CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-615

Medical Review(s)

Review and Evaluation of Clinical Data

NDA: 21-615, 21-169, 21-224
Drug: Reminyl (galantamine)
Route: oral
Indication: mild to moderate dementia of Alzheimer's type
Submitted materials: Johnson and Johnson submissions dated December 29, 2004; November 30, 2004; September 28, 2004; August 23, 2004
Sponsor: Johnson and Johnson
Reviewer: Alice T.D. Hughes, MD

1 Background

In July, 2004, the Division first became aware of reports of medication errors resulting from name confusion between Reminyl (galantamine) and Amaryl (glimepiride), an oral hypoglycemic. These cases were identified during review by the Division of Medication Errors and Technical Support (DMETS) of the extended release formulation of galantamine for which Johnson and Johnson was seeking approval. The eight reports of medication errors initially identified included instances in which Amaryl was mistakenly administered to patients with Alzheimer's disease in place of Reminyl, leading to various adverse events including severe hypoglycemia and one death. After the identification of these reports, Johnson and Johnson launched a risk management program to help prevent prescribing and dispensing errors with Reminyl. Concurrently, they began efforts to identify, test, and obtain trademark approval for alternative proprietary names to prepare for the possibility of a name change becoming necessary.

As Johnson and Johnson's risk management plan was being developed and implemented, the Division learned of additional reports of medication errors due to confusion between Reminyl and Amaryl. One of these errors, in which a patient's Reminyl prescription was refilled with Amaryl, had resulted in death.[1] After this second death resulting from a medication error was reported, the Division convened a teleconference on November 10, 2004 with Johnson and Johnson, during which it requested a change in the proprietary name of galantamine. Johnson and Johnson agreed that a name change for galantamine coincident to the launch of the new extended release formulation was appropriate. They agreed to submit a plan detailing a strategy for making the transition from Reminyl to the new name for all galantamine formulations.

In this memorandum, I will briefly summarize the risk management plan for preventing medication errors due to name confusion between Reminyl and Amaryl that Johnson and Johnson has developed and launched. I will then discuss in detail the plan that Johnson and Johnson has proposed for making the transition from Reminyl to the new trademark name following the anticipated approval of the extended-release formulation of galantamine.

[1] This death, which occurred on May 13, 2003, was reported by the Associated Press on October 16, 2004.

2 Risk management plan

In collaboration with the Division, Johnson and Johnson developed a multi-pronged campaign to educate pharmacists, physicians, patients, and caregivers regarding the potential for and prevention of medication errors resulting from name confusion between Reminyl and Amaryl.

2.1 Completed or planned measures

The following components of this program have been completed or are currently being implemented:

Interventions targeting multiple groups

- Press release was issued by Johnson and Johnson on October 22, 2004
- Sales force training

Interventions for pharmacists

- "Dear Pharmacist" letter was sent on October 19, 2004
- Letters to the editor of pharmacy journals
    - On October 27, 2004, letters were sent to the editors of the following pharmacy journals: Annals of Pharmacotherapy, American Journal of Health-System Pharmacy, Drug Topics, Formulary, and Pharmacy Times
    - The letter was published in the American Journal of Health-System Pharmacy in January, 2005 and in Drug Topics in November 2004.
    - The remaining three journals declined to publish the letter.
- Pharmacy "shelf-talkers"
    - These items, which warned pharmacists to avoid confusing Reminyl and Amaryl, were distributed in October, 2004.
- Pop-up alerts on pharmacy computer systems
    - These alerts are intended to appear when either Reminyl or Amaryl is entered into pharmacy computer systems
- Educational advertisements in pharmacy journals
    - Johnson and Johnson has proposed that journal advertisements appear in six pharmacy journals: American Journal of Health-System Pharmacy, Consultant Pharmacist, Drug Topics, Hospital Pharmacy, Pharmacy Practice News, and US Pharmacist
    - These advertisements, which are to be published in both pharmacy and medical journals, warn prescribers and pharmacists that medication errors have occurred due to confusion between Reminyl and Amaryl and make recommendations for preventing such errors
- Convention panels and flashcards to be displayed or distributed at key pharmacy meetings

Interventions for physicians

- "Dear Healthcare Professional" letter was sent on October 15, 2004

- Educational advertisements in medical journals
    - Johnson and Johnson's educational advertisement, which will be identical in both pharmacy and medical journals, is slated to be published in the following medical journals: American Family Physician, American Medical News, Archives of Internal Medicine, Consultant, Family Practice News, Internal Medicine News, JAMA, Medical Economics, New England Journal of Medicine, Advance for Nurse Practitioners, Clinical Advisor, Archives of Neurology, Neurology, Neurology Reviews, Neurology Today, Clinical Psychiatry, Journal of Clinical Psychiatry, Psychiatric Times, and Caring for the Ages
- Convention panels and flashcards to be displayed or distributed at key medical meetings

Interventions for patients/caregivers

- Patient/caregiver advocacy group outreach
- Caregiver awareness brochure
    - Johnson and Johnson created a new page and a pocket card for their brochure for caregivers of patients with Alzheimer's disease.
    - The new page is entitled "Make sure you receive Reminyl at the pharmacy." It states that on "a few rare occasions" patients have received Amaryl accidentally instead of Reminyl. Pictures of all available Reminyl tablets are provided and the oral solution is described. Patients and caregivers are advised to take the following steps to ensure that they "always get the right medication":
        - ask physicians to repeat the names of prescribed medications
        - ask physicians or nurses to write down the names of all medications and (and to have these written names with them when they go to the pharmacy)
        - request medication brochures from physicians
        - ask pharmacists to double-check that the medications that the patients have received is correct
        - read package inserts accompanying all prescriptions
    - The pocket card lists signs and symptoms of hypoglycemia, advises patients or caregivers to call a doctor if they notice these symptoms, and lists treatments for hypoglycemia.
- Updated Reminyl sample pack
    - The current Reminyl sample pack will be updated with a message that Reminyl is indicated to treat Alzheimer's disease.

2.2 Discontinued components of original risk management plan proposal

In view of the decision to change Reminyl's name, Johnson and Johnson does not intend to implement all of the components of the risk management plan that they originally proposed in August, 2004. The following components of the original plan have been abandoned because they are either impractical or no longer relevant in the face of Reminyl's impending name change:

3 Proposal for transition to new proprietary name

In a submission dated December 29, 2004, Johnson and Johnson outlined their plan for transitioning to a new name for all galantamine products following the approval of the new extended-release formulation of galantamine. The cornerstone of Johnson and Johnson's plan is a staged approach. They propose to launch the extended-release product under the new name while retaining the name Reminyl for the immediate-release galantamine products. Approximately three months after the launch of the extended-release formulation, they plan to initiate the name change of the twice-daily products.

Initially, they will use both Reminyl and the new name on the label of the immediate-release products to facilitate the transition. After at least three months of marketing the dual-labeled immediate-release products, they plan to phase the name Reminyl out entirely. They state that as long as any products with the name Reminyl are on the market, the risk management plan for preventing errors due to name confusion with Amaryl will continue. Pharmacy software alerts, advertisements in medical and pharmacy journals, distribution of the revised caregiver awareness brochure, distribution of the updated Reminyl sample pack, and displays of convention panels and flashcards at medical and pharmacy meetings will be ongoing during the launch of the extended-release formulation of galantamine and the transition to a new name for Reminyl.

Johnson and Johnson asserts that their general approach was devised based on feedback from physicians, pharmacists, and Alzheimer's disease advocacy groups; these groups advised that a staged approach was preferable given the patient population's memory impairment and resistance to change. Johnson and Johnson states that keeping the Reminyl name for a limited period of time following the introduction of the extended-release formulation will allow for adequate education of patients and caregivers regarding the new name and new formulation.

To accompany the transition to the new name for all galantamine products, Johnson and Johnson proposes implementing a multi-pronged communication plan to educate pharmacists, prescribers, caregivers and patients about the new name and the availability of the new formulation. They propose the following timeline and communication plan for the launch of the new product and the transition to the new name for all galantamine products:

3.1 Phase I: launch of extended-release product with new name

In this phase, Johnson and Johnson will launch the new extended-release formulation of galantamine under the new trademark name. The communication plan during this phase will be focused on educating pharmacists, prescribers, caregivers, and patients regarding the availability of the new formulation of galantamine with the new name. Johnson and Johnson proposes to undertake the following actions during this phase of the transition:

3.1.1 Activities to be implemented after approval of new name

- Immediately after approval of the new proprietary name, prescribers, pharmacists, wholesalers, and payors will be notified of the new once-daily formulation and its name. Information regarding converting patients from the twice- to once-daily formulation will be part of these communications. The pending name change for the immediate-release products will also be announced, which will facilitate expedient depletion of existing inventory levels of Reminyl from the supply chain.
- A template letter that pharmacists can distribute to their customers taking Reminyl will be sent to all pharmacies. This letter will:
    - Announce the availability of a once-daily formulation with a new name
    - Emphasize the convenience of the new formulation

    - Refer patients to their doctors for additional information
    - Refer patients to a coupon towards the purchase of the new extended-release formulation of galantamine that will be available on the website of SharingCare, a support program run by Johnson and Johnson for patients with Alzheimer's disease and their caregivers
- A pharmacy counter display to be made available through sales representatives covering approximately 50,000 pharmacies. This display will:
    - Announce the availability of the new product and emphasize its convenience
    - Refer patients to their physicians regarding changing their prescription to the new formulation
    - Provide patients with a coupon towards their next purchase of the new extended-release product
- Letters and materials emphasizing the availability of the new formulation and its convenience will be prepared for account managers to present to major payors

3.1.2 Activities to be implemented once new extended-release product is available in pharmacies

Johnson and Johnson predicts that extended-release galantamine will be available at the retail level four to eight weeks following its approval with the new proprietary name. They state that the extended-release formulation of galantamine will be preferentially advertised and detailed by sales representatives over the immediate-release formulation of galantamine. Once the extended-release formulation is available at the retail level, they plan to implement the following components of their transition plan:

- Press release announcing the availability of the new extended-release product with the new trademark name
- Communications to Sharing Care enrollees
    - Direct and e-mail contact will be made with the all Sharing Care enrollees. Johnson and Johnson estimates that over 24,000 patients or caregivers will be reached in this manner
        - The draft letter that Johnson and Johnson has submitted announces that a new version of Reminyl is being introduced, announces its new name, emphasizes the new product's convenience, and counsels patients or caregivers to speak to their physicians regarding changing their medication from Reminyl to the new formulation.
        - The letter does not mention the reasons for the name change and does not announce the impending name change of the immediate-release Reminyl products.
- Updated webpages for Reminyl.com and SharingCare.com
    - The websites will announce that an extended-release formulation of galantamine has been approved, stating that this product is "the active ingredient of Reminyl in a new, more convenient once-daily formulation that is generally safe and well tolerated." The websites will give advice regarding converting patients from the immediate- to the extended-release

formulations of galantamine and provide pictures of the immediate- and extended-release tablets.
    - As is the case with all communications that Johnson and Johnson is proposing as part of their risk management program, the proposed website language does not communicate either the reason for the name change or the impending name change for the immediate-release products.
- New insert for the six-week Reminyl sample pack
    - An insert will be placed in the sample pack discussed above in section 2.1. The draft insert submitted by Johnson and Johnson announces that the name Reminyl will soon be changing and announces that this product with the new proprietary name will also be available in a once-daily formulation. Patients or their caregivers are advised to speak to their physicians if they are interested in this "new, convenient formulation."
    - Johnson and Johnson states that the goal of the insert is to facilitate the conversion of patients started on Reminyl to the new once-daily formulation of galantamine.
- Physicians and pharmacist conversion flashcards and tear-pads
    - Sales representatives will use "conversion flashcards" to educate physicians and pharmacists regarding the transition of patients currently receiving Reminyl to the new extended-release formulation. Physicians and pharmacists will be left with tear-pads containing the same information to use as a reference tool. Johnson and Johnson predicts that sales representatives will reach approximately 30,000 physicians, 9,000 long-term care facilities, and 15,000 pharmacies with these tools.
- Core visual aid
    - The core visual aid will be the primary teaching tool used by sales representatives. Johnson and Johnson anticipates that they will reach approximately 30,000 physicians, 9,000 long-term care facilities, and 15,000 pharmacies with this tool.
    - The core visual aid introduces the new name and formulation, presents clinical trial efficacy data, discusses how to switch patients from Reminyl to the new formulation of galantamine, discusses the safety and tolerability of the extended-release formulation compared to Reminyl, and presents safety information regarding the extended-release product.
    - The core visual aid is intended to be used by the sales representatives as a tool for discussion but is not intended to be left with physicians or pharmacists.
- Direct mail campaign
    - Johnson and Johnson will send a "Dear Doctor" letter to approximately 30,000 physicians. This letter announces the availability of "the new once-daily formulation of Reminyl" and counsels prescribers regarding converting patients from Reminyl to the new extended-release formulation of galantamine.

