Johnson & Johnson Pharmaceutical Research & Development

Guideline for the Preparation of

Investigator's Brochures

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INTRODUCTION

The Investigator's Brochure (IB) is a compilation of all relevant nonclinical and clinical data for a drug undergoing clinical investigation. It is an important source of information for clinical investigators, Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), and regulatory agencies. It is a dynamic document that evolves over time to reflect an increasing body of nonclinical and clinical data as the drug progresses through the various stages of clinical development. The preparation and updating of the IB is a collaborative process that involves extensive interactions among individuals from various functional areas.

Information contained in the IB enables potential investigators to evaluate the drug and determine their interest in the clinical program and their ability to conduct the proposed clinical investigation(s). The IB is used by IRBs, IECs, and regulatory agencies to assess whether a proposed clinical study or group of studies is acceptable from a risk/benefit standpoint and to determine whether there are adequate data to justify the dosage regimen, duration, and other aspects of the proposed clinical trial(s). The IB provides investigators with sufficient background information to discuss the benefits and risks of the drug with potential study subjects as part of the informed consent process. Finally, the IB serves as an up-to-date reference manual for investigators during the clinical study.

The IB is included in the initial filing of an Investigational New Drug Application (IND) or Clinical Trials Exemption (CTX) and, in some countries, is the primary document required by regulatory agencies to initiate clinical studies.

The purpose of this guideline is to provide uniform standards for the format and content of IBs for all Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) compounds. Guidelines are also provided for the use of data from various sources, including preliminary data from completed studies, data from ongoing studies, and information from postmarketing surveillance. The information in these Guidelines is based on the guidelines for Investigator's Brochures contained in the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice, 1996. These Guidelines should be used in conjunction with SOP 103 "Preparation and Revision of the Investigator's Brochure."

GENERAL FORMAT AND CONTENT OF THE INVESTIGATOR'S BROCHURE

The major components and general organization of an IB are given in the IB template and explained further below. The Table of Contents for the IB template is shown in Guideline Attachment 1. The content and emphasis of the IB for a given compound will change over time as the drug progresses through clinical development. For example, the IB for a drug in Phase 2/3 of clinical development will have greater emphasis on clinical data than will the initial IB for a new drug (Drug Evaluation). The initial IB will be based largely on summaries of animal data from nonclinical research reports and, for the purposes of expediting a new IND or CTX, may vary in some respects from the complete format given in the template and described in this section. As the IB is updated, subsections shown in the template (but not the main headings of sections) may be deleted if not applicable, or modified to suit the type of drug and specific information available. If appropriate, certain subheadings may be retained with the explanation that the data are not yet available. In general, the majority of subsections specified in the template are applicable to most drugs in clinical development.

Every attempt should be made to limit the main text of the IB to 100 pages or fewer. To make the IB user friendly, information should be organized clearly and concisely, using tables and graphs to the greatest extent possible. There should be full disclosure of the data, i.e., negative findings as well as positive findings should be presented.

Generally, data to be included in an IB will be those available in published reports (i.e., reports issued in-house) at the time the IB is being updated. However, in some cases, the Global Medical Leader (GML) or project team may decide that unpublished data should be included. In such cases, the published data or analyses will be referred to in the text of the IB as "preliminary data" or "preliminary analyses" and referenced to the Laboratory Notebook No. or the study number (for nonclinical data) as "data on file at J&JPRD," or as "draft report," as appropriate. Data from studies that were not conducted under Good Laboratory Practices (GLP), e.g., pilot studies, are usually not included in the IB. In some instances, however, the project team may decide that such non-GLP data are of sufficient quality and importance to be included.

As a general rule, there should be a single IB for each drug or combination product in clinical development. Thus, information pertaining to different formulations, dosage forms, strengths, routes of administration, or indications should be compiled into the

IB for that compound. Moreover, the IB should be prepared so as to be suitable for worldwide use.

While safety and efficacy results and conclusions from specific studies may be presented in the IB, no overall claims should be made regarding the safety or efficacy of an investigational drug.

As indicated in the template, each major section of the IB starts with an Overview, which contains 1 or 2 paragraphs summarizing the main points presented in the section. These Overview sections may be used for the Summary at the beginning of the IB.

The following sections of the IB end with a list of references: Introduction (if applicable), Chemistry, Nonclinical Studies, and Effects in Humans. References should be numbered in the order in which they appear in the foregoing section. A citation that appears in 2 sections, e.g., the Nonclinical Studies and Effects in Humans sections, will appear in both reference lists. References to published and unpublished data, as well as to internal research reports, should be listed in the References section according to the most recent Style Guidelines for Clinical Documents.

Title Page; Table of Contents

Items required on the Title Page and the Table of Contents from the template are shown in Guideline Attachment 1.

Summary

The IB Summary, which should generally be no more than 2 pages in length, summarizes the rationale for the drug and should highlight the significant chemical, pharmacologic, pharmacokinetic/metabolic, toxicologic, and clinical information available, as relevant to the stage of development of the investigational product. This Summary section should consist largely of the 1- to 2-paragraph Overview sections contained in the main text.

The IB Summary should contain the headings and subheadings shown in the template.

List of Abbreviations and Definition of Terms

A list of the abbreviations used in the brochure, as well as a list of definitions for specialized or unusual terms or units of measure used in the report, should be provided. Any abbreviated term should be spelled out at its first appearance in the text, followed by the abbreviation indicated in parentheses. Thereafter, only the abbreviation should be used.

MAIN TEXT OF THE IB

1. INTRODUCTION

A brief introduction should be provided that contains the chemical name of the product (as well as the generic and trade names when approved), all active ingredients, the pharmacologic class of the drug and the drug's position within the class (e.g., expected advantages), mechanism of action, scientific rationale, intended use, and the general approach to be followed in evaluating the investigational product. Examples of Introductions are given in Guideline Attachments 2.1 and 2.2.

2. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATIONS

Items to be included in this section are organized under the subheadings shown in the template (see Guideline Attachment 1). It should be noted that the Formulation Information section should include excipients as well as active ingredients. The Other Pertinent Information section may include information on important physical and chemical characteristics, such as physical constants, pKa values, pH (if a solution), partition coefficient, melting point, isomers, and polymorphs. This should also include information on stability, storage, and handling, as appropriate. Additional information (e.g., origin, method of isolation or manufacture, molecular biology) may also be pertinent for natural or biotechnology products. Examples of sections on Physical, Chemical, and Pharmaceutical Properties and Formulations are given in Guideline Attachments 3.1 and 3.2.

3. NONCLINICAL STUDIES

3.1. Nonclinical Pharmacology [Microbiology]

The pharmacologic effects of the drug in vitro and in animal models should be summarized in sufficient detail to assist the investigator in evaluating the activity and therapeutic index of the drug. In vivo and in vitro microbiologic activity should be described in this section, if applicable.

3.1.1. Overview

This section includes a concise (1 or 2 paragraphs) summary of key results and conclusions from all relevant pharmacologic and mechanism of action studies, describing the pharmacologic profile of the drug and its significance relative to the drug's proposed therapeutic use.

3.1.2. Pharmacologic Effects

This section summarizes the pharmacologic aspects of the investigational product from in vitro and in vivo studies and, where appropriate, its significant metabolites. Such a summary should include studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding and specificity) as well as those that assess safety (e.g., special studies to assess pharmacologic actions other than the intended therapeutic effect[s]).

For the above summary, a tabular format (with limited accompanying text) should be used if possible. Alternatively, single brief paragraphs describing individual studies may be used if that format provides a more effective presentation of the data. A limited number of small figures or tables may be used to present the most important or representative results. NOTE: As pharmacodynamic and efficacy data become available from human studies, this section may be condensed into a short review of nonclinical pharmacologic findings.

An example of a Nonclinical Pharmacology section is given in Guideline Attachment 4.

3.2. Pharmacokinetics and Product Metabolism in Animals

Overview

This section provides a concise (1 or 2 paragraphs) summary of key results and conclusions from relevant nonclinical pharmacokinetic and metabolism studies, identifying important qualitative or quantitative differences in absorption, distribution, metabolism, or elimination of the drug across species.

Additional Sections

These sections include summaries of the pharmacokinetics, biological transformation, and disposition of the investigational product in species used for pharmacology and toxicology studies. Specific topics are listed in the template. It should be noted that while some subsections (e.g., Methods of Analysis) may be deleted if not considered useful, it may be important to retain other subsections (e.g., Placental Transfer) even if data are not yet available, inserting text stating that data are not yet available.

To the greatest extent possible, each subsection should include tables that allow presentation of data from multiple studies. For example, data for

relevant pharmacokinetic parameters such as peak concentration (C_{max}), time to peak concentration (t_{max}), volume of distribution (V_d), area under the concentration x time curve (AUC), half-life ($t_{1/2}$), and clearance may be listed by route of administration, frequency of dosing (single vs. multiple), and species, as appropriate. Data for repeated dose studies should include the above parameters plus the time required to reach steady state.

In the section on metabolites (Section 3.2.5.1), it is important to include information, if available, on whether the metabolites have biological activity, as well as pharmacokinetic details related to accumulation and excretion.

An example of a section on Pharmacokinetics and Product Metabolism in Animals is given in Guideline Attachment 5.

3.3. Toxicology

Overview

This section includes a brief overview of the types of animal toxicology studies conducted and a concise (1- or 2-paragraph) summary of the results and conclusions from these studies.

Additional Sections

In the major subsections under Toxicology (see Guideline Attachment 1), data should be presented in tables that include elements of the study design together with results. Information within the tables should be arranged in a logical sequence; for example, by animal species and duration of the study. Examples of toxicology tables appear in Guideline Attachment 6.

A Toxicokinetics subsection should appear in the Toxicology section, if applicable. Toxicokinetics refers to pharmacokinetic data obtained as part of animal toxicology studies. Such data are used to calculate animal to human exposure ratios, i.e., the blood concentrations animals are exposed to at a given dose relative to the blood concentrations humans will be exposed to at that dose. The blood concentrations used are either $AUC_{0\text{-}xhours}$ or C_{max} values obtained from animal and human pharmacokinetic studies. Data on toxicokinetics/exposure ratios are placed in the Toxicology section because the exposure ratios allow the toxicology findings to be translated into the *possible* risks humans may be exposed to at various clinical doses. Examples of toxicokinetics tables are given in Guideline Attachment 7.

4. EFFECTS IN HUMANS

Available data concerning the pharmacologic activity, pharmacokinetics, efficacy, and safety of the drug in humans, including healthy volunteers and patient populations, should be summarized in the appropriate subsections that appear under this heading. Information from early Phase 1 and 2 studies, particularly that pertaining to pharmacologic effects and efficacy, should be further condensed as data from controlled clinical trials in the intended patient population(s) become available. As in other sections of the IB, summary tables and graphs should be used extensively in lieu of lengthy narrative descriptions.

Cut-off date: A cut-off date should be used for establishing what clinical data will be included in the IB. For example, all data available from completed and analyzed clinical studies as of the Cut-off date will be summarized in the brochure. Also, the number of subjects enrolled in ongoing clinical studies as of the Cut-off date should be included in the Table of Studies.

4.1. Overview

This section is divided into the following 2 sections:

4.1.1. Summary of Results

This section provides a concise (1- to 2-paragraph) summary of key pharmacodynamic, pharmacokinetic, efficacy, and safety data as well as conclusions from the various clinical studies.

4.1.2. Design of Studies

This section includes a brief description of the design of the different clinical studies (or groups of studies), with emphasis on the design features critical to the interpretation of results presented in this section.

A table(s) of completed and ongoing studies categorizing the various studies is provided as appropriate (e.g., by indication, by study design, by route of administration). These tables should contain appropriate information such as study and reference number, indication/study population, design, treatment groups, dose/duration, and number of subjects enrolled, completed, and, if applicable, included in the safety data summaries as of a specified cut-off date. Examples of study design tables are given in Guideline Attachment 8. NOTE: For reasons of confidentiality, the names of study investigators are not included in tables or text.

4.2. Pharmacokinetics and Product Metabolism in Humans

This section summarizes the key pharmacokinetic data, such as C_{max}, t_{max}, V_d, AUC, $t_{1/2}$, elimination constant (K_{el}), across studies if possible (see example, Guideline Attachment 9). Data on metabolites, plasma protein binding, and routes of clearance, may be included with a brief comparison to previously discussed animal data.

This section also includes data from other special studies, including studies of drug-drug interactions and studies of the effects of food, diseases, or demographic characteristics on pharmacokinetic properties. The writer should refer to the nonclinical section (Section 3.2) for guidance on topics that may be relevant (or even more relevant) to the Human Pharmacokinetics and Metabolism section. Cross-referencing between the human and nonclinical sections may be used. For example, if human in vitro protein-binding data are presented in the nonclinical section, a cross-reference to that data should be included here.

A discussion of blood levels of the drug in relationship to pharmacologic activity/efficacy and toxicity is included as appropriate.

The significance of the above data with respect to the clinical use of the drug (e.g., selection of dose and dose interval, duration of therapy, timing of doses relative to meals) should be noted and any potential problems described (e.g., high first-pass effect, dependence on renal or hepatic function).

NOTE: The pharmacokinetic data in this section should be organized and presented in a logical manner (e.g., healthy volunteers vs. selected patient populations, route of administration, and frequency of dosing [e.g., single vs. multiple dosing]), using descriptive subheadings if necessary.

4.3. Safety and Efficacy

4.3.1. Pharmacodynamics

This section contains the results of dose-response or blood-level response studies, including short-term studies of therapeutic response or of the principal pharmacodynamic effect(s) thought to be related to the therapeutic action of the drug (e.g., effects of a β-blocker on heart rate during exercise). It also includes information on any biochemical or physiologic markers of activity.

This section summarizes studies of pharmacodynamic properties other than the specific property thought to be related to therapeutic activity (e.g., hemodynamic studies, electrophysiologic studies, and studies of effects on renal or GI function).

NOTE: Data in this section should be organized and presented by study population (e.g., healthy volunteers vs. selected patient populations) and specific pharmacodynamic effect, using descriptive subheadings if necessary.

4.3.2. Efficacy

Efficacy data from completed clinical studies should be organized and presented by indication, dosage form, route of administration, and study design, as appropriate. Appropriate subheadings should be included to reflect these major subsections.

Within each of the major subsections, data for a given efficacy variable should be presented for each study using descriptive subheadings corresponding to individual efficacy variables or groups of variables (e.g., reduction in seizure frequency, mycologic results). Although efficacy data for a given variable generally will not be pooled across studies, data from different studies should be displayed side-by-side in a manner consistent with that presented in an integrated summary of efficacy.

4.3.3. Safety and Tolerability

This section should present safety information from all clinical studies, with separate subsections and summary tables for clinical pharmacology studies in healthy volunteers and controlled clinical trials in selected patient populations (including different target indications and special populations such as geriatric, pediatric, and renally impaired patients). In addition, any significant safety findings from investigator-sponsored studies, postmarketing studies, and postmarketing surveillance information should be noted.

Consistent with the presentation of efficacy data, safety data of a given type should be presented across studies rather than as a study-by-study review. Moreover, data should be pooled across studies as appropriate and, for completed studies, compared across treatment groups. In particular, adverse event data from all studies of a given category (e.g., controlled trials in a

specific patient population) should be combined and summarized in a single table whenever possible.

4.3.3.1. Nature and Frequency of Adverse Events

This section summarizes the incidence of adverse events in completed studies (or appropriate categories of completed studies) and includes a table(s) summarizing the incidence rates by body system and adverse events for the control group(s) and increasing doses of study drug. This summary may include all adverse events or may be limited to those occurring above a specified frequency, as appropriate. An example is given in Guideline Attachment 10.

In addition, this section should summarize discontinuations due to individual adverse events (e.g., nausea) or categories of adverse events (e.g., gastrointestinal complaints), as appropriate. This may include a table summarizing the percentages of subjects who discontinued study therapy due to adverse events (categorized by body system/adverse event as noted above).

This section should also include an assessment of the causal relationship of adverse events to the study drug and should provide other pertinent clinical information or assessment of the observed adverse event profile, as appropriate.

4.3.3.2. Deaths and Other Serious Adverse Events

A listing of individual deaths by treatment group (including age and sex of the subject, dosage regimen/duration, and cause of death) should be provided along with an assessment of their relationship to the study drug and any other pertinent clinical information. NOTE: In cases where there are a large number of deaths due to progression of the underlying disease or other factors (e.g., studies in cancer patients), a table summarizing the causes of deaths should be substituted for an individual subject listing.

Other serious adverse events reported during clinical studies should be summarized in this section, along with information regarding their frequency, causal relationship to the study drug, and any other pertinent clinical information or assessment. This may include a table summarizing the incidence of serious adverse events by body system/adverse event and treatment group (see example, Guideline Attachment 11.1); when possible,

serious adverse events resulting in discontinuation should be summarized separately from those not resulting in discontinuation.

The IB need not contain a listing of individual cases of serious adverse events; however, in the early phases of clinical investigation, i.e., through Phase 2, it may be useful to list individual cases of serious adverse events (see example, Guideline Attachment 11.2). The GML (or Clinical Scientist for Drug Evaluation) and Drug Safety Officer should be consulted as to whether serious adverse events that have occurred in the ongoing studies (which usually remain blinded) should be included in the IB. However, all individual reports of serious, unexpected and drug-related* adverse events (SUAs), whether or not from completed or blinded studies, should be identified in the brochure. Also, an indication should be given that such reports have been forwarded to regulatory authorities and clinical investigators as SUAs.

NOTE: Narrative descriptions of individual deaths or other serious adverse events need not be included in the IB unless such cases are rare or sufficiently heterogeneous so as to preclude generalizations. In addition, certain cases may require additional explanation.

