CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020606

TRADE NAME: Imodium Advanced Chewable Tablets

GENERIC NAME: Loperadmide HCL/Simethicone

SPONSOR: McNeil Consumer Products Company

APPROVAL DATE: 06/25/97

NDA 20-606

McNeil Consumer Products Company
Attention: Vivian Chester
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Chester:

Please refer to your new drug application dated July 28, 1995, received July 31, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets.

We acknowledge receipt of your submissions dated December 23, December 27, and December 31, 1996 and February 19, April 11, and June 20, 1997. The User Fee goal date for this application is June 30, 1997.

This new drug application provides for control of the symptoms of diarrhea plus bloating, pressure and cramps commonly referred to as gas.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on June 20, 1997. Accordingly, the application is approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

6-26-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-606
HFD-180/Div. files
HFD-180/CSO/B.Strongin
HFD-180/H.Gallo-Torres
HFD-180/J.Canchola
HFD-180/E.Duffy
HFD-180/A.Al-Hakim
HFD-720/W.J.Chen
HFD-002/ORM (with labeling)
HFD-103/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)
HFI-20/Press Office (with labeling)

Drafted by: BS/June 25, 1997/c:\wpfiles\n\20606706.0
Initialed by: L.Talarico/June 25, 1997
final: BS/June 25, 1997

BS/6-25-97

APPROVAL (AP)

NDA 20-606

McNeil Consumer Products Company
Attention: Vivian Chester
7050 Camp Hill Road
Fort Washington, PA 19034

JUL 23 1996

Dear Ms. Chester:

Please refer to your July 28, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets.

We acknowledge receipt of your amendments dated October 10, October 20, October 30, December 6, and December 14, 1995 and March 20, April 17, and April 25, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit a satisfactory response to our letter dated July 22, 1996 requesting additional chemistry information.

In addition, it will be necessary for you to submit final printed labeling (FPL) identical in content to the enclosed marked-up draft labeling. Please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
Telephone: (301) 443-0483

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:
Original NDA 20-606
HFD-180/Div. Files
HFD-2/M.Lumpkin
HFD-80
HFD-180/B.Strongin
HFD-180/J.Canchola
HFD-180/E.Duffy
HFD-180/A.Al-Hakim
HFD-720/M.Huque
HFD-720/W.J.Chen
HFD-870/L.Kaus
HFD-103/P.Botstein
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

BS/7-23-96

SF 7/23/96

drafted: BS/July 18, 1996/c:\wpfiles\n\20606607.0
r/d Initials: S.Fredd/July 23, 1996
Final: BS/July 23, 1996

APPROVABLE (AE)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

JUN 24 1997

Application Number: NDA 20-606

Name of Drug: Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets

Sponsor: McNeil Consumer Products Company

Material Reviewed

Submission Date(s): December 23, 1996

Receipt Date(s): December 26, 1996

Content: Revised Draft Labeling submitted in response to an AE letter

Background and Summary Description

NDA 20-606 was submitted July 28, 1995 for Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets for the control of the symptoms of diarrhea, including Traveler's Diarrhea, and associated gas symptoms including abdominal pain, bloating, and cramping. McNeil Consumer Products markets OTC loperamide in liquid (NDA 19-487) and caplet (NDA 19-860) dosage forms, while simethicone in a 500 mg maximum daily dose is an approved ingredient in the antiflautlent monograph. The application was approvable July 22, 1996 pending a complete response to a chemistry, manufacturing, and controls IR letter dated the same day and final printed labeling identical in content to the marked-up draft labeling attached to the action letter. A complete response to the AE letter was submitted December 27, 1996 and the user fee due date is June 30, 1997. Revised draft labeling submitted December 23, 1996 is the subject of this review. The Division of Over-the-Counter Drug Products (HFD-560) reviewed the labeling for format and content and compared it to the marked-up draft labeling attached to AE letter. The marked-up draft labeling attached to the AE letter, the new marked-up draft labeling, and HFD-560's review are attached, and their comments are reflected herein.

Review

I. Six Count Carton

A. Front Panel

1. The established names of the active ingredients, loperamide HCL/simethicone, are in the middle, below their pharmacologic categories, anti-diarrheal and anti-gas.

The format of the statement of identity was changed from that in the marked-up draft labeling. The new format does not comply with 21 CFR 201.61 which states that the established name of the drug (loperamide HCL/simethicone) should be followed by the pharmacologic category or principal intended action (anti-diarrheal/anti-gas). This can be corrected by moving the established names above the pharmacologic categories.

2. The established names, loperamide HCL/simethicone, appear to be smaller than in the marked-up draft labeling.

Per 21 CFR 201.10(g)(2), the established names , "...shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined.". The firm should enlarge the established names to at least the size used in the marked-up draft attached to the approvable letter.

3. The sentence in the lower left corner has been revised. In the marked up draft labeling attached to the July 22, 1996 AE letter the sentence read:

> "CONTROLS THE SYMPTOMS OF DIARRHEA AND ASSOCIATED GAS SYMPTOMS."

In the draft labeling submitted December 23, 1996, it read:

> "Control The Symptoms of Diarrhea Plus:
>
> - o Cramps
> - o Bloating
> - o _____ Pressure"

The symptom "gas pain" must be deleted since it is not consistent with the language in the July, 1996 marked-up draft labeling and the antiflatulent monograph.

HFD-560 contends that the word "cramps" might be confused with "menstrual cramps" by consumers and recommends that the sentence, "Controls the symptoms of diarrhea, plus bloating, pressure, and cramps commonly referred to as gas.", be used in its place. Alternatively, if the firm would rather use a bulleted format, HFD-560 proposed:

"Controls The Symptoms of Diarrhea Plus:

- **Gas cramps**
- **Gas bloating**
- **Gas pressure".**

It is this reviewers contention that, since this sentence is directly below the pharmacologic category, anti-gas, the word "cramps" is not likely to be confused with "menstrual cramps". The same point was made at the October 17, 1996 labeling meeting with the firm and is reflected on page 3 of the minutes to that meeting. Dr. Hugo Gallo-Torres recommended that the firm change to the sentence format and new text recommended by HFD-560 which is consistent with language used in the marked-up draft labeling.

4. The word "new" is included in the top left corner.

   The word "new" may only be used for six months.

5. The phrase, "Patented - Only from the makers of Imodium A-D" is included in the top section.

   HFD-560 recommends moving the word "patented" to the second bullet in the top section of the back panel. The bullet would read, "This unique, patented formula is only from the makers of Imodium A-D.".

   Since it is stated in the minutes to the October 17, 1996 labeling meeting with the firm that, "The word 'patented' may be included on the front panel of the Imodium Advanced labeling as requested.", I suggest we do not recommend moving this word.

B. Back Panel

1. The pharmacologic categories and established names are placed in the middle of the top section under the trade name, Imodium Advanced.

   As recommended in comment I.A.1, the established names should be placed to the left of the pharmacologic categories.

2. A proposed rule to establish a standardized format for the labeling of all over-the-counter drugs was published in Volume 62 of the Federal Register on page 9,024 on February 27, 1997.

Per HFD-560, if the proposed rule becomes finalized the following changes would be required:

a. The following headings in this order should be the first information appearing on the back or side panel: "Active Ingredients", "Purposes", "Uses", "Warnings", and "Directions".

b. The heading "Active Ingredients" should be followed by "in each (insert dosage form)".

c. The hyphens in the words anti-diarrheal and anti-gas under the heading "Purpose" should be deleted to conform with the OTC monographs.

d. Under the heading "Warnings", the phrase "Ask a Doctor before Use" should replace "Do Not Use Without Asking a Doctor".

Since this is only a proposed rule, it is not fair to the firm or consistent with the recommendations included in the marked-up draft labeling to require these changes. This reviewer suggests recommending these changes if the proposed rule becomes final.

3. Three bulleted phrases are included in the top section, above the "Active Ingredients", "Uses", "Directions", "Dosage" and "Warnings" headings.

HFD-560 recommends moving the bullets to a side panel so that the "Warnings" and "Directions" headings can be made larger and more legible.

Similar sized and bolded bullets were included in the same location of the back panel in the July, 1996 marked-up draft without a request that they be moved. Similar sized and bolded bullets as well as "Warnings" and "Directions" sections unbolded and with a small font are also included in the back panel of the approved labeling for NDA 19-860, Imodium A-D Caplets. Requiring the firm to move the bullets would be inconsistent with the marked-up draft labeling and the approved labeling for Imodium A-D Caplets and is not recommended.

4. The word "new" is included in the first bullet in the top section.

The word "new" may only be used for six months.

5. The phrase, "[redacted]" is included in the first bullet in the top section and under the heading, "Uses".

As stated in I.A.3., this phrase is inconsistent with the language recommended in the marked-up draft labeling and the antiflatulent monograph and it should be revised to be consistent with the language used on the front panel.

6. The following directions are included in the middle section:

"See the chart below for the correct dose:

- o Chew the first dose and take with water after the first loose stool.
- o If needed, chew the next dose and take with water after the next loose stool.
- o Drink plenty of clear liquids to prevent dehydration."

HFD-560 had the following comments regarding this section:

a. "Although the chart indicated the maximum number of doses per day, the directions do not make it clear to the consumer that more than one 'next dose' can be taken. This could be corrected by adding an 's' on dose in 'next dose'.

b. It is not clear whether one should swallow the chewable tablet with water or just chew it and after the next loose stool, drink water. We recommend changing the sequence of the sentences to read:

- **o After the first loose stool, chew the first dose followed by water.**
- **o If needed, after the next loose stool, chew the next dose followed by water. This step may be repeated 1 time if needed."**

The firm's language was recommended in a July 11, 1996 HFD-560 labeling review. Requiring further revision presents the firm with a "moving target". In addition, the previous language is clear and more accurate since children 9 - 11 years may take four "next

doses" before reaching the maximum daily dose. This reviewer agrees with comment "a", but recommends against comment "b".

7. The statement, "Children under 6 years old (up to 47 lbs): Consult a physician. Not intended for use in children under 6 years old." is included under the "Dosage" heading.

   HFD-560 considers this statement redundant and possibly confusing and recommends changing it to, "Children under 6 years of age: Ask a doctor.". The firm's language is consistent with the July, 1996 marked-up draft labeling and with language in the approved labeling for Imodium A-D Caplets. Requiring a change is not recommended.

8. The phrase, "You also have a high fever (over 101°)" is included under the "Warnings" heading.

   The word "also" should be deleted.

C. Top and Bottom Panels

1. See comments I.A.1. and I.A.2. above.

2. A 1-800 number for the product is suggested.

II. Blister Backing

The labeling for the blister backing is adequate.

III. Two Count Pouch

See all comments above.

Conclusions

The recommendations stated above have been incorporated into marked up draft labeling to accompany the action letter.

Brian Strongin
Consumer Safety Officer

Carrie L. Tolentino MD 6-24-97

cc:
Original
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/L.Talarico, M.D.

draft: BS/April 9, 1997/c:\wpfiles\n\20606704.0
r/d Initials:
final:

CSO REVIEW
ATTACHMENTS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-606

Name of Drug: Imodium Advanced (loperamide/simethicone) Chewable Tablets

Sponsor: McNeil Consumer Products Company

NOV 14 1995

Material Reviewed

Submission Date(s): July 28, 1995

Receipt Date(s): July 31, 1995

Background and Summary Description: This application was submitted for the control of the symptoms of diarrhea, including Traveler's Diarrhea, and associated gas symptoms including abdominal pain, bloating and cramping. The sponsor is requesting approval for over-the-counter use.

This application contains four clinical studies in support of efficacy. The studies, which include a pilot study and three pivotal studies, are double-blind, placebo controlled and utilize a factorial design. They were designed to compare the efficacy of the loperamide/simethicone combination product with either component alone in relieving diarrhea and/or gas-related symptoms.

Loperamide capsules have been approved for prescription use since December 28, 1976 under the tradename Imodium, and Imodium A-D liquid was approved for over-the-counter use on March 1, 1988. I have included data about the various prescription and over-the-counter loperamide products in the table below.

NDA #	BRAND NAME	ACTION DATE/TYPE	Rx/OTC	INDICATION
17-694	Imodium 2mg Capsules	12/28/76 Approval	Rx	Acute diarrhea, chronic diarrhea with IBD
19-487	Imodium A-D Liquid	3/1/88 Approval	OTC	Diarrhea, Traveler's Diarrhea
19-860	Imodium A-D Caplets	11/22/89 Approval	OTC	Diarrhea, Traveler's Diarrhea

Simethicone is the subject of the Final Monograph for Antiflatulent Products for Over-the-Counter Human Use in 21 CFR 332.

Review

Filing Issues

1. Case report tabulations for adequate and well controlled studies, as described on page 20 of the February 1987 edition of the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications", could not be located. The completed form FDA 356H did not indicate that case report tabulations were included in the application, and these could not be identified in a comprehensive search of the volumes. In addition, they were

not indicated in the indices to either the NDA or final reports for the pivotal studies.

2. English translation of case report forms, as described on page 21 of the above Guideline and 21 CFR 314.50(g)(2), could not be located. The translation was not listed in the index to the NDA, nor could it be located in the volume containing case report forms.

Conclusions

A 45-day planning/filing meeting was held on September 18, 1995. A refuse-to-file letter was sent on September 20, 1995 citing the above deficiencies. Note: In an October 11, 1995 response to our refusal to file letter, the firm provided the locations of the case report tabulations, and the English translation of the case report forms. The firm also agreed to reformat the case report tabulations such that data was provided on an individual patient basis as opposed to categorization by other variables (i.e. demographic data, physical exam, previous meds). The firm agreed to provide the reformatted tables by October 27, 1995.

Brian Strongin
Consumer Safety Officer

cc:

Original
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/SFredd

draft: BS/October 13, 1995/c:\wpfiles\reviews\20606510.0
r/d Initials: B.Strongin/October 13, 1995,October 24, 1995
K.Johnson/October 16, 1995, November 6, 1995
S.Fredd/November 9, 1995
final: BS/November 9, 1995

11/14/95

CSO REVIEW

McNEIL

McNEIL CONSUMER PRODUCTS COMPANY, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034-2299 (215) 233-7000

APR 11 1997

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® Advanced Chewable Tablets
NDA 20-606
Amendment No. 10

Dear Dr. Fredd:

The purpose of this amendment is to update the patent information for IMODIUM® Advanced Chewable Tablets. On March 18, 1997, US Patent No. 5,612,054 covering the composition of the drug product was issued. The general patent information and patent declaration required for New Drug Applications under 21 USC 355 (b) or (c) are attached. This is the second patent that has issued for this product. The required patent information and patent declaration for US Patent No. 5,248,505 covering the method of use of the product were submitted to this NDA with the original filing on July 28, 1995.

Should you have any questions, please contact Janet A. Uetz at (215) 233-8368 or me at (215) 233-7010.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Vice President, Regulatory Affairs

cc: B. Strongin (HFD-180)
p:\jau133

13.0 PATENT INFORMATION

1. General

   a. Patent Number and Expiration Date
   5,612,054 / September 28, 2010

   b. Type of Patent
   Drug Product

   c. Name of Patent Owner
   McNeil-PPC, Inc.

   d. US Agent
   McNeil-PPC, Inc.

2. Declaration (for formulation, composition, or method of use patents)

   The undersigned declares that Patent No. 5,612,054 covers the formulation, composition, and/or method of use of Loperamide HCl/Simethicone Chewable Tablets. This product is submitted for approval in this new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act.

   Name Bernard F. Plantz

   Bernard F. Plantz

   Title Senior Patent Attorney

   Date 4/9/97

13.0 PATENT INFORMATION
21 USC 355 (b) or (c)

13.0 PATENT INFORMATION

1. General

   a. Patent Number and Expiration Date
   5,248,505/September 28,2010

   b. Type of Patent
   Method of Use

   c. Name of Patent Owner
   McNeil-PPC, Inc.

   d. US Agent
   McNeil-PPC, Inc.

2. Declaration (for formulation, composition, or method of use patents)

The undersigned declares that Patent No. 5,248,505 covers the formulation, composition, and/or method of use of Loperamide HCl/Simethicone Chewable Tablets. This product is submitted for approval in this new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act.

Name Bernard F. Plantz
Bernard F. Plantz

Title Senior Patent Attorney

Date 7-21-95

EXCLUSIVITY SUMMARY for NDA # 20-606 SUPPL # NA

Trade Name Imodium Advanced Chewable Tablets
Generic Name loperamide HCL/simethicone
Applicant Name McNeil Consumer Products HFD- 180

Approval Date June 25, 1997

JUN 26 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-487 IMODIUM A-D LIQUID

NDA # 19-860 IMODIUM A-D CAPLETS

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_X_/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

   _____

   _____

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   YES /___/ NO /_X_/

   (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 92-202

Investigation #2, Study # 92-209

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /__/	NO /_X_/
Investigation #2	YES /__/	NO /_X_/
Investigation #3	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /__/	NO /_X_/
Investigation #2	YES /__/	NO /_X_/
Investigation #3	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # 92-202

Investigation #_, Study # 92-209

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /_X_/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 !

YES /__/ Explain _____ ! NO /__/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /_X_/

If yes, explain: _____

Brian Strongin 6/25/97
Signature Date
Title: Project Manager

[signature] 6-25-97
Signature of Division Director Date
Acting

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-606 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF D-180 Trade and generic names/dosage form: Imodium Advanced (loperamide/~~simethicone) Chewable Tabs~~ Action: (AP) AE NA

Applicant McNeil Consumer Products Company Therapeutic Class 4,7 S

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application DIARRHEA/GAS (For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Brian Strongin/Project Manager
Signature of Preparer and Title

6/25/97
Date

cc: Orig NDA/PLA/PMA # 20-606
HF D-180 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

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15.0 CERTIFICATION STATEMENTS

15.0 CERTIFICATION STATEMENTS

DEBARMENT CERTIFICATION

McNeil Consumer Products Company certifies that it did not and will not use in any capacity the services of any person debarred under subsection 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act (21 USC 335a and 335b) in connection with this New Drug Application.

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PENTIUM CHIP CERTIFICATION

McNeil Consumer Products Company certifies that no computer with a flawed Pentium chip was used in the analysis of any data submitted in this New Drug Application.

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-606
Date of Submission:	07-28-95
Date Received at CDER:	07-31-95
Date Received at HFD-180:	08-01-95
Date Assigned to MO:	08-07-95
Date of Filing Decision:	08-18-95
Date MOR Completed:	04-23-96

APR 29 1996

Applicant: McNeil Consumer Products Company
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Name of Drug: Fixed Drug Combination: Loperamide HCl + Simethicone
USAN: Loperamide HCl
USP: Simethicone
Trade: Imodium® Advanced Chewable Tablet
Chemical: Loperamide HCl= 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinedinebutyramine monohydrochloride

Simethicone= mixture of α-(trimethylsillyl)-ω-methylpoly[oxy(di-Methylsilylene)] and silicon dioxide

Dosage Form: Chewable tablet

Category: Antidiarrheal

Formulation: Loperamide HCl 2mg + Simethicone 125mg per tablet:

Ingredients	mg/Tablet
Simethicone(	
Simethicone USP	
Sorbitol NF	
Dextrates NF	
Tribasic Ca phosphate NF	
Loperamide HCl	
Loperamide HCl USP	
Dextrates NF	
Flavor,	
Sodium saccharin USP	
Stearic acid NF	
Tribasic Ca phosphate NF	

Proposed Clinical Indications: "*Controls the symptoms of diarrhea, including Traveler's Diarrhea, and associated gas symptoms including abdominal pain, bloating and cramping*".

Dosage and Route of Administration: p.o., as follows:

Adult and Children (12 years and older): Take two tablets after the first loose bowel movement and 1 tablet after each subsequent loose bowel movement buts no more than 4 tablets a day for no more than 2 days.

Children 9-11 years (60-95 lbs): Take 1 tablet after the first loose bowel movement and ½ tablet after each subsequent loose bowel movement but no more than 3 tablets a day for no more than 2 days.

Children under 6 years old (up to 47 lbs: Consult a physician. Not intended for use in children under 6 years old.

Related IND: [redacted]

NDA: 19-487: Loperamide HCl liquid, OTC; McNeil; Approved on 03-01-88.

19-860: Loperamide HCl caplets, OTC; McNeil; Approved on 11-22-89.

Manufacturing, and Controls: Chemistry review assigned to John J. Gibbs, Ph.D.

Pharmacology: Review assigned to Jasti B. Choudary, Ph.D.

Clinical Background: Loperamide HCl, a synthetic piperidine opioid, was approved in the USA as an antidiarrheal prescription drug in oral dosages up to 16 mg/day in 1977. Subsequently in 1988 it was made available as an antidiarrheal OTC drug in dosages up to 8 mg/day for 2 days. In 1991 its use was also approved for the symptomatic relief of traveler's diarrhea.

Simethicone, a silicon dioxide complex, is a defoaming compound, and it is available in the USA as an OTC antiflatulent drug in divided daily oral dosages up to 500 mg/day.

Acute nonspecific diarrhea is a common self-limiting condition, that despite its morbidity can be managed symptomatically. It is often associated with gas-related symptoms such as abdominal pain or cramps, abdominal distension, flatulence, nausea, and vomiting

The applicant planned and performed 3 clinical pivotal studies to evaluate the efficacy and safety of a fixed combination of Loperamide HCl and Simethicone in the symptomatic relief of acute nonspecific diarrhea, and the efficacy and safety of Loperamide alone in the relief of gas pain or cramps associated with acute diarrhea.

In support of the proposed clinical indications, the applicant submitted for review the reports of 3 pivotal, controlled clinical studies performed under protocols 92-202, 92-209, and 93-333. In addition, the applicant also submitted for review the report of a clinical pharmacokinetics study performed under protocol 94-428, and a report of a pilot study, performed under protocol 89-950.

Controlled Clinical Studies

■ 1. Protocol 92-202. A single center, 2 x 2 factorial, randomized, double-blind, placebo controlled, parallel clinical study to evaluate the efficacy and safety of a fixed combination of Loperamide and Simethicone, Loperamide alone, Simethicone alone, and placebo, given p.o. for 48 hours, in the treatment of acute nonspecific diarrhea, associated with gas-related abdominal symptoms, and additionally, the efficacy of Loperamide alone in the relief of diarrhea-associated gas pain or cramps.

The study was performed under the direction of Esteban Ortiz Pavon, M.D. in Acapulco, Guerrero, Mexico, from 08/93 to 12/94.

The original protocol was to be a multicenter study involving 120 subjects per treatment group with a total sample size of 480 patients. The sample size estimation was based on previous pilot clinical data derived from related studies, assuming the detection of a significant difference of 7 hours between treatment group means, an $\alpha=.05$, a $1-\beta=.80$, and 2-tailed tests.

Patient inclusion criteria were to include male and female subjects, 18 years of age or older with **acute diarrhea, and onset of illness less than 48 hours, accompanied by moderately severe gas-related abdominal pain, cramps, pressure, or bloating.** These subjects were to have **a minimum of 3 unformed stools within 24 hours prior to entry** into the study. An **unformed stool was** defined as **a watery or soft stool.** Female patients were to be menopausal, or else be on an effective anticonceptive treatment.

Criteria for patient exclusion were to comprise severe diarrheal illness requiring hospitalization, parenteral hydration or antibiotic treatment; patients with blood or pus in stools, orthostatic hypotension, inability to take fluids and medication by the oral route, hypersensitivity to **Loperamide or Simethicone**; a recent history of therapy with antibiotics or antimicrobials that interfere with bacterial intestinal flora; or antidiarrheal or promotility drugs or antiflatulents, such as opiates, adsorbents, antimotility drugs, anticholinergics, bismuth salts, metoclopramide, domperidone, cisapride, **Simethicone**, or activated charcoal; analgesic therapy; pregnant women, nursing mothers, or women with menstrual or pelvic discomfort; and previous participation in the study.

Patients were not to take other antidiarrheal, promotility, antiflatulent, antacid, analgesic, or antibiotic drugs while in the study. In addition, patients were to be advised not to consume alcoholic and carbonated beverages, non-potable water, and food and beverages containing milk or milk products.

Baseline observations were to include medical history, physical examination, vital signs, weight, **onset of diarrheal illness, number of unformed stools in the previous 24 hours, time of last stool and its consistency, and the intensity of the gas-related abdominal discomfort in the preceding hour.**

Selected patients were to be randomized in blocks of 12, with 3 patients per treatment cell. Patients were to record in their diaries abdominal symptoms and the number and characteristics of bowel movements during the 48 hours of the study.

Treatments were to comprise the following 4 cells:

8 chewable tablets, each containing 0mg Loperamide HCl, and 125mg Simethicone;

8 chewable tablets, each containing 2mg Loperamide HCl, and 0mg Simethicone;

8 chewable tablets, each containing 2mg Loperamide HCl, and 125mg Simethicone;

8 chewable tablets, each containing 0mg Loperamide HCl, and 0mg Simethicone.

Patients were to chew thoroughly and swallow the initial dose of two tablets under the supervision of study personnel, and to chew and swallow one tablet only after each unformed stool, without exceeding 4 tablets in any 24-hour period, during 2 days.

Subjects were to record in their diaries during 48 hours, **the time and quantity of medication taken, time of bowel movements and consistency of stools, such as formed (hard or normal), or unformed (soft or watery), and the intensity of gas-related abdominal discomfort.** Furthermore, subjects were to **record the intensity of gas-related abdominal symptoms every hour during the first 8 hours of study, and at 12, 24, 36, NS 48 hours, and at each evening and morning during the study, using a scale of 0=absent, 1=mild, 2=moderate, 3=moderately-severe, and 4=severe.**

After completion of the study, and within 72 hours of entry, subjects were to return for a second visit to return their diaries and unused study medication. At 48 hours or at the time of discontinuation from the study, **patients were to record the time for complete relief of diarrhea, and the time for complete relief of gas-related abdominal discomfort. In addition, subjects were to record their evaluation of treatment efficacy in the relief of gas-related abdominal symptoms and diarrhea, on a scale of 0=poor, 1=fair, 2=good, 3=very good, and 4=excellent.**

The primary efficacy endpoints were to be the relief of diarrhea, as determined by the time to the last unformed stool, and time to complete relief of gas-related abdominal discomfort. **Use of *rescue medications* for treatment failures, were to be at the discretion of the investigator.**

Survival analysis was to be applied to primary endpoints. Rescued patients were to be censored. Differences from baseline for maximum symptom intensity were to be analyzed by ANOVA with investigator and drug as factors in the model. Symptom intensity ratings during the first 8 hours of treatment, could be stratified and analyzed by repeated measures ANOVA.

*Assessment of the efficacy of **Loperamide alone** in the relief of gas-related pain or cramps was to be done.* Frequency of unformed stools in each of the 12-hour intervals was to be analyzed by repeated measures ANOVA, stratified by stool frequency at baseline. Global effectiveness for overall illness, diarrhea, and abdominal discomfort was to be analyzed by ANOVA.

An interim analysis might be done when half of the sample size had been entered, to assess the model sensitivity to distinguish between drug treatments and placebo, and to decide if the study should be terminated or not. **The efficacy endpoints to be analyzed were the time to complete relief of gas-related abdominal discomfort, and the time to the last unformed stool, with a calculation of the conditional probability that the differences between treatment groups will reach statistical significance when the trial is completed.**

The results of the interim analysis were not to be disclosed to the investigators and monitors involved. **No adjustments to α were to be made because the intent of the interim analysis was to determine the sensitivity of the model only.**

Drug safety was to be determined by the proportion of drug adverse reactions. These proportions were to be compared statistically.

Results

Interim Analysis

A sample of 199 patients had been randomized to treatments. Of these, the applicant excluded 9 patients from analysis **[Table 1]**.

Table 1. Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Included in an Interim Analysis to Determine if Loperamide+Simethicone, or Its Components Could be Distinguished From Placebo. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

Treatment	Eligible Patients	Ineligible Patients	TOTAL
1	49	1	50
2	46	2	48
3	48	3	51
Placebo	47	3	50
TOTAL	190	9	199

Six(6) patients were excluded from analysis because they took more than 5 tablets in 24 hours, **3 patients** took one dose with no unformed stool occurrence, and **1 patient** failed to take a dose after an unformed stool. Two **rescued** patients were not excluded.

There were no significant differences at baseline between treatment groups in demographic characteristics, onset of diarrhea, abdominal discomfort, or abdominal pain **[Table 2]**.

Table 2. Demographic and Baseline Data of Patients with Acute Diarrhea and Gas-Related Abdominal Symptoms, Randomized to Treatment with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

Baseline Data	TREATMENT 1 (N=50)	2 (N=48)	3 (N=51)	Placebo (N=50)	TOTAL	p
Sex						.3448
Male	20	24	24	29	97	
Female	30	24	27	21	102	
TOTAL	50	48	51	50	199	
Race						.5332
White	49	47	51	50	197	
Black	1	1	0	0	2	
Onset Illness(h)						
Mean	20.8	20.9	19.7	20.6	20.5	.9176
Median	21.9	21.3	20.0	21.1	21.0	
Range						
Unformed Stools Prior 24h						
Mean	5.5	5.6	5.5	5.6	5.5	.8893
Median	5.0	5.5	5.0	5.5	5.0	
Range						
Abd Discomfort						
Mod-Severe	49	46	50	49	194	.5560
Severe	1	2	1	0	4	
Gas Pain/Cramps						
Mod-Severe	50	46	50	50	196	.3903
Severe	0	2	1	0	3	

➤ **Endpoints:**

• **Time to Complete Relief of Gas-Related Abdominal Discomfort:** Data were analyzed by **survival analysis.** Patients who did not have complete relief were considered censored. Comparison of survival curves by **Log-rank and Wilcoxon tests** indicated that the median time(h) to complete relief of abdominal discomfort, and the proportion of patients who did not experienced relief, were significantly different between placebo and treatments 1-3 **[Table 3]**.

Table 3. Time(h) to Complete Relief of Gas-Related Abdominal Discomfort in 199 Adult Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

Treatment	Median Time (h) Complete Relief	Percent Without Relief
1	5.2	2.0
2	36.0	28.3
3	21.2	6.2
Placebo	48.0	55.3
Log-rank, p	.0001	
Wilcoxon, p	.0001	

Pairwise comparisons of treatments showed that treatments were significantly different from each other [Table 4].

Table 4. Comparison of Time(h) to Complete Relief of Abdominal Discomfort in 199 Adult Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

		P*, vs			
Statistic	Treatment	1	2	3	Placebo
Log-rank	1		.0001	.0001	.0001
	2			.0188	.0025
	3				.0001
	Placebo				
Wilcoxon	1		.0001	.0001	.0001
	2			.0392	.0026
	3				.0001
	Placebo				

*No α adjustment for multiple comparisons

• Time(h) to Last Unformed Stool: Two definitions, A and B, not included in the protocol, were analyzed:

Definition A= The elapsed time from initial dose to:

- the time of the last unformed stool where only unformed stools are subsequently reported, or
- the beginning of a 24-hour period without stools following unformed stools, or
- the end of the period of observation if unformed stools continue throughout the study.

Any unformed stool occurring after a 24-hour stool-free period, is considered a different episode, and it is ignored.

Definition B= The elapsed time from the initial dose to the time of the last unformed stool where only formed stools or no stools are subsequently reported.

Survival analysis by log-rank (Mantel-Haenszel) and generalized Wilcoxon tests, indicated that for both definitions, A and B, the median time(h) to the last unformed stool was significantly different among treatment groups [Table 5].

Table 5. Median Time(h) to Last Unformed Stool in 199 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

	Definition A			Definition B		
	Stool Category			Stool Category		
Treatment	3-5	≥6	All	3-5	≥6	All
1	6.5	5.0	6.0	7.1	7.0	7.0
2	19.5	9.7	11.5	19.5	10.5	12.0
3	33.5	42.2	35.6	33.5	42.2	35.6
Placebo	36.5	46.0	46.0	36.5	46.0	39.0
Log-rank, p	.0001	.0001	.0001	.0001	.0001	.0001
Wilcoxon, p	.0001	.0001	.0001	.0001	.0001	.0001

Pairwise comparisons of median times(h) between treatments, showed that treatments 1 and 2 were significantly different from treatment 3 and placebo. In addition, treatment 3 was not significantly different from placebo [Table 6].

Table 6. Comparison of Median Time(h) to Last Unformed Stool in 199 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

			P*, vs			
Statistic	Treatment		1	2	3	Placebo
				Definition A		
	1	A		.0328	.0001	.0001
Log-rank	2	B			.0001	.0001
	3	C				.0870
	Placebo	CD				
	1	A		.0122	.0001	.0001
Wilcoxon	2	B			.0001	.0001
	3	C				.2132
	Placebo	CD				
				Definition B		
	1	A		.0626	.0001	.0001
Log-rank	2	AB			.0001	.0001
	3	C				.1877
	Placebo	CD				
	1	A		.0266	.0001	.0001
Wilcoxon	2	B			.0001	.0001
	3	C				.3752
	Placebo	CD				

*No adjustment for multiple comparisons; Single letter=Not significantly different at $\alpha \leq .05$

• **Maximum Intensity of Gas Pain/Cramps:** The maximum intensity of gas pain/cramps was analyzed during the first 8 hours of treatment as the change from baseline, using repeated measures ANOVA. Patients who did not have or did not rate their baseline gas pain, and those patients with more than two missing points were excluded from analysis.

The least squares means of gas pain intensity differences from baseline during the first 8 hours of treatment, were greater for treatment 1 and treatment 3 compared to treatment 2 and placebo, and for treatment 2 compared to placebo [Table 7].

Table 7. Mean Intensity of Gas Pain/Cramps During the First 8 Hours of Treatment in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo During 48 Hours. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

	Treatment Hour							
Treatment	1	2	3	4	5	6	7	8
1	.02	.55	1.17	1.67	1.94	2.21	2.34	2.49
2	.02	.09	.27	.42	.49	.67	.80	.94
3	.00	.21	.57	.83	1.06	1.40	1.58	1.77
Placebo	.00	.02	.06	.15	.25	.34	.47	.53

Pairwise comparison of treatments indicated that treatment 1 was significantly better than placebo, treatment 2, and treatment 3 in decreasing the severity of gas pain/cramps from the second or third hour of dosing. Moreover, treatment 3 was significantly better than placebo and treatment 2 from the third or fourth hour of dosing. No significant difference between treatment 2 and placebo was evident until the eighth hour of treatment [Table 8].

Table 8. Comparison of Differences From Baseline of Gas Pain/Cramps Intensity During the First 8 Hours of Dosing in 199 Adult Patients with acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

	P* at Indicated Dosing Hour							
Comparison	1	2	3	4	5	6	7	8
Treatment 1 vs Placebo	.9098	.0030	.0001	.0001	.0001	.0001	.0001	.0001
Treatment 2 vs Placebo	.9039	.6918	.2493	.1509	.1892	.0731	.0717	.0271
Treatment 3 vs Placebo	1.000	.2882	.0051	.0002	.0001	.0001	.0001	.0001
Treatment 1 vs 2	.9921	.0109	.0001	.0001	.0001	.0001	.0001	.0001
Treatment 1 vs 3	.9093	.0541	.0009	.0001	.0001	.0001	.0001	.0001
Treatment 2 vs 3	.9034	.5141	.1053	.0241	.0019	.0001	.0001	.0001

*Unadjusted for multiple comparisons

➤ Adverse Events: No adverse events were reported.

➤ Probability of Statistical Significance at the End of the Study: Considering the two endpoints, e.g., time to complete relief of gas-related abdominal discomfort, and time to complete relief of diarrhea, assuming an estimated sample size of 480 patients, and an eligibility rate similar to that of the 199 patients evaluated, treatments 1, 2, and 3 could yield a significant difference for the time to complete relief of abdominal discomfort when compared with placebo. In contrast, treatments 1 and 2, but not treatment 3, could yield a significant difference compared with placebo for the time to the last unformed stool, using both definition A and B [Table 9].

Table 9. Probability of Statistical Significance at the End of the Study Between Loperamide and Simethicone, Alone and in Combination, and Placebo in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort. NDA 20-606. Protocol 92-202: Interim Analysis. (Applicant's Table)

Variable (h)	Treatment	Δ from Placebo	Probability of Significance
Time to Complete Relief of Abdominal Discomfort	1	28.7	1.000
	2	8.9	.994
	3	16.7	1.000
Time to Last Unformed Stool, Definition A	1	27.0	1.000
	2	21.3	1.000
	3	.6	.062
Time to Last Unformed Stool, Definition B	1	25.2	1.000
	2	20.1	1.000
	3	.082	.028

Applicant's Conclusions: "Based on these analyses, the model appears to be sensitive in separating the active treatments from placebo. Therefore no changes will be made to the study".

Reviewer's Conclusions: Results from the **interim analysis** showed that the coded active treatments could be distinguished from placebo treatment. However, the question still remains weather or not the level of significance should be readjusted, and the sample size recalculated.

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Results From the Completed Clinical Study

A total of 483 patients were enrolled in the study. Of these, 124 patients took the combination of Loperamide plus Simethicone, 123 patients took Loperamide alone, 123 patients took Simethicone alone, and 123 took placebo [Table 10].

Table 10. Demographic and Baseline Variables of Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours.

Variable	Loperamide+ Simethicone (N=124)	Loperamide (N=122)	Simethicone (N=123)	Placebo (N=122)	TOTAL (N=491)	p
Sex						.3470
Male	55	65	58	66	244	
Female	69	57	65	56	247	
Race						.8730
White	123	121	123	122	489	
Black	1	1	0	0	2	
Age (y)						.4715
Mean±SD	28.9	30.3	29.4	29.9	29.6	
Range						
Onset Ill (h)						
Mean±	18.9	17.0	17.7	18.1	18.0	.4602
Median	18.5	16.0	17.8	17.7	17.5	
Range						
Unformed Stools Prior 24h						
Mean±	4.9	4.8	4.9	5.0	4.9	.7909
Median	5.0	5.0	5.0	5.0	5.0	
Range						
Abd Discomfort						
Mean	3.17	3.05	3.04	3.02	3.07	
Missing	0	0	0	1	1	
Mod-Severe	103	116	118	119	456	
Severe	21	6	5	2	34	
Gas Pain/Cramps						
Mean	3.16	3.04	3.04	3.02	3.07	
Missing	0	0	0	0	0	
Mod-Severe	104	117	118	120	459	
Severe	20	5	5	2	32	
Gas Pressure/ Bloating						
Mean	3.17	3.03	3.03	3.02	3.06	
Missing	2	0	1	0	3	
Mode-Severe	101	118	118	120	457	
Severe	21	4	4	2	31	

Of the 491 patients entered in the study, 2 patients (#77 Loperamide, and #107 placebo), were excluded by the applicant from the efficacy evaluation in the intent-to-treat analysis, leaving a subset of 491 patients. In addition, 25 patients were also excluded by the applicant from efficacy evaluation in the per protocol analysis, leaving a subset of 468 patients [Table 11].

TABLE 11. Patient Subsets Analyzed for Efficacy By the Applicant in the Intent-To-Treat and Per Protocol Analyses. NDA 20-606: Protocol 92-202. (MO's Table)

Treatment Group	Entered	Intent-To-Treat Excluded	Intent-To-Treat Analyzed	Per Protocol Excluded	Per Protocol Analyzed
Loperamide+ Simethicone	124	0	124	2	122
Loperamide	123	1	122	4	119
Simethicone	123	0	123	9	114
Placebo	123	1	122	10	113
TOTAL	493	2	491	25	468

Thirty-eight(38) patients discontinued the study before the end of the 48-hour study period, because of the use of rescue medication, or the symptoms resolved, concomitant illness, use of NSAIDs or antibiotics, or because the patient decided to discontinue [Table 12]. These patients were excluded from some analyses by the applicant.

Table 12. Study Discontinuation of Adults Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606: Protocol 92-202. (MO's Table)

Reason for Discontinuation	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo	TOTAL
Use of rescue medication	0	1	10	11	22
Symptoms resolved	4	3	0	0	7
Concomitant illness	0	0	1	2	3
Patient's decision	0	1	0	2	3
Use of NSAIDs	1	1	0	0	2
Use of antibiotic	1	0	0	0	1
TOTAL	6	6	11	15	38

Seventy-four percent(74%) of the patients in the intent-to-treat subset, had 3 to 5 unformed stools within 24 hours of randomization to treatment, compared with 26% of subjects who had 6 or more unformed stools [Table 13].

Table 13. Baseline Frequency of Unformed Stools in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table, modified by MO)

Stool Category	No. Stools	Loperamide+ Simethicone (N=124)	Loperamide (N=122)	Simethicone (N=123)	Placebo (N=122)	TOTAL (N=491)
1	3-5	95	91	91	86	363(74)
2	≥6	29	31	32	36	128(26)

Efficacy Analysis

As mentioned in the review of the protocol, the primary efficacy endpoint for the relief of diarrhea was the time to the last unformed stool, whereas that for the relief of gas-related symptoms was the time to complete relief of gas-related abdominal discomfort.

In addition, the following secondary efficacy endpoints were analyzed:

- Time to first unformed stool;
- Number of unformed stools;
- Time to complete relief of diarrhea;
- Maximum intensity of gas-related abdominal discomfort, including overall, gas pain/bloating, and gas pressure/bloating; and
- End of study patient's evaluation of overall illness, diarrhea, and abdominal discomfort relief.

The applicant performed both intent-to-treat and per protocol analyses.

Intent-to-Treat Analysis

- Primary Efficacy Endpoints:

- Time to Last Unformed Stool (TTLUS): Time when objective signs of diarrhea have stopped. Two(2) definitions A and B, not included in the protocol, were applied in the analysis:

Definition A= For patients who completed the study, and for patients who discontinued the study because the diarrhea resolved, TTLUS equaled the time from the initial dose to:

- the last unformed stool, where only formed stools or no stools were subsequently reported, or
- the start of a 24-hour period without stooling, following unformed stools.

Definition B= For patients who completed the study, and for patients who discontinued the study because the diarrhea resolved, TTLUS was the time from the initial dose to:

- the last unformed stool, where only formed stools or no stools were subsequently reported.

Unformed stools occurring after a 24-hour stool-free period, were considered as a different episode, and were ignored.

If no unformed stools were observed, TTLUS was zero. When treatment was discontinued for reasons other than resolution of diarrhea, TTLUS was censored at the time of discontinuation (hours from initial dose).

Data were analyzed by survival analysis. Comparison of the survival curves by the Log-rank (Mantel-Haenszel) and generalized Wilcoxon statistic, showed that *the median survival time (h)for the combination of Loperamide plus Simethicone was significantly shorter than the median survival time for Loperamide alone, Simethicone alone, and placebo for both definitions and stools categories* [Table 14].

