinogenicity (including supportive toxicokinetics evaluations)*

A brief rationale should explain why the studies were chosen and the basis for high-dose selection. Individual studies should be summarised in the following order:

- Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Other studies

*2.3.6.6 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations)*

Studies should be summarised in the following order, giving brief details of the methodology and highlighting important findings:

- Fertility and early embryonic development
- Embryo-fetal development
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted.

If modified study designs are used, the sub-headings should be modified accordingly.

*2.3.6.7 Local Tolerance*

If local tolerance studies have been performed, they should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings.

*2.3.6.8 Other Toxicity Studies (if available)*

If other studies have been performed, they should be summarised. When appropriate, the rationale for conducting the studies should be provided.

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not reported elsewhere)
- Dependence
- Studies on metabolites
- Studies on impurities
- Other studies

*2.3.6.9 Discussion and Conclusions*

This section should provide an opportunity to discuss the toxicologic evaluation and the significance of any issues that arise. Tables or figures summarizing this information are recommended.

*2.3.6.10 Tables and Figures*

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

### 2.3.7 The Toxicology Tabulated Summary (see Appendix B)

**Examples of Tables and Figures for Written Summaries (Appendix A)**

The tables and figures in Appendix A are presented merely as examples. Applicants should provide tables and figures using a format appropriate to the product.

Study references should be included in the table or text.

Tables should include statistics, if appropriate.

**Nonclinical Tabulated Summaries**

It is recommended that summary tables for the nonclinical information in the Common Technical Document be provided in the format outlined in this Guideline. Applicants can modify the format if needed to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

This Guideline is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed. Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

The recommended formats for the tables in the Nonclinical Tabulated Summaries are provided in Appendices B and C, which follow. Appendix B contains templates for use in preparation of the tables. The templates are annotated (in italics) to provide guidance on their preparation. (The italicized information should be deleted when the tables are prepared.) Appendix C provides examples of the summary tables. The purpose of the examples is to provide additional guidance on the suggested content and format of the Tabulated Summaries. However, it is the responsibility of the applicant to decide on the best possible presentation of the data for each product. Authors should keep in mind that, in some regions, a review of the Tabulated Summaries (in conjunction with the Written Summaries) represents the primary review of the nonclinical information. Presentation of the data in the formats provided as templates and examples should ensure that a sufficient level of detail is available to the reviewer and should provide concise overviews of related information.

When a juvenile-animal study has been conducted, it should be tabulated using the template appropriate for the type of study.

The order of presentation given for the Nonclinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries.

# THE ORGANISATION OF MODULE 4: NONCLINICAL STUDY REPORTS

This guideline presents an agreed format for the organisation of the nonclinical reports in the Common Technical Document for applications that will be submitted to Regulatory Authorities. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual-animal data is in the study report or as an appendix to the study report.

4.1 Table of Contents

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

*Study Reports*

The study reports should be presented in the following order:

4.2 Pharmacology

- 4.2.1 Primary Pharmacodynamics
- 4.2.2 Secondary Pharmacodynamics
- 4.2.3 Safety Pharmacology
- 4.2.4 Pharmacodynamic Drug Interactions

4.3 Pharmacokinetics

- 4.3.1 Analytical Methods and Validation Reports (if separate reports are available)
- 4.3.2 Absorption
- 4.3.3 Distribution
- 4.3.4 Metabolism
- 4.3.5 Excretion
- 4.3.6 Pharmacokinetic Drug Interactions (nonclinical)
- 4.3.7 Other Pharmacokinetic Studies

4.4 Toxicology

- 4.4.1 Single-Dose Toxicity (in order by species, by route)
- 4.4.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.4.3 Genotoxicity
  - 4.4.3.1 In vitro
  - 4.4.3.2 In vivo (including supportive toxicokinetics evaluations)
- 4.4.4 Carcinogenicity (including supportive toxicokinetics evaluations)
  - 4.4.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.4.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.4.4.3 Other studies

4.4.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

4.4.5.1 Fertility and early embryonic development

4.4.5.2 Embryo-fetal development

4.4.5.3 Prenatal and postnatal development, including maternal function

4.4.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.4.6 Local Tolerance

4.4.7 Other Toxicity Studies (if available)

4.4.7.1 Antigenicity

4.4.7.2 Immunotoxicity

4.4.7.3 Mechanistic studies (if not included elsewhere)

4.4.7.4 Dependence

4.4.7.5 Metabolites

4.4.7.6 Impurities

4.4.7.7 Other

4.5 Key Literature References

# APPENDIX A

## Examples of Tables and Figures for Written Summaries

The tables and figures in Appendix A are presented merely as examples. Applicants should provide tables and figures using a format appropriate to the product.

Study references should be included in the table or text.

Tables should include statistics, if appropriate.

**Table X**

**Binding of X and its Major Metabolites and Comparators**

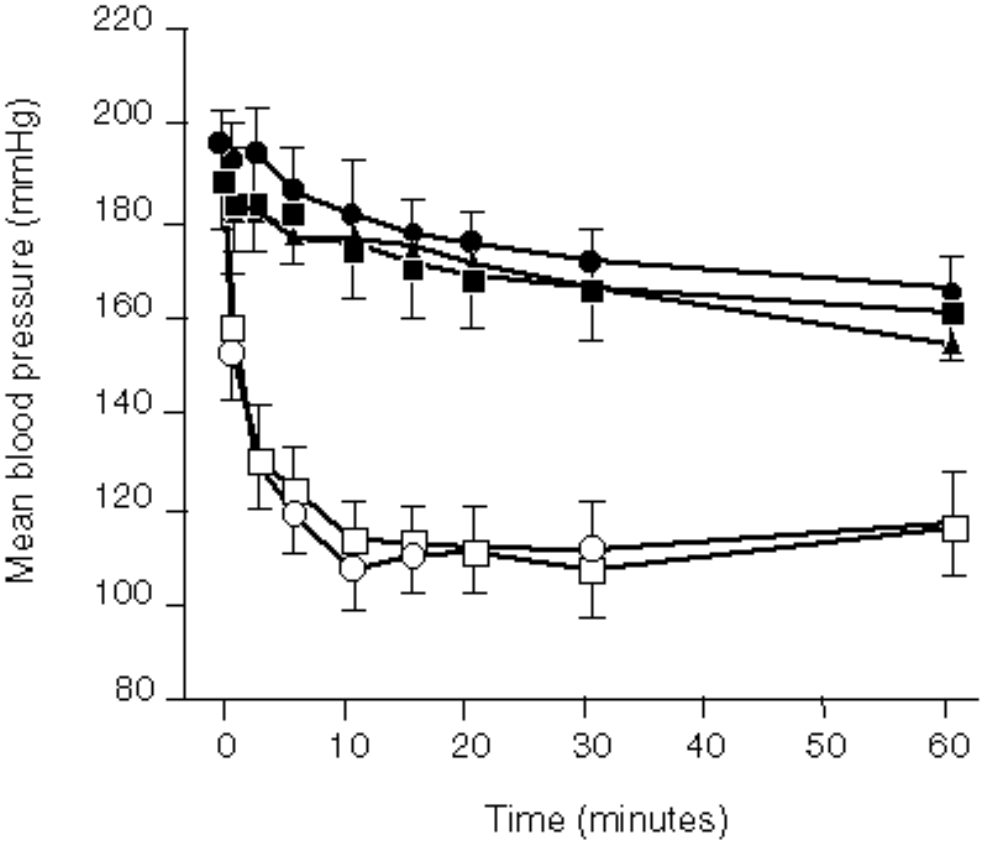
**to Human $X_2$ and $X_3$ Receptors**

| Compound | $X_2$ $K_i1$(nM) | $X_2$ $K_i2$(nM) | $X_3$ $K_i1$(nM) | $X_3$ $K_i2$(nM) |
|---|---|---|---|---|
| **1** | 538 | 2730 | 691 | 4550 |
| **2** | 2699 | 1050 | 2.0 | 181 |
| **3** | 578 | 14.4 | 141 | 10400 |
| **4** | 20 | 100 | 10.7 | 7.9 |
| **5** | 2100 | 3.1 | 281 | 28 |
| **6** | 7.5 | 8.4 | 44 | 2.8 |
| **7** | 3.11 | 3.76 | 1.94 | 1.93 |

$K_i1$ and $K_i2$ represent the high and low affinity binding sites respectively (Data from Study Number).

**Figure X**

**Blood pressure following chronic dosing with X to SHR[a]**




**Blood pressure following chronic dosing with X to SHR[a][ref].** Hypotensive effect of saline i.v. infusion over 5 min (▲) compared to X, 3 mg/kg i.v. infusion to SHR pretreated twice daily with saline, 1 mL/kg p.o., for 7 (❍) or 14 (❒) days or X, 25 mg/kg p.o., for 7 (●) or 14 (■) days. Saline pretreated statistical significances: $p<0.05$, all other points after challenge $p<0.01$. Values represent mean ± s.e.m.

[a]SHR= spontaneous hypertensive rat (n=5 per group)

**Table X**

**Model-independent pharmacokinetic parameters for X in mice following single oral doses at 2, 10 and 30 mg/kg [ref]**

| **Parameter (units)** | **Parameter value** | | | | | |
|---|---|---|---|---|---|---|
| **Sex** | **Males** | | | **Females** | | |
| Dose (mg/kg) | 2 | 10 | 30 | 2 | 10 | 30 |
| $C_{max}$ (ng/mL) | 4.9 | 20.4 | 30.7 | 5.5 | 12.9 | 28.6 |
| $T_{max}$ (h) | 0.8 | 0.4 | 0.3 | 0.4 | 0.5 | 0.3 |
| $AUC_{0-t}$ (ng.h/mL) | 21.6 | 80.5 | 267 | 33.3 | 80 | 298 |
| $AUC_{0-inf}$ (ng.h/mL) | 28.3 | 112 | 297 | 40.2 | 90 | 327 |

Pharmacokinetic parameters were determined in pooled plasma from three animals at each time

**Table X**

**Excretion of radioactive material following single doses of [$^{14}$C]X to male mice [ref]**

| **Dose (mg/kg)/ route** | | **Percentage of administered dose** | | |
|---|---|---|---|---|
| | | **Urine*** | **Faeces** | **Total+** |
| 2.8 | i.v. | 88.1 ± 7.4 | 5.5 ± 0.7 | 93.6 ± 6.9 |
| 8.8 | p.o. | 89.4 ± 4.7 | 6.9 ± 1.4 | 95.3 ± 3.4 |

Excretion was determined over 168 hours after dosing

Values are means ± S.D. (n= 5 for p.o. and 5 for i.v.)

* - includes radioactivity in cage wash (22.1% after p.o. and 21.7% after i.v.)

+ - includes radioactivity in the carcass

**Table X**

**Concentrations of radioactive material in the tissues of male rats after a single intravenous dose of [$^{14}$C]X at 1.75 mg/kg [refs]**

| Tissue | Concentration (ng equiv.*/g) | | | | |
|---|---|---|---|---|---|
| | **1 h** | **6 h** | **24 h** | **48 h** | **72 h** |
| Blood | 105 | 96.6 | 2.34 | 2.34 | 3.65 |
| Plasma | 142 | 175 | 3.12 | ND | ND |
| Adrenals | 656 | 49.2 | 14.3 | 9.63 | ND |
| Bone marrow | 359 | 31.5 | ND | ND | ND |
| Brain | 116 | 9.37 | ND | ND | ND |
| Eyes | 124 | 28.9 | 4.69 | ND | ND |
| Fat | 490 | 44.0 | 10.2 | 6.25 | 5.47 |
| Heart | 105 | 26.6 | ND | ND | ND |
| Kidneys | 1280 | 651 | 21.6 | 13.3 | 9.63 |
| Large intestine | 570 | 2470 | 39.3 | 12.0 | ND |
| Liver | 875 | 380 | 133 | 87.7 | 64.6 |
| Lungs | 234 | 59.1 | 7.55 | ND | ND |

* - ng of X free base equivalent/g.
N= 5 animals/time point
ND - Not detected

**Table X**

**Excretion of radioactive material following single doses of [$^{14}$C]X to male rats [refs]**

| Dose (mg/kg)/ route | | Percentage of administered dose | | | |
|---|---|---|---|---|---|
| | | **Urine** | **Faeces** | **Bile** | **Total** |
| 1.75 | i.v. | 61.3 ± 9.3 | 30.3 ± 4.1 | - | 95.2 ± 5.0 |
| 1.75 | p.o. | 57.4 ± 3.8 | 37.0 ± 3.4 | - | 95.2 ± 1.5 |
| 2 | p.o. | 72.3 ± 0.8 | 26.9 ± 1.9 | - | 99.5 ± 1.1 |
| 20 | p.o. | 23.5 ± 6.3 | 0.5 ± 0.2 | 76.0 ± 5.9 | 100 ± 0.8 |
| 220 | p.o. | 67.1 ± 9.0 | 24.8 ± 5.0 | - | 93.3 ± 6.8 |

Excretion was determined over 168 h period in Wistar rats:Values are means ± S.D. (n=5); - not assayed; Total includes radioactivity in the carcass and cage washings

**Table X**

**Comparative pharmacokinetic data and systemic exposure to X following oral administration to mice, rats, dogs and patients [ref]**

| Species (formulation) | Dose (mg/kg/day) | Systemic (plasma) exposure | | References |
|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | AUC (ng.h/mL)# | |
| Man (tablet) | 0.48$ | 36.7 | 557 | X |
| Mouse (solution) | 8.8 | 68.9 (1.9)* | 72.7 (0.2)* | Y |
| | 21.9 | 267 (7.3)* | 207 (0.5)* | |
| | 43.8 | 430 (11.7)* | 325 (0.7)* | |
| Rat (solution) | 50 | 479 (13.0)* | 1580 (2.8)* | Z |
| Dogs (solution) | 1.5 | 5.58 (0.2)* | 15.9 (<0.1)* | V |
| | 5 | 24.8 (0.7)* | 69.3 (0.1)* | |
| | 15 | 184 (5.0)* | 511 (0.9)* | |

Data presented are for male and female animals and are after daily repeated oral administration (at the end of the 60-day mouse study, 14 day rat study, and 1 year dog study). Data for man are extrapolated from dose normalised data obtained in male and female patients following t.i.d regimen.

# - $AUC_{0-6}$ in the mouse, $AUC_{0-t}$ in the rat and in the dog and dose normalised $AUC_{0-\tau}$ x 24 in man. $ - calculated from the total daily dose assuming a bodyweight of 50 kg for man. * - Numbers in parentheses represent ratios of exposure in animals to those in patients

**Table X**

**Incidence of Proliferative Interstitial (Leydig) Cell Lesions in Rats [ref]**

| | Dose Groups | | | |
|---|---|---|---|---|
| **Lesion** | **Control** | **3 mg/kg** | **30 mg/kg** | **100 mg/kg** |
| Hyperplasia (only) | x/50 (%) | x/50 (%) | x/50 (%) | x/50 (%) |
| Adenoma (only) | x/50 (%) | x/50 (%) | x/50 (%) | x/50 (%) |
| Adenoma + Hyperplasia | x/50 (%) | x/50 (%) | x/50(%) | x/50 (%) |
| Total* | x/50 (%) | x/50 (%) | x/50 (%) | x/50 (%) |

* Adenoma and/or Hyperplasia

# APPENDIX B

## The Nonclinical Tabulated Summaries- Templates

**The Nonclinical Tabulated Summaries– Templates**

2.3.3 Pharmacology
- 2.3.3.1 Pharmacology: Overview
- 2.3.3.2 Primary Pharmacodynamics*
- 2.3.3.3 Secondary Pharmacodynamics*
- 2.3.3.4 Safety Pharmacology
- 2.3.3.5 Pharmacodynamic Drug Interactions*

2.3.5 Pharmacokinetics
- 2.3.5.1 Pharmacokinetics: Overview
- 2.3.5.2 Analytical Methods and Validation Reports*
- 2.3.5.3 Pharmacokinetics: Absorption after a Single Dose
- 2.3.5.4 Pharmacokinetics: Absorption after Repeated Doses
- 2.3.5.5 Pharmacokinetics: Organ Distribution
- 2.3.5.6 Pharmacokinetics: Plasma Protein Binding
- 2.3.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals
- 2.3.5.8 Pharmacokinetics: Other Distribution Study
- 2.3.5.9 Pharmacokinetics: Metabolism In Vivo
- 2.3.5.10 Pharmacokinetics: Metabolism In Vitro
- 2.3.5.11 Pharmacokinetics: Possible Metabolic Pathways
- 2.3.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes
- 2.3.5.13 Pharmacokinetics: Excretion
- 2.3.5.14 Pharmacokinetics: Excretion into Bile
- 2.3.5.15 Pharmacokinetics: Drug-Drug Interactions
- 2.3.5.16 Pharmacokinetics: Other

2.3.7 Toxicology
- 2.3.7.1 Toxicology: Overview
- 2.3.7.2 Toxicokinetics: Overview of Toxicokinetics Studies
- 2.3.7.3 Toxicokinetics: Overview of Toxicokinetics Data
- 2.3.7.4 Toxicology: Drug Substance
- 2.3.7.5 Single-Dose Toxicity
- 2.3.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies
- 2.3.7.7 Repeat-Dose Toxicity: Pivotal Studies
- 2.3.7.8 Genotoxicity: In Vitro
- 2.3.7.9 Genotoxicity: In Vivo
- 2.3.7.10 Carcinogenicity
- 2.3.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies

2.3.7.12 Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation (Pivotal)

2.3.7.13 Reproductive and Developmental Toxicity – Effects on Embryo-Fetal Development (Pivotal)

2.3.7.14 Reproductive and Developmental Toxicity – Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)

2.3.7.15 Studies in Juvenile Animals[a]

2.3.7.16 Local Tolerance

2.3.7.17 Other Toxicity Studies

* : Tabulated Summary is optional. It is preferable to include text tables and figures with the Nonclinical Written Summary.