3.2 Phase 2: name change for immediate-release product

Johnson and Johnson proposes initiating this phase of the transition approximately three months after the extended-release formulation is launched and available at the retail level. At this time, the renamed immediate-release product will be made available to wholesalers and direct purchasing consumers and products labeled solely as Reminyl will no longer be shipped. Initially, the renamed immediate-release product will have a dual label; the text "formerly known as Reminyl" will appear beneath the new name in a smaller font. The generic name will also appear on the label in parentheses beneath the new name.

The renamed immediate-release product will be marketed with a dual label for a minimum of three months following its launch. At this point, the "formerly Reminyl" statement will be removed from the label and inventory with this statement "will be allowed to exit the supply chain naturally." In contrast, there will be active reverse distribution of all products labeled solely as Reminyl. Johnson and Johnson states that at the completion of their proposed plan for transitioning to a new trademark for galantamine, retailers will be directed to return all tablets and oral solution labeled solely as Reminyl through a third party reverse distribution agency. A credit for returned Reminyl products will be provided. At this point, the risk management plan for preventing medication errors due to confusion between Reminyl and Amaryl will be discontinued.

Johnson and Johnson proposes the following communications during this phase of the transition:

3.2.1 Communications to be initiated prior to retail availability of renamed immediate-release formulations

- Calls will be made and/or letters sent to all direct purchasing customers several weeks prior to shipping the renamed immediate-release products with the dual labels.
- One month prior to the retail availability of the renamed twice-daily product, the following communications will begin and will be continued for four months (drafts of the materials are not provided):
    - Sales force promotion to physicians regarding the name change of the twice-daily formulation
    - Journal advertising targeted to physicians and pharmacists
    - Public relations directed to professional societies

3.2.2 Communications to be initiated concurrently with the retail availability of the renamed twice-daily product

- Faxes and on-line alerts will be sent to pharmacies informing them of the name change and the immediate availability of the renamed immediate-release products.
- The following communications to patients and their caregivers will be undertaken during this phase of the transition:

- E-mails and a letter will be sent to all Sharing Care enrollees
    - The draft letter provided informs patients and caregivers of the name change for Reminyl, informs them of the availability of an extended-release formulation, and advises them to talk with their physicians about switching to the extended-release formulation. The letter also discusses the side effects of galantamine.
- Letters will also be sent to patients receiving Reminyl through third party databases describing the name change
- Patient advocacy groups will be contacted
- The websites Reminyl.com and Sharingcare.com will be updated with information targeted to consumers
    - The draft webpage Johnson and Johnson has provided announces the name change as well as the availability of the new extended-release formulation of galantamine

- Revised Reminyl sample pack insert
    - The insert for the Reminyl sample pack that Johnson and Johnson proposes using in this phase of the transition plan appears to be identical to the insert they plan to use during phase 1 of the transition plan as discussed above in section 3.1.2.
        - They do no state when they plan to cease production of the Reminyl sample pack or whether the sample pack will have a dual label at any point during the transition.
- "Dear Doctor" letter will be sent to approximately 30,000 physicians
    - The draft letter submitted by Johnson and Johnson informs physicians of Reminyl's name change and informs them of the availability of the new, "more convenient" extended-release formulation of galantamine.

4 Reviewer comment

In my view, Johnson and Johnson's overall proposal for transitioning to a new name for its galantamine products has several flaws. The staged approach introduces the potential for medication errors due to confusion between available galantamine formulations. The potential for confusion that is always present when a new formulation of an existing medication is marketed would be heightened by the fact that the immediate- and extended-release formulations of galantamine will have different names for several months. Prescribers, patients, and pharmacists might not realize that the extended-release formulation of galantamine has the same active ingredient as Reminyl and some patients may receive both drugs in error. It is difficult to predict whether the presence of a dual-labeled product during the transition period will mitigate or increase the potential for confusion. Although the dual label will link Reminyl with the new name, the dual-labeled product will not be released until three months after the launch of the extended-release formulation. The presence of a dual-labeled product will increase the number of galantamine products with different labels that are on the market. For approximately three months, there will be multiple uniquely labeled galantamine products available—

the new extended-release product with the new name, the immediate-release products labeled solely as Reminyl, and the immediate-release products labeled both with the new name and a statement that the drug was "formerly known as Reminyl."

Johnson and Johnson's proposed communication plan materials do not address the potential for confusion between differently-named formulations of galantamine. They should be very clear in all communications that the extended-release formulation of galantamine with the new name has the same active ingredient as Reminyl. They should also explicitly state in each communication the names of the galantamine products that are on the market at the time of the communication. Their educational plan materials should contain a statement warning against prescribing, taking, or dispensing two differently-labeled galantamine products concurrently.

In my view, the potential for medication errors due to confusion between galantamine formulations could also be mitigated by greater clarity in the educational materials regarding the overall transition plan. The materials that Johnson and Johnson proposes using in phase 1 of their transition scheme do not mention that their plan is ultimately to change Reminyl's name or cite the reason that the name change is occurring . I think that this is critical information to communicate, particularly to prescribers and pharmacists, and its absence is a major flaw in Johnson and Johnson's overall plan. If Johnson and Johnson intends for physicians and pharmacists to educate patients and caregivers regarding the name change for Reminyl, it is critical that they be apprised of the overall plan up front and that they be prepared for the eventual name change of Reminyl. Waiting to impart this information to prescribers and pharmacists until the immediate-release products with the new name are about to go on the market does not appear to serve any useful purpose and could potentially increase confusion. Citing the reason for the name change in all materials may help reduce medication errors due to confusion between Amaryl and Reminyl and would link the name change transition plan with the ongoing risk management plan for preventing errors due to name confusion.

In addition to these overarching problems with Johnson and Johnson's proposal, a number of specific components of their transition plan need further clarification:

- Reminyl starter pack
    - Johnson and Johnson should clarify when distribution of the Reminyl starter pack will cease.
    - They should also clarify whether the starter pack will be dually labeled for a period of time.
    - They should clarify whether they will be producing the starter pack under the new name. If they do intend to continue to distribute starter packs for immediate-release galantamine, they should clarify when the starter pack with the new name will be available.
- Reverse distribution plan
    - Johnson and Johnson should clarify exactly when reverse distribution of Reminyl will begin and end and how reverse distribution will be implemented. None of the submitted materials directed to pharmacists mention reverse distribution of Reminyl, which seems to be an oversight.

- The transition plan states that reverse distribution of the Reminyl that is remaining on the market will be initiated at the end of the name change transition scheme. In my view, reverse distribution should begin earlier in order to shorten the period of time that galantamine products with more than one proprietary name are on the market.
- Johnson and Johnson should specify how reverse distribution of Reminyl will be tracked. Because they plan to cease their active name confusion risk management plan when there are no products labeled solely as Reminyl remaining on the market, it is important that they have a plan in place for monitoring the volume of Reminyl products that remain on the market.

- Caregiver awareness brochure
  - The caregiver awareness brochure could be a useful vehicle regarding communicating with patients and caregivers regarding the new formulation and the new name. Johnson and Johnson's current transition plan does not appear to make use of the caregiver awareness brochure. The Division should inquire how Johnson and Johnson plans to modify their caregiver awareness brochure to educate patients regarding the new name and new formulation.

5 Division response and future of name change transition

The Division met with Johnson and Johnson on January 24, 2005 to discuss the proposed plan for changing the name of all galantamine products subsequent to the approval of a new proprietary name. At the January 24 meeting, the Division expressed concerns regarding the potential for confusion inherent in Johnson and Johnson's staged approach. The Division also requested that the communication plan materials cite the reason for the name change.

Johnson and Johnson responded that they were willing to modify the timing of their name change for the immediate-release formulations even though feedback from prescribers, pharmacists, and patient advocacy groups had led them to believe that a staged approach would minimize confusion, provide continuity for patients receiving Reminyl, and allow adequate time for patient and caregiver education. Johnson and Johnson agreed to launch the dual-labeled immediate-release galantamine products (labeled with both the new name and the "formerly Reminyl" statement) at the same time that they launched the extended-release formulation of galantamine with the new name. They agreed to accelerate the reverse distribution of products labeled solely as Reminyl. They agreed to modify their proposed communications to be consistent with this new timeline and resubmit a comprehensive transition plan to the Division. They agreed to state the reason for the name change for all galantamine products in their educational materials.

The following actions related to the name change will also be pursued by either the Division or Johnson and Johnson:

- The Division will forward all proposed educational materials directed to patients to the Division of Surveillance, Research, and Communication Support (DSRCS) for their review and comment once the revised materials are received
- Johnson and Johnson will contact the Institute for Safe Medication Practices (ISMP) regarding placing an item in their newsletter regarding the name change
- After the new name is approved, the Division will contact the FDA Patient Safety News producers to suggest that they broadcast a segment regarding the name change and the name change transition plan.

On March 31, 2005, DNDP approved the name Razadyne and Razadyne ER to replace Reminyl. The sponsor's updated transition plan will be reviewed in a separate document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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5/16/05 12:22:55 PM
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Review and Evaluation of Clinical Data

NDA	**21615**
Sponsor:	**Johnson & Johnson**
Drug:	**Galantamine**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Briefing Package**
Correspondence Date:	**12/29/04**
Date Received By Reviewer:	**1/3/05**
Date Review Completed	**1/24/05**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Introduction

This submission consists of a Briefing Package for a meeting that is to be held between the Division and sponsor to discuss a plan to implement a change in the proprietary name for galantamine hydrobromide (hitherto referred to as "Reminyl®"). The implementation of this change in proprietary name is to accompany the launch of an extended-release formulation of galantamine.

3 formulations of Reminyl® are discussed in this submission

- An approved immediate-release tablet formulation
- An approved oral solution formulation
- An extended-release capsule formulation, whose approval is currently pending

The impetus for the transition plan contained in this submission is 2-fold

- A number of reports of prescribing and dispensing errors apparently resulting from confusion between the names "Reminyl®" and "Amaryl®." [Amaryl® is an oral anti-diabetic drug]. These reports have included accounts of two deaths
- The recent approval of an extended-release formulation of galantamine, hitherto referred to as Reminyl® Extended-Release Capsules

Reminyl® Extended-Release capsules have been developed under Investigational New Drug Application (IND) 61703. The immediate-release tablet and oral solutions formulations of galantamine, Reminyl®, had earlier been developed by this sponsor for the treatment of Alzheimer's Disease under IND 51538. NDAs 21169 and 21224, for the use of the immediate-release tablet and oral solution forms, respectively, of galantamine in the treatment of mild-to-moderate dementia of the Alzheimer's type were approved in 2001. Later in 2001, a supplemental NDA (SCM-001) was approved for the use of immediate-release tablet and oral solution formulations of synthetic galantamine (for the treatment of mild-to-moderate dementia of the Alzheimer's type), instead of the plant-derived drug substance approved earlier.

NDA 21615, originally submitted on 2/24/03, sought the approval of Reminyl® Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. The Division responded to that application with a Not-Approvable action letter on 12/23/03. Subsequently, the sponsor submitted a earlier Complete Response to the Not-Approvable letter on 5/27/04, to which the Division responded with a further Not-Approvable action letter on 7/27/04. A Dispute Resolution Request package was then submitted directly to Dr R. Temple, Office Director, which was received by his office on 9/27/04. Dr Temple's response to that Request was provided to the sponsor on 10/27/04 and concluded that the key deficiency in this application, the lack of substantial evidence of efficacy, had been adequately addressed in the original NDA and subsequent Amendments. A further submission, a Complete Response (dated 10/27/04) to the second Not-Approvable letter, followed Dr Temple's response to the Dispute Resolution Request, and was approved on 12/27/04.

The sponsor has proposed that Reminyl® Extended-Release capsules be administered once daily, whereas it is recommended in the package insert for the currently approved immediate-release and oral solution formulations of Reminyl® that they be administered twice daily.

Note that a risk management plan, agreed to by this Division and by the sponsor, is currently in existence as a means of addressing the confusion in name between "Reminyl®" and "Amaryl®." The existing plan does not provide for a change in the proprietary name "Reminyl®."

An earlier, but incomplete, version of this transition plan was submitted as a briefing package on 12/3/04. The meeting scheduled in association with that submission was postponed, in order that the current briefing package could be reviewed.

This submission is cross-referenced to NDAs 21169 and 21224. The sponsor notes in the submission, that all references to the twice daily formulation are equally applicable to both the immediate-release tablet and to the oral solution formulation.

2. Contents Of Submission

The contents of this submission are provided under the following main headings

- Introduction
- Overall timing and implementation plan
- Conversion plan for patients to once-daily regime
- Transition plan for name change to the currently marketed products

In addition, the submission contains an appendix whose intention is to provide clinical justification for switching patients from twice-daily immediate-release galantamine to once-daily extended-release galantamine

3. Contents Of Review

In this review, I will address the following contents of this submission (only) and in the same order as below

- Stated objectives of the meeting and of the transition plan
- Steps in the transition plan
- New proprietary names proposed by sponsor
- Data supporting the sponsor's plan for conversion from a twice-daily to a once-daily regimen

The other components of this submission will be reviewed by the Safety Group within this Division and Division of Medication Errors and Technical Support (DMETS) of the Office of Drug Safety.