Table 14. Median Time(h) to Last Unformed Stool in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Tables, modified by MO)

	Definition A			Definition B		
	Stool Category			Stool Category		
Treatment	3-5	≥6	Both	3-5	≥6	Both
Loperamide+ Simethicone	11.2	7.0	9.5	11.5	7.5	9.7
Loperamide	25.0	11.0	22.9	25.0	12.0	23.4
Simethicone	31.3	35.6	32.4	31.3	35.6	32.5
Placebo	36.5	46.0	38.8	36.6	46.0	39.0
Log-rank, p	.0001	.0001	.0001	.0001	.0001	.0001
Wilcoxon, p	.0001	.0001	.0001	.0001	.0001	.0001

Pairwise comparisons indicated that *the combination of Loperamide+Simethicone was significantly better than placebo and Simethicone alone in decreasing the median survival time(h) to the last unformed stool, regardless of the definition and stool category at baseline. For definitions A and B, the combination was significantly better than Loperamide alone only for stool category 1 (3-5 unformed stools at baseline). In addition, Loperamide alone was significantly better than placebo for both definitions and both stool categories* [Table 15].

Table 15. Comparison of Median Time(h) to Last Unformed Stool in Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Baseline Stools/ Statistic	P*, Loperamide+Simethicone vs Loperamide	P*, Loperamide+Simethicone vs Simethicone	P*, Loperamide+Simethicone vs Placebo	Loperamide vs Placebo
		Definition A		
3-5				
Log-rank	.0003	.0001	.0001	.0001
Wilcoxon	.0001	.0001	.0001	.0001
≥6				
Log-rank	.1769	.0001	.0001	.0001
Wilcoxon	.1301	.0001	.0001	.0001
Both				
Log-Rank	.0001	.0001	.0001	.0001
Wilcoxon	.0001	.0001	.0001	.0001
		Definition B		
3-5				
Log-rank	.0003	.0001	.0001	.0001
Wilcoxon	.0001	.0001	.0001	.0001
≥6				
Log-rank	.1776	.0001	.0001	.0001
Wilcoxon	.1571	.0001	.0001	.0001
Both				
Log-rank	.0002	.0001	.0001	.0001
Wilcoxon	.0001	.0001	.0001	.0001

*Unadjusted for multiple comparisons

For both stool frequency definitions, A and B, the cumulative percentages of patients with last unformed stool, 36 hours after the initial dose, was 91%, 81%, 58%, and 38% for the combination, Loperamide alone, Simethicone alone, and placebo, respectively [Table 16].

Table 16. Cumulative Percentages of Adult Patients with Last Unformed Stool After Initial Dose of Loperamide and Simethicone, Alone and in Combination, or Placebo. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

	Percentage of Patients at Indicated Hour												
Treatment	0	4	8	12	16	20	24	28	32	36	40	44	48
						Definition A							
Loperamide+ Simethicone	15	28	46	55	59	62	71	85	88	91	91	93	100
Loperamide	4	15	22	35	39	42	53	70	76	81	82	84	100
Simethicone	0	0	2	4	6	9	17	31	45	58	66	71	100
Placebo	0	3	3	5	5	6	8	18	28	38	46	50	100
						Definition B							
Loperamide+ Simethicone	14	26	44	54	58	60	69	84	87	91	92	93	100
Loperamide	4	14	21	34	38	41	52	69	76	81	82	84	100
Simethicone	0	0	2	4	6	9	17	30	45	59	67	71	100
Placebo	0	2	2	6	6	7	8	17	27	37	45	49	100

• **Time to Complete Relief of Gas-Related Abdominal Discomfort:** Data were analyzed by survival analysis. Patients who did not have complete relief within 48 hours were censored and assigned a time of 48 hours.

The median survival time(h) for complete relief of abdomina discomfort was significantly **shorter for the combination compared with its components, or placebo [Table 17].**

Table 17. Time(h) to Complete Relief of Gas-Related Abdominal Discomfort in Adult Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo For 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Treatment	Median Time(h)
Loperamide+ Simethicone	12
Loperamide	42
Simethicone	21
Placebo	48
Log-rank, p	.0001
Wilcoxon, p	.0001

Pairwise comparisons of treatments indicated that *the combination of Loperamide plus Simethicone was significantly better than its components and placebo in the complete relief of gas-related abdominal discomfort. In addition, Loperamide alone was significantly better than placebo in the complete relief of these symptoms* **[Table 18].**

Table 18. Comparisons of Time(h) to Complete Relief of Gas-Related Abdominal Discomfort in Adult Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

	P*, Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
Log-rank	.0001	.0001	.0001	.0001
Wilcoxon	.0001	.0001	.0001	.0001

*Unadjusted for multiple comparisons

The cumulative percentages of patients with complete relief of gas-related abdominal discomfort are shown in **Table 19.** ***The combination of Loperamide plus Simethicone yielded higher percentages of patients with complete relief than its components and placebo, at each time interval. In addition, Simethicone alone produced higher rates than Loperamide alone and placebo.***

Table 19. Cumulative Percentages of Adult Patients with "Complete Relief of Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

	Percentage of Patients at Indicated Hour												
Treatment	0	4	8	12	16	20	24	28	32	36	40	44	48
Loperamide+ Simethicone	0	13	41	52	60	68	81	85	85	89	92	93	94
Loperamide	0	2	7	11	11	16	32	34	34	44	46	59	69
Simethicone	0	2	25	34	37	46	62	64	64	68	74	75	90
Placebo	0	0	3	6	7	7	10	11	13	17	23	26	39

■ Secondary Efficacy Endpoints:

• Time(h) to First Unformed Stool (TTFUS): Time from initial dose to first unformed bowel movement, occurring ≥30 minutes after the initial dose:

Survival median time to first unformed stool was significantly greater for the Loperamide+Simethicone combination than for its components and placebo [Table 20].

Table 20. Time(h) to First Unformed Stool in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

	Median Time(h) After Initial Dose Baseline Stools		
Treatment	3-5	≥6	Both
Loperamide+ Simethicone	4.58	5.00	5.00
Loperamide	3.33	5.50	3.50
Simethicone	3.25	2.12	3.00
Placebo	3.50	2.50	3.00
Log-rank, p	.0001	.0001	.0001
Wilcoxon, p	.0003	.0001	.0001

Pairwise comparison of treatments indicated that *the combination of Loperamide plus Simethicone was significantly better than Loperamide alone in the 3-5 stool frequency, but not in the ≥6 stools frequency. In addition, the combination was significantly better than Simethicone alone and placebo in both stool categories combined. Loperamide alone was significantly better than placebo for both stool categories combined, and also for the ≥6 stool category* [Table 21].

Table 21. Comparison of Time(h) to First Unformed Stool in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. Applicant's Table)

Baseline Stools/ Statistic	P*, Loperamide+Simethicone vs Loperamide	Simethicone	Placebo	Loperamide vs Placebo
3-5				
Log-rank	.0001	.0001	.0001	.5366
Wilcoxon	.0005	.0001	.0004	.9497
≥6				
Log-rank	.5381	.0003	.0001	.0001
Wilcoxon	.5640	.0002	.0001	.0007
Both				
Log-rank	.0006	.0001	.0001	.0036
Wilcoxon	.0012	.0001	.0001	.0368

*Unadjusted for multiple comparisons

• Number of Unformed Stools: The number of unformed stools in each 12-hour period was utilized to compare treatments in a 3 factor repeated measures ANOVA, including treatment, baseline stool category, and period. Results from this analysis showed a significant treatment x baseline stool category interaction over time [Table 22].

Table 22. Summary of Repeated Measures ANOVA of Number of Unformed Stools in Adult Patients with Acute Nonspecific Diarrhea, and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Factor	P
Drug	.0001
Baseline Stool Category	.2327
Drug x Baseline Stool Category	.0001
Period*	.0001
Period x Drug*	.0001
Period x Baseline Stool Category*	.0334
Period x Drug x Baseline Stool Category*	.0236

*df adjusted with Greenhouse-Geiser epsilon

Pairwise comparison of treatments within each baseline stool category, indicated that patients on the loperamide+Simethicone combination had significantly fewer unformed stools than patients on Simethicone alone and placebo, in both stool categories. In addition, patients in the 3-5 baseline stool category and on the Loperamide+Simethicone combinantion, had significantly fewer unformed stools during the first and third 12-hour periods, than patients on Loperamide [Table 23].

Patients on Loperamide alone had significantly less unformed stools than patients on placebo in all the 12-hours periods, irrespective of baseline stool categories.

Table 23. Comparison of Number of Unformed Stools per 12-Hour Periods in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Stool Category	Time(h)	P*, Loperamide+Simethicone vs Loperamide	P*, Loperamide+Simethicone vs Simethicone	P*, Loperamide+Simethicone vs Placebo	P*, Loperamide vs Placebo
	0-12	.0050	<.0001	<.0001	<.0003
3-5	12-24	.0764	.0001	<.0001	<.0001
	24-36	.0139	<.0001	<.0001	<.0001
	36-48	.0872	.0001	<.0001	<.0001
	0-12	.1693	<.0001	<.0001	<.0001
≥6	12-24	.3114	<.0001	<.0001	.0005
	24-36	.6760	<.0001	<.0001	<.0001
	36-48	.9076	.0018	<.0001	<.0001
	0-12	.0099	<.0001	<.0001	<.0001
Both	12-24	.0793	<.0001	<.0001	<.0001
	24-36	.1143	<.0001	<.0001	<.0001
	36-48	.3443	<.0001	<.0001	<.0001

*Unadjusted for multiple comparisons

• Time to Complete Relief of Diarrhea: These data were analyzed by survival analysis. Patients who did not have complete relief of diarrhea within 48 hours, were considered censored at 48h.

Comparison of median survival times(h) by log-rank and generalized Wilcoxon tests, showed a significant difference between the fixed combination of Loperamide and Simethicone and its components, and placebo, regardless of the baseline stool category [Table 24].

Table 24. Median Time(h) to Complete Relief of Diarrhea in Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Semithicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Treatment	Baseline Stool Category 3-5	≥6	Both
Loperamide+ Simethicone	23.5	21.5	23.1
Loperamide	33.0	26.0	31.0
Simethicone	44.0	48.0	45.3
Placebo	48.0	48.0	48.0
Log-rank, p	.0001	.0001	.0001
Wilcoxon, p	.0001	.0001	.0001

Pairwise comparisons of treatments indicated that the combination of Loperamide plus Simethicone, was significantly better than its components and placebo in the complete relief of diarrhea. However, the combination was not significantly better than Loperamide alone in patients with 6 or more unformed stools at baseline. In addition, Loperamide alone was significantly better than placebo in all the baseline stool categories [Table 25].

Table 25. Comparison of Time(h) to Complete Relief of Diarrhea in Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Baseline Stools/ Statistic	P*, Loperamide+Simethicone vs Loperamide	Loperamide+Simethicone vs Simethicone	Loperamide+Simethicone vs Placebo	Loperamide vs Placebo
3-5				
Log-rank	.0001	.0001	.0001	.0001
Wilcoxon	.0001	.0001	.0001	.0001
≥6				
Log-rank	.1099	.0001	.0001	.0001
Wilcoxon	.0738	.0001	.0001	.0001
Both				
Log-rank	.0001	.0001	.0001	.0001
Wilcoxon	.0001	.0001	.0001	.0001

*Unadjusted for multiple comparisons

The cumulative percentage of patients with complete relief of diarrhea was progressively greater for the Loperamide+Simethicone combination than for the components alone and placebo, at each 12-hour period [Table 26].

Table 26. Percentage of Patients with Complete Relief of Diarrhea Among Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

	Percentage of Patients at Indicated Hour												
Treatment	0	4	8	12	16	20	24	28	32	36	40	44	48
Loperamide+ Simethicone	0	6	17	27	28	36	52	64	77	84	85	90	93
Loperamide	0	0	4	10	11	11	27	43	51	63	65	75	84
Simethicone	0	0	0	1	1	1	6	13	24	30	37	43	66
Placebo	0	1	2	2	2	2	4	6	7	15	20	28	44

- **Intensity (severity) of Gas-Related Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating:**

Intensity changes from baseline at time point intervals were analyzed by repeated measures ANOVA. Patients with two missing values, or those who did not rate the initial discomfort intensity, or did not have any gas-related symptoms at entry, were excluded form analysis.

In the 0-8 hour period, there was clear improvement of overall abdominal discomfort, gas pain/cramps, and gas pressure/bloating in favor of the loperamide+Simethicone combination over its components and placebo, from hour 3 to 8. Simethicone appeared to be better than Loperamide alone and placebo in the relief of these symptoms from hour 4 to 8 [Table 27].

Table 27. Mean Differences From Baseline of Gas-Related Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating Severity in the First 8 Hours of Dosing with Loperamide and Simethicone, Alone and in Combination, or Placebo to Adult Patients with Acute Nonspecific Diarrhea. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Period 0-8 Hour	Loperamide+ Simethicone (N=124)	Loperamide (N=121)	Simethicone (N=123)	Placebo (N=121)
		Overall Abdominal Discomfort		
1	.05	.02	.02	.02
2	.27	.06	.10	.02
3	.65	.15	.29	.06
4	1.03	.23	.48	.12
5	1.38	.28	.76	.20
6	1.71	.42	1.13	.30
7	1.98	.61	1.39	.38
8	2.25	.72	1.62	.48
		Gas Pain/Cramps		
1	.05	.02	.02	.02
2	.28	.05	.11	.02
3	.62	.14	.30	.06
4	1.01	.22	.48	.12
5	1.37	.27	.76	.21
6	1.70	.42	1.13	.31
7	1.96	.61	1.39	.40
8	2.24	.71	1.63	.47
		Gas Pressure/Bloating		
1	.05	.01	.01	.02
2	.27	.04	.09	.02
3	.60	.13	.28	.06
4	.97	.21	.47	.12
5	1.35	.26	.74	.21
6	1.69	.41	1.12	.32
7	1.93	.61	1.38	.39
8	2.23	.70	1.64	.48

Pairwise treatment comparisons, during the first 8 hours of dosing, showed that *the combination of Loperamide plus Simethicone was significantly better than placebo and Loperamide alone from hour 3 through 8 in relieving the intensity of all 3 variables of gas-related symptoms. In addition, the combination was significantly better than Simethicone alone from hour 3 through 8. Loperamide alone was significantly better than placebo from hour 7 through 8 for the 3 variables* [Table 28].

Table 28. Comparison of Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating Severity in Adult Patients with Acute Diarrhea, In the First 8 Hours of Dosing with Loperamide and Simethicone, Alone and in Combination, or Placebo. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

	P*, Loperamide+Simethicone vs			Loperamide
Time(h)	Loperamide	Simethicone	Placebo	vs Placebo
		Overall Abdominal Discomfort		
1	.8245	.7559	.7590	.9327
2	.0293	.0752	.0111	.7197
3	<.0001	.0002	<.0001	.3753
4	<.0001	<.0001	<.0001	.2673
5	<.0001	<.0001	<.0001	.4510
6	<.0001	<.0001	<.0001	.2090
7	<.0001	<.0001	<.0001	.0215
8	<.0001	<.0001	<.0001	.0138
		Gas Pain/Cramps		
1	.7425	.7394	.7409	.9989
2	.0200	.0790	.0091	.7812
3	<.0001	.0008	<.0001	.4171
4	<.0001	<.0001	<.0001	.2982
5	<.0001	<.0001	<.0001	.5446
6	<.0001	<.0001	<.0001	.2630
7	<.0001	<.0001	<.0001	.0315
8	<.0001	<.0001	<.0001	.0138
		Gas Pressure/Bloating		
1	.6745	.6734	.7359	.9335
2	.0203	.0679	.0118	.8471
3	<.0001	.0012	<.0001	.4678
4	<.0001	<.0001	<.0001	.3396
5	<.0001	<.0001	<.0001	.6026
6	<.0001	<.0001	<.0001	.3316
7	<.0001	<.0001	<.0001	.0255
8	<.0001	<.0001	<.0001	.0296

Changes from baseline of the intensity of gas-related abdominal discomfort, gas pain/cramps, and gas pressure/bloating after the first 8 hours of treatment was analyzed by ANOVA, using initial severity and treatment as factors.

Pairwise comparisons of treatments indicated that the combination *of Loperamide plus Simethicone was significantly better than Loperamide alone and placebo in decreasing the severity of gas-related symptoms at all time points. The combination was also significantly better than Simethicone, except in the second morning and at the end of the study. Loperamide was significantly better than placebo at all time points* [Table 28].

Table 28. Comparison of Mean Differences From Baseline of Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating Intensity in Adult Patients with Acute Diarrhea After 8 Hours of Dosing with Loperamide and Simethicone, Alone and in Combination, or Placebo. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Time(h) After Initial Dose	P*, Loperamide+Simethicone vs Loperamide	Simethicone	Placebo	Loperamide vs Placebo
		Abdominal Discomfort		
12	.0001	.0008	.0001	.0100
Bedtime 1	.0001	.0001	.0001	.0217
Next Morning 1	.0001	.0090	.0001	.0001
24	.0001	.0087	.0001	.0001
36	.0001	.0224	.0001	.0001
Bedtime 2	.0001	.0122	.0001	.0001
Next Morning 2	.0001	.1049	.0001	.0001
48	.0002	.1962	.0001	.0001
		Gas Pain/Cramps		
12	.0001	.0006	.0001	.0157
Bedtime 1	.0001	.0002	.0001	.0389
Next Morning 1	.0001	.0083	.0001	.0001
24	.0001	.0110	.0001	.0001
36	.0001	.0385	.0001	.0001
Bedtime 2	.0001	.0168	.0001	.0001
Next Morning 2	.0001	.0966	.0001	.0001
48	.0001	.1844	.0001	.0001
		Gas Pressure/Bloating		
12	.0001	.0013	.0001	.0168
Bedtime 1	.0001	.0005	.0001	.0340
Next Morning 1	.0001	.0122	.0001	.0001
24	.0001	.0139	.0001	.0001
36	.0001	.0351	.0001	.0001
Bedtime 2	.0001	.0200	.0001	.0001
Next Morning 2	.0001	.1020	.0001	.0001
48	.0002	.2119	.0001	.0001

*Unadjusted for multiple comparisons

• **End of Study Patients' Evaluations:** The data from the patients' evaluations of treatment efficacy in the relief of overall diarrheal illness, diarrhea, and gas-related abdominal discomfort, were analyzed by a two factor (baseline stool category, and treatment) ANOVA. *There was a significant effect of treatment and frequency of stools at baseline for overall, diarrhea and abdominal discomfort relief. Moreover, there were significant treatment by stool category interactions for overall and diarrhea relief* [Table 29].

Table 29. Evaluation of Treatment Efficacy in the Relief of Diarrheal Illness, Diarrhea, and Gas-Related Abdominal Discomfort By Adult Patients with Acute Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Patients' Evaluation of Relief	P*		
	Treatment	Baseline Stool Category	Treatment x Stool Category
Overall	.0001	.0462	.0303
Diarrhea	.0001	.0062	.0035
Abd Discomfort	.0001	.0266	.6595

*ANOVA

Comparison of mean symptom relief by treatment, showed a greater mean relief for overall illness, diarrhea, and abdominal discomfort by the Loperamide+Simethicone combination, compared with its components alone and placebo in all baseline stool categories. Loperamide alone yielded a greater mean relief than placebo and Simethicone alone, except for mean relief of abdominal discomfort [Table 30].

Table 30. Mean Relief of Overall Illness, Diarrhea, and Abdominal Discomfort in Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Relief	Baseline Stool Category	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo
Overall Illness	3-5	2.68	1.59	1.37	.63
	≥6	3.24	1.94	1.09	.81
	Both	2.96	1.78	1.23	.72
Diarrhea	3-5	2.67	1.95	1.24	.57
	≥6	3.17	2.74	.91	.83
	Both	2.92	2.34	1.07	.70
Abd Discomfort	Both	2.97	1.52	1.86	.75

Pairwise treatment comparisons indicated that the Loperamide+Simethicone combination was significantly better than Loperamide alone, Simethicone alone, and placebo in the mean relief of overall diarrheal illness, diarrhea, and abdominal discomfort for both baseline stool categories. However, the combination was similar to Loperamide alone in the category of 6 stools or more [Table 31].

Table 31. Comparison of Mean Relief of Overall Diarrheal Illness, Diarrhea, and Abdominal Discomfort by Loperamide and Simethicone, Alone and in Combination, or Placebo Given for 48 Hours to Adult Patients with Acute Diarrhea, and Gas-Related Abdominal Discomfort. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Relief	Baseline Stool Category	P*, Loperamide+Simethicone vs Loperamide	Loperamide+Simethicone vs Simethicone	Loperamide+Simethicone vs Placebo	Loperamide vs Placebo
Overall Illness	3-5	.0001	.0001	.0001	.0001
	≥6	.0001	.0001	.0001	.0001
	Both	.0001	.0001	.0001	.0001
Diarrhea	3-5	.0001	.0001	.0001	.0001
	≥6	.1230	.0001	.0001	.0001
	Both	.0003	.0001	.0001	.0001
Abd Discomfort	Both	.0001	.0001	.0001	.0001

*Unadjusted for multiple comparisons

Per Protocol Analysis

All the results from the per protocol analysis for every efficacy endpoint, were very similar to those already reviewed under the intent-to-treat analysis. Thus, the per protocol analysis will not be done, to avoid duplication.

Safety

A sample of 491 patients were included in the analysis of adverse events. As described in the protocol for this study, subjects could take up to 8 tablets of the assigned medication in the 48-hour study period.

As shown in Table 32, about 50% of the study subjects took ≤3 Loperamide+Simethicone tablets, compared with about 50% of patients in the placebo group who took up to 6 tablets.

Table 32. Frequency Distribution of Number of Tablets of Loperamide Plus Simethicone, Loperamide, Simethicone, or Placebo Taken During the 48-Hour Study Period by 491 Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table, modified by MO)

	Number of Subjects							
No. of Tablets	Loperamide+ Simethicone (N=124)	Cum %	Loperamide (N=122)	Cum %	Simethicone (N=123)	Cum %	Placebo (N=122)	Cum %
2	18	14	5	4	0	0	0	0
3	43	49	25	25	2	2	3	2
4	26	70	39	57	20	18	16	16
5	20	86	21	74	24	37	13	26
6	6	91	10	82	28	60	28	49
7	2	93	3	84	14	71	13	60
8	9	100	19	100	35	100	49	100

Twenty-one(21) patients reported adverse events. Eight(8) patients took the Loperamide plus Simethicone combination, 5 took Loperamide, 2 took Simethicone, and 6 took placebo. Of the 22 adverse events reported, 7 were considered to be drug-related or possible drug-related [Table 33].

Table 33. Adverse Events Reported by Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in combination, or Placebo. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Composite of Applicant's Tables)

Adverse Events	Simethicone (N=124)	Loperamide (N=122)	Simethicone (N=123)	Placebo (N=122)	TOTAL (N=491)
No. Of Reports	8	5	2	7	22
Pts. Reporting	8(6)	5(4)	2(2)	6(5)	21(4)
Drug-Related or Possible Related	4(3)	1(1)	0	2(2)	7(1)
Serious	0	0	0	0	0
Death	0	0	0	0	0

()=percent

Most of the adverse events involved the digestive system and the body as a whole. The most frequent drug-related adverse event associated with the combination was nausea **[Table 34]. No serious adverse reactions or deaths were reported.**

Table 34. Drug-Related Adverse Events Reported by 491 Adult Subjects with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo. NDA 20-606. Protocol 92-202: Intent-To-Treat. (Applicant's Table)

Body System	Adverse Event	Loperamide+ Simethicone (N=124)	Loperamide (N=122)	Simethicone (N=123)	Placebo (N=122)
Body as a Whole	Headache	0	0	0	2
Digestive	Nausea	4(3)	1(1)	0	0

()=Percent

Two(2) placebo-treated, and 1 Simethicone-treated patients were discontinued from the study because of non-drug-related adverse events. These events included lumbar pain in the Simethicone-treated, and rheumatic pain in one placebo, and cough and pharyngitis in the other placebo-treated patient.

□ **Applicant's Conclusions: "Loperamide HCl 2mg and simethicone 125mg administered as a combination chewable tablet,...is more effective than either of its components in relieving the symptoms of diarrhea...and gas-related abdominal symptoms, including bloating/distension and abdominal pain/cramps in patients with acute diarrheal illness with concomitant gas-related intestinal symptoms...**

Loperamide HCl 2mg and simethicone 125mg taken as a combination chewable tablet is well tolerated with an incidence of adverse experiences no different than placebo when administered as a two-tablet initial dose followed by one tablet after each unformed stool up to a maximum of four tablets in a 24-hour period...".

□ **Reviewer's Conclusions:** *This single center , factorial, randomized, double-blind clinical study to evaluate the efficacy and safety of a fixed combination of Loperamide HCl 2mg and Simethicone 125mg in a chewable tablet dosage form, versus its components alone an placebo, in the relief of acute nonspecific diarrhea with gas-related abdominal symptoms in adult outpatients, showed the combination was significantly more effective than its components and placebo in the relief of acute diarrhea and abdominal discomfort, including gas pain/cramps, and gas pressure/bloating.*

These results indicate that the components of the fixed combination did make a contribution to the effects of the combination in the relief of acute nonspecific diarrhea, and the associated gas-related abdominal symptoms.

In addition, *this clinical study showed that Loperamide alone was significantly better than Simethicone alone and placebo in the relief of relief of diarrhea, and significantly better than placebo in the relief of gas-related abdominal discomfort.*

No serious adverse events were reported. The most frequent adverse reaction associated with the combination was nausea.

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■ 2. Protocol 92-209: A multicenter, parallel, factorial, randomized, placebo controlled, double blind clinical study to evaluate the efficacy and safety of a fixed combination of Loperamide and Simethicone , versus its components alone and placebo, in the relief of acute nonspecific diarrhea with gas-related abdominal discomfort, and the efficacy and safety of Loperamide alone in the relief of diarrhea- associated gas pain or abdominal cramps in adult outpatients.

The study was performed from September, 1993 through August, 1994 in Cancun, QR, Mexico by Jose Alba V., M.D., and Juan C. Martinez, and in Puerto Vallarta, Jalisco., Mexico by Jorge E. Ruiz R., M.D.

A sample size of 480 subjects, with 120 subjects for each of 4 treatment groups, was calculated to detect a significant difference of at least 7h in the mean time to complete relief of gas-related abdominal discomfort between treatments groups, with an α=.05, 1-β=.80, and 2-tail tests.

Subjects were to be enrolled for 48 hours, and they were to record the time and consistency of stools, and the intensity (severity), and time to complete relief of the gas-related abdominal discomfort.

Patient inclusion criteria were to comprise adult male and female outpatients with acute diarrhea of less than 48h duration, and at least 3 unformed stools within 24h prior to entry into the study, and to have moderately severe gas-related abdominal discomfort one hour prior to entry. Female subjects were to be menopausal, or else to have used appropriate anticonceptive measures 3 months prior to the study. An unformed stool was defined as any watery or soft bowel movement.

Exclusion criteria were to involve patients with severe diarrhea requiring hospitalization, or outpatient parenteral hydration, or antibiotic therapy. In addition, patients should not have an oral temperature of >102F, blood or pus in the stools, signs or symptoms of orthostatic hypotension, chronic gastrointestinal, hepatic or renal disease, or any significant medical condition, inability to take medications or fluids orally, hypersensitivity to loperamide or simethicone, antibiotic or other therapy which might interfere with enteral bacterial flora 7 days prior to the study, or a history of treatment with antidiarrheal, promotility, antiflatulent, antacid, antibiotic, or analgesic drugs within 6 to 12 hours prior to the study.

Patients were to be advised not to drink alcoholic or carbonated beverages, or non-potable water, or beverages containing milk, or to eat foods containing milk or milk products during the study.

Baseline measurements were to include medical history, physical examination, date and time of diarrhea onset, number of unformed stools in the preceding 24 hours; date, time, and consistency of last stool; intensity of gas-related abdominal discomfort within the previous hour, and type of discomfort, e.g., gas pain or cramps, or gas pressure or bloating.

Each patient was to be assigned to a code number corresponding to one of the 4 treatment groups. Patients were to be randomized to treatments in blocks of 12 each. In addition, patients were to be given a diary to record symptoms and the date, time and consistency of stools (formed=hard or normal, or unformed=soft or watery), and the time and quantity of medication taken for 48 hours.

Treatments were to include the following 4 groups:

- 8 chewable tablets containing Loperamide HCl 0mg and Simethicone 125mg
- 8 chewable tablets containing Loperamide HCl 2mg and Simethicone 0mg
- 8 chewable tablets containing Loperamide HCl 2mg and Simethicone 125mg
- 8 chewable tablets containing Loperamide HCl 0mg and Simethicone 0mg (placebo)

Patients were to take the initial dose of study medication under the observation of the investigator. The initial dose was to consist of 2 tablets which were to chewed and swallowed, followed by 1 tablet after each unformed stool, without exceeding 4 tablets in any 24-hour period.

Patients were to record in their diaries the time and quantity of study medication taken, as well as the time and consistency of stools, and the maximum intensity of the gas-related abdominal discomfort hourly during the first 8 hours of dosing, and at 12, 24, 36, and 48 hours, and each evening and morning during the study. Abdominal discomfort, gas pain/cramps, and gas pressure/bloating were to be rated on a scale of 0=absent, 1=mild, 2=moderate, 3=moderately severe, and 4=severe.

At the end of the study or after discontinuation from the study, patients were to record the time of complete relief of diarrhea and the gas-related abdominal discomfort. In addition, the subjects were to record an evaluation of the treatment efficacy on a scale of 0=poor, 1=fair, 2=good, 3=very good, and 4=excellent. After completion of the study, and within 24 hours of entry, the patients were to return their diaries and unused medication.

The primary efficacy endpoints were to be time to the last unformed stool, and time to complete relief of gas-related abdominal discomfort. All other measurements were to be considered secondary efficacy endpoints.

Survival analysis was to be used for analysis of time to complete relief of abdominal discomfort, time to first unformed stool, and time to rescue. Patients rescued before reaching the endpoint, were to be censored at the time of rescue. Ratings of the intensity of gas-related abdominal discomfort were to be analyzed as differences from baseline by ANOVA. Repeated measures ANOVA was to be utilized for analysis of frequency of unformed stools during each 12-hour interval, stratified by the baseline stool frequency into 2 strata (3-5 unformed stools, and ≥6 unformed stools). ANOVA was to be applied to the analysis of patients' ratings of treatment efficacy.

An interim analysis could have been done when half of the patients had been entered, to assess a model sensitivity and to decide about the continuation or discontinuation of the study. The following conditions were to be met: 1) the results will not be known to the principal and associates; 2) the treatment code will not be disclosed to the clinical monitors; 3) only the primary endpoints will be analyzed with a calculation of the conditional probability that the observed differences between treatment groups will reach statistical significance at the completion of the study. No adjustment of α was considered necessary.

Safety was to be assessed by the incidence of adverse reactions. Tabulations of all adverse reactions were to be provided and compared statistically.

Results

Interim Analysis

The *two primary endpoints analyzed* were the *time to complete relief of gas-related abdominal discomfort, and the time to the last unformed stool*. In addition, the severity of gas pain/cramps was analyzed to evaluate the efficacy of Loperamide in the relief of gas-related abdominal discomfort.

A sample of 229 patients had been randomized to treatments. Of these, 59 patients had received placebo, 55 had received treatment 1, 58 had received treatment 2, and 57 had received treatment 3 [Table 35].

Table 35. Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo, Evaluated in the Interim Analysis. NDA 20-606: Protocol 92-209. (Applicant's Table)

	Treatment									
	Placebo		1		2		3		TOTAL	
Investigator	Eval	Excl	Eval	Excl	Eval	Excl	Eval	Excl	Eval	Excl
Alba	12	6	13	3	14	1	16	0	55	10
Martinez	16	11	27	0	27	1	25	1	95	13
Ruiz	13	1	11	1	15	0	15	0	54	2
TOTAL	41	18	51	4	56	2	56	1	204	25

Eval=Evaluated; Excl=Excluded

The applicant excluded **25 patients from analysis.** Of these, **18 patients had received placebo, 4 patients treatment 1, 2 patients treatment 2, and 1 patient treatment 3.** Most of the exclusions were due to dosing violations **[Table 36].**

Table 36. Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide And Simethicone, Alone and in Combination, or Placebo For 48 Hours, Excluded From Analysis. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table, Modified by MO)

Reason for Exclusion	No. Pts.
Exceeded daily dose	20
No dose after unformed stool	2
> 1 dose after unformed stool	2
Lost to follow-up	1
TOTAL	25

Nine(9) patients discontinued treatment before completion of the study, but they were included in the analysis **[Table 37].**

Table 37. Study Discontinuation by Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table,, modified by MO)

Reason for Discontinuation	No. of Patients
Diarrhea resolved	1
Use of rescue medication	5
Treatment failure	3
TOTAL	9

There were no significant differences between treatment groups at baseline [Table 38].

Table 38. Demographic and Other Baseline Data of Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

	Treatment					
Baseline Variable	Placebo (N=59)	1 (N=55)	2 (N=58)	3 (N=57)	TOTAL (N=229)	P
Sex						.0678
Male	34	23	33	38	128	
Female	25	32	25	19	101	
Race						.1683
White	58	49	53	51	211	
Black	1	0	1	2	4	
Other	0	6	4	4	14	
Age(y)						
Mean	35.3	33.8	33.5	35.4	34.5	.6749
Median	32	33	31	33	32	
Range						
Onset Illness(h)						
Mean	15.3	16.8	13.7	13.5	14.8	.0558
Median	14.3	15.5	14.0	12.9	14.3	
Range						
Unformed Stools Prior 24h						
Mean	5.4	5.9	5.5	5.5	5.6	.2167
Median	5.0	6.0	5.5	5.0	6.0	
Range						
Abd Discomfort						.3867
Mod-Severe	55	50	56	53	214	
Severe	4	5	1	3	13	
Gas Pain/Cramps						.5743
Mean	2.9	3.0	3.0	2.9	3.0	
None	0	0	0	1	1	
Mild	2	1	1	2	6	
Moderate	3	2	3	4	12	
Mod-Severe	51	46	48	43	188	
Severe	3	6	5	6	2	

However, **significant differences were found between investigators** for sex, race, onset of illness, abdominal discomfort, and gas pain/cramps **[Table 39]**.

Table 39. Demographic and Other Baseline Data, By Investigator, of Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

Baseline Variable	Alba (N=65)	Martinez (N=108)	Ruiz (N=56)	P
Sex				
Male	34	48	46	.0001
Female	31	60	10	
Race				
White	61	107	43	.0001
Black	3	1	0	
Other	1	0	13	
Age(y)				
Mean	36.9	33.5	33.5	.0849
Median	33	32	32	
Range				
Onset Illness(h)				
Mean	17.8	15.1	10.7	.0001
Median	15	15.5	10	
Range				
Unformed Stools Prior 24h				
Mean	5.4	5.7	5.5	.4473
Median	5	6	5.5	
Range				
Abd Discomfort				
Mod-Severe	58	105	51	.0390
Severe	7	2	4	
Gas Pain/Cramps				
Mean	2.69	3.01	3.20	.0001
None	0	0	1	
Mild	6	0	0	
Moderate	12	0	0	
Mod-Severe	43	105	40	
Severe	4	2	14	

Results

Endpoints:

- **Time to Complete Relief of Gas-Related Abdominal Discomfort:** Patients recorded this outcome at the end of the 48-hour study period, or at the time of study discontinuation. ***Survival analysis*** *indicated that* ***survival median time(h) and the proportion of patients without relief for treatment 3, were significantly less than that for placebo and treatments 1 and 2*** **[Table 40].**

Table 40. Time(h) to Complete Relief of Abdominal Discomfort in 229 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

Treatment	Median Time (h) Complete Relief	Percent No Relief
1	24.0	13.7
2	19.5	21.4
3	9.2	3.6
Placebo	22.5	26.8
Log-rank, p	.0001	
Wilcoxon, p	.0001	

Pairwise comparisons of treatments also showed that treatment 3 was significantly better than placebo and treatments 1 and 2. No significant differences between treatments 1 and 2, and placebo were found [Table 41].

Table 41. Comparison of Time to Complete Relief of Abdominal Discomfort in 229 Adult Patients with Acute Nonspecific Diarrhea,, Treated with Loperamide and Simethicone, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

Pairwise Comparison	P*, Survival Analysis Log-Rank	Wilcoxon
Placebo vs Treatment 1	.3518	.9327
Placebo vs Treatment 2	.2745	.1418
Placebo vs Treatment 3	.0001	.0001
Treatment 1 vs 2	.6690	.1003
Treatment 1 vs 3	.0001	.0001
Treatment 2 vs 3	.0006	.0022

*Unadjusted for multiple comparisons

- **Time(h) to the Last Unformed Stool: Two definitions were considered:**

o **Definition A= the time elapsed from initial dose to:**

I. **the time of last unformed stool where only unformed stools are subsequently reported, or**

ii. **the beginning of a 24-hour period without stools, following unformed stools, or**

iii. **end of observation if unformed stools continue throughout the study.**

o Definition B= the time elapsed from initial dose to the time of last unformed stools, where only formed or no stools are subsequently reported.

Survival analysis indicated that the median survival times(h) were significantly different for treatments 1 and 3, compared with placebo and treatment 2 for both definitions and stool categories [Table 42].

Table 42. Median Times(h) to Last Unformed Stool in 229 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

	Definition A			Definition B		
Treatment	3-5	≥6	Both	3-5	≥6	Both
1	13.7	5.7	6.7	13.7	5.7	6.7
2	22.8	23.0	22.8	23.5	24.8	24.1
3	5.9	6.2	6.1	5.9	6.2	6.1
Placebo	29.4	23.8	25.2	34.0	24.7	25.9
Log-rank, p	.0001	.0001	.0001	.0001	.0001	.0001
Wilcoxon, p	.0013	.0001	.0001	.0002	.0001	.0001

Pairwise comparisons of treatments showed that for both definitions, *treatments 1, 2, and 3 were significantly better than placebo, treatments 1 and 3 were significantly better than treatment 2, and treatments 1 and 3 were not significantly different* [Table 43].

Table 43. Comparison of Time(h) to Last Unformed Stool in 229 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

Pairwise	Definition A		Definition B	
Comparison	Log-Rank	Wilcoxon	Log-Rank	Wilcoxon
Placebo vs Treatment 1	.0001	.0001	.0001	.0001
Placebo vs Treatment 2	.0150	.0451	.0076	.0366
Placebo vs Treatment 3	.0001	.0001	.0001	.0001
Treatment 1 vs 2	.0148	.0070	.0093	.0024
Treatment 1 vs 3	.1570	.2244	.1682	.2281
Treatment 2 vs 3	.0001	.0001	.0001	.0001

• Intensity of Gas Pain/Cramps:

Mean differences of intensity of gas pain/cramps from baseline, during the first 8 hours of dosing, were greater for the active treatments compared with placebo, and for treatment 1 compared to treatment 2 and 3 from 2 to 8 hours [Table 44].

Table 44. Mean Differences From Baseline of Gas pain/Cramps Intensity, During the First 8 Hours of Dosing, in 229 Adult Subjects with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

Treatment	1	2	3	4	5	6	7	8
1	.22	.86	1.22	1.81	1.95	2.13	2.16	2.21
2	.31	.69	1.47	1.67	1.74	1.83	2.00	2.15
3	.33	.82	1.00	1.23	1.66	1.78	1.93	2.16
Placebo	.28	.59	.82	1.05	1.54	1.53	1.80	1.72

Pairwise comparison of treatments of mean differences from baseline during the first 8 hours of dosing, yielded significant differences between treatment 1 vs placebo at 4 and 6 hours, treatment 2 vs placebo at 3 and 4 hours, treatment 1 vs treatment 3 at 4 hours, and treatment 2 vs treatment 3 at 3 hours. No significant differences between treatment 3 and placebo, and treatment 1 and 2 were detected [Table 45].

Table 45. Comparison of Gas Pain/Cramps Severity during the First 8 Hours of Dosing in 229 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

Pairwise	P* at Indicated Hour							
Comparison	1	2	3	4	5	6	7	8
Treatment 1 vs Placebo	.8130	.2647	.1097	.0022	.0951	.0160	.1398	.0471
Treatment 2 vs Placebo	.8898	.6469	.0053	.0073	.3745	.1898	.3935	.0590
Treatment 3 vs Placebo	.7918	.2813	.4194	.4058	.5738	.2524	.5305	.0398
Treatment 1 vs 2	.6928	.4578	.2744	.5451	.3640	.1992	.4625	.8104
Treatment 1 vs 3	.5898	.8427	.3027	.0070	.1745	.1036	.2844	.8302
Treatment 2 vs 3	.8977	.5140	.0161	.0241	.6695	.7777	.7537	.9634

*Unadjusted for multiple comparisons

Safety: One patient on treatment 3 had moderate nausea.

- Probability of Statistical Significance at the Completion of the Study:

The probability of achieving statistical significance between the active treatments and placebo for the time to complete relief of gas-related abdominal discomfort, and time to complete relief of diarrhea (time to the last unformed stool) at the completion of the study, was calculated assuming that 480 patients would be entered into the study with a probability similar to that of the 229 patients analyzed.

For the time to complete relief of gas-related abdominal discomfort, there was a high probability of detecting a significant difference vs placebo for treatments 2 and 3, whereas a high probability was evident for the time to last unformed stool for all the 3 active treatments vs placebo [Table 46].

Table 46. Estimation of Probability of Significant Statistical Difference at the End of the Study, Between Active and Placebo Treatments. NDA 20-606. Protocol 92-209: Interim Analysis. (Applicant's Table)

Endpoint(h)	Treatment	Difference From Placebo	P of Statistical Significance
	1	.40	.039
Complete Relief	2	4.99	.685
Abd Discomfort	3	14.91	1.000
	1	14.50	1.000
Last Unformed	2	6.63	.950
Stool, Def A	3	17.94	1.000
	1	15.29	1.000
Last Unformed	2	6.67	.948
Stool, Def B	3	18.72	1.000

= Reviewer's Opinion: *The data analysis indicated that the active treatments were distinguishable from placebo. However, the question remains if α should be readjusted for data analysis at the completion of the study.*

Results from Completed Study

A total of 485 adult patients were randomized to treatments by the 3 participating clinical investigators. Of these, 121 subjects received Loperamide plus Simethicone, 120 received Loperamide alone, 123 received Simethicone alone, and 121 received placebo [Table 47].