[a] : When a juvenile-animal study has been conducted, it should be tabulated using the template appropriate for the type of study and located in Section 3.6.

**2.3.3.1 Pharmacology** **Overview** **Test Article**: (1)

| Type of Study | Test System | Method of Administration | Testing Facility | Study Number*(4)* | Location Vol. | Location Page |
|---|---|---|---|---|---|---|
| **1.1 Primary Pharmacodynamics** *(2)* | | | | | *(3)* | |
| **1.2 Secondary Pharmacodynamics** | | | | | | |
| **1.3 Safety Pharmacology** | | | | | | |
| **1.4 Pharmacodynamic Drug Interactions** | | | | | | |

*Notes:* *(1) International Nonproprietary Name (INN)*
*(2) There should be one line for each pharmacology report, in the same order as the CTD. Reports that contain a GLP Compliance Statement should be identified in a footnote.*
*(3) The location of the Technical Report in the CTD should be indicated.*
*(4) Or Report Number (on all tables).*

**2.3.3.4 Safety Pharmacology*(1)*** **Test Article:** *(2)*

| Organ Systems Evaluated | Species/ Strain | Method of Admin. | Doses[a] (mg/kg) | Gender and No. per Group | Noteworthy Findings | *GLP* Compliance | Study Number*(3)* |
|---|---|---|---|---|---|---|---|

*Notes:* *(1) All safety-pharmacology studies should be summarized.*
*(2) International Nonproprietary Name (INN).*
*(3) Or Report Number (on all tables).*

a - Single dose unless specified otherwise.

**2.3.5.1 Pharmacokinetics** **Overview** **Test Article:** *(1)*

| Type of Study | Test System | Method of Administration | Testing Facility | Study Number | Location Vol. | Location Page |
|---|---|---|---|---|---|---|
| | | | | | *(3)* | |
| **2.2 Absorption** *(2)* | | | | | | |
| **2.3 Distribution** | | | | | | |
| **2.4 Metabolism** | | | | | | |
| **2.5 Excretion** | | | | | | |
| **2.6 Pharmacokinetic Drug Interactions** | | | | | | |
| **2.7 Other** | | | | | | |

*Notes:* *(1) International Nonproprietary Name (INN).*
*(2) There should be one line for each pharmacokinetics report, in the same order as the CTD. Reports that contain a GLP Compliance Statement should be identified in a footnote.*
*(3) The location of the Technical Report in the CTD should be indicated.*

**2.3.5.3 Pharmacokinetics: Absorption after a Single Dose**

**Test Article:** *(1)*
**Location in CTD:** Vol. Page
**Study No.**

| | | | | | |
|---|---|---|---|---|---|
| **Species** | _____ | _____ | _____ | _____ | _____ |
| **Gender (M/F) / Number of animals** *(4)* | | | | | |
| **Feeding condition** | | | | | |
| **Vehicle/Formulation** | | | | | |
| **Method of Administration** | | | | | |
| **Dose (mg/kg)** | | | | | |
| **Sample (Whole blood, plasma, serum etc.)** | | | | | |
| **Analyte** | | | | | |
| **Assay** *(2)* | | | | | |
| **PK parameters:** | | | | | |

**Additional Information:** *(3)*

*Notes:* *(1) International Nonproprietary Name (INN).*
*(2) For example, HPLC, LSC with $^{14}C$-labeled compound.*
*(3) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.*
*(4) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included.*

**2.3.5.4 Pharmacokinetics: Absorption after Repeated Doses** **Test Article:**

*[Data may be tabulated as in the format of 2.2.1 if applicable.]*

***Format A***

**2.3.5.5 Pharmacokinetics: Organ Distribution**

**Test Article:**
**Location in CTD:** Vol. Page
**Study No.**

**Species:**
**Gender (M/F)/Number of animals:**
**Feeding condition:**
**Vehicle/Formulation:**
**Method of Administration:**
**Dose (mg/kg):**
**Radionuclide:**
**Specific Activity:**
**Sampling time:**

| | Concentration (unit) | | | | | |
|---|---|---|---|---|---|---|
| **Tissues/organs** | **T(1)** | **T(2)** | **T(3)** | **T(4)** | **T(5)** | **$t_{1/2?}$** |

**Additional information:**

***Alternate Format B***

**2.3.5.5 Pharmacokinetics: Organ Distribution**

**Test Article:**
**Location in CTD:** Vol. Page
**Study No.**

**Species:**
**Gender (M/F) / Number of animals:**
**Feeding condition:**
**Vehicle/Formulation:**
**Method of Administration:**
**Dose (mg/kg):**
**Radionuclide:**
**Specific Activity:**
**Analyte/Assay (unit):**
**Sampling time:**

| Tissues/organs | $C_t$ | | Last time-point | | | | |
|---|---|---|---|---|---|---|---|
| | conc. | T/P[1)] | conc. | T/P[1)] | Time | AUC | $t_{1/2?}$ |

**Additional information:**

**[1)] [Tissue]/[Plasma]**

**2.3.5.6 Pharmacokinetics: Plasma Protein Binding** **Test Article:**

**Study system:**
**Target entity, Test system and method:**

| Species | Conc. tested | % Bound | Study No. | Location in CTD Vol. | Page |
|---|---|---|---|---|---|

**Additional Information:**

**2.3.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals** ***(1)***

**Test Article:** ***(2)***

**Location in CTD:** Vol. Page

**Study No.**

**Placental transfer**

**Species:**
**Gestation day / Number of animals:**
**Vehicle/Formulation:**
**Method of Administration:**
**Dose (mg/kg):**
**Analyte:**
**Assay:**

| **Time (hr)** | _____ | _____ | _____ | _____ | _____ |
|---|---|---|---|---|---|
| **Concentration / Amount (% of dose)** | | | | | |
| **Dam** ***(3)*****:** | | | | | |
| **Fetus** ***(3)*****:** | | | | | |

**Additional Information:**

**Location in CTD:** Vol. Page

**Study No.**

**Excretion into milk**

**Species:**
**Lactating date / Number of animals:**
**Feeding condition:**
**Vehicle/Formulation:**
**Method of Administration:**
**Dose (mg/kg):**
**Analyte:**
**Assay:**

| **Time [hr]** | _____ | _____ | _____ | _____ | _____ |
|---|---|---|---|---|---|
| **Concentration:** | | | | | |
| **Milk:** | | | | | |
| **Plasma:** | | | | | |
| **Milk / plasma:** | | | | | |
| **Neonates:** | | | | | |

**Additional Information:**

**Notes for Table 2.3.3**

*(1)* Even if the data are obtained in reproduction toxicology studies, they should be presented in this table.
*(2)* International Nonproprietary Name (INN).
*(3)* The tissue sampled should be described; e.g., plasma for dams, fetal concentrations.

**2.3.5.8 Pharmacokinetics: Other Distribution Study**

**Test Article:**

**2.3.5.9 Pharmacokinetics: Metabolism *In Vivo*** **Test Article:**

**Gender(M/F) / Number of animals:**
**Feeding condition:**
**Vehicle/Formulation:**
**Method of Administration:**
**Dose (mg/kg):**
**Radionuclide:**
**Specific Activity:**

| | | | | % of Compound in Sample | | | | Location in CTD | |
|---|---|---|---|---|---|---|---|---|---|
| **Species** | **Sample** | **Sampling Time or Period** | **% of Dose in Sample** | **Parent** | **M1** | **M2** | **Study No.** | **Vol** | **Page** |
| | Plasma | | | | | | | | |
| | Urine | | | | | | | | |
| | Bile | | | | | | | | |
| | Feces | | | | | | | | |
| | Plasma | | | | | | | | |
| | Urine | | | | | | | | |
| | Bile | | | | | | | | |
| | Feces | | | | | | | | |
| | Plasma | | | | | | | | |
| | Urine | | | | | | | | |
| | Bile | | | | | | | | |
| | Feces | | | | | | | | |

**Additional Information:**

Note: *Human data should be included for comparison, if available.*

**2.3.5.10 Pharmacokinetics: Metabolism *In Vitro***

**Test Article:**
**Location in CTD:** Vol. Page
**Study No.**

**Study system:**

| **Time** | _____ | _____ | _____ | _____ | _____ |
|---|---|---|---|---|---|
| **Concentration:** | | | | | |
| **Compounds** | | | | | |
| **Parent** | | | | | |
| **M-1** | | | | | |
| **M-2** | | | | | |

**Additional Information:**

*Note: Human data should be included for comparison, if available.*

**2.3.5.11 Pharmacokinetics: Possible Metabolic Pathways** **Test Article:**

*(Illustrate possible metabolic map indicating species in which metabolic reactions occur.)*

**2.3.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes**

**Test Article:**
**Location in CTD:** Vol. Page
**Study No.**

*Note: Nonclinical studies only.*

**Type of study:**

**Method:**

**Tabulated results:**

**Additional Information:**

**2.3.5.13 Pharmacokinetics: Excretion** **Test Article:** ***(1)***

| **Species** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gender (M/F) / Number of animals** *(3)* | | | | | | | | | | | | |
| **Feeding condition** | | | | | | | | | | | | |
| **Vehicle/Formulation** | | | | | | | | | | | | |
| **Method of Administration** | | | | | | | | | | | | |
| **Dose (mg/kg)** | | | | | | | | | | | | |
| **Analyte** | | | | | | | | | | | | |
| **Assay** | | | | | | | | | | | | |
| **Excretion route** ***(4)*** | **Urine** | **Feces** | **Total** | **Urine** | **Feces** | **Total** | **Urine** | **Feces** | **Total** | **Urine** | **Feces** | **Total** |
| **Time** | | | | | | | | | | | | |
| **0 - T hr** | | | | | | | | | | | | |

**Study number**
**Location in CTD**

**Additional Information:** ***(2)***

*Notes:* *(1) International Nonproprietary Name (INN).*
*(2) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.*
*(3) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included. May be combined with the Absorption Table, if appropriate.*
*(4) Other routes (e.g., biliary, respiratory) should be added, if performed.*

***2.3.5.14 Pharmacokinetics: Excretion into Bile*** ***Test Article:***

*[Data may be tabulated as in the format of 2.2.1 if applicable.]*

**2.3.5.15 Pharmacokinetics: Drug-Drug Interactions**

**Test Article:**
**Location in CTD:** Vol. Page
**Study No.**

**Type of study:**

**Method:**

**Tabulated results:**

**Additional Information:**

***2.3.5.16 Pharmacokinetics: Other***

**Test Article:**
**Location in CTD:** Vol. Page
**Study No.**

**Type of study:**

**Method:**

**Tabulated results:**

**Additional Information:**

**2.3.7.1 Toxicology** **Overview** **Test Article:** ***(1)***

| Type of Study | Species and Strain | Method of Administration | Duration of Dosing | Doses (mg/kg[a]) | GLP Compliance | Testing Facility | Study Number | Location Vol. Page |
|---|---|---|---|---|---|---|---|---|
| **3.1 Single-Dose Toxicity** | *(2)* | | | | | | | *(3)* |
| **3.2 Repeat-Dose Toxicity** | | | | | | | | |
| **3.3 Genotoxicity** | | | | | | | | |
| **3.4 Carcinogenicity** | | | | | | | | |
| **3.5 Reproductive and Developmental Toxicity** | | | | | | | | |
| **3.6 Local Tolerance** | | | | | | | | |
| **3.7 Other Toxicity Studies** | | | | | | | | |

*Notes: (1) International Nonproprietary Name (INN).*
*(2) There should be one line for each toxicology report, in the same order as the CTD.*
*(3) The location of the Technical Report in the CTD should be indicated.*

a - Unless otherwise specified. For Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

**2.3.7.2 Toxicokinetics** **Overview of Toxicokinetics Studies** **Test Article:** ***(1)***

| Type of Study | Test System | Method of Administration | Doses (mg/kg) | GLP Compliance | Study Number | Location Vol. | Location Page |
|---|---|---|---|---|---|---|---|
| *(2)* | | | | | | *(3)* | |

*Notes: (1) International Nonproprietary Name (INN).*
*(2) There should be one line for each toxicokinetics report, in the same order as the CTD (Section 3, Toxicology).*
(3) *The location of the Technical Report in the CTD should be indicated.*

**2.3.7.3 Toxicokinetics** **Overview of Toxicokinetics Data** **Test Article:** ***(1)***

***(2)***

*Notes: (1) International Nonproprietary Name (INN).*
*(2) A one- to three-page summary (tables and/or figures) of steady-state toxicokinetic data should be prepared in a format that facilitates comparisons across species, including humans.*

**2.3.7.4 Toxicology** **Drug Substance** **Test Article:** ***(1)***

| **Batch No.** | **Purity (%)** | **Specified Impurities ( )** | **Study Number** | **Type of Study** |
|---|---|---|---|---|
| PROPOSED SPECIFICATION: | | | | |
| *(2)* | | | | *(3)* |

*Notes:* *(1) International Nonproprietary Name (INN).*
*(2) All batches used in the Toxicology studies should be listed, in approximate chronological order.*
*(3) The Toxicology studies in which each batch was used should be identified.*

**2.3.7.5 Single-Dose Toxicity** ***(1)*** **Test Article:** *(2)*

| Species/ Strain | Method of Administration (Vehicle/ Formulation) | Doses (mg/kg) | Gender and No. per Group | Observed Maximum Non-Lethal Dose (mg/kg) | Approximate Lethal Dose (mg/kg) | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|---|

*Notes:* *(1) All single-dose toxicity studies should be summarized, in the same order as the CTD. Footnotes should be used to indicate special features, such as unusual duration, infusion rate, or age of test subjects.*
*(2) International Nonproprietary Name (INN).*

**2.3.7.6 Repeat-Dose Toxicity** **Non-Pivotal Studies *(1)*** **Test Article:** *(2)*

| Species/ Strain | Method of Administration (Vehicle/ Formulation) | Duration of Dosing | Doses (mg/kg) | Gender and No. per Group | NOAEL[a] (mg/kg) | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|---|

*Notes:* *(1) All repeat-dose toxicity studies (including all range-finding toxicity studies), other than the definitive GLP studies specified by ICH Guideline M3, should be summarized, in the same order as the CTD. Footnotes should be used to indicate special features, such as unusual age of test subjects.*

*(2) International Nonproprietary Name (INN).*

_____

a - No Observed Adverse-Effect Level.