4. Objectives Of Meeting And Transition Plan

The stated objectives of the meeting are as follows

- To discuss the sponsor's plans for the introduction of a new once-daily extended-release formulation under a new proprietary name
- To discuss the sponsor's proposal for transition to the new proprietary name for the currently marketed products (immediate-release tablet and oral solution formulations of Reminyl®)

The overall objectives of the transition plan are as follows

- To support the introduction of the new formulation (i.e., extended-release galantamine capsules) under a new proprietary name; in furthering this objective, the plan will include data and promotional materials that aid in the conversion of patients currently administered the twice daily tablet Reminyl® tablet formulation to the once-daily galantamine capsule formulation
- To support the transition in proprietary name for the immediate-release tablet and oral solution formulations

5. Steps In Transition Plan

The sponsor has proposed the following sequence of steps as constituting the transition

1. Launch of extended-release galantamine capsules under the new proprietary name, supported by dose conversion information
2. Communication to wholesalers and direct purchase customers of the pending name change for the currently marketed formulations (IR tablets and oral solution)
3. Shipment of dual-labeled tablets and oral solution to distribution centers, simultaneous with communication to physicians and pharmacists of the name change.
4. Retail stocking in local pharmacies of dual-labeled tablets and oral solution
5. Communication to patients and caregivers of name change upon retail availability
6. Phase out of dual-labeled packaging to new TRADEMARK only
7. Discontinuation of the Risk Management Program communicating potential of dispensing errors between REMINYL and AMARYL

6. New Proprietary Names Proposed By Sponsor

The alternative proprietary names proposed by the sponsor are [ ] and [ ]

7. Data To Support Plan For Conversion From A Twice-Daily To A Once-Daily Regimen

The sponsor proposes that patients taking a twice daily dose of immediate-release galantamine tablets or galantamine oral solution, begin taking once-daily extended-release capsules without dose titration, and using the same total daily dose.

7.1 Overview

The plan for converting patients from twice-daily to once-daily galantamine is based on a review of pharmacokinetic and clinical data comparing the once-daily and twice-daily formulations

The pharmacokinetic data is derived from a study in young normal volunteers and a new pharmacokinetic simulation designed to predict plasma concentrations in patients with Alzheimer's Disease following an immediate conversion from twice-daily to once-daily galantamine

The clinical data includes a summary of efficacy and safety data from patients who participated in both GAL-INT-10 and its open-label uncontrolled extension, GAL-INT-21. Study GAL-INT-10 formed the basis for the approval of the extended-release formulation of galantamine.

7.2 Clinical Data

The clinical data provided in this submission are derived from patients who participated in Study GAL-INT-21.

An outline of Studies GAL-INT-10 and GAL-INT-21 is provided below followed by data from both studies

7.2.1 Summary Of Studies GAL-INT-10 And GAL-INT-21

7.2.1.1 Study GAL-INT-10

This study is summarized below

Objective:	Efficacy and safety of Reminyl® CR in mild-to-moderate Alzheimer's Disease
Design:	Randomized, double-blind, placebo-controlled, parallel-arm study
Key Inclusion Criteria:	• Male or female • Probable Alzheimer's disease by NINCDS-ADRDA criteria • Mini-Mental Status Examination score 10-24 **and** ADAS-Cog score of at least 18

Dose Groups:	Placebo Reminyl® ER 16 to 24 mg q.d. Reminyl® IR 8 mg to 12 mg b.i.d
Duration:	26 weeks
Randomized Population:	Placebo → 324 patients Reminyl® ER 16 to 24 mg q.d. → 327 patients Reminyl® IR 8 mg to 12 mg b.i.d → 320 patients
Primary Efficacy Measures:	• ADAS-Cog • CIBIC-Plus
Secondary Efficacy Measures:	• ADAS-Cog/13 • ADAS-Cog/10 • ADAS-Cog/mem • Percentage of responders on standard ADAS-Cog using 0, 4, 7 and 10 points of improvement as cut-off • Percentage of subjects with "improved" or "no change" on the CIBIC-Plus. • Neuropsychiatry Inventory • Alzheimer's Disease Cooperative Study-ADL

7.2.1.2 Study GAL-INT-21

This study is summarized below

Primary Objective:	To evaluate the long-term safety of controlled-release galantamine in Alzheimer's Disease
Design:	Open-label uncontrolled trial
Key Inclusion Criteria:	Completion of Study GAL-INT-10
Dosage:	Reminyl® ER 16 to 24 mg q.d.
Duration:	12 months
Original Projected Sample Size:	700 patients
Safety Outcome Measures:	Adverse events, vital signs, safety laboratory tests, electrocardiograms, and physical examinations
Efficacy Outcome Measures:	ADAS-Cog, Neuropsychiatry Inventory, ADCS-ADL
Status	Ongoing

The dosing regimen for this study was as follows

- Patients enrolled in this study were to be titrated to a dose of Reminyl® ER of either 16 mg q.d. or 24 mg q.d.
- All patients were to initially receive Reminyl® ER in a dose of 8 mg q.d. for 4 weeks, followed by a dose of 16 mg q.d. for at least 8 weeks.
- After Week 12 the dose could be increased to 24 mg q.d., based on safety and tolerability
- At or beyond Week 12, dose adjustments could be made only twice (including the initial increase to 24 mg q.d.). A decrease to 16 mg q.d. could be made based on safety and tolerability, but once such a decrease was made, the dose would have to remain unchanged for the remainder of the trial.

7.2.2 *Disposition*

The disposition of patients in GAL-INT-21 is summarized below, tabulated according to treatment assignment in the immediately preceding study GAL-INT-10. The patients enrolled in GAL-INT-21 included 233 individuals who had been treated with immediate-release galantamine in GAL-INT-10. The table is copied from the submission

Trial Medication Termination Reasons
(Study GAL-INT-21: Safety Analysis Set)

Status Termination Reasons	PLA/ GAL-ER (N=253) n (%)	GAL-IR/ GAL-ER (N=233) n (%)	GAL-ER/ GAL-ER (N=236) n (%)	Total (N=722) n (%)
Completed	188 (74)	171 (73)	188 (80)	547 (76)
Discontinued	65 (26)	62 (27)	48 (20)	175 (24)
Death	5 (2)	10 (4)	5 (2)	20 (3)
Adverse event	27 (11)	26 (11)	12 (5)	65 (9)
Insufficient response	2 (1)	1 (<1)	0	3 (<1)
Subject ineligible to continue the trial	0	2 (1)	2 (1)	4 (1)
Subject lost to follow-up	4 (2)	4 (2)	5 (2)	13 (2)
Subject withdrew consent	14 (6)	5 (2)	9 (4)	28 (4)
Subject non-compliant	5 (2)	5 (2)	6 (3)	16 (2)
Other	7 (3)	9 (4)	9 (4)	25 (3)

Percentage for each category in a group was calculated based on all subjects for that group as denominator.
PLA/GAL-ER, GAL-IR/GAL-ER, GAL-ER/GAL-ER=Treatment sequence during GAL-INT-10 (DB), GAL-INT-21 (OL).
DB: Double-blind. OL: Open-label. PLA: Placebo

7.2.3 *Efficacy Data: ADAS-Cog*

The next table, copied from the submission, indicates changes in the ADAS-Cog in all 3 treatment groups (as defined in Study GAL-INT-10) during both studies. Week 26 represents the start of the open-label extension study GAL-INT-21

Summary of ADAS-cog/11 – Change From Baseline
(Study GAL-INT-21: Efficacy Analysis Set)

Subject Grouping Assessment Time	N	Mean (SD)	Mean Change From Baseline (SD)
PLA/GAL-ER			
Baseline	250	25.5 (9.20)	
Week 8	250	25.6 (10.51)	0.1 (4.86)
Week 12	246	25.5 (10.76)	0.1 (5.33)
Wk 26/initial	238	26.1 (11.15)	1.1 (5.66)
Month 12	203	26.2 (11.26)	1.5 (6.37)
Month 18	177	28.4 (13.06)	4.2 (8.38)
Endpoint LOCF	215	28.6 (12.82)	3.7 (8.16)
GAL-IR/GAL-ER			
Baseline	228	26.8 (9.56)	
Week 8	226	24.5 (9.43)	-2.1 (4.93)
Week 12	224	23.6 (9.23)	-2.8 (4.86)
Wk 26/initial	213	24.3 (10.10)	-2.0 (6.09)
Month 12	181	26.3 (11.12)	0.4 (6.79)
Month 18	151	26.9 (11.78)	1.9 (7.33)
Endpoint LOCF	189	27.8 (12.19)	1.8 (7.68)
GAL-ER/GAL-ER			
Baseline	233	25.9 (9.12)	
Week 8	232	24.1 (9.33)	-1.8 (4.90)
Week 12	231	23.6 (9.15)	-2.3 (5.33)
Wk 26/initial	228	24.5 (10.68)	-1.4 (5.19)
Month 12	202	26.2 (11.47)	0.5 (6.54)
Month 18	171	28.3 (12.43)	3.6 (8.07)
Endpoint LOCF	214	29.3 (12.83)	3.5 (7.96)
GAL-IR(ER)/GAL-ER			
Baseline	461	26.3 (9.34)	
Week 8	458	24.3 (9.37)	-2.0 (4.91)
Week 12	455	23.6 (9.18)	-2.5 (5.11)
Wk 26/initial	441	24.4 (10.39)	-1.7 (5.64)
Month 12	383	26.2 (11.29)	0.5 (6.65)
Month 18	322	27.6 (12.13)	2.8 (7.77)
Endpoint LOCF	403	28.6 (12.54)	2.7 (7.87)

Analysis includes subjects entering open-label phase with baseline data.
Note: PLA/GAL-ER, GAL-IR/GAL-ER, GAL-ER/GAL-ER=Treatment sequence during GAL-INT-10 (DB), GAL-INT-21 (OL). GAL-IR(ER)/GAL-ER=Combination of GAL-IR/ER and GAL-ER/GAL-ER.
Baseline=Baseline of GAL-INT-10, WK 26/Initial=Initial visit of GAL-INT-21.
Endpoint LOCF: last observation carried forward from any timepoint post Week 26/initial visit.

The sponsor points out that those who received the IR and ER formulations of galantamine in Study GAL-INT-10 had similar scores at Week 26 and at Month 12 of GAL-INT-21, thus suggesting that there was no loss of efficacy with conversion of patients from twice-daily to once-daily galantamine through re-titration

7.2.4 Efficacy Data: ADCS-ADL

The next table, copied from the submission, indicates changes in the ADCS-ADL in all 3 treatment groups (as defined in Study GAL-INT-10) during both studies.

Week 26 again represents the start of the open-label extension study GAL-INT-21

Summary of ADCS-ADL – Change From Baseline
(Study GAL-INT-21: Efficacy Analysis Set)

Subject Grouping Assessment Time	N	Mean (SD)	Mean Change From Baseline (SD)
PLA/GAL-ER			
Baseline	252	55.2 (14.84)	
Week 8	251	54.8 (16.18)	-0.4 (7.60)
Week 12	251	54.9 (15.98)	-0.3 (7.58)
Wk 26/initial	246	53.2 (16.89)	-2.0 (9.37)
Month 12	211	50.9 (18.33)	-4.6 (10.33)
Month 18	185	48.2 (19.26)	-8.1 (12.15)
Endpoint LOCF	220	47.6 (19.56)	-7.9 (12.27)
GAL-IR/GAL-ER			
Baseline	232	52.6 (15.62)	
Week 8	232	53.6 (15.96)	0.9 (7.08)
Week 12	232	53.9 (15.71)	1.2 (7.82)
Wk 26/initial	227	51.6 (17.06)	-1.0 (8.90)
Month 12	195	49.2 (19.07)	-4.0 (11.94)
Month 18	170	46.8 (19.97)	-7.0 (13.21)
Endpoint LOCF	202	46.1 (19.70)	-6.8 (13.44)
GAL-ER/GAL-ER			
Baseline	235	54.1 (14.80)	
Week 8	235	55.2 (15.25)	1.1 (6.87)
Week 12	235	54.3 (15.57)	0.2 (8.24)
Wk 26/initial	232	54.2 (15.81)	0.0 (8.52)
Month 12	209	50.8 (17.94)	-3.9 (11.28)
Month 18	178	47.3 (19.76)	-8.3 (13.03)
Endpoint LOCF	218	46.8 (19.12)	-7.9 (13.03)
GAL-IR(ER)/GAL-ER			
Baseline	467	53.4 (15.21)	
Week 8	467	54.4 (15.61)	1.0 (6.97)
Week 12	467	54.1 (15.62)	0.7 (8.04)
Wk 26/initial	459	52.9 (16.47)	-0.5 (8.72)
Month 12	404	50.0 (18.48)	-4.0 (11.59)
Month 18	348	47.0 (19.84)	-7.7 (13.12)
Endpoint LOCF	420	46.5 (19.38)	-7.4 (13.23)

Analysis includes subjects entering open-label phase with baseline data.
Note: PLA/GAL-ER, GAL-IR/GAL-ER, GAL-ER/GAL-ER=Treatment sequence during GAL-INT-10 (DB), GAL-INT-21 (OL). GAL-IR(ER)/GAL-ER=Combination of GAL-ER/IR and GAL-ER/GAL-ER.
Baseline=Baseline of GAL-INT-10, WK 26/Initial=Initial visit of GAL-INT-21.
Endpoint LOCF: last observation carried forward from any time point post Week 26/Initial visit.