Table 47. Demographic and Other Baseline Data of Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo in a Factorial Design for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

Variable	Loperamide+ Simethicone (N=121)	Loperamide (N=120)	Simethicone (N=123)	Placebo (N=121)	TOTAL (N=485)	p*
Sex						
Male	76	58	76	75	285	.0697
Female	45	62	47	46	200	
Race						
White	111	109	112	115	447	.3025
Afro-Amer	3	0	4	1	8	
Other	7	11	7	5	30	
Age(y)						
Mean±SD	36.1±9.98	34.7±10.38	34.8±10.44	35.9±12.01	35.4±	.6234
Range						
Onset Ill(h)						
Mean±	14.6±6.95	16.8±8.33	13.8±6.26	14.2±7.30	14.8±7.31	.0073
Median	13.5	15.5	13.0	13.0	14.0	
Range						
Unformed Stools Prior 24h						
Mean±SD	5.6±1.38	5.8±1.75	5.6±1.22	5.5±1.57	5.6±1.49	.4843
Median	6.0	5.0	5.0	5.0	5.0	
Range						
Abdominal Discomfort						
Mean±SD	3.06±.235	3.07±.252	3.03±.180	3.07±.264	3.06±.234	.5188
Missing	1	1	2	0	4	
Mod-Severe	113	111	117	112	453	
Severe	7	8	4	9	28	
Gas Pain/ Cramps						
Mean ±SD	2.90±.614	2.97±.486	2.92±.586	2.86±.567	2.91±.565	.5312
Missing	1	1	2	0	4	
None	1	0	0	0	1	
Mild	3	3	4	6	16	
Moderate	14	7	14	11	46	
Mod-Severe	91	100	91	98	380	
Severe	11	9	12	6	38	
Gas Pressure/ Bloating						
Mean±SD	3.02±.389	3.03±.223	3.01±.241	3.00±.342	3.01±.306	.8520
Missing	1	1	2	0	4	
None	0	0	0	0	0	
Mild	1	0	0	0	1	
Moderate	5	1	3	7	16	
Mod-Severe	105	113	114	107	439	
Severe	9	5	4 4	7	25	

* Fisher's exact test for categorical, and ANOVA for continuous data

Of the 485 patients randomized to treatments, 2 patients (1 Loperamide+Simethicone pt. #275, and 1 Loperamide-treated pt. #349) were lost to follow-up, and they were excluded form the intent-to-treat efficacy analysis by the applicant, leaving 483 patients for this analysis. In addition, for the per protocol (evaluable patients) analysis the applicant excluded 8 patients from the Loperamide alone, 10 patients from the Simethicone alone, and 29 patients from the placebo group, leaving a subset of 437 patients for this analysis [Table 48].

Table 48. Patient Subsets Evaluated by the Applicant for Efficacy of Loperamide and Simethicone, Alone and in Combination, or Placebo in Adult Subjects with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated for 48 Hours. NDA 20-606. Protocol 92-209. (Applicant's Table, modified by MO)

Treatment Group	No. Pts Entered	Intent-To-Treat		Per Protocol	
		Excluded	Analyzed	Excluded	Analyzed
Loperamide+ Simethicone	121	1	120	1	120
Loperamide	120	1	119	8	112
Simethicone	123	0	123	10	113
Placebo	121	0	121	29	92
TOTAL	485	2	483	48	437

Fifteen(15) patients were discontinued from the study because the symptoms resolved in less than 48 hours (1 Loperamide), the treatment failed (1 Simethicone, 4 placebo), or the patient took rescue medication (2 Loperamide, 3 Simethicone, 4 placebo) [Table 49]

Table 49. Study Discontinuations Among Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209. Applicant's Table, modified by MO)

Reasons for Discontinuation	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo
Symptoms resolved	0	1	0	0
Treatment failure	0	0	1	4
Rescue medication	0	3	4	4*
TOTAL	0	4	5	8

*2 pts. included in the per protocol analysis by the applicant

Stratification patients by the frequency of unformed stools in the 24 hours prior to randomization, e.g., 3-5 stools (Category 1), or ≥6 stools (Category 2), showed a similar distribution in all the treatment groups both in the intent-to-treat, and the per protocol subsets [Table 50].

Table 50. Frequency of Unformed Stools 24 Hours Prior to the Study Among Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606: Protocol 92-209. (Applicant's Table)

Cat	No. Stools	Investigator	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo	TOTAL No.	TOTAL %
			Intent-To-Treat					
1	3-5	All	56	60	63	69	248	51
2	≥6	All	64	59	60	52	235	49
Both	Both	All	120	119	123	121	483	100
		Alba	39	39	41	41	160	33
Both	Both	Martinez	39	41	41	41	162	33
		Ruiz	42	39	41	39	161	33
			Per Protocol					
1	3-5	All	56	59	56	51	222	51
2	≥6	All	64	53	57	41	215	49
Both	Both	All	120	112	113	92	437	100
		Alba	39	34	36	30	139	32
Both	Both	Martinez	39	40	37	27	143	33
		Ruiz	42	38	40	35	155	35

The primary efficacy endpoints **analyzed were the *time to the last unformed stool, and the time to complete relief of gas-related abdominal discomfort*.** In addition, several ***secondary efficacy endpoints*** **were analyzed, as shown below:**

- **Time to first unformed stool**
- **Number of unformed stools**
- **Time to complete relief of diarrhea**
- **Maximum intensity of gas-related abdominal discomfort, gas pain/cramps, and gas pressure/bloating**
- **End of study patient's evaluation of therapies.**

Efficacy Analysis

Intent-To-Treat Analysis

There were no significant differences between treatment groups at baseline in demographic and clinical variables, except for onset(h) of illness which was significantly longer for the Loperamide compared with the fixed combination, Simethicone alone, and placebo groups. This imbalance appeared to be caused by patients enrolled by Alba. In addition, significant differences between investigators were found for all the baseline variables [Table 51].

Table 51. Demographic and Clinical Baseline Data, By Investigator, of Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-92-209: Intent-To-Treat. (Applicant's Table)

Variable	Alba (N=160)	Martinez (N=164)	Ruiz (N=161)	P
Sex				
Male	87	78	120	.0001
Female	73	86	41	
TOTAL	160	164	161	
Race				
White	153	163	131	.0001
Afro-Amer	5	1	2	
Other	2	0	28	
TOTAL	160	164	161	
Age(y)				
Mean	39.1	32.3	34.9	.0001
Range				
Onset Ill(h)				
Mean	17.9	14.9	11.7	.0001
Median	15.3	15.5	11.0	
Range				
Unformed Stools Prior 24h				
Mean	5.3	5.5	6.0	.0001
Median	5.0	5.0	6.0	
Range				
Abd Discomfort				
Mean	3.09	3.02	3.07	.0159
Missing	0	2	2	
Mod-Severe	146	159	148	
Severe	14	3	11	
Gas Pain/Cramps				
Mean	2.59	3.02	3.13	.0001
Missing	0	2	2	
None	0	0	1	
Mild	14	0	2	
Moderate	45	0	1	
Mod-Severe	94	159	127	
Severe	7	3	28	
Gas Pressure/ Bloating				

Mean	2.97	3.01	3.06	.0001
Missing	0	2	2	
None	0	0	0	
Mild	1	0	0	
Moderate	13	0	3	
Mod-Severe	136	160	143	
Severe	10	2	13	

▪ Primary Efficacy Endpoints:

• Time(h) to Last Unformed Stool (TTLUS): That is, time to disappearance of objectives signs of diarrhea. Two definitions were applied in the analysis:

o Definition A= For patients who completed the study, or discontinued the study because the diarrhea stopped, TTTLUS was the elapsed time(h) from initial dose to:

1. The time of the last unformed stool, where only formed stools or no stools were subsequently reported, or
2. The beginning of a 24-hour period without stools, following unformed stools.

o Definition B= For patients who completed the study, or discontinued it because the diarrhea resolved, TTLUS was the time elapsed from the initial dose to the time of the last unformed stool, where only formed stools were subsequently reported.

Survival analysis showed that for both definitions, *the combination of Loperamide and Simethicone was significantly better than Simethicone alone and placebo in decreasing the median time(h) to the last unformed stool, regardless of the unformed stool frequency at baseline or the investigator involved. Similarly, Loperamide alone was significantly better than placebo in accomplishing the same effect* [Table 52].

Table 52. Median Time (h) to Last Unformed Stool in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	Stool Category		Investigators			
Treatment	3-5	≥6	Alba	Martinez	Ruiz	All
			Definition A			
Loperamide+ Simethicone	6.2	9.1	8.0	2.0	12.7	7.6
Loperamide	12.0	10.5	16.5	2.3	20.1	11.5
Simethicone	26.0	26.1	29.2	7.5	30.3	26.0
Placebo	28.6	29.5	25.0	24.0	32.7	29.4
Log-rank, p	.0001	.0001	.0001	.0001	.0001	.0001
Wilcoxon, p	.0001	.0001	.0001	.0001	.0001	.0001
			Definition B			
Loperamide+ Simethicone	7.6	10.0	9.0	2.2	18.7	8.7
Loperamide	12.9	12.5	16.5	2.7	20.1	12.5
Simethicone	26.3	27.9	29.2	10.2	32.0	27.0
Placebo	30.8	30.0	27.0	26.2	32.8	30.5
Log-rank, p	.0001	.0001	.0001	.0001	.0001	.0001
Wilcoxon, p	.0001	.0001	.0001	.0001	.0001	.0001

Pairwise comparison of treatments yielded similar results.~ *Under both definitions, A and B, the combination of Loperamide and Simethicone was significantly better than Simethicone alone and placebo in decreasing the median time(h) to the last unformed stool. Also, Loperamide alone was significantly better than placebo in decreasing the time to last unformed stool. In contrast, the combination appeared to be significantly better than Loperamide alone only under definition A for investigator Alba* [Table 53].

Table 53. Comparison of Time(h) to Last Unformed Stool in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

Stool Category	Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
		Definition A		
3-5				
Log-rank	.1573	.0001	.0001	.0001
Wilcoxon	.0422	.0001	.0001	.0001
≥6				
Log-rank	.0428	.0001	.0001	.0002
Wilcoxon	.2468	.0001	.0001	.0001
Both				
Log-rank	.0123	.0001	.0001	.0001
Wilcoxon	.0232	.0001	.0001	.0001
Alba				
Log-rank	.0477	.0001	.0001	.0304
Wilcoxon	.0238	.0001	.0001	.0012
Martinez				
Log-rank	.4111	.0001	.0001	.0001
Wilcoxon	.8683	.0078	.0001	.0001
Ruiz				
Log-rank	.1295	.0001	.0001	.0001
Wilcoxon	.0794	.0001	.0001	.0001
		Definition B		
3-5				
Log-rank	.5128	.0007	.0001	.0001
Wilcoxon	.2133	.0001	.0001	.0001
≥6				
Log-rank	.0519	.0001	.0001	.0003
Wilcoxon	.2002	.0001	.0001	.0001
Both				
Log-rank	.0586	.0001	.0001	.0001
Wilcoxon	.0709	.0001	.0001	.0001
Alba				
Log-rank	.0906	.0001	.0001	.0204
Wilcoxon	.0484	.0001	.0001	.0008
Martinez				
Log-rank	.1881	.0001	.0001	.0001
Wilcoxon	.6825	.0053	.0001	.0001
Ruiz				
Log-rank	.9032	.0001	.0001	.0001
Wilcoxon	.6781	.0001	.0001	.0001

For both definitions A and B, the cumulative percentage of patients with last unformed stool was greater for the combination than for Loperamide alone, Simethicone alone and placebo at all time intervals [Table 54].

Table 54. Cumulative Percentage of Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	Percentage of Patients at indicated Time(h)												
	Definition A												
Treatment	0	4	8	12	16	20	24	28	32	36	40	44	48
Loperamide+ Simethicone	14	36	53	65	71	73	83	93	95	97	97	97	100
Loperamide	12	25	39	50	59	65	78	84	85	91	94	95	100
Simethicone	8	16	21	26	30	30	41	56	63	74	84	89	100
Placebo	3	8	12	16	21	23	34	43	56	69	77	83	100
	Definition B												
Loperamide+ Simethicone	13	33	48	60	66	68	78	88	92	95	96	97	100
Loperamide	11	24	36	48	56	62	77	82	85	91	94	95	100
Simethicone	8	15	18	23	26	27	38	53	59	72	83	88	100
Placebo	3	8	11	15	19	21	30	39	53	66	75	81	100

• Time to Complete Relief of Gas-Related Abdominal Discomfort: Data were analyzed by survival analysis. Patients without complete relief within 48 hours were censored, and assigned a time of 48h. Survival functions were compared by log-rank and Wilcoxon tests.

Median time(h) survival to complete relief of gas-related abdominal discomfort was significantly shorter for the combination compared with Loperamide alone, Simethicone alone, and placebo for the pooled data, and for each investigator [Table 55].

Table 55. Time(h) to Complete Relief of Gas-Related Abdominal Discomfort in Adult Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	Investigators			
Treatment	Alba	Martinez	Ruiz	All
Loperamide+ Simethicone	16.5	9.5	13.1	12.0
Loperamide	48.0	21.7	23.3	24.0
Simethicone	48.0	11.5	23.2	23.2
Placebo	48.0	13.0	23.5	23.5
Log-rank, p	.0001	.0001	.0023	.0001
Wilcoxon, p	.0001	.0001	.0025	.0001

Pairwise comparison of treatments showed that *the combination of Loperamide plus Simethicone, was significantly better than Loperamide alone, Simethicone alone, and placebo in decreasing the time to complete relief of abdominal discomfort when the pooled data or the data form the individual investigators were analyzed, except for Martinez, where no significant difference between the combination and Simethicone was found. Moreover, no significant difference between Loperamide alone and placebo was detected* [Table 56].

Table 56. Comparison of Time(h) to Complete Relief of Gas-Related Abdominal Discomfort in Adult Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

Investigators	P*, Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
All				
Log-rank	.0001	.0001	.0001	.5705
Wilcoxon	.0001	.0001	.0001	.8820
Alba				
Log-rank	.0005	.0001	.0001	.7840
Wilcoxon	.0001	.0001	.0001	.8382
Martinez				
Log-rank	.0001	.0858	.0004	.8554
Wilcoxon	.0001	.5436	.0100	.1586
Ruiz				
Log-rank	.0065	.0081	.0013	.3588
Wilcoxon	.0062	.0046	.0038	.6427

*Unadjusted for multiple comparisons

■ Secondary Efficacy Endpoints:

• Time to First Unformed Stool: Survival analysis indicated that *the combination of Loperamide plus Simethicone was significantly better than placebo, but not significantly different from either Loperamide alone or Simethicone alone in delaying the median time(h) to the first unformed stool, for all investigators and baseline stool categories combined* [Table 57].

Table 57. Median Time(h) to First Unformed Stool in Adult Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	Stool Category		Investigators			
Treatment	3-5	≥6	Alba	Martinez	Ruiz	All
Loperamide+ Simethicone	3.62	3.50	2.50	2.83	7.21	3.50
Loperamide	4.37	2.75	2.33	2.50	7.33	3.33
Simethicone	3.25	2.75	2.25	3.25	6.25	3.08
Placebo	2.75	2.75	2.67	1.75	5.33	2.75
Log-rank, p	.0231	.0096	.1217	.0108	.1749	.0005
Wilcoxon, p	.0427	.1249	.6498	.0637	.0824	.0054

Pairwise treatment comparisons showed *significant differences between the combination and placebo for all baseline stool categories, and Martinez. In addition, Loperamide was significantly better than placebo for all baseline stool categories* [Table 58].

Table 58. Comparison of Median Time(h) to First Unformed Stool in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

Stool Cat	P*, Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
3-5				
Log-rank	.5676	.3784	.0059	.0163
Wilcoxon	.4947	.2934	.0099	.0362
≥6				
Log-rank	.5230	.0780	.0011	.0178
Wilcoxon	.3041	.2214	.0138	.2264
Both				
Log-rank	.4028	.0899	.0001	.0016
Wilcoxon	.2389	.1142	.0005	.0249
Alba				
Log-rank	.1292	.0698	.0503	.4106
Wilcoxon	.2735	.2780	.3780	.8813
Martinez				
Log-rank	.9204	.9180	.0116	.0122
Wilcoxon	.6937	.9614	.0215	.0752
Ruiz				
Log-rank	.5368	.1191	.0582	.1229
Wilcoxon	.7161	.1140	.0302	.0506

*Unadjusted for multiple comparisons

• Number of Unformed Stools: Pairwise comparisons of treatments indicated that the mean number of unformed stools for all the investigators combined, was significantly less for the combination of Loperamide plus Simethicone than for Simethicone alone and placebo in all 12-hour periods. In addition, Loperamide alone was significantly better than placebo for all investigators, and for Martinez up to the 24-36 hour period [Table 59].

Table 59. Comparison of Mean Number of Unformed Stools in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

		P*, Loperamide+Simethicone vs			Loperamide
Investigators	Time(h)	Loperamide	Simethicone	Placebo	vs Placebo
All	0-12	.0447	.0001	.0001	.0001
	12-24	.1115	.0072	.0001	.0014
	24-36	.1363	.0001	.0001	.0001
	36-48	.3222	.0282	.0033	.0469
Alba	0-12	.1528	.0651	.1581	.9638
	12-24	.6618	.0289	.0400	.1003
	24-36	.2163	.0087	.0373	.3650
	36-48	.8246	.0437	.4456	.5803
Martinez	0-12	.0777	.0005	<.0001	<.0001
	12-24	.0976	.2331	<.0001	<.0001
	24-36	.1136	.0416	<.0001	.0003
	36-48	.1257	.5496	.0011	.0794
Ruiz	0-12	.7667	.0754	.0047	.0104
	12-24	.4976	.2017	.0931	.3069
	24-36	.8220	.0081	.0003	.0001
	36-48	.98445	.2416	.2514	.2386

*Unadjusted for multiple comparisons

• Time to Complete Relief of Diarrhea: Survival analysis showed that, *the median survival time(h) to complete relief of diarrhea was significantly shorter for the combination of Loperamide plus Simethicone compared with Loperamide alone and placebo for all investigators, and Alba alone. No significant difference between the combination and Loperamide alone was evident for Martinez and Ruiz* [Table 60].

Table 60. Median Time(h) to Complete Relief of Diarrhea in Adult Subjects with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	Median Time(h) to Complete Relief of Diarrhea			
Treatment	All	Alba	Martinez	Ruiz
Loperamide+ Simethicone	19.6	22.0	5.8	33.8
Loperamide	23.3	25.0	5.7	35.3
Simethicone	35.5	37.0	24.8	45.4
Placebo	38.3	32.0	31.1	47.5
Log-rank, p	.0001	.0001	.0001	.0001
Wilcoxon, p	.0001	.0001	.0001	.0001

Pairwise comparison of treatments demonstrated that the combination was significantly better than Loperamide alone, Simethicone alone, and placebo for pooled investigators, and for Alba. However, for Martinez and Ruiz the combination was significantly better than Simethicone alone and placebo only. In addition, Loperamide alone was significantly better than placebo for the pooled, and also for individual investigators [Table 61].

Table 61. Comparison of Time(h) to Complete Relief of Diarrhea in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

Investigators	P*, Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
All				
Log-rank	.0441	.0001	.0001	.0001
Wilcoxon	.0292	.0001	.0001	.0001
Alba				
Log-rank	.0452	.0001	.0001	.0563
Wilcoxon	.0250	.0001	.0001	.0061
Martinez				
Log-rank	.1580	.0001	.0001	.0001
Wilcoxon	.2631	.0001	.0001	.0001
Ruiz				
Log-rank	.7862	.0271	.0001	.0001
Wilcoxon	.4825	.0051	.0001	.0003

*Unadjusted for multiple comparisons

At each 112-hour time interval, there was a greater cumulative percentage of patients with complete relief of diarrhea in the combination group, compared with the Loperamide alone, Simethicone alone, and placebo groups [Table 62].

Table 62. Percentage of Patients with Complete Relief of Diarrhea Among Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	Percentage of Patients at Indicated Time(h)												
Treatment	0	4	8	12	16	20	24	28	32	36	40	44	48
Loperamide+ Simethicone	0	18	31	41	44	51	63	73	76	79	83	85	95
Loperamide	0	10	23	27	31	35	53	62	64	71	76	79	91
Simethicone	0	7	11	13	14	15	26	33	40	51	57	60	80
Placebo	0	4	6	8	10	11	16	23	35	43	47	52	69

• Gas-Related Abdominal Discomfort Intensity: Differences from baseline were analyzed by for overall abdominal discomfort, gas pain/cramps, and gas pressure/bloating by repeated measures ANOVA.

Pairwise treatment comparisons during the first 8 hours of treatment, showed that *the combination of Loperamide plus Simethicone was significantly better than placebo from hour 3 through 8, and significantly better than Loperamide alone from hour 5 through 8 for all 3 measurements. In contrast, the combination was significantly better than Simethicone alone at hour 6 and 8, only for overall discomfort. Loperamide alone was not significantly better than placebo for any of the 3 measurements* [Table 63].

Table 63. Comparison of Mean Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating Intensity, During First 8 Hours of Dosing, in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Symptoms Related Symptoms, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	P*, Loperamide+Simethicone vs			Loperamide
Time(h)	Loperamide	Simethicone	Placebo	vs Placebo
	Overall Abdominal Discomfort			
1	.8367	.6613	.8887	.9466
2	.2155	.7355	.1779	.9176
3	.0673	.3127	.0129	.5165
4	.1139	.2817	.0044	.2063
5	.0309	.0997	.0015	.3162
6	.0382	.0472	.0060	.5060
7	.0025	.1852	.0005	.6570
8	.0003	.0417	.0011	.7181
	Gas Pain/Cramps			
1	.2592	.5923	.4581	.6957
2	.2648	.4230	.1153	.6489
3	.2749	.6004	.0058	.0962
4	.0894	.7498	.0009	.1075
5	.0341	.0971	.0005	.1713
6	.0276	.0643	.0001	.0725
7	.0267	.0247	.0001	.0871
8	.0119	.0697	.0001	.1599
	Gas Pressure/Bloating			
1	.4325	.9772	.9476	.3950
2	.2165	.3525	.1567	.8590
3	.1734	.0837	.0073	.1878
4	.1444	.2891	.0043	.1625
5	.0233	.0399	.0005	.2213
6	.0288	.0120	.0034	.4573
7	.0011	.0106	<.0001	.3683
8	.0014	.0045	.0002	.6212

*Unadjusted for multiple comparisons

Differences from baseline of gas-related abdominal symptoms after 8 hours of treatment were also analyzed by repeated measures ANOVA. Pairwise comparison of treatments showed that *the combination of Loperamide plus Simethicone was significantly better than placebo, Loperamide alone, and Simethicone alone at all time points for overall abdominal discomfort intensity.*

In contrast, for gas pain/cramps the combination was significantly better than Loperamide at 12-hour and bedtime 1, and Simethicone alone at 12-hour, 24-hour, bedtime 1, and next morning 1. For gas pressure/bloating, the combination was significantly better than placebo at all time points; than Loperamide alone at 12-hour, 36-hour, and bedtime 1, and than Simethicone alone at all time points but the 48-hour. In addition, for the gas pain/cramps intensity, Loperamide alone was significantly better than placebo for the gas pain/cramps intensity at 36-hour, 48-hour, bedtime 2, and next morning 2 [Table 64].

Table 64. Comparison of Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating Intensity, After 8 Hours of Dosing, in Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Symptoms, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

Time Period	P*, Loperamide+Simethicone vs Loperamide	P*, Loperamide+Simethicone vs Simethicone	P*, Loperamide+Simethicone vs Placebo	P*, Loperamide vs Placebo
	Overall Abdominal Discomfort			
12 Hours	.0017	.0019	.0002	.5380
Bedtime 1	.0001	.0001	.0001	.8280
Next Morning 1	.0001	.0001	.0004	.6537
24 Hours	.0005	.0001	.0007	.9556
36 Hours	.0018	.0002	.0001	.3394
Bedtime 2	.0027	.0001	.0001	.2195
Next Morning 2	.0430	.0002	.0053	.4354
48 Hours	.0429	.0010	.0016	.2517
	Gas Pain/Cramps			
12 Hours	.0385	.0166	.0006	.1499
Bedtime 1	.0028	.0082	.0001	.0915
Next Morning 1	.0777	.0125	.0020	.1813
24 Hours	.0852	.0360	.0033	.2149
36 Hours	.1871	.0991	.0003	.0184
Bedtime 2	.3184	.0503	.0025	.0416
Next Morning 2	.8239	.0581	.0020	.0042
48 Hours	.9238	.1176	.0033	.0025
	Gas Pressure/Bloating			
12 Hours	.0037	.0034	.0003	.4408
Bedtime 1	.0001	.0001	.0001	.5020
Next Morning 1	.0119	.0016	.0006	.3684
24 Hours	.0505	.0010	.0034	.3277
36 Hours	.0254	.0034	.0041	.4791
Bedtime 2	.0577	.0020	.0016	.2027
Next Morning 2	.0768	.0259	.0044	.2729
48 Hours	.0995	.0553	.0031	.1858

*Unadjusted for multiple comparisons

• End of Study Patients' Evaluations: Patients evaluations of treatments efficacy in the relief of gas-related abdominal discomfort and diarrhea, were analyzed by ANOVA.

Pairwise comparison of treatments showed that the combination of Loperamide plus Simethicone was significantly better than placebo, Loperamide alone, and Simethicone alone in the relief of overall illness, diarrhea, and abdominal discomfort. Moreover, Loperamide alone was significantly better than placebo in the relief of overall illness, and diarrhea [Table 65].

Table 65. Comparison of Relief of Overall Illness, Diarrhea, and Abdominal Discomfort as Rated by Adults Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	P*, Loperamide+Simethicone vs			Loperamide
Relief	Loperamide	Simethicone	Placebo	vs Placebo
Overall Illness	.0025	.0001	.0001	.0001
Diarrhea	.0052	.0001	.0001	.0001
Abdominal Discomfort	.0001	.0001	.0001	.2057

*Unadjusted for multiple comparisons

▪ Per Protocol Efficacy Analysis (Applicant's Evaluable Patients): *The results from the per protocol analysis, for both the primary and secondary efficacy endpoints, were similar to the results already reviewed under the Intent-To-Treat analysis, and will not be reviewed to avoid duplication.*

▶ Safety Analysis

Four hundred eighty-four(484) patients were included in the analysis of adverse events. One Loperamide-treated patient (#275) was lost to follow-up and was excluded from analysis.

Patients could have taken up to 8 tablets of the study medication during the 48-hour study period, or 4 tablets every 24 hours. As shown in Table 66, 26(21%) of 121 Loperamide, 36(30%) OF 119 Loperamide, 85(69%) of Simethicone, and 97(80%) of placebo-treated patients took 5 or more tablets during the 48-hour study period.

Table 66. Frequency of Number of Study Medication Tablets Taken by 484 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

	Loperamide+ Simethicone		Loperamide		Simethicone		Placebo	
Tablets	No.	%	No.	%	No.	%	No.	%
2	16	13	13	11	10	8	4	3
3	40	33	23	19	8	6	6	5
4	39	32	47	39	20	16	14	12
5	19	16	19	16	28	23	30	25
6	2	2	6	5	19	15	17	14
7	2	2/21	1	1/30	18	15/69	17	14/80
8	3	2	10	8	20	16	33	27
TOTAL	121	100	119	100	123	100	121	100

Six(6) patients reported 9 adverse events. No significant differences in the number of patients reporting adverse events were found between treatment groups. Three(3) patients (1 Loperamide+Simethicone, 1 Simethicone, 1 placebo) 4 drug-related or possible drug-related adverse reactions [Table 67].

Table 67. Adverse Events Reported by 484 Adult Patients with Acute Nonspecific Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Composite of Applicant's Tables)

Adverse Events	Loperamide+ Simethicone (N=121)	Loperamide (N=119)	Simethicone (N=123)	Placebo (N=121)	TOTAL
All*					
No. Pts. Affected	1	0	3	2	6
No. Reported	2	0	4	3	9
Drug or Possible Drug-Related**					
No. Pts. Affected	1	0	1	1	3
No. Reported	2	0	1	1	4
Serious	0	0	0	0	0
Deaths	0	0	0	0	0

* p=.385, ** p=.695, Fisher's exact test

The 4 drug-related of possible drug-related adverse events involved the digestive system, and included 2 moderate nausea reports by 1 Loperamide+Simethicone, (pt. #442), 1 moderate nausea report by 1 placebo (pt. #476), and 1 severe abdominal pain by 1 Simethicone-treated subject (pt. #104) [Table 68].

Table 68. Drug-Related Adverse Reactions Reported Among 494 Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 92-209: Intent-To-Treat. (Applicant's Table)

System	Adverse Reaction	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo	TOTAL
Body as a Whole	Abd pain	0	0	1	0	1
Digestive	Nausea	2	0	0	1	3
TOTAL		2	0	1	0	4

Two(2) patients (#104 Simethicone, and #40 placebo) were discontinued from the study because of an adverse event. Patient #104 received Simethicone and developed severe abdominal pain which was considered drug-related. The other patient #104 developed dehydration due to an intestinal infection which was considered not to be drug-related.

Applicant's Conclusions: "*Loperamide HCl (2mg) and simethicone (125mg)* administered as a combination chewable tablet, dosed as a two-tablet initial dose followed by one tablet taken after each unformed stool up to a maximum of four tablets in a 24-hour period, is effective in relieving both the symptoms of diarrhea,...*is more effective than either of its components or placebo in relieving the symptoms of diarrhea...and gas-related abdominal discomfort associated with diarrheal illness with concomitant gas-related intestinal symptoms.*

Loperamide HCl (2mg) tablets dosed as a two-tablet initial dose followed by one tablet after each unformed bowel movement up to a maximum of four tablets in a 24-hour period *is effective in treating diarrhea*, but not effective in providing relief of gas pain or cramping in patients with acute diarrheal illness with concomitant gas-related intestinal symptoms".

Reviewer's Conclusions: This factorial, randomized, placebo controlled, double blind, parallel, and multicenter clinical study to evaluate the efficacy and safety of a fixed combination of Loperamide HCl 2mg plus Simethicone 125mg, its separate components and placebo in the relief of acute nonspecific diarrhea with gas-related abdominal discomfort in adult subjects has shown that *the fixed combination is significantly better than each of its components, and placebo in the relief of acute diarrhea with concurrent abdominal discomfort associated with gas pain or cramps, and gas pressure or bloating. These results indicated that the components made a contribution to the effects of the combination.*

In addition, the study also provided evidence that *Loperamide alone was significantly better than placebo in the relief of acute nonspecific diarrhea*, but not in the relief of abdominal discomfort and associated symptoms.

No serious adverse reactions were associated with the fixed combination. A low incidence of moderate nausea was reported.

■ 3. Protocol 93-333. A multi-site, factorial, randomized, parallel, placebo controlled, and double blind clinical study to evaluate the efficacy and safety of a fixed combination of Loperamide plus Simethicone, its components and placebo, in a chewable tablet dosage form, in the treatment of acute nonspecific diarrhea with gas-related abdominal discomfort, and the efficacy of Loperamide alone in the relief of gas pain or cramps associated with acute diarrhea, in adult subjects. The study was performed under the direction of Guillermo Rodriguez Gomez, M.D. in four clinics in San Jose, Costa Rica, CA, from November, 1993 through April, 1994.

♦ Comments: The experimental design, including sample size estimation, inclusion and exclusion criteria, primary and secondary efficacy endpoints are similar to those of protocols 92-202 and 92-209. Thus no written review of this protocol will be performed to avoid unneeded duplication.

However, two important departures from the original protocol inclusion criteria were arbitrarily implemented:

1. Age was changed from ≥18y to ≥12y
2. Onset of acute diarrheal illness was changed from ≤48h to 53h

The most important change was the exceedingly long onset of illness, that will render treatment outcomes meaningless and not significantly different from placebo, and even no treatment if such control group would have been included. These predictable outcomes are obvious because acute nonspecific diarrhea, despite its morbidity, is a self-limited and short-lived disease that will clear in a short time. On these bases, the investigational evaluation of the efficacy of an antidiarrheal agent will require the inclusion of subjects preferably with onset of illness of ≤24h.

Although an interim analysis was described in the protocol, there is no report of this analysis available in NDA 20-606.

▣ **Efficacy Analysis**

As described in the protocol, 2 primary efficacy endpoints were analyzed:

1. *Time to the last unformed stool,* and

2. *Time to complete relief of gas-related abdominal discomfort.*

In addition, the following *secondary efficacy endpoints* were analyzed:

- Time to first unformed stool
- Number of unformed stools
- Time to complete relief of diarrhea
- Maximum intensity of gas-related abdominal discomfort, gas pain/cramps, and gas pressure/bloating
- End of study patients' evaluations of therapy.

The applicant performed both *intent-to-treat and per protocol* (evaluable patients) analyses.

♦ Comments: Because both the intent-to-treat and the per protocol analysis yielded similar results, only the intent-to-treat analysis will be written to avoid duplication of the review.

■

Results

A total of 480 patients were randomized to treatments, and exactly 120 patients were allocated into each of the 4 treatment groups [Table 69].

Table 69. Demographic and Clinical Baseline Data of Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Randomized to Treatment with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606: Protocol 93-333. (Applicant's Table)

Variable	Loperamide+ Simethicone (N=120)	Loperamide (N=120)	Simethicone (N=120)	Placebo (N=120)	TOTAL (N=480)	P p
Sex						
Male	62	44	48	62	216	.0320
Female	58	76	72	58	264	
Race						
White	118	118	119	120	475	.2010
Black	0	2	0	0	2	
Other	2	0	1	0	3	
Age(y)						
Mean	32.7	33.9	35.4	34.8	34.2	.4303
Range						
Age Group						
<18	0	1	0	0	1	
18-64	117	112	115	113	457	
≥65	3	7	5	7	22	
Onset Ill(h)						
Mean	20.2	21.2	21.6	21.8	21.2	.6422
Median	19.5	20.0	23.0	23.0	21.0	
Range						
Unformed Stools Prior 24h						
Mean	8.8	8.9	8.7	8.2	8.7	.7094
Median	8.0	8.0	8.0	7.0	8.0	
Range						
Abd Discomfort						
Mean	3.2	3.2	3.2	3.2	3.2	.6271
Missing	2.0	2.0	2.0	3.0	9.0	
Moderate	0	1	0	0	1	
Mod-Severe	89	95	91	90	365	
Severe	29	22	27	27	105	
Gas Pain/Cramps						
Mean	3.2	3.2	3.2	3.2	3.2	.8397
Missing	2.0	2.0	2.0	3.0	9.0	
None	0	0	1	1	2	
Mild	1	1	0	2	4	
Moderate	2	2	2	2	8	
Mod-Severe	84	84	89	81	338	
Severe	31	31	26	31	119	

Gas Pressure/ Bloating					
Mean	3.2	3.2	3.3	3.2	3.2
Missing	4.0	2.0	2.0	3.0	11.0
None	0	1	0	0	1
Mild	2	2	1	1	6
Moderate	1	2	1	1	5
Mod-Severe	87	79	83	83	332
Severe	26	34	33	32	125

In the evaluation of efficacy, of the 480 patients randomized to treatments the *applicant excluded 9 patients who did not return their diaries from by intent-to-treat analysis, and 124 patients form the per protocol analysis* [Table 70].

Table 70. Patient Subsets Evaluated For Efficacy by the Applicant in the Intent-To-Treat and Per Protocol Analyses. NDA 20-606: Protocol 93-333. (Applicant's Table, modified by MO)

Treatment Group	No. Entered	Intent-To-Treat		Per Protocol	
		Included	Excluded	Included	Excluded
Loperamide+ Simethicone	120	118	2	90	30
Loperamide	120	118	2	90	30
Simethicone	120	118	2	91	29
Placebo	120	117	3	85	35
TOTAL	480	471	9	356	124

The applicant's reasons for patients exclusions from the per protocol analysis, are listed in Table 71.

Table 71. Applicant's Reasons for Patient Exclusions from the Per Protocol Analysis of Efficacy. NDA 20-606: Protocol 93-333. (Applicant's Table, modified and corrected by MO)

Reason for Exclusion	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo	TOTAL
No diary returned	2	2	2	3	9
Onset ≥53h	1	2	0	0	3
<3 unformed stools prior 24h	1	0	0	0	1
Prohibited medication	4	3	3	1	11
≥5 tablets in 24h	7	11	12	10	40
Took 2 tablets after initial dose	0	0	1	2	3
No dose after unformed stool	12	10	8	13	43
Took dose with no unformed stool	3	2	3	6	14
TOTAL	30	30	29	35	124

Because of the low number of patients entered in site 4, this site was combined with site 1 for efficacy analyses.

Patients were stratified by the frequency of stools at baseline, e.g., Category 1=3-5 stools, Category 2 ≥6 stools [Table 72].

Table 72. Stool Frequency at Baseline Among Adult Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606: Protocol 93-333. (Applicant's Table, truncated by MO)

Analysis	Stool Cat	Stool Freq	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo	TOTAL
Intent-To-Treat			118	118	118	117	471
	1	3-5	118	118	118	117	471
	2	≥6	24	24	23	40	111
Per Protocol			90	90	91	85	356
	1	3-5	20	20	17	30	87
	2	≥6	70	70	74	55	269

Intent-To-Treat

- Primary Efficacy Endpoints:

- Time to Last Unformed Stool: *There were no significant differences in the median survival times(h) between the combination and its components alone and placebo, either by stool category or definition, or by site of study* [Table 73].

Table 73. Median Time(h) to Last Unformed Stool in Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

Treatment Group	Stool Frequency 3-5	Stool Frequency ≥6	Sites 1+4	Sites 2	Sites 3	Sites All
			Definition A			
Loperamide+ Simethicone	4.7	13.0	13.0	5.9	7.2	9.5
Loperamide	9.5	9.0	12.0	5.9	8.5	9.0
Simethicone	6.8	19.7	16.6	18.8	23.5	19.0
Placebo	18.0	23.0	20.9	27.5	6.0	20.8
Log-rank, p	.5886	.0104	.1183	.0446	.3359	.0149
Wilcoxon, p	.4429	.0277	.3874	.0155	.1504	.0393
			Definition B			
Loperamide+ Simethicone	5.7	21.0	22.6	6.6	8.0	13.9
Loperamide	9.5	14.0	20.0	5.9	9.2	12.0
Simethicone	11.5	21.0	21.6	18.8	25.0	20.0
Placebo	20.4	27.0	24.0	27.5	15.7	24.0
Log-rank, p	.3674	.0703	.2529	.1302	.7107	.0487
Wilcoxon, p	.4238	.0595	.4513	.0485	.2548	.0393

Pairwise comparison of treatments did provide the same results. In addition, Loperamide alone was significantly better than placebo in decreasing the median survival time(h) to last unformed stool [Table 74].

Table 74. Comparison Median Time(h) to Last Unformed Stool in Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

Stools	P*, Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
		Definition A		
3-5				
Log-rank	.9817	.9983	.3795	.1970
Wilcoxon	.3321	.5645	.1428	.3758
≥6				
Log-rank	.0453	.8436	.2267	.0006
Wilcoxon	.2244	.3079	.1496	.0067
Both				
Log-rank	.0619	.8074	.2511	.0007
Wilcoxon	.4594	.2347	.0938	.0084
Site 1+4				
Log-rank	.0412	.7635	.6602	.0100
Wilcoxon	.3198	.7329	.4876	.0827
Site 2				
Log-rank	.8613	.6620	.0383	.0079
Wilcoxon	.7763	.1235	.0192	.0064
Site 3				
Log-rank	.7790	.2803	.6523	.9000
Wilcoxon	.7704	.0623	.7736	.9554
		Definition B		
3-5				
Log-rank	.6519	.9346	.4069	.0545
Wilcoxon	.6032	.5428	.1653	.1557
≥6				
Log-rank	.1212	.6350	.2828	.0067
Wilcoxon	.3645	.5546	.0895	.0077
Both				
Log-rank	.1001	.7176	.3423	.0038
Site 1+4				
Log-rank	.1087	.5281	.7730	.0525
Wilcoxon	.4436	.6770	.4590	.1131
Site 2				
Log-rank	.7059	.9657	.1160	.0220
Wilcoxon	.7763	.2272	.0434	.0146
Site 3				
Log-rank	.8615	.4571	.8805	.4672
Wilcoxon	.9710	.1176	.4061	.3737

*Unadjusted for multiple comparisons

• Time to Complete Relief of Gas-Related Abdominal Discomfort: The median survival times(h) for the combination, its components, and placebo were not significantly different from each other, except for Site 2 and severe discomfort, where the time was significantly shorter for the combination and Loperamide alone compared with placebo [Table 75].

Table 75. Median Time(h) to Complete Relief of Abdominal Discomfort in Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20 -606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

		Abdominal Discomfort		Sites		
Treatment	All	Mod-Severe	Severe	1+4	2	3
Loperamide+ Simethicone	44.0	44.0	43.2	45.0	22.5	47.5
Loperamide	41.5	42.0	35.7	43.0	23.0	42.0
Simethicone	40.5	40.5	43.5	41.0	35.5	46.9
Placebo	46.5	45.0	>48	48.0	>48	41.7
Log-rank, p	.2556	.6764	.0589	.6823	.0348	.8041
Wilcoxon, p	.3615	.7229	.1121	.6614	.0993	.7315

Similar results were obtained by pairwise comparison of treatments [Table 76].

Table 76. Comparison of Time(h) to complete Relief of Abdominal Discomfort In Patients with Acute Nonspecific Diarrhea, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

Abd Discomfort	P*, Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
Mod-Severe				
Log-rank	.9657	.6854	.0905	.0755
Wilcoxon	.9897	.6262	.5109	.5171
Severe				
Log-rank	.4600	.3029	.0432	.0130
Wilcoxon	.4763	.4073	.0755	.0218
Both				
Log-rank	.8560	.8790	.0905	.0755
Wilcoxon	.7923	.9714	.1546	.1087
Site 1+4				
Log-rank	.9790	.8014	.3428	.4055
Wilcoxon	.8595	.5436	.4638	.4667
Site 2				
Log-rank	.9000	.7957	.0093	.0072
Wilcoxon	.7918	.5856	.0214	.0181
Site 3				
Log-rank	.7193	.8919	.4605	.6745
Wilcoxon	.6592	.8292	.4223	.6912

*Unadjusted for multiple comparisons

■ Secondary Efficacy Endpoints:

• Time to First Unformed Stool: *Median survival time(h) for the combination and Loperamide alone were significantly shorter than placebo only in site 3. No other significant differences between treatments were found* [Table 77].

Table 77. Median Time(h) to First Unformed Stool in Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

	Baseline Stools		Sites			
Treatment	3-5	≥6	1+4	2	3	All
Loperamide+ Simethicone	14.7	4.0	4.0	3.2	7.0	4.2
Loperamide	2.7	4.2	3.9	3.0	5.0	4.0
Simethicone	4.0	3.2	6.0	2.2	4.0	3.5
Placebo	5.0	3.5	4.2	5.0	3.0	4.0
Log-rank, p	.3212	.1022	.3779	.1482	.0157	.1691
Wilcoxon, p	.3278	.2654	.6471	.4057	.0242	.4031

Pairwise comparisons of treatments showed also a significant difference in shorter median survival time(h) between the combination and placebo, and between Loperamide alone and placebo at site 3 only [Table 78].

Table 78. Comparison of Time(h) to First Unformed Stool in Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

Baseline Stools	P*, Loperamide+Simethicone vs			Loperamide
Statistic	Loperamide	Simethicone	Placebo	vs Placebo
3-5				
Log-rank	.0972	.3069	.0906	.7536
Wilcoxon	.0830	.3241	.1669	.4462
≥6				
Log-rank	.3843	.2439	.2070	.0388
Wilcoxon	.5465	.2520	.3116	.1263
Both				
Log-rank	.9918	.1166	.0976	.1140
Wilcoxon	.7998	.1470	.2181	.3716
Site 1+4				
Log-rank	.5498	.9777	.5372	.9964
Wilcoxon	.1905	.6902	.5186	.4983
Site 2				
Log-rank	.6571	.0995	.5452	.2729
Wilcoxon	.6019	.2810	.9406	.5968
Site 3				
Log-rank	.9781	.0604	.0485	.0077
Wilcoxon	.6193	.2080	.1240	.0035

*Unadjusted for multiple comparisons

• Number of Unformed Stools: *The mean number of stools was significantly lower in the 12-24 hour period for the combination group compared with placebo. No other significant differences were detected* [Table 79].