**2.3.7.7 *(1)* Repeat-Dose Toxicity** *(2)* **Report Title:** **Test Article:** (*3*)

**Species/Strain:** **Duration of Dosing:** **Study No.**
**Initial Age:** **Duration of Postdose:** **Location in CTD:** Vol. Page
**Date of First Dose:** **Method of Administration:**
**Vehicle/Formulation:** **GLP Compliance:**

**Special Features:**
**No Observed Adverse-Effect Level:**

| **Daily Dose (mg/kg)** | 0 (Control) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Number of Animals** | M: | F: | M: | F: | M: | F: | M: | F: |
| **Toxicokinetics: AUC ( )** ***(4)*** | *(5)* | | | | | | | |
| **Noteworthy Findings** | | | | | | | | |
| **Died or Sacrificed Moribund** | | | | | | | | |
| **Body Weight (%[a])** | | | | | | | | |
| **Food Consumption (%[a])** | *(5)* | | | | | | | |
| **Water Consumption ( )** | *(5)* | | | | | | | |
| **Clinical Observations** | | | | | | | | |
| **Ophthalmoscopy** | | | | | | | | |
| **Electrocardiography** | | | | | | | | |

\- No noteworthy findings. + Mild ++ Moderate +++ Marked *(6)*
*(7)* * - p<0.05 ** - p<0.01
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

**2.3.7.7 *(1)* Repeat-Dose Toxicity** **Study No. (Continued)**

| **Daily Dose (mg/kg)** | 0 (Control) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Number of Animals** | M: | F: | M: | F: | M: | F: | M: | F: |
| **Hematology** | | | | | | | | |
| **Serum Chemistry** | | | | | | | | |
| **Urinalysis** | | | | | | | | |
| **Organ Weights[a] (%)** | | | | | | | | |
| **Gross Pathology** | | | | | | | | |
| **Histopathology** | | | | | | | | |
| **Additional Examinations** | | | | | | | | |
| **Postdose Evaluation:** | | | | | | | | |
| **Number Evaluated** *(8)* | | | | | | | | |

\- No noteworthy findings.

*(7)* * - $p<0.05$ ** - $p<0.01$

a - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

Notes for Table 3.2.2

*(1)* The tables should be numbered consecutively: 3.2.2A, 3.2.2B, 3.2.2C etc.

*(2)* There should be one table for each of the repeat-dose toxicity studies specified by ICH Guideline M3, as well as any other repeat-dose toxicity studies that could be considered pivotal.

*(3)* International Nonproprietary Name (INN).

*(4)* Steady-state AUC, Cmax, Css, or other toxicokinetic information supporting the study. If from a separate study, the Study Number should be given in a footnote.

*(5)* ONLY NOTEWORTHY FINDINGS SHOULD BE PRESENTED. If additional parameters (other than those in the Template) showed noteworthy changes, these should be added to the tables. In general, data at end of dosing period can be shown; however, if there were additional noteworthy findings at earlier timepoints, these should be included. Footnotes should be used as needed to provide additional information about the tests or the results.

*(6)* Or other scale, as appropriate.

*(7)* Methods of statistical analyses should be indicated.

*(8)* All parameters that still show drug-related changes should be listed. This section should be deleted if the study does not include a Postdose Evaluation.

*(9)* When appropriate, information on animals that were necropsied early should be presented separately.

**2.3.7.8 *(1)* Genotoxicity: In Vitro** **Report Title:** **Test Article:** *(2)*

**Test for Induction of:** **No. of Independent Assays:** **Study No.**
**Strains:** **No. of Replicate Cultures:** **Location in CTD:** Vol. Page
**Metabolizing System:** **No. of Cells Analyzed/Culture:**
**Vehicles:** **For Test Article:** **For Positive Controls:** **GLP Compliance:**
**Treatment:** **Date of Treatment:**
**Cytotoxic Effects:**
**Genotoxic Effects:**

| Metabolic Activation | Test Article | Concentration or Dose Level *( (3) )* | | | | | |
|---|---|---|---|---|---|---|---|
| Without Activation | | | | | | | |
| | | *(4)* | | | | | |
| With Activation | | | | | | | |

*Notes:* *(1) The tables should be numbered consecutively: 3.3.1A, 3.3.1B, etc. Results of replicate assays should be shown on subsequent pages.*
*(2) International Nonproprietary Name (INN).*
*(3) Units should be inserted.*
*(4) If precipitation is observed, this should be inserted in a footnote.*
*(5) Methods of statistical analyses should be indicated.*

*(5)* * - $p<0.05$ ** - $p<0.01$

**2.3.7.9 *(1)* Genotoxicity: In Vivo** **Report Title:** **Test Article:** *(2)*

**Test for Induction of:**
**Species/Strain:**
**Age:**
**Cells Evaluated:**
**No. of Cells Analyzed/Animal:**
**Special Features:**
**Toxic/Cytotoxic Effects:**
**Genotoxic Effects:**
**Evidence of Exposure:**

**Treatment Schedule:**
**Sampling Time:**
**Method of Administration:**
**Vehicle/Formulation:**

**Study No.**
**Location in CTD:** Vol. Page

**GLP Compliance:**
**Date of Dosing:**

| Test Article | Dose (mg/kg) | No. of Animals | _____ | _____ | _____ | _____ |
|---|---|---|---|---|---|---|

*Notes:* *(1) The tables should be numbered consecutively: 3.3.2A, 3.3.2B, etc.*
*(2) International Nonproprietary Name (INN).*
*(3) Methods of statistical analysis should be indicated.*

*(3)* * - $p<0.05$ ** - $p<0.01$).

**2.3.7.10 *(1)*Carcinogenicity** **Report Title:** **Test Article:** *(2)*

**Species/Strain:** **Duration of Dosing:** **Study No.**
**Initial Age:** **Method of Administration:** **Location in CTD:** Vol. Page
**Date of First Dose:** **Vehicle/Formulation:**
**Treatment of Controls:** **GLP Compliance:**

**Basis for High-Dose Selection:** *(3)*
**Special Features:**

| **Daily Dose (mg/kg)** | 0 (Control) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Gender** | M | F | M | F | M | F | M | F |
| **Toxicokinetics: AUC ( ) *(4)*** | | | | | | | | |
| **Number of Animals** | | | | | | | | |
| **At Start** | | | | | | | | |
| **Died/Sacrificed Moribund** | | | | | | | | |
| **Terminal Sacrifice** | | | | | | | | |
| **Survival (%)** | *(5)* | | | | | | | |
| **Body Weight (%[a])** | | | | | | | | |
| **Food Consumption (%[a])** | | | | | | | | |

*(6)* * - p<0.05 ** - p<0.01
a - At 6 months. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

**2.3.7.10 *(1)* Carcinogenicity** **Study No. (Continued)**

| **Daily Dose (mg/kg)** | (Control) | | 0 (Control) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number Evaluated** | M: | F: | M: | F: | M: | F: | M: | F: | M: | F: |
| **Number of Animals with Neoplastic Lesions: *(7)*** | | | | | | | | | | |
| **Noteworthy Findings:** | | | | | | | | | | |
| **Gross Pathology** | | | | | | | | | | |
| **Histopathology - Non-Neoplastic Lesions** | | | | | | | | | | |

\- No noteworthy findings.
* - p<0.05 ** - p<0.01

Notes for Table 3.4

*(1)* Tables should be numbered consecutively: 3.4A, 3.4B, etc. There should be one table for each carcinogenicity study.

*(2)* International Nonproprietary Name (INN).

*(3)* From ICH Guideline S1C.

*(4)* Steady-state AUC, Cmax, Css, or other toxicokinetic information supporting the study. If the information is from a separate study, the Study Number should be given in a footnote.

*(5)* If additional parameters showed drug-related changes, these should be added to the tables. Footnotes should be used as needed to provide additional information about the tests or the results.

*(6)* Methods of statistical analysis should be indicated.

*(7)* Drug-related lesions should be listed first. Then other lesions should be listed by alphabetically ordered organs/tissues.

**2.3.7.11 Reproductive and Developmental Toxicity** **Non-Pivotal Studies** ***(1)*** **Test Article:** *(2)*

| Species/ Strain | Method of Administration (Vehicle/ Formulation) | Dosing Period | Doses mg/kg | No. per Group | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|

*Notes:* *(1) All reproduction toxicity studies (including all relevant range-finding studies) other than the definitive GLP studies specified by ICH Guideline M3 should be summarized, in the same order as the CTD. However, investigative studies should be summarized using a more detailed template.*

*(2) International Nonproprietary Name (INN).*

**2.3.7.12** ***(1)*** **Reproductive and Developmental Toxicity - Report Title: Test Article:** *(2)*

**Fertility and Early Embryonic Development to Implantation** ***(3)***

| | | |
|---|---|---|
| **Design similar to ICH 4.1.1?** | **Duration of Dosing:** M: | **Study No.** |
| **Species/Strain:** | **Day of Mating:** ***(8)*** F: | **Location in CTD:** Vol. Page |
| **Initial Age:** | **Day of C-Section:** | |
| **Date of First Dose:** | **Method of Administration:** | **GLP Compliance:** |
| **Special Features:** | **Vehicle/Formulation:** | |

**No Observed Adverse-Effect Level:**

**$F_0$ Males:**

**$F_0$ Females:**

**$F_1$ Litters:**

| **Daily Dose (mg/kg)** | **0 (Control)** |
|---|---|
| **Males** Toxicokinetics: AUC ( ) *(4)* | |
| No. Evaluated | |
| No. Died or Sacrificed Moribund | |
| Clinical Observations | |
| Necropsy Observations | |
| Body Weight (%[a]) | |
| Food Consumption (%[a]) | |
| Mean No. Days Prior to Mating | |
| No. of Males that Mated | |
| No. of Fertile Males | *(5)* |

\- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*

*(7)* * - p<0.05 ** - p<0.01

a - After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

**2.3.7.12 *(1)* Reproductive and Developmental Toxicity** **Study No.** **(Continued)**

| **Daily Dose (mg/kg)** | **0 (Control)** |
|---|---|
| **Females** Toxicokinetics: AUC ( ) *(4)* | |
| No. Evaluated | |
| No. Died or Sacrificed Moribund | |
| Clinical Observations | |
| Necropsy Observations | |
| Premating Body Weight (%[a]) | |
| Gestation Body Weight (%[a]) | |
| Premating Food Consumption (%[a]) | |
| Gestation Food Consumption (%[a]) | |
| Mean No. Estrous Cycles/14 days | |
| Mean No. Days Prior to Mating | |
| No. of Females Sperm-Positive | |
| No. of Pregnant Females | |
| No. Aborted or with Total Resorption of Litter | |
| Mean No. Corpora Lutea | |
| Mean No. Implantations | |
| Mean % Preimplantation Loss | |
| Mean No. Live Conceptuses | |
| Mean No. Resorptions | |
| No. Dead Conceptuses | |
| Mean % Postimplantation Loss | |

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*

*(7)* * - p<0.05 ** - p<0.01

a - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

Notes for Tables 3.5.2, 3.5.3, and 3.5.4

*(1)* If there are multiple studies of this type, the tables should be numbered consecutively: 3.5.2A, 3.5.2B, 3.5.3A, 3.5.3B, etc.

*(2)* International Nonproprietary Name (INN).

*(3)* If a modified study design is used, tables should be modified accordingly.

*(4)* Steady-state AUC, Cmax, or other toxicokinetic information supporting the study. If the information is from a separate study, the Study Number should be given in a footnote.

*(5)* POSSIBLE PRESENTATIONS OF THE RESULTS ARE SHOWN IN THESE TEMPLATES. DATA PRESENTATION SHOULD BE FLEXIBLE AND APPROPRIATE ACCORDING TO OPTIMAL STATISTICAL ANALYSIS AND THE DESIGN OF THE STUDY. If additional parameters showed drug-related changes, these should be added to the tables. Footnotes should be used as needed to provide additional information about the tests or the results.

*(6)* Or other scale as appropriate.

*(7)* Methods of statistical analysis should be indicated.

*(8)* Day of mating should be indicated; e.g., Day 0 or Day 1

**2.3.7.13 *(1)* Reproductive and Developmental Toxicity - Report Title: Test Article:** *(2)*
**Effects on Embryo-Fetal Development *(3)***

**Design similar to ICH 4.1.3?**
**Duration of Dosing:**
**Day of Mating:** *(8)*
**Study No.**

**Species/Strain:**
**Day of C-Section:**
**Location in CTD:** Vol. Page

**Initial Age:**
**Method of Administration:**

**Date of First Dose:**
**Vehicle/Formulation:**
**GLP Compliance:**

**Special Features:**
**No Observed Adverse-Effect Level:**
**$F_0$ Females:**
**$F_1$ Litters:**

| **Daily Dose (mg/kg)** | **0 (Control)** |
|---|---|
| **Dams/Does:** Toxicokinetics: AUC **()** *(4)* | |
| No. Pregnant | |
| No. Died or Sacrificed Moribund | *(5)* |
| No. Aborted or with Total Resorption of Litter | |
| Clinical Observations | |
| Necropsy Observations | |
| Body Weight (%[a]) | |
| Food Consumption (%[a]) | |
| Mean No. Corpora Lutea | |
| Mean No. Implantations | |
| Mean % Preimplantation Loss | |

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)* G = Gestation day
*(7)* * - $p<0.05$ ** - $p<0.01$
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

**2.3.7.13 *(1)* Reproductive and Developmental Toxicity** **Study No. (Continued)**

| **Daily Dose (mg/kg)** | | **0 (Control)** |
|---|---|---|
| Litters: | No. Litters Evaluated | |
| | No. Live Fetuses | |
| | Mean No. Resorptions | |
| | No. of Litters with Dead Fetuses | |
| | Mean % Postimplantation Loss | |
| | Mean Fetal Body Weight (g) | |
| | Fetal Sex Ratios | |
| | Fetal Anomalies: | |
| | Gross External | |
| | Visceral Anomalies | |
| | Skeletal Anomalies | |
| | Total Affected Fetuses (Litters) | |

- No noteworthy findings.
* - p<0.05 ** - p<0.01

**2.3.7.14** ***(1)*** **Reproductive and Developmental Toxicity - Report Title: Test Article:** *(2)*
**Effects on Pre- and Postnatal Development, Including Maternal Function** ***(3)***

**Design similar to ICH 4.1.2?** **Duration of Dosing:** **Study No.**
**Day of Mating:** ***(8)***
**Species/Strain:** **Method of Administration:** **Location in CTD:** Vol. Page
**Initial Age** **Vehicle/Formulation:**
**Date of First Dose:** **Litters Culled/Not Culled:** **GLP Compliance:**
**Special Features:**
**No Observed Adverse-Effect Level:**
**$F_0$ Females:**
**$F_1$ Males:**
**$F_1$ Females:**

| **Daily Dose (mg/kg)** | **0 (Control)** |
|---|---|
| $F_0$ Females: Toxicokinetics: AUC ( ) *(4)* | |
| No. Pregnant | |
| No. Died or Sacrificed Moribund | |
| No. Aborted or with Total Res. Of Litter | |
| Clinical Observations | |
| Necropsy Observations | *(5)* |
| Gestation Body Weight (%[a]) | |
| Lactation Body Weight (%[a]) | |
| Gestation Food Consumption (%[a]) | |
| Lactation Food Consumption (%[a]) | |
| Mean Duration of Gestation (days) | |
| Abnormal Parturition | |

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)* G = Gestation day
*(7)* * - p<0.05 ** - p<0.01) L = Lactation day
a - At end of gestation or lactation. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

**2.3.7.14 *(1)* Reproductive and Developmental Toxicity** **Study No. (Continued)**

| **Daily Dose (mg/kg)** | | **0 (Control)** |
|---|---|---|
| $F_1$ Litters: | No. Litters Evaluated | |
| (Preweaning) | Mean No. of Implantations | |
| | Mean No. Pups/Litter | |
| | Mean No. Liveborn Pups/Litter | |
| | No. of Litters with Stillborn Pups | |
| | Postnatal Survival to Day 4 | |
| | Postnatal Survival to Weaning | |
| | No. of Total Litter Losses | |
| | Change in Pup Body Weights[a] (g) | |
| | Pup Sex Ratios | |
| | Pup Clinical Signs | |
| | Pup Necropsy Obs. | |
| $F_1$ Males: | No. Evaluated Postweaning | |
| (Postweaning) | Per Litter | |
| | No. Died or Sacrificed Moribund | |
| | Clinical Observations | |
| | Necropsy Observations | |
| | Body-Weight Change[b] (g) | |
| | Food Consumption (%[c]) | |
| | Preputial Separation | |
| | Sensory Function | |
| | Motor Activity | |
| | Learning and Memory | |
| | Mean No. Days Prior to Mating | |
| | No. of Males that Mated | |
| | No. of Fertile Males | |

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - p<0.05 ** - p<0.01
a - From birth to weaning.
b - From weaning to mating.
c - At end of postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