4.3.3.3. Clinical Laboratory Abnormalities

Significant trends in clinical laboratory data should be noted, including any available information on the nature and frequency of marked abnormalities in individual laboratory analyses (e.g., ALT) or groups of analyses (e.g., liver function tests).

NOTE: The IB should not summarize the results of all clinical laboratory analyses and need not describe individual cases of marked laboratory abnormalities unless such cases are rare or heterogenous as a group or if certain cases require additional explanation.

4.3.3.4. Other Safety Observations

Significant findings resulting from various other safety monitoring tests or observations should be identified briefly in this section.

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* For purposes of reporting, JRF/PRI Drug Safety and Surveillance (DSS) considers any event to be drug-related if it is evaluated as "possibly, probably or definitely" drug-related either by the investigator or DSS.

4.4. Marketing Experience

The IB should identify countries where the investigational product has been approved for marketing. Any significant information arising from marketed use should be summarized (e.g., formulations, dosages, routes of administration, adverse reactions). The IB should also identify countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing.

5. SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATORS

This section should include an overall assessment of the safety profile of the drug based on prior clinical and nonclinical experience with this drug and other drugs of the same class. It should identify contraindications and possible risks and adverse reactions (including recognition and treatment of potential drug interactions and potential overdose/abuse potential) to be anticipated from use of the drug. In addition, it should describe any general precautions, warnings, or special steps that should be taken by the investigator to ensure the safety of subjects in the clinical studies. Although some general guidance may be provided in the IB regarding safety monitoring tests, dosing precautions, etc., additional specific instructions should be provided in individual study protocols.

Section 5 of the IB template specifies subheadings that may be useful for the Summary of Data and Guidance for Investigators. Depending on the drug, specific subheadings may be modified.

For drugs which have a final, approved Core Data Sheet, that Core Data Sheet should be used as the Summary of Data and Guidance for Investigators. For marketed drugs, the physician's circular for the country where the investigation is being performed should also be appended to the IB (see Section 7).

- **Core Data Sheet:** A J&JPRD document, presented in modified SmPC format, that contains all the supported knowledge about the product generated during development, drives new product development, and is the single unifying document from which all other local labels will be derived.

- **Target Core Data Sheet:** The Core Data Sheet tailored to anticipated labeling for the targeted indication.

For investigational drugs, the Target Core Data Sheet may be used as *a guide* in the preparation of the Guidance for Investigators section. Care must be taken not to copy anything from the Target Core Data Sheet that represents anticipated, rather than actual, findings. In cases where a drug is marketed but is being studied for a new indication(s), the main text of the IB should focus on the nonclinical and clinical data specific to the unapproved indications for which the drug is currently under investigation, and should reference the physician's circular for other information. At most, the nonclinical and clinical information reflected in the physician's circular should be briefly summarized in the main text of the IB; no tables-of-studies pertaining to these data need to be included in the main text. A sample Section 5, Summary of Data and Guidance for Investigators, appears in Guideline Attachment 12.

6. PUBLICATIONS (IF APPLICABLE)

In accordance with FDA regulations, copies of published articles on prior clinical studies of the drug may be appended to the IB. Copies of other key publications may also be appended as appropriate.

7. PHYSICIAN'S CIRCULAR (IF APPLICABLE)

For marketed drugs, a copy of the physician's circular (i.e., the U.S. package insert or its equivalent in other countries) should be included in the IB. Inclusion of the physician's circular(s) will substitute for a detailed presentation of animal and human data pertinent to the approved indications. The physician circular(s) included in the core IB should be specific to the country (or countries) in which the IB is being used, and therefore will vary depending on the study site. The clinical team is responsible for ensuring that the appropriate physician's circular is included with the IB provided to each of its study investigators. The physician's circular, because it may vary for different investigators, will not be paginated. NOTE: Draft labelling for the investigational drug (e.g., new drug entity, new indications) should not be included in the IB.

INFORMATION UPDATES (ADDENDA)

Information updates (addenda), usually based on memos or letters that have been sent to investigators reporting serious and unexpected adverse events, may be prepared between formal updates of the IB as appropriate. The addenda will be archived electronically in Documentum but a printed copy will not be issued to Global

Information Custody and Standards (GICS) for paper archival. The investigators will be instructed by Clinical to place a copy of these information updates into a tabbed section at the end of the IB for reference. NOTE: Addenda will not be paginated.

ATTACHMENTS TO THIS GUIDELINE

Attachment 1: Title Page and Table of Contents from the Template

[Logo will go here]

Johnson & Johnson Pharmaceutical Research & Development[, L.L.C.]
[a division of Janssen Pharmaceutica N.V.]
[a division of Janssen-Cilag Ltd.]

Investigator's Brochure

[R][RWJ-][JNJ][number] (generic name, if applicable)

[Month Year]

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Attachment 1: Title Page and Table of Contents from the Template (Continued)

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Attachment 1: Title Page and Table of Contents from the Template (Continued)

TABLE OF CONTENTS (CONTINUED)

Attachment 1: Title Page and Table of Contents from the Template (Continued)

TABLE OF CONTENTS (CONTINUED)

Attachment 2.1: Sample Introduction for a Compound in Drug Evaluation

1. INTRODUCTION

Ongoing release of mast cell-derived mediators such as histamine, β tryptase, prostaglandin D_2 and leukotriene C_4 contribute to the symptoms of both asthma and allergic rhinitis.[1,2]

Asthma is a chronic inflammatory airway disorder that causes recurring bouts of coughing, wheezing, chest tightness, and difficult breathing due to airway obstruction. An asthmatic attack involves widespread but variable broncho-constriction and inflammation of airway tissues, including swelling, and mucus production.

Asthma is underdiagnosed and undertreated yet its prevalence, particularly among children, is increasing worldwide.[3] Asthma prevalence among children, currently about 7%,[4] and among young adults has increased over the past 2 decades,[5] climbing by nearly 50% in many countries,[6] and is estimated to be 6% to 10% in older people.[7] Hospitalizations attributed to asthma also rose and asthma mortality increased by more than 40% between the mid-1970s and mid-1980s among people 5 to 34 years old.[8] Asthma-related mortality nearly doubled between 1980 and 1993 among Americans 5 to 24 years old.[4]

Bronchodilators are currently used to treat asthma, including beta-agonists, theophylline, and anticholinergic agents, but have disadvantages. Beta-agonists potently and rapidly relieve asthma symptoms but can induce tolerance.[9,10] Theophylline metabolism can be markedly affected by age, diet, disease state, and drug interactions[11,12] and proper dosing requires care and periodic serum level monitoring. Anticholinergic agents are generally less potent with a slower onset of action than beta-agonists and, therefore, are more useful in the treatment of chronic obstructive pulmonary disease.[13]

The anti-inflammatory medications, cromolyn and nedocromil, are used in mild, persistent asthma.[14] Leukotriene D4 antagonists and 5-lipoxygenase inhibitors provide only modest improvement in asthma management.[15] Inhaled corticosteroids are the first-line therapy for chronic treatment of asthma[11] and chronic obstructive pulmonary disease,[14] with systemic corticosteroids being reserved for severe exacerbations that are refractory to bronchodilators.[13,14] Corticosteroid therapy, especially when administered systemically, can result in hypothalamic-pituitary-adrenal axis suppression,

Attachment 2.1: Sample Introduction for a Compound in Drug Evaluation (Continued)

osteoporosis, cataracts, hyperglycemia, hypertension, dermal thinning and striae, avascular necrosis, and growth retardation.[13]

Allergic rhinitis is characterized by sneezing, rhinorrhea, nasal blockage, and anosmia. Allergic rhinitis occurs mostly in patients aged 15 to 25 years and is rarely observed in patients older than 45 years. The prevalence of allergic rhinitis in young adults is approximately 10% and about 50% of the patients seek medical advice.[15]

At present, the pharmacotherapy of allergic rhinitis is aimed at alleviating symptoms. Thus, histamine H_1 antagonists are efficacious against sneezing and rhinorrhea but less so against nasal blockage, whereas α adrenoceptor agonists are effective decongestants but have limited efficacy against the other symptoms of allergic rhinitis. Although the cromoglycates are effective against all symptoms except anosmia, the effectiveness of these agents is sub-optimal. By far the most effective agents are topical and oral steroids.[16] However, concerns over the side effects of these drugs may limit their use.[13]

RWJ-56423 is an inhibitor of mast cell β tryptase. Mast cell β tryptase is a tetrameric serine protease with multiple physiological activities and is released upon immunoglobulin E (IgE)-dependent mast cell activation. Among the physiological effects of mast cell β tryptase are degradation of bronchodilator neuropeptides such as vasoactive intestinal polypeptide, generation of kinins, induction of tissue remodeling either via extracellular matrix changes or fibroblast induction and smooth muscle cell proliferation and the induction of inflammatory responses.[17,18]

Because of these multiple physiological effects, β tryptase is believed to be an attractive target for the development of drugs with a novel mechanism of action to treat atopic disease. RWJ-56423 is a reversible competitive inhibitor of β tryptase with anti-inflammatory activity in a sheep model for asthma. RWJ-56423 will be developed for the treatment of asthma and allergic rhinitis as an inhalation (i.h.) therapy and topical therapy, respectively.

Summaries in this Investigators Brochure reflect nonclinical data available through July 2001.

Attachment 2.1: Sample Introduction for a Compound in Drug Evaluation (Continued)

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Attachment 2.2: Sample Introduction for a Compound in Phase 2 or 3

1. INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) belong to the steroid/thyroid/retinoid superfamily of nuclear receptors.[1] These receptors control a variety of genes in several pathways of lipid metabolism. Three related PPAR isotypes, designated α, β (or δ), and |, have been identified. Agonists that bind to the PPAR| receptor reduce insulin resistance and thereby produce antihyperglycemic effects. This mechanism makes such agonists potentially useful in the treatment of Type 2 diabetes.

RWJ-XXXXXX is a novel thiazolidinedione which functions as a modulator (i.e., a milieu-specific partial or full agonist) when it binds to PPAR|; such modulators are sometimes referred to as Selective PPAR Modulators or SPARMS. It is currently being investigated for the treatment of Type 2 diabetes. Two thiazolidinediones currently marketed for this therapeutic use are rosiglitazone (Avandia®, Glaxo SmithKline) and pioglitazone (Actos®, Takeda Pharmaceuticals America/Eli Lilly & Company).

The first thiazolidinedione to be marketed as an antihyperglycemic agent, troglitazone (Rezulin®, Parke-Davis), was associated with idiosyncratic hepatotoxicity and very rare cases of liver failure, liver transplants, and death during postmarketing clinical use.[2,3] In controlled clinical trials conducted pre-approval in patients with Type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3X the upper limit of normal [ULN]) compared to placebo.[2,3] Because concern about potential adverse hepatic effects has extended to thiazolidinediones as a class, it is instructive to review ALT data from thiazolidinedione clinical trials presented by the U.S. FDA at an Endocrinologic and Metabolic Drugs Advisory Committee on May 19, 2000.[4] The data, which were obtained from New Drug Applications for troglitazone, rosiglitazone, and pioglitazone, show marked differences between troglitazone and each of the other two drugs (see below):[4]

Attachment 2.2: Sample Introduction for a Compound in Phase 2 or 3 (Continued)

Percentage of Subjects Treated with Thiazolidinediones having Specific ALT Elevations: Data from Clinical Studies Presented in New Drug Applications for 3 Thiazolidinediones

Liver Function Test	Troglitazone (N=2,510) ULN=34	Placebo for Troglitazone (N=475) ULN=34	Rosiglitazone (N=4,421) ULN=48	Pioglitazone (N=3,650) ULN=34
ALT >3x ULN[a]	1.9%	0.6%	0.25%	0.33%
ALT >5 x ULN	1.7%	--	0.23%	0.25%
ALT >8 x ULN	0.9%	0	0.05%	0.03%
ALT >30 x ULN	0.2%	0	0	0

[a] ULN = Upper limit of the normal range.

As reported in labeling for rosiglitazone and pioglitazone, the incidence of ALT >3X the ULN in controlled clinical trials was no greater for rosiglitazone or pioglitazone than for placebo treatment.[2,3] In controlled clinical trials of rosiglitazone, 0.2% of patients treated with rosiglitazone had elevations in ALT >3X the ULN compared to 0.2% on placebo and 0.5% on active comparators.[2] In controlled clinical studies of pioglitazone, a total of 4 of 1,526 patients (0.26%) treated with pioglitazone and 2 of 793 treated with placebo (0.25%) had ALT values >3X the ULN.[3] The ALT elevations in patients treated with rosiglitazone or pioglitazone were reversible and were not clearly related to therapy with these thiazolidinediones.[2,3]

The above data reveal the importance of close monitoring of ALT values in clinical studies of a new thiazolidinedione and further suggest that serious liver toxicity may be predictable from less serious transaminase elevations for this drug class.

Thiazolidinediones may be important therapeutic agents in Type 2 diabetics for reasons other than the reduction of hyperglycemia. Research on other thiazolidinediones has shown that they have the potential to decrease blood pressure, correct diabetic dyslipidemia, improve fibrinolysis, and decrease carotid artery intima-media thickness in humans.[5] Whether such effects will reduce cardiovascular disease in patients with Type 2 diabetes, however, will only be determined with long-term clinical trials.

Attachment 2.2: Sample Introduction for a Compound in Phase 2 or 3 (Continued)

References

1. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. Endocrine Revs 1999;20:649-688. Product information for ACTOS® (pioglitazone hydrochloride) tablets.

2. Product information for AVANDIA® brand of rosiglitazone maleate tablets. Physician's Desk Reference, 55th ed. Montvale, NJ: Medical Economics Company, Inc.; 2001.

3. Product information for ACTOS® (pioglitazone hydrochloride) tablets. Physician's Desk Reference, 55th ed. Montvale, NJ: Medical Economics Company, Inc.; 2001.

4. U.S. Food and Drug Administration. A presentation of the data and rationale for the regulatory action regarding the withdrawal from the U.S. market of Rezulin® (troglitazone, Parke-Davis Pharmaceutical Research, a Division of Warner-Lambert) for the treatment of type 2 diabetes mellitus. Presentation to the Endocrinologic and Metabolic Drugs Advisory Committee, May 19, 2000.

5. Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of thiazolidinediones. Ann Int Med 2001;134:61-71.

Attachment 3.1: Sample Chemistry Section

2. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

2.1. Product Identification

2.1.1. Generic Name

The USAN (United States Approved Name) for RWJ-XXXXXX is xxxxglitazone, although this generic name has not yet been confirmed as the World Health Organization INN (International Nonproprietary Name).

2.1.2. RWJ Number

The investigational drug designations are:

Free base: RWJ-XXXXXX-000

Benzoate salt: RWJ-XXXXXX-024

Early preclinical Discovery studies were performed using batches of drug substance designated as RWJ-XXXXXX-300. The 300 suffix indicates the type of analyses done on the batch of drug substance, it does not indicate the form of the drug substance (salt or freebase). The actual form of the drug substance corresponding to the batch designation RWJ-XXXXXX-300 is the freebase (RWJ-XXXXXX-000).[1]

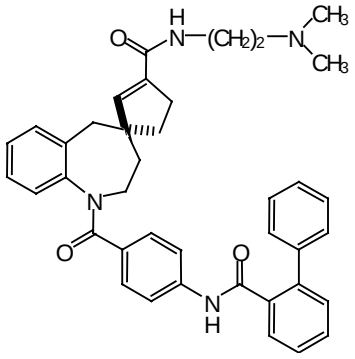
2.1.3. Chemical Name

(4*R*)-1-[4-[([1,1'-biphenyl]-2-ylcarbonyl)amino]benzoyl]-*N*-[2-(dimethylamino) ethyl]-1,2,3,5-tetrahydrospiro[4*H*-1-benzazepine-4,1'-[2]cyclopentene]-3'-carboxamide, benzoate (salt)[2]

2.2. Physical and Chemical Characteristics

2.2.1. Chemical Structure

The structure of RWJ-XXXXXX is shown below:[3,4]



Attachment 3.1: Sample Chemistry Section (Continued)

2.2.2. Molecular Formula

The molecular formula[5] is:

Free base:	$C_{39}H_{40}N_4O_3$	(RWJ-XXXXXX-000)
Benzoate salt:	$C_{39}H_{40}N_4O_3 \bullet C_7H_6O_2$	(RWJ-XXXXXX-024)

2.2.3. Molecular Weight

The molecular weight[5] is:

Free base:	612.77 daltons	(RWJ-XXXXXX-000)
Benzoate salt:	734.88 daltons	(RWJ-XXXXXX-024)

2.2.4. Solubility

The solubility of RWJ-XXXXXX-024 is presented in Table 1.[6a]

Table 1: Solubility of RWJ-XXXXXX-024

Solvent	pH	Solubility[a]
0.1 N HCl	1.03	Slightly soluble
Water	5.95	Insoluble
0.1 N NaOH	12.68	Insoluble
0.5% HPMC	6.75	Insoluble

[a] According to USP Descriptive and Relative Solubility Classification:[6b]

Sparingly soluble:	From 30 to 100 parts solvent per 1 part solute, i.e. 10 to 33 mg/mL
Slightly soluble:	From 100 to 1000 parts solvent per 1 part solute, i.e. 1 to 10 mg/mL
Practically insoluble:	Over 10000 parts solvent per 1 part solute, i.e. less than 0.1 mg/mL

Key: HCl = hydrochloric acid; NaOH = sodium hydroxide;
HPMC = hydroxypropyl methylcellulose, Methocel®

2.2.5. Physical Appearance

White solid.[7]

2.2.6. Formulation Information

The oral formulation for RWJ-XXXXXX-024 will be prepared as a XX-mg/mL and YY-mg/mL suspension dispersed in an aqueous solution of 0.5% weight/weight (w/w) hydroxypropyl methycellulose (Methocel®). The formulation should be stored refrigerated (2-8°C; 36-46°F) and protected from light prior to use, but allowed to warm up to room temperature for at least 1 hour prior to dose preparation. The placebo formulation will be supplied as a 10-mg/mL microcrystalline cellulose suspension. Detailed instructions for resuspension of the formulation and dose preparation in the oral dispenser will accompany the supply shipment to the clinical study site.