Table 79. Mean Number of Unformed Stools in Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone or in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

	Mean±SE			
Time(h)	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo
0-12	1.54±.16	1.75±.16	1.88±.17	1.86±.14
12-24	.48±.16	.64±.16	.87±.17	1.05±.14
24-36	.63±.16	.58±.16	.78±.17	.85±.14
36-48	.20±.16	.13±.16	.35±.17	.44±.14

Similar results were obtained by pairwise treatment comparisons [Table 80].

Table 80. Comparison of Mean Number of Stools in Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

	P*, Loperamide+Simethicone vs			Loperamide
Time(h)	Loperamide	Simethicone	Placebo	vs Placebo
0-12	.3645	.1464	.1349	.6034
12-24	.4928	.0938	.0086	.0588
24-36	.8414	.5421	.3136	.2162
36-48	.7779	.5063	.2528	.1479

*Unadjusted for multiple comparisons

• Time to Complete Relief of Diarrhea: *Patients on Loperamide alone had a significantly shorter median survival time(h) to complete relief of diarrhea, than placebo* [Table 81].

Table 81. Median Time(h) to Complete Relief of Diarrhea In Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 933-333: Intent-To-Treat. (Applicant's Table)

	Baseline Stool Category		
Treatment	3-5	≥6	Both
Loperamide+ Simethicone	30.0	26.5	27.2
Loperamide	21.4	27.3	26.0
Simethicone	28.0	30.4	30.0
Placebo	31.0	34.5	33.0
Log-rank, p	.1002	.0796	.0553
Wilcoxon, p	.1518	.1282	.0703

Pairwise comparison of treatments showed that both baseline stool categories, Loperamide alone was significantly better than placebo in shortening the median survival time to complete relief of diarrhea [Table 82].

Table 82. Comparison of Time(h) to Complete Relief of Diarrhea in Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

Baseline Stools	P*, Loperamide+Simethicone vs			Loperamide
Statistics	Loperamide	Simethicone	Placebo	vs Placebo
3-5				
Log-rank	.0480	.8696	8101	.0277
Wilcoxon	.1140	.9391	.9770	.0294
≥6				
Log-rank	.4258	.6855	0886	.0130
Wilcoxon	.7839	.8440	.0563	.0224
Both				
Log-rank	.1500	.6338	.2173	.0064
Wilcoxon	.3467	.9017	.1170	.0071

*Unadjusted for multiple comparisons

- Intensity of Gas-Related Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating: *There were no significant differences between treatments in the mean change from baseline of any of the 3 symptoms intensity during the first 8 hours of treatment* [Table 83].

Table 83. Comparison of Mean Change from Baseline in Abdominal Discomfort, Gas Pain/Cramps, and Gas Pressure/Bloating Intensity in Patients with Acute Diarrhea, During the First 8 Hours of Treatment with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

Time (h)	P*, Loperamide+Simethicone vs Loperamide	P*, Loperamide+Simethicone vs Simethicone	P*, Loperamide+Simethicone vs Placebo	P*, Loperamide vs Placebo
		Abdominal Discomfort		
1	.8163	.1637	.7489	.5919
2	.7636	.4113	.8094	.5968
3	.8804	.6584	.4778	.4087
4	.5804	.4314	.6923	.8628
5	.5696	.2784	.9492	.5311
6	.3390	.1296	.2610	.9042
7	.3312	.2223	.1310	.6362
8	.6685	.3417	.2096	.4412
		Gas Pain/Cramps		
1	.3141	.0012	.2102	.8076
2	.6209	.0408	.4468	.7909
3	.3009	.0499	.1244	.6167
4	.4290	.3538	.8554	.5393
5	.3495	.4960	.6552	.6209
6	.3823	.5562	.7668	.2392
7	.7599	.9922	.2801	.1643
8	.4974	.5240	.5363	.1926
		Gas Pressure/Bloating		
1	.7979	.2224	.4092	.5524
2	.7737	.5683	.5244	.3355
3	.8122	.3869	.2801	.1696
4	.4892	.7938	.8785	.5749
5	.8886	.9117	.6621	.5475
6	.4221	.6814	.4859	.9129
7	.6277	.9206	.6444	.9810
8	.9257	.8800	.5176	.4399

*Unadjusted for multiple comparisons

After 8 hours of treatment, there was no evidence of significant differences between treatments in mean differences from baseline of gas-related symptoms intensity [Table 84].

Table 84. Comparison of Differences from Baseline of Gas-Related Symptoms Intensity in Patients with Acute Diarrhea, After 8 Hours of Treatment with Loperamide and Simethicone, Alone and in Combination, or Placebo. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

	P*. Loperamide+Simethicone vs			Loperamide
Time(h)	Loperamide	Simethicone	Placebo	vs Placebo
		Abdominal Discomfort		
12	.8557	.2925	.0617	.1120
Bedtime 1	.9063	.5230	.2104	.2816
Next morning 1	.8720	.2288	.0361	.0633
24	.3662	.2188	.4404	.1047
36	.2489	.4665	.1717	.0154
Bedtime 2	.8278	.1753	.0562	.1097
Next morning 2	.9665	.1134	.0469	.0630
48	.4710	.1155	.0723	.3186
		Gas Pain/Cramps		
12	.4533	.6868	.2049	.0454
Bedtime 1	.6456	.3904	.2034	.4094
Next morning 1	.7722	.0974	.2191	.3405
24	.3356	.6567	.7099	.1807
36	.1733	.7424	.8052	.1101
Bedtime 2	.8138	.4459	.0945	.0585
Next morning 2	.6602	.1043	.1017	.0378
48	.9066	.1750	.1758	.2196
		Gas Pressure/ Bloating		
12	.9472	.9959	.4240	.3731
Bedtime 1	.9323	.7777	.7046	.7583
Next morning	.8622	.1927	.1743	.1060
24	.3383	.8992	.4589	.0797
36	.0503	.5205	.7660	.0215
Bedtime 2	.7124	.5783	.1456	.0585
Next morning 2	.6229	.1006	.0163	.0424
48	.2370	.0651	.0117	.1540

*Unadjusted for multiple comparisons

• End of Study Patients' Evaluation of Treatment Efficacy: *There were no significant differences between treatments on mean scores of treatment efficacy on the relief of diarrhea or abdominal discomfort* [Table 85].

Table 85. End of Study Treatment Efficacy Evaluations by Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

Relief	Loperamide+ Simethicone	Loperamide	Simethicone	Placebo	p
Diarrhea	2.82	2.94	2.70	2.78	.5309
Abd Discomfort	2.44	2.39	2.19	2.27	.5264
Both	2.73	2.75	2.49	2.65	.3995

Pairwise treatment comparisons did not find any significant differences between treatment groups [Table 86].

Table 86. Comparison of End of Study Treatment Efficacy Evaluations by Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Intent-To-Treat. (Applicant's Table)

	P*, Loperamide+Simethicone vs			Loperamide
Relief	Loperamide	Simethicone	Placebo	vs Placebo
Diarrhea	.4725	.4640	.7891	.3251
Abd Discomfort	.7852	.1771	.3715	.5340
Both	.9084	.1544	.6468	.5658

*Unadjusted for multiple comparisons

■ Per protocol analysis: *The results from this analysis were similar to those already reviewed in the intent-to-treat analysis. To avoid duplication, the per protocol analysis will not be duplicated.*

■ Safety

Of the 480 patients randomized to treatments, 7 patients (2 Loperamide+Simethicone, 1 Loperamide, 2 Simethicone, and 2 placebo) were lost to follow-up, and they were excluded from safety analysis by the applicant, leaving a subset of 473 patients for safety analysis.

Patients could have chewed 4 tablets in 24 hours, or up to 8 tablets in the 48-hour study period. Forty-five(45) or 38% of 118 patients in the Loperamide+Simethicone group took 5 or more tablets during the study, compared to 48(40%) of 119 patients in the Loperamide, 55(47%) of 118 patients in the Simethicone, and 58(49%) of 118 patients in the placebo groups [Table 87].

Table 87. Frequency Distribution of Tablets Taken by 473 Patients with Acute Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Safety. (Applicant's Table)

No.	Loperamide+ Simethicone		Loperamide		Simethicone		Placebo		TOTAL	
Tablets	No.	%	No.	%	No.	%	No.	%	No.	%
Unknown	0	0	1	1	0	0	1	1	2	0
2	25	21	24	20	20	17	17	14	86	18
3	24	21	23	19	16	14	16	13	79	17
4	24	21	23	19	27	23	26	22	100	21
5	17	14	13	11	14	12	8	7	52	11
6	4	3	(38)12	10(40)	9	7(47)	14	12(49)	39(44)	8
7	5	4	3	3	7	6	7	6	22	5
8	19	16	20	17	25	21	29	25	93	20
TOTAL	118	100	119	100	118	100	118	100	473	100

()=Percent

There were 78 adverse events reported by 44 patients. Of these, 12 patients took the combination, 14 took Loperamide alone, 11 took Simethicone alone, and 7 took placebo. A pregnancy, labeled as a serious adverse event, occurred in 1 Simethicone patient. No deaths were reported [Table 88].

Table 88. Adverse Events Reported by 473 patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Safety. (Applicant's Table)

Adverse Events	Loperamide+ Simethicone (N=118)	Loperamide (N=119)	Simethicone (N=118)	Placebo (N=118)	TOTAL (N=473)
No. Patients	12	14	11	7	44
No. Reports	19	31	16	12	78
Serious	0	0	1	0	1
Deaths	0	0	0	0	0

Fisher's exact test, p=.446

Of the 78 adverse events reported, 64 reports were considered to be drug-related or possible drug-related [Table 89].

Table 89. Drug-Related or Possible Drug-Related Adverse Events Among 473 Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Safety. (Applicant's Table)

Adverse Events	Loperamide+ Simethicone (N=118)	Loperamide (N=119)	Simethicone (N=118)	Placebo (N=118)	TOTAL (N=473)
No. Patients	10	11	6	5	32
No. Reports	17	28	9	10	64
Serious	0	0	0	0	0

The most frequent adverse events associated with the combination of Loperamide plus Simethicone, were taste perversion, dizziness, nausea, and dry mouth [Table 90]. No patient was withdrawn from the study because of an adverse reaction.

Table 90. Drug-Related Adverse Reactions Reported by 473 Patients with Acute Nonspecific Diarrhea and Gas-Related Abdominal Discomfort, Treated with Loperamide and Simethicone, Alone and in Combination, or Placebo for 48 Hours. NDA 20-606. Protocol 93-333: Safety. (Applicant's Table)

System	Adverse Reaction	Loperamide+ Simethicone (N=118)	Loperamide (N=119)	Simethicone (N=118)	Placebo (N=118)	TOTAL (N=473)
Body as a Whole	Chills	1	0	0	0	1
	Pain	0	1	1	1	4
	Abd pain	0	0	1	0	1
Digestive	Constipation	0	1	2	2	1
	Dry mouth	2	3	0	0	5
	Nausea	2	1	2	1	6
	Other	0	1	0	0	1
Nervous	Dizziness	0	2	2	5	9
	Somnolence	1	1	0	0	0
Skin	Rash	1	0	1	0	2
	Sweat	1	0	0	0	1
Special Senses	Taste Perversion	9	18	0	1	28

▶ Applicant's Conclusions: "Loperamide HCl (2mg) and simethicone (125mg) administered as a combination chewable tablet, dosed as a two-tablet initial dose followed by one tablet... after each unformed stool up to a maximum of four tablets in a 24-hour period and loperamide alone demonstrated similar clinical efficacy in relieving the diarrheal symptoms,...(but it) did not demonstrate any consistent statistically significant differences compared with either its components or placebo in relieving the symptoms of gas-related abdominal discomfort...Loperamide HCl (2mg)...did not differ from placebo in providing relief of gas pain/cramps...".

The combination "is well tolerated when administered to patients with acute diarrheal illness with concomitant gas-related intestinal symptoms...".

▶ Reviewer's Conclusions: This factorial, randomized, multisite clinical study to evaluate the comparative efficacy of a fixed Loperamide plus Simethicone combination, its components, and placebo in the relief of acute nonspecific diarrhea and gas related abdominal symptoms, did not show that the combination was significantly better than its components alone and placebo in the relief of diarrhea and concurrent gas-related symptoms.

Loperamide alone was significantly better than placebo in the relief of acute diarrhea, but not in the relief of concurrent gas-related abdominal discomfort.

The most frequent adverse events related to the combination were taste changes, nausea, and dry mouth.

Review of OTC Labeling

- Comments: The sections of the proposed draft labeling do not follow the format required in the TFM for OTC antidiarrheal drug products [Fed Reg 1986;51:16138-16149]. In addition, the applicant intercalated several promotional statements that are not appropriate in a label.

Recommendations

1. NDA 20-606 for the OTC use of the fixed combination of Loperamide HCl 2mg and Simethicone 125mg, in a chewable tablet dosage form, for the control of diarrhea, including traveler's diarrhea, and associated gas-related symptoms of abdominal pain, cramps, and bloating, is approvable.

Two(2) well controlled, factorial clinical studies [protocols Nos. 92-202 and 92-209] showed that the fixed combination, was significantly better than its components alone and placebo in the relief of acute nonspecific diarrhea and associated gas-related abdominal symptoms.

2. The applicant should be requested to delete all the promotional statements from the draft labeling, and to rearrange the headings of the draft labeling to conform with the labeling format and content required in the TFM for OTC antidiarrheal drug products, and in 21 CFR 332 for OTC antiflatulent drug products, and to submit the revised draft labeling for review.

Jose G. Canchola, M.D., M.P.H.

cc:
NDA 20-606
HFD-180
HFD-180/SFredd
HFD-180/JCanchola
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
f/t 4/26/96 jgw
MED\N\20606604.0JC

4/29/96
Concur with rec. 1 & 2.
We will send them marked up labeling we think is approvable.

Stonger

ADDENDUM TO MOR OF NDA 20-606

NDA Amendment No. 6 dated April 25, 1996. The applicant submitted a revised draft labeling for both the carton and pouch.

The revised labeling does not include promotional statements, and the heading sections are presented in the proper sequence.

Conclusions: The proposed draft labeling is adequate.

RECOMMENDATION: NDA 20-606 should be approved for the OTC use of the fixed combination of Loperamide and Simethicone in the control of acute nonspecific diarrhea, including traveler's diarrhea, and gas-related abdominal symptoms.

Jose G. Canchola

Jose G. Canchola, M.D., M.P.H.

cc:
NDA 20-606
HFD-180
HFD-180/SFredd
HFD-180/JCanchola
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
f/t 4/30/96 jgw
MED\N\20606604.1JC

4/30/96

STATISTICAL REVIEW AND EVALUATION

Date: **June 19, 1996**

NDA: 20-606

Applicant: McNeil Consumer Products Company

Name of Drug: Loperamide HCL/Simethicone Chewable Tablets

Indication: For the control of the symptoms of diarrhea and associated gas.

Document Reviewed: NDA Vol. 1 - 16; Dated 28 July 1995.

Medical Reviewer: This review has been discussed with medical officer, Jose Canchola, MD., (HFD-180).

I. Introduction

This statistical review pertains two main trials, Study #s 92-202 and 92-209, which the sponsor has submitted for the claim that the combination therapy loperamide/simethicone is more effective than its components or placebo in treating acute diarrhea and gas related abdominal discomfort. Loperamide as a single component is effective in treating acute diarrhea and simethicone in relieving gas related discomfort. These two trials are of factorial designs, each with 4 treatment arms: loperamide & simethicone combination, loperamide alone, simethicone alone, and placebo.

The sponsor has submitted two additional trials, # 92-210 and # 93-333. Since trial #92-210 was discontinued due to slow enrollment and the statistical results of trial #93-333 performed by the sponsor were not considered for approval, these two trials are not addressed in this statistical review.

In this review, two major endpoints are considered: 1) time to last unformed stool (TTLUS) and 2) time to complete relief of gas-related symptoms (TTCRGAD). The statistical hypotheses focussed on are i) for TTLUS, the combination is better than placebo and simethicone; ii) for TTCRGAD, the combination is better than placebo and loperamide.

II. Study 92-202/U.S. Study

2.1 Design

This study was a randomized, parallel, double-blind, single-site (multi-site was planned in the protocol), placebo-controlled trial. A total of 480 completed patients (120 in each treatment group) was planned. A total of 493 patients entered into the study. Patients who met the inclusion criteria entered one of the following four treatment groups in randomization blocks of twelve patient. The treatment groups were loperamide HCL 2mg/simethicone 125 mg, loperamide HCL 2mg, simethicone 125 mg, and placebo. The study had a double-blind treatment period of 48 hours. Patients who entered this treatment period were dispensed eight tablets. Patients took two tablets initially, followed by one tablet after each unformed stool, up to a total of four tablets in any 24-hour period. Patients recorded the time and consistency of each bowel movement and other relevant efficacy measurements during this 48 hour treatment period.

The primary efficacy measure for the relief of diarrhea symptoms was the time to the last unformed stool. The primary efficacy measure for the relief of gas-related symptoms was the time to complete relief of gas-related abdominal discomfort. Time to last unformed stool (TTLUS) established the time when objective signs of diarrhea stopped. The sponsor considered two working definitions, A and B, of TTLUS. For patients who completed the study (or discontinued because their diarrhea resolved), TTLUS was the elapsed time from initial dose to the time of the last unformed stool where only formed stool or no stools were subsequently reported. The difference between Definition A and Definition B is that Definition A set TTLUS equal to zero if the first unformed stool occurred after a 24-hour period without stooling since the patient entered the study. Please see Appendix A for detail of theses two definitions. Definition B is more practical than definition A to define time to last unformed stool and will be used in this reviewer's assessment.

2.2 Sponsor's statistical analysis and results

The sponsor used Survival analysis technique to analyze time to last unformed stool and time to complete relief of gas-related abdominal discomfort (TTCRGAD). Comparisons among the survival curves of the patients in the four treatment groups (loperamide/simethicone, loperamide, simethicone, and placebo) were made using both the log-rank and generalized Wilcoxon tests.

In addition, the secondary endpoint, maximum intensity ratings of gas-related abdominal discomfort (MIRGAD) was analyzed at various time points as differences from baseline using ANOVA techniques.

The sponsor summarized the baseline characteristics by treatment in the sponsor's Table 2 of Volume 1.11. The baseline characteristics analyzed in this study were sex, race, age, weight, treatment delay, number of unformed stools in the prior 24 hours, initial overall abdominal discomfort, and initial gas pain/cramps. The treatment groups appeared balanced with respective to the baseline characteristics analyzed.

Finally, based on the analysis results of TTLUS (for both definition A and definition B), TTCRGAD, and MIRGAD, the sponsor made efficacy claims in favor of a treatment strategy when patients were given two-tablet initial dose followed by one tablet taken after each unformed stool up to a maximum of four tablets in a 24-hour period. The efficacy claims included:

"1) Loperamide HCL 2mg and simethicone 125 mg administered as a combination chewable tablet is effective in relieving both the symptoms of diarrhea and gas-related abdominal discomfort for patients with acute diarrhea illness with concomitant gas-related intestinal symptoms.

2) Loperamide HCL 2mg and simethicone 125 mg administered as a combination chewable tablet is more effective than either of its components or placebo in relieving both the symptoms of diarrhea and gas-related abdominal discomfort for patients with acute diarrhea illness with concomitant gas-related intestinal symptoms.

3) Loperamide HCL 2mg tablets is effective in providing relief of gas-related abdominal symptoms, including bloating/distension and abdominal pain/cramps for patients with acute diarrhea illness with concomitant gas-related intestinal symptoms."

2.3 Reviewer's Analyses and Comments

In order to validate the sponsor's efficacy claim for this study, this reviewer did 1) survival analysis, and 2) crude rate analysis . The purpose of these analyses was to check the robustness of the sponsor's claimed results.

1) Survival Analysis.

Survival analysis using Cox's proportional Hazard Model was employed to analyze the following variables:

a) time to last unformed stool (TTLUS),
b) time to first formed stool (TTFFS), and
c) time to complete relief of gas-related abdominal discomfort (TTCRGAD).

In order to perform the survival analyses , the three variables, TTLUS, TTFFS, and TTCRGAD were developed by this reviewer. The variable TTLUS was computed based on Definition B described in Appendix A. However, if last record of the patient was unformed stool, time to last unformed stool was classified as a censored time as is done in a standard survival analysis when no event occurs to the end of the study period.

Variable TTFFS was the elapsed time from initial dose to the time of the first formed stool where only formed stools were subsequently reported or the first formed stool for the patient was at the last record. On the other hand, if the last record of the patient still indicated unformed stool, the censored

time of the time to first formed stool was the number of hours from the initial dose to the time of the unformed stool showed in the last record. Finally, the time to complete relief of gas-related abdominal discomfort was set to 48 hours and declared as a censored time if its value was missing from the data diskette submitted by the sponsor.

This reviewer first performed the survival analysis with Cox's proportional hazard model on the four treatment groups, loperamide & simethicone combination, loperamide alone, simethicone, and placebo to detect if the hazard functions for the four treatment groups in each of the three variables, TTLUS, TTFFS, and TTCRGAD are equal. The statistical results indicated that the hazard functions of the four treatment groups in each of the three variables were significantly different (three P values all equal to 0.0001).

The survival analysis with Cox's proportional hazard model was used to perform the following five pairwise comparisons: loperamide & simethicone combination vs. loperamide alone, loperamide & simethicone combination vs. simethicone alone, loperamide & simethicone combination vs. placebo, loperamide alone vs. placebo, and simethicone alone vs. placebo. This was done for each of the three variables, TTLUS, TTFFS, and TTCRGAD, to validate the efficacy of the new drug loperamide & simethicone combination, claimed by the sponsor. The statistical results for both the pairwise comparisons and the risk ratios are presented in this reviewer's Table 2.3.1 (below). Here, in Table 2.3.1, we denote L+S for loperamide & simethicone combination, L for loperamide alone, and S for simethicone alone.

Table 2.3.1 (Reviewer)/Study 92-202
Survival Analysis For The Pairwise Comparisons
(2-sided P-Values and Risk Ratios in Parenthesis)

Endpoints	L+S vs. L	L+S vs. S	L+S vs. Placebo	L vs. Placebo	S vs. Placebo
TTLUS	0.0028 (1.52)	0.0001 (3.50)	0.0001 (5.87)	0.0001 (3.97)	0.001 (1.84)
TTFFS	0.0002 (1.68)	0.0001 (3.96)	0.0001 (6.06)	0.0001 (3.63)	0.0077 (1.64)
TTCRGAD	0.0001 (3.5)	0.0001 (1.72)	0.0001 (7.60)	0.0001 (2.42)	0.0001 (4.26)

Note:

1. **P value less than 0.05 indicated that the recovering time for a patient taking the first drug in the pairwise comparison is less than that of a patient taking the second drug.**
2. **Risk ratio greater than one indicated that patients taking first drug in the pairwise comparison had larger opportunity to recover than those patients taking second drug.**

Results in Table 2.3.1 indicates that the loperamide & simethicone combination is superior to loperamide alone, simethicone alone, and placebo in treating the diarrhea and relieving the gas-related abdominal discomfort. In addition, both loperamide alone and simethicone alone are

significantly better than placebo for both symptoms.

The survival distributions for the four treatment groups on the three variables, TTLUS, TTFFS, and TTCRGAD, were estimated by Kaplan-Meier method and are presented in Figure 1 through Figure 3 (attached). These figures also indicated that the patients in the group of loperamide & simethicone combination had the shortest diarrhea and abdominal discomfort times in comparison to those in the other treatment groups.

2) Crude Rate Analysis

This reviewer performed a crude rate analysis for the first 24-hour treatment period to detect the early treatment effect and for the total 48-hour treatment period for validating the overall treatment effect. The crude rate analysis is more conservative; it compares the rates formed by the total # of events in the numerator over the total # of patients randomized in the denominator. It is an intent-to-treat analysis. Table 2.3.2 (below) shows the results of this crude analysis.

Table 2.3.2 (Reviewer)/Study 92-202
Crude Rate Analysis Results
Response Rates

		Loperamide & Simethicone	Loperamide	Simethicone	Placebo
Control Of Diarrhea	24-Hour	84/124 (68%)	62/120 (52%)	19/120 (16%)	8/116 (7%)
	48-hour	109/124 (88%)	97/120 (81%)	74/120 (62%)	46/116 (40%)
Control Of Gas-related Discomfort	24-Hour	101/124 (81%)	39/120 (33%)	75/120 (63%)	13/116 (11%)
	48-hour	117/124 (94%)	83/120 (69%)	102/120 (85%)	45/116 (39%)

Table 2.3.2 (Reviewer)/Study 92-202
Crude Rate Analysis Results
2-Sided P-Values (Chi-Square test)

		L+S Vs. L	L+S Vs. S	L+S Vs. Placebo	L Vs. Placebo	S Vs. Placebo
Control Of Diarrhea	24-Hour	0.01	0.001	0.001	0.001	0.031
	48-Hour	0.128	0.001	0.001	0.001	0.001
Control Of Gas-related Discomfort	24-Hour	0.001	0.001	0.001	0.001	0.001
	48-Hour	0.001	0.016	0.001	0.001	0.001

The results in Table 2.3.2 (Reviewer) validate the results in favor of the loperamide & simethicone combination therapy by a conservative statistical approach.

III. Study 92-209/U.S. Study

3.1 Design

This study was a randomized, parallel, double-blind, multi-site, placebo-controlled trial. A total of 480 completed patients (120 in each treatment group) was planned. A total of 485 patients were entered into the study with 483 eligible for the intent to treat analysis and 437 eligible for the per protocol analysis. Patients who met the inclusion criteria were randomly assigned to one of the following four treatment groups in randomization blocks of twelve patient. The treatment groups were loperamide HCL 2mg/simethicone 125 mg, loperamide HCL 2mg, simethicone 125 mg, and placebo. The study had a double-blind treatment period of 48 hours. Patients who entered this treatment period were dispensed eight tablets. Patients took two tablets initially, followed by one tablet after each unformed stool, up to a total of four tablets in any 24-hour period. Patients recorded the time and consistency of each bowel movement and other relevant efficacy measurement during this 48 hour treatment period.

The primary efficacy measures for the relief of diarrhea and gas-related symptoms were the same as Study 92-202.

3.2 Sponsor's statistical analysis and results

The sponsor used Survival analysis technique to analyze the time to last unformed stool and time to complete relief of gas-related abdominal discomfort (TTCRGAD). Comparisons among the survival curves of the patients in the four treatment groups were made using both the log-rank and generalized Wilcoxon tests.

In addition, the secondary endpoint, maximum intensity ratings of gas-related abdominal discomfort (MIRGAD) was analyzed at various time points as differences from baseline using ANOVA techniques.

The results of statistical analyses on the demographic and baseline characteristics by treatment groups and investigators were listed form Table 4 through Table 10 of Volume 1.14. The baseline characteristics analyzed in this study were sex, race, age, age group, weight, height, temperature, treatment delay, number of unformed stools in the prior 24 hours, initial overall abdominal discomfort, initial gas pain/cramps, and initial gas pressure/bloating. The results indicated that there was a significant difference among treatments for treatment delay for the all patient data sets, and sex for the per protocol data set.

Table 3.2.1 (below) provides the overall test results of the Survival analyses on time to last unformed stool by Definition B and time to complete relief of gas-related abdominal discomfort, which are copied from sponsor's Table 13 and Table 27 of Volume 1.14, respectively.

Table 3.2.1 (Sponsor) Overall Test P-Values (ITT)

Time to last unformed stool (Definition B)

Test	Loperamide/ Simethicone vs Loperamide	Loperamide/ Simethicone vs Simethicone	Loperamide/ Simethicone vs Placebo	Loperamode vs Placebo
Log Rank	0.0586	0.0001	0.0001	0.0001
Wilcoxon	0.0709	0.0001	0.0001	0.0001

Table 3.2.1 (Sponsor) Overall Test P-Values (ITT)

Time to complete relief of gas-related abdominal discomfort

Test	Loperamide/ Simethicone vs Loperamide	Loperamide/ Simethicone vs Simethicone	Loperamide/ Simethicone vs Placebo	Loperamode vs Placebo
Log Rank	0.0001	0.0001	0.0001	0.5750
Wilcoxon	0.0001	0.0001	0.0001	0.8820

Table 3.2.1 (Sponsor) indicates that the loperamide/simethicone combination was not significantly superior to loperamide alone in treating diarrhea (p values equal to 0.058 and 0.07 for Log Rank test and Wilcoxon test, respectively). Similarly, the overall-all test results of the survival analysis on time to complete relief of abdominal discomfort showed that the loperamide alone was not significantly superior to placebo (p values equal to 0.5705 and 0.8820 for Log Rank test and Wilcoxon test, respectively). In addition, in the discussion section of Volume 1.14, the sponsor commented that "treatment with loperamide alone or simethicone had no effect on the duration of abdominal discomfort symptoms compared to placebo".

3.3 Reviewer's Aanalyses and Comments

In order to validate the sponsor's efficacy claim for this study, this reviewer did 1) survival analysis, and 2) crude rate analysis. The purpose of these analyses was to check the robustness of the sponsor's claimed results.

1) Survival Analysis.

Survival analysis using Cox's proportional Hazard Model was employed to analyze the following variables based on the data set pooled over three investigators and data set for each investigator:

a) time to last unformed stool (TTLUS),
b) time to first formed stool (TTFFS), and
c) time to complete relief of gas-related abdominal discomfort (TTCRGAD).

In order to perform the survival analyses , the three variables, TTLUS, TTFFS, and TTCRGAD were developed by this reviewer.

Variable TTLUS was computed based on Definition B described in Appendix A. However, if last record of the patient was unformed stool, time to last unformed stool was classified as a censoring time as is done in a standard survival analysis when no event occurs to the end of the study period. The variable TTFFS was the elapsed time from initial dose to the time of the first formed stool where only formed stools were subsequently reported or the first formed stool for the patient was at the last record. On the other hand, if the last record of the patient still indicated unformed stool, the censored time of the time to first formed stool was the number of hours from the initial dose to the time of the unformed stool showed in the last record. Finally, the time to complete relief of gas-related abdominal discomfort was set to 48 hours and declared as a censored time if its value was missing from the data diskette submitted by the sponsor.

Since the results of survival analysis based on the data set pooled over three investigators and data set for each investigator are similar, the statistical methods and results based on the data set pooled over three investigators are discussed below.

This reviewer first performed the survival analysis with Cox's proportional hazard model on the four treatment groups, loperamide & simethicone combination, loperamide alone, simethicone, and placebo to detect if the hazard functions for the four treatment groups in each of the three variables, TTLUS, TTFFS, and TTCRGAD are equal. The statistical results indicated that, for the overall test, the hazard functions of the four treatment groups in each of the three variables were significantly different (three P values all equal to 0.0001).

The survival analysis with Cox's proportional hazard model was used to perform the following five pairwise comparisons: loperamide & simethicone combination vs. loperamide alone, loperamide & simethicone combination vs. simethicone alone, loperamide & simethicone combination vs. placebo, loperamide alone vs. placebo, and simethicone alone vs. placebo. This was done for each of the three variables, TTLUS, TTFFS, and TTCRGAD, to validate the efficacy of the new drug loperamide & simethicone combination, claimed by the sponsor. The statistical results for both the pairwise comparisons and the risk ratios are presented in Table 3.3.1 (below).

Table 3.3.1 (Reviewer)/Study 92-209
Survival Analysis For The Pairwise Comparisons
(2-sided P-Values and Risk Ratios in Parenthesis)

Endpoints	L+S vs. L	L+S vs. S	L+S vs. Placebo	L vs. Placebo	S vs. Placebo
TTLUS	0.1755 (1.22)	0.0001 (2.38)	0.0001 (3.30)	0.0001 (2.68)	0.0739 (1.35)
TTFFS	0.1052 (1.27)	0.0002 (1.76)	0.0001 (2.34)	0.0001 (1.92)	0.0582 (1.37)
TTCRGAD	0.0001 (2.22)	0.0001 (1.98)	0.0001 (2.30)	0.50 (1.11)	0.3026 (1.17)

Note:

1. **P value less than 0.05 indicated that the recovering time for a patient taking the first drug in the pairwise comparison is less than that of a patient taking the second drug.**
2. **Risk ratio greater than one indicated that patients taking first drug in the pairwise comparison had larger opportunity to recover than those patients taking second drug.**

Results in Table 3.3.1 confirms the following: 1) with respect to treatment of acute diarrhea, the loperamide & simethicone combination is more effective than placebo and simethicone, 2) with respect to gas-related symptoms, the loperamide & simethicone combination is more effective than placebo, loperamide, and simethicone.

The survival distributions for the four treatment groups on the three variables, TTLUS, TTFFS, and TTCRGAD, were estimated by Kaplan-Meier method and presented in Figure 4 through Figure 6 (attached). The figures for the three variables TTLUS, TTFFS, and TTCRGAD supported the results indicated by Table 3.3.1.

2) Crude Rate Analysis

This reviewer also performed a crude rate analysis similar to those performed for the Study# 92-202. Table 3.3.2 (below) provides the detail results of the crude rate analyses.

Table 3.3.2 (Reviewer)/Study 92-209
Crude Rate Analysis Results
Response Rates

		Loperamide & Simethicone	Loperamide	Simethicone	Placebo
Control Of Diarrhea	24-Hour	87/116 (75%)	83/115 (72%)	47/120 (39%)	33/115 (29%)
	48-hour	97/116 (84%)	92/115 (80%)	81/120 (68%)	65/115 (57%)
Control Of Gas-related Discomfort	24-Hour	96/116 (83%)	58/115 (50%)	66/120 (55%)	60/115 (52%)
	48-hour	105/116 (91%)	89/115 (77%)	90/120 (75%)	80/115 (70%)

2-Sided P-Values (Chi-Square test)

		L+S Vs. L	L+S Vs. S	L+S Vs. Placebo	L Vs. Placebo	S Vs. Placebo
Control Of Diarrhea	24-Hour	0.626	0.001	0.001	0.001	0.09
	48-Hour	0.476	0.004	0.001	0.001	0.083
Control Of Gas-related Discomfort	24-Hour	0.001	0.001	0.001	0.792	0.664
	48-Hour	0.007	0.002	0.001	0.179	0.352

Results from Table 3.3.2 (Reviewer) indicated that the loperamide & simethicone combination is superior to simethicone alone and placebo in treating the diarrhea symptom. Similarly, the loperamide & simethicone combination is superior to simethicone alone, loperamide alone, and placebo in relieving gas-related abdominal discomfort. Therefore, the results of the crude rate approach also support the loperamide & simethicone combination therapy. In addition, loperamide

alone is significantly better than placebo in treating the diarrhea symptom but is not significantly better than placebo in relieving the gas-related abdominal discomfort. Finally, simethicone alone is not significantly better than placebo in both of treating the diarrhea symptom and relieving the gas-related abdominal discomfort.

IV. Summary and conclusion

For study 92-202, the loperamide & simethicone combination is superior to loperamide alone, simethicone alone, and placebo in treating the diarrhea and relieving the gas-related abdominal discomfort. In addition, both loperamide alone and simethicone alone are significantly better than placebo for both symptoms. Therefore, the results of this study are in favor of the loperamide & simethicone combination therapy.

For study 92-209, the results of this reviewer's analyses confirm the following: 1) with respect to treatment of the acute diarrhea, the loperamide & simethicone combination is more effective than placebo and simethicone, 2) with respect to the gas-related symptom, the loperamide & simethicone combination is more effective than placebo, loperamide, and simethicone. In addition, loperamide alone is significantly better than placebo in treating the diarrhea symptom but is not significantly better than placebo in relieving the gas-related abdominal discomfort. Finally, simethicone alone is not significantly better than placebo in relieving the diarrhea symptom and in relieving the gas-related abdominal discomfort.

Wen-Jen Chen

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Huque Huque 6/19/96

Dr. Smith Y/Smith 6/19/96

cc: Original NDA 20-606

HFD-180/Dr. Fredd
HFD-180/Dr. Canchola
HFD-180/Mr. Strongin
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Chen
HFD-720/File Copy

Figure 1

Estimates of The four Survival Functions For Variable TTLUS
(STUDY 92-202)

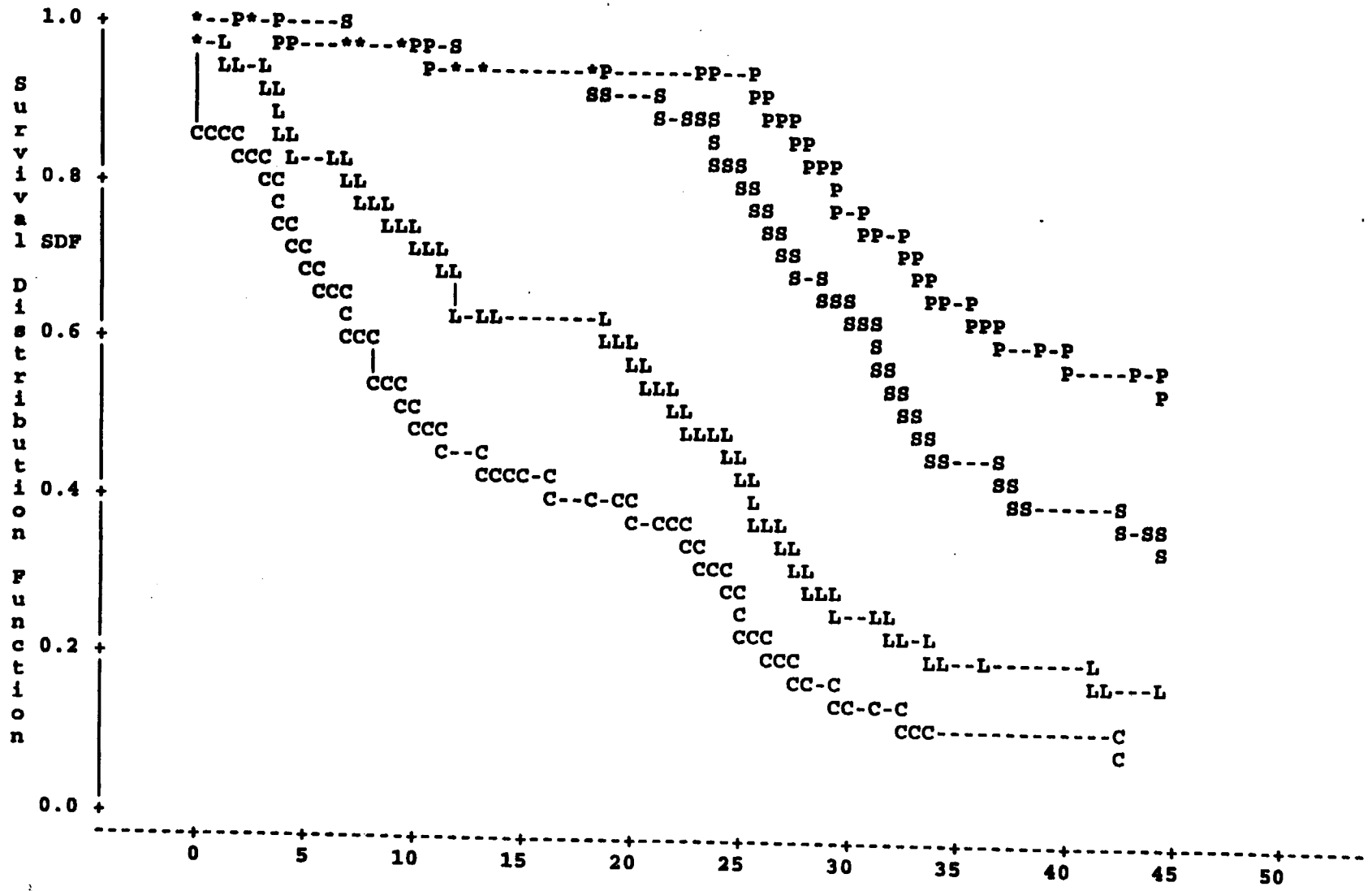


Figure 2

Estimates of The Four Survival Functions For Variable TTFFS
(STUDY 92-202)

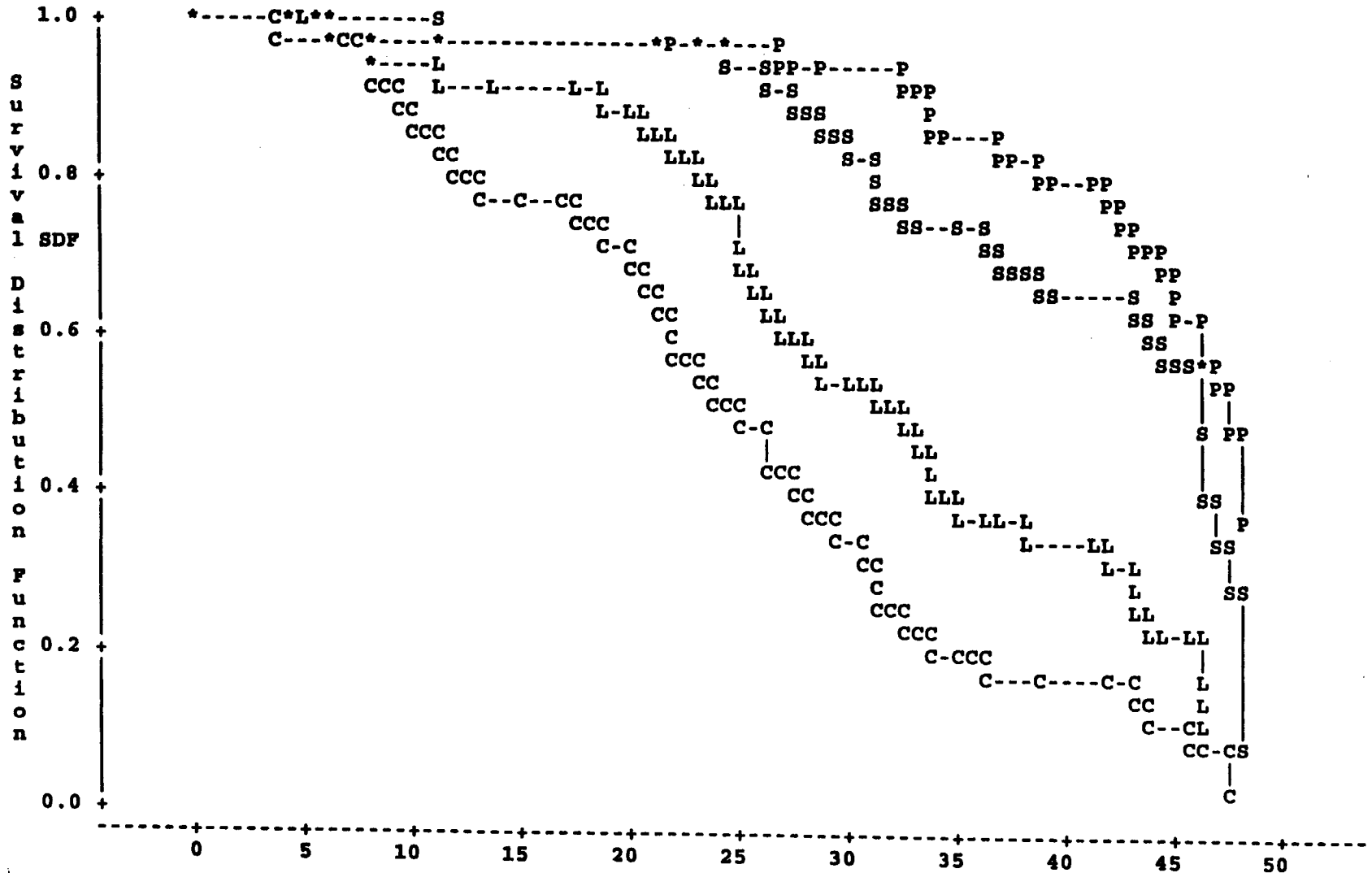


Figure3

Estimates of The Four Survival Functions For Variable TTCRGAD
(STUDY 92-202)