**2.3.7.14 *(1)* Reproductive and Developmental Toxicity** **Study No. (Continued)**

| **Daily Dose (mg/kg)** | | **0 (Control)** |
|---|---|---|
| $F_1$ Females: | No. Evaluated Postweaning | |
| (Postweaning) | No. Died or Sacrificed Moribund | |
| | Clinical Observations | |
| | Necropsy Observations | |
| | Premating Body-Weight Change[a] (g) | |
| | Gestation Body-Weight Change (g) | |
| | Premating Food Consumption (%[b]) | |
| | Gestation Food Consumption (%[b]) | |
| | Mean Age of Vaginal Patency (days) | |
| | Sensory Function | |
| | Motor Activity | |
| | Learning and Memory | |
| | Mean No. Days Prior to Mating | |
| | No. of Females Sperm-Positive | |
| | No. of Pregnant Females | |
| | Mean No. Corpora Lutea | |
| | Mean No. Implantations | |
| | Mean % Preimplantation Loss | |
| $F_2$ Litters: | Mean No. Live Conceptuses/Litter | |
| | Mean No. Resorptions | |
| | No. of Litter with Dead Conceptuses | |
| | No. Dead Conceptuses | |
| | Mean % Postimplantation Loss | |
| | Fetal Body Weights (g) | |
| | Fetal Sex Ratios (% males) | |
| | Fetal Anomalies | |

\- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*

*(7)** - $p<0.05$ ** - $p<0.01$

a - From weaning to mating

b - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

**2.3.7.14 *(1)* Reproductive and Developmental Toxicity Study No. (Continued)**

| **Daily Dose (mg/kg)** | | **0 (Control)** |
|---|---|---|
| $F_1$ Females: | No. Evaluated Postweaning | |
| (Postweaning) | No. Died or Sacrificed Moribund | |
| | Clinical Observations | |
| | Necropsy Observations | |
| | Premating Body-Weight Change[a] (g) | |
| | Gestation Body-Weight Change (g) | |
| | Premating Food Consumption (%[b]) | |
| | Gestation Food Consumption (%[ab]) | *Note: Alternate* |
| | Mean Age of Vaginal Patency (days) | *Format for* |
| | Sensory Function | *Natural Parturition.* |
| | Motor Activity | |
| | Learning and Memory | |
| | Mean No. Days Prior to Mating | |
| | No. of Females Sperm-Positive | |
| | No. of Pregnant Females | |
| | Mean Duration of Gestation | |
| | Abnormal Parturition | |
| $F_2$ Litters: | No. Litters Evaluated | |
| | Mean No. of Implantations | |
| | Mean No. Pups/Litter | |
| | Mean No. Liveborn Pups/Litter | |
| | Mean No. Stillborn Pups/Litter | |
| | Postnatal Survival to Day 4 | |
| | Postnatal Survival to Weaning | |
| | Change in Pup Body Weights[a] (g) | |
| | Pup Sex Ratios | |
| | Pup Clinical Signs | |
| | Pup Necropsy Obs. | |

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*

*(7)* * - $p<0.05$ ** - $p<0.01$

a - From birth to mating.

b - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

**2.3.7.15 Local Tolerance** ***(1)*** **Test Article:** *(2)*

| Species/ Strain | Method of Administration | Doses (mg/kg) | Gender and No. per Group | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|

*Notes: (1) All local-tolerance studies should be summarized.*
*(2) International Nonproprietary Name (INN).*

**2.3.7.16 Other Toxicity Studies** ***(1)*** **Test Article:** *(2)*

| Species/ Strain | Method of Administration | Duration of Dosing | Doses (mg/kg) | Gender and No. per Group | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|

*Notes: (1) All supplementary toxicity studies should be summarized.*
*(2) International Nonproprietary Name (INN).*

# APPENDIX C

## The Nonclinical Tabulated Summaries - Examples

EXAMPLE

**2.3.3.1 Pharmacology** **Overview** **Test Article:** Curitol Sodium

| Type of Study | Test System | Method of Administration | Testing Facility | Study Number | Location Vol. | Location Page |
|---|---|---|---|---|---|---|
| **1.1 Primary Pharmacodynamics** | | | | | | |
| Antiviral activity vs. VZV | Human embryonic lung fibroblasts | In vitro | Sponsor Inc. | 95401 | 1 | 1 |
| Antiviral activity vs. VZV | | In vitro | Sponsor Inc. | 95402 | 1 | 20 |
| Antiviral activity vs. HSV | Clinical isolates | In vitro | Sponsor Inc. | 95406 | 1 | 30 |
| Antiviral activity vs. CMV | Human embryonic lung fibroblasts | In vitro | Sponsor Inc. | 95408 | 1 | 45 |
| Antiviral activity vs. VZV | | Gavage | Sponsor Inc. | 95411 | 1 | 55 |
| Antiviral activity vs. SVV | Human embryonic lung fibroblasts<br>ICR mice<br>African Green monkeys | Nasogastric Intubation | Sponsor Inc. | 95420 | 1 | 100 |
| **1.2 Secondary Pharmacodynamics** | | | | | | |
| Antimicrobial activity | Gram-positive and gram-negative bacteria; yeasts | In vitro | Sponsor Inc. | 95602 | 1 | 200 |
| **1.3 Safety Pharmacology** | | | | | | |
| Effects on central nervous system[a] | Mice, rats, rabbits, and cats | Gavage | Sponsor Inc. | 95703 | 2 | 1 |
| Effects on cardiovascular system | Dogs | Gavage, i.v. | Sponsor Inc. | 95706 | 2 | 75 |
| **1.4 Pharmacodynamic Drug Interactions** | | | | | | |
| Interactions with anti-HIV activity of AZT | Human T lymphocytes | In vitro | Sponsor Inc. | 95425 | 2 | 200 |

a - Report contains a GLP Compliance Statement.

EXAMPLE

**2.3.3.4 Safety Pharmacology** **Test Article:** Curitol Sodium

| Organ Systems Evaluated | Species/ Strain | Method of Admin. | Doses[a] (mg/kg) | Gender and No. per Group | Noteworthy Findings | GLP Compliance | Study Number |
|---|---|---|---|---|---|---|---|
| CNS | CD-1 Mice | Gavage | 0, 10, 50, 250 | 10M | Slight prolongation of hexobarbital anesthesia (≥10 mg/kg). No analgesic, anticonvulsive, or cataleptic properties. No effects on coordination, traction, or spontaneous motility. | Yes | 92201 |
| Renal, GI, CNS, and Hemostasis | CD-1 Mice | Gavage | 0, 10, 50, 250 | 6M | Slight increases in urinary excretion of sodium and potassium (≥50 mg/kg). No effects on GI transit time (charcoal meal), pupillary diameter, blood coagulation time, or urine volume. | No | 92205 |
| Cardiovascular | Mongrel Dogs | Intravenous | 0, 3, 10, 30 | 3M | Dose-related transient decreases in blood pressure and increases in heart rate and respiratory rate (all doses). Minor ECG changes at 30 mg/kg. No effects on cardiac output, stroke volume, or total peripheral resistance. | Yes | 92210 |

a - Single dose unless specified otherwise.

EXAMPLE

**2.3.5.1 Pharmacokinetics** **Overview** **Test Article:** Curitol Sodium

| Type of Study | Test System | Method of Administration | Testing Facility | Study Number | Location Vol. | Page |
|---|---|---|---|---|---|---|
| **2.2 Absorption** | | | | | | |
| Absorption and excretion | Rats | Gavage, i.v. | Sponsor Inc. | 93302 | 1 | 1 |
| Absorption and excretion | Dogs | Gavage, i.v. | Sponsor Inc. | 93304 | 1 | 25 |
| Absorption and excretion | Monkeys | Gavage, i.v. | Sponsor Inc. | 93306 | 1 | 50 |
| **2.3 Distribution** | | | | | | |
| Single-dose tissue distribution | Rats | Gavage | Sponsor Inc. | 93307 | 1 | 100 |
| Repeat-dose tissue distribution | Rats | Gavage | Sponsor Inc. | 93308 | 1 | 125 |
| Plasma protein binding | Mice, rats, dogs, | In vitro | Sponsor Inc. | 93311 | 1 | 150 |
| Plasma protein binding | monkeys, Humans, rats, dogs | Tablets/Gavage/ Capsules | Sponsor Inc. | 93312 | 1 | 200 |
| **2.4 Metabolism** | | | | | | |
| Metabolites in blood, urine, and feces | Rats | Gavage | Sponsor Inc. | 93402 | 1 | 250 |
| Metabolites in blood, urine, and feces | Dogs | Gavage | *Sponsor Inc.* | 93407 | 1 | 300 |
| **2.5 Excretion** | | | | | | |
| Absorption and excretion | Rats | Gavage, i.v. | Sponsor Inc. | 93302 | 1 | 1 |
| Absorption and excretion | Dogs | Gavage, i.v. | Sponsor Inc. | 93304 | 1 | 25 |
| Absorption and excretion | Monkeys | Gavage, i.v. | Sponsor Inc. | 93306 | 1 | 50 |
| **2.6 Pharmacokinetic Drug Interactions** | | | | | | |
| Interaction with AZT[a] | Rats | Gavage | Sponsor Inc. | 94051 | 1 | 350 |

a - Report contains a GLP Compliance Statement.

EXAMPLE

**2.3.5.3 Pharmacokinetics: Absorption after a Single Dose** **Test Article:** Curitol Sodium

**Location in CTD** Volume 1, Page 258
**Study number** 95104

| **Species** | **Mouse** | **Rat** | **Dog** | **Monkey** | **Human** |
|---|---|---|---|---|---|
| **Gender (M/F) / Number of animals** | 4M | 3M | 4F | 2M | 6M |
| **Feeding condition** | Fed | Fasted | Fasted | Fed | Fasted |
| **Vehicle/Formulation** | Suspension 10% acacia | Suspension 10% acacia | Capsule | Suspension 10% acacia | Tablet |
| **Method of Administration** | Gavage | Gavage | Capsule | Gavage | Oral |
| **Dose (mg/kg)** | 15 | 8 | 5 | 5 | 4 mg |
| **Sample (Whole blood, plasma, serum etc.)** | Plasma | Plasma | Plasma | Plasma | Plasma |
| **Analyte** | TRA[a] | MM-180801 | MM-180801 | MM-180801 | MM-180801 |
| **Assay** | LSC | HPLC | HPLC | HPLC | HPLC |
| **PK parameters:** | | | | | |
| **Tmax (hr)** | 4.0 | 1.0 | 3.3 | 1.0 | 6.8 |
| **Cmax (ng/ml or ng-eq/ml)** | 2,260 | 609 | 172 | 72 | 8.2 |
| **AUC (ng or ng-eq x hr/ml)** | 15,201 | 2,579 | 1,923 | 582 | 135 |
| **(Time for calculation – hr)** | (0-72) | (0-24) | (0.5-48) | (0-12) | (0-24) |
| **T 1/2 (hr)** | 10.6 | 3.3 | 9.2 | 3.2 | 30.9 |
| **(Time for calculation – hr)** | (7-48) | (1-24) | (24-96) | (1-12) | (24-120) |

**Additional Information:**

A single oral dose was well absorbed in mice, rats, dogs, and monkeys.

In a study examining the concentration of compound in the portal vein and inferior vena cava, 30 minutes after a dose to rats, the concentration of compound was approximately 15-fold higher in the portal circulation compared to systemic circulation. This result indicated extensive metabolism and/or biliary secretion of compound in the rat.

a - Total radioactivity, $^{14}C$

EXAMPLE

***Format A***

**2.3.5.5 Pharmacokinetics: Organ Distribution**

**Test Article:** Curitol Sodium

**Location in CTD:** Vol. 21 Page 1
**Study No.** 95207

**Species:** Rat
**Gender (M/F)/Number of animals:** 3M/each time point
**Feeding condition:** Fasted
**Vehicle/Formulation:** Solution/Water
**Method of Administration:** Oral Gavage
**Dose (mg/kg):** 10
**Radionuclide:** $^{14}C$
**Specific Activity:** $2x10^5$ Bq/mg
**Sampling time:** 0.25, 0.5, 2, 6, 24, 96, and 192 hr

| | Concentration (mcg/mL) | | | | | |
|---|---|---|---|---|---|---|
| **Tissues/organs** | **0.25** | **0.5** | **2** | **6** | **24** | **$t_{1/2}$** |
| **Blood** | 9.2 | 3.7 | 1.8 | 0.9 | 0.1 | |
| **Plasma** | 16.5 | 7.1 | 3.2 | 1.6 | 0.2 | |
| **Brain** | 0.3 | 0.3 | 0.2 | 0.1 | nd | |
| **Lung** | 9.6 | 14.1 | 7.3 | 2.9 | 0.1 | |
| **Liver** | 73.0 | 54.5 | 19.9 | 12.4 | 3.2 | |
| **Kidney** | 9.6 | 13.2 | 4.9 | 3.8 | 0.6 | |
| **Testis** | 0.3 | 0.5 | 0.6 | 0.5 | 0.1 | |
| **Muscle** | 1.0 | 1.2 | 0.8 | 0.3 | nd | |

**Additional information:**

Heart, thymus, adrenal, spleen, stomach, intestine,….are examined but not shown.

nd = Not detected.

EXAMPLE

***Alternate Format B***

**2.3.5.5 Pharmacokinetics: Organ Distribution**

**Test Article:** Curitol Sodium

**Location in CTD:** Vol. 21 Page 1
**Study No.** 95207

**Species:** Rat
**Gender (M/F) / Number of animals:** 3M/each time point
**Feeding condition:** Fed
**Vehicle/Formulation:** Solution/Saline
**Method of Administration:** Intravenous
**Dose (mg/kg):** 1
**Radionuclide:** Non-labeled compound
**Specific Activity:** -
**Analyte/Assay:** Unchanged compound (mcg/mL)/HPLC
**Sampling time:** 10 min, 1, 4, 8, 24, 48, 96, and 168 hr

| Tissues/organs | $C_{1hr}$ | | Last time-point | | | AUC | $t_{1/2}$ |
|---|---|---|---|---|---|---|---|
| | conc. | T/P[1)] | conc. | T/P[1)] | Time | | |
| **Heart** | 1.4 | 0.08 | 0.44 | 22 | 48 | 57.3 | 37.3 |
| **Liver** | 4.5 | 6 | 1.85 | 92.5 | 48 | 290 | 51.7 |
| **Kidney** | 2.8 | 0.20 | 1.07 | 53.5 | 48 | 126 | 36.3 |
| **Spleen** | 6.5 | 8.6 | 3.5 | 175 | 48 | 410 | 46.9 |

**Additional information:**

[1)] **[Tissue]/[Plasma]**

EXAMPLE

**2.3.5.6 Pharmacokinetics: Protein Binding** **Test Article:** Curitol Sodium

**Study system:** In vitro
**Target entity, Test system and method:** Plasma, Ultrafiltration

| Species | Conc. tested | % Bound | Study No. | Location in CTD Vol. | Page |
|---|---|---|---|---|---|
| **Rat** | 1 - 100uM | 82.1 - 85.4 | 95301 | 21 | 150 |
| **Dog** | 1 - 100uM | 83.5 - 88.2 | 95301 | 21 | 150 |
| **Human** | 1 - 100uM | 75.2 - 79.4 | 96-103-03 | 45 | 1 |

**Additional Information:**

EXAMPLE

**2.3.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals**

**Test Article:** Curitol Sodium

**Location in CTD:** Vol. 22 Page 1
**Study No.** 95702

**Placental transfer**
**Species:** Rat
**Gestation day / Number of animals:** 14 and 19 days gestation/3 animals at each time point
**Vehicle/Formulation:** Solution/Water
**Method of Administration:** Oral gavage
**Dose (mg/kg):** 5
**Analyte:** Total radioactivity, $^{14}C$
**Assay:** LSC

| Time (hr) | 14 days/30 min | 14 days/24 hr | 19 days/30 min | 19 days/24 hr |
|---|---|---|---|---|
| **Concentration / Amount (% of dose)** | | | | |
| **Maternal plasma** | 12.4 | 0.32 | 13.9 | 0.32 |
| **Placenta** | 3.8 | 0.14 | 3.3 | 0.32 |
| **Amniotic fluid** | 0.07 | 0.04 | 0.04 | 0.13 |
| **Whole fetus** | 0.54 | 0.03 | 0.39 | 0.10 |

**Additional Information:**
Maternal blood, liver, kidney, ovary, uterus were also examined but not shown.

**Location in CTD:** Vol. 22 Page 102
**Study No.** 95703

**Excretion into milk**
**Species:** Rat
**Lactating date / Number of animals:** day 7/3
**Feeding condition:** Fed
**Vehicle/Formulation:** Solution/Water
**Method of Administration:** Oral gavage
**Dose (mg/kg):** 5
**Analyte:** Total radioactivity, $^{14}C$
**Assay:** LSC

| Time [hr] | 1 | 2 | 4 | 6 | 8 | 24 |
|---|---|---|---|---|---|---|
| **Concentration:** | | | | | | |
| **Milk:** | 0.6 | 0.8 | 1.0 | 1.1 | 1.3 | 0.4 |
| **Plasma:** | 1.5 | 1.4 | 1.2 | 0.8 | 0.6 | 0.1 |
| **Milk / plasma:** | 0.40 | 0.57 | 0.83 | 1.4 | 2.2 | 4.0 |
| **Neonates** | | | | | | |

**Additional Information:**

**2.3.5.9 Pharmacokinetics: Metabolism *In Vivo*** **Test Article:** Curitol Sodium

**Gender (M/F) / Number of animals:** **Rats:** 4M **Dogs:** 3F **Humans:** 8M
**Feeding condition:** Fed
**Vehicle/Formulation:** **Rats:** Solution/water **Dogs:** Capsules **Humans:** 75-mg tablets
**Method of Administration:** **Rats:** Gavage* **Dogs:** Oral Capsule* **Humans:** Oral Tablet
**Dose (mg/kg):** **Rats:** 5 mg/kg **Dogs:** 5 mg/kg **Humans:** 75 mg
**Radionuclide:** $^{14}C$
**Specific Activity:** 2 x $10^5$ Bq/mg



| | | | | % of Compound in Sample | | | | Location in CTD | |
|---|---|---|---|---|---|---|---|---|---|
| **Species** | **Sample** | **Sampling Time or Period** | **% of Dose in Sample** | **Parent** | **M1** | **M2** | **Study Number** | **Vol.** | **Page** |
| Rats | Plasma | 0.5 hr | - | 87.2 | 6.1 | 3.4 | *95076* | 26 | 101 |
| | Urine | 0-24 hr | 2.1 | 0.6 | n.d. | 0.2 | | | |
| | Bile | 0-4 hr | 28.0 | 15.5 | 7.2 | 5.1 | | | |
| | Feces | - | - | - | - | - | | | |
| Dogs | Plasma | 0.5 hr | - | 92.8 | n.d. | 7.2 | 95082 | 26 | 301 |
| | Urine | 0-24 hr | 6.6 | 6.4 | n.d. | n.d. | | | |
| | Bile | 0-4 hr | 32.0 | 28.5 | 2.8 | n.d. | | | |
| | Feces | - | - | - | - | - | | | |
| Humans | Plasma | 1 hr | - | 87.5 | trace | 12.5 | CD-102 | 42 | 1 |
| | Urine | 0-24 hr | 5.5 | 2.4 | 2.9 | n.d. | | | |
| | Bile | - | - | - | - | - | | | |
| | Feces | - | - | - | - | - | | | |

Additional Information

* - Intraduodenal administration for collection of bile.
n.d. - None detected.