Attachment 3.1: Sample Chemistry Section (Continued)

2.2.7. Other Pertinent Information

Nonclinical PK and GLP toxicology studies have been performed with RWJ-XXXXXX-024 (lot F). This lot was tested according to J&JPRD specifications and released by J&JPRD Quality Assurance for use in the clinical studies.

The storage condition and expiry date for the drug product are indicated on the label.

2.3 Chemistry References

1. Robert Chen. J&JPRD Research Notebook 15098, page 173.

2. Hua M. Zhong. J&JPRD Research Notebook 17122, page 123.

3. Ryall R. Proof of structure for RWJ-339489, memo by J. Weber. Spectral Report AR-0131-01, AR-0157-01 (18 May 2001).

4. Hua M. Zhong. J&JPRD Research Notebook 16316, pages 163 and 184.

5. Hua M. Zhong. J&JPRD Research Notebook 17122, page 121.

6. (a) Barry Fegely. J&JPRD Research Notebook 17153, pages 91 to 95. (b) General Notices and Requirements/Test and Assays/Solubility. In United States Pharmacopeia, 24th Ed. Rockville, MD: US Pharmacopeial Convention; 1995:10.

7. Arthur Micheel, J&JPRD Research Notebook 17126, page 53.

Attachment 3.2: Sample Chemistry Section for a Compound with Multiple Formulations

2. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

2.1 Product Identification

2.1.1. Generic Name

Not assigned.

2.1.2. Trade Name

Not assigned.

2.1.3. RWJ Number

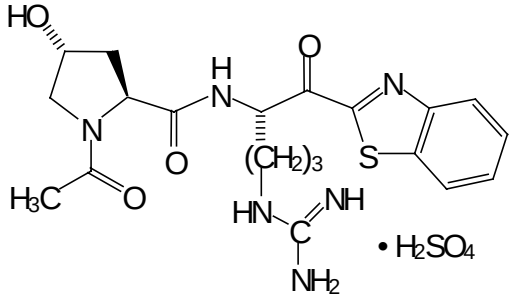
RWJ-BBBBB-180 (sulfate salt)

2.1.4. Chemical Name

1-acetyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl) butyl]-4-hydroxy-(2S,4R)-2 pyrrolidinecarboxamide, mono sulfate

2.2. Physical and Chemical Characteristics

2.2.1. Chemical Structure



2.2.2. Molecular Formula

Sulfate salt:	$C_{20}H_{26}N_6O_4S \cdot H_2SO_4$	(RWJ-BBBBB-180)
Free base:	$C_{20}H_{26}N_6O_4S$	(RWJ-BBBBB)
Hydrochloride salt:	$C_{20}H_{26}N_6O_4S \cdot 2.5HCl \cdot 2.2H_20$	(RWJ-AAAAA-002)

RWJ-BBBBB is a single diastereomer (having the stereochemistry depicted in the structure above, the L-arginine moiety) and has been isolated as the sulfate salt. RWJ-AAAAA is a mixture of diastereomers (RWJ-BBBBB [L-arginine diastereomer] and RWJ-CCCCCC [D-arginine diastereomer]) and has been isolated as the HCl salt. RWJ-BBBBB can epimerize to RWJ-AAAAA (mixture of diastereomers) under a variety of conditions.

Attachment 3.2: Sample Chemistry Section for a Compound with Multiple Formulations (Continued)

The drug identification suffix, –180, indicates the sulfate salt of RWJ-BBBBB. However, throughout the majority of this document the compound is simply referred to as RWJ-BBBBB. Some values, such as concentrations and potencies, are expressed as the free base even though a salt form was actually used.

2.2.3. Molecular Weight

Sulfate salt:	544.61	(RWJ-BBBBB-180)
Free base:	446.53	(RWJ-BBBBB)
Hydrochloride salt:	577.32	(RWJ-AAAAA-002)

2.2.4. Solubility

The solubility of RWJ-BBBBB-180 is presented in Table 1.

Table 1: Solubility of RWJ-BBBBB-180

Solvent	pH	Solubility[a]
0.1 N HCl	1.0	Sparingly soluble
Water	1.5	Sparingly soluble
0.1 N NaOH	3.6	Slightly soluble
0.5% HPMC	1.6	Sparingly soluble
Simulated Intestinal Fluid	2.0	Sparingly soluble
pH4 Citrate Buffer	2.0[b]	Soluble
pH7 Phosphate Buffer	1.9[b]	Sparingly soluble
Ethanol		Very slightly soluble
Methanol		Slightly soluble
Octanol		Practically insoluble
Hexane		Practically insoluble

[a] According to USP Descriptive and Relative Solubility Classification:

Soluble	From 10 to 30 parts solvent per 1 part solute
Sparingly soluble	From 30 to 100 parts solvent per 1 part solute
Slightly soluble	From 100 to 1000 parts solvent per 1 part solute
Very slightly soluble	From 1000 to 10000 parts solvent to 1 part solute
Practically insoluble	Over 10000 parts solvent to 1 part solute

[b] Buffer capacity broken by pH lowering effect of sulfate salt.

2.2.5. Physical Appearance

Tan or light yellowish brown powder.

2.2.6. Formulation Information

Formulations used for pharmacokinetic studies were prepared in 0.1 M dibasic phosphate buffer (pH 7); concentrations were 1 mg/mL (dog, intravenous [i.v.]), 10 mg/mL (rat, i.v.; dog, p.o.), and 15 mg/mL (rat, p.o.). The formulation used in the range-finding i.h. toxicology studies was

Attachment 3.2: Sample Chemistry Section for a Compound with Multiple Formulations (Continued)

RWJ-BBBBB-180 (sulfate salt) at a concentration of 35 mg/mL (concentration expressed as the free base) in 0.1 M sodium phosphate. The formulation used in the dog i.v. cardiovascular safety study was prepared as a solution (0.3, 1, or 3 mg/mL) in citrate buffered 0.9% sodium chloride solution (pH 4). The formulation used in the 28-day i.h. toxicology studies was RWJ-BBBBB-180 (sulfate salt) at a concentration of 35 mg/mL (concentration expressed as the free base) in citrate buffer (pH 4). The solution was stored frozen and then thawed prior to dosing. Nonclinical studies of pharmacokinetics and metabolism used RWJ-BBBBB-180 (sulfate salt) while the in vitro metabolism study used RWJ-AAAAA-002 (hydrochloride salt). RWJ-BBBBB is converted in vitro to RWJ-AAAAA (a mixture of diastereomers), in rat, dog, and human plasma within 2 hours at 37°C, pH 7.4 (final ratio of RWJ-BBBBB [L-arginine diastereomer]: RWJ-CCCCCC [D-arginine diastereomer] approximately 65:35).

The clinical formulation is a sterile freeze-dried powder stored in 20-mL glass Type-I vials. Each vial will contain 60 mg RWJ-BBBBB (expressed as free base), 40 mg anhydrous citric acid, and the amount of sodium hydroxide needed to bring the solution pH to pH 4 prior to freeze-drying. The freeze-dried powder will be stored at 2 to 8°C, protected from light, and is readily reconstituted for nebulization in 5 mL of sterile aqueous 0.45% sodium chloride solution to attain isotonicity.

The stability of the reconstituted drug product has been investigated over 20 hours at room temperature (approximately 29°C). Based on these findings, the solution is to be used for nebulization within 6 hours of reconstitution with normal saline. Over this period of time the diastereomer form (RWJ-CCCCCC) remains less than 10% when compared with RWJ-BBBBB.

The use of pH 4 maintains the concentration of RWJ-CCCCCC at a very low level throughout nebulization. The citrate concentration is 0.8%, well below concentrations (2 through 8%) which cause cough in healthy subjects.

The freeze-dried formulation is stable for at least 3 months at 2 to 8°C and at 23 to 27°C, maintaining a diastereomeric purity of 95%

(5% RWJ-CCCCCC). The level of unknown impurities remains unchanged at approximately 1%.

The placebo vials will contain 40 mg anhydrous citric acid, pH-adjusted to pH 4 with NaOH, isotonicity achieved with 0.45% NaCl (same formulation as the reconstituted active) in a total volume of 5.0 mL. The placebo will be provided as a solution not as freeze-dried powder.

2.2.7. Other Pertinent Information

The batch of RWJ-BBBBB-180 used in both toxicology and in planned clinical studies has a potency of 78.1% as the free base (95.2% as the sulfate salt). The bulk of the remaining mass balance is accounted for by chromatographic impurities (2.22%), moisture (1.18%), residual solvents (2-propanol 0.13%), and inorganic materials (magnesium 0.19%).

RWJ-BBBBB-180 melts at approximately 223°C and degrades immediately thereafter. Studies performed at The R. W. Johnson Pharmaceutical Research Institute (RWJPRI) demonstrate that RWJ-BBBBB-180 is very stable in the solid state when protected from light and high humidity. The compound is not stable in solution, especially at high pH. The primary degradation pathway in the absence of light is epimerization at the arginine α-carbon to produce the other diastereomeric form (RWJ-CCCCCC), which also exhibits inhibition of tryptase and trypsin, in the low nanomolar range (see Section 3.1.1). Approximately a 1:1 ratio of diastereomers is produced in 6 hours at room temperature at pH 7. Significant photodegradation was also observed when an aqueous solution of RWJ-BBBBB was exposed to 765 watts per square meter (W/m^2) ultraviolet-visual (UV-Vis) irradiation.

Inhaled RWJ-BBBBB will be delivered in clinical studies using a Trudell AeroEclipse™ breath-actuated nebulizer, whose output has been characterized for mass output (filter) and particle size (Anderson Cascade Impaction) in combination with a breathing simulator. The following parameters were used for breathing simulation: tidal volume (600 mL), breathing ratio (10 breaths/minute), inspiration: expiration ratio (1:2 at inspiratory time 2 seconds). The output of the nebulizer was constant over time using a RWJ-BBBBB solution at 12 mg/mL (Table 2). Ascending doses will be delivered with variable numbers of breaths (1 to 120 breaths).

Attachment 3.2: Sample Chemistry Section for a Compound with Multiple Formulations (Continued)

Anderson 8-stage impactor size distribution data demonstrated that 72% to 74% of the output consisted of particles smaller than 4.7 µm, which will provide efficient delivery and deposition of the drug in the small airways.

Table 2: Recovery of 12-mg/mL Dose of RWJ-BBBBB in Breathing Simulation

	Nebulization Time			
	Start	Start - Mid	Mid - End	Entire
Mass Recovered	0 to 1 min	1 to 8 min	8 to 16 min	0 to 16 min
Mean (SEM), µg	1860 (200)	14850 (1130)	13030 (1600)	29750 (1690)
Coefficient of variation, %	11%	8%	12%	6%
Output, µg/min	1860	2120	1630	1860

Data was generated using the Trudell nebulizer.
Min = minute.

At the proposed strength of 12 mg/mL for clinical studies, foaming of the solution is expected and should not be a concern. There is no evidence of pH change during nebulization.

3.1. Nonclinical Pharmacology

3.1.1. Overview

RWJ-ZZZZZ-300 is a potent, selective, nonpeptide antagonist of the motilin receptor. RWJ-ZZZZZ-300 competitively inhibits binding of radiolabelled motilin to membranes prepared from rabbit colon with an inhibition constant (K_i) of 18 nM. RWJ-ZZZZZ-300 also inhibits radiolabelled binding to membranes prepared from rabbit antrum (K_i = 9 nM) and duodenum (K_i = 82 nM).

RWJ-ZZZZZ-300 binding affinity and functional antagonistic activity were evaluated in preparations containing either endogenous (human antral muscle) or cloned human motilin receptors. RWJ-ZZZZZ-300 was a potent inhibitor of motilin binding to both endogenous and cloned human receptors. In cells containing endogenous or cloned motilin receptors, motilin-induced intracellular calcium mobilization was inhibited by RWJ-ZZZZZ-300. RWJ-ZZZZZ-300 had no functional agonistic activity in these cells.

RWJ-ZZZZZ-300 also antagonizes in vitro motilin- and EM-induced contractions of rabbit duodenal smooth muscle strips with K_i values of 89 nM and 28 nM, respectively. RWJ-ZZZZZ-300 appears specific for the motilin receptor since it antagonizes neither acetylcholine-induced contractions of rabbit longitudinal duodenal smooth muscle or potassium chloride (KCl)-induced contractions of rabbit aorta in vitro.

The receptor affinity of RWJ-ZZZZZ-300 was determined in vitro from motilin- and EM-induced contractility studies in rabbit longitudinal duodenal smooth muscle. Antagonist potency was expressed as the negative log of the receptor affinity (pA2). When pA2 values (6.96 and 7.8, for motilin- and EM-induced contractions, respectively) were converted, they agreed well with K_i values obtained in the binding studies. Similar pA2 values were obtained in segments of whole rabbit duodenum.

There were no significant cardiovascular effects at an intravenous (i.v.) cumulative dose of 10 mg/kg in rats. In anesthetized rats, a slight indication of mild and transient central nervous system (CNS) stimulation at 100 mg/kg p.o. was observed. In anesthetized dogs, RWJ-ZZZZZ-300 produced a moderate decrease in heart rate (HR) at 1 to 10 mg/kg i.v. and a

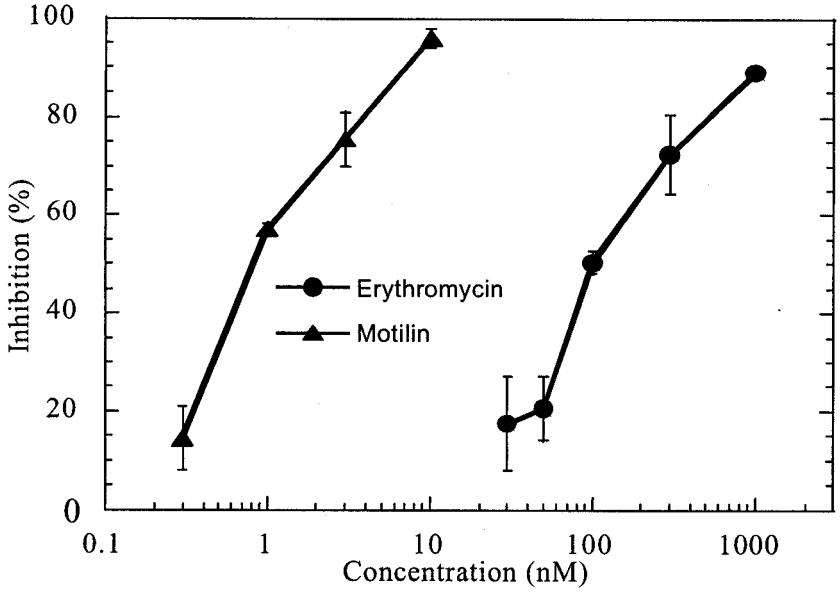
moderate, transient decrease in mean arterial pressure (MAP) at 10 mg/kg i.v.

3.1.2. Receptor Binding

3.1.2.1. Motilin and EM

Motilin, EM, and test compounds were evaluated for the ability to inhibit the binding of ^{125}I-motilin to crude membrane preparations of rabbit colon smooth muscle. Both motilin and EM exhibited a concentration-dependent inhibition of radiolabelled motilin binding to rabbit colon membranes with IC_{50} values of 1.08 and 136 nM, respectively (Figure 1; Table 3).[1] Studies were conducted to compare the ability of motilin and EM to compete for radiolabelled motilin binding in rabbit colon versus antral stomach and duodenum (Tables 3 and 4).[1] Motilin and EM inhibited binding in a concentration-dependent manner in both antral and duodenal membranes, however differences in potency between tissues were observed. Motilin and EM exhibited the same rank order of potency in the three tissues; both were most potent in antrum, less potent in colon, and least potent in duodenum.