The sponsor interprets the above results as follows

- After the initial 26 weeks of treatment (in the GAL-INT-10 study), there were no differences in ADCS-ADL scores between the 2 galantamine treatment arms

- In the first 6 months of GAL-INT-21, the group that shifted from twice-daily to once-daily galantamine had "similar or less decline" on the ADCS-ADL than the group that continued once-daily galantamine.

7.2.5 Safety Data: Incidence Of Adverse Events

The next table, copied from the submission, indicates the incidence of adverse events in patients enrolled in Study GAL-INT-21, based on their treatment assignment in Study GAL-INT-10.

Incidence of Adverse Events by WHO System Organ Class and Preferred Term – Treatment-Emergent Analysis (≥5%)
(Study GAL-INT-21: Safety Analysis Set)

System Organ Class Preferred Term	PLA/ GAL-ER (N=253) n (%)	GAL-IR/ GAL-ER (N=233) n (%)	GAL-ER/ GAL-ER (N=236) n (%)	Total (N=722) n (%)
Total no. subjects with adverse events	191 (75)	178 (76)	177 (75)	546 (76)
Psychiatric disorders	69 (27)	82 (35)	63 (27)	214 (30)
Agitation	20 (8)	21 (9)	17 (7)	58 (8)
Depression	13 (5)	11 (5)	13 (6)	37 (5)
Anorexia	14 (6)	10 (4)	7 (3)	31 (4)
Insomnia	7 (3)	12 (5)	5 (2)	24 (3)
Aggressive reaction	4 (2)	12 (5)	7 (3)	23 (3)
Gastrointestinal system disorders	79 (31)	57 (24)	61 (26)	197 (27)
Nausea	31 (12)	13 (6)	17 (7)	61 (8)
Diarrhea	24 (9)	13 (6)	20 (8)	57 (8)
Vomiting	22 (9)	8 (3)	9 (4)	39 (5)
Constipation	13 (5)	6 (3)	11 (5)	30 (4)
Body as a whole – general disorders	64 (25)	55 (24)	60 (25)	179 (25)
Injury	20 (8)	23 (10)	21 (9)	64 (9)
Central & peripheral nervous system disorders	62 (25)	48 (21)	31 (13)	141 (20)
Dizziness	26 (10)	15 (6)	10 (4)	51 (7)
Headache	12 (5)	13 (6)	7 (3)	32 (4)
Urinary system disorders	41 (16)	34 (15)	40 (17)	115 (16)
Urinary tract infection	27 (11)	18 (8)	21 (9)	66 (9)
Urinary incontinence	10 (4)	7 (3)	14 (6)	31 (4)
Metabolic and nutritional disorders	42 (17)	34 (15)	34 (14)	110 (15)
Weight decrease	16 (6)	13 (6)	14 (6)	43 (6)
Secondary terms	44 (17)	31 (13)	35 (15)	110 (15)
Fall	27 (11)	26 (11)	19 (8)	72 (10)
Respiratory system disorders	42 (17)	26 (11)	32 (14)	100 (14)
Rhinitis	12 (5)	4 (2)	6 (3)	22 (3)

Note: PLA/GAL-ER, GAL-IR/GAL-ER, GAL-ER/GAL-ER =Treatment sequence during GAL-INT-10 (DB), GAL-INT-21 (OL).

The sponsor considers the above table to indicate that the incidence of adverse events in those originally treated with once-daily galantamine was comparable to those originally treated with twice-daily galantamine. A slightly higher incidence of agitation and insomnia in those who originally received the IR formulation, as compared with those who originally received the ER formulation, has been

explained by the sponsor as being, in part, related to the higher Neuropsychiatry Inventory scores in the former group at the end of GAL-INT-10.

7.3 GAL-NED-8 Phase I Bioavailability Data

7.3.1 Objectives

The primary objective of this study was to evaluate the effects of food on the bioavailability of galantamine at steady-state after the administration of the 24 mg once-daily extended-release tablet

A secondary objective of the study was to evaluate the relative steady-state bioavailability of galantamine from the 24 mg once-daily extended-release capsule compared with the immediate-release tablet

7.3.2 Design

This was a randomized, open-label, 3-way crossover study comparing the following regimes

GAL-ER 24 mg QD in a fasted state (Treatment A)
GAL-ER 24 mg QD in a fed state (Treatment B)
GAL-IR 12 mg BID in a fasted state (Treatment C))

7.3.3 Pharmacokinetic Results

A comparison of the pharmacokinetic parameters for Treatments A and C are in the following table, which I have copied from the submission

Galantamine Pharmacokinetic Parameters
(Study GAL-NED-8)

	Arithmetic mean ± SD		LS mean treatment ratio[a] (90% CI)
Parameters	ER capsule fasted Treatment A (N = 22)	IR tablet fasted Treatment C (N = 22)	A/C
AUC_{24h} (ng.hr/mL)	968 ± 193	1050 ± 239	93 (90 - 96)
C_{max} (ng/mL)	63.0 ± 12.0	84.3 ± 21.4[b]	76 (71- 80)
C_{min} (ng/mL)	18.8 ± 4.6	21.7 ± 7.9	89 (83 - 96)
t_{max} (h)	4.4 ± 1.7	1.2 ± 0.6[b]	-

[a] Parameter values were analyzed on a logarithmic scale with least-squares means were transformed back to the original scale. The t_{max} values were analyzed on the original scale using a nonparametric method.
[b] Related to the first intake for Treatment C.

Based on the above results

- Treatment A has been assumed to be bioequivalent to Treatment C, based on the AUC_{0-24} and C_{min}.

- The C_{max} of the ER capsule is 76% that of the IR tablet, slightly below the lower boundary of the bioequivalence criteria (80% to 125%)

7.3.4 Safety Results

The sponsor has summarized the safety data for this study as follows

- Treatment with the ER capsule was better tolerated than treatment with the IR tablet
- The evaluation of vital signs, electrocardiograms, and safety laboratory tests revealed no safety concerns with either formulation.

7.4 Pharmacokinetic Simulation Of Conversion In Patients With Alzheimer's Disease

7.4.1 Objectives

The purpose of the simulation study was to compare the concentration-time profile of galantamine when the formulation used was changed from the twice-daily IR formulation to the once-daily ER formulation

7.4.2 Dosing Regimes Simulated

Two sets of changing dose regimes were simulated

- The IR tablet administered in a dose of 8 mg BID for 7 days, followed by the ER tablet administered in a dose of 16 mg QD for 7 days
- The IR tablet administered in a dose of 12 mg BID for 7 days, followed by the ER tablet administered in a dose of 24 mg QD for 7 days

7.4.3 Methods

These are described further in the submission, but are too complex for this reviewer to understand. They have, however, been reviewed by Dr Sally Yasuda of the Office of Clinical Pharmacology and Biopharmaceutics.

The simulations used data from 3 completed pharmacokinetic studies of galantamine and were based on a 2-compartment linear disposition model.

7.4.4 Results

The results of the above simulations are summarized in the table below, which I have copied from the submission

Non-compartmental PK Characteristics Derived From the Simulated Profiles					
		IR 8 mg b.i.d.	ER 16 mg q.d.	IR 12 mg b.i.d	ER 24 mg q.d.
		Female / Male	Female / Male	Female / Male	Female / Male
Tmax, hr	1st day of ER	[redacted]	5.5 / 5.5	[redacted]	5.5 / 5.5
Tmax, hr	steady state	1 / 1	5.5 / 6	1 / 1	5.5 / 6
Cmax, ng / mL	1st day of ER	[redacted]	80.6 / 66.2	[redacted]	121 / 99.4
Cmax, ng / mL	steady state	81.7 / 66.3	77.0 / 63.0	123 / 99.5	115 / 94.5
Cmin, ng / mL	1st day of ER	[redacted]	27.3 / 24.5	[redacted]	40.5 / 36.8
Cmin, ng / mL	steady state	32.9 / 29.1	26.5 / 23.7	49.4 / 43.6	39.7 / 35.5
AUC, ng.hr / mL	1st day of ER	[redacted]	1351 / 1144	[redacted]	2027 / 1715
AUC, ng.hr / mL	steady state	1294 / 1092	1290 / 1089	1941 / 1638	1936 / 1634

7.4.5 Conclusions

The sponsor has concluded the following from the above simulations

- When switching from the IR tablet to the ER capsule, C_{max}, C_{min}, and AUC after the first day of dosing with the ER formulation is very similar to that seen with the IR formulation at steady state

- On the first day after switching, a slight increase in AUC (4%) occurred, followed by a return to the same AUC as observed at steady state with the IR formulation

- At steady-state, C_{max} and C_{min} are ~ 5% and ~18% lower for the ER formulation than for the IR formulation

8. Comments

- This submission consists of a Briefing Package for a meeting that is to be held between the Division and sponsor to discuss a plan to implement a change in the proprietary name for galantamine hydrobromide (hitherto referred to as "Reminyl®"). The implementation of this change in proprietary name is to accompany the launch of an extended-release formulation of galantamine, which was recently approved for marketing. Immediate-release tablet and oral solution formulations of galantamine are currently approved for marketing under the proprietary name "Reminyl®"

- The impetus for the change in proprietary name is the receipt by this Agency of a number of reports of prescribing and dispensing errors where there was confusion between the names "Reminyl®" and "Amaryl®"; Amaryl® is an oral anti-diabetic drug; at the present time, these reports include those for 2 deaths that have resulted from Amaryl® being prescribed instead of Reminyl®. These reports have been the subject of a number of discussions between the sponsor, and the Agency; a Risk

Management Program, albeit without a change proprietary name, has been developed, agreed to by this Division, and already initiated.

- The change in proprietary name is to be initiated with the launch of the extended-release formulation and is to later extend to the currently marketed immediate-release and oral solution formulations of galantamine. Full details of the transition plan are in the current submission.

- In this submission, the sponsor proposes that patients taking a twice daily dose of immediate-release galantamine tablets or galantamine oral solution, who wish to change to the extended-release formulation, begin taking once-daily extended-release capsules (in the same total daily dose) without titration. Data in the current submission appear to support the proposed transition.

9. Meeting With Sponsor: January 24, 2005

A meeting between this Division and this sponsor was held today. Representatives of DMETS were present at the meeting

The following were the key items discussed and agreements reached between the Division and sponsor

9.1 New Product Name

- DMETS has recommended that the product name [ ] not be used since it has the potential for being confused for the product names of other marketed drugs [the Division of Drug Marketing, Advertising, and Communications (DDMAC) had, however, found this name to be acceptable]; this Division therefore recommended against its use

- Notwithstanding the recommendation from DDMAC against the use of the product name [ ] DMETS is currently reviewing this name for the possibility that its use could result in errors, such as might occur during dispensing and prescribing. The negative recommendation from DDMAC does not preclude the possibility that, if the assessment by DMETS is favorable, the sponsor might be able to use the name [ ] instead of Reminyl®

- Two additional proprietary names very recently proposed by the sponsor [ ] are currently under review by both DMETS and DDMAC.

9.2 Transition Plan

- The Division was concerned that over a specific period in the transition process, at least 3 differently labeled containers for galantamine formulations would be available and would create a potential for medication errors. The 3 different labels would be those for

    - The extended-release formulation using the new proprietary name
    - The immediate-release formulation using the old and new proprietary names
    - The immediate-release formulation using the old proprietary name

  After a lengthy discussion, it was decided that this concern could best be addressed by launching the extended-release formulation labeled with the new proprietary name as the same time as the release of containers labeled with both the old and new proprietary names.

- The Division recommended that communications to physicians, pharmacists, and others during the transition process be more explicit and detailed than they are currently; for example, it should be made very clear that the new and old product names apply to the same drug, and the use of both the old and new formulations together warned against. There were additional discussions about the recipients and text of these communications

- The sponsor has proposed that patients taking a twice daily dose of immediate-release galantamine tablets or galantamine oral solution, who wish to change to the extended-release formulation, begin taking once-daily extended-release capsules in the same total daily dose without titration. This proposal is acceptable to the Division

- Several communications that are part of the transition package state that extended-release galantamine has the same efficacy as the immediate-release formulation and that the former is better tolerated than the latter. The Division indicated that these statements may not be adequately supported by the results of Study GAL-INT-10

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 1/24/05
cc:

HFD-120
NDA 21615

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/s/

Ranjit Mani
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MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA	**21615**
Sponsor:	**Johnson & Johnson**
Drug:	**Reminyl® Extended-Release**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Complete Response**
Correspondence Date:	**10/27/04**
Date Received / Agency:	**10/27/04**
Date Review Completed	**12/14/04**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission is a Complete Response to the most recent of two Not-Approvable letters that were issued by this Division in regard to this application.