EXAMPLE

**2.3.5.13 Pharmacokinetics: Excretion** **Test Article:** Curitol Sodium

| **Species** | Rat | | | Rat | | | Dog | | | Dog | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gender (M/F) / Number of animals** | 4M | | | 4M | | | 3M | | | 3M | | |
| **Feeding condition** | Fasted | | | Fasted | | | Fasted | | | Fasted | | |
| **Vehicle/Formulation** | Solution<br>Water | | | Solution<br>Saline | | | Capsule | | | Solution<br>Saline | | |
| **Method of Administration** | Oral | | | Intravenous | | | Oral | | | Intravenous | | |
| **Dose (mg/kg)** | 10 | | | 5 | | | 10 | | | 5 | | |
| **Analyte** | TRA[a] | | | TRA[a] | | | TRA[a] | | | TRA[a] | | |
| **Assay** | LSC | | | LSC | | | LSC | | | LSC | | |
| **Excretion route** | **Urine** | **Feces** | **Total** | **Urine** | **Feces** | **Total** | **Urine** | **Feces** | **Total** | **Urine** | **Feces** | **Total** |
| **Time** | | | | | | | | | | | | |
| **0 - 24 hr** | 26 | 57 | 83 | 22 | 63 | 85 | 20 | 29 | 49 | 23 | 42 | 65 |
| **0 - 48 hr** | 30 | 65 | 95 | 27 | 69 | 96 | 25 | 65 | 90 | 28 | 78 | 96 |
| **0 - 72 hr** | 31 | 65 | 97 | 28 | 70 | 98 | 26 | 73 | 99 | 29 | 72 | 101 |
| **0 - 96 hr** | 31 | 67 | 98 | 29 | 70 | 99 | 26 | 74 | 100 | 29 | 73 | 102 |

| | | |
|---|---|---|
| **Study number** | 95102 | 95156 |
| **Location in CTD** | Volume 20, Page 75 | Volume 20, Page 150 |

**Additional Information:**

a - Total radioactivity; percent recovery, $^{14}C$

EXAMPLE

**2.3.5.14 Pharmacokinetics: Excretion into Bile** **Test Article:** Curitol Sodium

| **Species** | **Rat** | | | **Rat** | | |
|---|---|---|---|---|---|---|
| **Gender (M/F) / Number of animals** | 4M | | | 4M | | |
| **Feeding condition** | Fasted | | | Fasted | | |
| **Vehicle/Formulation** | Solution<br>Water | | | Solution<br>Saline | | |
| **Method of Administration** | Oral | | | Intravenous | | |
| **Dose (mg/kg)** | 10 | | | 5 | | |
| **Analyte** | TRA[a] | | | TRA[a] | | |
| **Assay** | LSC | | | LSC | | |
| **Excretion route** | **Bile** | **Urine** | **Total** | **Bile** | **Urine** | **Total** |
| **Time** | | | | | | |
| **0 - 2 hr** | 37 | - | 37 | 75 | - | 75 |
| **0 - 4 hr** | 50 | - | 50 | 82 | - | 82 |
| **0 - 8 hr** | 62 | - | 62 | 86 | - | 86 |
| **0 - 24 hr** | 79 | 9 | 86 | 87 | 11 | 98 |
| **0 - 48 hr** | 83 | 10 | 93 | 88 | 11 | 99 |

**Study number** 95106
**Location in CTD** Volume 20, Page 150

**a - Total radioactivity; percent recovery, $^{14}C$**

EXAMPLE

**2.3.7.1 Toxicology** **Overview** **Test Article:** Curitol Sodium

| Type of Study | Species and Strain | Method of Administration | Duration of Dosing | Doses (mg/kg[a]) | GLP Compliance | Testing Facility | Study Number | Location Vol. | Location Page |
|---|---|---|---|---|---|---|---|---|---|
| **3.1 Single-Dose Toxicity** | CD-1 Mice | Gavage | - | 0, 1000, 2000, 5000 | Yes | Sponsor Inc. | 96046 | 1 | 1 |
| | | Intravenous | - | 0, 100, 250, 500 | Yes | CRO Co. | 96047 | 1 | 100 |
| | Wistar Rats | Gavage | - | 0, 1000, 2000, 5000 | Yes | Sponsor Inc. | 96050 | 1 | 200 |
| | | Intravenous | - | 0, 100, 250, 500 | Yes | CRO Co. | 96051 | 1 | 300 |
| **3.2 Repeat-Dose Toxicity** | CD-1 Mice | Diet | 3 Months | 0, 62.5, 250, 1000, 4000, 7000 | Yes | CRO Co. | 94018 | 2 | 1 |
| | Wistar Rats | Diet | 2 Weeks | 0, 1000, 2000, 4000 | No | Sponsor Inc. | 94019 | 3 | 1 |
| | | Gavage | 2 Weeks | 0, 500, 1000, 2000 | No | Sponsor Inc. | 94007 | 3 | 200 |
| | | Gavage | 3 Months | 0, 200, 600, 1800 | Yes | Sponsor Inc. | 94214 | 4 | 1 |
| | | Gavage | 6 Months | 0, 100, 300, 900 | Yes | Sponsor Inc. | 95001 | 5 | 1 |
| | Beagle Dogs | Capsules | 1 Month | 0, 10, 40, 100 | Yes | Sponsor Inc. | 94020 | 6 | 1 |
| | | Capsules | 9 Months | 0, 5, 20, 50 | Yes | Sponsor Inc. | 96041 | 7 | 1 |
| | Cynomolgus Monkeys | Gavage | 5 Days | 0, 500, 1000 | No | CRO Co. | 94008 | 8 | 1 |
| **3.3 Genotoxicity** | S. typhimurium and E. coli | In Vitro | - | 0, 500, 1000, 2500, and/or 5000 mcg/plate | Yes | Sponsor Inc. | 96718 | 9 | 1 |
| | Human Lymphocytes | In Vitro | - | 0, 2.5, 5, 10, 20, and 40 mcg/ml | Yes | CRO Co. | 97634 | 9 | 100 |
| | Wistar Rats | Gavage | 3 Days | 0, 1000, 2000 | Yes | Sponsor Inc. | 96037 | 9 | 200 |

a - Unless otherwise specified. For Single-Dose Toxicity and Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

(Continued)

EXAMPLE

**2.3.7.1 Toxicology** **Overview (Continued)** **Test Article:** Curitol Sodium

| Type of Study | Species and Strain | Method of Administration | Duration of Dosing | Doses (mg/kg) | GLP Compliance | Testing Facility | Study Number | Location Vol. | Location Page |
|---|---|---|---|---|---|---|---|---|---|
| **3.4 Carcinogenicity** | CD-1 Mice | Diet | 21 Months | 0, 0, 25, 100, 400 | Yes | CRO Co. | 95012 | 10 | 1 |
| | Wistar Rats | Gavage | 24 Months | 0, 0, 25, 100, 400 | Yes | Sponsor Inc. | 95013 | 12 | 1 |
| **3.5 Reproduction Toxicity** | Wistar Rats | Gavage | a | 0, 5, 30, 180 | Yes | CRO Co. | 96208 | 14 | 1 |
| | Wistar Rats | Gavage | F: G6 - G15[b] | 0, 10, 100, 1000 | Yes | Sponsor Inc. | 94211 | 15 | 1 |
| | NZW Rabbits | Gavage | F: G6 - G18[b] | 0, 1, 5, 25 | Yes | CRO Co. | 97028 | 16 | 1 |
| | Wistar Rats | Gavage | F: G6 - L21[b] | 0, 7.5, 75, 750 | Yes | Sponsor Inc. | 95201 | 17 | 1 |
| **3.6 Local Tolerance** | NZW Rabbits | Dermal | 1 Hour | 0, 15 mg | No | Sponsor Inc. | 95015 | 18 | 1 |
| **3.7 Other Toxicity Studies** | | | | | | | | | |
| **3.7.1 Antigenicity** | Guinea Pigs | Subcutaneous | Weekly for 3 weeks | 0, 5 mg | No | CRO Co. | 97012 | 18 | 20 |
| **3.7.2 Impurities** | Wistar Rats | Gavage | 2 Weeks | 0, 1000, 2000 | Yes | Sponsor Inc. | 97025 | 18 | 200 |

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a - Males: 4 weeks prior to mating. Females - 2 weeks prior to mating through Gestation Day 7.
b - G = Gestation Day L = Lactation Day

EXAMPLE

**2.3.7.2 Toxicokinetics** **Overview of Toxicokinetics Studies** **Test Article:** Curitol Sodium

| Type of Study | Test System | Method of Administration | Doses (mg/kg) | GLP Compliance | Study Number | Location Vol. | Location Page |
|---|---|---|---|---|---|---|---|
| Three-month range-finding study | Mice | Diet | 62.5, 250, 1000, 4000, 7000 | Yes | 94018 | 2 | 1 |
| Two-week toxicity study | Rats | Gavage | 500, 1000, 2000 | No | 94007 | 3 | 200 |
| Six-month toxicity study | Rats | Gavage | 100, 300, 900 | Yes | 95001 | 5 | 1 |
| One-month toxicity study | Dogs | Capsules | 10, 40, 100 | Yes | 94020 | 6 | 1 |
| Nine-month toxicity study | Dogs | Capsules | 5, 20, 50 | Yes | 96041 | 7 | 1 |
| Carcinogenicity study | Mice | Diet | 25, 100, 400 | Yes | 95012 | 10 | 1 |
| Carcinogenicity study | Rats | Gavage | 25, 100, 400 | Yes | 95013 | 12 | 1 |
| Toxicokinetics study | Rabbits | Gavage | 1, 5, 25 | No | 97231 | 16 | 1 |

EXAMPLE

**2.3.7.3 Toxicokinetics** **Overview of Toxicokinetics Data** **Test Article:** Curitol Sodium

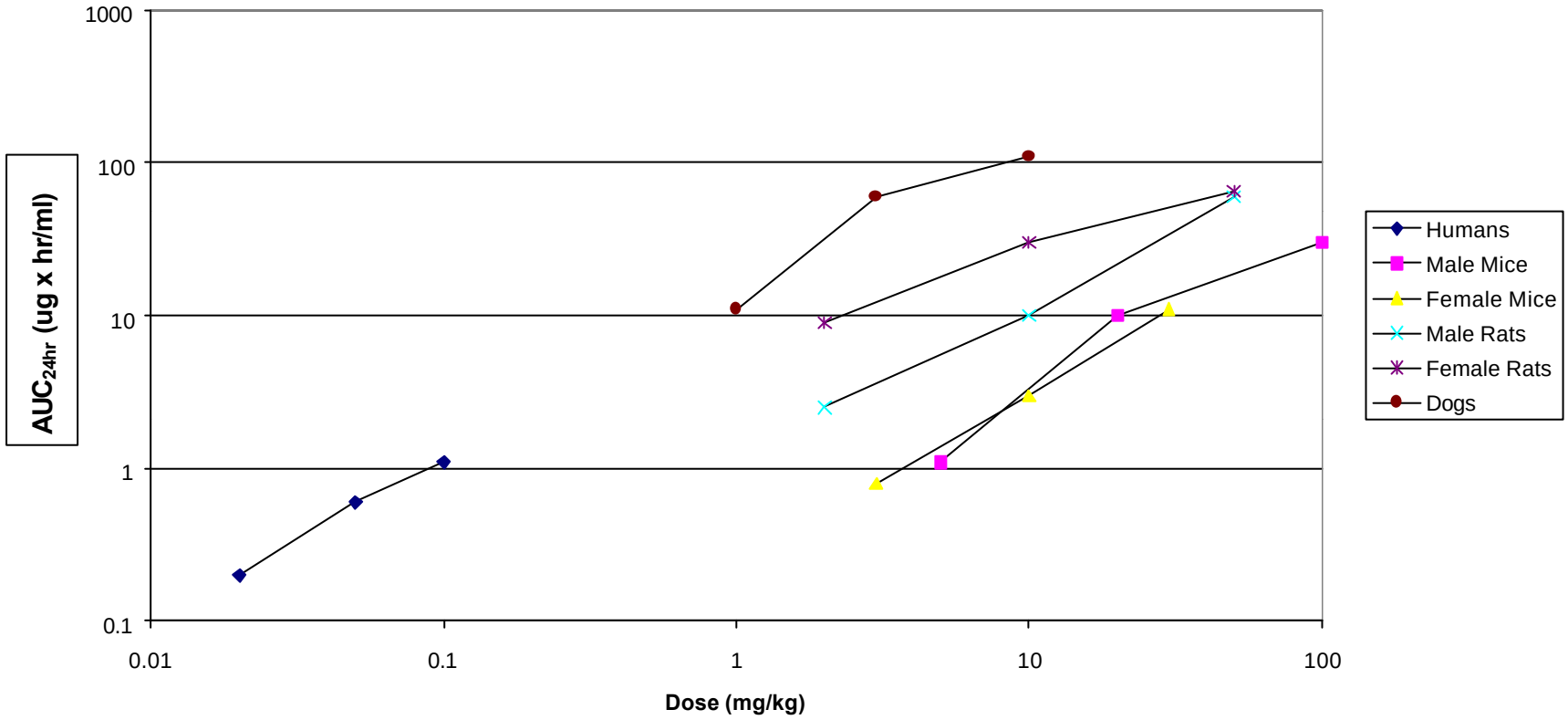
| | Steady-State AUC (mcg-hr/ml) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Daily Dose** | **Mice**[a] | | **Rats**[b] | | | **Female** | |
| **(mg/kg)** | **M** | **F** | **M** | **F** | **Dogs**[c] | **Rabbits**[b] | **Humans**[f] |
| 1 | | | | | | 9 | 3 |
| 5 | | | | | 3 | 25 | |
| 10 | | | | | 4 | | |
| 20 | | | | | 10 | | |
| 25 | 10 | 12 | 6 | 8 | | 273 | |
| 40 | | | | | 10 | | |
| 50 | | | | | 12 | | |
| 62.5 | 35 | 40 | | | | | |
| 100 | 40 | 48 | 25[d], 20[e] | 27[d], 22[e] | 40 | | |
| 250 | 120 | 135 | | | | | |
| 300 | | | 68 | 72 | | | |
| 400 | 815 | 570 | 90 | 85 | | | |
| 500 | | | 125 | 120 | | | |
| 900 | | | 200 | 190 | | | |
| 1000 | 2,103 | 1,870 | 250 | 240 | | | |
| 2000 | | | 327 | 321 | | | |
| 4000 | 4,975 | 3,987 | | | | | |
| 7000 | 8,241 | 7,680 | | | | | |

_____

a - In diet.
b - By gavage.
c - In capsules. Males and females combined.
d - Six-month toxicity study.
e - Carcinogenicity study.
f - Protocol 147-007.