Figure 1: Effect of Motilin and EM on ^{125}I-Motilin Binding to Rabbit Colon Membranes



Attachment 4: Sample Nonclinical Pharmacology Section (Continued)

Table 3: Binding of Motilin to Rabbit Antrum, Duodenum, and Colon Membranes

Parameter	Antrum	Duodenum	Colon
IC_{50} (95% C.L.)	0.4 nM (0.05-3.18 nM)	18.3 nM (5.8-58.2 nM)	1.08 nM (0.2-6.37 nM)
K_d	0.61 (0.19) nM	14.6 (3.5) nM	0.9 (0.3) nM
B_{max}	39 (4) fmole/mg	--	51(1) fmole/mg

Table 4: Competitive Binding of EM to Rabbit Antrum, Duodenum, and Colon Membranes

Parameter	Antrum	Duodenum	Colon
IC_{50} (95% C.L.)	69.5 nM (10-480 nM)	507.5 nM (59-4323 nM)	136 nM (34-537 nM)
K_i	66.0 nM	507.0 nM	130 nM

3.1.2.2. RWJ-ZZZZZ

Racemic RWJ-67849 and the purified enantiomers, RWJ-68022 and RWJ-ZZZZZ, exhibited competition for ^{125}I-motilin binding to the rabbit colon motilin receptor (Figure 2).[2] RWJ-ZZZZZ-300 was the most potent inhibitor with an affinity approximately 100-fold less than the best peptide antagonist, ANQ-11526 (Table 5).[2]

Figure 2: Competitive Inhibition of ^{125}I-Motilin for Binding to the Rabbit Colon Motilin Receptor

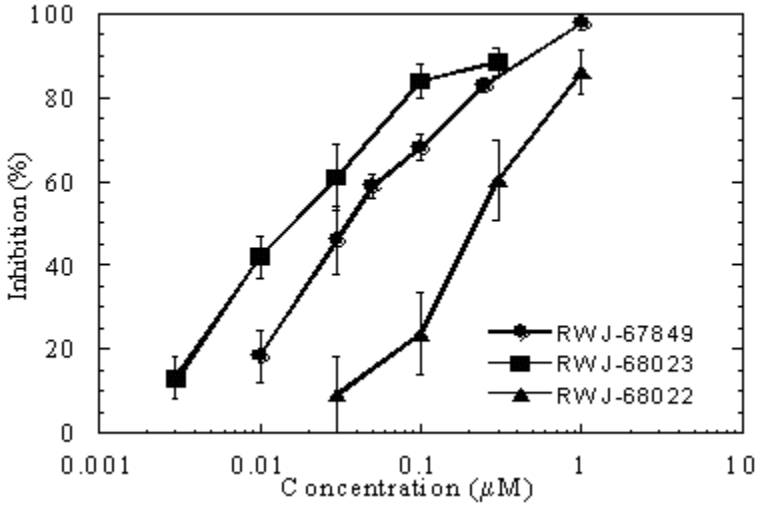


Table 5: Competitive Binding of RWJ-67849 and Its Enantiomers to Rabbit Colon Membranes

Parameter	RWJ-67849	RWJ-ZZZZZ	RWJ-68022	ANQ-11526
IC_{50} (95% C.L.)	42 nM (12-146 nM)	19 nM (2.6-137 nM)	218 nM (41-1153 nM)	0.27 nM (0.06-1.2 nM)
K_i	40.3 nM	18.2 nM	209 nM	0.25 nM

The results in Tables 6 and 7 demonstrate marked differences in the ability of motilin and EM to displace ^{125}I-motilin from antrum, duodenum, and colon membranes.[1] As shown in Table 6, RWJ-ZZZZZ-300 exhibited the same rank order of potency in these tissues as did motilin and EM; all three were most potent in antrum, less potent in colon, and least potent in duodenum.[1]

Table 6: Competitive Binding of RWJ-ZZZZZ-300 to Rabbit Antrum, Duodenum, and Colon Membranes

Parameter	Antrum	Duodenum	Colon
IC_{50} (95% C.L.)	9.9 nM (1.6 - 60 nM)	86.9 nM (20.2 - 374.7 nM)	19 nM (12 - 146 nM)
Ki	9.4 nM	82 nM	18.2 nM

RWJ-ZZZZZ-300 inhibited the binding of motilin to human antral tissue with an IC_{50} of 135 nM (Table 7).[1] The identical ratio of IC_{50} values for all ligands suggests that they bind at the same site in the human antral tissue but with less affinity.

Table 7: Competitive Binding of Motilin, EM, and RWJ-ZZZZZ-300 to Rabbit and Human Antral Stomach Membranes

Parameter	Motilin	EM	RWJ-ZZZZZ
Rabbit IC_{50}	0.4 nM	69.5 nM	9.9 nM
Human IC_{50}	6.0 nM	800 nM	135 nM
Human/Rabbit	15.0	11.5	13.6

3.1.2.3. Human Motilin Receptors

3.1.2.3.1. Receptor Binding

Binding affinity of RWJ-ZZZZZ-300 was evaluated in preparations containing either endogenous (human antral muscle) or cloned human motilin receptor. RWJ-ZZZZZ-300 potently inhibited binding of porcine motilin to both receptor populations (Table 8). Although the IC_{50} was lower in endogenous (32 nM) than in cloned (114 nM) receptors, the ratio of IC_{50}

values for porcine motilin in the two preparations were the same as that of RWJ-ZZZZZ (3.55 and 3.6, respectively). Therefore, in both preparations, the nonpeptide RWJ-ZZZZZ-300 was approximately 30 times less potent than the natural ligand agonist, motilin.[3]

Table 8: Inhibition[a] of ^{125}I-Motilin Binding to Human Antral Membranes and Cloned Human Motilin Receptor by Porcine Motilin and RWJ-ZZZZZ-300

Preparation	Motilin IC_{50} (nM)	RWJ-ZZZZZ IC_{50} (nM)
Human antral membrane	1.00 (0.10)	32 (3)
Cloned human motilin receptor	3.55 (0.05)	114 (38)

[a] Each value represents the mean (SE) of 3-4 determinations.

3.1.2.3.2. Motilin-Induced Intracellular Calcium Mobilization

Studies in two cell lines, human TE671 cells containing endogenous motilin receptors and Motilin-HEK cells expressing cloned human motilin receptors, evaluated intracellular calcium mobilization. Porcine motilin induced a dose-related increase in intracellular calcium mobilization in both cell lines (Table 9). ED_{50} values for TE671 and Motilin-HEK cells were 25 nM and 3 nM, respectively (Table 10). In addition to this difference in motilin sensitivity, the maximal change in intracellular calcium mobilization induced by motilin in Motilin-HEK cells was 10 times greater than that induced in TE671 cells. These results are likely due to a greater number of motilin receptors in the clone preparation.[3]

Table 9: Percent Stimulation[a] of Intracellular Calcium Mobilization by Porcine Motilin in Human TE671 Cells and Motilin-HEK Cells

Porcine Motilin	Stimulation of Calcium Mobilization (%)	
(nM)	TE671 Cells	Motilin-HEK Cells
0.1	—	2 (0)
0.3	—	9 (1)
1	0 (4)	38 (3)
3	6 (0)	53 (3)
10	24 (8)	85 (5)
30	57 (9)	92 (5)
100	67 (7)	100 (3)
300	85 (9)	—
1000	100 (10)	—

[a] Each value represents the mean (SE) of 3 values expressed as a percent of the maximal response observed.

Table 10: Motilin-Induced Intracellular Calcium Mobilization in Human TE671 Cells and Motilin-HEK Cells

	TE671 Cells	Motilin-HEK Cells
Motilin ED_{50}	25 nM	3 nM
Maximal fluorescent response[a]	3618	34502
Fold increase over vehicle	13	73

[a] Maximal fluorescent response values are means of maximal relative fluorescent units measured in motilin dose-response studies in TE671 cells (n=6) and Motilin-HEK cells (n=4).

3.1.2.3.3. Functional Antagonism

RWJ-ZZZZZ-300 and its less active enantiomer, RWJ-68022-300, as well as the racemic mixture, RWJ-67849-300, were evaluated for functional agonist and antagonist activities (Table 11). In human TE671 cells containing endogenous motilin receptors, RWJ-ZZZZZ-300 inhibited porcine motilin with a K_i of 10 nM while RWJ-68022-300 was 18 times less potent. Similarly, in Motilin-HEK cells expressing cloned human motilin receptors, RWJ-ZZZZZ-300 inhibited motilin with a K_i of 20 nM while RWJ-68022-300 was 15 times less potent in this cell line. Since motilin receptor sequences in both cell lines have been verified as identical, the difference in RWJ-ZZZZZ-300 K_i values is probably due to more motilin receptors in the cloned preparation (when compared with the antral muscle preparation). No agonist activity was observed for any of the compounds at concentrations up to 3 μM.[3]

Table 11: Inhibition[a] of Motilin-Induced Intracellular Calcium Mobilization in Human TE671 and Motilin-HEK Cells by RWJ-ZZZZZ-300, RWJ-68022-300, and RWJ-67849-300

	TE671 Cells	Motilin-HEK Cells
Compound	K_i (nM)	K_i (nM)
RWJ-ZZZZZ-300	10 (3)	20 (5)
RWJ-68022-300	185 (25)	303 (37)
RWJ-67849-300	18 (4)	53 (11)

[a] K_i values represent means (SE) of 3-5 determinations.

3.1.3. Tissue Strip Activity

3.1.3.1. Motilin and EM

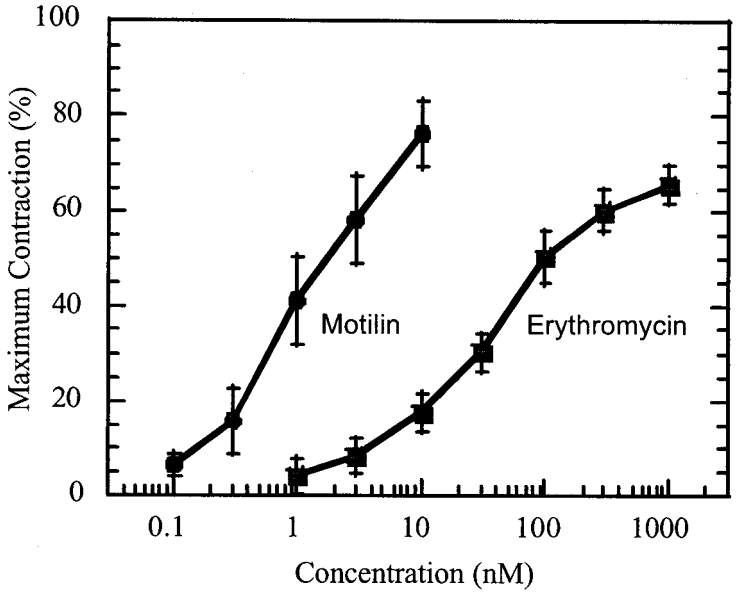
Motilin- and EM-induced contractions of rabbit longitudinal duodenal muscle strips in vitro were utilized to characterize the efficacy of potential motilin antagonists.[4] The tissue was equilibrated with two initial contractions induced by acetylcholine (100 μM), with the second designated

as 100% maximal contraction of the tissue. Both motilin and EM induced a concentration-dependent increase in contractility with EC_{50} values of 1.87 and 155 nM, respectively (Table 12; Figure 3). Based on these results, potential motilin antagonists were tested for the ability to block either 4 nM motilin-induced or 1 μM EM-induced contractions (agonist concentrations that induce 50-70% maximal contraction).

Table 12: Acetylcholine-, Motilin-, and EM-Induced Contractility of Rabbit Longitudinal Duodenal Muscle In Vitro

Parameter	Acetylcholine	Motilin	EM
EC_{50}	4200 nM	1.87 nM	155 nM
95% C.L.	950-18500 nM	0.65-5.4 nM	56-429 nM

Figure 3: Motilin- and EM-Induced Contractility of Rabbit Longitudinal Duodenal Muscle



3.1.3.2. RWJ-ZZZZZ

Racemic RWJ-67849 and the purified enantiomers, RWJ-68022 and RWJ-ZZZZZ-300, exhibited concentration-dependent inhibition of motilin-induced duodenal strip contractions (Table 13; Figure 4) as did the peptide motilin antagonist, ANQ-11526.[4] RWJ-ZZZZZ-300 was more potent than RWJ-68022, but equipotent with the racemic mixture, RWJ-67849 (Table 13). When RWJ-ZZZZZ-300 was tested against motilin, an IC_{50} of 280 nM (95% C.L. = 98-800 nM; K_i = 89.2 nM) was obtained (Table 13)[4] and the pA2 was 6.96 ± 0.13 (Table 14). Transformation of the contractility

dose-response data, according to the method of Schild,[5] produced a plot with a slope close to 1 (Table 14), demonstrating that RWJ-ZZZZZ-300 interacted with a single population of receptors. From the same plot, the pA2 value (negative log of antagonist receptor affinity) was determined using functional data. The pA2 values obtained with RWJ-ZZZZZ-300 (6.96 ± 0.13, Table 14) agree well with the K_i for RWJ-ZZZZZ-300 in the rabbit duodenum (89.2 nM, negative log 7.05, Table 13).[4]

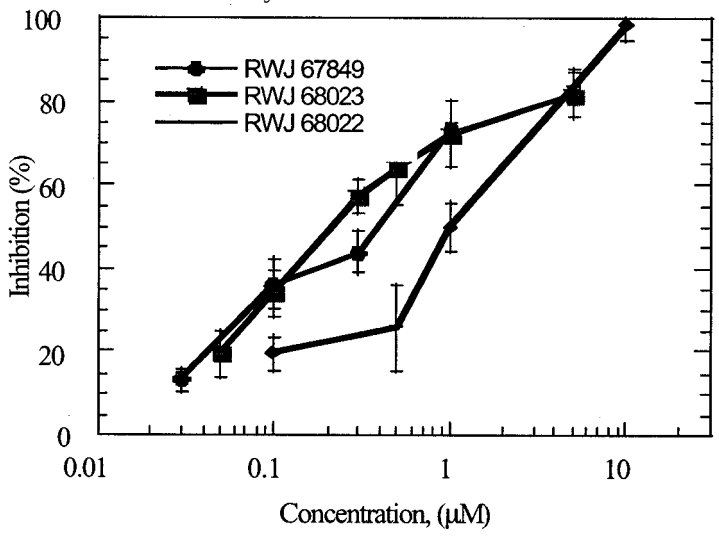
Table 13: Inhibition of Motilin-Induced Rabbit Duodenal Muscle Contraction by RWJ-ZZZZZ-300 and Its Enantiomers

Parameter	RWJ-67849	RWJ-ZZZZZ	RWJ-68022	ANQ-11526
IC_{50} (95% C.L.)	285 nM (100-810 nM)	280 nM (98-800 nM)	890 nM (256-3090 nM)	9.8 nM (3-32 nM)
K_i	90 nM	89.2 nM	283.5 nM	3.8 nM

Table 14: pA2 Values for RWJ-ZZZZZ-300 on Motilin- and EM-Induced Contractility of Rabbit Longitudinal Duodenal Muscle In Vitro

Parameter	Motilin	EM
pA2	6.96	7.80
Standard Error	0.13	0.16
95% C.L.	5.35-8.56	5.81-9.79
R	0.979	0.985

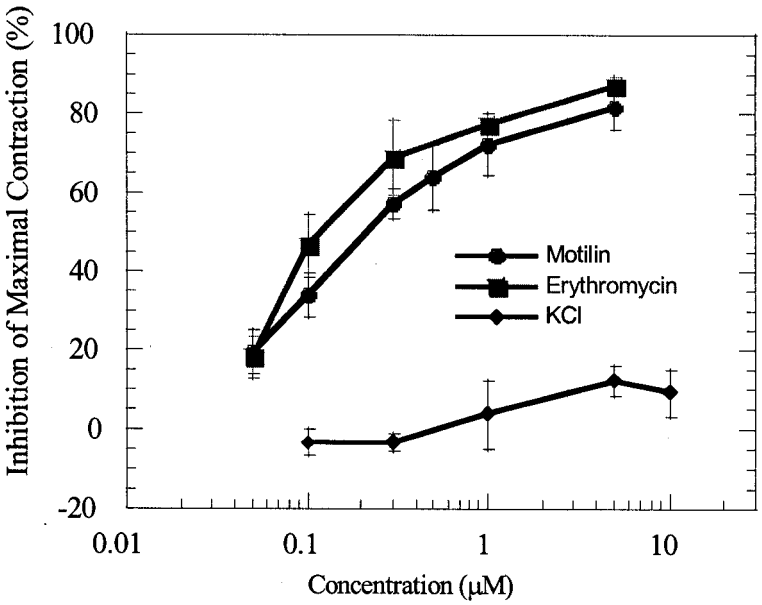
Figure 4: Inhibition of Motilin-Induced Contractions of Rabbit Duodenum by RWJ-ZZZZZ-300



EM and its derivatives have been shown to possess motilin-like activity and to displace ^{125}I-motilin bound to duodenal muscle.[6-9] These data suggest that

motilin and EM share the same receptor; therefore, a motilin antagonist should inhibit the contractile response to EM. RWJ-ZZZZZ-300 did inhibit EM-induced contractions with an IC_{50} of 212 nM (95% C.L. = 67-669 nM; K_i = 28.45 nM) and a pA2 of 7.8 ± 0.16 (Table 14; Figure 5).[4]

Figure 5: Effect of RWJ-ZZZZZ-300 on Motilin-, EM-Induced Contractions of Rabbit Duodenum and KCl-Induced Contractions of Rabbit Aorta In Vitro



RWJ-ZZZZZ-300 antagonism of motilin and EM was shown to be selective. The contractile response induced by 10 μM acetylcholine (Table 15) on rabbit duodenum muscle was not inhibited by RWJ-ZZZZZ-300 at concentrations more than ten times greater than its IC_{50} for motilin-induced contractions (Table 6). In addition, RWJ-ZZZZZ-300 did not inhibit contraction of rabbit aortic rings produced by a near maximal concentration of KCl, 30 mM (Figure 5).

Table 15: Effect of RWJ-ZZZZZ-300 on Acetylcholine-Induced Contractility on Rabbit Longitudinal Duodenal Muscle In Vitro

Concentration (μM)	% Maximum Contraction Produced by Acetylcholine $1E^{-4}$ M		
RWJ-ZZZZZ-300	Mean	Standard Error	Number Tissues
0.00	55.91	4.18	21
0.01	70.00	4.42	7
0.05	70.21	5.28	8
0.10	75.16	3.53	12
0.50	73.63	6.03	7
1.00	61.90	12.85	4
5.00	47.27	6.89	4

Similar studies were performed using 3 cm segments of whole rabbit duodenum from either fed or fasted rabbits. Cumulative concentration response curves to Leu_{13}-motilin, pEC_{50}, and pA2 values were estimated.

The results indicated and confirmed that RWJ-ZZZZZ-300 is a competitive and potent motilin receptor antagonist in the isolated rabbit duodenum, yielding affinity estimates between pA2 values of 7.6 and 8.2. Since the curves were slightly depressed by RWJ-ZZZZZ-300 (no full surmountability), the Schild criteria for competitive antagonism were not fully met. The narrow range of calculated pA2 values, however, indicates the robustness of the values and are very similar to reported affinity values above (Table 14). Fasting of the rabbits for three days did not affect response parameters to Leu_{13}-motilin.