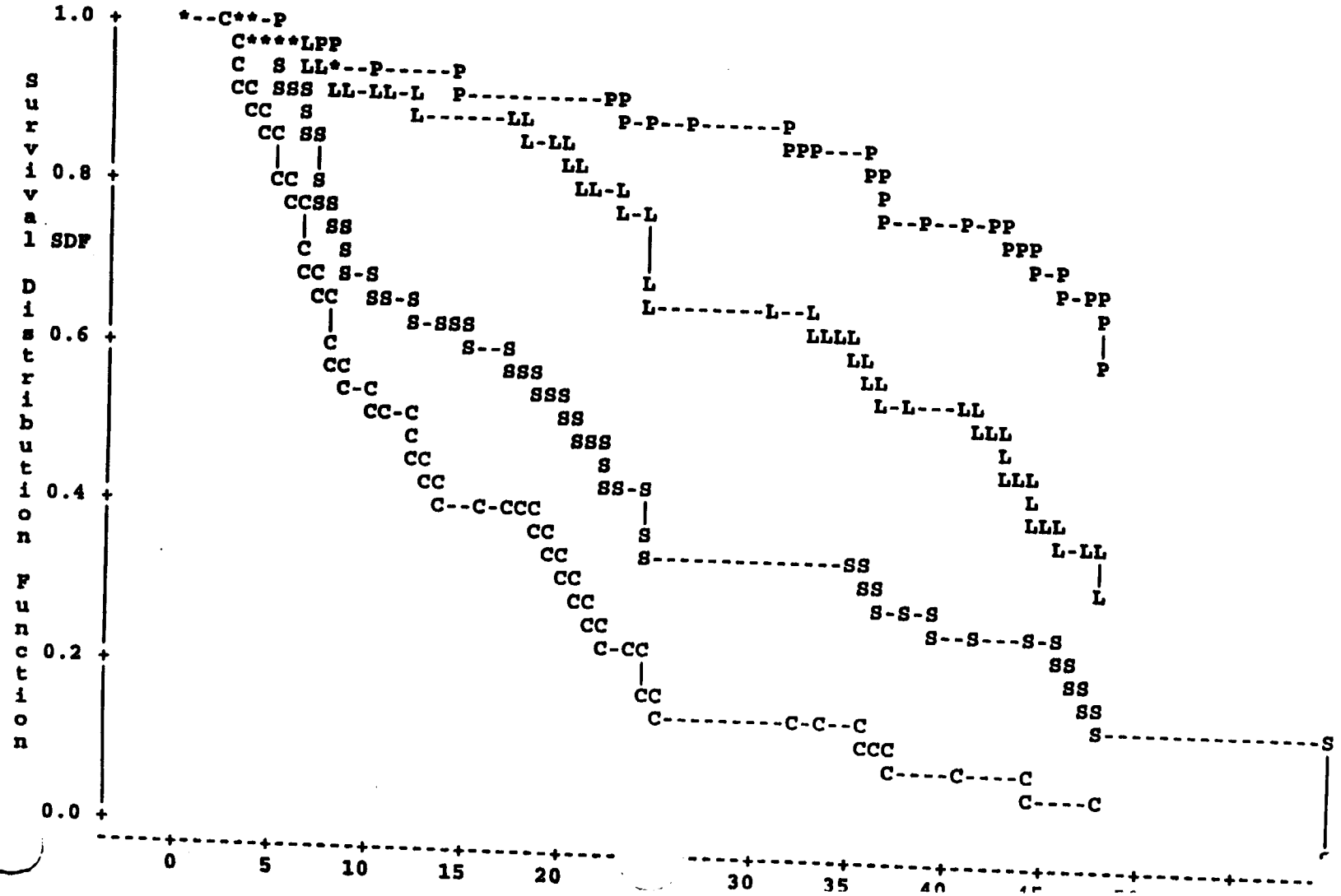


Figure 4

Estimates of The four Survival Functions For Variable TTLUS
(STUDY 92-209)

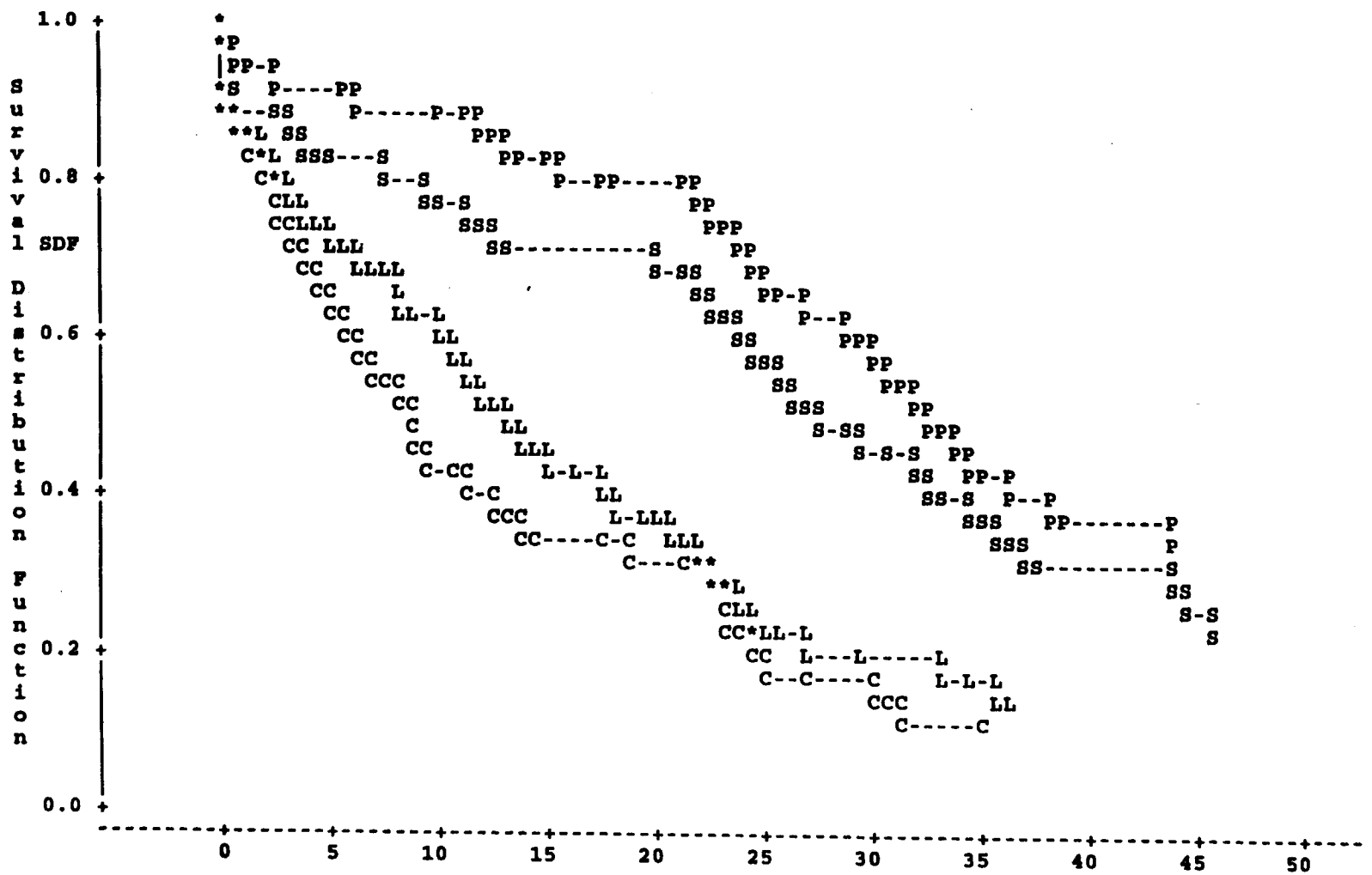


Figure 5

Estimates of The Four Survival Functions For Variable TTFFS
(STUDY 92-209)

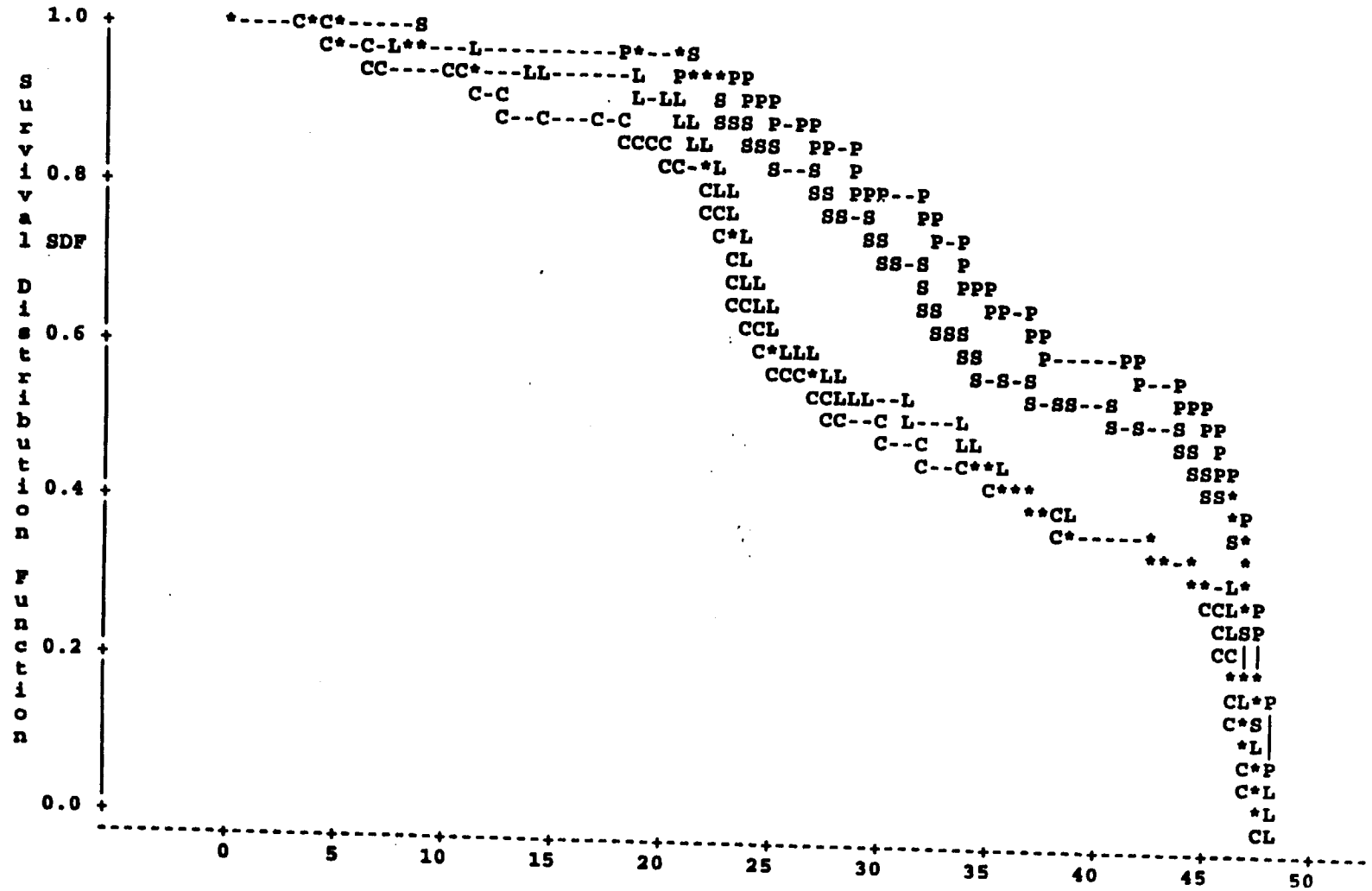
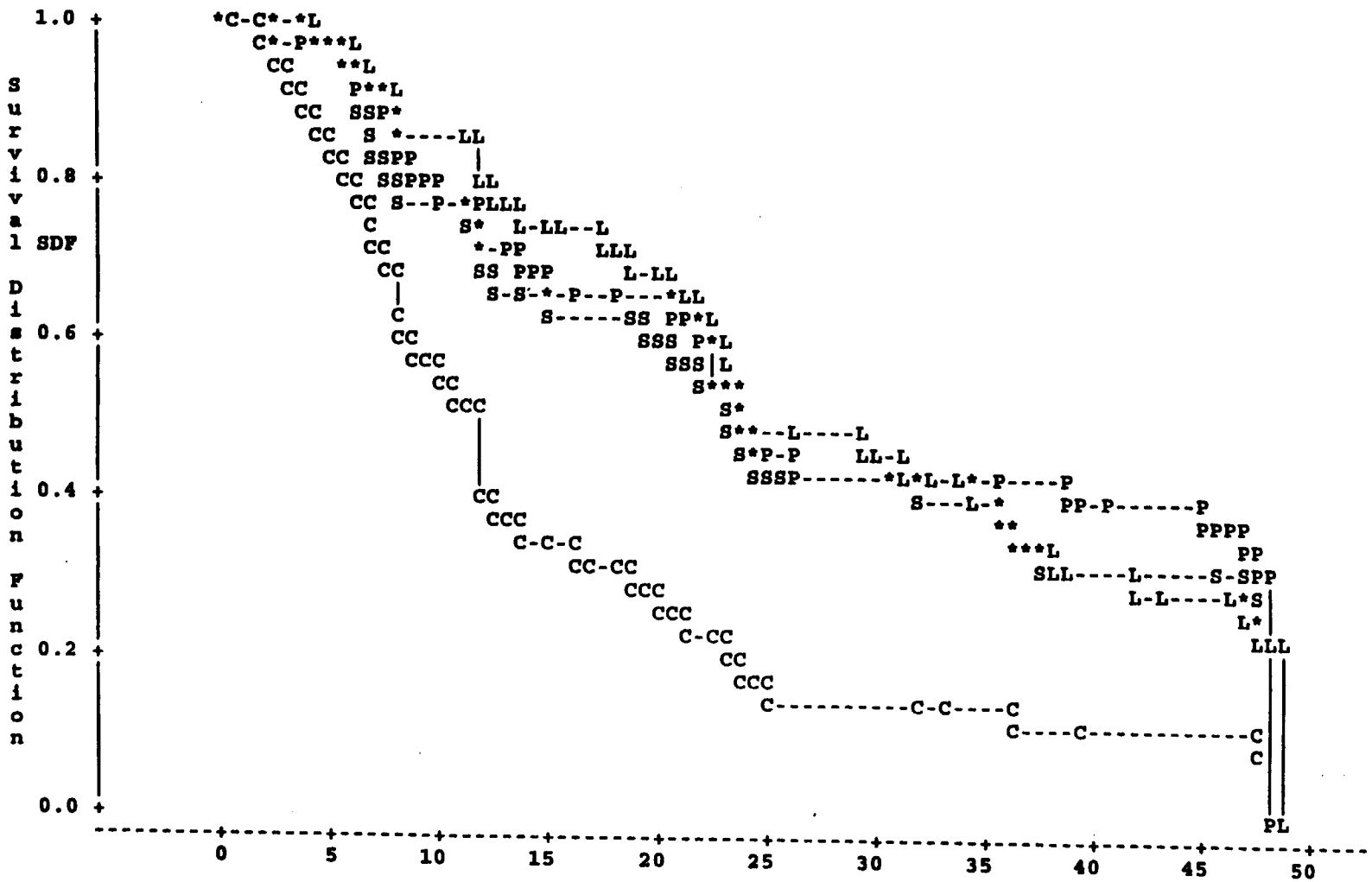


Figure 6

Estimates of The Four Survival Functions For Variable TTCRGAD
(STUDY 92-209)



Appendix A

Definitions for the Time To Last Unformed Stool (TTLUS)

Definition A: For patients who completed the study (or discontinued because their diarrhea resolved), TTLUS was the elapsed time from initial dose to the time of the last unformed stool where only formed stool or no stools were subsequently reported.

In this definition, if the first unformed stool occurred after a 24-hour period without stooling since patient entering the study, or no unformed stools were observed then TTLUS was zero.

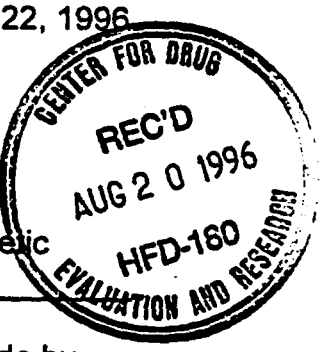
If a patient discontinued for reasons other than resolution of diarrhea, then TTLUS was censored at the number of hours from the initial dose to study discontinuation.

Definition B: For patients who completed the study (or discontinued because their diarrhea resolved), TTLUS was the elapsed time from initial dose to the time of the last unformed stool where only formed stool or no stools were subsequently reported. If no unformed stools were observed then TTLUS was zero. Patients who discontinued for reasons other than resolution of diarrhea, TTLUS were censored at the number of hours from the initial dose to study discontinuation.

Hrangin AUG 20 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA 20-606 Submission Dates: April 17, 1996
Loperamide HCl/Simethicone Chewable Tablets Received by DPEII:April 22, 1996
Imodium Advanced™
2 mg loperamide HCl/125 mg simethicone
McNeil Consumer Products Company



Type of submission: Response to request for gender analysis of pharmacokinetic study Biostudy 134.

Background:
The review of submission dated 7/28/95 was completed and a request was made by the reviewer, Dr. Phil Colangelo that a gender analysis of the pharmacokinetic data be undertaken for Biostudy 134. The sponsors have responded by completing the gender analysis.

Gender analysis method and results:
This was a bioequivalence study consisting of a three-way, crossover study. The study consisted of 24 subjects with equal representation of males and females. The three treatments were two formulations of the loperamide/simethicone (2mg/125 mg) combination chewable tablet and the reference, Imodium™ capsules 2 mg strength. A total single dose of 8 mg was administered in each treatment arm. The model used to analyze the data was:

Y = Weight sequence gender sequence*gender subject(sequence*gender) period product product*gender weight*product *sequence*product*period*gender*

Using this model the interaction term *"sequence*product*period*gender"* was not significant at the $p<0.1$ level. This interaction term was excluded from the model and the data were re-analyzed. The model used was:

Y = Weight sequence gender sequence*gender subject(sequence*gender) period product product*gender weight*product

No terms showed significance at the p 0.05 level. The analysis was repeated dropping the weight term. No gender effect was found in the data analyzed and there was no significant gender*product interaction.

A summary of the results can be found in the Appendix to this review. The SAS data set was provided by the sponsors and the results were checked by the reviewer.

Recommendation:
The sponsors have satisfied the request to analyze by gender the pharmacokinetic data from Biostudy 134 as described in the letter to the sponsors dated 12/11/95. There was no statistically significant gender effect found. This completes the review for DPEII.

8/7/96

Lydia C. Kaus, M.S., Ph.D.
Team Leader, Gastrointestinal and
Coagulation Drug Products, DPE II

FT initialed by
Mei-Ling Chen, Ph.D.
Director, DPEII

cc:NDA20-606, HFD-180, HFD-870(MChen, Kaus), HFD-850 (Lesko), HFD-850 (Chron, Bott, Reviewer), HFD-340(Viswanathan), HFD-205(FOI)

APPENDIX A

RESULTS OF ANALYSIS FOR MODEL ONE

MODEL ONE:

Y = Weight
Sequence
Gender
Sequence*Gender
Subject(Sequence*Gender)
Period
Product
Product*Gender
Weight*Product
Sequence*Product*Period*Gender

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL 85-134 12:46 Monday, March 25, 1996
STATISTICAL ANALYSIS OF DATA

General Linear Models Procedure

Dependent Variable:

Source	DF	Mean Square	F Value	Pr > F
Model	1	0.52933541	18.96	0.0001
Error	17	0.02791327		
Corrected Total	18			

R-Square	C.V.
0.953783	5.602631

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	1	0.17304706	6.20	0.0178
SEQUENCE	2	0.74252596	26.60	0.0001
GENDER	1	0.69724909	24.98	0.0001
SEQUENCE*GENDER	2	0.07152150	2.56	0.0919
SUBJE(SEQUEN*GENDER)	17	0.96961593	34.74	0.0001
PERIOD	2	0.00041003	0.01	0.9854
PRODUCT	2	0.20303819	7.27	0.0023
PRODUCT*GENDER	2	0.00205139	0.07	0.9293
WEIGHT*PRODUCT	2	0.00973543	0.35	0.7080
SEQU*PROD*PERI*GENDE	6	0.02884633	1.03	0.4210

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.67651966	24.24	0.0001
GENDER	1	0.69724909	24.98	0.0001
SEQUENCE*GENDER	2	0.07152150	2.56	0.0919
SUBJE(SEQUEN*GENDER)	17	0.96961593	34.74	0.0001
PERIOD	2	0.00024478	0.01	0.9913
PRODUCT	2	0.00530205	0.19	0.8279
PRODUCT*GENDER	2	0.01074305	0.38	0.6835
WEIGHT*PRODUCT	2	0.00139546	0.05	0.9513
SEQU*PROD*PERI*GENDE	6	0.02884633	1.03	0.4210

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.62530496	22.40	0.0001
GENDER	1	0.81106060	29.06	0.0001
SEQUENCE*GENDER	2	0.07152150	2.56	0.0919
SUBJE(SEQUEN*GENDER)	17	0.96961593	34.74	0.0001
PERIOD	2	0.00004960	0.00	0.9982
PRODUCT	2	0.00314649	0.11	0.8937
PRODUCT*GENDER	2	0.00538093	0.19	0.8256
WEIGHT*PRODUCT	2	0.00139546	0.05	0.9513
SEQU*PROD*PERI*GENDE	6	0.02884633	1.03	0.4210

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134 12:46 Monday, March 25, 1996
STATISTICAL ANALYSIS OF DATA

General Linear Models Procedure

Dependent Variable:

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.54951668	19.69	0.0001
GENDER	1	1.86774677	66.91	0.0001
SEQUENCE*GENDER	2	0.57053529	20.44	0.0001
SUBJE(SEQUEN*GENDER)	17	0.96961593	34.74	0.0001
PERIOD	2	0.00004960	0.00	0.9982
PRODUCT	2	0.00314649	0.11	0.8937
PRODUCT*GENDER	2	0.00538093	0.19	0.8256
WEIGHT*PRODUCT	2	0.00139546	0.05	0.9513
SEQU*PROD*PERI*GENDE	6	0.02884633	1.03	0.4210

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source	DF	Mean Square	F Value	Pr > F
GENDER	1	0.81106060	0.84	0.3732
SEQUENCE	2	0.62530496	0.64	0.5371
SEQUENCE*GENDER	2	0.07152150	0.07	0.9292

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.26512565	-0.46	0.6488	0.57697298
C-317 - IMODIUM	-0.07281698	-0.13	0.9003	0.57697298
C-604 - C-317	-0.19230867	-0.33	0.7409	0.57697298

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134 12:46 Monday, March 25, 1996
STATISTICAL ANALYSIS OF DATA

General Linear Models Procedure

Dependent Variable: LAUCINF

Source		Mean Square	F Value	Pr > F
Model	37	0.42511261	23.85	0.0001
Error	34	0.01782418		
Corrected Total	71			

R-Square	C.V.
0.962901	4.121098

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	1	0.08358196	4.69	0.0375
SEQUENCE	2	0.63421155	35.58	0.0001
GENDER	1	0.49936335	28.02	0.0001
SEQUENCE*GENDER	2	0.10680320	5.99	0.0059
SUBJE(SEQUEN*GENDER)	17	0.78547673	44.07	0.0001
PERIOD	2	0.00447176	0.25	0.7795
PRODUCT	2	0.02713348	1.52	0.2327
PRODUCT*GENDER	2	0.00003749	0.00	0.9979
WEIGHT*PRODUCT	2	0.02038043	1.14	0.3307
SEQU*PROD*PERI*GENDE	6	0.03450681	1.94	0.1031

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0			
SEQUENCE	2	0.57961566	32.52	0.0001
GENDER	1	0.49936335	28.02	0.0001
SEQUENCE*GENDER	2	0.10680320	5.99	0.0059
SUBJE(SEQUEN*GENDER)	17	0.78547673	44.07	0.0001
PERIOD	2	0.00149232	0.08	0.9199
PRODUCT	2	0.00794080	0.45	0.6442
PRODUCT*GENDER	2	0.01190407	0.67	0.5194
WEIGHT*PRODUCT	2	0.00429608	0.24	0.7872
SEQU*PROD*PERI*GENDE	6	0.03450681	1.94	0.1031

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0			
SEQUENCE	2	0.52284645	29.33	0.0001
GENDER	1	0.63194041	35.45	0.0001
SEQUENCE*GENDER	2	0.10680320	5.99	0.0059
SUBJE(SEQUEN*GENDER)	17	0.78547673	44.07	0.0001
PERIOD	2	0.00189780	0.11	0.8993
PRODUCT	2	0.00370267	0.21	0.8134
PRODUCT*GENDER	2	0.00485445	0.27	0.7632
WEIGHT*PRODUCT	2	0.00429608	0.24	0.7872
SEQU*PROD*PERI*GENDE	6	0.03450681	1.94	0.1031

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134 12:46 Monday, March 25, 1996
STATISTICAL ANALYSIS OF DATA

General Linear Models Procedure

Dependent Variable: LAUCINF

Source		Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.39413225	22.11	0.0001
GENDER	1	1.53058225	85.87	0.0001
SEQUENCE*GENDER	2	0.54993975	30.85	0.0001
SUBJE(SEQUEN*GENDER)	17	0.78547673	44.07	0.0001
PERIOD	2	0.00189780	0.11	0.8993
PRODUCT	2	0.00370267	0.21	0.8134
PRODUCT*GENDER	2	0.00485445	0.27	0.7632
WEIGHT*PRODUCT	2	0.00429608	0.24	0.7872
SEQU*PROD*PERI*GENDE	6	0.03450681	1.94	0.1031

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source	DF	Mean Square	F Value	Pr > F
GENDER	1	0.63194041	0.80	0.3823
SEQUENCE	2	0.52284645	0.67	0.5268
SEQUENCE*GENDER	2	0.10680320	0.14	0.8738

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.11215492	-0.24	0.8093	0.46105738
C-317 - IMODIUM	0.18225797	0.40	0.6951	0.46105738
C-604 - C-317	-0.29441288	-0.64	0.5274	0.46105738

APPEARS THIS WAY
ON ORIGINAL

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General Linear Models Procedure

Dependent Variable: LCMAX

Source	DF	Mean Square	F Value	Pr > F
Model	37	0.49702328	9.57	0.0001
Error	34	0.05191218		
Corrected Total	71			

R-Square	C.V.
0.912427	-1036.285

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	1	0.48264217	9.30	0.0044
SEQUENCE	2	0.48866850	9.41	0.0006
GENDER	1	0.29354558	5.65	0.0232
SEQUENCE*GENDER	2	0.08135202	1.57	0.2233
SUBJE(SEQUEN*GENDER)	17	0.82134304	15.82	0.0001
PERIOD	2	0.04420826	0.85	0.4356
PRODUCT	2	1.04449647	20.12	0.0001
PRODUCT*GENDER	2	0.01173212	0.23	0.7989
WEIGHT*PRODUCT	2	0.02148944	0.41	0.6643
SEQU*PROD*PERI*GENDE	6	0.04449138	0.86	0.5359

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.45755858	8.81	0.0008
GENDER	1	0.29354558	5.65	0.0232
SEQUENCE*GENDER	2	0.08135202	1.57	0.2233
SUBJE(SEQUEN*GENDER)	17	0.82134304	15.82	0.0001
PERIOD	2	0.04790090	0.92	0.4072
PRODUCT	2	0.01598328	0.31	0.7370
PRODUCT*GENDER	2	0.03285227	0.63	0.5372
WEIGHT*PRODUCT	2	0.00200457	0.04	0.9622
SEQU*PROD*PERI*GENDE	6	0.04449138	0.86	0.5359

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.45171358	8.70	0.0009
GENDER	1	0.37026147	7.13	0.0115
SEQUENCE*GENDER	2	0.08135202	1.57	0.2233
SUBJE(SEQUEN*GENDER)	17	0.82134304	15.82	0.0001
PERIOD	2	0.04228473	0.81	0.4513
PRODUCT	2	0.00839358	0.16	0.8514
PRODUCT*GENDER	2	0.01697402	0.33	0.7233
WEIGHT*PRODUCT	2	0.00200457	0.04	0.9622
SEQU*PROD*PERI*GENDE	6	0.04449138	0.86	0.5359

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General Linear Models Procedure

Dependent Variable: LCMAX

Source		Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.48411294	9.33	0.0006
GENDER	1	1.85822592	35.80	0.0001
SEQUENCE*GENDER	2	0.68481516	13.19	0.0001
SUBJE(SEQUEN*GENDER)	17	0.82134304	15.82	0.0001
PERIOD	2	0.04228473	0.81	0.4513
PRODUCT	2	0.00839358	0.16	0.8514
PRODUCT*GENDER	2	0.01697402	0.33	0.7233
WEIGHT*PRODUCT	2	0.00200457	0.04	0.9622
SEQU*PROD*PERI*GENDE	6	0.04449138	0.86	0.5359

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source	DF	Mean Square	F Value	Pr > F
GENDER	1	0.37026147	0.45	0.5110
SEQUENCE	2	0.45171358	0.55	0.5869
SEQUENCE*GENDER	2	0.08135202	0.10	0.9062

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.44702279	-0.57	0.5737	0.78683703
C-317 - IMODIUM	-0.20669818	-0.26	0.7944	0.78683703
C-604 - C-317	-0.24032461	-0.31	0.7619	0.78683703

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ON ORIGINAL

General Linear Models Procedure
Least Squares Means

PRODUCT	AUCTLQC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN
A:C-604	Non-est	Non-est	Non-est	Non-est	Non-est
B:C-317	Non-est	Non-est	Non-est	Non-est	Non-est
C:IMODIUM	Non-est	Non-est	Non-est	Non-est	Non-est

PRODUCT	THALF LSMEAN	LAUCTLQC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
A:C-604	Non-est	Non-est	Non-est	Non-est
B:C-317	Non-est	Non-est	Non-est	Non-est
C:IMODIUM	Non-est	Non-est	Non-est	Non-est

PERIOD	AUCTLQC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN	THALF LSMEAN
1	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est
2	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est
3	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est

PERIOD	LAUCTLQC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
1	Non-est	Non-est	Non-est
2	Non-est	Non-est	Non-est
3	Non-est	Non-est	Non-est

GENDER	AUCTLQC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN	THALF LSMEAN
FEMALE	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est
MALE	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est

GENDER	LAUCTLQC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
FEMALE	Non-est	Non-est	Non-est
MALE	Non-est	Non-est	Non-est

APPENDIX B

RESULTS OF ANALYSIS FOR MODEL TWO

MODEL TWO:

Y = Weight
Sequence
Gender
Gender*Sequence
Subject(Sequence*Gender)
Period
Product
Product*Gender
Weight*Product

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General Linear Models Procedure

Dependent Variable:

Source		Mean Square	F Value	Pr > F
Model		0.62620426	22.32	0.0001
Error		0.02805323		
Corrected Total				

R-Square	C.V.
0.945354	5.616659

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	1	0.17304706	6.17	0.0173
SEQUENCE	2	0.74252596	26.47	0.0001
GENDER	1	0.69724909	24.85	0.0001
SEQUENCE*GENDER	2	0.07152150	2.55	0.0908
SUBJE(SEQUEN*GENDER)	17	0.96961593	34.56	0.0001
PERIOD	2	0.00041003	0.01	0.9855
PRODUCT	2	0.20303819	7.24	0.0021
PRODUCT*GENDER	2	0.00205139	0.07	0.9296
WEIGHT*PRODUCT	2	0.00973543	0.35	0.7089

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.67651966	24.12	0.0001
GENDER	1	0.69724909	24.85	0.0001
SEQUENCE*GENDER	2	0.07152150	2.55	0.0908
SUBJE(SEQUEN*GENDER)	17	0.96961593	34.56	0.0001
PERIOD	2	0.00024478	0.01	0.9913
PRODUCT	2	0.00530205	0.19	0.8285
PRODUCT*GENDER	2	0.01074305	0.38	0.6843
WEIGHT*PRODUCT	2	0.00973543	0.35	0.7089

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.62866469	22.41	0.0001
GENDER	1	0.80721654	28.77	0.0001
SEQUENCE*GENDER	2	0.07152150	2.55	0.0908
SUBJE(SEQUEN*GENDER)	17	0.96961593	34.56	0.0001
PERIOD	2	0.00024478	0.01	0.9913
PRODUCT	2	0.00943852	0.34	0.7163
PRODUCT*GENDER	2	0.01074305	0.38	0.6843
WEIGHT*PRODUCT	2	0.00973543	0.35	0.7089

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.95227803	33.95	0.0001

LOPERAMIDE TABLETS VS CAPSULE STUDY
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General Linear Models Procedure

Dependent Variable:

Source			Mean Square	F Value	Pr > F
GENDER	1		1.89011000	67.38	0.0001
SEQUENCE*GENDER	2		0.57053529	20.34	0.0001
SUBJE(SEQUEN*GENDER)	17		0.96961593	34.56	0.0001
PERIOD	2		0.00024478	0.01	0.9913
PRODUCT	2		0.00943852	0.34	0.7163
PRODUCT*GENDER	2		0.01074305	0.38	0.6843
WEIGHT*PRODUCT	2		0.00973543	0.35	0.7089

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source	DF		Mean Square	F Value	Pr > F
GENDER	1		0.80721654	0.83	0.3743
SEQUENCE	2		0.62866469	0.65	0.5354
SEQUENCE*GENDER	2		0.07152150	0.07	0.9292

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.24791005	-0.47	0.6419	0.52899036
C-317 - IMODIUM	0.18447516	0.35	0.7291	0.52899036
C-604 - C-317	-0.43238520	-0.82	0.4186	0.52899036

LOPERAMIDE TABLETS VS CAPSULE STUDY
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General Linear Models Procedure

Dependent Variable: LAUCINF

Source		Mean Square	F Value	Pr > F
Model	31	0.50071373	24.63	0.0001
Error	40	0.02032658		
Corrected Total	71			

R-Square	C.V.
0.950226	4.400887

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	1	0.08358196	4.11	0.0493
SEQUENCE	2	0.63421155	31.20	0.0001
GENDER	1	0.49936335	24.57	0.0001
SEQUENCE*GENDER	2	0.10680320	5.25	0.0094
SUBJE(SEQUEN*GENDER)	17	0.78547673	38.64	0.0001
PERIOD	2	0.00447176	0.22	0.8035
PRODUCT	2	0.02713348	1.33	0.2747
PRODUCT*GENDER	2	0.00003749	0.00	0.9982
WEIGHT*PRODUCT	2	0.02038043	1.00	0.3759

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0			
SEQUENCE	2	0.57961566	28.52	0.0001
GENDER	1	0.49936335	24.57	0.0001
SEQUENCE*GENDER	2	0.10680320	5.25	0.0094
SUBJE(SEQUEN*GENDER)	17	0.78547673	38.64	0.0001
PERIOD	2	0.00149232	0.07	0.9293
PRODUCT	2	0.00794080	0.39	0.6792
PRODUCT*GENDER	2	0.01190407	0.59	0.5615
WEIGHT*PRODUCT	2	0.02038043	1.00	0.3759

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0			
SEQUENCE	2	0.52639333	25.90	0.0001
GENDER	1	0.62626217	30.81	0.0001
SEQUENCE*GENDER	2	0.10680320	5.25	0.0094
SUBJE(SEQUEN*GENDER)	17	0.78547673	38.64	0.0001
PERIOD	2	0.00149232	0.07	0.9293
PRODUCT	2	0.01927499	0.95	0.3959
PRODUCT*GENDER	2	0.01190407	0.59	0.5615
WEIGHT*PRODUCT	2	0.02038043	1.00	0.3759

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0			
SEQUENCE	2	0.78579154	38.66	0.0001

LOPERAMIDE TABLETS VS CAPSULE STUDY
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General Linear Models Procedure

Dependent Variable: LAUCINF

Source		Mean Square	F Value	Pr > F
GENDER	1	1.50263240	73.92	0.0001
SEQUENCE*GENDER	2	0.54993975	27.06	0.0001
SUBJE(SEQUEN*GENDER)	17	0.78547673	38.64	0.0001
PERIOD	2	0.00149232	0.07	0.9293
PRODUCT	2	0.01927499	0.95	0.3959
PRODUCT*GENDER	2	0.01190407	0.59	0.5615
WEIGHT*PRODUCT	2	0.02038043	1.00	0.3759

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source	DF	Mean Square	F Value	Pr > F
GENDER	1	0.62626217	0.80	0.3844
SEQUENCE	2	0.52639333	0.67	0.5246
SEQUENCE*GENDER	2	0.10680320	0.14	0.8738

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.18136405	-0.40	0.6893	0.45028604
C-317 - IMODIUM	0.42286664	0.94	0.3533	0.45028604
C-604 - C-317	-0.60423070	-1.34	0.1872	0.45028604

LOPERAMIDE TABLETS VS CAPSULE STUDY
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General Linear Models Procedure

Dependent Variable: LCMAX

Source			Mean Square	F Value	Pr > F
Model	31		0.58461010	11.51	0.0001
Error	40		0.05079906		
Corrected Total	71				
	R-Square	C.V.			
	0.899183	-1025.115			

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	1	0.48264217	9.50	0.0037
SEQUENCE	2	0.48866850	9.62	0.0004
GENDER	1	0.29354558	5.78	0.0209
SEQUENCE*GENDER	2	0.08135202	1.60	0.2143
SUBJE(SEQUEN*GENDER)	17	0.82134304	16.17	0.0001
PERIOD	2	0.04420826	0.87	0.4266
PRODUCT	2	1.04449647	20.56	0.0001
PRODUCT*GENDER	2	0.01173212	0.23	0.7948
WEIGHT*PRODUCT	2	0.02148944	0.42	0.6580

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.45755858	9.01	0.0006
GENDER	1	0.29354558	5.78	0.0209
SEQUENCE*GENDER	2	0.08135202	1.60	0.2143
SUBJE(SEQUEN*GENDER)	17	0.82134304	16.17	0.0001
PERIOD	2	0.04790090	0.94	0.3980
PRODUCT	2	0.01598328	0.31	0.7318
PRODUCT*GENDER	2	0.03285227	0.65	0.5292
WEIGHT*PRODUCT	2	0.02148944	0.42	0.6580

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.45253519	8.91	0.0006
GENDER	1	0.36705443	7.23	0.0104
SEQUENCE*GENDER	2	0.08135202	1.60	0.2143
SUBJE(SEQUEN*GENDER)	17	0.82134304	16.17	0.0001
PERIOD	2	0.04790090	0.94	0.3980
PRODUCT	2	0.02077907	0.41	0.6670
PRODUCT*GENDER	2	0.03285227	0.65	0.5292
WEIGHT*PRODUCT	2	0.02148944	0.42	0.6580

Source	DF	Mean Square	F Value	Pr > F
WEIGHT	0	.	.	.
SEQUENCE	2	0.82555259	16.25	0.0001

General Linear Models Procedure

Dependent Variable: LOMAX

Source		Mean Square	F Value	Pr > F
GENDER	1	1.95231058	38.43	0.0001
SEQUENCE*GENDER	2	0.68481516	13.48	0.0001
SUBJE(SEQUEN*GENDER)	17	0.82134304	16.17	0.0001
PERIOD	2	0.04790090	0.94	0.3980
PRODUCT	2	0.02077907	0.41	0.6670
PRODUCT*GENDER	2	0.03285227	0.65	0.5292
WEIGHT*PRODUCT	2	0.02148944	0.42	0.6580

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source	DF	Mean Square	F Value	Pr > F
GENDER	1	0.36705443	0.45	0.5128
SEQUENCE	2	0.45253519	0.55	0.5863
SEQUENCE*GENDER	2	0.08135202	0.10	0.9062

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.44516774	-0.63	0.5353	0.71184297
C-317 - IMODIUM	0.18025101	0.25	0.8014	0.71184297
C-604 - C-317	-0.62541876	-0.88	0.3849	0.71184297

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General Linear Models Procedure
Least Squares Means

PRODUCT	AUCTLOC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN
A:C-604	Non-est	Non-est	Non-est	Non-est	Non-est
B:C-317	Non-est	Non-est	Non-est	Non-est	Non-est
C:IMODIUM	Non-est	Non-est	Non-est	Non-est	Non-est

PRODUCT	THALF LSMEAN	LAUCTLOC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
A:C-604	Non-est	Non-est	Non-est	Non-est
B:C-317	Non-est	Non-est	Non-est	Non-est
C:IMODIUM	Non-est	Non-est	Non-est	Non-est

PERIOD	AUCTLOC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN	THALF LSMEAN
1	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est
2	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est
3	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est

PERIOD	LAUCTLOC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
1	Non-est	Non-est	Non-est
2	Non-est	Non-est	Non-est
3	Non-est	Non-est	Non-est

GENDER	AUCTLOC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN	THALF LSMEAN
FEMALE	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est
MALE	Non-est	Non-est	Non-est	Non-est	Non-est	Non-est

GENDER	LAUCTLOC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
FEMALE	Non-est	Non-est	Non-est
MALE	Non-est	Non-est	Non-est

APPENDIX C

RESULTS OF ANALYSIS FOR MODEL THREE

MODEL THREE:

Y = Sequence
Gender
Sequence*Gender
Subject(Sequence*Gender)
Period
Product
Product*Gender

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General Linear Models Procedure

Dependent Variable:

Source		Mean Square	F Value	Pr > F
Model		0.66871935	24.60	0.0001
Error		0.02718095		
Corrected Total				