**EXAMPLE**

**2.3.7.3 Toxicokinetics** **Overview of Toxicokinetics Data** **Test Article : Curitol Sodium**




Steady-state $AUC_{24hr}$ values of unchanged MM-180801 in humans after repeated oral administration of 1, 2.5, and 5 mg OD, in comparison with those in mice in the carcinogenicity study, rats in the 6-month toxicity study, and dogs in the 9-month toxicity study.

EXAMPLE

**2.3.7.4 Toxicology** **Drug Substance** **Test Article:** Curitol Sodium

| Batch No. | Purity (%) | Specified Impurities[a] | | | Study Number | Type of Study |
|---|---|---|---|---|---|---|
| | | A | B | C | | |
| PROPOSED SPECIFICATION: | ≥95 | ≤ 0.1 | ≤ 0.2 | ≤ 0.3 | - | - |
| LN125 | 98.2 | 0.1 | 0.1 | 0.2 | 94007 | Two-Week Oral Range-Finding Study in Rats |
| | | | | | 94008 | Five-Day Oral Range-Finding Study in Monkeys |
| | | | | | 96718 | Ames Test |
| 94NA103 | 99.1 | 0.2 | 0.1 | 0.2 | 96046 | Single-Dose Oral Study in Mice |
| | | | | | 96050 | Single-Dose Oral Study in Rats |
| | | | | | 94214 | Three-Month Oral Study in Rats |
| | | | | | 94020 | One-Month Oral Study in Dogs |
| | | | | | 97634 | Human Lymphocytes Assay In Vitro |
| 95NA215 | 97.3 | 0.1 | 0.3 | 0.1 | 96047 | Single-Dose Intravenous Study in Mice |
| | | | | | 96051 | Single-Dose Intravenous Study in Rats |
| | | | | | 96037 | Micronucleus Test in Rats |
| | | | | | 94211 | Embryo-Fetal Development Study in Rats |
| | | | | | 97028 | Embryo-Fetal Development Study in Rabbits |
| 95NB003 | 94.6 | 0.2 | 0.3 | 0.4 | 94019 | Two-Week Palatability Study in Rats |
| | | | | | 97012 | Antigenicity Study in Hamsters |
| 96NB101 | 99.0 | 0.4 | 0.1 | 0.0 | 94018 | Three-Month Dietary Range-Finding Study in Mice |
| | | | | | 95001 | Six-Month Oral Study in Rats |
| | | | | | 95002 | One-Year Oral Study in Dogs |
| | | | | | 95012 | Dietary Carcinogenicity Study in Mice |
| | | | | | 95013 | Oral Carcinogenicity Study in Rats |
| | | | | | 96208 | Fertility and Early Embryonic Development Study in Rats |
| | | | | | 95015 | Dermal Irritation Study in Rabbits |

a - Area percent.

EXAMPLE

**2.3.7.5 Single-Dose Toxicity** **Test Article:** Curitol Sodium

| Species/ Strain | Method of Administration (Vehicle/ Formulation) | Doses (mg/kg) | Gender and No. per Group | Observed Maximum Non-Lethal Dose (mg/kg) | Approximate Lethal Dose (mg/kg) | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|---|
| CD-1 Mice | Gavage (Water) | 0, 1000, 2000, 5000 | 10M 10F | ≥5000 ≥5000 | >5000 | ≥2000: Transient body-weight losses.<br>5000: Decreased activity, convulsions, collapse. | 96046 |
| | Intravenous (Saline) | 0, 100, 250, 500 | 10M 10F | 250 250 | >250 <500 | ≥250: Body-weight losses.<br>500: 3M and 2F died. | 96047 |
| Wistar Rats | Gavage (CMC Suspension) | 0, 1000, 2000, 5000 | 5M 5F | 2000 ≥5000 | >2000 <5000 | ≥2000: Transient body-weight losses; inactivity; chromorhinorrhea.<br>5000: 2M died. | 96050 |
| | Intravenous (5% Dextrose) | 0, 100, 250, 500 | 5M 5F | 250 ≥500 | >250 <500 | ≥250: Body-weight losses in males.<br>500: 3M died. | 96051 |

EXAMPLE

**2.3.7.6 Repeat-Dose Toxicity** **Non-Pivotal Studies** **Test Article:** Curitol Sodium

| Species/ Strain | Method of Administration (Vehicle/ Formulation) | Duration of Dosing | Doses (mg/kg) | Gender and No. per Group | NOAEL[a] (mg/kg) | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|---|
| CD-1 Mice | Diet | 3 Months | 0, 62.5, 250, 1000, 4000, and 7000 | 10M, 10F | M:4000<br>F: 1000 | ≥4000: Lower body weights; gastric erosions/ulcers in some mice.<br>7000: 4M and 6F died/ sacrificed; lower body weights; single-cell necrosis in liver. | 94018 |
| Wistar Rats | Diet | 2 Weeks | 0, 1000, 2000, and 4000 | 5M, 5F | 1000 | ≥2000: Lower body weights.<br>4000: 2M and 1F sacrificed moribund. | 94019 |
| | Gavage (Water) | 2 Weeks | 0, 500, 1000, and 2000 | 5M, 5F | 1000 | 2000: Lower body weights; single-cell necrosis in liver. | 94007 |
| Beagle Dogs | Gavage (CMC Suspension) | 5 Days | 0, 500, and 1000 | 1M, 1F | <500 | ≥500: Weight losses, inappetence. | 94008 |

_____

a - No Observed Adverse-Effect Level.

EXAMPLE #1

**2.3.7.7A Repeat-Dose Toxicity** **Report Title:** MM-180801: Three-Month Oral Toxicity Study in Rats **Test Article:** Curitol Sodium

**Species/Strain:** Wistar Rats
**Initial Age:** 5 Weeks
**Date of First Dose:** 15 Jan 94

**Duration of Dosing:** 3 Months
**Duration of Postdose:** 1 Month
**Method of Administration:** Gavage
**Vehicle/Formulation:** Aqueous Solution

**Study No.** 94214
**Location in CTD:** Vol. 4 Page 1

**GLP Compliance:** Yes

**Special Features:** None
**No Observed Adverse-Effect Level:** 200 mg/kg

| **Daily Dose (mg/kg)** | 0 (Control) | | 200 | | 600 | | 1800 | |
|---|---|---|---|---|---|---|---|---|
| **Number of Animals** | M:30 | F:30 | M:20 | F:20 | M:20 | F:20 | M:30 | F:30 |
| **Toxicokinetics: AUC (mcg-hr/ml):** | | | | | | | | |
| **Day 1** | - | - | 30 | 28 | 130 | 125 | 328 | 302 |
| **Day 28** | - | - | 52 | 47 | 145 | 140 | 400 | 380 |
| **Day 90** | - | - | 50 | 51 | 160 | 148 | 511 | 475 |
| **Noteworthy Findings** | | | | | | | | |
| **Died or Sacrificed Moribund** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Body Weight (%[a])** | 394 g | 244 g | 0 | -1 | -10* | -11* | -25** | -45** |
| **Food Consumption (%[a])** | 20.4 g | 17.2 g | 0 | -1 | -1 | -8* | -30** | -50** |
| **Clinical Observations** | | | | | | | | |
| **Hyperactivity** | - | - | - | - | - | + | - | ++ |
| **Chromorhinorrhea, reddish-stained coat, white feces** | - | - | - | - | - | - | ++ | ++ |
| **Emaciated, piloerection, stilted gait** | - | - | - | - | - | - | - | ++ |
| **Ophthalmoscopy** | - | - | - | - | - | - | - | - |

- No noteworthy findings. + Mild ++ Moderate +++ Marked
Dunnett's Test: *- p<0.05 ** - p<0.01
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

EXAMPLE #1

**2.3.7.7A Repeat-Dose Toxicity** **Study No. 94214 (Continued)**

| **Daily Dose (mg/kg)** | 0 (Control) | | 200 | | 600 | | 1800 | |
|---|---|---|---|---|---|---|---|---|
| **Number of Animals** | M:30 | F:30 | M:20 | F:20 | M:20 | F:20 | M:30 | F:30 |
| **Hematology** | | | | | | | | |
| **Hemoglobin (g/dl)** | 15.8 | 15.0 | 15.7 | 14.9 | 15.8 | 14.6 | 14.0* | 13.1* |
| **Erythrocyte Count (x10$^6$/mm$^3$)** | 8.1 | - | 7.9 | - | 8.1 | - | 7.4* | - |
| **MCH** | - | 22 | - | 21 | - | 22 | - | 19* |
| **MCHC** | - | 34 | - | 34 | - | 34 | - | 30* |
| **Platelet Count (x10$^3$/mm$^3$)** | 846 | 799 | 825 | 814 | 914 | 856 | 931* | 911* |
| **Serum Chemistry** | | | | | | | | |
| **Creatinine (IU/L)** | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 1.1* | 1.1* |
| **Proteins g/dl)** | - | 6.7 | - | 6.6 | - | 6.6 | - | 5.0** |
| **Cholesterol (mg/dl)** | 96 | - | 86 | - | 90 | - | 105* | - |
| **ALT (IU/L)** | 67 | 56 | 60* | 52 | 55* | 47* | 53* | 58 |
| **AST (IU/L)** | 88 | 92 | 96 | 90 | 87* | 84* | 85* | 93 |
| **Bilirubin (mg/dl)** | 0.18 | 0.20 | 0.17 | 0.20 | 0.18 | 0.20 | 0.22** | 0.26** |
| **Calcium (mEq/L)** | - | 10.7 | - | 10.8 | - | 10.8 | - | 9.8** |
| **Phosphorus (mEq/L)** | 9.3 | - | 9.3 | - | 9.3 | - | 8.2* | - |
| **Urinalysis** | | | | | | | | |
| **Protein Conc. (mg/dl)** | | | | | | | | |
| **pH** | 260 | 49 | 102 | 34 | 123 | 54 | 126* | 22* |
| **Glucose (mg/dl)** | 7.5 | - | 7.5 | - | 7.2 | - | 6.3** | - |
| **Urine Volume (ml)** | - | 0 | - | 0 | - | 20 | - | 98** |
| | - | 18 | - | 18 | - | 16 | - | 12* |

- No noteworthy findings.
Dunnett's Test: *- p<0.05 **- p<0.01

(Continued)

EXAMPLE #1

**2.3.7.7A Repeat-Dose Toxicity** **Study No. 94214 (Continued)**

| **Daily Dose (mg/kg)** | 0 (Control) | | 200 | | 600 | | 1800 | |
|---|---|---|---|---|---|---|---|---|
| **Number of Animals** | M:30 | F:30 | M:20 | F:20 | M:20 | F:20 | M:30 | F:30 |
| **Organ Weights[b] (%)** | | | | | | | | |
| **Kidney** | 3.01 g | 1.75 g | 0 | +5* | +1 | +8** | +12** | +20** |
| **Liver** | 15.9 g | 8.01 g | 0 | +1 | +10* | +12* | +12* | +20** |
| **Gross Pathology** | | | | | | | | |
| **Number examined** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **Kidneys: Pallor** | 0 | 0 | 0 | 0 | 0 | 5 | 1 | 2 |
| **Glandular Stomach: Discoloration** | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 4 |
| **Histopathology** | | | | | | | | |
| **Number examined** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **Kidneys: Tubular dilatation** | 0 | 0 | 0 | 0 | 0 | 6 | 3 | 4 |
| **Mild** | 0 | 0 | 0 | 0 | 0 | 6 | 1 | 0 |
| **Moderate** | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 4 |
| **Glandular Stomach: Erosions** | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 9 |
| **Additional Examinations** | - | - | - | - | - | - | - | - |
| **Postdose Evaluation:** | | | | | | | | |
| **Number Evaluated** | 10 | 10 | 0 | 0 | 0 | 0 | 10 | 10 |
| **Body Weight [a] (%)** | 422 g | 265 g | -1 | -2 | -3 | -4 | -10* | -20** |
| **Kidney Weight[b] (%)** | 3.24 g | 1.81 g | 0 | -1 | -1 | 0 | +8* | +10 |

- No noteworthy findings.

Dunnett's Test: * - $p<0.05$ **- $p<0.01$

a - At end of postdose recovery period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

EXAMPLE #2

**2.3.7.7B Repeat-Dose Toxicity** **Report Title:** MM-180801: One-Month Oral Toxicity Study in Dogs **Test Article:** Curitol Sodium

**Species/Strain:** Beagle Dogs
**Initial Age:** 5-6 Months
**Date of First Dose:** 2 Feb 94

**Duration of Dosing:** 1 Month
**Duration of Postdose:** None
**Method of Administration:** Oral
**Vehicle/Formulation:** Gelatin Capsules

**Study No.** 94020
**Location in CTD:** Vol. 6 Page 1

**GLP Compliance:** Yes

**Special Features:** Hepatic enzyme induction evaluated at termination.
**No Observed Adverse-Effect Level:** 10 mg/kg

| **Daily Dose (mg/kg)** | 0 (Control) | | 10 | | 40 | | 100 | |
|---|---|---|---|---|---|---|---|---|
| **Number of Animals** | M:3 | F:3 | M:3 | F:3 | M:3 | F:3 | M:3 | F:3 |
| **Toxicokinetics: AUC (mcg-hr/ml):** | | | | | | | | |
| **Day 1** | - | - | 5 | 6 | 10 | 12 | 40 | 48 |
| **Day 28** | - | - | 4 | 5 | 8 | 11 | 35 | 45 |
| **Noteworthy Findings** | | | | | | | | |
| **No. Died or Sacrificed Moribund** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Body Weight (%[a])** | 9.8 kg | 9.2 kg | 0 | 0 | -1 | -19** | 0 | -18** |
| **Clinical Observations:** | | | | | | | | |
| **Hypoactivity (after dosing)** | - | - | - | - | - | - | + | ++ |
| **Ophthalmoscopy** | - | - | - | - | - | - | - | - |
| **Electrocardiography** | - | - | - | - | - | - | - | - |
| **Hematology** | - | - | - | - | - | - | - | - |
| **Serum Chemistry** | | | | | | | | |
| **ALT (IU/L): Week 2** | 22 | 25 | 24 | 27 | 21 | 24 | 48* | 69** |
| **Week 4** | 25 | 27 | 26 | 25 | 23 | 25 | 54* | 84** |

- No noteworthy findings. + Mild ++ Moderate +++ Marked
Dunnett's Test: * - p<0.05 ** - p<0.01
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

EXAMPLE #2

**2.3.7.7B Repeat-Dose Toxicity** **Study No. 94020 (Continued)**

| **Daily Dose (mg/kg)** | 0 (Control) | | 10 | | 40 | | 100 | |
|---|---|---|---|---|---|---|---|---|
| **Number of Animals** | M:3 | F:3 | M:3 | F:3 | M:3 | F:3 | M:3 | F:3 |
| **Organ Weights[a] (%)** | | | | | | | | |
| **Liver** | 339 g | 337 g | +1 | -1 | +17** | +16** | +23** | +21** |
| **Gross Pathology** | - | - | - | - | - | - | - | - |
| **Histopathology** | | | | | | | | |
| **Number Examined** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Liver: Centrilobular hypertrophy** | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 |
| **Additional Examinations** | | | | | | | | |
| **Hepatic Enzyme Induction** | - | - | - | - | - | - | - | - |

- No noteworthy findings.