3.1.4. Cardiovascular

3.1.4.1. Effects in Anesthetized Rats

RWJ-ZZZZZ-300 had no significant hemodynamic or electrocardiographic effects at doses up to and including 10 mg/kg i.v. in anesthetized rats.[10] Rats were anesthetized with pentobarbital and catheters placed in the carotid artery and jugular vein for measuring arterial pressure and infusing drug, respectively. Lead II ECG was also recorded. RWJ-ZZZZZ-300 was administered as five-minute i.v. infusions of 0.1, 0.2, 0.7, 2 and 7 mg/kg every 15 minutes, yielding cumulative doses of 0.1, 0.3, 1, 3, and 10 mg/kg. RWJ-ZZZZZ-300 had no effect on MAP and HR through 10 mg/kg i.v. RWJ-ZZZZZ-300 also had no effect on PR interval, QRS width, QT interval, and ECG morphology through 10 mg/kg i.v.

3.1.4.2. Effects in Anesthetized Dogs

Male or female mongrel dogs were anesthetized with pentobarbital (35 mg/kg i.v.) and surgical anesthesia was maintained by a continuous i.v. infusion of pentobarbital (3.5 mg/kg/h).[11] RWJ-ZZZZZ-300 was administered as five-minute i.v. infusions of 0.1, 0.2, 0.7, 2, and 7 mg/kg for cumulative doses of 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Measurements were made immediately after and at five and 10 minutes after the end of i.v. infusions.

RWJ-ZZZZZ-300 did not affect MAP except for a moderate and transient decrease at 10 mg/kg (Figure 6, filled symbols) but caused moderate, dose-related decreases in HR between 1 and 10 mg/kg (Figure 6, open symbols). Peak positive and negative left ventricular pressures (dP/dt) were not affected except for a slight decline at 10 mg/kg, perhaps attributable to the decreases in MAP and HR. RWJ-ZZZZZ-300 had no effect on mean pulmonary arterial pressure and did not significantly affect PR interval or QRS width through 10 mg/kg. QT interval rose slightly at 10 mg/kg but this was due to the decrease in HR since corrected QT interval (QTc, Bazet formula) was unchanged through 10 mg/kg (Figure 7). There were no changes in respiratory rate.[11]

Figure 6. Effect of RWJ-ZZZZZ-300 on MAP and HR in Anesthetized Dogs

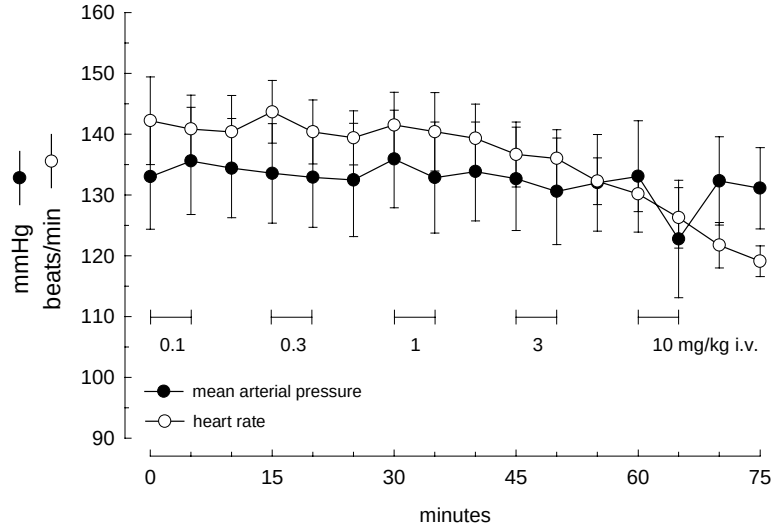
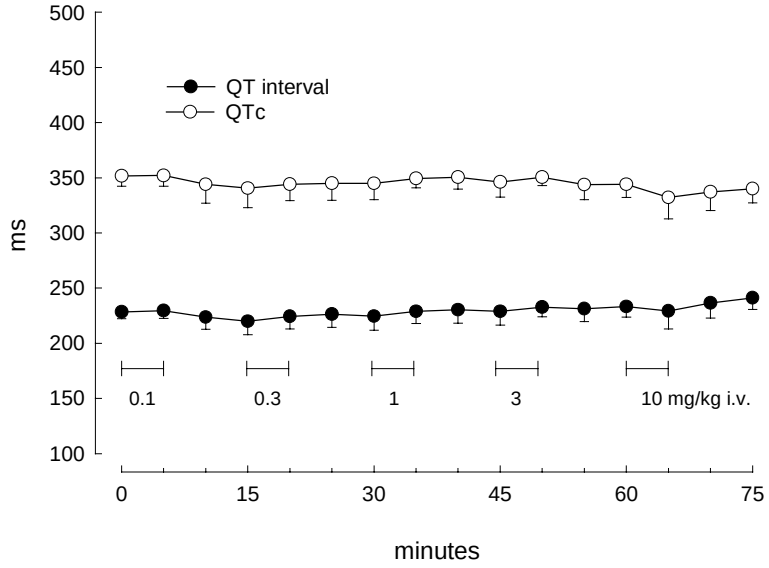


Figure 7: Effect of RWJ-ZZZZZ-300 on QT and Corrected QT (QTc) Intervals in Anesthetized Dogs



3.1.5. Central Nervous System

No physical or behavioral signs were observed in rats administered RWJ-ZZZZZ-300 at 1 and 10 mg/kg p.o.[12] However, at 100 mg/kg p.o. a slight and transient increase in startle response was observed, indicative of mild and transient CNS stimulation or activation. Compared with the vehicle control group, no change in body temperature was observed in rats one hour after administration of 1, 10, and 100 mg/kg p.o. RWJ-ZZZZZ-300. Rats were retained for two weeks and, throughout this period, all rats appeared normal.

3.1.6. Selectivity

RWJ-ZZZZZ-300 was submitted for evaluation of 35 receptor-binding assays at 10 μM. Five assays generated evaluations in functional (tissue) assays at 30 μM. RWJ-ZZZZZ-300 was inactive in all functional assays.

3.1.7. Migrating Motor Complex

A dog study investigating the effects of 1 or 2 mg/kg RWJ-ZZZZZ or placebo on the migrating motor complex in the dog gastrointestinal tract is ongoing. Preliminary data indicate effects at 1 mg/kg (unpublished data, RWJPRI).

3.2. Pharmacokinetics and Product Metabolism in Animals

3.2.1. Summary of Absorption, Pharmacokinetics and Distribution

An overview of the nonclinical pharmacokinetics and product metabolism of RWJ-68023-300 can be found in the Summary section of this brochure. Table X summarizes the studies performed to evaluate the absorption, pharmacokinetics and distribution of RWJ-68023-300 in nonclinical studies.

Table X: Comparative Parmacokinetic Parameters of RWJ-zzzzzz Following Oral or Intravenous Administration in Rats and Dogs

Study Type	Species Sex (N)	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(O-\infty)}$ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (mL/kg·h)	F (%)	Vd_{ss} (mL/kg)
Single-dose	Rat								
i.v. bolus	Male (4)	5.0	3403	N/A	1193	3.2	4281	N/A	6107
	Female (4)	5.0	2558	N/A	2457	6.2	2044		9836
Single-dose	Dog								
i.v. bolus	Male (4)	1.0	769	N/A	460	12.2	2177	N/A	11164
	Female (4)	1.0	893	N/A	486	10.3	2153		7381

Results/Comments: RWJ 68023-300 was slowly eliminated in rats and dogs after i.v. bolus administration ($t_{1/2}$ = 3.2 to 6.2 and 10.3 to 12.2 hours, respectively). The mean steady-state volume of distribution (Vd_{ss}) greatly exceeded total body water in both rat (6107 to 9836 mL/kg)[13] and dog (7381 to 11164 mL/kg),[14] indicating extensive distribution outside of plasma.

Single-dose	Rat								
Oral	Male (4)	50.0	1012	4.0	7386	3.6	7167	61.9	N/A
	Female (4)	50.0	2389	7.0	32042	6.6	1607	130.4	
Single-dose	Dog								
Oral	Male (2)	1.0	3.0	0.5	8.5	6.1	68716	1.8	N/A
	Female (4)	1.0	N/M	N/M	N/M	N/M	N/M	N/M	

Results/Comments: In rats, the bioavailability of RWJ 68023-300 following a single oral dose was absorbed slowly (t_{max}=4.0 to 7.0 hours) and well (bioavailability 61.9% to 130.4%) and was slowly eliminated following oral administration ($t_{1/2}$=3.6 to 6.6 hours). The $t_{1/2}$ after oral administration was similar to the $t_{1/2}$ after i.v. bolus administration. In dogs, RWJ 68023-300 was rapidly absorbed (t_{max}=0.5 hours), but the bioavailability was low (1.8%).

Multiple-dose four-hour i.v. infusion toxicokinetic studies were conducted in rats[15,16] and dogs[17,18] in support of the five-day dose range-finding and 14-day toxicity studies (Table 18). In general, the drug exposure, expressed as C_{max} and AUC, was dose-related following both single- and multiple-dose administration in these species. The inverse concentration-dependent adsorption of RWJ-ZZZZZ-048 by infusion tubing that was observed in these studies may, in part, explain the more than dose-proportional increases in exposure, at least in the five-day studies where it was not corrected for. In general, the C_{max} and AUC values did not change significantly from the first day to the last day of dosing, suggesting no accumulation or change in clearance of RWJ-ZZZZZ-048 over time. There were no sex-related differences in RWJ-ZZZZZ-048 pharmacokinetic parameters. The $t_{1/2}$ ranged from 0.5 to 12.6 hours in rats and 4.2 to 15.3 hours in dogs.

Attachment 5: Sample Pharmacokinetics and Product Metabolism in Animals Section (Continued)

Table 18: Mean Pharmacokinetic Parameters for RWJ-ZZZZZ-048 Following Multiple 4-Hour Infusions

Species/ [Reference]	Sex	n	Day	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/kg·h)
Sprague-Dawley Rat [a]	Male	2	1	1.2	3.8	10.4[b]	NC	NC
[15]		1	1	6.0	97.5	504.9	3.6	NC
		2	1	12.0	364.3	1661.1	3.3	NC
		2	1	24.0	1078	4920.0	3.2	NC
	Female	2	1	1.2	1.8	NC	NC	NC
		2	1	6.0	97.4	347.2	1.2	NC
		2	1	12.0	437.9	1960.7	3.1	NC
		2	1	24.0	852.1	5641.1	4.6	NC
	Male	2	5	1.2	8.9	32.4[c]	0.5	NC
		2	5	24.0	869.2	5334.4[c]	8.0	NC
	Female	1	5	1.2	3.8	14.1[c]	0.7	NC
		2	5	24.0	1760	11987.9[c]	3.9	NC
Sprague-Dawley Rat [d]	Male	4	1	20.0	3940	28212	3.6	811
[16]		4	1	40.0	5030	37605	3.8	1109
		4	1	90.0	18349	174580	5.2	537
	Female	4	1	20.0	3550	23594	4.3	850
		4	1	40.0	7067	56072	5.2	722
		2	1	90.0	18229	187817	5.7	481
	Male	4	10	20.0	3501	19483[c]	4.0	1020
		4	10	40.0	10417	97398[c]	11.0	1040
		1	10	90.0	4449	29057[c]	4.9	2979
	Female	3	10	20.0	2900	22005[c]	12.6	3279
		3	10	40.0	6798	52303[c]	4.7	779
		2	10	90.0	14194	144532[c]	3.3	710
Beagle Dog[e]	Male	1	1	3.2	217.0	1082	4.7	NC
[17]		1	1	12.8	1154	5407	4.2	NC
	Female	1	1	3.2	155.9	783	5.1	NC
		1	1	12.8	1631	7482	4.7	NC
	Male	1	5	3.2	232.8	1287[c]	6.9	NC
		1	5	12.8	1399	6419[c]	5.0	NC
	Female	1	5	3.2	160.4	846[c]	5.3	NC
		1	5	12.8	2125	10132[c]	5.3	NC
Beagle Dog[d]	Male	3	1	10.0	1194	6053	7.3	1739
[18]		3	1	30.0	4270	26548	7.5	1143
		3	1	80.0	13839	102063	8.1	801
	Female	3	1	10.0	1117	5469	8.4	1899
		3	1	30.0	3477	16781	7.7	1799
		3	1	80.0	12908	89532	6.8	894
	Male	3	14	10.0	1605	8319[c]	9.6	118
		3	14	30.0	5986	38332[c]	11.2	669
		3	14	80.0	21924	161251[c]	15.3	367
	Female	3	14	10.0	1297	7001[c]	13.2	119
		3	14	30.0	4799	27371[c]	13.3	937
		2	14	80.0	14673	119063[c]	10.1	580

[a] RWJ-ZZZZZ-048 in 5% dextrose (Lot No. 14031-127, S-8939, RWJPRI Lot A)
[b] AUC(0-5h)
[c] AUC(0-24h)
[d] RWJ-ZZZZZ-048 in 5% dextrose (Lot No. A-11-002)
[e] RWJ-ZZZZZ-048 in 5% dextrose (Lot No. 14031-127, S-8940, RWJPRI Lot A)
NC = not calculated

Attachment 5: Sample Pharmacokinetics and Product Metabolism in Animals Section (Continued)

3.2.2. Metabolism

A study was conducted to investigate the in vitro metabolism of the racemic mixture (RWJ-67849), containing the active enantiomer RWJ-ZZZZZ, in male rat and pooled male and female human hepatic S9 fractions.[19] RWJ-67849 was incubated with rat and human hepatic S9 fractions in a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-generating system at 37°C for 60 minutes. The unchanged RWJ-67849 and metabolites were characterized, identified, and quantified using Sciex API-III (ionspray)-MS, MS/MS, and methyl derivatization (diazomethane) methodologies.

The results indicated that RWJ-67849 was not extensively metabolized in the rat and human hepatic S9 systems (Table 19). After 60-minute incubations, the parent compound accounted for approximately 83-85% (rat) to 87-89% (human) of the sample analytes. Four metabolites were tentatively identified. N-oxidation appears to be the predominant in vitro metabolic pathway for RWJ-67849 in both species. The proposed in vitro metabolic pathways for RWJ-67849 in the rat and human are shown in Figure 8.

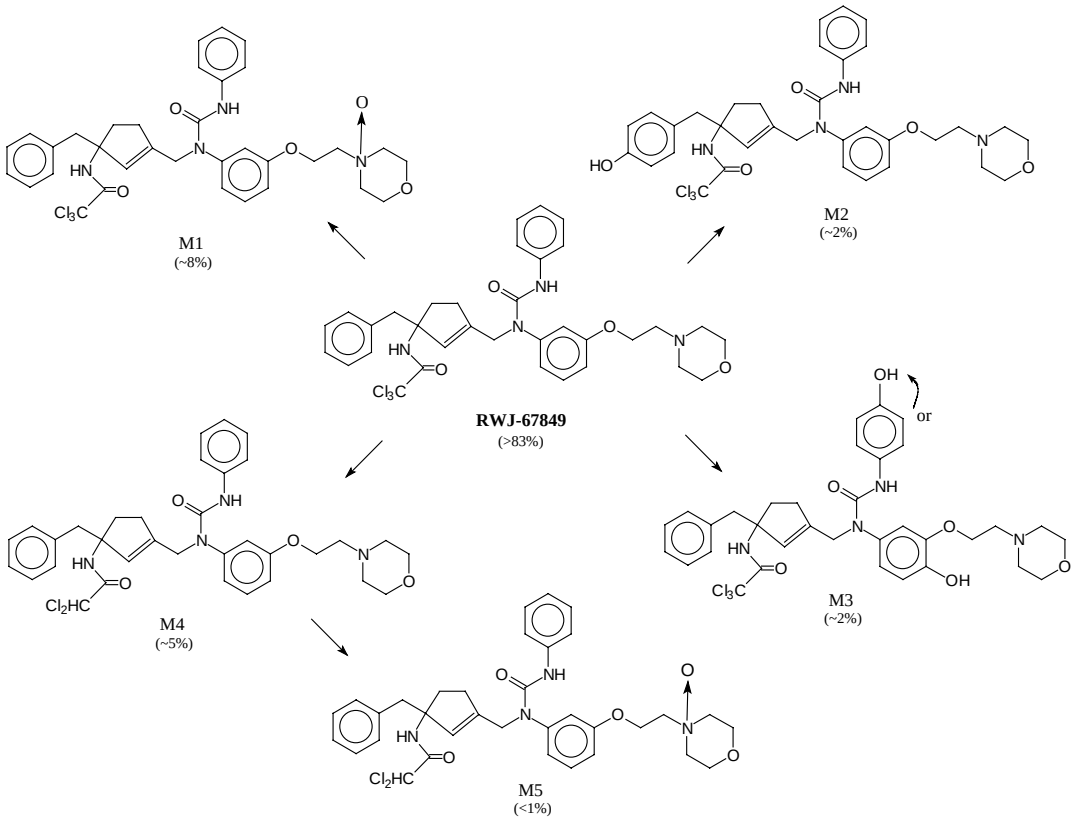
Table 19: Relative Percent of Sample[a] for RWJ-67849 and Its Metabolites after 60-Minute Incubation in Hepatic S9 of Rat and Human

Analyte	Rat (%)	Human (%)
RWJ-67849	83-85	87-89
M1: (RWJ-67661) RWJ-67849-N-oxide	7	7-8
M2: OH-ph-RWJ-67849	5	2
M3: dechloro-RWJ-67849	5	2-3
M4: dechloro-RWJ-67849-N-oxide	<1	<1

[a] Values are expressed as percentages of total ion current for each metabolite for the sample matrix only and, due to potential differences in the degree of ionization of each metabolite, are not absolutely quantitative.