R-Square	C.V.
0.944406	5.528649

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.77361063	28.46	0.0001
GENDER	1	0.08585092	3.16	0.0828
SEQUENCE*GENDER	2	0.00384451	0.14	0.8685
SUBJE(SEQUEN*GENDER)	18	0.96339449	35.44	0.0001
PERIOD	2	0.00041003	0.02	0.9850
PRODUCT	2	0.20303819	7.47	0.0017
PRODUCT*GENDER	2	0.00205139	0.08	0.9274

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.78116452	28.74	0.0001
GENDER	1	0.08585092	3.16	0.0828
SEQUENCE*GENDER	2	0.00384451	0.14	0.8685
SUBJE(SEQUEN*GENDER)	18	0.96339449	35.44	0.0001
PERIOD	2	0.00058975	0.02	0.9785
PRODUCT	2	0.20303819	7.47	0.0017
PRODUCT*GENDER	2	0.00205139	0.08	0.9274

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.75817845	27.89	0.0001
GENDER	1	0.08593636	3.16	0.0826
SEQUENCE*GENDER	2	0.00384451	0.14	0.8685
SUBJE(SEQUEN*GENDER)	18	0.96339449	35.44	0.0001
PERIOD	2	0.00058975	0.02	0.9785
PRODUCT	2	0.20303819	7.47	0.0017
PRODUCT*GENDER	2	0.00205139	0.08	0.9274

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.89841409	33.05	0.0001
GENDER	1	0.07701984	2.83	0.0997
SEQUENCE*GENDER	2	0.00384451	0.14	0.8685
SUBJE(SEQUEN*GENDER)	18	0.96339449	35.44	0.0001
PERIOD	2	0.00058975	0.02	0.9785
PRODUCT	2	0.20303819	7.47	0.0017
PRODUCT*GENDER	2	0.00205139	0.08	0.9274

LOPERAMIDE TABLETS VS CAPSULE STUDY
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General Linear Models Procedure

Dependent Variable:

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source			Mean Square	F Value	Pr > F
GENDER	1		0.08593636	0.09	0.7686
SEQUENCE	2		0.75817845	0.79	0.4703
SEQUENCE*GENDER	2		0.00384451	0.00	0.9960

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.16781726	-3.53	0.0010	0.04759285
C-317 - IMODIUM	-0.14916045	-3.13	0.0031	0.04759285
C-604 - C-317	-0.01865681	-0.39	0.6970	0.04759285

LOPERAMIDE TABLETS VS CAPSULE STUDY
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General Linear Models Procedure

Dependent Variable: LAUCINF

Source			Mean Square	F Value	Pr > F
Model	29		0.53384016	26.26	0.0001
Error	42		0.02032914		
Corrected Total	71				
	R-Square	C.V.			
	0.947731	4.401165			

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.65542945	32.24	0.0001
GENDER	1	0.09471764	4.66	0.0366
SEQUENCE*GENDER	2	0.02255144	1.11	0.3393
SUBJE(SEQUEN*GENDER)	18	0.77596666	38.17	0.0001
PERIOD	2	0.00447176	0.22	0.8035
PRODUCT	2	0.02713348	1.33	0.2742
PRODUCT*GENDER	2	0.00003749	0.00	0.9982

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.66375653	32.65	0.0001
GENDER	1	0.09471764	4.66	0.0366
SEQUENCE*GENDER	2	0.02255144	1.11	0.3393
SUBJE(SEQUEN*GENDER)	18	0.77596666	38.17	0.0001
PERIOD	2	0.00444350	0.22	0.8046
PRODUCT	2	0.02713348	1.33	0.2742
PRODUCT*GENDER	2	0.00003749	0.00	0.9982

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.63493242	31.23	0.0001
GENDER	1	0.09656051	4.75	0.0350
SEQUENCE*GENDER	2	0.02255144	1.11	0.3393
SUBJE(SEQUEN*GENDER)	18	0.77596666	38.17	0.0001
PERIOD	2	0.00444350	0.22	0.8046
PRODUCT	2	0.02713348	1.33	0.2742
PRODUCT*GENDER	2	0.00003749	0.00	0.9982

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.75191568	36.99	0.0001
GENDER	1	0.05758962	2.83	0.0998
SEQUENCE*GENDER	2	0.02255144	1.11	0.3393
SUBJE(SEQUEN*GENDER)	18	0.77596666	38.17	0.0001
PERIOD	2	0.00444350	0.22	0.8046
PRODUCT	2	0.02713348	1.33	0.2742
PRODUCT*GENDER	2	0.00003749	0.00	0.9982

LOPERAMIDE TABLETS VS CAPSULE STUDY
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General Linear Models Procedure

Dependent Variable: LCMAX

Source			Mean Square	F Value	Pr > F
Model	29		0.62344601	12.62	0.0001
Error	42		0.04940337		
Corrected Total	71				
	R-Square	C.V.			
	0.897050	-1010.934			

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.52551924	10.64	0.0002
GENDER	1	0.01705539	0.35	0.5600
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.04420826	0.89	0.4163
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.52287898	10.58	0.0002
GENDER	1	0.01705539	0.35	0.5600
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.03767509	0.76	0.4728
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.54280824	10.99	0.0001
GENDER	1	0.01658612	0.34	0.5654
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.03767509	0.76	0.4728
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.66850748	13.53	0.0001
GENDER	1	0.00208762	0.04	0.8381
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.03767509	0.76	0.4728
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

General Linear Models Procedure

Dependent Variable: LCMAX

Source			Mean Square	F Value	Pr > F
Model	29		0.62344601	12.62	0.0001
Error	42		0.04940337		
Corrected Total	71				
	R-Square	C.V.			
	0.897050	-1010.934			

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.52551924	10.64	0.0002
GENDER	1	0.01705539	0.35	0.5600
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.04420826	0.89	0.4163
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.52287898	10.58	0.0002
GENDER	1	0.01705539	0.35	0.5600
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.03767509	0.76	0.4728
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.54280824	10.99	0.0001
GENDER	1	0.01658612	0.34	0.5654
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.03767509	0.76	0.4728
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

Source	DF	Mean Square	F Value	Pr > F
SEQUENCE	2	0.66850748	13.53	0.0001
GENDER	1	0.00208762	0.04	0.8381
SEQUENCE*GENDER	2	0.02688107	0.54	0.5844
SUBJE(SEQUEN*GENDER)	18	0.81984470	16.59	0.0001
PERIOD	2	0.03767509	0.76	0.4728
PRODUCT	2	1.04449647	21.14	0.0001
PRODUCT*GENDER	2	0.01173212	0.24	0.7897

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General Linear Models Procedure

Dependent Variable: LAUCINF

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source		Mean Square	F Value	Pr > F
GENDER	1	0.09656051	0.12	0.7284
SEQUENCE	2	0.63493242	0.82	0.4570
SEQUENCE*GENDER	2	0.02255144	0.03	0.9714

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.06004376	-1.46	0.1521	0.04115939
C-317 - IMODIUM	-0.05624678	-1.37	0.1790	0.04115939
C-604 - C-317	-0.00379699	-0.09	0.9269	0.04115939

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General Linear Models Procedure

Dependent Variable: LCMAX

Tests of Hypotheses using the Type III MS for SUBJE(SEQUEN*GENDER) as an error term

Source			Mean Square	F Value	Pr > F
GENDER	1		0.01658612	0.02	0.8885
SEQUENCE	2		0.54280824	0.66	0.5279
SEQUENCE*GENDER	2		0.02688107	0.03	0.9678

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
C-604 - IMODIUM	-0.37492253	-5.84	0.0001	0.06416344
C-317 - IMODIUM	-0.34600741	-5.39	0.0001	0.06416344
C-604 - C-317	-0.02891512	-0.45	0.6546	0.06416344

LOPERAMIDE TABLETS VS CAPSULE STUDY
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STATISTICAL ANALYSIS OF DATA

General Linear Models Procedure
Least Squares Means

PRODUCT	AUCTLQC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN
A:C-604	20.6096759	27.0623467	0.95524074	6.54351852	0.03213852
B:C-317	20.8215509	27.3528273	0.98940741	5.91851852	0.03211075
C:IMODIUM	24.0615509	28.7743512	1.36232407	4.25185185	0.03869119

PRODUCT	THALF LSMEAN	LAUCTLQC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
A:C-604	22.1290567	2.91771535	3.21408910	-0.15113193
B:C-317	22.7133117	2.93637216	3.21788608	-0.12221682
C:IMODIUM	18.2519034	3.08553261	3.27413286	0.22379060

PERIOD	AUCTLQC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN	THALF LSMEAN
1	21.7159082	27.4765656	1.12565741	5.42590623	0.03420234	20.8068876
2	21.6980359	27.6138630	1.12335244	5.44363672	0.03385125	21.2635654
3	22.0788337	28.0990967	1.05796237	5.84434594	0.03488688	21.0238188

PERIOD	LAUCTLQC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
1	2.97875292	3.22493050	0.01801732
2	2.97551890	3.23022741	-0.00716806
3	2.98534829	3.25095013	-0.06040742

GENDER	AUCTLQC LSMEAN	AUCINF LSMEAN	CMAX LSMEAN	TMAX LSMEAN	KELM LSMEAN	THALF LSMEAN
FEMALE	22.0704398	27.7377250	1.15511111	5.17500000	0.03539400	20.5682272
MALE	21.5914120	27.7219585	1.04953704	5.96759259	0.03323297	21.4946207

GENDER	LAUCTLQC LSMEAN	LAUCINF LSMEAN	LCMAX LSMEAN
FEMALE	2.94456488	3.19785496	-0.00106518
MALE	3.01518186	3.27288373	-0.03197359

~~OCT 25 1995~~

NOV 2 1995

NDA: 20-606 **Submission Date:** ~~June 22, 1995~~ 9/28/95

Loperamide HCl/Simethicone Chewable Tablets
IMODIUM *ADVANCED*®
2mg loperamide HCl/125mg simethicone

Sponsor: McNeil Consumer Products Company

Type of Submission: Bioequivalence study to support approval of a chewable tablet dosage form

OCPB Reviewer: Philip Colangelo, Pharm.D., Ph.D.

Synopsis:

In this submission the sponsor included one study (Biostudy 134) which assessed the *in vivo* bioequivalence of loperamide between the proposed marketing (i.e., production batch size) and clinical trials formulations of the loperamide/simethicone chewable tablet and also evaluated the bioavailability of these two formulations relative to the 2mg IMODIUM® capsule. The results are summarized as follows:

Biostudy 134 (Protocol 84-428): "A Comparison of the Pharmacokinetics of the Two Formulations of Loperamide/Simethicone Chewable Tablets (C-604 and C-317) and IMODIUM® Capsules Administered in the Fasted State to Healthy Adults"

The study design was a randomized, 3-way crossover in 24 healthy male (n=12) and female (n=12) subjects in which each subject received the maximum daily loperamide (8mg) and simethicone (500mg) doses with the following treatments on three different occasions separated by a 1 week washout period: marketing tablet (Lot #C-604-3J) x 4 tablets; clinical trials tablet (Lot #C-317-5C) x 4 tablets; IMODIUM® 2mg capsule x 4 capsules. Mean loperamide plasma concentrations and pharmacokinetic parameters were nearly identical for the proposed marketing and clinical formulations. The 90% confidence intervals for AUC(tlqc) (90.8%, 106%), AUC(inf) (93.1%, 107%), and Cmax (87.4%, 108%), using the 2 one-sided tests, were within the 80% to 125% range for the comparison between the proposed marketing and clinical formulations.

The pharmacokinetic comparisons (i.e., using 90% bioequivalence confidence intervals) between the chewable tablet formulations with the capsule indicated that while the extent of total loperamide absorption was equivalent (i.e., 90% C.I. for AUC(inf) (88.0%, 101%) for both chewable formulations), the rate of absorption was slower and maximum loperamide concentrations were lower for both the proposed marketing and clinical trials chewable tablets (i.e., Tmax prolonged by ~45%, Cmax reduced by ~30% for both chewable formulations). Both the rate and extent of absorption were significantly less during the first 8 to10 hours following chewable tablet administration (i.e., 90 % C.I. for AUC(tlqc) (78.2%, 91.4%) for marketing *vs* capsule, (79.7%, 93.2%) for clinical *vs* capsule; 90% C.I. for Cmax (61.8%, 76.4%) for marketing *vs* capsule, (63.6%, 78.7%) for clinical *vs* capsule). The sponsor noted that this slower rate and lower extent of absorption for the chewable tablet suggested that more loperamide remains locally in the gastrointestinal tract at the site of action.

The sponsor also performed the USP *in vitro* defoaming test on the proposed marketing and clinical trials chewable tablet formulations to measure the functional ability of

simethicone to collapse bubbles produced by a foaming soap solution (1g octoxynol-9/100ml water). For simethicone tablets, the specification is a [redacted] All currently marketed simethicone products are evaluated for their antiflatulant activity using this test. For this submission, the sponsor performed (1) the standard *in vitro* defoaming test on crushed tablets, [redacted] The modified test on whole tablets was performed at the suggestion of the Agency. The results are as follows:

[redacted]

In conclusion, the results from Biostudy 134 indicated that the proposed marketing chewable tablet formulation of loperamide/simethicone was bioequivalent (i.e., with respect to loperamide absorption) to the formulation used in previouly conducted clinical trials. In addition, although the extent of total loperamide absorption from the two chewable tablet formulations was equivalent to that of the capsule, the rate of absorption was significantly slower for the chewable tablets, resulting in significantly lower maximum loperamide plasma concentrations. This would be expected since absorption from the chewable tablet requires tablet particle disintegration and dissolution to occur, whereas, absorption from the capsule would require only dissolution. The results of the USP *in vitro* defoaming tests indicated that the antiflatulent activity of simethicone was similar and within the limits of acceptance for the proposed marketing and clinical trials chewable tablet formulations.

General Comment:

1. Since 12 males and 12 females were studied in Biostudy 134, it is recommended that the sponsor perform an analysis of the loperamide pharmacokinetic data by gender.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed Biostudy 134 and the *in vitro* defoaming test results submitted in this NDA and found them to be acceptable. Comment 1 is of general nature and may be conveyed to the sponsor as deemed appropriate.

ON ORIGINAL

Philip M. Colangelo 10/20/95
Philip Colangelo, Pharm.D., Ph.D.
Pharmacokinetics Evaluation Branch II

RD Initialed by Lydia Kaus, Ph.D. LSK 10/23/96

FT Initialed by Mei Ling Chen, Ph.D. [illegible] 10/21/95

cc: NDA 20-606; HFD-180(Clinical Review); HFD-426(Fleischer); HFD-427 (MLChen, Colangelo), HFD-340(Viswanathan); Chron; Drug; Reviewer; HFD-19 (FOI)

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Background:

The sponsor has submitted this NDA for the combination of loperamide HCl 2mg/simethicone 125mg as a chewable tablet. It is intended to be marketed as an OTC product for the control of acute episodes of diarrhea, including Traveler's diarrhea, and associated gas symptoms such as abdominal pain, bloating, and cramping. Both loperamide and simethicone have been previously approved for OTC use - loperamide (Imodium A-D®) is available as 2mg caplets and 1mg/5ml liquid; simethicone is available in tablet and liquid form as a single-ingredient product or in combination with antacids. The maximum approved daily OTC doses are 8mg for loperamide and 500mg for simethicone. The proposed labeling for Imodium *ADVANCED*® tablets follows these same dosing guidelines, i.e., maximum of 4 tablets/day. Loperamide has also been approved for prescription use as 2mg hard gelatin capsules (Imodium®).

Oral absorption for both drugs is minimal and it is postulated that they exert their pharmacological effects locally within the gastrointestinal tract. However, assessment of the *in vivo* bioequivalence of loperamide formulations has been based on the measurement of loperamide plasma concentrations following maximum doses of 8mg.

The *in vivo* bioequivalence of simethicone (an inert silicon polymer) cannot be assessed by conventional assay methods since silicon polymer does not appear to be absorbed systemically. Simethicone appears under the FDA monograph for Antiflatulent Products for OTC Human Use (21 CFR 332) and is therefore generally recognized as safe and effective. Although the ____ assessment of simethicone bioequivalence may not be necessary, the antiflatulant activity of simethicone formulations can be evaluated *in vitro* using a USP defoaming test. For simethicone tablets, this test is a measure of the functional ability of crushed tablets to collapse bubbles produced by a foaming soap solution (1g octoxynol-9/100ml water). The specification is ____ All currently marketed simethicone products are evaluated using this test.

Previous discussions were held between the Divisions of Biopharmaceutics, Gastrointestinal Drugs/Coagulation Products and the sponsor regarding the issue of adequate assessment of bioequivalence of simethicone in this combination tablet. The sponsor's original proposal for this NDA submission was to evaluate the pharmacokinetics of loperamide ____ using a previously validated ____ method and to assess simethicone activity using the standard *in vitro* defoaming test on crushed tablets. The FDA responded with 5 suggestions, which were initiated by the Div. of Biopharm., for the sponsor to consider (see **Attachment 1**). Of these suggestions, the sponsor chose the first, i.e., to perform the standard *in vitro* defoaming test on crushed tablets and ____

ATTACHMENT 1:

CORRESPONDENCE BETWEEN FDA AND MCNEIL CONSUMER PRODUCTS

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

APPENDIX 1:

STUDY SUMMARIES

1. **Biostudy 134 (Protocol 84-428)**: "A Comparison of the Pharmacokinetics of the Two Formulations of Loperamide/Simethicone Chewable Tablets (C-604 and C-317) and IMODIUM® Capsules Administered in the Fasted State to Healthy Adults"

Volumes: 7, 8 of 27 **Pages**: 06-000045 to 06-000378B

Investigator & Location:

Study Dates: 1/9/95 to 4/22/95

Objective:
The primary objective of this study was to evaluate the *in vivo* bioequivalence of loperamide between the proposed marketing (C-604) and clinical trial (C-317) formulations of the loperamide/simethicone chewable tablet in healthy volunteers. In addition, the bioavailability of loperamide from these two chewable tablet formulations relative to the commercially marketed IMODIUM® capsule were compared in the same group of subjects.

Formulations:
Loperamide/Simethicone Chewable Tablets - 2mg loperamide HCl/125mg simethicone; Lot #C-604-3J - Production Batch Size of the Proposed Marketing Formulation; Control No. Z-4104

Loperamide/Simethicone Chewable Tablets - 2mg loperamide HCl/125mg simethicone; Lot #C-317-5C - Clinical Trial Formulation; Control No. Z-4105

IMODIUM® Capsules (Janssen) - 2mg; Control No. Z-4106

The major difference between the marketing and clinical formulations was that the marketing tablet used Simethicone and the clinical tablet used Simethicone See **Appendix 2** for the quantitative comparison of the two chewable tablet formulations.

Methods:
The study design was a randomized, 3-way crossover in 24 healthy male (n=12) and female (n=12) subjects in which each subject received the maximum daily loperamide (8mg) and simethicone (500mg) doses with the following treatments on three different occasions separated by a 1 week washout period:

Treatment A = marketing tablet (Lot #C-604-3J) x 4 tablets
Treatment B = clinical tablet (Lot #C-317-5C) x 4 tablets
Treatment C = IMODIUM® capsule x 4 capsules

The subjects fasted for at least 10 hours prior to and for 4 hours after dosing. The IMODIUM® capsules were administered with 200ml of water. For adminsitration of the chewable tablets, the subjects were instructed to thoroughly chew and swallow the tablets, then swish 200ml of water around the mouth to remove any tablet particles that may be caught in the teeth, and then swallow the water.

Plasma samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, and 48 hours postdose for determination of loperamide plasma concentrations.

Results:
In **Appendix 2**, the individual plasma loperamide concentration-time data and pharmacokinetic parameters are provided for each treatment in Tables 1 through 3 and 5 through 6, respectively. The results of the statistical analyses for both untransformed and log-transformed data and Westlake's 95% confidence intervals are also provided in Tables 7 through10 of **Appendix 2**.

The comparison of mean plasma loperamide plasma concentration-time profiles are illustrated in Figures 1 through 4 for the three treatments. The mean pharmacokinetic parameters are summarized in Table 1 and the statistical results are summarized in Tables 2, 3, and 4.

Table 1 shows that the mean pharmacokinetic parameters are nearly identical for both the proposed marketing and clinical formulations and Figures 1 and 2 illustrate that the mean plasma loperamide concentrations are nearly superimposable. As shown in Table 2, the 90% confidence intervals for AUCTLQC (90.8%, 106%), AUCINF (93.1%, 107%), and Cmax (87.4%, 108%) were all within the range for the comparison between the proposed marketing and clinical formulations. The sponsor concluded that the two formulatioins are bioequivalent.

For the comparison between either the proposed marketing or clinical chewable tablets and IMODIUM® capsules, Figures 1, 3, and 4 show that the mean loperamide plasma concentrations following either chewable tablet formulation were lower than the capsules for up to 10 hours postdose. The ANOVA detected significantly lower loperamide concentrations from 0.5 to 8 hours postdose for both chewable tablet formulations ($p < 0.05$). As shown in Table 1, the mean AUCTLQC values for either proposed marketing or clinical chewable tablet formulations were reduced by ~14% *vs* the capsules, while the mean AUCINF values differed by only ~5%. Consistent with these findings, the 90% confidence intervals for the comparison of AUCTLQC between either of the chewable tablet formulations and the capsule fell outside of the acceptance range for bioequivalence (i.e, Table 3: (78.2%, 91.4%) for marketing *vs* capsule; Table 4: (79.7%, 93.2%) for clinical *vs* capsule). However, the 90% confidence intervals were within the acceptance range for the comparison of AUCINF for both chewable tablet formulations and the capsule (i.e, Table 3: for marketing *vs* capsule; Table 4:) for clinical *vs* capsule). The mean Tmax estimates were ~45% longer for both chewable formulations than those following capsule administration and mean Cmax values were ~30% lower. The ANOVA detected significant diferences for Tmax between either chewable formulation and the capsule ($p < 0.05$) and the 90% confidence intervals fell outside the acceptance range for Cmax (i.e., Table 3: for marketing *vs* capsule; Table 4:

for clinical *vs* capsule). The mean estimates for KELM and T½ were also statistically different between the two chewable tablet formulations and the capsules ($p < 0.05$). The sponsor concluded that the chewable tablet formulations (proposed marketing or clinical) and the IMMODIUM® capsules were equivalent with respect to the extent of total loperamide absorbed (i.e., AUCINF), but that the rate of loperamide absorption from either chewable tablet formulation (i.e., Cmax, Tmax) was slower than the capsules. The rate and extent of absorption was significantly less during the first 8 to 10 hours following tablet administration. The sponsor also noted that this slower rate and extent of absorption for the chewable tablet suggested that more loperamide remains locally in the gastrointestinal tract at the site of action.

Conclusions:
The results from this study of 12 male and 12 female volunteers fulfilled the sponsor's primary objective, i.e., the proposed marketing chewable tablet formulation of loperamide/simethicone (Lot #C-604-3J) was bioequivalent to the formulation used in previouly conducted clinical trials (Lot #C-317-5C).

As a secondary objective, the sponsor also compared the pharmacokinetics of the chewable tablet and IMODIUM® capsule formulations. Although the extent of loperamide absorption from the two chewable tablet formulations was equivalent to that of the capsule, the rate of absorption was slower for the chewable tablets, resulting in lower maximum loperamide plasma concentrations. This would be expected since absorption from the chewable tablet requires tablet particle disintegration and dissolution to occur, whereas, absorption from the capsule would require only dissolution. The rate and extent of loperamide absorption was significantly less from the chewable tablets during the first 8 to 10 hours postdose when comapred to capsule administration. Also, the mean loperamide T½ estimates following chewable tablet administration were found to be statistically longer than that following capsule administration. These results indicated that the chewable tablet and capsule formulations are not bioequivalent.

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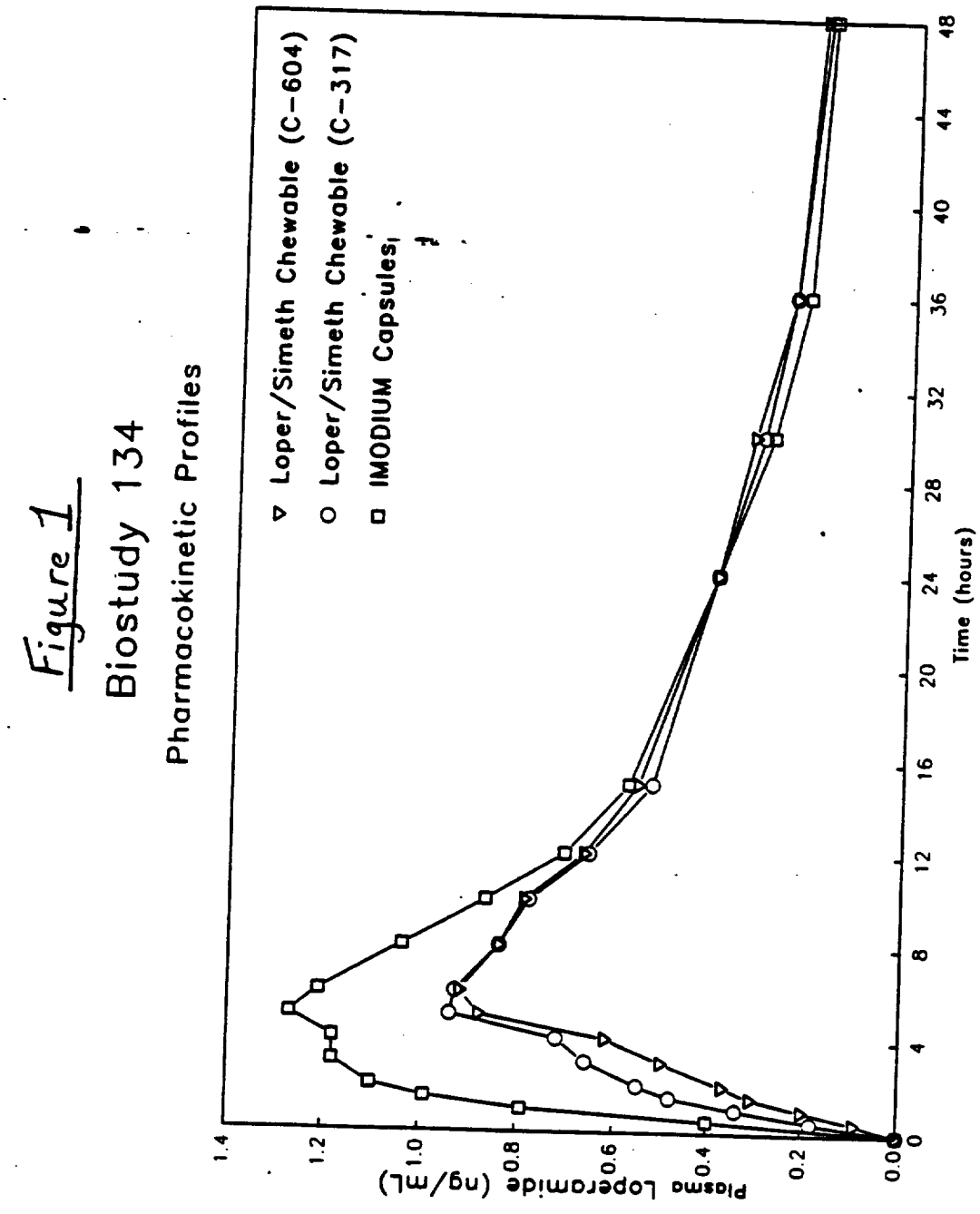
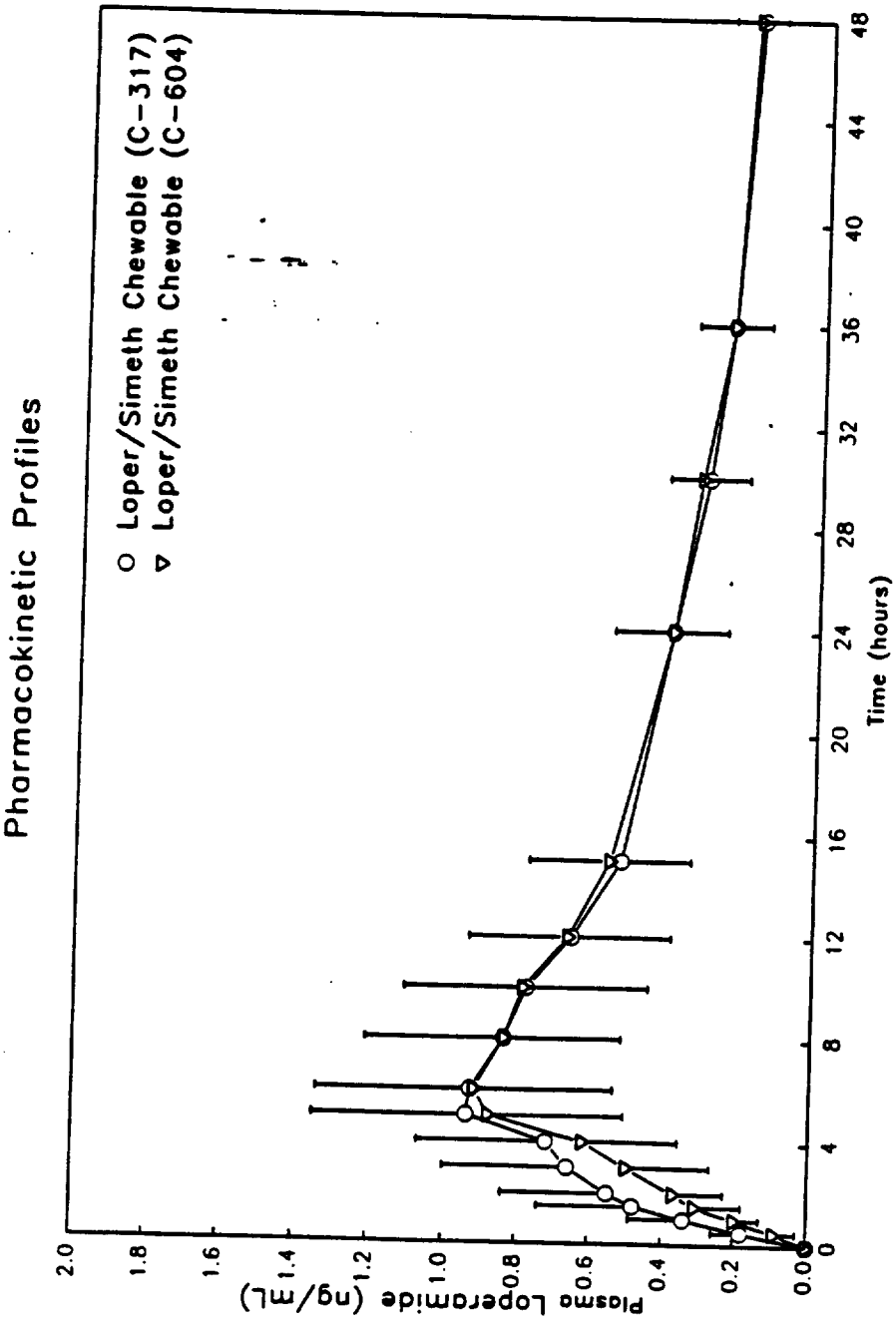
Figure 6.3.1



C-604/s6/11

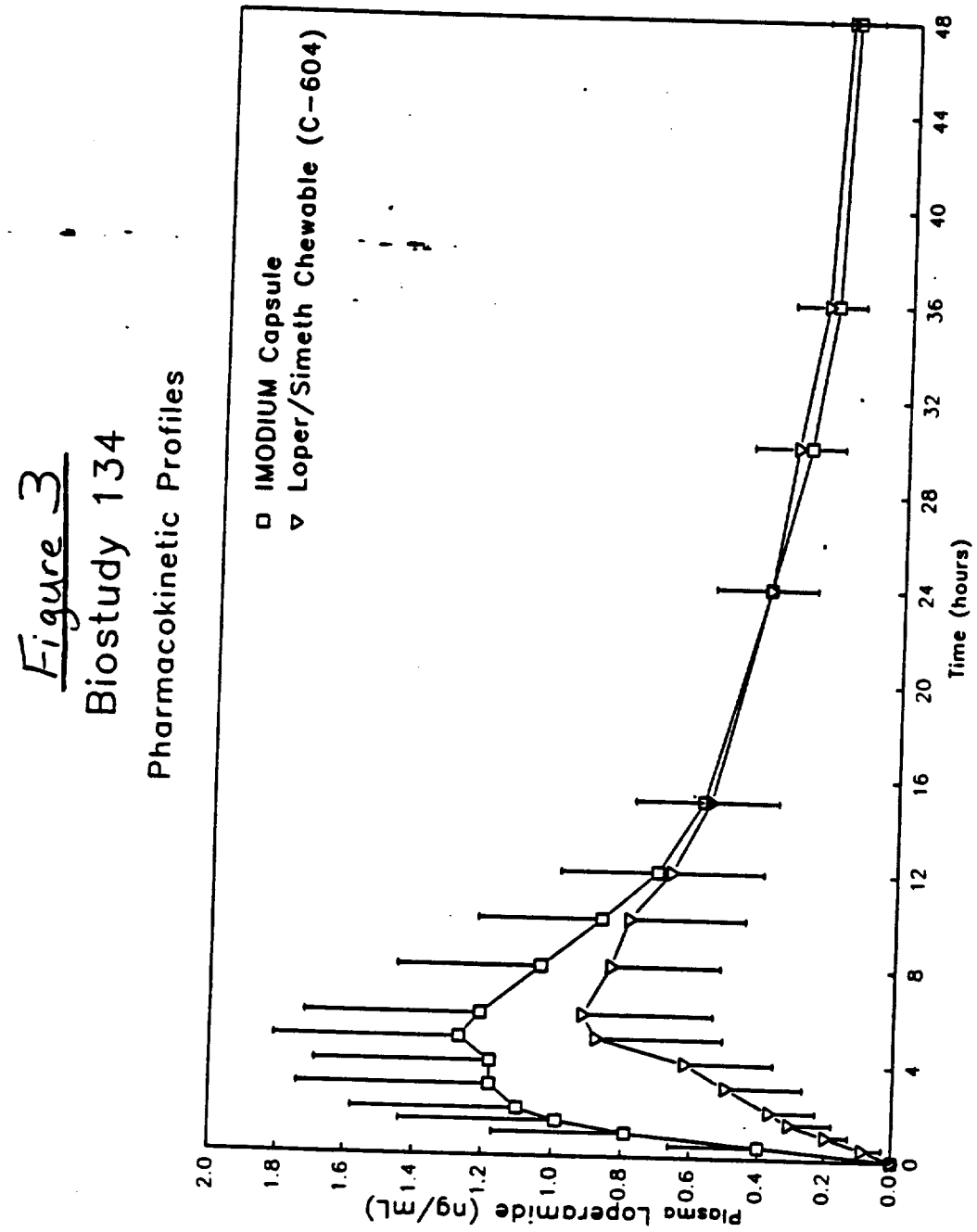
Loperamide HCl/Simethicone Chewable Tablets
NDA 20-606
McNeil Consumer Products Company

Figure 6.3.2



C-604/s6/12

Figure 6.3.3



C-604/s6/13

Figure 6.3.4

Figure 4
Biostudy 134
Pharmacokinetic Profiles

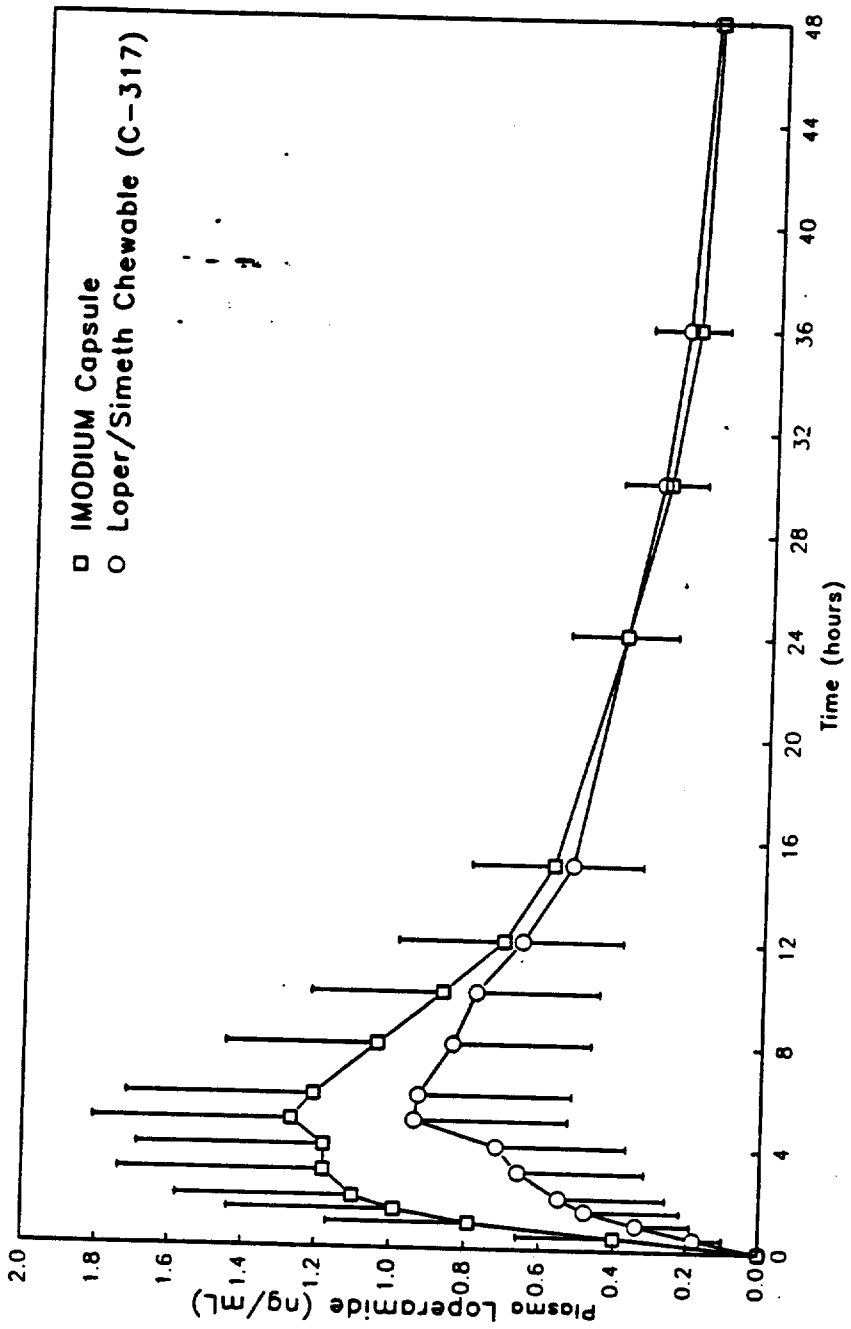


Table 1

6.3.1 Loperamide Pharmacokinetic Parameters from Bioavailability Study 134

Study Number†	Route	Dosage Form	N	Mean (± S.D.) [% C.V.] AUC (ng·hr/mL)	AUC$_{INF}$ (ng·hr/mL)	C$_{MAX}$ (ng/mL)	T$_{MAX}$ (hr)	k_{el} (hr^{-1})	$t_{1/2}$ (hr)	LAUC	LAUC$_{INF}$	LC$_{MAX}$
134	oral	4 Loperamide/Simethicone Chewable Tablets (2mg/125mg per tablet) *Marketing Formulation* C-604-3J	24	20.7 (7.7) [37]	27.2 (9.3) [34]	0.95 (0.37) [39]	6.6 (1.7) [26]	0.032 (0.005) [16]	22.2 (3.6) [16]	2.920 (0.578)	3.218 (0.485)	-0.157 (0.537)
		4 Loperamide/Simethicone Chewable Tablets (2mg/125mg per tablet) *Clinical Formulation* C-317-5C	24	20.9 (7.9) [38]	27.5 (10.1) [37]	0.99 (0.42) [42]	6.0 (1.3) [22]	0.032 (0.007) [22]	22.0 (5.6) [25]	2.939 (0.526)	3.222 (0.494)	-0.126 (0.540)
		4 IMODIUM® Capsules (2mg per capsule) 93N363A	24	24.1 (9.0) [37]	28.9 (10.3) [36]	1.36 (0.54) [40]	4.3 (1.6) [37]	0.039 (0.005) [14]	18.3 (2.6) [14]	3.088 (0.514)	3.276 (0.478)	0.218 (0.453)

† Protocol 94-428

Table 2

Table 6.3.2 Comparison of Proposed Marketing and Clinical Formulations of the Loperamide/Simethicone Chewable Tablet

Parameter	Mean (± SD) CV% Marketing Formulation C-604-3J	Clinical Formulation C-317-5C	90% Confidence Intervals (2 one-sided t-tests)	Pr > |T|	Power %
AUC	20.67 (7.68) 37%	20.88 (7.93) 38%	90.8 to 107	0.8353	98
AUCINF	27.18 (9.33) 34%	27.47 (10.06) 37%	91.9 to 106	0.8020	100
CMAX	0.95 (0.37) 39%	0.99 (0.42) 42%	83.8 to 109	0.6499	73
Geometric Means					
LAUC	18.54	18.89	90.8 to 106	0.6907	99
LAUCINF	24.99	25.08	93.1 to 107	0.9252	100
LCMAX	0.86	0.88	87.4 to 108	0.6487	87

Table 3

Table 6.3.3 Comparison of Loperamide/Simethicone Chewable Tablets (Proposed Marketing Formula) and IMODIUM® Capsules

Parameter	Mean (± SD) CV% Chewable Tablets C-604-3J	IMODIUM® Capsules	90% Confidence Intervals (2 one-sided t-tests)	Pr > |T|	Power
AUC	20.67 (7.68) 37%	24.12 (8.97) 37%	78.6 to 92.7	0.0014	100
AUCINF	27.18 (9.33) 34%	28.90 (10.30) 36%	87.4 to 101	0.1441	100
CMAX	0.95 (0.37) 39%	1.36 (0.54) 40%	60.8 to 79.3	0.0001	94
Geometric Means					
LAUC	18.54	21.93	78.2 to 91.4	0.0008	99
LAUCINF	24.99	26.53	88.0 to 101	0.1426	100
LCMAX	0.86	1.24	61.8 to 76.4	0.0001	87

Table 4

Table 6.3.4 Comparison of Loperamide/Simethicone Chewable Tablets (Clinical Formula) and IMODIUM® Capsules

Parameter	Mean (± SD) CV% Chewable Tablets C-317-5C	IMODIUM® Capsules	90% Confidence Intervals (2 one-sided t-tests)	Pr > |T|	Power
AUC	20.88 (7.93) 38%	24.12 (8.97) 37%	79.5 to 93.6	0.0026	100
AUCINF	27.47 (10.06) 37%	28.90 (10.30) 36%	88.4 to 102	0.2235	100
CMAX	0.99 (0.42) 42%	1.36 (0.54) 40%	63.3 to 81.8	0.0001	94
Geometric Means					
LAUC	18.89	21.93	79.7 to 93.2	0.0025	99
LAUCINF	25.08	26.53	88.0 to 101	0.1689	100
LCMAX	0.88	1.24	63.6 to 78.7	0.0001	87

2. *In Vitro* Defoaming Tests for the Release of Simethicone From the Chewable Tablet Formulations Used in **Biostudy 134**: Proposed Marketing (C-604-3J); Clinical Trials (C-317-5C)

Volumes: 7 of 27 **Pages**: 06-000039 to 06-000044

Introduction:
The *in vivo* bioequivalence of simethicone (an inert silicon polymer) cannot be assessed by conventional assay methods since silicon polymer does not appear to be absorbed systemically. Simethicone appears under the FDA monograph for Antiflatulent Products for OTC Human Use (21 CFR 332) and is therefore generally recognized as safe and effective. Although the *in vivo* assessment of simethicone bioequivalence may not be necessary, the antiflatulant activity of simethicone formulations can be evaluated *in vitro* using a USP defoaming test. For simethicone tablets, this test is a measure of the functional ability of crushed tablets to collapse bubbles produced by a foaming soap solution (1g octoxynol-9/100ml water). The specification is a [redacted] All currently marketed simethicone products are evaluated using this test.