NDA 21615, originally submitted on 2/24/03, sought the approval of Reminyl® Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. The Division responded to that application with a Not-Approvable action letter on 12/23/03. Subsequently, the sponsor submitted a earlier Complete Response to the Not-Approvable letter on 5/27/04, to which the Division responded with a further Not-Approvable action letter on 7/27/04; prior to the Complete Response being submitted, a meeting (End-of-Review Conference) was held between the Division and sponsor on 2/17/04, to discuss the initial Not-Approvable action letter.

On 9/3/04, the sponsor then submitted a Briefing Package for an End-of-Review Conference. While that conference, scheduled for 9/22/04, was cancelled after an internal Agency meeting, a Dispute Resolution Request package was then submitted directly to Dr R. Temple, Office Director, which was received by his office on 9/27/04. Dr Temple's response to that Request was provided to the sponsor on 10/27/04 and concluded that the key deficiency in this application, the lack of substantial evidence of efficacy, had been adequately addressed in the original NDA and subsequent Amendments. The current submission follows Dr Temple's response to the Dispute Resolution Package.

The original application under NDA 21615 was based mainly on the results of one Phase III randomized, double-blind, placebo-controlled efficacy study (GAL-INT-10), an uncontrolled, open-label extension to GAL-INT-10, and several pharmacokinetic trials.

Four-Month and Seven-Month Safety Updates to the original application under NDA 21615 were submitted on 6/19/03 and 10/3/03, respectively, and were reviewed with the original application.

Reminyl® Extended-Release capsules have been developed under Investigational New Drug Application (IND) 61703. The immediate-release tablet and oral solutions formulations of galantamine, Reminyl®, had earlier been developed by this sponsor for the treatment of Alzheimer's Disease under IND 51538. NDAs 21169 and 21224, for the use of the immediate-release tablet and oral solution forms, respectively, of galantamine in the treatment of mild-to-

moderate dementia of the Alzheimer's type were approved in 2001. Later in 2001, a supplemental NDA (SCM-001) was approved for the use of immediate-release tablet and oral solution formulations of synthetic galantamine (for the treatment of mild-to-moderate dementia of the Alzheimer's type), instead of the plant-derived drug substance approved earlier.

The sponsor had earlier proposed that Reminyl® Extended-Release capsules be administered once daily, whereas it is recommended in the package insert for the currently approved immediate-release formulation of Reminyl® that that drug formulation be administered twice daily.

Please see my reviews of the original application under NDA 21615, the sponsor's Briefing Package for the meeting held on 2/17/04, the earlier Complete Response dated 5/27/04, and the Briefing Package of 9/3/04 for further details.

The extended-release formulation of Reminyl® is referred to in this review, interchangeably, as "Reminyl® ER", "GAL-ER", or "GAL-CR". The immediate-release formulation is referred to in this review, interchangeably, as "Reminyl® IR" or "GAL-IR". The terms "IR" and "ER" are used in this review as a substitute for "immediate-release" and "extended-release," respectively.

2. Contents Of Submission

The submission contains the following

- Cover letter
- Proposal for addressing the name of the formulation under review
- Proposed Labeling
- Chemistry information: Dissolution specifications
- Additional attachments, including a formal dispute resolution request

3. Contents Of Review

This review will address the following items in the same order as below

- Cover letter (the section of my review that addresses this item will also outline the sponsor's proposal for addressing the name of the formulation under review)
- Summary of Study GAL-INT-10
- Text of initial Not-Approvable Letter (dated 12/23/04)
- Summary of meeting with sponsor on February 17, 2004
- Summary of Complete Response to Not-Approvable Letter (dated 5/27/04)

- Text of second Not-Approvable Letter (dated 7/27/04)
- Contents of Briefing Package (dated 9/3/04)
- Summary of Agency response to Dispute Resolution Request
- Chemistry data in submission
- Proposed labeling
- Edited labeling
- Comments
- Recommendation

4. Cover Letter

The cover letter accompanying this submission addresses 3 areas, which I have summarized under the following headings

4.1 History Of Application

The history of this application and the basis for the current submission are outlined.

4.2 Name Of Formulation

4.2.1 Background

In July 2004, the Division became aware of a number of reports of prescribing and dispensing errors where there was confusion between Reminyl® and Amaryl®, an oral anti-diabetic drug; at the present time, these reports include those for 2 deaths that have resulted from Amaryl® being prescribed instead of Reminyl®. These reports have been the subject of a number of discussions between the sponsor, this Division (and especially its Safety Group), and the Division of Medication Errors and Technical Support (DMETS); a Risk Management Program, albeit without a change in the name "Reminyl®," has been developed, agreed to by the Division, and initiated. However, as a result of these dispensing errors, the DMETS staff recommended earlier that the name "Reminyl® ER" not be approved for the formulation currently under review

4.2.2 Cover Letter

The section of the cover letter that addresses this matter states the following

- The sponsor states in the cover letter that the name "Reminyl® ER" should be retained for the formulation under review unless the Agency

makes a formal decision that the name "Reminyl®" should be changed; otherwise confusion is likely to result from the extended-release and immediate-release formulations having different trade names. Full justification for retaining the name "Reminyl® ER" is provided elsewhere in this submission and may be summarized as follows

- The use of a proprietary name for the Reminyl® ER formulation that is different from that for the immediate-release formulation of Reminyl® could result in both formulations being inadvertently administered concomitantly and with the potential for serious adverse events
- A change in the proprietary name for Reminyl® ER could result in the new proprietary name being confused with the trade names of other marketed drugs, and, therefore, in further marketing and dispensing errors
- Patients with Alzheimer's Disease who are already taking the Reminyl® immediate-release formulation may be reluctant to accept the Reminyl® ER formulation if the brand name has been altered
- The existing Agency and pharmaceutical industry standard for naming extended-release formulations, consists of adding a modifier (e.g., "XR," "XL," "LA," ER") to the existing base brand name of the immediate-release formulation
- The creation of a trade name for the extended-release formulation by the addition of a modifier, such as the above, to the proprietary name for the immediate-release formulation makes it less, rather than more, likely, that errors of prescribing and/or dispensing will occur, and will enhance the Risk Management Program. For example, Reminyl® ER is less likely to be confused for Amaryl®.

- The sponsor recognizes that the Risk Management Program currently being implemented for the immediate-release formulation of Reminyl® will need to be expanded to include the extended-release formulation once approved.

- Efforts to find alternatives to the name "Reminyl®" are continuing, and a new name will be implemented should the Agency determine that a name change is needed or should the Risk Management Program not result in a decrease in prescribing or dispensing errors

4.2.3 Dissolution Specifications

In an e-mail message dated February 5, 2004, the Agency had proposed dissolution specifications for the extended-release formulation of Reminyl®. The sponsor has now agreed to these specifications, which are provided in an appendix to the submission.

5. Summary Of Study GAL-INT-10

The following is an outline of the main features and key efficacy data for Study GAL-INT-10

Note that an efficacy study for the extended-release formulation was required for the following reasons

- Although the IR and ER formulations of Reminyl® were technically bioequivalent based on C_{min} and AUC, these parameters were considered significantly lower for the ER formulation
- The IR and ER formulations were not bioequivalent based on the C_{max}, which was again lower for the ER formulation (estimated ratio of means: 0.76)

The following table, derived from data contained in the original submission of this application compares pharmacokinetic parameters for the 24 mg once-daily extended-release formulation and the 12 mg BID immediate-release formulation, when both were administered in the fasting state in the pharmacokinetic study, GAL-NED-8

	Arithmetic mean ± SD		LS mean treatment ratio[a] (90% CI)
Parameters	ER capsule fasted (N = 22)	IR tablet fasted (N = 22)	ER/IR
AUC_{24h} (ng.hr/mL)	968 ± 193	1050 ± 239	93 (90 - 96)
C_{max} (ng/mL)	63.0 ± 12.0	84.3 ± 21.4	76 (71- 80)
C_{min} (ng/mL)	18.8 ± 4.6	21.7 ± 7.9	89 (83 - 96)
t_{max} (h)	4.4 ± 1.7	1.2 ± 0.6	-

[a] Parameter values were analyzed on a logarithmic scale with least-squares means were transformed back to the original scale. The t_{max} values were analyzed on the original scale using a nonparametric method.

5.1 Outline Of Study

The study is outlined in the following table

Protocol	GAL-INT-10
Objective	Efficacy and safety of Reminyl® ER in mild-to-moderate Alzheimer's Disease
Design	Randomized, double-blind, placebo-controlled, parallel-arm study
Key Inclusion Criteria	• Male or female • Probable Alzheimer's disease by NINCDS-ADRDA criteria • Mini-Mental Status Examination score 10-24 **and** ADAS-Cog score of at least 18
Dose Groups	▪ Placebo ▪ Reminyl® ER 16 to 24 mg q.d. ▪ Reminyl® IR 8 mg to 12 mg b.i.d
Duration	26 weeks
Randomized Population	Placebo → 324 patients Reminyl® ER 16 to 24 mg q.d. → 327 patients Reminyl® IR 8 mg to 12 mg b.i.d → 320 patients
Primary Efficacy Measures	▪ ADAS-Cog ▪ CIBIC-Plus
Secondary Efficacy Measures	• ADAS-Cog/13 ▪ ADAS-Cog/10 ▪ ADAS-Cog/mem

- Percentage of responders on standard ADAS-Cog using 0, 4, 7 and 10 points of improvement as cut-off
- Percentage of subjects with "improved" or "no change" on the CIBIC-Plus.
- Neuropsychiatry Inventory
- Alzheimer's Disease Cooperative Study-ADL

Primary Efficacy Analysis Methods

ADAS-Cog: ANOVA
CIBIC-Plus: Cochran-Mantel-Haenszel Test
Primary Dataset: Observed Cases
Primary Comparison: Reminyl® ER vs Placebo

5.2 Results

5.2.1 Disposition

The disposition of all randomized patients is summarized in the following table, which I have taken from the original NDA submission

Trial Termination Reasons
(Study GAL-INT-10: All Randomized Subjects Analysis Set)

All Randomized Subjects Status Termination Reasons	PLACEBO (N=324) n (%)	GAL IR (N=327) n (%)	GAL CR (N=320) n (%)
Randomized and treated	320 (99)	326 (100)	319 (100)
Completed	266 (82)	251 (77)	251 (78)
Discontinued	54 (17)	75 (23)	68 (21)
Adverse event	15 (5)	24 (7)	28 (9)
Subject withdrew consent	21 (6)	23 (7)	18 (6)
Subject non-compliant	7 (2)	14 (4)	8 (3)
Other[a]	11 (3)	14 (4)	14 (4)

[a]Other reasons for discontinuation includes subject lost to follow-up, insufficient response, death, and subject violating protocol criteria. 8 subjects died during this trial. None of these deaths were related to study medication.

5.2.2 Primary Efficacy Measures

5.2.3 ADAS-Cog

The results of the primary analysis of the ADAS-Cog are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline	305	26.1 (0.54)	--	306	27.3 (0.55)	--	300	26.3 (0.54)	--	
Week 8	289	25.8 (0.63)	0.0 (0.30)	286	25.4 (0.58)	-1.7 (0.30)	284	24.6 (0.58)	-1.5 (0.30)	0.001
Week 12	275	25.9 (0.66)	0.0 (0.32)	268	24.0 (0.57)	-2.6 (0.31)	269	23.9 (0.57)	-2.2 (0.32)	0.001
Week 26	**248**	**26.4 (0.72)**	**1.3 (0.36)**	**227**	**24.7 (0.69)**	**-1.8 (0.42)**	**240**	**24.8 (0.69)**	**-1.4 (0.34)**	**<0.001**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS)
GAL-IR vs Placebo at Week 26 p 0.001

5.2.4 CIBIC-Plus

The results of the primary analysis of the CIBIC-Plus are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)	(Cum %)	n (%)	(Cum %)	n (%)	(Cum %)	P value[a]
N at Week 26	259		240		246		
Markedly improved	3 (1.2)	(1.2)	3 (1.3)	(1.3)	3 (1.2)	(1.2)	
Moderately improved	9 (3.5)	(4.6)	14 (5.8)	(7.1)	14 (5.7)	(6.9)	
Mildly improved	41 (15.8)	(20.5)	36 (15.0)	(22.1)	43 (17.5)	(24.4)	
No change	94 (36.3)	(56.8)	93 (38.8)	(60.8)	90 (36.6)	(61.0)	
Mildly worse	70 (27.0)	(83.8)	67 (27.9)	(88.8)	69 (28.0)	(89.0)	
Moderately worse	36 (13.9)	(97.7)	25 (10.4)	(99.2)	23 (9.3)	(98.4)	
Markedly worse	6 (2.3)	(100.0)	2 (0.8)	(100.0)	4 (1.6)	(100.0)	0.086

[a] GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
Cum % cumulative percent
Note: Percentages calculated with the number of subjects at Week 26 as denominator
GAL-IR vs. Placebo at Week 26: p 0.223.