Attachment 5: Sample Pharmacokinetics and Product Metabolism in Animals Section (Continued)

Figure 8: Proposed In Vitro Metabolic Pathways for RWJ-67849 (Racemic Mixture Containing RWJ-ZZZZZ)



3.2.3. Excretion

RWJ-ZZZZZ-300 was slowly eliminated from plasma in rats[13] and dogs,[14] after i.v. or oral administration, with a $t_{1/2}$ of 3.2 to 6.6 hours in rats and 6.1 to 12.2 hours in dogs.

3.2.4. Bioanalytical Summary

LC-MS/MS assays were used to support the preclinical pharmacokinetic and toxicokinetic studies. The lower limits of quantification for assays conducted by Phoenix International, Montreal, Canada were 1.0 ng/mL[14,15,17] and 10 ng/mL.[16,18] For assays conducted by RWJPRI, Spring House, PA, this limit was 1.0 ng/mL.[13]

Attachment 5: Sample Pharmacokinetics and Product Metabolism in Animals Section (Continued)

3.2.5. Interspecies Scaling

The plasma concentration data and the pharmacokinetic parameters from the i.v. bolus pharmacokinetic studies in rats[13] and dogs[14] were used for interspecies scaling. The data were averaged across gender and doses.

Allometric scaling[20] was then performed on the pharamcokinetic parameters versus body weight to predict the human parameters (Table 20). The plasma concentrations expected to be obtained following selected proposed doses administered as i.v. infusions were predicted by simulations using a two-compartment model (Table 21, Figure 9).

Table 20: Predicted Pharmacokinetic Parameters for RWJ-ZZZZZ-300 in 70 kg Healthy Volunteers from Simulation Using a Two-Compartment Model

Parameter			Predicted
CL		(mL/h)	112121
Vd_{ss}		(mL)	299401
$t_{1/2}$		(h)	9.7
C_{max}	@ 8.7 mg[a]	(ng/mL)	67.5
$AUC_{0-\infty}$	@ 8.7 mg[a]	(ng·h/mL)	77.6
C_{max}	@ 52.0 mg[a]	(ng/mL)	403.5
$AUC_{0-\infty}$	@ 52.0 mg[a]	(ng·h/mL)	463.8
C_{max}	@ 156.0 mg[a]	(ng/mL)	1210.5
$AUC_{0-\infty}$	@ 156.0 mg[a]	(ng·h/mL)	1391.4

[a] 45-minute i.v. constant-rate infusion

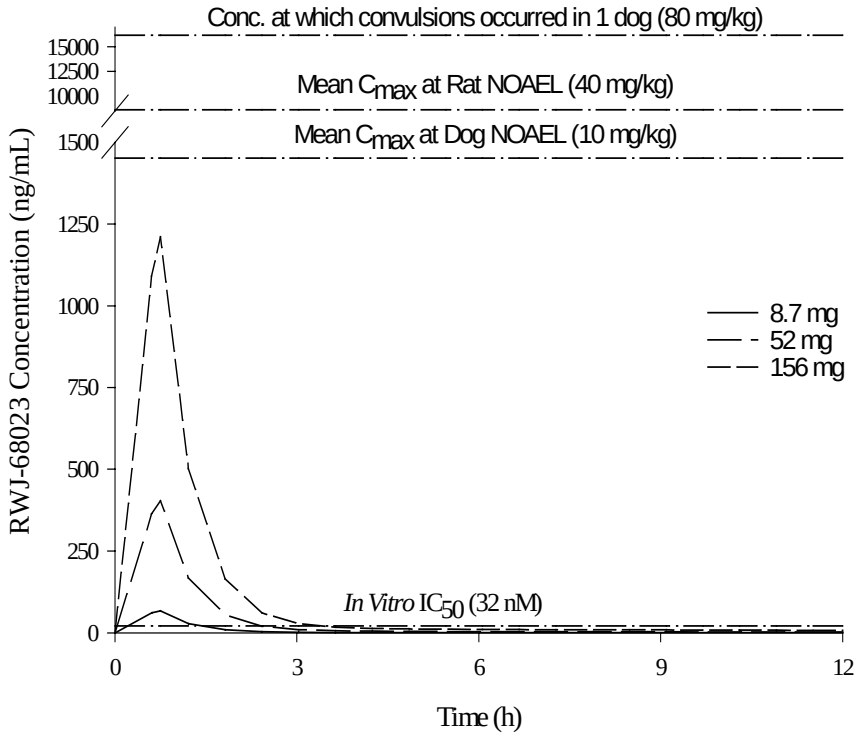
Table 21: Predicted Doses to Achieve Target Plasma Concentrations for RWJ-ZZZZZ-300 in Healthy 70 kg Volunteers

Target Plasma Concentration (ng/mL)	(nM)	Predicted Dose[a] (mg)
67.5	100	8.7
403.5	600	52.0
1210.5	1800	156.0

[a] 45-minute i.v. constant-rate infusion

Attachment 5: Sample Pharmacokinetics and Product Metabolism in Animals Section (Continued)

Figure 9: Predicted RWJ-ZZZZZ Plasma Concentrations for 70 kg Humans Following Each I.V. Infusion Regimen



NOAELs were 40 mg/kg/day (Day 10 data, rats) and 10 mg/kg/day (Day 14 data, dogs); C_{max} values in rats and dogs were 8606 and 1451 ng/mL, respectively.[16,18] Convulsions occurred twice at the end of the 4h infusion in one dog administered 80 mg/kg in the 14-day study;[18] Day 1 C_{max} (16158 ng/mL) for that dog is shown.

These data show that predicted plasma concentrations after 45-minute constant- rate i.v. infusions of RWJ-ZZZZZ-300 at doses of 8.7-156 mg (over 45 minutes) in a 70 kg human should remain below the mean C_{max} values measured at the No Adverse Effect Levels (NOAELs) found in male and female rats (8608 ng/mL) and dogs (1451 ng/mL). The exposure ratios for both C_{max} and AUC are presented in Tables 22 and 23.

Attachment 5: Sample Pharmacokinetics and Product Metabolism in Animals Section (Continued)

Table 22: Exposure Ratios Predicted for RWJ-ZZZZZ in Human Relative to Rat NOAEL Following 10 Daily Four-Hour I.V. Infusions of RWJ-ZZZZZ (40 mg/kg/day)

Human Dose (mg)	C_{max}		AUC	
45 min infusion	male	female	male	female
8.7	154	101	1255	674
52	25.8	16.9	210	113
156	8.61	5.62	70.0	37.6

Note: All animal data are multiple dose [AUC (0-24h)].[16] The human data are from a predicted single-dose data set [AUC (0-∞)], based on interspecies scaling.

Exposure Ratio = $\frac{\text{AUC (animal)}}{\text{AUC (human)}}$

Table 23: Exposure Ratios Predicted for RWJ-ZZZZZ in Human Relative to Dog NOAEL Following 14 Daily Four-Hour I.V. Infusions of RWJ-ZZZZZ-048 (10 mg/kg/day)

Human Dose (mg)	C_{max}		AUC	
45 min infusion	male	female	male	female
8.7	23.8	19.2	107	90.2
52	3.98	3.21	17.9	15.1
156	1.33	1.07	5.98	5.03

Note: All animal data are multiple dose [AUC (0-24h)].[18] The human data are from a predicted single dose data set [AUC (0-∞)], based on interspecies scaling.

Exposure Ratio = $\frac{\text{AUC (animal)}}{\text{AUC (human)}}$

Attachment 6: Sample Toxicology Tables

Table 6: Repeated Dose Toxicity Studies of RWJ-XXXXXX (Continued)

Study Type [Reference]	Species No. animals	Dose (Route) Treatment Duration	Results
5-Day intravenous toxicity study [52]	Rat 5/sex/group plus 3/sex/group for drug exposure assessment	0 (vehicle), 0.2 or 1.0 mg/kg/day (i.v., once daily) 5 days	0.2 and 1.0 mg/kg: No drug-related effects on mortality, clinical observations, body weight, hematology, coagulation, clinical chemistry, or urinalysis parameters. No organ weight, gross, or microscopic changes related to i.v. administration of RWJ-XXXXXX. NOAEL was 1.0 mg/kg/day.
4-Week repeated dose toxicity [53]	Rat 6/sex/group	0 (vehicle), 30, 100, 300 and 1000 mg/kg/day (Oral, once daily) 4 weeks	30 mg/kg: No adverse effects. 100 mg/kg: ↓Body weight gain and ↓food consumption (F); ↓ovary weights 300 mg/kg: Additional findings included ↓body weight gain and food consumption (M); ↑adipocytes in bone marrow (F). 1000 mg/kg: Additional findings included ↓ Hb (M); ↑adipocytes in bone marrow (M).
13-Week repeated dose toxicity study followed by a 5-week recovery study [54],[55]	Rat 18 for control and high-dose groups (6/sex/group retained for 5-week recovery) 12/sex/group for other dosage groups	0 (vehicle), 10, 30, 100, and 300 mg/day (Oral, once daily) 13 weeks	10 and 30 mg/kg: No adverse effects. 100 mg/kg: ↓Body weight gain and ↓food consumption (F); ↓reticulocyte count (M); ↓ovary weights; ↓lipid droplets in the hepatocytes (M); hypertrophy of centrilobular hepatocytes (M); ↑adipocytes in the bone marrow; a ↓ in hematopoietic cells in the bone marrow. 300 mg/kg: Additional findings include ↓RBC and Hb; ↓Hct (M); ↓reticulocyte count (F); ↓triglycerides (M); ↑relative kidney weight (F); hypertrophy of centrilobular hepatocytes (F); ↑apoptotic bodies in the acinar cells in the pancreas (F). All changes were reversible except for ↓ovary weights. Electron microscopic exam of formalin-fixed liver tissues indicated the hypertrophy of hepatocytes was related to slight proliferation of the smooth endoplasmic reticulum (SER).
13-Week dose-ranging study to select doses for a second rat carcino-genicity study [43]	Rat 10/sex/group (main study) and 10/sex/group for toxicokinetic study	0 (vehicle), 100, 300, 600 and 1000 mg/kg/day (Oral, once daily) 13 weeks	No unscheduled mortalities or treatment-related clinical signs. 100 mg/kg: ↓Body weight gains (F); slight ↓platelets (F); unremarkable clinical chemistry except for ↓thyroxine with no changes in thyroid histology; ↑heart weight; dose-related ↑adipocytes in the sternal bone marrow. 300 mg/kg: ↓RBC, Hb, Hct (F); slight ↓platelets (F); unremarkable clinical chemistry except for ↓thyroxine with no changes in thyroid histology;↑liver weights (F) with no gross or histopathologic correlates; ↑kidney weight (M); dose-related diffuse epithelial hypertrophy and multifocal tubular epithelial hyperplasia in kidneys; dose-related ↑adipocytes in the sternal bone marrow. 600 mg/kg: Additional findings included ↓body weight gains (F); ↑liver weights (M). 1000 mg/kg: Markedly ↓body weight gain (21%) (F) Induction of cytochrome P-450 isoforms in the liver was found (see Section 3.2.4.3.2). A NOAEL for toxicity was not established.

KEY: ↓ = decreased; ↑ = increased; F = females; M = males. Other abbreviations are defined on pp. 11-12.

Table X: Single and Multiple-Dose Toxicity Studies for RWJ-241947

Study Type	Species (N)	Route/ Duration	Dose	C_{max} (ng/mL)	AUC (ng·h/mL)	Results/Comments
Single-dose, range-finding	Rat (10) (2/group) 1 male 1 female	i.v. infusion over 10-20 minutes	20 mg/kg 40 mgkg 60 mgkg 90 mg/kg 180 mg/kg			Three males (180 mg/kg) died after receiving 75-80% of dose. Clinical observations during and for 1-2 hrs post dose included convulsions at ≥90 mg/kg, and salivation and respiratory distress at ≥40 mg/kg. Red urinary discharge observed within 2 hrs post dose (1 male in the 90 and 180 mg/kg groups). No lesions observed in gross pathology.
		i.v. infusion over 4 hrs. (femoral catheter)	90 mg/kg 180 mg/kg			Both rats in the 90-mg/kg group remained within normal limits. After ~3 hrs of dosing, both rats in the 180-mg/kg group exhibited ↓ activity, ↓ rate of respiration and ↑ salivation. At the end of the dosing period the condition of both rats had significantly declined. The male exhibited severe convulsions, labored breathing, prostration, cyanosis, hypothermia, ↑ salivation and died 2 hrs post dosing. The female exhibited severe convulsions, moderately ↓ activity, ataxia, ↓ respiration, and ↑ salivation, but its condition slightly improved 2 hrs post dosing and included head bobbing, ↓ activity, ↑ salivation ↓ respiratory rate and hunched posture. No significant findings observed in the gross pathology examination. NOAEL = 90 mg/kg over the 4 hr dosing period.
Single-dose, range-finding	Dog (3) 1 male 1 male 1 female	i.v. infusion (5mL/min over 7 min) and 0.33mL/min	80 mg/kg			One male dosed at 5mL/min exhibited clonic and tonic convulsions after ~1/3 of the intended 80 mg/kg dose was administered. Convulsions ceased after ~5 minutes and dog recovered. One male and 1 female (0.33mL/min) tolerated dosing much better; clinical observations included fine tremors, discolored emesis in the female and watery ocular discharge, ↑ licking and fecal abnormalities (soft, watery and/or mucoid) in both dogs.

Table X: Single and Multiple-Dose Toxicity Studies for RWJ-241947

Study Type	Species (N)	Route/ Duration	Dose	C_{max} (ng/mL)	AUC (ng·h/mL)	Results/Comments
Multiple-dose	Rat (128) Pre-cannulated 10/sex/group	4 hr i.v. infusion 1x/day for 2 weeks	0 mg/kg 20 mg/kg 40 mg/kg 90 mg/kg			Study terminated at 10 days due to occlusion of the infusion lines and septic complications from catheterization/infusion process. Infusion of 90 mg/kg associated with ↓ body weight and/or ↓ food consumption; therefore, NOAEL = 40 mg/kg. No opthamoloscopic findings. No evidence in clinical lab data of an effect of RWJ 68023-048. No histopathologic findings attributed to RWJ 68023.
Multiple-dose	Dog (24) 12 male 12 female	4 hr i.v. infusion 1x/day for 2 weeks	0 mgkg 10 mg/kg 30 mg/kg 80 mg/kg			One female (80 mg/kg group) experinced convulsions on Days 2 and 10 (C_{max} on Day 1 = 16158 ng/mL), moribundity/sacrifice on Day 13; compound-related changes included evidence of liver disease and aspiration pneumonia (likely cause of moribundity) and bilirubinuria. Animals in the 80-mg/kg group experienced hypoactivity, emesis, discolored/abnormal feces, and weight loss/poor appetite. No opthalomoscopic or ECG effects observed. One female (80 mg/kg) had elevations in alkaline phosphatase, ALT, total bilirubin values, and a slight ↑ in AST at Day 14; high urine volume and a ↓ in urinary solutes was further evidence of liver disease. ↑ liver weight observed in the 80 mg/kg group. Most animals in the 30 and 80 mg/kg groups exhibited ↑ hepatocellular and Kupffer cell pigmentation. ↑ or severity of thymic lymphoid depletion also seen in 80 mg/kg males and 30 and 80 mg/kg females. NOAEL = 10 mg/kg/day

Attachment 6: Sample Toxicology Tables (Continued)

Table 12: Genotoxicity Studies with RWJ-XXXXXX

Test [Reference]	Test system	RWJ-241947 Concentration/dose	Result
Bacterial reverse mutation test [77]	*Salmonella typhimurium*: TA98, TA1535, TA100, TA1537 *E. coli*: WP2 *uvrA*$^-$	Direct method and metabolic activation method: 100, 200, 500, 1000, 2000, 5000 µg/plate	Negative
Chromosomal aberration test [78]	Chinese hamster lung-derived fibroblast cell line	Direct method: 24hr 12.5, 25, 50, 100 µg/mL 48hr 7.5, 15, 30, 60 µg/mL Metabolic activation method (with or without S9mix) 6hr treatment + 18hr recovery 25, 50, 100, 125, 150, 175, 200 µg/mL	Negative Positive
Micronucleus test in mice [79]	Male ICR (Crj:CD-1, SPF) mice	0, 500, 1000, 2000 mg/kg, **SINGLE ORAL GAVAGE**	Negative
Rat unscheduled DNA synthesis test (hepatocyte) [80]	Male Fischer rats	0, 500, 1000, 2000 mg/kg, Single oral gavage	Negative

Attachment 7: Sample Toxicokinetic Tables

Table 11: Summary of Toxicokinetics and Exposure Ratios Based on Total Plasma Concentrations of RWJ-XXXXXX-000 in Male and Female Mice, Rats, Monkeys, and Pregnant Rabbits

Study (Sampling time)	Dose (mg/kg)	Dose Ratio [a]	Cmax (ng/mL)	Exposure Ratio; Cmax[a]	AUC(0-24) (ng•h/mL)	Exposure Ratio; AUC(0-24) [a]
13-week oral toxicity study in rats[b]						
Males (week 13)	10	11	5900	1.6	67500	1.0
	30	32	13200	3.5	152000	2.4
	100	106	14800	3.9	187000	2.9
	300	317	17600	4.7	249000	3.9
Females (week 13)	10	11	7300	1.9	62400	1.0
	30	32	12100	3.2	109000	1.7
	100	106	17700	4.7	133000	2.1
	300	317	21500	5.7	212000	3.3
13-week oral toxicity study in monkeys						
Males (day 84)	10	11	11700	3.1	225000	3.5
	30	32	17000	4.5	310000	4.8
	100	106	21300	5.7	397000	6.2
	300	317	32200	8.5	595000	9.2
Females (day 84)	10	11	12800	3.4	225000	3.5
	30	32	18900	5.0	346000	5.4
	100	106	34500	9.2	558000	8.7
	300	317	42500	11.3	736000	11.4
26-week oral toxicity study in rats[c]						
Males (day 182)	4	4	4300	1.1	67000	1.0
	20	21	9900	2.6	143000	2.2
	100	106	14100	3.7	225000	3.5
Females (day 182)	4	4	5300	1.4	39000	0.6
	20	21	5300	1.4	70200	1.1
	100	106	12600	3.3	128000	2.0
26-week oral toxicity study in monkeys[d]						
Males (week 25)	8	8	10200	2.7	197000	3.1
Males (week 25)	40	42	19900	5.3	387000	6.0
Males (week 13)	300 (150)[e]	317(159)	38600	10.2	728000	11.3
Females (week 25)	8	8	12200	3.2	235000	3.6
Females (week 25)	40	42	22600	6.0	424000	6.6
Females (week 25)	300 (150)[e]	317(159)	20300	5.4	311000	4.8

[a] Dose and exposure ratios are based upon clinical dose of 80 mg/day (0.945 mg/kg/day for 17 days), which gave a mean plasma C_{max} of 3768 ng/mL and a mean plasma AUC(0-24h) of 64391 ng*h/mL in male and female subjects (PHI-005 results).