Dunnett's Test: * - p<0.05 ** - p<0.01

a - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

EXAMPLE #1

**2.3.7.8A Genotoxicity: In Vitro** **Report Title:** MM-180801: Ames Reverse-Mutation Study in Salmonella and E. Coli **Test Article:** Curitol Sodium

**Test for Induction of:** Reverse mutation in bacterial cells **No. of Independent Assays:** 2 **Study No.** 96669
**Strains:** S. typhimurium and E. coli **No. of Replicate Cultures:** 3 **Location in CTD:** Vol. 10 Page 211
**Metabolizing System:** Aroclor-induced rat liver S9, 7.1% **No. of Cells Analyzed/Culture:** -
**Vehicles:** **Test Article:** DMSO **Positive Controls:** DMSO **GLP Compliance:** Yes
**Treatment:** Plate incorporation for 48 hr. **Date of Treatment:** Feb. 1996
**Cytotoxic Effects:** None.
**Genotoxic Effects:** None.

| Metabolic Activation | Test Article | Dose Level (mcg/plate) | Assay #1 Revertant Colony Counts (Mean ±SD) | | | | |
|---|---|---|---|---|---|---|---|
| | | | TA 98 | TA 100 | TA 1535 | TA 1537 | WP2 uvrA |
| Without | DMSO | 100 mcl/plate | 24 ± 9 | 129 ± 4 | 15 ± 4 | 4 ± 2 | 17 ± 3 |
| Activation | MM-180801 | 312.5 | 24 ± 6 | 128 ± 11 | 12 ± 4 | 4 ± 2 | 14 ± 2 |
| | | 625 | 32 ± 9 | 153 ± 9 | 9 ± 2 | 8 ± 2 | 17 ± 5 |
| | | 1250 | 30 ± 4 | 152 ± 12 | 9 ± 3 | 9 ± 2 | 18 ± 4 |
| | | 2500 | 27 ± 5 | 140 ± 6 | 9 ± 3 | 5 ± 1 | 19 ± 1 |
| | | 5000[a] | 30 ± 3 | 137 ± 21 | 15 ± 1 | 7 ± 2 | 13 ±4 |
| | 2-Nitrofluorene | 2 | 696 | | | | |
| | Sodium azide | 1 | | 542 | 468 | | |
| | 9-Aminoacridine | 100 | | | | 515 | |
| | MMS | 2.5 mcl/plate | | | | | 573 |
| With | DMSO | 100 mcl/plate | 27 ± 6 | 161 ± 12 | 12 ± 5 | 5 ± 1 | 21 ± 8 |
| Activation | MM-180801 | 312.5 | 31 ± 4 | 142 ± 8 | 12 ± 5 | 4 ± 2 | 17 ± 3 |
| | | 625 | 30 ± 1 | 156 ± 15 | 17 ± 2 | 9 ± 5 | 23 3 |
| | | 1250 | 33 ± 2 | 153 ± 13 | 13 ± 3 | 8 ± 2 | 18 ± 3 |
| | | 2500 | 35 ± 8 | 160 ± 4 | 10 ± 2 | 8 ± 2 | 19 ± 5 |
| | | 5000[a] | 31 ± 4 | 153 ± 5 | 9 ± 4 | 7 ± 1 | 17 ±4 |
| | 2-Aminoanthracene | 2.5 | 1552 | 1487 | 214 | 61 | |
| | | 10 | | | | | 366 |

a - Precipitation.

EXAMPLE #2

**2.3.7.8B Genotoxicity: In Vitro** **Report Title:** MM-180801: Cytogenetics Study in Primary Human Lymphocytes **Test Article:** Curitol Sodium

**Test for Induction of:** Chromosome aberrations **No. of Independent Assays:** 1 **Study No.** 96668
**Strains:** Primary human lymphocytes **No. of Replicate Cultures:** 2 **Location in CTD:** Vol. 10 Page 245
**Metabolizing System:** Aroclor-induced rat liver S9, 5% **No. of Cells Analyzed/Culture:** 100
**Vehicles:** **Test Article:** DMSO **Positive Controls:** DMSO **GLP Compliance:** Yes
**Treatment:** Continuous treatment for 24-hr without S9; pulse treatment 5 hr and recovery time 24 hr with and without S9. **Date of Treatment:** Aug. 1996
**Cytotoxic Effects:** Dose-related decreases in mitotic indices.
**Genotoxic Effects:** Chromosome aberrations without S9 at 10 and 20 µg/ml, and with S9 at 50 and 200 µg/ml.

| Metabolic Activation | Test Article | Concentration (mcg/ml) | Cytotoxicity[a] (% of control) | Aberrant Cells Mean % | Abs/Cell | *Total polyploid cells* |
|---|---|---|---|---|---|---|
| Without Activation | DMSO | - | 100 | 2.0 | 0.02 | 4 |
| | MM-180801 | 2.5 | 78 | 3.0 | 0.03 | 3 |
| | | 5 | 59 | 4.0 | 0.05 | 4 |
| | | 10 | 36 | 16.5** | 0.20 | 2 |
| | | 20 | 32 | 35.0** | 0.55 | 3 |
| | Mitomycin | 0.10 | 52 | 38.5** | 0.64 | 5 |
| With Activation | DMSO | - | 100 | 4.0 | 0.04 | 3 |
| | MM-180801 | 2.5 | 91 | 4.5 | 0.05 | 3 |
| | | 10 | 88 | 4.5 | 0.05 | 2 |
| | | 50 | 80 | 9.5* | 0.10 | 4 |
| | | 200 | 43 | 34.0** | 0.66 | 3 |
| | Cyclophosphamide | 4 | 68 | 36.5** | 0.63 | 6 |

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$
a - Based on mitotic indices.

EXAMPLE #1

**2.3.7.9A Genotoxicity: In Vivo** **Report Title:** MM-180801: Oral Micronucleus Study in Rats **Test Article:** Curitol Solution

**Test for Induction of:** Bone-marrow micronuclei
**Species/Strain:** Wistar Rats
**Age:** 5 Weeks
**Cells Evaluated:** Polychromatic erythrocytes
**No. of Cells Analyzed/Animal:** 2000
**Special Features:** None.

**Treatment Schedule:** Three daily doses.
**Sampling Time:** 24 hr after last dose.
**Method of Administration:** Gavage.
**Vehicle/Formulation:** Aqueous solution.

**Study No:** 96683
**Location in CTD:** Vol. 10 Page 502

**GLP Compliance:** Yes
**Date of Dosing:** July 1996

**Toxic/Cytotoxic Effects:** At 2000 mg/kg, clinical signs, two deaths, and decreases in bone-marrow PCEs.
**Genotoxic Effects:** None.
**Evidence of Exposure:** Overt toxicity at 2000 mg/kg.

| Test Article | Dose (mg/kg) | No. of Animals | Mean % PCEs (±SD) | Mean % MN-PCEs (±SD) |
|---|---|---|---|---|
| Vehicle | 0 | 5M | 52 ± 1.9 | 0.20 ± 0.12 |
| MM-180801 | 2 | 5M | 54 ± 3.7 | 0.25 ± 0.16 |
| | 20 | 5M | 49 ± 3.1 | 0.20 ± 0.07 |
| | 200 | 5M | 50 ± 2.1 | 0.26 ± 0.08 |
| | 2000 | 3M | 31 ± 2.5 | 0.12 ± 0.03 |
| Cyclophosphamide | 7 | 5M | 51 ± 2.3 | 2.49 ± 0.30** |

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$

EXAMPLE #2

**2.3.7.9B Genotoxicity: In Vivo** **Report Title:** MM-180801: Oral DNA Repair Study in Rats **Test Article:** Curitol Solution

**Test for Induction of:** Unscheduled DNA synthesis
**Species/Strain:** Wistar Rats
**Age:** 5 Weeks
**Cells Evaluated:** Hepatocytes.
**No. of Cells Analyzed/Animal:** 100
**Special Features:** None.
**Toxic/Cytotoxic Effects:** None.
**Genotoxic Effects:** None.
**Evidence of Exposure:** Toxicokinetics - See Study No. 94007, Two-Week Oral Toxicity Study in Rats.

**Treatment Schedule:** Single dose.
**Sampling Time:** 2 and 16 hr.
**Method of Administration:** Gavage.
**Vehicle/Formulation:** Aqueous solution.

**Study No:** 51970
**Location in CTD:** Vol. 11 Page 2

**GLP Compliance:** Yes
**Date of Dosing:** Jan. 1997

| Test Article | Dose (mg/kg) | No. of Animals | Time hr | Nuclear Mean ± SD | Cytoplasm Mean ± SD | NG Mean ± SD | % IR Mean ± SD | NGIR Mean ± SD |
|---|---|---|---|---|---|---|---|---|
| Vehicle | 0 | 3M | 16 | 3.5 ± 0.2 | 7.3 ± 0.3 | -3.8 ± 0.4 | 0 ± 0 | - |
| MM-180801 | 2 | 3M | 2 | 3.0 ± 1.1 | 5.5 ± 1.4 | -2.6 ± 0.4 | 0 ± 0 | - |
| | 2 | 3M | 16 | 4.1 ± 0.5 | 6.5 ± 0.8 | -2.4 ± 0.2 | 0 ± 0 | - |
| | 20 | 3M | 2 | 3.9 ± 0.2 | 6.9 ± 0.3 | -3.0 ± 0.1 | 1 ± 0 | 5.7 ± 0.4 |
| | 20 | 3M | 16 | 3.6 ± 0.3 | 6.3 ± 0.4 | -2.7 ± 0.2 | 0 ± 0 | - |
| | 200 | 3M | 2 | 4.2 ± 0.2 | 7.5 ± 0.3 | -3.4 ± 0.2 | 0 ± 0 | - |
| | 200 | 3M | 16 | 3.1 ± 0.3 | 5.3 ± 0.3 | -2.2 ± 0.1 | 0 ± 0 | - |
| | 2000 | 3M | 2 | 4.8 ± 0.4 | 8.2 ± 0.7 | -3.4 ± 0.4 | 0 ± 0 | - |
| | 2000 | 3M | 16 | 2.7 ± 0.1 | 4.8 0.3 | -2.1 ± 0.3 | 0 ± 0 | - |
| DMN | 10 | 3M | 2 | 10.7 ± 3.0 | 5.8 ± 1.0 | 4.9 ± 2.1 | 41 ±15 | 11.4 ± 0.4 |

Nuclear = Nuclear grain count; the number of grains over the nucleus.
Cytoplasm = Cytoplasmic grain count; the highest grain count from 2 nuclear-sized areas adjacent to the nucleus.
NG = Net grains/nucleus; the nuclear count minus the cytoplasmic count.
% IR = Percentage of cells with at least 5 NG.
NGIR = Average net grains/nucleus of cells in repair.

EXAMPLE

**2.3.7.10 Carcinogenicity** **Report Title:** MM-180801: Dietary Carcinogenicity Study in Mice **Test Article:** Curitol Sodium

**Species/Strain:** CD-1 Mice
**Initial Age:** 6 Weeks
**Date of First Dose:** 20 Sep 95
**Duration of Dosing:** 21 months
**Method of Administration:** Diet
**Vehicle/Formulation:** In Diet
**Treatment of Controls:** Drug-Free Diet
**Study No.** 95012
**Location in CTD:** Vol. 4 Page 1
**GLP Compliance:** Yes

**Basis for High-Dose Selection:** Toxicity-based endpoint.
**Special Features:** 12 additional males and 12 additional females per drug-treated group bled at 6 months for toxicokinetic monitoring and then removed from the study.

| **Daily Dose (mg/kg)** | 0 (Control) | | 25 | | 100 | | 400 | |
|---|---|---|---|---|---|---|---|---|
| **Gender** | M | F | M | F | M | F | M | F |
| **Toxicokinetics:** | | | | | | | | |
| **AUC on Day 28 (mcg-hr/ml[a])** | - | - | 10 | 12 | 40 | 48 | 815 | 570 |
| **Css on Day 180 (mcg/ml)** | - | - | 0.4 | 0.5 | 1.7 | 0.3 | 34 | 24 |
| **Number of Animals:** | | | | | | | | |
| **At Start** | 60 | 60 | 60[c] | 60 | 60 | 60 | 60 | 60 |
| **Died/Sacrificed Moribund** | 16 | 16 | 15 | 13 | 18 | 20 | 27 | 25 |
| **Terminal Sacrifice** | 44 | 44 | 44[c] | 47 | 42 | 40 | 33 | 35 |
| **Survival (%)** | 67 | 73 | 75 | 80 | 71 | 68 | 56 | 59 |
| **Body Weight (%[b])** | 33g | 31g | 0 | 0 | -7* | 0 | -13** | -19** |
| **Food consumption (%[b])** | 6g/day | 5g/day | 0 | 0 | -9* | -8* | -17** | -15** |

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$

a - From Study No. 95013.

b - At 6 months. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)

c - One missing mouse could not be evaluated.

(Continued)

EXAMPLE

**2.3.7.10 Carcinogenicity** **Study No. 95012 (Continued)**

| Daily Dose (mg/kg) | 0 (Control) | | 25 | | 100 | | 400 | |
|---|---|---|---|---|---|---|---|---|
| **Number Evaluated** | M: 60 | F: 60 | M: 59 | F: 60 | M: 60 | F: 60 | M: 60 | F: 60 |
| **Number of Animals with Neoplastic Lesions:** | | | | | | | | |
| **Skin: Hemangioma** | 0 | 1 | 1 | 0 | 6[b] | 1 | 13[b] | 0 |
| **Hemangiosarcoma** | 1 | 3 | 2 | 2 | 9 | 11 | 18[a] | 24[a] |
| **Adrenal: Adrenocortical adenoma** | 4 | 1 | 2 | 0 | 4 | 3 | 3 | 1 |
| **Adrenocortical adenocarcinoma** | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Adenoma + Adenocarcinoma** | 4 | 1 | 2 | 0 | 4 | 3 | 3 | 1 |
| **Pheochromocytoma** | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 |
| **Bone: Osteochondrosarcoma** | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Osteoma** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Epididymis: Sarcoma, undifferentiated** | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| **Gallbladder: Adenoma** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **Harderian gland: Adenoma** | 4 | 2 | 3 | 1 | 3 | 4 | 3 | 1 |
| **Kidney: Renal cell adenoma** | 1 | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| **Liver: Hepatocellular adenoma** | 3 | 1 | 4 | 2 | 3 | 1 | 4 | 1 |
| **Hepatocellular carcinoma** | 2 | 1 | 1 | 2 | 3 | 1 | 0 | 1 |
| **Hepatocellular adenoma + carcinoma** | 3 | 2 | 4 | 3 | 5 | 2 | 4 | 1 |
| **Lung: Alveolar/bronchiolar adenoma** | 13 | 10 | 11 | 11 | 14 | 7 | 13 | 4 |
| **Alveolar/bronchiolar carcinoma** | 4 | 0 | 1 | 1 | 2 | 2 | 1 | 1 |
| **Adenoma + carcinoma** | 15 | 10 | 11 | 12 | 15 | 9 | 13 | 5 |

a - Trend analysis, p<0.005
b - Trend analysis, p<0.025

(Continued)

EXAMPLE

**2.3.7.10 Carcinogenicity** **Study No. 95012 (Continued)**

| **Daily Dose (mg/kg)** | 0 (Control) | | 25 | | 100 | | 400 | |
|---|---|---|---|---|---|---|---|---|
| **Number Evaluated** | M: 60 | F: 60 | M: 59 | F: 60 | M: 60 | F: 60 | M: 60 | F: 60 |
| **Mediastinum: Sarcoma, undifferentiated** | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Oviduct: Adenoma** | | 1 | | 1 | | 0 | | 0 |
| **Pancreas: Islet cell adenoma** | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Peritoneum: Osteosarcoma** | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| **Seminal vesicle: Adenoma** | 0 | | 1 | | 0 | | 0 | |
| **Stomach: Osteochondrosarcoma** | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Thymus: Thymoma** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Thyroid: Follicular cell adenoma** | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Uterus: Papillary cystadenoma** | | 1 | | 0 | | 2 | | 0 |
| **Whole animal: Lymphosarcoma** | 6 | 13 | 4 | 11 | 3 | 12 | 5 | 11 |
| **Whole animal: Histiocytic sarcoma** | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Noteworthy Findings:** | | | | | | | | |
| **Gross Pathology** | - | - | - | - | - | - | - | - |
| **Histopathology - Non-Neoplastic Lesions** | | | | | | | | |
| **Liver: Hepatocellular hypertrophy** | 4 | 2 | 3 | 2 | 4 | 1 | 40** | 45** |
| **Testes: Hypospermatogenesis** | 1 | | 2 | | 15* | | 30** | |

- No noteworthy findings.
Fisher Exact Test: * - p<0.05 ** - p<0.01

EXAMPLE

**2.3.7.11 Reproductive and Developmental Toxicity** **Non-Pivotal Studies** **Test Article:** Curitol Sodium

| Species/ Strain | Method of Administration (Vehicle/ Formulation) | Dosing Period | Doses mg/kg | No. per Group | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|
| Wistar Rats | Gavage (Water) | G6 through G15 | 0, 500, 1000, 2000 | 8 Pregnant Females | ≥1000: Deaths; weight losses; decreased food consumption; clinical signs; resorptions. | 94201 |
| NZW Rabbits | Gavage (CMC Suspension) | 13 Days | 0, 5,15, 45 | 6 Nonpregnant Females | ≥15: Decreased weight gain and food consumption.<br>45: Four does died. | 97020 |

G – Gestation day

EXAMPLE

**2.3.7.12 Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation**

**Report Title:** MM-180801: Oral Study of Effects on Fertility and Early Embryonic Development in Rats

**Test Article:** Curitol Sodium

**Design similar to ICH 4.1.1?** Yes
**Species/Strain:** Wistar Rats
**Initial Age:** 10 Weeks
**Day of Mating:** Day 0
**Date of First Dose:** 3 Mar 97
**Special Features:** None
**No Observed Adverse-Effect Level:**
**$F_0$ Males:** 100 mg/kg
**$F_0$ Females:** 100 mg/kg
**$F_1$ Litters:** 1000 mg/kg

**Duration of Dosing:** M: 4 weeks prior to mating
F: 2 weeks prior to mating, through day 7 of gestation
**Day of C-Section:** Day 16 of gestation
**Method of Administration:** Gavage
**Vehicle/Formulation:** Aqueous solution.