The results of the analysis of the CIBIC-Plus using the intent-to-treat (identical to classical intent-to-treat) dataset, and applying the last-observation-carried-forward (LOCF) method of imputation is in the following table, which I have copied from the original NDA submission

(Study GAL-INT-10: LOCF/CITT Data)

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)[b]	Cum %	n (%)[b]	Cum %	n (%)[b]	Cum %	P value[a]
LOCF-CITT at Endpoint[b]	301		302		296		
Markedly improved	3 (1.0)	(1.0)	3 (1.0)	(1.0)	3 (1.0)	(1.0)	
Moderately improved	11 (3.7)	(4.7)	15 (5.0)	(6.0)	14 (4.7)	(5.7)	
Mildly improved	48 (15.9)	(20.6)	46 (15.2)	(21.2)	49 (16.6)	(22.3)	
No change	111 (36.9)	(57.5)	127 (42.1)	(63.2)	114 (38.5)	(60.8)	
Mildly worse	80 (26.6)	(84.1)	78 (25.8)	(89.1)	81 (27.4)	(88.2)	
Moderately worse	41 (13.6)	(97.7)	30 (9.9)	(99.0)	29 (9.8)	(98.0)	
Markedly worse	7 (2.3)	(100.0)	3 (1.0)	(100.0)	6 (2.0)	(100.0)	0.216

[a] GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
[b] The endpoint was defined as the last available observation up to 14 days after the last dose of study medication
Cum % cumulative percent
Note Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at endpoint: p 0.144 (LOCF CITT)

5.2.5 Selected Secondary Efficacy Measures

5.2.6 ADCS-ADL

The results of the analysis of the ADCS-ADL, using the Observed Cases dataset, are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline	308	54.5 (0.87)	--	310	52.0 (0.90)	--	303	53.5 (0.88)	--	
Week 8	294	53.8 (0.98)	-0.7 (0.45)	292	52.6 (0.93)	0.9 (0.42)	290	54.5 (0.94)	0.8 (0.41)	0.013
Week 12	281	54.2 (0.99)	-0.3 (0.46)	279	52.8 (0.95)	1.1 (0.47)	276	54.1 (0.94)	0.4 (0.48)	0.321
Week 26	**258**	**52.4 (1.09)**	**-2.4 (0.60)**	**242**	**50.9 (1.12)**	**-1.0 (0.57)**	**245**	**53.9 (1.03)**	**0.0 (0.55)**	**0.003**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p=0.088.

5.2.7 Neuropsychiatry Inventory

The results of the analysis of the Neuropsychiatry Inventory, using the Observed Cases dataset, are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	P value[a]
Baseline	308	10.3 (0.69)	--	310	12.6 (0.76)	--	304	11.2 (0.79)	--	
Week 8	295	10.2 (0.70)	0.1 (0.48)	292	11.5 (0.68)	-1.2 (0.61)	291	10.4 (0.85)	-0.8 (0.53)	0.226
Week 12	281	9.5 (0.70)	-0.6 (0.56)	279	11.0 (0.75)	-1.9 (0.74)	276	9.6 (0.84)	-1.5 (0.62)	0.320
Week 26	**258**	**10.3 (0.82)**	**0.1 (0.66)**	**242**	**11.5 (0.83)**	**-1.2 (0.83)**	**245**	**10.0 (0.76)**	**-0.6 (0.69)**	**0.451**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p 0.203.

6. Text Of Initial Not-Approvable Letter

Key text from the Not Approvable action letter of 12/23/03 is reproduced verbatim below

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Lack of Substantial Evidence of Effectiveness:

The supporting clinical efficacy study GAL-INT-10 fails to provide evidence of effectiveness of extended-release galantamine.

As you know, the current regulatory standard for a demonstration of effectiveness for treatments of Alzheimer's Disease is the showing of statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure. Unfortunately, Reminyl ER was not shown to be superior to placebo on the CIBIC-Plus (for the intent-to-treat population on the last observation carried forward analysis, the between-treatment contrast yields p=0.22). Thus, based on the pre-specified primary efficacy analysis, this study must

be considered not to have shown substantial evidence of effectiveness of Reminyl® Extended-Release Capsules.

While the between-treatment comparison on the ADCS-ADL, a secondary efficacy measure that also can be acceptable as a co-primary measure of overall functioning (when so designated prospectively), was nominally significant ($p<0.001$), the negative finding on the protocol specified global measure (the CIBIC-Plus) makes relying on any analysis of further outcome variables inappropriate, because to do so inflates the overall Type I error for the study.

Before this application can be approved, you must submit a single adequate and well-controlled investigation that demonstrates superiority of Reminyl ER to placebo on two prospectively designated outcomes of the sort described above.

7. Summary Of Meeting With Sponsor: February 17, 2004

The following is an extract of the key elements of the meeting minutes

7.1.1 Discussion Points and Decisions (agreements) reached:

The meeting was requested by the sponsor to discuss the Division's December 23, 2003 Not Approvable letter for the controlled-release formulation of Reminyl®. The sponsor's and Division's viewpoints about the results of Study GAL-INT-10, and the next steps that the sponsor might take in obtaining approval of Reminyl® ER for the treatment of mild to moderate dementia of the Alzheimer's type, were discussed. The discussion included an outline of the sponsor's views as to why there was no evidence for the efficacy of either the extended-release or immediate-release formulations of Reminyl® on the CIBIC-Plus analysis in that study.

Based on that discussion, the following were the key agreements reached at the meeting

- The sponsor was advised to submit a detailed argument that addresses, on clinical and statistical grounds, why the results of the ADCS-ADL analysis for Study GAL-INT-10 should be considered in lieu of those for the CIBIC-Plus, in attempting to establish that that study is "positive".

- The sponsor proposed that another means of establishing the efficacy of the extended-release formulation of Reminyl® might be the demonstration of a correlation between exposure (based on AUC) and clinical effect, in a small study using the immediate-release formulation of Reminyl® alone, given the similarity in AUC between the 2 formulations of Reminyl®. The Division will comment more fully on such a proposal once more details are submitted. Such a proposal should clearly describe how a link between clinical effectiveness and pharmacokinetic exposure will be established.

- The sponsor proposed that a further efficacy study of the extended-release formulation of Reminyl® use the ADAS-Cog and ADCS-ADL as primary efficacy measures and be of 3 months duration. This proposal will in all likelihood be acceptable to the Division, although 3 months is the minimum duration for an efficacy study in Alzheimer's Disease.

- A submission comprising one or more of the above would be considered a response to the Division's Not-Approvable action letter.

The sponsor asked if the nomenclature to be used for the proposed new formulation in labeling – Reminyl® ER (galantamine hydrobromide) Extended Release Capsules had been agreed to by the Division of Medication Errors and Technical Support (DMETS). The Division stated that the final opinion of DMETS was pending, however, preliminarily it appeared to be acceptable.

8. Summary Of Complete Response To Initial Not-Approvable Letter

The following is my summary of the Complete Response to the initial Not-Approvable Letter. As noted earlier, the Complete Response was dated 5/27/04.

In that submission, the sponsor had performed a number of additional analyses of the CIBIC-Plus. The sponsor contended that the results of these additional analyses, together with the analyses of the ADAS-Cog and ADCS-ADL described in the original application, provided substantial evidence of the effectiveness of the Reminyl® Extended-Release formulation in mild to moderate dementia of the Alzheimer's type.

The new CIBIC-Plus analyses, which were all performed using the intent-to-treat, last-observation-carried-forward dataset (based on a Cochran-Mantel-Haenszel model using rank scores and stratified by study site) are further summarized below

- The sponsor now contended that the Cochran-Mantel-Haenszel test model used for the protocol-specified analysis of the CIBIC-Plus, which used modified ridit scores and was stratified by region (US vs. non-US), may not have been appropriate since, in that analysis, US and non-US centers were equally weighted, whereas US centers contributed 69% of those enrolled in the study. The sponsor was now of the view that, since randomization was stratified by study site, a more appropriate Cochran-Mantel-Haenszel test model for analysis of the CIBIC-Plus was one that used rank scores and was stratified by study site. The sponsor then used the latter model to demonstrate what appears to be a nominally statistically significant superiority of both the extended- and immediate-release formulations of Reminyl® over placebo on the CIBIC-Plus, with p-values of 0.030 and 0.027, respectively; these results were considered by the sponsor to more accurately reflect the overall treatment effects of both formulations of Reminyl® on that measure

- A number of baseline variables contributing to CIBIC-Plus outcome were identified by logistic regression analysis; these variables were screening Mini-Mental Status Examination score, baseline ADAS-Cog score, and prior cholinomimetic use. 3 separate analyses of the CIBIC-Plus were then performed using Cochran-Mantel-Haenszel test models; each was stratified for one of the variables considered of prognostic importance, and for country. In each of the 3 analyses the extended-release formulation of galantamine showed a nominally

statistically significant superiority to placebo; in each model, the immediate-release formulation showed either a nominally statistically significant superiority to placebo, or a superiority that approached nominal statistical significance

- Since US centers contributed about 69% of subjects to this study and since these subjects were considered by the sponsor to be more homogenous, a CIBIC-Plus analysis was performed confined to the US centers alone. This analysis, too, appeared to show a nominally statistically significant superiority of each Reminyl® formulation to placebo (p-values of 0.026 and 0.029 for the extended- and immediate-release formulations, respectively)

9. Text Of Second Not Approvable Letter

Key text from the Not Approvable action letter of 7/27/04 is reproduced verbatim below

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

You have presented numerous post hoc re-analyses of the CIBIC-Plus, all of which achieve nominal significance, and which you suggest establish that Reminyl ER is statistically significantly superior to placebo on this outcome measure. However, we believe that it is inappropriate to rely on the results of post hoc analyses unless a compelling argument can be made for disregarding the protocol-specified analyses (as we noted in our December 23, 2003 letter, relying on additional analyses in the face of a negative result on the primary analysis inflates the Type I error for the study). We do not believe that you have provided any convincing rationale for considering the protocol-specified analysis of the CIBIC-Plus to be inappropriate, and, therefore, replaceable by other analyses. Indeed, the protocol-specified analysis of this outcome measure was standard for this measure, and was reasonable in all fundamental aspects. The fact that you have identified numerous other analyses of this outcome measure that you believe, after the fact, are more appropriate, does not constitute, in our view, sufficient justification for rejecting the results of the original analysis. Therefore, given our view that the protocol-specified analysis was sound, we consider it inappropriate to accept as definitive analyses done retrospectively, after a non-significant finding on the original analysis.

Further, even if we were convinced that the protocol-specified analysis of the CIBIC-Plus was inappropriate, the alternative analyses you performed are not clearly appropriate on their own terms. For example, in the analysis in which you stratified by study site, you adopted a rule for pooling small centers that, in addition to being obviously unplanned (and therefore only one of many possible pooling schemes), was itself problematic, given that it resulted in a single "center" that was much larger than any other center in the study. The creation of this very large single "center" could have tended to obscure the effects of center in the analysis. Similarly, you have not adequately justified the appropriateness of the several other specific analyses you have performed, given the extraordinarily large number of analyses that could have been performed.

10. Summary Of Contents Of Briefing Package Dated September 3, 2004

This Briefing Package was intended to form the basis for an End-of-Review conference and its contents are summarized below

10.1 Background

The sponsor stated the following

- Galantamine extended-release capsules are a once-daily formulation consisting of 8, 16, and 24 mg of galantamine hydrobromide in each of 3 capsule sizes

- Each capsule shell contains [ ] sugar spheres coated in 3 layers, as follows

    - An inner layer containing [ ] of the total active ingredient (galantamine hydrobromide) content which is released over 24 hours

    - A [ ] membrane which provides for controlled release of galantamine via diffusion

    - An outer layer of immediate-release galantamine hydrobromide containing the remaining [ ] of the total active ingredient

- A single daily 8 mg dose of the extended-release capsule of galantamine is equivalent to 4 mg twice daily of the immediate-release tablet of galantamine, based on the AUC_{0-24}. [Reviewer's note: The bioequivalence of the 2 formulations was confirmed when the original submission under this application was reviewed]

- The efficacy of galantamine extended-release capsule was investigated in Study GAL-INT-10, a randomized, double-blind, placebo controlled study in patients with mild to moderate dementia of the Alzheimer's type. In this study,

    - The 2 co-primary efficacy endpoints were the ADAS-Cog, a cognitive measure, and the CIBIC-Plus, a functional/global instrument

    - An "acceptable alternative global/functional endpoint," the ADCS-ADL, was also included in the trial design as the key secondary endpoint (reviewer's note: there is no evidence from the study protocol that the ADCS-ADL was a pre-specified key secondary endpoint).