[b] Reference 54.

[c] Reference 56.

[d] Reference 63.

[e] Dose changed from 300 mg/kg to 150 mg/kg during Week 15

Attachment 7: Sample Toxicokinetic Tables (Continued)

Table 22: Exposure Ratios Predicted for RWJ-zzzzz in Human Relative to Rat NOAEL Following 10 Daily Four-Hour I.V. Infusions of RWJ-ZZZZZ (40 mg/kg/day)

Human Dose (mg)	C_{max}		AUC	
45 min infusion	male	Female	male	female
8.7	154	101	1255	674
52	25.8	16.9	210	113
156	8.61	5.62	70.0	37.6

Note: All animal data are multiple dose [AUC (0-24h)].[16] The human data are from a predicted single-dose data set [AUC (0-∞)], based on interspecies scaling.

Exposure Ratio = $\frac{\text{AUC (animal)}}{\text{AUC (human)}}$

Table 23: Exposure Ratios Predicted for RWJ-zzzzz in Human Relative to Dog NOAEL Following 14 Daily Four-Hour I.V. Infusions of RWJ-ZZZZZ-048 (10 mg/kg/day)

Human Dose (mg)	C_{max}		AUC	
45 min infusion	male	female	male	female
8.7	23.8	19.2	107	90.2
52	3.98	3.21	17.9	15.1
156	1.33	1.07	5.98	5.03

Note: All animal data are multiple dose [AUC (0-24h)].[18] The human data are from a predicted single dose data set [AUC (0-∞)], based on interspecies scaling.

Exposure Ratio = $\frac{\text{AUC (animal)}}{\text{AUC (human)}}$

Attachment 8: Sample Clinical Study Design/Enrollment Tables

Table 13: Completed Clinical Studies of RWJ-XXXXXX (Continued)

Protocol No. (Country)	Study Design/Enrollment Status
PHI-005 Phase 1 (U.S.)	Open-label, randomized, parallel-group study to assess the safety and PK of three doses (40, 60, and 80 mg) of RWJ-XXXXXX in 30 healthy volunteers (5 males and 5 females per group). The urinary excretion of RWJ-XXXXXX metabolites and the urinary ratios of 6-hydroxycortisol to cortisol were also determined. On Day 1 and Days 8 through 17, subjects received single doses of either 40 mg, 60 mg, or 80 mg of RWJ-XXXXXX. No. Subjects Enrolled/Completed: 30/26 Treated with RWJ-XXXXXX: 30
PHI-006 Phase 1 (U.S.)	Open-label, randomized, parallel group, study in healthy volunteers (24 males and 24 females) to evaluate the effects of 40 mg or 80 mg of RWJ-XXXXXX on the PK of midazolam, thereby assessing the ability of RWJ-XXXXXX to induce cytochrome P-450 3A4. The effect of RWJ-XXXXXX on the protein-binding of midazolam was also studied. All subjects received 5 mg midazolam i.v. (one 2.5-mg injection followed by a second 2.5-mg injection 5 minutes later, each administered over 2 minutes) on Days 1, 10, and 21. Two hours prior to midazolam administration on Days 10 and 21, subjects also received either 40 mg or 80 mg of RWJ-XXXXXX. Subjects received RWJ-XXXXXX once daily on Days 8 through 21. Safety evaluations were also performed. No. Subjects Enrolled/Completed: 48/41 Treated with RWJ-XXXXXX: 42
PHI-007 Phase 1 (U.S.)	Open-label, randomized, parallel-group study in 48 healthy male and female volunteers to evaluate the effects of RWJ-XXXXXX and rosiglitazone on the PK of Glucotrol® glipizide. The primary objective was to assess the potential of RWJ-XXXXXX to induce cytochrome P-450 2C9. All subjects received 15 mg glipizide on Days 1, 10, and 21. Subjects (N=24) randomized to RWJ-XXXXXX received 80 mg of RWJ-XXXXXX once daily following breakfast on Days 8 through 21. Subjects randomized to rosiglitazone (N=24) received 4 mg of rosiglitazone twice daily (one 4-mg tablet following breakfast and one 4-mg tablet approximately 12 hours later) on Days 8 through 21. Safety evaluations were also performed. No. Subjects Enrolled/Completed: 48/43 Treated with RWJ-XXXXXX: 24
PHI-008 Phase 1 (U.K.)	Open-label, single oral-dose study in 6 healthy, male subjects. The objective was to elucidate metabolite structures and to determine the routes of excretion and PK of RWJ-XXXXXX and RWJ-XXXXXX metabolites in blood, plasma, urine, and feces following administration of a single 80-mg oral dose of $^{14[}$C] RWJ-XXXXXX. Blood samples were obtained at 26 time points following administration of the radiolabeled compound over a 22-day period. Urine and fecal samples were collected quantitatively for 504 hours post-dose. No. Subjects Enrolled/Completed: 6/6 Treated with RWJ-XXXXXX: 6
PHI-017 Phase 1 (U.S.)	Open-label, single-center study to evaluate the potential of RWJ-XXXXXX to alter the metabolism and/or PK of acetaminophen. Eighteen healthy adults (9 males and 9 females) received multiple daily 1000-mg doses of acetaminophen on Days 1, 2, 15, and 16, while single daily 80-mg doses of RWJ-XXXXXX were administered on Days 3-16. Blood samples were drawn for 24 hours after dosing on Days 2 and 16 to determine the effect of RWJ-XXXXXX on the PK of acetaminophen. Safety evaluations were also performed. No. Subjects Enrolled/Completed: 18/18 Treated with RWJ-XXXXXX: 18

RXXXXX and GEM Combination Therapy Trials

Study No. Country Start/Stop Dates	Study Objective/ Population	Phase/ Trial Design	No. Patients Planned/ Accrued	R115777 Dose Level and Schedule	Assessments
RXXXXXX-USA-4 USA 03 Nov 1998	***Objective:*** To determine the MTD, PK, and safety of RXXXXXX in combination with a fixed dose of GEM ***Population:*** **Part A*:*** Patients with advanced incurable cancer. **Part B**: Patients with NSCLC	Phase 1, single center, dose escalation trial	33/33	***Starting dose:*** RXXXXXX (100 mg BID, orally) + GEM (1000 mg/m^2, i.v. over 30 min) ***Duration of treatment:*** 28-day cycles (RXXXXXX, continuously; GEM, weekly for 3 weeks followed by 1 week of rest) ***Dosage:*** RXXXXXX (successive cohort dose escalation: 100-300 mg BID, orally for 28 days) + GEM (1000 mg/m^2, i.v. over 30 min each week for 3 weeks followed by 1 week of rest) Dose modifications of study drugs (interruption and/or reduction) based on occurrence of hematologic or non-hematologic toxicities	Safety (AEs, clinical lab tests, PE, vital signs, eye exam), efficacy (tumor status, ECOG-PS, FACT-G QOL), PK, and PD (PBL protein analysis)
RXXXXXX-INT-11 USA; Europe 04 Nov 1999	***Objective:*** To determine whether administration of RXXXXXX plus GEM improves median survival time by ≥36% when compared to that of GEM plus placebo. ***Population:*** Patients with pathologically confirmed, locally advanced, unresectable or metastatic, pancreatic adenocarcinoma.	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial.	688/688	***Starting dose:*** either RXXXXXX (200 mg BID, orally) or placebo + GEM (1000 mg/m^2, i.v. over 30 min) ***Duration of treatment*:** 7-day cycles ***Dosage:*** RXXXXXX (200 mg BID, orally) or placebo, continuously; GEM (1000 mg/m^2 i.v. over 30 min) each week for 7 weeks with 1week rest, followed by GEM weekly for 3 weeks with 1 week rest for the remainder of treatment Dose modifications of study drugs (interruption and/or reduction) based on occurrence of hematologic or non-hematologic toxicities	Safety (AEs, clinical lab tests, PE, vital signs, eye exam, ECG), efficacy (survival, PFS and RR), PK, DNA and ras mutation analysis

Attachment 9: Sample Clinical Pharmacokinetics Table

Table 17: Mean (SD) Plasma Pharmacokinetic Parameter Estimates of RWJ-XXXXXX Following Multiple Daily Oral Doses of RWJ-XXXXXX in Subjects with Type 2 Diabetes

Study No.	Dose	No. Subjects	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng.h/mL)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
DIAB-001	5 mg	7	350 (83)	3.0 (1.3)	6585 (1668)	43.0 (11.0)	8.73 (1.51)
	10 mg	8	630 (189)	2.4 (1.1)	11425 (3381)	38.0 (11.0)	10.6 (2.0)
	20 mg	6	1153 (170)	3.0 (1.1)	19878 (2493)	32.0 (14.0)	11.5 (1.7)
	40 mg	5	1800 (362)	2.4 (0.9)	31762 (7133)	28.4 (8.9)	15.3 (3.7)
PHI-002	40 mg	24	2130 (684)	2.8 (2.3)	36199 (11992)	33.8 (8.8)	13.6 (3.9)
PHI-003	40 mg	24	1994 (656)	3.4 (2.4)	34320 (14834)	31.6 (10.9)	15.1 (5.1)

Attachment 10: Sample Adverse Reaction Summary Table

Table X: Adverse Events (Excluding Endometrial Hyperplasia) Reported With A Subject Incidence of ≥5% in Any Treatment Group, Summarized by Body Systems and Preferred Terms
(1-Year Studies: Combined Data from Studies N93-072, C-101, and 102/103)

Body System Preferred Term	Continuous 1 mg E_2 (N=356) n (%)	Cyclophasic 1 mg E_2/ 30 µg NGM (N=360) n (%)	Cyclophasic 1 mg E_2/ 90 µg NGM (N=579) n (%)	Cyclophasic 1 mg E_2/ 180 µg NGM (N=362) n (%)	Continuous 2 mg E_2 (N=250) n (%)	Cyclophasic 2 mg E_2/ 30 µg NGM (N=49) n (%)	Cyclophasic 2 mg E_2/ 90 µg NGM (N=262) n (%)	Cyclophasic 2 mg E_2/ 180 µg NGM (N=474) n (%)	2 mg E_2/ 1 mg NETA Reference (N=216) n (%)	Total (N=2,908) n (%)
Reproductive disorders, female										
Breast Pain Female	43 (12)	65 (18)	92 (16)	61 (17)	47 (19)	2 (4)	57 (22)	129 (27)	54 (25)	550 (19)
Dysmenorrhea	46 (13)	47 (13)	48 (8)	61 (17)	40 (16)	4 (8)	31 (12)	60 (13)	12 (6)	349 (12)
Vaginitis	41 (12)	47 (13)	42 (7)	26 (7)	23 (9)	4 (8)	25 (10)	40 (8)	19 (9)	267 (9)
Vaginal Hemorrhage[a]	24 (7)	10 (3)	11 (2)	27 (7)	40 (16)	6 (12)	24 (9)	25 (5)	0	167 (6)
Intermenstrual Bleeding[a]	0	1 (<1)	41 (7)	1 (<1)	0	0	0	86 (18)	35 (16)	164 (6)
All Vaginal Bleeding[a]	24 (7)	11 (3)	52 (9)	28 (8)	40 (16)	6 (12)	24 (9)	111 (23)	35 (16)	331 (11)
Leukorrhea	20 (6)	18 (5)	15 (3)	7 (2)	15 (6)	1 (2)	9 (3)	12 (3)	15 (7)	112 (4)
Body as a whole-general disorders										
Back Pain	55 (15)	44 (12)	69 (12)	45 (12)	23 (9)	7 (14)	26 (10)	58 (12)	23 (11)	350(12)
Influenza-like Symptoms	36 (10)	41 (11)	64 (11)	19 (5)	13 (5)	7 (14)	13 (5)	38 (8)	24 (11)	255 (9)
Pain	29 (8)	23 (6)	37 (6)	10 (3)	9 (4)	3 (6)	10 (4)	31 (7)	22 (10)	174 (6)
Fatigue	14 (4)	18 (5)	32 (6)	20 (6)	9 (4)	4 (8)	13 (5)	24 (5)	7 (3)	141 (5)
Edema Generalized	12 (3)	23 (6)	17 (3)	10 (3)	10 (4)	1 (2)	8 (3)	21 (4)	8 (4)	110 (4)
Injury	18 (5)	19 (5)	9 (2)	16 (4)	7 (3)	1 (2)	6 (2)	3 (1)	0	79 (3)
Respiratory system disorders										
Upper Resp Tract Infection	111 (31)	99 (28)	121 (21)	78 (22)	43 (17)	10 (20)	45 (17)	45 (9)	10 (5)	562 (19)
Sinusitis	39 (11)	48 (13)	44 (8)	39 (11)	23 (9)	6 (12)	19 (7)	23 (5)	3 (1)	244 (8)
Pharyngitis	21 (6)	15 (4)	38 (7)	15 (4)	9 (4)	4 (8)	8 (3)	21 (4)	7 (3)	138 (5)
Bronchitis	7 (2)	25 (7)	22 (4)	19 (5)	3 (1)	0	3 (1)	11 (2)	11 (5)	101 (3)
Coughing	13 (4)	12 (3)	28 (v5)	9 (2)	3 (1)	2 (4)	2 (1)	11 (2)	17 (8)	97 (3)

[a] Vaginal bleeding was coded using the preferred term 'vaginal hemorrhage' in Studies N93-072 and 102/103 and using the term 'intermenstrual bleeding' in Study C-101. The category 'All Vaginal Bleeding,' which is not a WHOART preferred term, combines the results for bleeding coded as 'vaginal hemorrhage' and bleeding coded as 'intermenstrual bleeding.'

(Continued)

Attachment 11.1: Sample Serious Adverse Event Table (Compound that Completed Phase 3 of Development)

Table 10: Incidence of Treatment-Emergent Serious Adverse Events (Excluding Endometrial Hyperplasia)[a] Reported for More Than One Subject
(One Year Studies: Combined Data from Studies N93-072, C-101, and 102/103)

Body System Preferred Term	Continuous 1 mg E_2 (N=356) n (%)	Cyclophasic 1 mg E_2/ 30 µg NGM (N=360) n (%)	Cyclophasic 1 mg E_2/ 90 µg NGM (N=579) n (%)	Cyclophasic 1 mg E_2/ 180 µg NGM (N=362) n (%)	Continuous 2 mg E_2 (N=250) n (%)	Cyclophasic 2 mg E_2/ 30 µg NGM (N=49) n (%)	Cyclophasic 2 mg E_2/ 90 µg NGM (N=262) n (%)	Cyclophasic 2 mg E_2/ 180 µg NGM (N=474) n (%)	2 mg E_2/ 1 mg NETA Reference (N=216) n (%)	Total (N=2,908) n (%)
Reproductive disorders, female										
Vaginal Hemorrhage	1 (<1)	0	0	0	3 (1)	0	1 (<1)	0	0	5 (<1)
Uterine Disorder	0	0	0	0	1 (<1)	0	1 (<1)	0	0	2 (<1)
Neoplasms										
Breast Neoplasm Malignant	0	1 (<1)	1 (<1)	1 (<1)	0	1 (2)	0	1 (<1)	0	4 (<1)
Neoplasm NOS	1 (<1)	0	1 (<1)	0	1[c] (<1)	0	2[d] (<1)	0	0	4 (<1)
Breast Neoplasm Female[b]	2 (1)	0	0	0	0	0	0	1 (<1)	0	3 (<1)
Ovarian Cyst	2 (1)	0	1 (<1)	0	0	0	0	0	0	3 (<1)
Uterine Neoplasm[b]	0	1 (<1)	2 (<1)	0	0	0	0	0	0	3 (<1)
Basal Cell Carcinoma	0	1 (<1)	1 (<1)	0	0	0	0	0	0	2 (<1)
Carcinoma	0	0	1[e] (<1)	0	0	0	0	1[f] (<1)	0	2 (<1)
Cervical Uterine Polyp	0	0	0	0	0	0	2 (1)	0	0	2 (<1)
Uterine Fibroid	1 (<1)	0	0	0	0	0	1 (<1)	0	0	2 (<1)
Body as a whole – general disorders										
Injury	0	5 (1)	0	0	0	0	0	0	0	5 (<1)
Chest Pain	0	0	0	0	1 (<1)	0	0	3 (1)	0	4 (<1)
Back Pain	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	3 (<1)
Allergic Reaction	0	0	0	0	0	1 (2)	0	1 (<1)	0	2 (<1)
Musculoskeletal system disorders										
Bone Disorder	0	0	1 (<1)	0	0	0	0	0	2 (1)	3 (<1)
Fracture Pathological	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	0	3 (<1)
Arthralgia	0	0	1 (<1)	0	0	0	0	0	1 (<1)	2 (<1)
Myopathy	0	0	1 (<1)	0	0	1 (2)	0	0	0	2 (<1)
Liver and biliary system disorders										
Cholelithiasis	1 (<1)	1 (<1)	4 (1)	0	0	0	0	1 (<1)	0	7 (<1)
Cholecystitis	0	1 (<1)	1 (<1)	0	1 (<1)	0	0	1 (<1)	0	4 (<1)

[a] Although the initial (safety) readings of biopsies by one pathologist were reported as serious adverse events in some studies, reference is made to the more definitive efficacy readings (see Tables 1, 4, and 5.
[b] Non-malignant neoplasms.
[c] Colon cancer.
[d] Endometrial cancer and thyroid Hurthle cell neoplasm, both in Study 072.
[e] Pulmonary carcinoma.
[f] Breast cancer. Other cases of breast cancer were coded under breast neoplasm, malignant.