**Study No.** 97072
**Location in CTD:** Vol. 6 Page 1
**GLP Compliance:** Yes

| Daily Dose (mg/kg) | | 0 (Control) | 10 | 100 | 1000 |
|---|---|---|---|---|---|
| **Males** | Toxicokinetics: AUC[b] (mcg-hr/ml) | - | 1.8 | 25 | 320 |
| | No. Evaluated | 22 | 22 | 22 | 22 |
| | No. Died or Sacrificed Moribund | 0 | 0 | 0 | 0 |
| | Clinical Observations: | | | | |
| | Salivation | - | - | + | ++ |
| | Necropsy Observations | - | - | - | - |
| | Body Weight (%[a]) | 452 g | 0 | 0 | -12* |
| | Mean No. Days Prior to Mating | 2.7 | 2.5 | 2.3 | 2.8 |
| | No. of Males that Mated | 22 | 21 | 22 | 22 |
| | No. of Fertile Males | 21 | 21 | 21 | 21 |

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - p<0.05 ** - p<0.01
a - After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
b - From Study No. 94220.

(Continued)

EXAMPLE

**2.3.7.12 Reproductive and Developmental Toxicity** **Study No. 97072 (Continued)**

| **Daily Dose (mg/kg)** | **0 (Control)** | **10** | **100** | **1000** |
|---|---|---|---|---|
| **Females** Toxicokinetics: AUC[b] (mcg-hr/ml) | - | 2.1 | 27 | 310 |
| No. Evaluated | 22 | 22 | 22 | 22 |
| No. Died or Sacrificed Moribund | 0 | 1 | 0 | 0 |
| Clinical Observations | | | | |
| Salivation | - | - | - | + |
| Necropsy Observations | - | - | - | - |
| Premating Body Weight (%[a]) | 175 g | 0 | 0 | -5* |
| Gestation Body Weight (%[a]) | 225 g | 0 | 0 | -12** |
| Premating Food Consumption (%[a]) | 14 g | 0 | 0 | -6* |
| Gestation Food Consumption (%[a]) | 15 g | 0 | 0 | -15** |
| Mean No. Estrous Cycles/14 days | 3.9 | 3.8 | 3.8 | 3.9 |
| Mean No. Days Prior to Mating | 2.1 | 2.3 | 2.5 | 2.2 |
| No. of Females Sperm-Positive | 21 | 22 | 22 | 21 |
| No. of Pregnant Females | 21 | 21 | 22 | 20 |
| Mean No. Corpora Lutea | 15.9 | 15.8 | 16.8 | 15.3 |
| Mean No. Implantations | 14.5 | 14.0 | 15.3 | 13.8 |
| Mean % Preimplantation Loss | 8.8 | 11.4 | 8.9 | 9.8 |
| Mean No. Live Conceptuses | 13.3 | 13.3 | 14.3 | 12.8 |
| Mean No. Resorptions | 1.2 | 0.7 | 1.0 | 1.0 |
| No. Dead Conceptuses | 0 | 0 | 0 | 0 |
| Mean % Postimplantation Loss | 8.3 | 5.0 | 6.5 | 7.2 |

- No noteworthy findings. + Mild ++Moderate +++Marked

Dunnett's Test * - $p<0.05$ ** - $p<0.01$

a - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b - From Study No. 94220.

EXAMPLE

**2.3.7.13 Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development**

**Report Title:** MM-180801: Oral Study of Effects on Embryo-Fetal Development in Rabbits

**Test Article:** Curitol Sodium

**Design similar to ICH 4.1.3?** Yes

**Duration of Dosing:** G6-G18

**Study No.** 97028

**Day of Mating:** Day 0

**Species/Strain:** NZW Rabbits

**Day of C-Section:** G29

**Location in CTD:** Vol. 6 Page 200

**Initial Age:** 5 months

**Method of Administration:** Gavage

**Date of First Dose:** 7 Aug 97

**Vehicle/Formulation:** Aqueous Solution

**GLP Compliance:** Yes

**Special Features:** None.

**No Observed Adverse-Effect Level:**

**$F_0$ Females:** 1 mg/kg

**$F_1$ Litters:** 5 mg/kg

| Daily Dose (mg/kg) | | 0 (Control) | 1 | 5 | 25 |
|---|---|---|---|---|---|
| **Dams/Does:** | Toxicokinetics: AUC[b] (mcg-hr/ml) | - | 2.6 | 31 | 345 |
| | No. Pregnant | 20 | 19 | 20 | 20 |
| | No. Died or Sacrificed Moribund | 0 | 1 | 1 | 0 |
| | No. Aborted or with Total Resorption of Litter | 0 | 0 | 0 | 3 |
| | Clinical Observations | - | - | - | ++ |
| | Necropsy Observations | - | - | - | - |
| | Body Weight (%[a]) | 3.2 kg | 0 | -15* | -20** |
| | Food Consumption (%[a]) | 60 g/day | 0 | -9* | -16** |
| | Mean No. Corpora Lutea | 9.4 | 9.3 | 9.4 | 10.4 |
| | Mean No. Implantations | 7.9 | 8.1 | 9.1 | 9.4 |
| | Mean % Preimplantation Loss | 15.8 | 13.1 | 4.0 | 8.9 |

- No noteworthy findings. + Mild ++Moderate +++Marked G = Gestation day

Dunnett's Test * - $p<0.05$ ** - $p<0.01$

a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b - From Study No. 97231.

(Continued)

EXAMPLE

**2.3.7.13 Reproductive and Developmental Toxicity** **Study No. 97028 (Continued)**

| **Daily Dose (mg/kg)** | | **0 (Control)** | **1** | **5** | **25** |
|---|---|---|---|---|---|
| Litters: | No. Litters Evaluated | 18 | 16 | 17 | 18 |
| | No. Live Fetuses | 140 | 126 | 148 | 86* |
| | Mean No. Resorptions | 0.2 | 0.3 | 0.4 | 4.7** |
| | No. Dead Fetuses | 1 | 0 | 0 | 0 |
| | Mean % Postimplantation Loss | 4.3 | 2.8 | 5.4 | 49.0** |
| | Mean Fetal Body Weight (g) | 44.82 | 42.44 | 42.14 | 42.39 |
| | Fetal Sex Ratios (% males) | 46.3 | 57.7 | 57.4 | 52.8 |
| | Fetal Anomalies: | | | | |
| | Gross External | | | | |
| | Lower jaw: Short | | | | |
| | No. Fetuses (%) | 0 | 0 | 0 | 7 (8.0)* |
| | No. Litters (%) | 0 | 0 | 0 | 5 (27.8)** |
| | Visceral Anomalies | | | | |
| | Tongue: Absent | | | | |
| | No. Fetuses (%) | 0 | 0 | 0 | 6 (6.9)* |
| | No. Litters (%) | 0 | 0 | 0 | 6 (33.3)** |
| | Skeletal Anomalies | | | | |
| | Mandible: Cleft | | | | |
| | No. Fetuses (%) | 0 | 0 | 0 | 10 (11.5)** |
| | No. Litters (%) | 0 | 0 | 0 | 8 (44.4)** |
| | Ribs: Cervical | | | | |
| | No. Fetuses (%) | 2 (1.4) | 0 | 1 (0.7) | 0 |
| | No. Litters (%) | 1 (5.6) | 0 | 1 (5.9) | 0 |
| | Sternebrae: Misshapen | | | | |
| | No. Fetuses (%) | 2 (1.4) | 1 (0.8) | 0 | 1 (1.2) |
| | No. Litters (%) | 2 (11.1) | 1 (6.3) | 0 | 1 (5.6) |
| | Total Affected Fetuses (Litters) | 2 (2) | 1 (1) | 0 | 15 (10) |

- No noteworthy findings.

Fisher Exact Test * - $p<0.05$ ** - $p<0.01$

EXAMPLE

**2.3.7.14 Reproductive and Developmental Toxicity -** Study of Effects on Effects on Pre- and Postnatal Development, Including Maternal Function

**Report Title:** MM-180801: Oral **Test Article:** Curitol Sodium Pre- and Postnatal Development in Rats

**Design similar to ICH 4.1.2?** Yes

**Duration of Dosing:** G6 - L21
**Day of Mating:** Day 0

**Study No.** 95201

**Species/Strain:** Wistar Rats
**Initial Age:** 9-10 Weeks
**Date of First Dose:** 8 Oct 95
**Special Features: None**

**Method of Administration:** Gavage
**Vehicle/Formulation:** Water
**Litters Culled/Not Culled:** Culled to 4/sex/litter

**Location in CTD:** Vol. 10 Page 1

**GLP Compliance:** Yes

**No Observed Adverse-Effect Level:**
**$F_0$ Females:** 7.5 mg/kg
**$F_1$ Males:** 75 mg/kg
**$F_1$ Females:** 75 mg/kg

| **Daily Dose (mg/kg)** | | **0 (Control)** | **7.5** | **75** | **750** |
|---|---|---|---|---|---|
| $F_0$ Females: | Toxicokinetics: AUC[b] (mcg-hr/ml) | - | 2.4 | 21 | 150 |
| | No. Pregnant | 23 | 21 | 22 | 23 |
| | No. Died or Sacrificed Moribund | 0 | 0 | 0 | 8 |
| | Clinical Observations | - | - | ++ | +++ |
| | Necropsy Observations | - | - | - | - |
| | Gestation Body Weight (%[a]) | 225 g | 0 | 0 | -25** |
| | Lactation Body Weight (%[a]) | 210 g | 0 | 0 | 0 |
| | Gestation Food Consumption (%[a]) | 15 g | 0 | 0 | -12* |
| | Lactation Food Consumption (%[a]) | 16 g | 0 | 0 | 0 |
| | Mean Duration of Gestation (days) | 22.1 | 22.2 | 22.1 | 23.5[+] |
| | Abnormal Parturition | - | - | - | - |

- No noteworthy findings. + Mild ++Moderate +++Marked G = Gestation day
Dunnett's Test * - p<0.05 ** - p<0.01 L = Lactation day
Kruskal-Wallis with Dunn's procedure + - p<0.05
a - At end of gestation or lactation. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
b - From Study No. 97227.

(Continued)

EXAMPLE

**2.3.7.14 Reproductive and Developmental Toxicity** **Study No. 95201 (Continued)**

| **Daily Dose (mg/kg)** | | **0 (Control)** | **7.5** | **75** | **750** |
|---|---|---|---|---|---|
| $F_1$ Litters: | No. Litters Evaluated | 23 | 21 | 22 | 15 |
| (Preweaning) | Mean No. Pups/Litter | 13.6 | 13.8 | 14.9 | 11.2++ |
| | Mean No. Liveborn Pups/Litter | 13.5 | 13.8 | 14.6 | 9.4++ |
| | Mean No. Stillborn Pups/Litter | 0.1 | 0.0 | 0.3 | 1.8+ |
| | Postnatal Survival to Day 4 | - | - | - | - |
| | Postnatal Survival to Weaning | - | - | - | - |
| | Change in Pup Body Weights[a] (g) | 60 | 58 | 62 | 53* |
| | Pup Sex Ratios (% males) | 51 | 53 | 49 | 51 |
| | Pup Clinical Signs | - | - | - | - |
| | Pup Necropsy Obs. | - | - | - | - |
| $F_1$ Males: | No. Evaluated Postweaning | 23 | 21 | 22 | 15 |
| (Postweaning) | No. Died or Sacrificed Moribund | - | - | - | - |
| | Clinical Observations | - | - | - | - |
| | Necropsy Observations | - | - | - | - |
| | Body Weight Change[b] (g) | 200 | 195 | 195 | 186* |
| | Food Consumption (%[b]) | 15 g | 0 | 0 | -11* |
| | Preputial Separation | - | - | - | - |
| | Sensory Function | - | - | - | - |
| | Motor Activity | - | - | - | - |
| | Learning and Memory | - | - | - | - |
| | Mean No. Days Prior to Mating | 2.4 | 3.3 | 2.9 | 3.5 |
| | No. of Males that Mated | 23 | 21 | 21 | 23 |
| | No. of Fertile Males | 23 | 21 | 19 | 20 |

- No noteworthy findings. + Mild ++Moderate +++Marked

Dunnett's Test * - p<0.05 ** - p<0.01

Kruskal-Wallis with Dunn's procedure + - p<0.05 ++ - p<0.01

a - From birth to weaning.

b - From weaning to mating. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

EXAMPLE

**2.3.7.14 Reproductive and Developmental Toxicity** **Study No. 95201 (Continued)**

| **Daily Dose (mg/kg)** | | **0 (Control)** | **7.5** | **75** | **750** |
|---|---|---|---|---|---|
| $F_1$ Females: | No. Evaluated Postweaning | 23 | 21 | 22 | 23 |
| (Postweaning) | No. Died or Sacrificed Moribund | 0 | 1 | 0 | 0 |
| | Clinical Observations | - | - | - | - |
| | Necropsy Observations | - | - | - | - |
| | Premating Body-Weight Change[a] (g) | 226 | 230 | 235 | 196* |
| | Gestation Body-Weight Change (g) | 153 | 160 | 144 | 158 |
| | Premating Food Consumption (%[b]) | 15 g | 0 | 0 | -13* |
| | Gestation Food Consumption (%[b]) | 16 g | 0 | 0 | 0 |
| | Mean Age of Vaginal Patency (days) | - | - | - | - |
| | Sensory Function | - | - | - | - |
| | Motor Activity | - | - | - | - |
| | Learning and Memory | - | - | - | - |
| | Mean No. Days Prior to Mating | 2.4 | 3.3 | 3.1 | 3.5 |
| | No. of Females Sperm-Positive | 23 | 21 | 21 | 23 |
| | No. of Pregnant Females | 23 | 21 | 20 | 21 |
| | Mean No. Corpora Lutea | 16.4 | 16.2 | 15.8 | 15.5 |
| | Mean No. Implantations | 15.8 | 15.2 | 14.4 | 14.9 |
| | Mean % Preimplantation Loss | 3.8 | 6.3 | 12.3 | 3.7 |
| $F_2$ Litters: | Mean No. Live Conceptuses/Litter | 15.0 | 14.9 | 13.6 | 14.4 |
| | Mean No. Resorptions | 0.8 | 0.3 | 0.8 | 0.5 |
| | No. Dead Conceptuses | 0 | 0 | 0 | 0 |
| | Mean % Postimplantation Loss | 5.1 | 2.2 | 5.2 | 3.4 |
| | Fetal Body Weights (g) | 3.69 | 3.65 | 3.75 | 3.81 |
| | Fetal Sex Ratios (% males) | 53 | 49 | 54 | 54 |
| | Fetal Anomalies | - | - | - | - |

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - p<0.05 ** - p<0.01

a - From weaning to mating
b - During postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

EXAMPLE

**2.3.7.16 Other Toxicity Studies** **Test Article:** Curitol Sodium

| Species/ Strain | Method of Administration | Duration of Dosing | Doses (mg/kg) | Gender and No. per Group | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|
| **3.7.1 Antigenicity** | | | | | | |
| Guinea Pigs | Subcutaneous | Weekly for 3 weeks; challenge 1 week later. | 0, 5 mg | 5M, 5F | Mildly positive delayed hypersensitivity reaction. No evidence of passive cutaneous anaphylaxis or systemic anaphylaxis. | 97012 |
| **3.7.2 Impurities** | | | | | | |
| WISTAR Rats | Gavage | 2 Weeks | 0, 1000, 2000 | 10M, 10F | MM-180801 fortified with 2% of the Z-isomer impurity; toxicologic effects comparable to MM-180801 without impurity. | 97025 |