    - A positive control arm, immediate-release galantamine, was added after discussions with the Agency in June 1999

10.2 Current Worldwide Regulatory Status Of Galantamine ER

The sponsor stated the following

- An application for authorization to market galantamine extended-release capsules was submitted in the first quarter of 2003 in the following countries: the United States, the European Union, Switzerland, Australia, Canada, New Zealand, Mexico, and Brazil. For all submissions
    - The formulation and composition of the drug product are identical
    - The site of manufacture for the active pharmaceutical ingredient, galantamine hydrochloride, is the same
    - The site of manufacture for the extended-release pellets is the same
- The Marketing Authorization Application in the European Union was submitted under a Mutual Recognition Procedure with Sweden as the Reference Member State (the Reference Member State is responsible for coordinating the approval process with the other Member State). Sweden approved the application in March 2004 for marketing and the application was then submitted to the remaining 16 European Concerned Member States in June 2004; the procedure is due to be completed on September 29, 2004.
- Galantamine extended-release capsules have so far been approved in the following countries: Australia, Sweden, Mexico, and Singapore. The product has been launched in Sweden and Mexico
- The approval of galantamine extended-release capsules is expected shortly in [ ] The sponsor states the following: "We are currently working with the healthy authorities in Canada, Switzerland and [ ] to resolve initial concerns."

10.3 Efficacy Of Galantamine ER

The following was stated by the sponsor

10.3.1 Overview

In Study GAL-INT-10

- A statistically significant difference in favor of GAL-ER and GAL-IR was observed, in comparison with placebo, for the ADAS-Cog
- For the CIBIC-Plus, the differences between the GAL-ER group and the placebo group, and between the GAL-IR group and placebo, did not reach statistical significance, using the protocol-specified method of analysis. In

this trial, the CIBIC-Plus demonstrated reduced assay sensitivity, as demonstrated by the "weaker" results for the GAL-IR group versus the placebo group, as compared with previous trials

- A statistically significant difference in favor of GAL-ER and GAL-IR compared with placebo was observed for the key secondary endpoint, a functional scale, the ADCS-ADL

The results described below are for the intent-to-treat analyses

10.3.2 Efficacy On The ADAS-Cog

Both the ER and IR arms of the GAL-INT-10 trial showed a clear superiority to placebo ($p < 0.001$)

10.3.3 Reduced Assay Sensitivity Of The CIBIC-Plus

- The results, when the GAL-ER and GAL-IR arms of this study were compared with placebo, on the CIBIC-Plus were similar; some analyses showed a statistically significant superiority for the galantamine arms, whereas others did not

- Evidence of reduced assay sensitivity is provided by the comparison of the GAL-IR group to placebo; whereas the immediate-release formulation of galantamine showed a statistically significant superiority to placebo on all 4 earlier trials, the same comparison did not reach statistical significance in GAL-INT-10 as indicated by the following table which I have copied from the submission

Study ITT/LOCF	Formulation	Cognition (ADAS-cog/11) P value vs Plac	Global (CIBIC-plus) P value vs Plac	Function (DAD or ADCS/ADL) P value vs Plac
Gal-INT-1 (6mths)	IR	<0.001	<0.05	NS (DAD)
Gal-USA-1 (6mths)	IR	<0.001	<0.05	NS (DAD)
Gal-INT-2 (3mths)	IR	<0.05	<0.05	<0.05 (DAD)
Gal-USA-10 (5mths)	IR	<0.001	<0.05	=0.002 (ADCS-ADL)
Gal-INT-10 (6mths)	IR	<0.001	NS (p=0.144)	=0.018 (ADCS-ADL)
	ER	<0.001	NS (p=0.216)	<0.001 (ADCS-ADL)

- Factors identified as potentially accounting for the reduced assay sensitivity of the CIBIC-Plus in Study GAL-INT-10 were as follows

- The inclusion of patients with milder dementia in Study GAL-INT-10 than in previous trials
- An imbalance between treatment groups in the severity of dementia at baseline
- Failure to properly weight data from individual centers in the protocol-specified analysis

- An analysis of the impact of these factors on the CIBIC-Plus results was provided in both the original application and in the Complete Response submitted May 27, 2004

- The additional post-hoc analyses of the CIBIC-Plus for GAL-INT-10 described above more accurately reflect the study results. To summarize these analyses

  - Screening Mini-Mental Status Examination scores for patients enrolled in GAL-INT-10 ranged from 10 to 24. When analyses of the CIBIC-Plus for GAL-INT-10 were confined to the subset with a screening Mini-Mental Status Examination score of 10 to 22 (the range for those enrolled in previous trials of immediate-release galantamine), both the GAL-ER and GAL-IR groups showed a statistically significant superiority to placebo
  - Baseline demographic data indicated that more of the mildly affected patients were randomized to the placebo group than to either of the galantamine groups. Additional post-hoc analyses were performed adjusting for baseline measures of disease severity that were found to be associated with response on the CIBIC-Plus. Each of these analyses yielded results that showed a statistically significant superiority for both galantamine arms over placebo
  - The protocol-specified analysis of the CIBIC-Plus used a method that did not reflect stratified randomization and used a method that resulted in greater weight being placed on data for a non-US subject than for a US subject. When a more design-based analysis, stratifying by center, was used, the analysis yielded results that showed a nominally statistically significant superiority on the CIBIC-Plus for both the GAL-ER and GAL-IR groups

- The sponsor acknowledges that, while, for the reasons already outlined, the statistical analyses which demonstrate a treatment effect on the CIBIC-Plus more accurately reflect the study results, these results are marginal and not as strong as for previous trials of the immediate-release formulation

10.3.4 Efficacy On Clinically Relevant Endpoints

- The current regulatory standard requires that the efficacy of drugs in the treatment of dementia of the Alzheimer's type be demonstrated by showing statistically significant results favoring the drug on each of 2 co-primary efficacy endpoints
    - A cognitive measure (the ADAS-Cog scale is generally recognized as an appropriate endpoint for assessing the effect on cognition)
    - A global or functional domain
- The ADAS-Cog scale is generally recognized as an appropriate endpoint for assessing the effect of a drug on cognition in dementia of the Alzheimer's type
- The 2 most commonly utilized global/functional scales are the CIBIC-Plus and ADCS-ADL. Further,
    - In GAL-INT-10, the choice of global/functional primary efficacy endpoint was arbitrary and the CIBIC-Plus was selected based on prior experience
    - The ADCS-ADL would have been equally acceptable as a co-primary endpoint, had it been specified prospectively
    - In this study, the ADCS-ADL demonstrated statistically significant evidence of efficacy for both the extended- and immediate-release formulations of galantamine ($p < 0.001$ and $p = 0.018$, respectively, at endpoint)

10.4 Sponsor's Conclusions

- The overall results of GAL-INT-10 support the effectiveness of GAL-ER in the treatment of mild to moderate dementia of the Alzheimer's type
- The CIBIC-Plus measure in this trial exhibited lowest assay sensitivity as demonstrated by the reduced effect of GAL-IR compared with previous trials. The reduced assay sensitivity is explicable by factors unique to the GAL-INT-10 trial
- Despite the reduced assay sensitivity, statistically significant positive results favoring the GAL-ER formulation over placebo were obtained on a cognitive endpoint (ADAS-Cog) and a functional outcome (ADCS-ADL), which are consistent with current regulatory standards required for the approval of such drugs

11. Summary Of Agency Response To Dispute Resolution Request

A Dispute Resolution Request package was submitted to Office of Drug Evaluation I on September 27, 2004. The package contained the following items

- Formal dispute resolution request, containing the sponsor's explanation for how evidence for the effectiveness of the Reminyl® ER formulation has already been demonstrated

- Additional items (documents previously submitted)

    - NDA 21615, as submitted on 2/23/03
    - Initial Not-Approvable letter, received by sponsor on 12/23/03
    - NDA 21615 End of Review Conference Briefing Package, submitted on 1/30/04
    - Agency minutes from the End of Review Conference, held on 2/17/04
    - NDA 21615 Resubmission to a Pending Application, and Complete Response to Not-Approvable letter of 12/23/03. Resubmission date 5/27/04
    - Second Not-Approvable letter, received by sponsor on 7/27/04
    - NDA 21615 End of Review Conference Briefing Package, submitted on 9/3/04

Dr Robert Temple, Director, Office Of Drug Evaluation I, has responded to this request in a memorandum dated October 26, 2004. Please refer to his memorandum for full details. Key elements of that memorandum are summarized below.

In his memorandum, Dr Temple has concluded that the sponsor has provided substantial evidence of the effectiveness or Reminyl® Extended-Release for the treatment of mild to moderate dementia of the Alzheimer's type. His basis for that conclusion is summarized as follows

- Galantamine is a well-evaluated drug and known to be effective as an immediate-release formulation in the treatment of Alzheimer's Disease; under those circumstances, an effect on the ADAS-Cog should be considered sufficient to establish that the extended-release formulation of that drug is effective

- The effect of the Reminyl® Extended-Release on the ADCS-ADL strongly supports that on the ADAS-Cog, despite not being essential to establish efficacy, and despite the ADCS-ADL not being a pre-specified primary efficacy measure

- The lack of an effect of Reminyl® Extended-Release on the CIBIC-Plus is greatly mitigated by the failure of the immediate-release formulation to have an effect on that measure in the GAL-INT-10 trial, given that there is no doubt from previous studies that the immediate-release formulation (and thus the galantamine molecule itself) affects both cognition and global function beneficially

- Several of the alternative analyses of the CIBIC-Plus conducted by the sponsor, and in particular the analysis which was stratified by center, have considerable merit, even if they are post-hoc

12. Chemistry Data (Dissolution Specifications) In Submission

12.1 Data In Submission

Dissolution specifications for the drug product (in accordance with Agency recommendations) have been supplied under 2 headings

- Control of critical steps and intermediates: galantamine hydrobromide controlled-release capsules equivalent to 8 mg, 16 mg, and 24 mg of galantamine

- Specifications: galantamine hydrobromide controlled-release capsules equivalent to 8 mg, 16 mg, and 24 mg of galantamine

Please see the submission for further details

12.2 Agency Review Of Data In Submission

The (interim) dissolution specifications recommended by the Agency, and agreed to by the sponsor in this submission, have been reviewed by Dr Ronald Kavanagh of the Office of Clinical Pharmacology and Biopharmaceutics.

Dr Kavanagh considers the application acceptable and has the following comments and recommendations

- He has recommended specific changes to the following sections of the sponsor's labeling proposal

    - Clinical Pharmacology: Metabolism and Elimination
    - Precautions
    - Dosage and Administration

- He provides full details of the interim dissolution specifications - these details are to be conveyed to the sponsor (these are more detailed than the interim dissolution specifications contained in the submission)

- He has asked that the sponsor be requested to make a Phase IV commitment to provide additional dissolution data within 6 months of approval in order to set final dissolution specifications (the specifics of these data are contained in his review)

13. Proposed Labeling

Changes have been proposed to the following sections of the currently-approved labeling for Reminyl®

- Description
- Clinical Pharmacology: Metabolism and Elimination
- Clinical Pharmacology: Clinical Trials
- Precautions
- Adverse Reactions
- Dosage and Administration
- How Supplied
- Storage and Handling

Changes proposed for each of these sections are outlined below (the changes use red strikethrough and underlined text)

[

]

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

[

]

14. Edited Labeling

The following initial proposal for changes to the current approved labeling for Reminyl® has been conveyed to the sponsor by the Division on December 1, 2004, in response to the sponsor's proposal contained in this submission.

Note that no changes have been made by the Division to sponsor's proposed changes to the Description, How Supplied, and Storage and Handling sections.

Changes proposed for each of these sections are outlined below (the changes use red strikethrough and underlined text)

[

]

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

] At the time of completion of this review, discussions between the Agency and sponsor regarding this transition were not complete. It was agreed, however, that this application would be approved without a firm proprietary name being decided upon, but with the launch of the new formulation occurring only after the proposed new proprietary name was agreed on.

It was also decided, based on communications between the Division and sponsor, that the extended-release formulation of galantamine would have labeling that was separate from the currently marketed immediate-release tablet and oral solution formulations]

The sponsor's modifications to the Division's labeling proposal of December 1, 2004 consist of

- Providing a proposed label for the extended-release capsule formulation only, while retaining all non-clinical and clinical information relevant to galantamine per se (and therefore to the extended-release formulation) that was based on studies using the immediate-release formulation

- Substituting "galantamine" or "galantamine immediate-release tablets" for REMINYL®, where appropriate

- Substituting "TRADEMARK extended release capsules" for "REMINYL® extended release capsules" [this substitution is intended to remain until such time as a new proprietary name is approved, when the product label is revised further]

- Making very minor modifications to the Clinical Trials, Precautions, Special Populations, and Adverse Reactions sections without changing the meaning of the text contained in those sections in any significant way

Note that the sponsor had initially failed to include the following statement in the Dosage and Administration section of the proposed labeling: "TRADEMARK should be administered once daily in the morning, preferably with food" (and thereby not provided any indication of how frequently, or what time of day, galantamine extended-release capsules should be taken, and how the intake of that formulation should relate to food). This omission was later corrected by the sponsor.