(Continued)

Attachment 11.2: Sample Serious Adverse Event Table (Compound in Phase 2 of Clinical Development)

Table 13: Serious Adverse Events Reported for Subjects Who Received Study Therapy in RWJ-XXXXXX Clinical Studies

Subject Sex/Age	Treatment (Daily)	Serious Adverse Event	Treatment Day of Onset[a]	Outcome	Relationship to Therapy[b]	Comment
Phase 1 Study PHI-005						
M/41	40 mg RWJ-XXXXXX	Psychosis (psychotic episode with agitation)	Day 16 or 17, hospitalized Day 18	Resolved with Tx by Day 34	Doubtful	Subject discontinued study drug 2 days early (at the time of the reported psychotic episode).
F/33	60 mg RWJ-XXXXXX	Drug exposure during pregnancy	See comment	Elective termination	Pregnancy not related	Pregnancy was diagnosed 5 days after study treatment was completed.
Phase 2a Study DIAB-001						
M/63	40 mg RWJ-XXXXXX	Myocardial infarction (anterior, no transmural development)	Day 16	Resolved with medication	Doubtful	Coronary atherosclerosis was newly reported at the time of the event. Study drug was discontinued.
M/52	20 mg RWJ-XXXXXX	Lymphangitis (toe infection)	Day 11	Resolved in 21 days with Tx	Unrelated	Hospitalization, surgery, and medication required. Study therapy temporarily interrupted.
F/69	10 mg RWJ-XXXXXX	Rectal carcinoma	Day 28 (end of study)	Surgery would be required	Unrelated	Diagnosed on biopsy as follow up to prior surgery for suspicious rectal cyst and rectal adenoma.
Phase 2a Study MCC-555-04						
M/67	Placebo	Cholecystitis (acute)	Day 10	Resolved	Unrelated	Subject treated with antibiotic.
Phase 2b Study DIAB-002						
M/63	Blinded[c] + metformin	Transient ischemic attack (left hemispheric)	Day 42	Symptoms resolved in 4 h	Possible	Study drug stopped for 2 days only. Concomitant therapy with clopidogrel was initiated.
M/45	Blinded[c] + metformin	Accidental injury (broken leg)	Day 74	Resolved in 40 days	Not related	Study drug stopped temporarily (3 days).
M/63	Blinded[c]	Myocardial infarction[d]	Day 44 (vague symptoms first reported on Day 28)	Symptoms resolved with treatment (see comment)	Not related	Angiography on Day 51 showed 95% obstruction of R coronary artery, and angioplasty and stent placement were performed. He was withdrawn from study therapy on Day 56 at Sponsor's request.

[a] Day 1 was the start of study drug (placebo or RWJ-XXXXXX) treatment.
[b] Relationship to study therapy as evaluated by the investigator.
[c] Blinded treatment could be placebo or 10, 20, 40, or 80 mg/day of RWJ-XXXXXX.
[d] Reported as expedited IND Safety Report, Manufacturer's Control No. JAOCAN2000001103.

Attachment 12: Sample Summary of Data and Guidance for Investigators Section

5. SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATORS

Description of RWJ-XXXXXX

RWJ-XXXXXXis a novel thiazolidinedione which is being studied as an antihyperglycemic agent for the treatment of Type 2 diabetes. The thiazolidinedione group of antidiabetic agents includes the marketed drugs rosiglitazone and pioglitazone.

RWJ-XXXXXX is a white to pale yellowish crystalline compound with a molecular weight of 381.42 daltons and an empirical formula of $C_{21}H_{16}FNO_3S$. It is being developed as a racemate.

RWJ-XXXXXX is available as white, film-coated tablets containing 10, 20, or 40 mg of RWJ-XXXXXX.

Pharmacology

In various animal models of Type 2 diabetes, RWJ-XXXXXX administration has been found to reduce elevated plasma glucose, HbA_{1C}, insulin, and triglyceride concentrations. RWJ-XXXXXX has been shown to bind to the peroxisome proliferator-activated receptor gamma (PPAR|) and to increase insulin sensitivity.

Pharmacokinetics

In clinical pharmacokinetic studies, absorption of orally-administered RWJ-XXXXXX was found to extend over a period of approximately 12 hours. The time to maximum plasma concentration (t_{max}) ranged from 3 or 4 hours at lower doses to 8 or 9 hours at higher doses. In combined data for all pharmacokinetic studies, there was a linear relationship between the dose of orally-administered RWJ-XXXXXX and C_{max} and between the dose and $AUC_{(0\text{-}24h \text{ or } 0\text{-}\Re)}$. The serum half-life ($t_{1/2}$) was generally in the range of 20 to 30 hours and, with repeated daily dosing, RWJ-XXXXXX concentrations achieved steady state in 5 to 7 days. In human plasma, 95% to 97% of RWJ-XXXXXX is bound to protein, mainly albumin.

The absolute bioavailability of orally-administered RWJ-XXXXXX in human subjects was found to be approximately 93%. The absorption of

Attachment 12: Sample Summary of Data and Guidance for Investigators Section (Continued)

RWJ-241947 is slightly greater under fed conditions (taken with a high-fat meal) than under fasted conditions.

No unchanged RWJ-XXXXXX is excreted in the urine. The following metabolites have been identified in human urine: M1 (O-desfluorobenzyl-RWJ-XXXXXX), M8 (a sulfate conjugate of M1), M9 (a glucuronide conjugate of M1), and M15 (a sulfate conjugate of RWJ-XXXXXX).

Pharmacodynamics/Efficacy

In normal subjects, exposure to RWJ-XXXXXX for up to 12 days was not associated with changes in plasma glucose, insulin or lipid levels. This is consistent with the results of studies where antidiabetic efficacy was only observed in animal models of Type 2 diabetes.

In a dose-ranging pilot study of subjects with Type 2 diabetes, median decreases in fasting plasma glucose following 28 days of treatment were found with 5-, 20-, and 40-mg/day doses of RWJ-XXXXXX; however, a dose-response relationship could not be established due to the small number of subjects in each treatment group and other factors related to study design.

Indications And Use

RWJ-XXXXXX is being developed for the treatment of hyperglycemia in patients with Type 2 diabetes mellitus whose hyperglycemia cannot be controlled by diet and exercise alone. It is expected that RWJ-XXXXXX will be investigated for use as a single agent and in combination with other orally acting antihyperglycemic drugs or insulin.

Contraindications

There is currently insufficient experimental evidence to determine the contraindications to RWJ-XXXXXX. However, RWJ-XXXXXX should not be administered to individuals with known hypersensitivity to thiazolidinediones.

RWJ-XXXXXX exerts its antihyperglycemic effect only in the presence of insulin. Therefore, RWJ-XXXXXX should not be used in patients with Type 1 diabetes not concurrently treated with insulin or used alone for the treatment of diabetic ketoacidosis.

Attachment 12: Sample Summary of Data and Guidance for Investigators Section (Continued)

Precautions

General

RWJ-XXXXXX is an investigational drug, with safety data in experimental animals, healthy male and female subjects, and a limited number of Type 2 diabetic patients. It is necessary that all subjects receiving RWJ-XXXXXX be closely followed by means of vital signs, body weight, plasma glucose concentrations, liver function tests, and other routine laboratory tests until sufficient experience is obtained to determine the safety of RWJ-XXXXXX.

Hypoglycemia

Hypoglycemia is not expected with use of RWJ-XXXXXX as monotherapy; however, hypoglycemia has been reported when other thiazolidinediones have been used in combination with sulfonylurea or insulin. The potential for hypoglycemia may also exist for RWJ-XXXXXX when it is used concomitantly with other agents that are known to have this effect.

Ovulation

Because RWJ-XXXXXX reduces insulin resistance, it is possible that reproductive-aged, anovulatory patients with insulin resistance could resume ovulation; therefore, adequate contraceptive measures should be used by women of childbearing potential who receive investigational RWJ XXXXXX.

In a 52-week toxicity study in monkeys, RWJ-XXXXXX was found to inhibit normal cycling and ovulation at an exposure ratio (based on plasma AUC values) that is 5 times the exposure women would receive at the highest anticipated clinical dose of 80 mg/day.

Effect on Ability to Drive and Use Machines

Because RWJ-XXXXXX lacks apparent effects on cognitive and psychomotor function, the use of RWJ-XXXXXX is not expected to affect the ability of patients to operate motor vehicles or machinery.

Drug Interactions

Pharmacodynamic Interactions

See *Hypoglycemia,* Precautions, General.

Attachment 12: Sample Summary of Data and Guidance for Investigators Section (Continued)

Pharmacokinetic Interactions

Results of a Phase 1 drug-drug interaction study with midazolam indicated that higher doses (i.e., 80 mg/day) of RWJ-XXXXXX induce CYP3A4, with no statistical evidence for induction at 40 mg/day. This induction may be characterized as mild. Nevertheless, it must be assumed that decreased efficacy of drugs metabolized by CYP3A4 may occur when they are used concomitantly with RWJ-XXXXXX.

RWJ-XXXXXX is highly bound (95.4% to 97.3%) to human plasma proteins. A potential therefore exists for RWJ-XXXXXX to displace other drugs that are also highly protein-bound. The concomitant administration of RWJ-XXXXXX with highly protein-bound drugs that have a narrow therapeutic range (e.g., coumarin) is therefore not recommended until the safety of such combinations has been established.

Carcinogenicity, Mutagenicity

Carcinogenicity studies of 104 weeks' duration have been conducted in the rat and mouse. In the rat, the highest dose studied (100 mg/kg/day) produced no observed adverse effects, and therefore the study is being repeated at doses that produce toxicity. In the mouse, an increased incidence of hemangiosarcoma was found in females at 10 and 30 mg/kg/day and in males at 30 mg/kg/day. At 30 mg/kg/day there was a higher incidence/severity of atrial thrombi, myocardial vacuolation, and cardiomyopathy, which were associated with increased mortality. Based on pharmacokinetic data from a 13-week mouse study and a human pharmacokinetic study, a dose of 30 mg/kg/day in the mouse represents approximately 5 to 7 times the exposure a patient would have at the highest anticipated clinical dose of 80 mg/day.

Four mutagenicity studies have been completed with RWJ-XXXXXX: (1) bacterial mutation, (2) in vivo-in vitro hepatocyte DNA repair, (3) in vitro chromosome aberration, and (4) bone marrow micronucleus test. With the exception of the in vitro chromosome aberration assay in which RWJ-XXXXXX was associated with an increase in structurally aberrant cells at cytotoxic dosages (≥175 μg/mL), RWJ-XXXXXX exhibited no genotoxic potential.

Attachment 12: Sample Summary of Data and Guidance for Investigators Section (Continued)

Acute and Subchronic Toxicity

RWJ-XXXXXX has little potential to produce acute toxicity. A single oral dose of 2000 mg/kg in rats and 1000 mg/kg in monkeys resulted in no clinical signs or gross postmortem changes.

The primary findings in the repeated dose toxicity studies involved the cardiovascular system and liver. Increased heart weight, lower red blood cell counts, and edema have been noted with RWJ-XXXXXX. These effects have been noted with other thiazolidinediones and have been attributed to drug-induced increased plasma volume. The predominant liver finding has been increased weight, related to hepatocyte hypertrophy. Increased adipocyte development/differentiation was frequently noted in the bone marrow as a manifestation of the pharmacologic activity of RWJ-XXXXXXas a PPARγ agonist. In a 52-week monkey study, RWJ-XXXXXX altered the menstrual cycle and inhibited ovulation.

RWJ-XXXXXX was evaluated, along with other thiazolidinediones, for effects on mouse bone marrow cell colony formation. Each of the tested compounds in this class showed some degree of colony formation inhibition, although RWJ-XXXXXX had the least inhibitory effect.

Antigenicity

Antigenicity tests using guinea pigs, mice and rats were negative.

Reproductive and Development Toxicity

In a combined fertility study in the rat, decreased fertility (decreased number of implants and live fetuses, and an increased index of postimplantation loss) was observed in the presence of maternal toxicity at the high dose of 300 mg/kg. A supplemental fertility study is being conducted to determine whether the decreased fertility observed in the first study was male or female mediated. No teratogenic effects were observed in rats at up to 300 mg/kg/day. At the highest dose studied (40 mg/kg/day) in an embryo-fetal development study in rabbits, 1.4% of fetuses per litter were affected with omphalocele. This incidence appeared to be higher than the historical background incidence. Taken together, the findings from nonclinical fertility and embryo-fetal toxicology studies suggest that women

Attachment 12: Sample Summary of Data and Guidance for Investigators Section (Continued)

of childbearing potential who receive RWJ-XXXXXX should use adequate contraception.

There are no adequate or well-controlled studies in pregnant women. RWJ-XXXXXX should not be used during pregnancy. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities as well as neonatal morbidity, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Lactation

It has not been determined whether RWJ-XXXXXX is secreted into human breast milk. The administration of RWJ-XXXXXX to nursing mothers is therefore not recommended.

Use In Elderly Patients

Only limited data have been obtained to date on the use of RWJ-XXXXXX in patients above the age of 65.

Use in Pediatrics

No data are available on the use of RWJ-XXXXXX in pediatric patients.

Use In Renal Dysfunction / Failure

Urinary excretion of the sulfated metabolite of M-1 accounts for up to 37% of the administered dose. However, no data are available on the effect of renal dysfunction/failure on the clearance of RWJ-XXXXXX, and therefore administration of RWJ-XXXXXX to patients with markedly compromised renal function is not recommended at this time outside of clinical trials specifically studying this population.

Adverse Reactions

In Phase 1 and 2 studies that have been completed and analyzed, adverse events reported most frequently during RWJ-XXXXXX treatment were headache and dizziness. As of August 1, 2001, 17 serious adverse event reports (not including three reports of pregnancy) had been received for

Attachment 12: Sample Summary of Data and Guidance for Investigators Section (Continued)

subjects treated with study drug in completed and ongoing studies. Reports (each representing one subject) for which the treatment is known to be RWJ-XXXXXX include psychosis, myocardial infarction, lymphangitis (toe infection) and rectal carcinoma. Reports for which the treatment remains blinded include transient ischemic attack, accidental injury, myocardial infarction, acute cholecystitis, chronic obstructive pulmonary disease with recurrent bronchitis, appendicitis, toe infection leading to limb amputation, coronary artery disease, vasovagal reaction, ovarian cancer, and bladder tumor (cancer), atrial fibrillation, and cervical intraepithelial neoplasia (CIN III). All of the events were evaluated by the investigators as either unrelated or of doubtful relationship to the study therapy except for the report of transient ischemic attack, which was evaluated as possibly related to therapy.

In the data available from short-term studies (treatment of 4 weeks or less), no trends have been observed for adverse changes in clinical laboratory tests, ECGs, vital signs, or body weight.

Cardiovascular Effects

Increased heart weight has been noted in dogs treated for 13 weeks with doses of 3 mg/kg/day, in rats treated for 26 weeks with doses of 100 mg/kg/day, and in monkeys treated for 52 weeks with doses of 100 mg/kg/day. In mice treated for 13 weeks, increased heart weight has been found at doses of 20 mg/kg/day, in mice treated for 13 weeks fine vacuolation of cardiomyocytes (correlating with mitochondrial swelling) has been observed at doses of 100 mg/kg/day, and myocardial hypertrophy has been observed at doses of 300 mg/kg/day.

CNS Effects

No CNS effects have been noted in the general pharmacology animal studies.

Other Effects

A general pharmacology screen showed a smooth muscle relaxing effect in vitro at high concentrations of RWJ-XXXXXX (10^{-5}M). However at the doses tested, no signs of a comparable effect were observed in vivo.

Attachment 12: Sample Summary of Data and Guidance for Investigators Section (Continued)

In a 26-week monkey oral toxicity study, slight edema (swollen eyelids/periorbital swelling) was noted in monkeys dosed at 40 mg/kg/day and higher.

Overdosage

No studies have been performed to determine a specific antidote to RWJ-XXXXXX. In cases of overdose, general supportive measures should be taken as appropriate.

Dosage And Administration

RWJ-XXXXXX should be administered orally as a film coated tablet.

The clinically effective dose of RWJ-XXXXXX has not yet been determined.

How Supplied

RWJ-XXXXXX is supplied as white, film coated tablets containing 10, 20, or 40 mg of RWJ-XXXXXX.