Methods:
The sponsor performed (1) the standard *in vitro* defoaming test on crushed tablets, and [redacted] The method and specifications for both tests used by the sponsor are provided in Table 1 and were in compliance with that outlined in the USP official monograph for simethicone products. The tests were performed by two different analysts to show reproducibility of the method, which requires judgement to note the time for a whole intact tablet or crushed sample to clear the foaming soap solution. Three determinations of defoaming times were made by each analyst.

Results:
The defoaming times for both tests with crushed tablets and whole intact tablets are provided in Table 2. The mean defoaming times for the crushed tablets were similar between the two formulations and did not exceed [redacted] The mean defoaming times for the whole tablets were also similar for the proposed marketing and clinical formulations, but were [redacted] than that for the crushed tablets. However, these defoaming times for the whole tablets remained well within the [redacted] specification. The sponsor noted that the [redacted] defoaming times for the whole intact tablets was to be expected. For a given analyst, defoaming time determinations were remarkably consistent for the crushed tablet test and slightly more variable for the whole tablet test.

Conclusions:

The results of the USP *in vitro* defoaming tests, either with crushed tablets or whole intact tablets, indicated that the antiflatulent activity of simethicone was similar and within the limits of acceptance for the proposed marketing and clinical trials chewable tablet formulations.

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Table 1

6.6.2 Proposed Defoaming Test Method and Specifications for Release

Dosage Form:	Loperamide HCl/Simethicone Chewable Tablet
Strength:	2 mg loperamide HCl / 125 mg simethicone
Sample:	
Medium:	
Volume:	
Medium Temperature:	
Apparatus:	
Shaking Speed:	
Shaking Time:	

Calculation of Defoaming Time:

Defoaming Time

t_2

t_1

Specification:

Not more than for defoaming activity of simethicone tablet formulations.

Table 2

Table 6.6.3 ***In Vitro*** **Defoaming Results for the Loperamide/ Simethicone Chewable Tablets**

SAMPLE	Analyst 1 Defoaming Time (seconds)	Analyst 2 Defoaming Time (seconds)
Proposed Marketing Formulation C-604-3J Crushed Tablet	Mean 3.8	Mean 2.4
Clinical Formulation C-317-5C Crushed Tablet	Mean 4.3	Mean 2.1
Proposed Marketing Formulation C-604-3J Whole Tablet	Mean 14.5	Mean 10.6
Clinical Formulation C-317-5C Whole Tablet	Mean 15.0	Mean 11.7

APPENDIX 2:

LOPERAMIDE HCL/SIMETHICONE CHEWABLE TABLET FORMULATION COMPARISONS: PROPOSED MARKETING (C-604-3) VS. CLINICAL TRIALS (C-317-5)

H. Investigational Formulations

Ingredients[1]	NDA Unit Formula C-604-3[2] (mg/tablet)
Loperamide HCl USP	
Microcrystalline Cellulose NF	
Simethicone USP	
Sorbitol NF	
Dextrates NF	
Tribasic Calcium Phosphate NF	
Dextrates NF	
Saccharin Sodium USP	
D&C Yellow	
FD&C Blue	
Tribasic Calcium Phosphate NF	
Total Unit Weights	

1 Variation in quantities of all excipients may be ± 10%.
2 Project Code changed from C-317 to C-604 due to a change from Simethicone to Simethicone USP.

02 [illegible]

APPENDIX 2:

BIOSTUDY 134 - LOPERAMIDE PLASMA CONCENTRATION-TIME DATA

Table 1

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL 85-134
DATA BY PRODUCT AND SUBJECT

PRODUCT=A:C-604

SUBJECT	PERIOD	0.0 HR	0.5 HR	1.0 HR	1.5 HR	2.0 HR	3.0 HR	4.0 HR	5.0 HR
1	1								
2	3								
3	1								
4	1								
5	2								
6	2								
7	3								
8	3								
9	3								
10	2								
11	2								
12	1								
13	2								
14	1								
15	2								
16	1								
17	3								
18	3								
20	3								
21	2								
22	1								
23	3								
24	2								
119	1								

SUBJECT	6.0 HR	8.0 HR	10 HR	12 HR	15 HR	24 HR	30 HR	36 HR	48 HR
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
20									
21									
22									
23									
24									
119									

Table 2

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
DATA BY PRODUCT AND SUBJECT

PRODUCT=B:C-317

SUBJECT	PERIOD	0.0 HR	0.5 HR	1.0 HR	1.5 HR	2.0 HR	3.0 HR	4.0 HR	5.0 HR
1	3								
2	2								
3	3								
4	3								
5	1								
6	1								
7	2								
8	2								
9	2								
10	1								
11	1								
12	3								
13	1								
14	3								
15	1								
16	3								
17	2								
18	2								
20	2								
21	1								
22	3								
23	2								
24	1								
119	3								

SUBJECT	6.0 HR	8.0 HR	10 HR	12 HR	15 HR	24 HR	30 HR	36 HR	48 HR
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
20									
21									
22									
23									
24									
119									

Table 3

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
DATA BY PRODUCT AND SUBJECT

PRODUCT=C:IMODIUM

SUBJECT	PERIOD	0.0 HR	0.5 HR	1.0 HR	1.5 HR	2.0 HR	3.0 HR	4.0 HR	5.0 HR
1	2								
2	1								
3	2								
4	2								
5	3								
6	3								
7	1								
8	1								
9	1								
10	3								
11	3								
12	2								
13	3								
14	2								
15	3								
16	2								
17	1								
18	1								
20	1								
21	3								
22	2								
23	1								
24	3								
119	2								

SUBJECT	6.0 HR	8.0 HR	10 HR	12 HR	18 HR	24 HR	30 HR	36 HR	48 HR
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
20									
21									
22									
23									
24									
119									

APPENDIX 2:

BIOSTUDY 134 - LOPERAMIDE PHARMACOKINETIC DATA

Table 4

Table 4.5.4 Treatment A (C-604) Product Loperamide Pharmacokinetic Parameter Values for Individual Subjects

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
DATA BY PRODUCT AND SUBJECT

PRODUCT=A:C-604

SUBJECT	PERIOD	SEQUENCE	AUCTLQC	AUCINF	CMAX	TMAX	KELM	THALF
1	1	1						
2	3	3						
3	1	1						
4	1	1						
5	2	2						
6	2	2						
7	3	3						
8	3	3						
9	3	3						
10	2	2						
11	2	2						
12	1	1						
13	2	2						
14	1	1						
15	2	2						
16	1	1						
17	3	3						
18	3	3						
20	3	3						
21	2	2						
22	1	1						
23	3	3						
24	2	2						
119	1	1						

06 000105

Table 5

Table 4.5.5 Treatment B (C-317) Product Loperamide Pharmacokinetic Parameter Values for Individual Subjects

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
DATA BY PRODUCT AND SUBJECT

PRODUCT=B:C-317

SUBJECT	PERIOD	SEQUENCE	AUCTLQC	AUCINF	CMAX	TMAX	KELM	THALF
1	3	1						
2	2	3						
3	3	1						
4	3	1						
5	1	2						
6	1	2						
7	2	3						
8	2	3						
9	2	3						
10	1	2						
11	1	2						
12	3	1						
13	1	2						
14	3	1						
15	1	2						
16	3	1						
17	2	3						
18	2	3						
20	2	3						
21	1	2						
22	3	1						
23	2	3						
24	1	2						
119	3	1						

06 000106

Table 6

Table 4.5.6 Treatment C (IMODIUM) Product Loperamide Pharmacokinetic Parameter Values for Individual Subjects

LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
DATA BY PRODUCT AND SUBJECT

PRODUCT=C:IMODIUM

SUBJECT	PERIOD	SEQUENCE	AUCTLQC	AUCINF	CMAX	TMAX	KELM	THALF
1	2	1						
2	1	3						
3	2	1						
4	2	1						
5	3	2						
6	3	2						
7	1	3						
8	1	3						
9	1	3						
10	3	2						
11	3	2						
12	2	1						
13	3	2						
14	2	1						
15	3	2						
16	2	1						
17	1	3						
18	1	3						
20	1	3						
21	3	2						
22	2	1						
23	1	3						
24	3	2						
119	2	1						

06 000107

APPENDIX 2:

BIOSTUDY 134 - LOPERAMIDE STATISTICAL DATA

Table 7

Table 4.5.7 Summary of Statistical Analysis of Loperamide Data

SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA
LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
A:(C-604) VS B:(C-317)

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	20.66656	20.87844	99.0
AUCINF	27.18262	27.47310	98.9
CMAX	0.950417	0.984583	96.5
TMAX	6.583333	5.958333	110
KELM	0.032028	0.032000	100
THALF	22.18586	22.77012	97.4

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(90.8; 107)	0.97954	0.8353
AUCINF	(91.9; 106)	0.99577	0.8020
CMAX	(83.8; 109)	0.73023	0.6499
TMAX	(99.5; 121)	0.84890	0.1157
KELM	(93.0; 107)	0.99554	0.9836
THALF	(89.7; 105)	0.98822	0.5786

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	2.919881	2.938538	18.5391	18.8882
AUCINF	3.218324	3.222121	24.9862	25.0813
CMAX	-0.156600	-0.127680	0.8550	0.8801

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	98.2	(90.8; 106)	0.98618	0.6907
AUCINF	99.6	(93.1; 107)	0.99752	0.9252
CMAX	97.1	(87.4; 108)	0.87327	0.6487

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS OF LOG TRANSFORMED VALUES.

06 000109

Table 8

Table 4.5.8 Summary of Statistical Analysis of Loperamide Data

SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA
LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
A:(C-604) VS C:(IMODIUM)

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	20.66656	24.11844	85.7
AUCINF	27.18262	28.89463	94.1
CMAX	0.950417	1.357500	70.0
TMAX	6.583333	4.291667	153
KELM	0.032028	0.038580	83.0
THALF	22.18586	18.30871	121

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(78.6;92.7)	0.99564	0.0014
AUCINF	(87.4; 101)	0.99781	0.1441
CMAX	(60.8;79.3)	0.94337	0.0001
TMAX	(138; 169)	0.57421	0.0001
KELM	(77.1;88.9)	0.99971	0.0001
THALF	(112; 131)	0.92850	0.0006

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	2.919881	3.087698	18.5391	21.9265
AUCINF	3.218324	3.278367	24.9862	26.5324
CMAX	-0.156600	0.218324	0.8550	1.2440

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	84.6	(78.2;91.4)	0.98618	0.0008
AUCINF	94.2	(88.0; 101)	0.99752	0.1426
CMAX	68.7	(61.8;76.4)	0.87327	0.0001

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

06 000110

Table 9

Table 4.5.9 Summary of Statistical Analysis of Loperamide Data

SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA
LOPERAMIDE TABLETS VS CAPSULE STUDY
MCNEIL BS-134
B:(C-317) VS C:(IMODIUM)

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	20.87844	24.11844	86.6
AUCINF	27.47310	28.89463	95.1
CMAX	0.984583	1.357500	72.5
TMAX	5.958333	4.291667	139
KELM	0.032000	0.038580	82.9
THALF	22.77012	18.30871	124

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(79.5;93.6)	0.99564	0.0026
AUCINF	(88.4; 102)	0.99781	0.2235
CMAX	(63.3;81.8)	0.94337	0.0001
TMAX	(124; 154)	0.57421	0.0001
KELM	(77.1;88.8)	0.99971	0.0001
THALF	(115; 134)	0.92850	0.0001

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	2.938538	3.087698	18.8882	21.9265
AUCINF	3.222121	3.278367	25.0813	26.5324
CMAX	-0.127680	0.218324	0.8801	1.2440

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	86.1	(79.7;93.2)	0.98618	0.0025
AUCINF	94.5	(88.4; 101)	0.99752	0.1689
CMAX	70.8	(63.6;78.7)	0.87327	0.0001

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

06 000111

Table 10

Table 4.5.10 Westlake's Symmetrical Confidence Limits

Westlake's 95% Symmetrical Confidence Limits

C-604 vs C-317

AUCTLQC	9.977
AUCINF	8.691
CMAX	16.680
TMAX	21.475
KELM	8.485
THALF	10.437

Westlake's 95% Symmetrical Confidence Limits

C-317 vs IMODIUM®

AUCTLQC	20.492
AUCINF	11.618
CMAX	36.726
TMAX	54.085
KELM	22.922
THALF	33.951

Westlake's 95% Symmetrical Confidence Limits

C-604 vs IMODIUM®

AUCTLQC	21.370
AUCINF	12.620
CMAX	39.243
TMAX	68.650
KELM	22.851
THALF	30.760

JUN 17 1997

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-606 **CHEM REVIEW #** 5 **REVIEW DATE:** February 21, 1997

SUBMISSION TYPE **DATES**

DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
Amendment (BC)	26APR96	01May96	10May96	3		
Amendment (BL)	26APR96	01May96	10MAY96	3		
Amendment (BC)	14DEC95	08JUL96	09JUL96	4		
Amendment (AC)	30DEC96	29JAN97	17Feb97	5		

NAME & ADDRESS OF APPLICANT:

McNeil Consumer Products Company,
7050 Camp Hill Road,
Fort Washington, PA 19034-2299

DRUG PRODUCT NAME:

Proprietary:	IMODIUM® Advanced Chewable Tablets
Nonproprietary/USAN:	Loperamide HCl/Simethicone
Code Name/#:	None
Chem.Type/Ther.Class:	1S

PHARMACOLOGICAL CATEGORY: Antidiarrheal agent

INDICATION: Control the symptoms of diarrhea and associated gas symptoms.

DOSAGE FORM: Chewable tablet

STRENGTH: Loperamide 2mg and Simethicone 125 mg Chewable tablet

ROUTE OF ADMINISTRATION: Oral
HOW DISPENSED? ____ RX ___√__ OTC

Chemical Name: Two active ingredients with the following names:
Loperamide hydrochloride; 4-(*p*-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutylamide monohydrochloride (figure 1).

Simethicone; α-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)], mixture with silicone dioxide, (figure 2).

Related Document: NDA 20-606

CONSULTS: Biostat III (Chen Wen-Jen)

STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT: Next page.

Figure 1. Loperamide hydrochloride

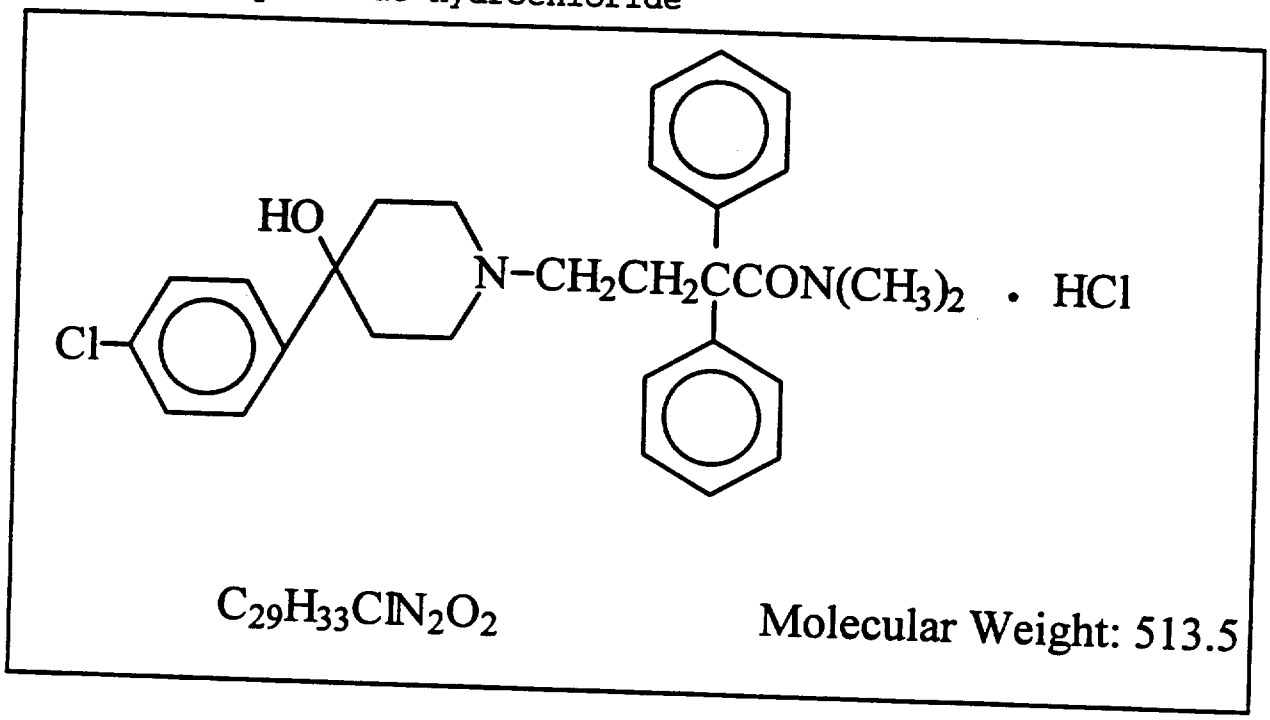
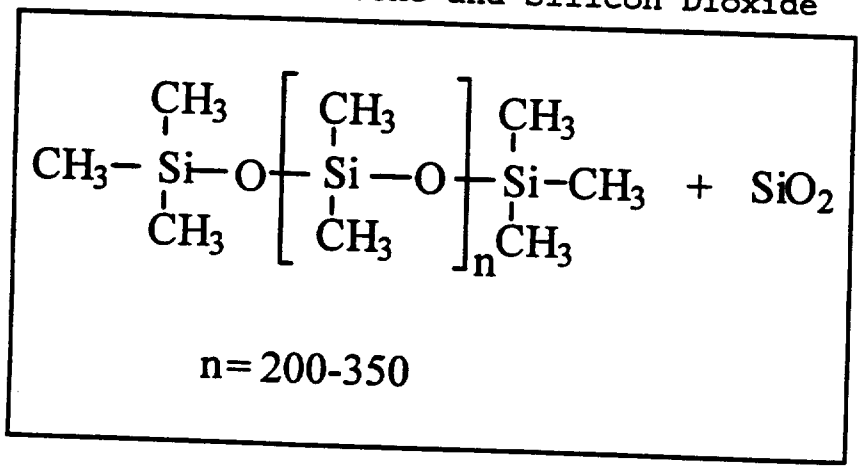


Figure 2. Simethicone and Silicon Dioxide



RECOMMENDATION/CONCLUSION:
The amendment (AC 12/27/96) contains satisfactory responses to our information request letter.
With these responses, the above application has no outstanding deficiencies/queries regarding the Chemistry, Manufacturing and Control section of the NDA. Acceptable EER is dated February 7, 1997.
Approval is recommended.

A Al-Hakim 6/17/97
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

Eric P. Duffy 6/17/97
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

CC:
NDA 20-606
HFD-180/Division file NDA 20-606
DISTRICT FILE
HFD-180/LTalarico
HFD-181/CSO/BStrongin
HFD-180/AAl-Hakim
HFD-180/EDuffy/6-16-97
AAH/dob **F/T 6/17/97/WP:** c:\wpfiles\chem\N\20606702.5AA

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-606 **CHEM REVIEW #** 4 **REVIEW DATE:** July 9, 1996

JUL 19 1996

SUBMISSION TYPE **DATES**

DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
Amendment (BC)	26APR96	01May96	10May96	3		
Amendment (BL)	26APR96	01May96	10MAY96	3		
Amendment (BC)	14DEC96	08JUL96	09JUL96	4		

NAME & ADDRESS OF APPLICANT:

McNeil Consumer Products Company,
7050 Camp Hill Road,
Fort Washington, PA 19034-2299

DRUG PRODUCT NAME:

Proprietary:	IMODIUM® Advanced Chewable Tablets
Nonproprietary/USAN:	Loperamide HCl/Simethicone
Code Name/#:	None
Chem.Type/Ther.Class:	1S

PHARMACOLOGICAL CATEGORY: Antidiarrheal agent

INDICATION: Control the symptoms of diarrhea and associated gas symptoms.

DOSAGE FORM: Chewable tablet

STRENGTH: Loperamide 2mg and Simethicone 125 mg Chewable tablet

ROUTE OF ADMINISTRATION: Oral
HOW DISPENSED? ____ RX __√__ OTC

Chemical Name: Two active ingredients with the following names:
Loperamide hydrochloride; 4-(*p*-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutylamide monohydrochloride (figure 1).

Simethicone; α-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)], mixture with silicone dioxide, (figure 2).

Related Document: NDA 20-606

CONSULTS: Biostat III (Chen Wen-Jen)

STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT: Next page.

Figure 1. Loperamide hydrochloride

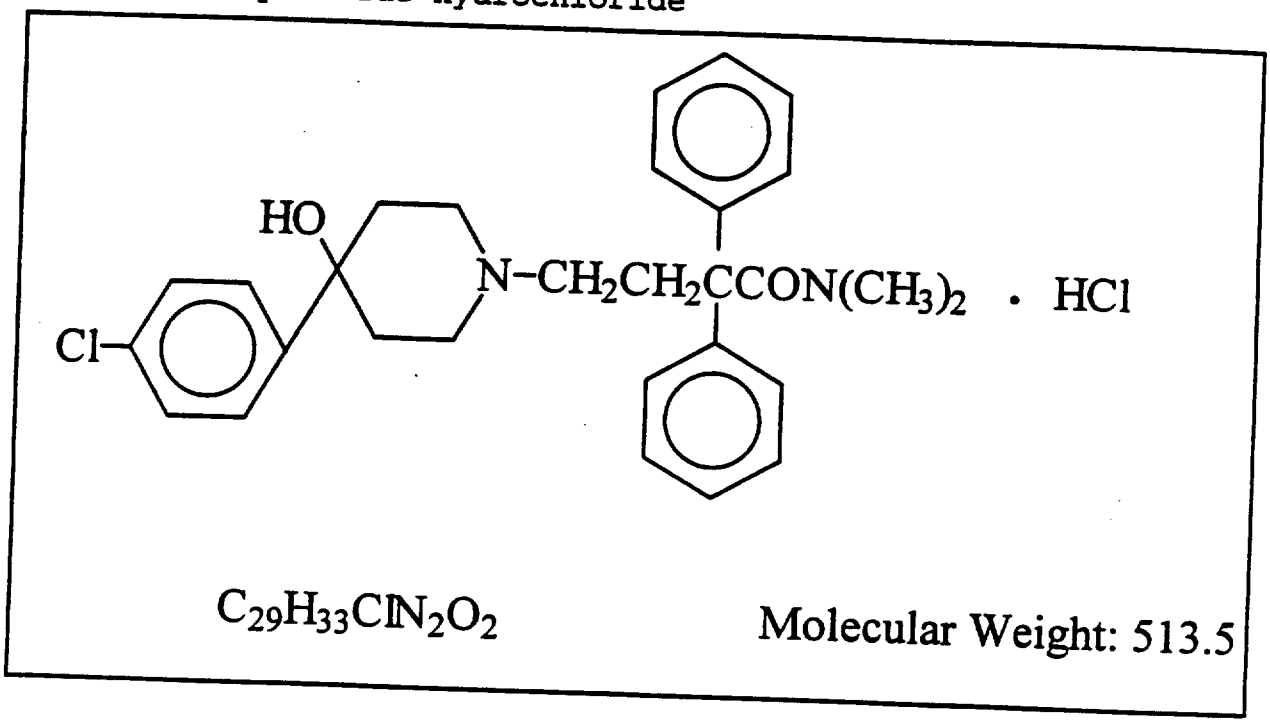
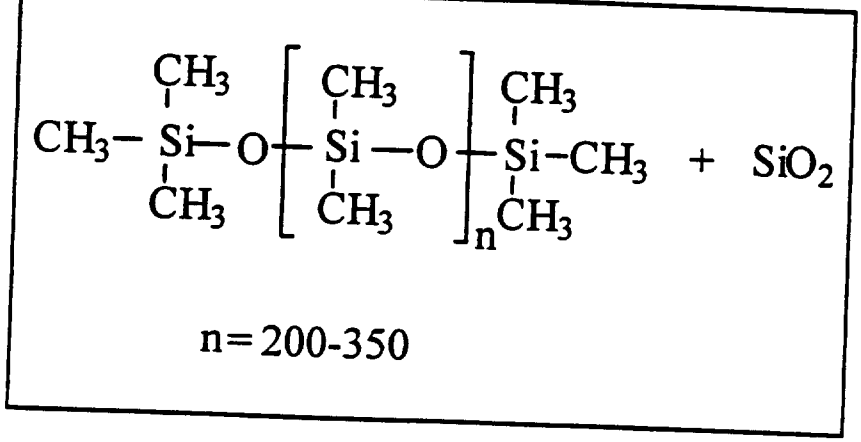


Figure 2. Simethicone and Silicon Dioxide



RECOMMENDATION/CONCLUSION: The new revised manufacturing process and in-process specifications for IMODIUM advanced chewable tablet, described in amendment BC 12/14/95, are acceptable.
Approval.

Ali Al-Hakim 7/19/96
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

Eric P. Duffy 7/19/96
Eric P. Duffy, Ph.D.
Acting Chemistry Team Leader

CC:
NDA 20-606
HFD-180/Division file NDA 20-606
DISTRICT FILE
HFD-180/SFredd
HFD-181/BStrongin
HFD-180/AAl-Hakim
HFD-180/EDuffy/7-17-96
AAH/dob F/T 7-18-96/WP: c:\wpfiles\chem\N\20606607.4AA

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-606 **CHEM REVIEW #** 3 **REVIEW DATE:** May 10, 1996

JUL 19 1996

SUBMISSION TYPE **DATES**

DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
Amendment (BC)	26APR96	01May96	10May96	3		
Amendment (BL)	26APR96	01May96	10MAY96	3		

NAME & ADDRESS OF APPLICANT:

McNeil Consumer Products Company,
7050 Camp Hill Road,
Fort Washington, PA 19034-2299

DRUG PRODUCT NAME:

Proprietary:	IMODIUM® Advanced Chewable Tablets
Nonproprietary/USAN:	Loperamide HCl/Simethicone
Code Name/#:	None
Chem.Type/Ther.Class:	1S

PHARMACOLOGICAL CATEGORY: Antidiarrheal agent

INDICATION: Control the symptoms of diarrhea and associated gas symptoms.

DOSAGE FORM: Chewable tablet

STRENGTH: Loperamide 2 mg and Simethicone 125 mg Chewable tablet

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED? ____ RX ___✓___ OTC

Chemical Name: Two active ingredients with the following names:
Loperamide hydrochloride; 4-(*p*-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutylamide monohydrochloride (figure 1).

Simethicone; α-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)], mixture with silicone dioxide, (figure 2).

Related Document: NDA 20-606

CONSULTS: Biostat III (Chen Wen-Jen)

STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT: Next page.

Figure 1. Loperamide hydrochloride

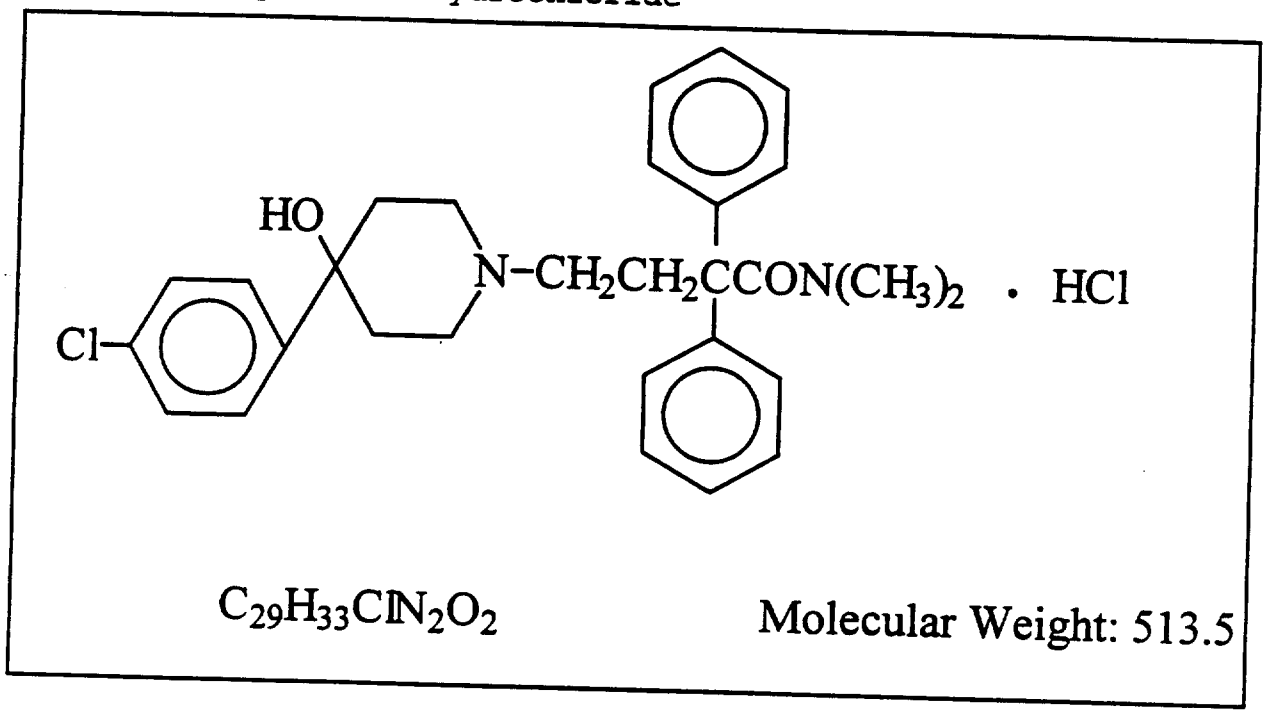
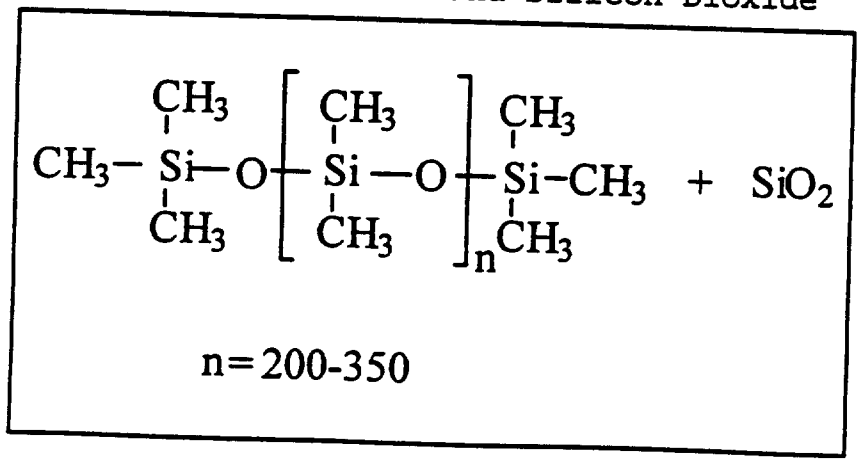


Figure 2. Simethicone and Silicon Dioxide



RECOMMENDATION/CONCLUSION: The new revised appearance specifications and the reformat for package labeling for IMODIUM advanced chewable tablet are acceptable.

Ali Al-Hakim 7/19/96
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

Eric P. Duffy 7/19/96
~~John J. Gibbs, Ph.D.~~
Acting Chemistry Team leader, HFD-180

CC:
NDA 20-606
HFD-180/Division file NDA 20-606
DISTRICT OFFICE
HFD-180/SFredd
HFD-180/BStrongin
HFD-180/AAl-Hakim
R/D init: 7-17-96
AAH/dob **F/T 7-18-96/WP**: c:\wpfiles\chem\N\20606605.3aa

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-606 CHEM REVIEW # 2 REVIEW DATE: April 02, 1996

MAY 30 1996

SUBMISSION TYPE DOCUMENT	DATES CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
Amendment (BS)	21MAR96	25MAR96	02APR96	2		

NAME & ADDRESS OF APPLICANT:
McNeil Consumer Products Company,
7050 Camp Hill Road,
Fort Washington, PA 19034-2299

DRUG PRODUCT NAME:

Proprietary:	IMODIUM® Advanced Chewable Tablets
Nonproprietary/USAN:	Loperamide HCl/Simethicone
Code Name/#:	None
Chem.Type/Ther.Class:	1S

PHARMACOLOGICAL CATEGORY: Antidiarrheal agent

INDICATION: Control the symptoms of diarrhea and associated gas symptoms.

DOSAGE FORM: Chewable tablet

STRENGTH: Loperamide 2 mg and Simethicone 125 mg Chewable tablet

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED? ___ RX ✓ OTC

CHEMICAL NAME: Two active ingredients with the following names:

Loperamide hydrochloride; 4-(*p*-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutylamide monohydrochloride (figure 1).

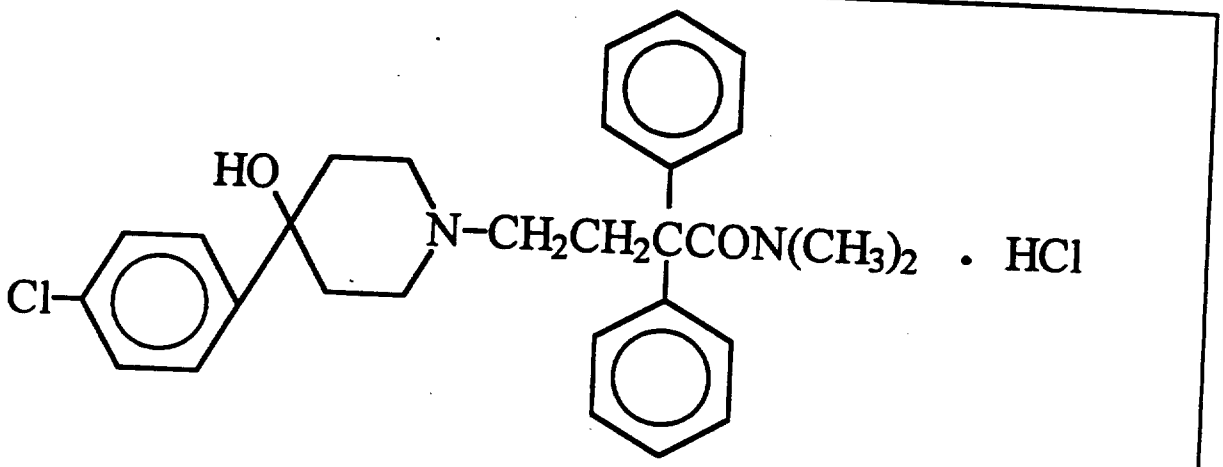
Simethicone; α-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)], mixture with silicone dioxide, (figure 2).

SUPPORTING DOCUMENT:

CONSULTS: Biostat III, Reviewer (Chen, Wen-Jen)

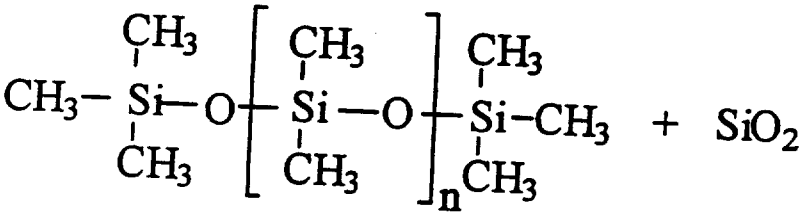
STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Figure 1. Loperamide hydrochloride



$C_{29}H_{33}ClN_2O_2$ Molecular Weight: 513.5

Figure 2. Simethicone and Silicon Dioxide



n=200-350

REMARKS/COMMENTS:
The firm has provided, in this amendment, 12 months stability data at the recommended storage conditions and 6 months at accelerated conditions. (Organon) has requested 24 expiration dating for the drug product. However, these data are not enough to extend the expiration dating to 24 months (as McNeil suggested). The agency has been using 12 months stability data to extend the expiration period to 18 months. Therefore, 18 months may be used as an expiration dating for the drug product based on the available stability data provided by the firm in this amendment.

RECOMMENDATION/CONCLUSION:
The stability data provided in this amendment may be used to extend the expiration dating to 18 months and not 24 months as requested by the firm. Therefore, only 18 months expiration period can be used by McNeil Consumer Products Company, at the present time, for their drug Imodium Advanced Chewable Tablets.

A Letter should be sent to the firm informing the applicant that, based on the available stability data, only 18 months expiration dating can be used for the drug product.

Ali Al-Hakim 5/30/96
Ali Al-Hakim, PH.D.
Review Chemist, HFD-180

5/30/96
John J. Gibbs, PH.D.
Chemistry Team leader, HFD-180

CC:
NDA 20-606
HFD-180/Division file NDA 20-606
HFD-180/SFredd
HFD-180/AAl-Hakim
HFD-180/BStrongin
HFD-180/MAdams for J.Gibbs/5-3-96
AAH/dob DRAFT 5-7-96\F/T 5-29-96\WP: c:\wpfiles\chem\N\20606604.2aa

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-606 CHEM REVIEW: #1 REVIEW DATE: January 29, 1996

SUBMISSION TYPE

DOCUMENT	CDER	DATES ASSIGNED	REVIEW	NUM	LETTER	ST
ORIGINAL	01AUG95	21Aug95*				

*Refuse to file : September 20, 1995
*New filing date: September 30, 1995

APR 12 1996

NAME & ADDRESS OF APPLICANT:
McNeil Consumer Products Company,
7050 Camp Hill Road,
Fort Washington, PA 19034-2299

DRUG PRODUCT NAME:

Proprietary:	IMODIUM® Advanced Chewable Tablets
Nonproprietary/USAN:	Loperamide HCL / Simethicone
Code Name/#:	None
Chem.Type/Ther.Class:	1S

PHARMACOLOGICAL CATEGORY: Antidiarrhea agent

INDICATION: Control the symptoms of diarrhea and associated gas symptoms.

DOSAGE FORM: Chewable tablet

STRENGTH: Loperamide 2mg and Simethicone 125 mg Chewable tablet

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED? __ RX ✓ OTC

Chemical Name: Two active ingredients with the following names:
- Loperamide hydrochloride; 4-(p-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutylamide monohydrochloride (figure 1).

- Simethicone;α-(Trimethylsilyl)-ω-methylpoly [oxy(dimethylsilylene)], mixture with silicone dioxide, (figure 2).

STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Figure 1. Loperamide hydrochloride

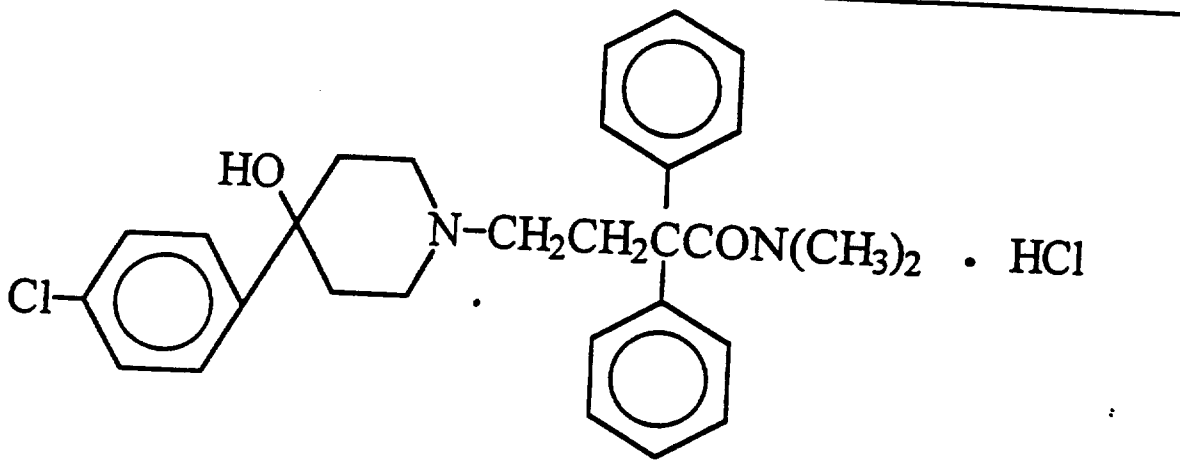
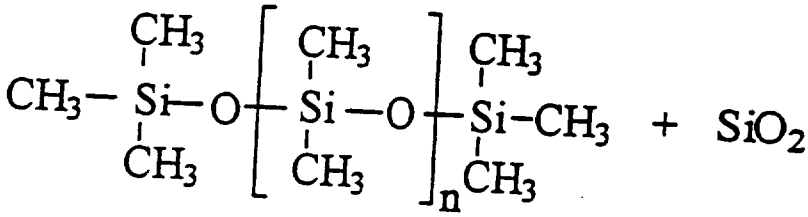


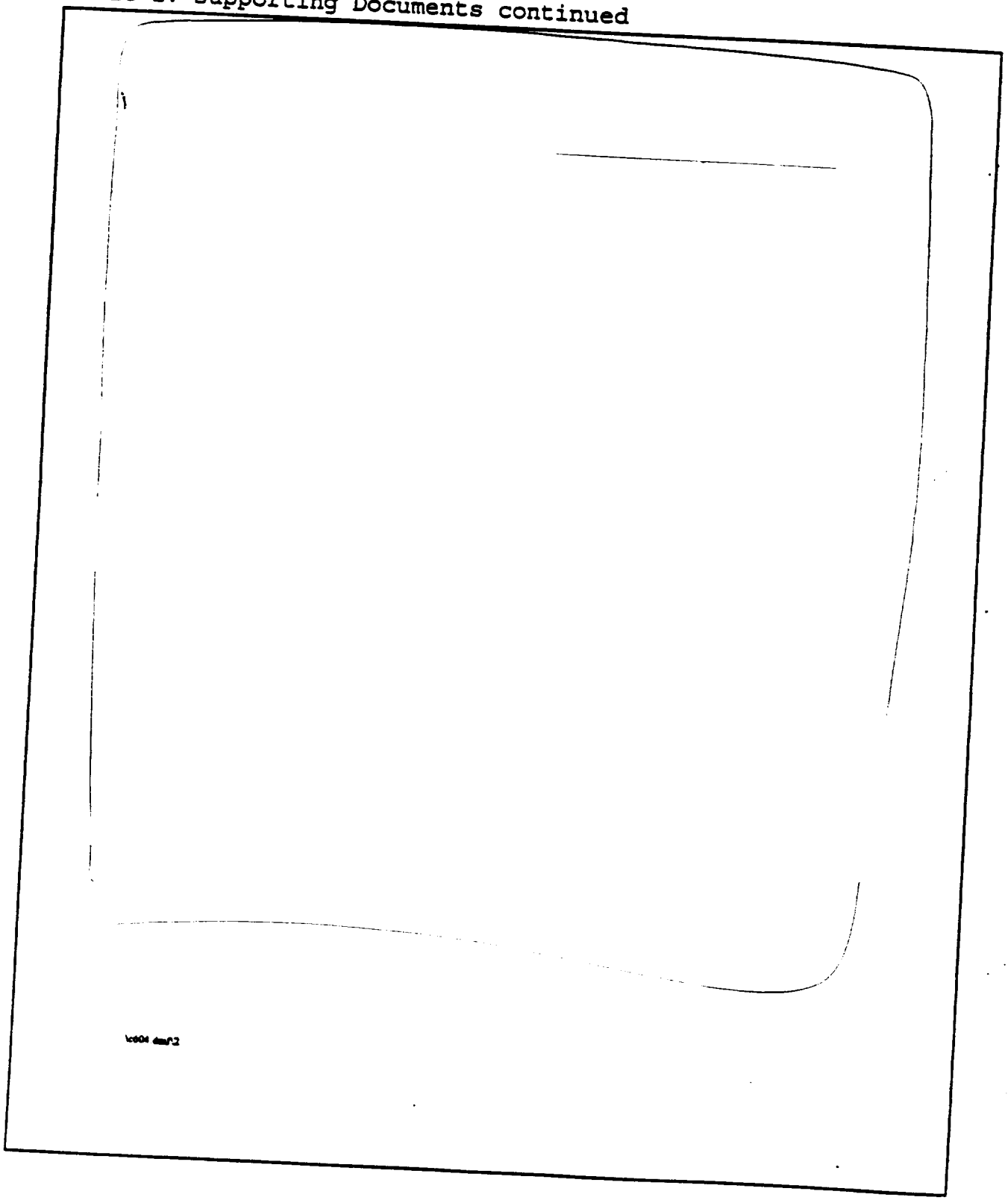
Figure 2. Simethicone and Silicon Dioxide



LOCATION OF INFORMATION INCORPORATED BY REFERENCE
LOPERAMIDE HCL/SIMETHICONE CHEWABLE TABLETS
NDA 20-606

Reference	Reference Description	Holder	Location of Information
NDA 19-037	Imodium Solution 1mg/5mL	Janssen Pharmaceutica	Original Submission Item 5
NDA 17-694	Imodium Capsule NDA	Janssen Pharmaceutica	Original Submission Item 5
NDA 17-690	Imodium Capsule NDA	Janssen Pharmaceutica	Original Submission Item 5

Table 1. Supporting Documents continued



RELATED DOCUMENTS (if applicable): See supporting documents (above).

CONSULTS: None

REMARKS/COMMENTS:
The applicant should provide additional essential information and related data regarding the drug product. Major issues of concern include the lack of a detailed sampling plan for the analytical tests and specifications and insufficient stability data.

In addition to the above items, there are some minor questions which need to be answered by the applicant. All of the deficiencies, including the above deficiencies are addressed in a draft deficiency letter to be sent to the applicant.

CONCLUSIONS & RECOMMENDATIONS:
The application is Not Approvable. The application is lacking some additional data (see above) which need to be included to complete the reviewing process of the chemistry, manufacturing and control section of the NDA. The applicant should be sent a letter explaining these deficiencies and requiring the submission of the corresponding additional data.

Ali Al-Hakim 4/10/96
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

4/12/96
John J. Gibbs, Ph.D.
Chemistry Team Leader, HFD-180

cc: NDA 20-606
HFD-180/Division File
HFD-180/SFredd
HFD-181/CSO
HFD-180/A.Al-Hakim
R/D Init: JGibbs/4-3-96
AAH/dob DRAFT 4-3-96/F/T 4-9-96
WP: c:\wpfiles\chem\N\20606601.1aa

N20606

N20606

K4.2

K4.2

Statistical Review - Stability Studies

NDA#: 20-606 Date: **May 30, 1996**

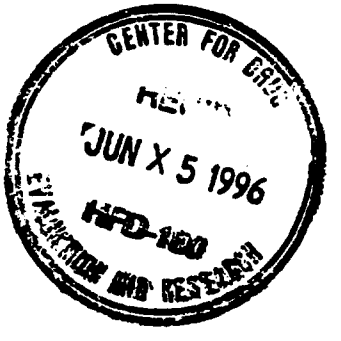
Applicant: McNeil Consumer Products Company

Name of drug: Imodium Advanced (loperamide/simethicone) Chewable Tablets

Documents reviewed: Original submission. Document dated March 20, 1996

I. Introduction: In this NDA submission McNeil Consumer Products Company has requested for an expiration dating period of 24 months for Imodium Advanced Chewable Tablets. Dr. Ali Al-Hakim, reviewing chemist, HFD-180 has requested the Division of Biometrics to perform statistical review and evaluation of the sponsor's stability data analyses.

II. Design



Number of package types: 2

Package configuration:

Package Type I. :
CR Blister

Package Type II. :
CR Pouch

Number of batches: 3; C-604-3G, C-604-3H, and C-604-3J.

Tested Parameters: Loperamide HCL and Simethicone.

Temperatures : 25° C/60% RH.

Specification limits:
Loperamide HCL:
Simethicone

Sampling times: For temperature 25°C/60%RH, all three batches were sampled at 0, 3, 6, 9, and 12 months.

III. Sponsor's analysis

The sponsor used the log-linear model to analyze the assay (potency) data: Loperamide HCL and Simethicone. The average of all 25°C/60%RH assy results for each test interval were used in the analysis. If separate intercepts and common slope were recommended by the regression analysis for the three batches, the model with the lowest intercept and common slope was used to project the expiration period. From the statistical analysis, the sponsor declared that the batches C-604-3G, C-604-3H, and C-604-3J for the two package types supported expiration period of 24 months.

IV. Reviewer's analysis

The reviewer analyzed the stability data using the SAS program developed by the Division of Biometrics, FDA. The procedures consist of the following two steps.

Step 1: Model selection (Test for pooling of stability batch data).

An assessment is made as to whether or not the degradation curves, considering all individual batches separately, are similar. If the degradation curves are similar, it is desirable to pool the data in order to obtain more precise estimates of expiration dating periods. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data, and applying statistical tests for equality of slopes and/or zero-time intercepts to these models. The following two conditions must be satisfied to allow such pooling of the data.

a) The test of hypothesis that a model with separate intercepts and separate slopes (H_1) fits the data better than a model with separate intercepts and common slope (H_0) should have a p-value of 0.25 or greater, (equality of slopes) and,

b) The test of hypothesis that a model with separate intercepts and the estimated common slope (H_1) fits the data better than a model with common intercept and common slope (H_0) should have a p-value of 0.25 or greater (equality of intercepts given parallel lines).

The rationale for using p-value of 0.25 for tests of this nature is presented in the paper of Bancroft "Analysis and inference for incompletely specified models involving the use of preliminary test of significance", Biometrics, pp. 427-442 (1964).

At the end of step 1, one of the following models is selected for the degradation curves,

a) separate intercepts and separate slopes,
b) separate intercepts and common slope,
c) common intercept and common slope.

Step 2: Construction of 95% lower and 95% upper confidence intervals for the mean degradation curve.

A 95% lower, and/or a 95% upper confidence intervals are constructed for the mean degradation curve based on model selected at step 1.

Acceptance criteria

In order to have an acceptable potency level of the assay under test, the 95% lower confidence bound should be above the lower specification limit and the 95% upper confidence bound should be below the upper specification limit when both upper and lower specification limits are required. However, if only one specification limit is needed, then either the 95% lower confidence bound should be above the lower specification limit or the 95% upper confidence bound should be below the upper specification limit.

Data analysis and results

In this review, two assays (Loperamide HCL and Simethicone) from each of the two package types (CR Blister and CR Pouch) with room temperature 25°C/60% RH were analyzed.

The p-values for the selections of the degradation models and the expiration dating periods on the two assays (Loperamide HCL and Simethicone) from each of the two package types (CR Blister and CR Pouch) are presented in Table 1 thru table 4, respectively. Based on the 0.25 model-selection criterion, the selected models for the two assays from each of the two package types along with their expiration dating periods are summarized in Table 4.1 (below).

Table 4.1 (reviewer) Summary on The Model Selection and The Expiration Date

Package Type	Assay	Selected Model	Expiration Date
CR Blister	Loperamide HCL	Common Slope & Separate Intercept	34 (Months)
CR Blister	Simethicone	Common Slope & Separate Intercept	30 (Months)
CR Pouch	Loperamide HCL	Common Slope & Separate Intercept	30 (Months)
CR Pouch	Simethicone	Separate Slope & Separate Intercept	38 (Months)

In addition, the 95% upper and 95% lower confidence bounds of the degradation lines for the three batches (C-604-3G, C-604-3H, and C-604-3J) from each of the two assays and two package types were calculated. However, for each assay and package type, the 95% upper and 95% lower confidence bounds generating the shortest expiration dating period among the three batches were presented in figure 1 thru figure 4, respectively.

The data of the Loperamide HCL and Simethicone for the two package types, CR Blister and CR Pouch, with the room temperatures 25°C/60% RH supported an expiration dating period of 24 months (2 years) for Imodium Advanced Chewable Tablets.

V. Summary

The sponsor submitted the data included Loperamide HCL and Simethicone in diskette. There were two package types: CR Blister and CR Pouch. The results of reviewer's analyses on Loperamide HCL and Simethicone for the two package types, CR Blister and CR Pouch, under the room temperature 25°C/60% RH showed that the data supported an expiration date of 24 months.

Wen-Jen Chen

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Huque Huque 5/30/96
Dr. Smith YSmith 5/31/96

cc: Original NDA20-606
HFD-180/Dr. Fredd
HFD-180/Dr. Al-Hakim
HFD-180/Mr. Strongin
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Chen
HFD-720 File Copy

Table 1 (Reviewer) Loperamide HCL For Package Type CR Blister
Room Temperature 25°C/60% RH

P Values For Model Testings

SOURCE	SS	DF	MS	F	P
A	58.71	4	14.68	6.9275	0.00787
B	58.25	2	29.12	13.7443	0.00184
C	0.47	2	0.23	0.1106	0.89650
D	19.07	9	2.12		
E	151001.02	6	25166.84		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Expiration Dating Periods

Batch Number	Estimated Expiration Date
C-604-3G	34 (Months)
C-604-3H	48 (Months)
C-604-3J	48 (Months)

Table 2 (Reviewer) Simethicone For Package Type CR Blister

Room Temperature 25°C/60% RH

P Values For Model Testings

SOURCE	SS	DF	MS	F	P
A	20.86	4	5.22	2.65148	0.10332
B	14.56	2	7.28	3.70026	0.06718
C	6.30	2	3.15	1.60270	0.25387
D	17.70	9	1.97		
E	158800.26	6	26466.71		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Expiration Dating Periods

Batch Number	Estimated Expiration Date
C-604-3G	30 (Months)
C-604-3H	34 (Months)
C-604-3J	35 (Months)

Table 3 (Reviewer) Loperamide HCL For Package Type CR Pouch
Room Temperature 25°C/60% RH

P Values For Model Testings

SOURCE	SS	DF	MS	F	P
A	72.75	4	18.19	4.93939	0.02196
B	72.39	2	36.19	9.82962	0.00545
C	0.36	2	0.18	0.04916	0.95228
D	33.14	9	3.68		
E	151677.12	6	25279.52		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Expiration Dating Periods

Batch Number	Estimated Expiration Date
C-604-3G	30 (Months)
C-604-3H	47 (Months)
C-604-3J	47 (Months)

Table 4 (Reviewer) Simethicone For Package Type CR Pouch
Room Temperature 25°C/60% RH

P Values For Model Testings

SOURCE	SS	DF	MS	F	P
A	4.11	4	1.03	1.28485	0.34518
B	1.47	2	0.73	0.91725	0.43396
C	2.64	2	1.32	1.65246	0.24476
D	7.20	9	0.80		
E	156860.73	6	26143.45		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Expiration Dating Periods

Batch Number	Estimated Expiration Date
C-604-3G	38 (Months)
C-604-3H	48 (Months)
C-604-3J	48 (Months)

Figure 1 (Reviewer) Expiration Date for Loperamide HCL and Package Type CR Blister
Room Temperature 25°C/60% RH

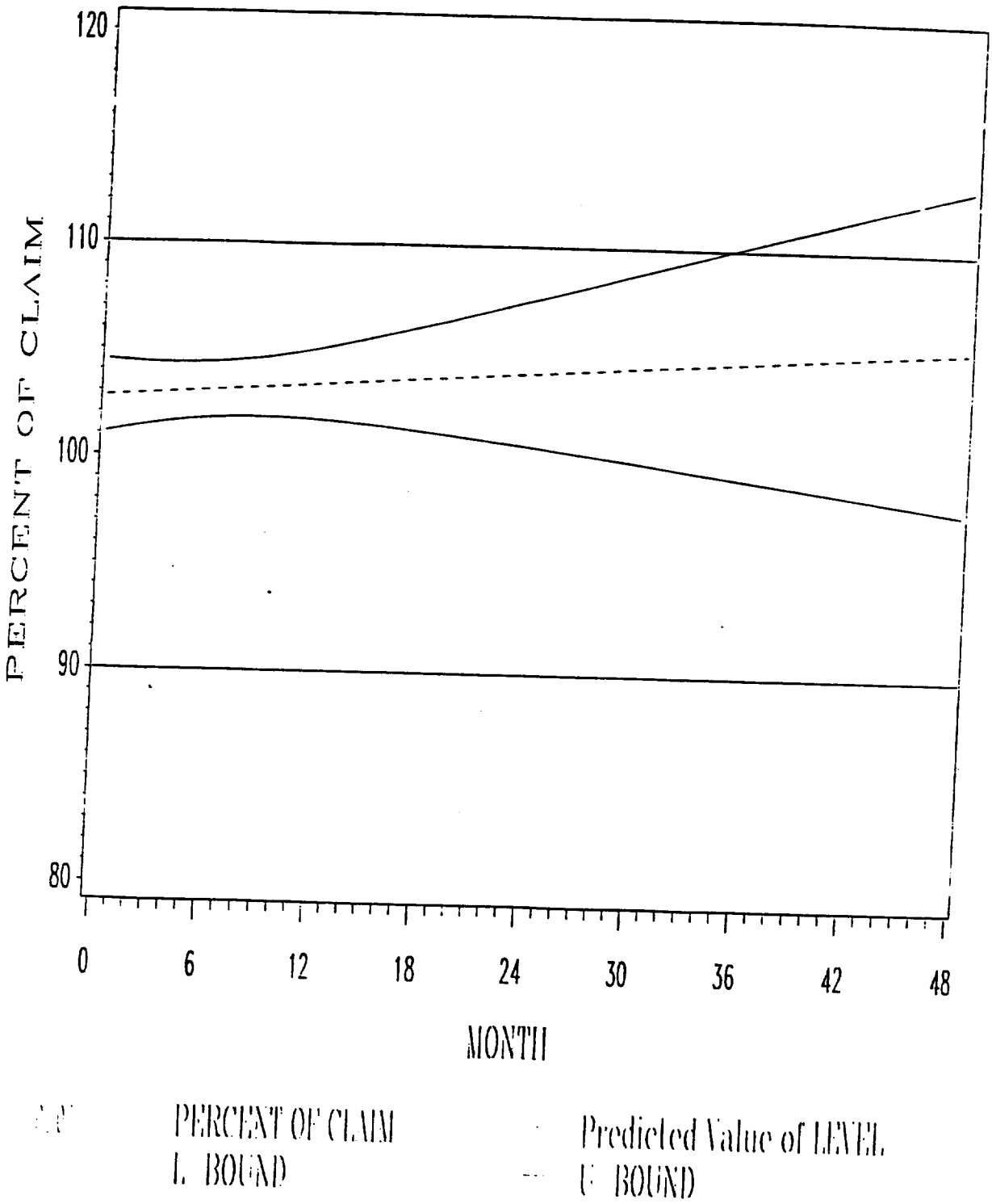


Figure (Reviewer) Expiration Date for Simethicone and Package Type CR Blister
Room Temperature 25°C/60% RH

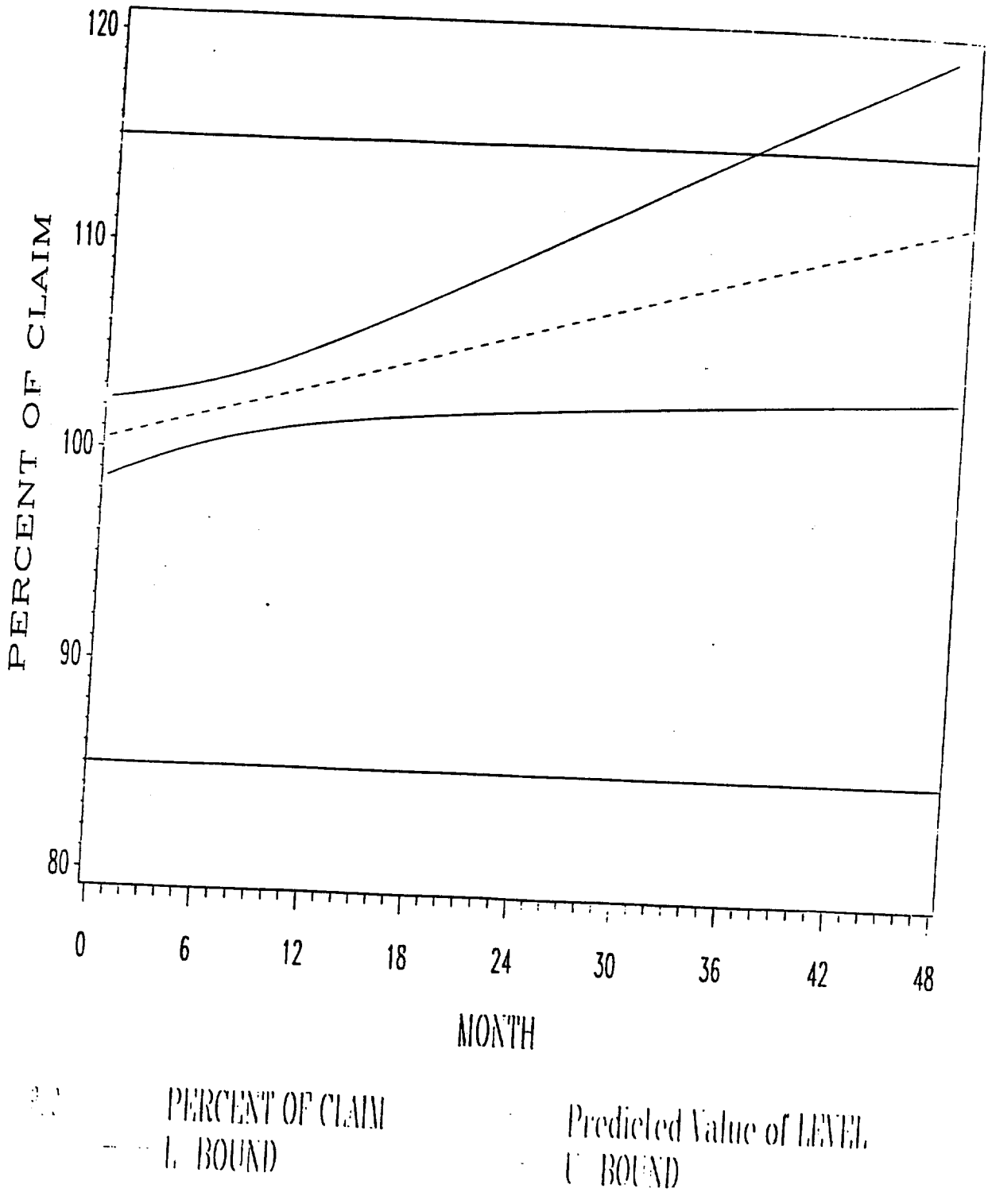


Figure 3 (Reviewer) Expiration Date for Loperamide HCL and Package Type CR Pouch Room Temperature 25°C/60% RH

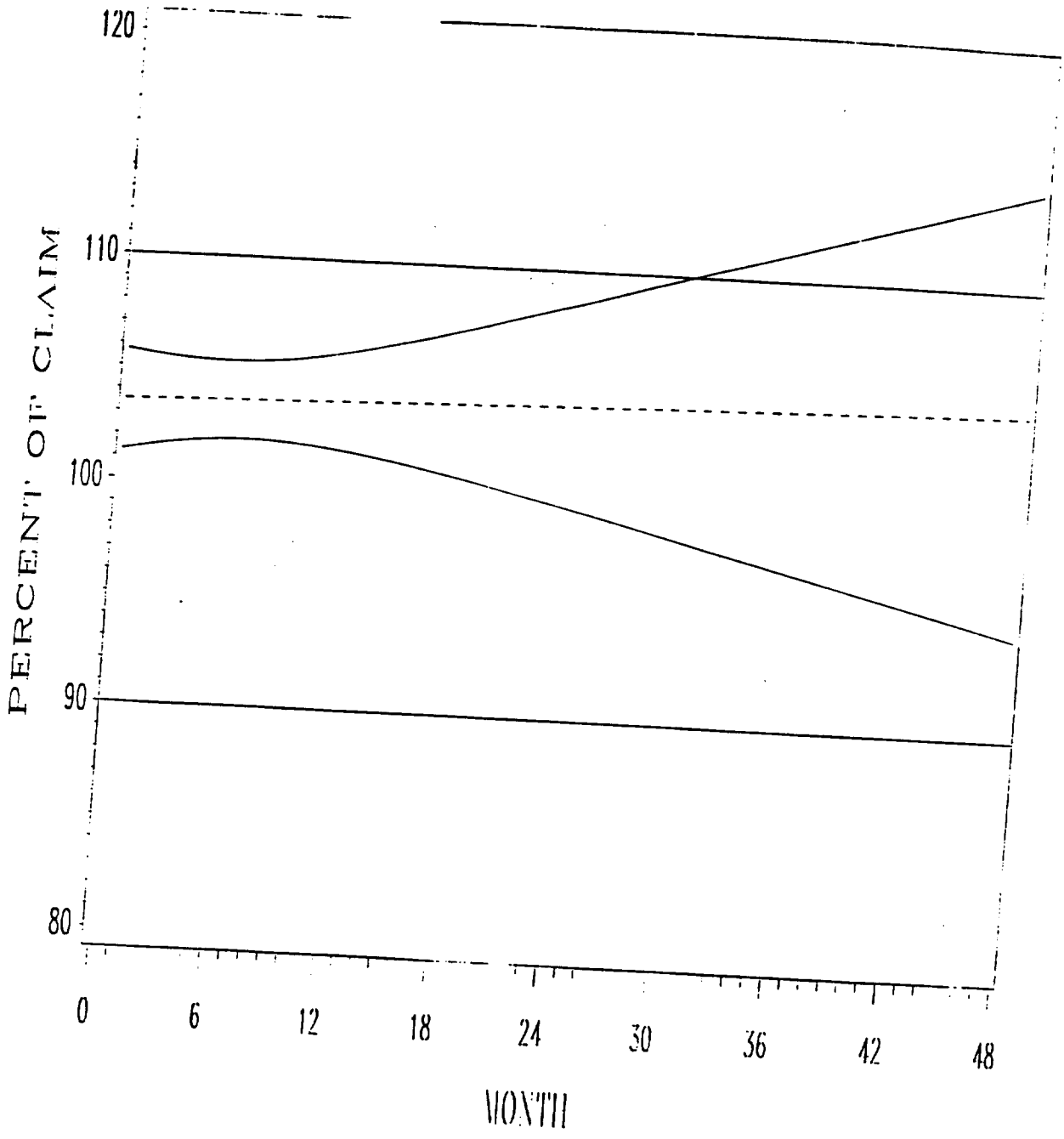
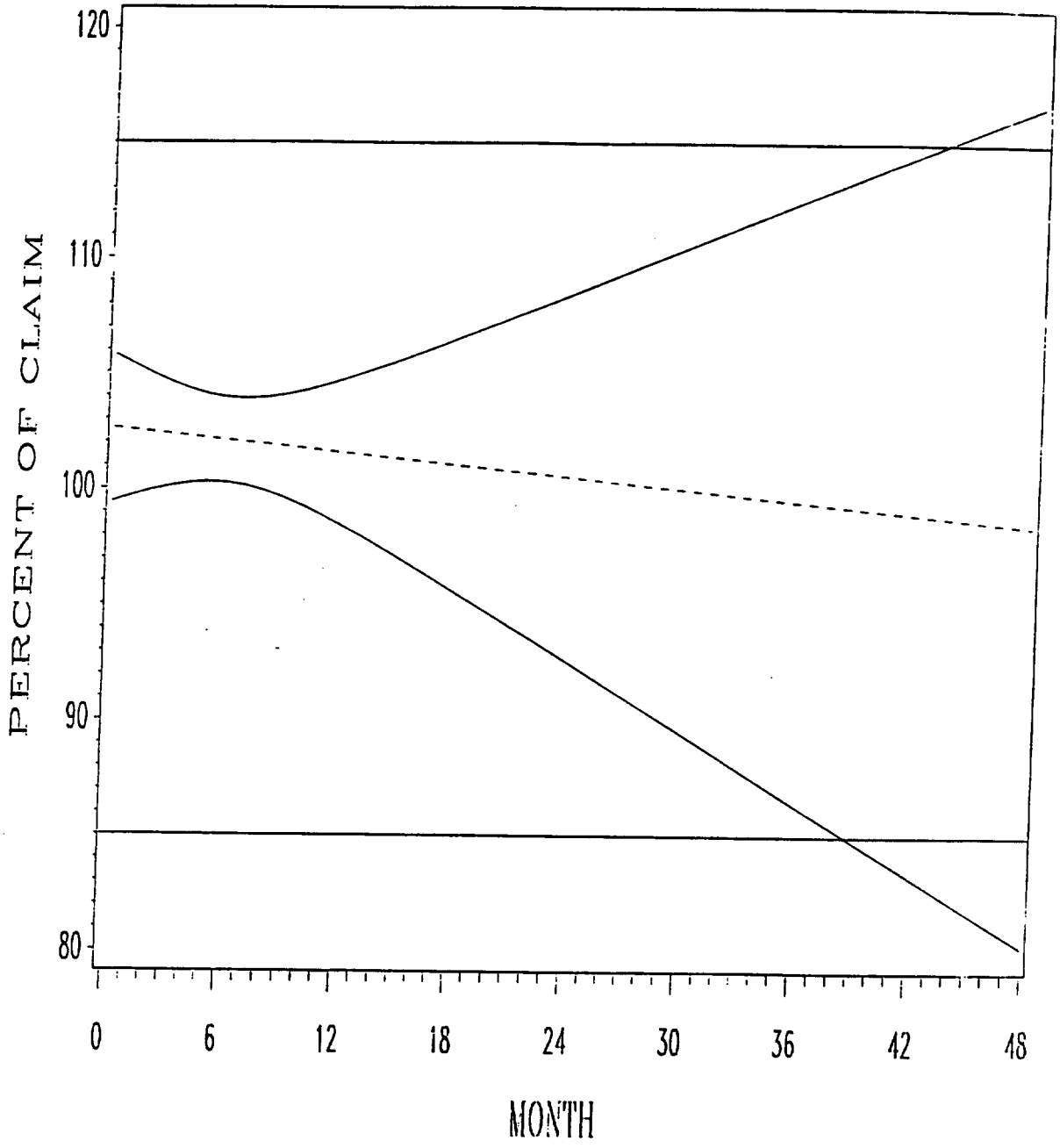


Figure 4 (Reviewer) Expiration Date for Simethicone and Package Type CR Pouch
Room Temperature 25°C/60% RH



REVIEW OF ENVIRONMENT ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

IMODIUM® ADVANCED CHEWABLE TABLETS

(Loperamide Hydrochloride and Simethicone)

NDA 20-606

Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Gastrointestinal and Coagulation Drug Product
HFD-180
Food and Drug Administration
Center for Drug Evaluation and Research

Finding of No Significant Impact

NDA 20-606

Imodium® Advanced Chewable Tablets (Loperamide Hydrochloride)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Loperamide Hydrochloride and Simethicone Chewable Tablets, McNeil Consumer Products Company has prepared an environmental assessment in accordance with 21 CFR 25.31a which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product.

Loperamide Hydrochloride and Simethicone is a synthetic drug that will be administered orally. The drug substances will be manufactured in and and the drug product will be manufactured in

Disposal of the chemical substances may result from waste generated during packaging, returned, recalled, or expired goods and user disposal of empty or partly used product and packaging. Packaging waste, returned or unused market packages, recalled and expired goods will be sent to licensed incineration or landfilled facilities.

The Center for Drug Evaluation and Research has concluded that

the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

6/17/97
DATE

Ali Al-Hakim

PREPARED BY:
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

6/17/97
DATE

Eric P. Duffy

DIVISION CONCURRENCE:
Eric P. Duffy, Ph.D.
Chemistry Team Leader

FONSI + paperwork held pending receipt of official submission w/ certifications

6/23/97
DATE

Nancy B Sager

CONCURRED:
Nancy B. Sager
Environmental Scientist
Center for Drug evaluation

Attachments

CC:
Original NDA 20-606/6 Stroup
HFD-357/FONSI File NDA 20-606
HFD-357/Docket File
HFD-205/FOI Copy
HFD-180/AAl-Hakim
R/D init: EDuffy/6-16-97
AH/dob F/T 6-17-97/WP: c:\wpfiles\chem\N\20606fon.1aa

Strongin

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-600) MPN II, (594-0365)

From: Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Brian Strongin Phone: (301) 443-0487

Date: August 7, 1995

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Imodium Advanced Chewable Tablets **NDA#:** 20-606

Established name, including form: loperamide/simethicone chewable tablets

Other trademarks by the same firm for companion products:

OTC Products

NDA 19-860	Imodium A-D Caplets	Approved
NDA 19-487	Imodium A-D Liquid	Approved

RX Product

NDA 17-694	Imodium Capsules	Approved

Indications for Use (may be a summary if proposed statement is lengthy):

Control of the symptoms of diarrhea, including Traveler's Diarrhea, and associated gas symptoms including abdominal pain, bloating and cramping.

Initial comments from the submitter: (concerns, observations, etc.)

No concerns at this time.

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

NDA 20-448
NDA 20-606

McNeil Consumer Product Company
Attention: Vivian Chester
7050 Camp Hill Road
Fort Washington, PA 19034-2299

NOV - 4 1996

Dear Ms. Chester:

Please refer to your new drug applications submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Imodium A-D (loperamide HCL) Chewable Tablets and Imodium Advanced (loperamideHCL/simethicone) Chewable Tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 17, 1996. The following represents our summary of the meeting.

MEMORANDUM OF MEETING

Meeting Date:	October 17, 1996
Time:	2PM - 3PM
Location:	Conference Room, 6B-45
Application:	NDA 20-448 Imodium A-D (loperamide HCL) Chewable Tablets
	NDA 20-606 Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets
External Meeting Requester:	McNeil Consumer Products Company
Type of Meeting:	Discussion of the marked-up draft labeling included with the June 14, 1996 approvable letter for NDA 20-448 and the July 23, 1996 approvable letter for NDA 20-606.
Meeting Chair:	Stephen Fredd, M.D.
Meeting Recorder:	Brian Strongin

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Stephen Fredd, M.D.	Director
Brian Strongin	Consumer Safety Officer

Division of Pharmaceutical Evaluation II (HFD-870)

Lydia Kaus, Ph.D.	Team Leader, Biopharmaceutics
Raj Pradhan, Ph.D.	Biopharmaceutics Reviewer

Division of OTC Drug Products (HFD-560)

Helen Cothran	Team Leader

External Constituent Attendees and Titles:

Vivian Chester	Vice President, Regulatory Affairs
Cathy Gelotte, Ph.D.	Assistant Director, Clinical Pharmacology
Michael Kaplan, M.D.	Associate Director, Clinical Development
Edward Nelson, M.D., Ph.D.	Vice President, Medical
Scott Snyder	Product Director, Marketing
Janet Uetz	Assistant Director, Regulatory Affairs

Background:

NDA 20-448 for Imodium A-D (loperamide HCL) Chewable Tablets was submitted March 14, 1994 for the control of the symptoms of diarrhea, including Traveler's Diarrhea. It was most recently approvable June 14, 1996 pending an adequate response to a chemistry, manufacturing, and controls and environmental assessment information request letter also dated June 14, 1996 and final printed labeling identical to the marked-up draft enclosed with the approvable letter. NDA 20-606 for Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets was submitted July 28, 1995 for the control of the symptoms of diarrhea, including Traveler's Diarrhea, and associated gas symptoms including abdominal pain, bloating, and cramping. It was approvable July 23, 1996 pending an adequate response to a chemistry, manufacturing, and controls and environmental assessment information request letter dated July 22, 1996 and final printed labeling identical to the marked-up draft enclosed with the approvable letter.

Meeting Objectives:

Discuss the comments and changes recommended by the Agency in the marked-up draft labeling

enclosed with the most recent approvable letters for these applications.

Discussion Points:

1. In the March 13, 1995 biopharmaceutics review for NDA 20-448, the reviewer commented that bioequivalence study subjects were required to take Imodium A-D Chewable tablets with water and expressed concerns about possible buccal absorption and toxicity if the tablet is not taken with water. Based on the biopharmaceutics review, the Division of Over-the-Drug Products recommended adding the phrase, "take with water" to the DIRECTIONS section of the labeling for Imodium A-D Chewable Tablets and Imodium Advanced Chewable Tablets. The phrase "take with water" was added to the marked-up draft labeling enclosed with the most recent approvable letters for both applications. In the background package for this meeting, the firm provided information indicating that buccal absorption may not occur and contended that these tablets need not be taken with water.

   Dr. Fredd reminded the firm that the approvable actions for NDA 20-448 were based on a bioequivalence study in which subjects were required to take the products with water. He asked them to provide data comparing the bioequivalence of each product when taken with and without water and recommended a comparative bioequivalence study. Concerning NDA 20-606, Dr. Fredd observed that although patients in the pivotal studies were not instructed to take the product with water, they were not prohibited from doing so and may have been instructed to drink plenty of liquids to prevent dehydration. He asked the firm to provide information indicating whether the drug was taken without water and suggested surveying patients.

   The firm also asked that the phrase, "... convenient to take anywhere, anytime", removed by the Agency, be included. Dr. Fredd explained that the word "anytime" must be removed since there are specific times when the drug should be taken, but indicated that the word "anywhere" was acceptable.

2. In the marked-up draft labeling enclosed with the most recent approvable letters for both applications, the Agency recommended that gas-related symptoms be described as, "...bloating, pressure, and cramps commonly referred to as gas." The firm contended that the word "cramps" could be confused with muscle or menstrual cramps by consumers. They proposed replacing the phrase recommended by the Agency with the phrase, "...plus gas pain, pressure, bloating and cramping commonly referred to as gas.". Dr. Fredd explained that the language recommended by the Agency is consistent with the labeling allowed for simethicone drug products approved under the antiflatulent monograph in 21 CFR 330.30(b) and suggested it remain unchanged. He added that since the product is clearly labeled "ANTI-DIARRHEAL, ANTI-GAS" consumer confusion regarding the word cramps should be minimal.

3. In the marked-up draft labeling included with the approvable letter for Imodium Advanced Chewable Tablets, the Agency recommended changing the phrase, "...the maximum dose of the medicine doctors recommend to relieve abdominal pain, bloating and cramping associated with gas" to the phrase, "...simethicone to relieve bloating, pressure, and cramps commonly referred to as gas". The firm suggested changing the Agency's wording to, "...a proven ingredient to relieve gas pain, pressure, bloating and cramping". Dr. Fredd recommended retaining the Agency's wording since it clearly identifies the anti-gas ingredient, simethicone.

4. In the marked-up draft labeling included with the approvable letter for Imodium Advanced Chewable Tablets, the Agency recommended removing the word "Patented". In response to the firm's request to reconsider the inclusion of this word, Dr. Fredd stated that the word "Patented" was acceptable.

5. In the marked-up draft labeling included with the approvable letter for Imodium A-D Chewable Tablets, the Agency recommended that the word "Chewable Tablets" rather than "ChewTab" be used to describe the dosage form. The firm proposed revising the description to "Imodium A-D ChewTab Chewable Tablets". Dr. Fredd recommended against using this description because it is redundant and may be confusing to consumers. In response to the firm, Dr. Fredd explained that the word "ChewTab" was removed based on the recommendation of the Division of Over-the-Counter Drug Products. He suggested requesting reconsideration of the acceptability of the term "ChewTab" from HFD-560 if desired.

Recommendations/Conclusions:

1. In support of their position that Imodium A-D Chewable and Imodium Advanced may be taken without water, the firm should submit a bioequivalence study comparing Imodium A-D Chewable taken with and without water and information describing whether Imodium Advanced was actually taken without water by the consumers during the clinical trials. While the word "anywhere" from the phrase "...convenient to take anywhere, anytime" is acceptable, the word "anytime" is unacceptable because it implies that unrestricted use is acceptable.

2. The Agency's recommended language describing gas-related symptoms in the marked-up draft labeling enclosed with the approvable letter for Imodium Advanced should be retained since it is consistent with the labeling for anti-flatulent products approved under the anti-flatulent monograph in 21 CFR 330.30(b).

3. The Agency's wording for the phrase, "...simethicone to relieve bloating, pressure, and cramps commonly referred to as gas" should be retained since it clearly identified simethicone as the anti-gas ingredient.

4. The word "Patented" may be included on the front panel of the Imodium Advanced labeling as requested.

5. The description, "Imodium A-D ChewTab Chewable Tablets", is redundant, possibly confusing and not recommended. The firm may consider asking the Division of Over-the-Counter Drug Products to reconsider their recommendation that the word "ChewTab" be deleted in favor of "Chewable Tablet".

If you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-606

McNeil Consumer Products Company
Attention: Paula Oliver
7050 Camp Hill Road
Fort Washington, PA 19034-2299

AUG 7 1995

Dear Ms. Oliver:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Imodium Advanced (Loperamide HCl/Simethicone) Chewable Tablets

Therapeutic Classification: Standard

Date of Application: July 28, 1995

Date of Receipt: July 31, 1995

Our Reference Number: 20-606

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 30, 1995 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Kati Johnson
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-606
HFD-180/Div. Files
HFD-80
HFD-180/CSO/K.Johnson

drafted: kj/August 3, 1995
c:\wpfiles\cso\n\20606508.0kj
ACKNOWLEDGEMENT (AC)

Strongin

NDA 20-606

DEC 1 1 1995

McNeil Consumer Products Company
Attention: Vivian Chester
Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Chester:

Please refer to your pending July 28, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium Advanced (loperamide/simethicone) Chewable Tablets.

We have completed our review of the pharmocokinetics section of your submission and request that a gender analysis of the pharmacokinetic data be done for Biostudy 134 ("A Comparison of the Pharmacokinetics of the Two Formulations of Loperamide/Simethicone Chewable Tablets (C-604 and C-317) and Imodium Capsules Administered in the Fasted State to Healthy Adults").

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-606

McNeil Consumer Products Company
Attention: Vivian Chester
7050 Camp Hill Road
Fort Washington, Pennsylvania 19034

JUL 22 1996

Dear Ms. Chester:

Please refer to your pending July 28, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium® Advanced (loperamide/simethicone) Chewable Tablets.

We also refer to your amendments dated December 14, 1995, and the March 20, and April 25, 1996.

We have completed our review of the chemistry, manufacturing and controls section of your submission and have the following comments, recommendations and requests:

1. Concerning the drug substance , samples for acceptance testing should be taken from the beginning, middle, and end of a given batch and the number of samples should be sufficient to assure batch homogeneity. Provide details of a revised sampling plan, or justify the use of one drum for sampling unless one drum represents one batch.

2. Describe the release tests performed at the facility and the acceptance tests and specifications performed at the facility for the

3. Concerning the methods of manufacturing of the

   A. Indicate the length of time the loperamide HCl drug substance may be held at before formulation into Provide stability data to support storing the bulk drug substance.

   B. Indicate the length of time the loperamide HCl may be stored at the facilities before simethicone is added. Provide data to support storing the

4. Concerning the drug product components:

   A. Describe the acceptance tests and specifications performed on the active ingredients.

B. Indicate which tests are performed on a routine basis for compendial excipients in the drug product.

5. Concerning the acceptance specifications and analytical methods for the drug substance and excipients:

A. Provide the sampling plan (points, time, intervals, etc.) for all the analytical methods used in testing the drug product and also for the container/closure system.

B. The [redacted] for loperamide showed different migration times (volume 1.6, 03-000129; lane 1,3, and 5). Provide a [redacted] showing similar retention times for loperamide spotted on the [redacted]

D. Provide [redacted] showing peaks for loperamide, loperamide trans N-oxide, [redacted]

6. Based on the stability data submitted in your amendment dated March 20, 1996 (twelve months at recommended storage conditions and six months of accelerated data), we consider an 18 month expiration dating period to be acceptable, provided that you continue your planned stability program and submit additional data to support this expiration period.

7. Provide additional information regarding the maltodextrin used in the early clinical trials batches, *e.g.*, (batch size, manufacturing method, particle size.

We also have the following requests concerning the environmental assessment (EA):

1. Indicate whether any intermediates are considered proprietary.

2. Provide information regarding the expected location of use of the drug product (hospitals, clinic, homes, etc.).

3. Provide data regarding the [redacted] of loperamide HCl and simethicone.

4. Since the EA will be made public by the FDA as required by regulations issued by the Council on Environmental Quality, information about the drug substance manufacturing

sites must be provided. In lieu of the information listed under format item 6 in 21 CFR 25.31a, the following certification from both drug substance manufacturers is acceptable:

A. They have been manufacturing this drug substance for commercial distribution for ten years.

B. The approval for this action will not affect the qualitative composition of the emissions relating to the manufacture of the drug substance.

C. They are in compliance with applicable federal, state, local and national emission requirements.

D. Approval of this action will have no effect upon compliance with federal, state, local or national emission requirements.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Strongin

NDA 20-606

JAN - 3 1997

McNeil Consumer Products Company
Attention: Vivian Chester
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Chester:

We acknowledge receipt on December 30, 1996 of your December 27, 1996 amendment to your new drug application (NDA) for Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets.

This amendment contains additional chemistry, manufacturing and controls information submitted in response to our July 23, 1996 approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is June 30, 1997.

Should you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research