The sponsor's labeling proposal of December 10, 2004, is therefore acceptable.

16. Comments

- This submission is a Complete Response to the second of two Not-Approvable action letters that have been issued by the Agency in response to this application and its Amendments.

- This New Drug Application, originally submitted on 2/24/03, seeks the approval of Reminyl® Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. The Division responded to that application with a Not-Approvable action letter on

12/23/03. Subsequently, the sponsor submitted a Complete Response to the Not-Approvable letter on 5/27/04, to which the Division responded with a further Not-Approvable action letter on 7/27/04; prior to the Complete Response being submitted, a meeting was held between the Division and sponsor on 2/17/04, to discuss the initial Not-Approvable action letter.

- Reminyl® Extended-Release Capsules are intended for once-daily administration, in contrast to the currently-approved immediate-release tablet and oral solution formulations which are recommended as twice daily doses.

- The evidence in the original submission under this NDA, in support of the efficacy of Reminyl® Extended Release capsules, consisted of a single study, GAL-INT-10, the design and results of which are further described below

    - This was a randomized, double-blind, placebo-controlled, parallel-arm study.

    - The study had 3 treatment arms: Reminyl® Extended-Release capsules 16 to 24 mg once daily; immediate-release Reminyl® tablets 8 to 12 mg twice daily; and placebo. The period of double-blind, parallel-arm treatment in this study was 26 weeks

    - Key inclusion criteria were the diagnosis of probable Alzheimer's Disease; a Mini-Mental Status Examination score at screening of 10 -24; and an Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) score at screening of at least 18.

    - 971 patients were enrolled in the study and randomized in about equal proportions to the 3 treatment groups

    - The primary efficacy measures were the ADAS-Cog and the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). There were 10 secondary efficacy measures, including the Alzheimer's Disease Cooperative Study – Activities Of Daily Living (ADCS-ADL) scale.

    - The primary efficacy analysis was performed, as specified in the protocol, on the observed cases dataset at Month 6, and the primary comparison was between the Reminyl® Extended-Release and placebo groups, again as specified in the protocol. The difference in this dataset, between the Reminyl® Extended-Release and placebo groups, for the mean change from baseline in the ADAS-Cog, was 2.7 points, and favored galantamine ($p \leq 0.001$). For the CIBIC-Plus, using the same dataset, 61% of those treated with extended-release galantamine, and 56.8% of those treated with placebo, either improved or showed no change ($p = 0.086$, when changes on the full 7-point scale were compared). Similar results were seen, on both primary efficacy parameters, when the Reminyl® Extended-Release and placebo groups were compared for the last-

observation-carried-forward and classical intent-to-treat datasets; the results were also similar when the immediate-release Reminyl® and placebo groups were compared.

- The protocol specified that evidence of the efficacy of extended-release galantamine was to be based on demonstrating a statistically significant ($p < 0.05$) treatment difference on both primary efficacy measures between that galantamine group and the placebo group.

- A comparison of the treatment groups on mean change from baseline to Week 26 scores for the ADCS-ADL using the observed cases dataset, revealed a mean difference between the Reminyl® Extended-Release and placebo groups of 2.4 points favoring galantamine ($p = 0.003$); a p-value of < 0.001 was seen in each instance when these groups were compared using the last-observed-carried-forward and classical intent-to-treat datasets

- The Agency's original Not Approvable action (12/23/03) on this application was based on the following

  - The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two prospectively-designated co-primary efficacy measures: a cognitive measure and a global/functional measure. In GAL-INT-10, Reminyl® Extended-Release capsules were not demonstrated to be superior to placebo on the CIBIC-Plus. Therefore this study could not be said to have shown substantial evidence of effectiveness

  - The comparison of the Reminyl® Extended-Release and placebo groups on the ADCS-ADL, a measure that could also be acceptable as a co-primary measure of efficacy, if prospectively designated, showed a nominally statistically significant treatment difference that favored the Reminyl® Extended-Release group. However, the negative finding on the protocol-specified global measure, the CIBIC-Plus, made relying on the results of any secondary efficacy measures inappropriate

- In the earlier Complete Response (5/27/04) to the initial Not-Approvable action, the sponsor had performed a number of additional analyses of the CIBIC-Plus. The sponsor contended that the results of these additional analyses, together with the analyses of the ADAS-Cog and ADCS-ADL described in the original application, provided substantial evidence of the effectiveness of the Reminyl® Extended-Release formulation in mild to moderate dementia of the Alzheimer's type.

  The new (post-hoc) CIBIC-Plus analyses, which were all performed using the intent-to-treat, last-observation-carried-forward dataset are briefly listed below, but are further described in Section 8. All analyses showed a

nominally statistically significant superiority of both the ER and IR formulations of galantamine over placebo

- An analysis in which protocol-specified Cochran-Mantel-Haenszel test model which was stratified by region (US vs. non-US) was modified to one stratified by study site.

- Analyses in which 3 baseline variables (screening Mini-Mental Status Examination score, baseline ADAS-Cog score, and prior cholinomimetic use) contributing to CIBIC-Plus outcome were identified by logistic regression analysis and were then each used as stratification factors in the same Cochran-Mantel-Haenszel model.

- An analysis confined to the US centers alone.

- The Agency's second Not-Approvable action, dated 7/27/04, was based on the following

  - The failure to provide a convincing argument for why the protocol-specified analysis of the CIBIC-Plus should be considered inappropriate, and, should, therefore be replaced by the post-hoc re-analyses of that measure, especially since the protocol-specified analysis of this outcome measure was standard for this measure, and was reasonable in all key aspects. In addition, as outlined in the earlier Not-Approvable action letter, the use of additional analyses after a negative primary analysis would inflate the Type I error for the study.

  - Concern that the alternative analyses proposed by the sponsor may not have been entirely appropriate in themselves

- The current submission relies on the following

  - The original submission under this application
  - A meeting held with the Division on February 17, 2004
  - The earlier Complete Response to the initial Not-Approvable letter
  - An End-of-Review Conference Briefing package submitted on September 3, 2004
  - The Dispute Resolution Request package submitted to Dr R. Temple on September 27, 2004 and Dr Temple's response in which he concluded that the key deficiency in this application, the lack of substantial evidence of efficacy, had been adequately addressed in the original NDA and subsequent Amendments. His basis for that conclusion was as follows

    - Since the galantamine is known to be effective (as an immediate-release formulation) in the treatment of Alzheimer's Disease, an effect on the ADAS-Cog alone should be sufficient to establish that the extended-release formulation of that drug is effective

    - The effect of the Reminyl® Extended-Release on the ADCS-ADL strongly supports that on the ADAS-Cog despite the ADCS-ADL not being a pre-specified primary efficacy measure

- The lack of an effect of Reminyl® Extended-Release on the CIBIC-Plus is mitigated by the failure of the immediate-release formulation to have an effect on that measure in the GAL-INT-10 trial, especially since there is no doubt from previous studies (with the immediate-release formulation) that the galantamine is a drug that affects both cognition and global function beneficially

- Several of the alternative, albeit post-hoc, analyses of the CIBIC-Plus conducted by the sponsor have considerable merit.

- My overall view of this application remains as follows

  - The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure.

  - The protocol for the GAL-INT-10 study specified that the efficacy of the extended-release galantamine formulation in that study was to be based on demonstrating a statistically significant superiority to placebo on both primary efficacy measures, the ADAS-Cog and CIBIC-Plus.

  - Since the treatment differences between extended-release galantamine and placebo on the CIBIC-Plus did not achieve or approach statistical significance using the protocol-specified analysis, this study has, according to all intents and purposes, failed to establish evidence for the efficacy of extended-release Reminyl® in mild-to-moderate Alzheimer's Disease.

  - The comparison of the Reminyl® Extended-Release and placebo groups on the ADCS-ADL showed a nominally statistically significant treatment difference favoring the Reminyl® Extended-Release group over placebo. While the ADCS-ADL would have been acceptable as a co-primary measure of efficacy in lieu of the CIBIC-Plus, if prospectively designated, it was one of 10 secondary efficacy measures in this study (albeit the only secondary efficacy measure other than the dichotomized CIBIC-Plus that could be considered a global or functional instrument), and these measures were subject to 90 separate analyses. Moreover, the lack of any evidence of efficacy on the protocol-specified global co-primary efficacy measure, the CIBIC-Plus, made relying on the results of any secondary efficacy measures inappropriate

  - Since the extended-release formulation of galantamine is intended to be taken once daily and will therefore be more convenient to use than the immediate-release formulation, for which twice daily dosing is recommended, the former formulation is likely to be used much frequently than the latter, when marketed. It is therefore especially important that evidence for the efficacy of the extended-release formulation should be clearly demonstrated prior to marketing approval being granted; such evidence is currently lacking.

- While the sponsor has also performed further analyses of the CIBIC-Plus, using Cochran-Mantel-Haenszel test models different from those used for the primary efficacy analyses, and although these further analyses have shown nominally statistically significant differences favoring extended-release galantamine over placebo, the new analyses are post-hoc, and their results are model-dependent, confined to a subgroup, or otherwise deficient. For those results that are model-dependent, the sponsor has not provided convincing evidence that the models that show "positive" results are more appropriate to use than those that do not. These analyses cannot therefore be considered to have met the "substantial evidence of effectiveness" standard

- I have noted Dr Temple's conclusion that, based on the results of Study GAL-INT-10, the extended-release formulation of Reminyl® has substantial evidence of efficacy (in the treatment of mild to moderate dementia of the Alzheimer's type), and have fully reviewed his reasons for arriving at that conclusion. I must, however, respectfully disagree with his conclusion for the following reasons

  - The effects of the immediate-release formulation of galantamine on the ADAS-Cog in the key studies that were the basis for approval of that formulation were small (indeed minimal), albeit statistically significant, when compared with placebo; but for the "positive" effects of this formulation on the global primary efficacy measure in these studies, the CIBIC-Plus, it would have been very difficult to conclude that the effects on the ADAS-Cog were clinically meaningful. On the same basis, the lack of a statistically significant benefit for the immediate-release formulation on the CIBIC-Plus in Study GAL-INT-10, could legitimately be interpreted as indicating that the small effect of that formulation on the ADAS-Cog, while statistically significant, was not clinically meaningful in that study, notwithstanding the effects of that formulation on both measures in earlier efficacy studies; this interpretation is, in my view, no less legitimate that concluding that because the efficacy of the immediate-release galantamine formulation had clearly been demonstrated on both the ADAS-Cog and CIBIC-Plus is early studies, the lack of an effect on the CIBIC-Plus in Study GAL-INT-10 may be discounted. The benefits of galantamine and of other approved drugs in the acetylcholinesterase inhibitor class are, in fact, marginal enough that variability in their efficacy across studies may be expected if a sufficiently large number of studies are done.

  - The CIBIC-Plus is a widely used and accepted primary efficacy measure in clinical drug trials in Alzheimer's Disease, including trials that have been the basis for approval of several drugs other than galantamine, and it is not easy to discount the lack of effect seen on this measure for both galantamine formulations in GAL-INT-10 as being an anomaly and not a true drug effect

  - While the ADCS-ADL may be appropriate, if prospectively designated as a primary efficacy measure, for use as a means of demonstrating that any

effect on the ADAS-Cog is clinically meaningful, it is inconsistent with our usual standard for drugs designated for the same indication, indeed unprecedented, to use it for the same purpose in Study GAL-INT-10, when the ADCS-ADL was one of several secondary efficacy measures (none of which were prospectively designated as being key), and when the results of the primary efficacy analysis were negative.

- It is increasingly likely that the extended-release formulation of galantamine will be the main, if not the sole, formulation, of that drug prescribed. Approval of that formulation should therefore, in my opinion, meet the same, albeit minimal, standard required for the immediate-release formulation

- In summary, I believe that substantial evidence for the efficacy of the extended-release formulation of galantamine in the treatment of mild to moderate dementia of the Alzheimer's type has NOT been established through Study GAL-INT-10. I, therefore, continue to recommend that the extended-release formulation of galantamine not be approved for marketing. However, given Dr Temple's response to the Dispute Resolution Request submitted by the sponsor, and his overriding determination that the immediate-release formulation of galantamine has shown substantial evidence of efficacy, the Division has proceeded with reaching agreement with the sponsor on the text of the product labeling for this formulation (see below).

- As indicated earlier in this review, the Agency has received a number of reports of prescribing and dispensing errors apparently resulting from confusion between the names "Reminyl®" and "Amaryl®;" Amaryl® is an oral anti-diabetic drug; at least 2 of these instances have led to patient deaths. In response to these errors, the DMETS staff recommended earlier that the name "Reminyl® ER" not be approved for the formulation currently under review.

  A Risk Management Program that attempts to address these errors has already been instituted in consultation with this Division.

  In a communication dated December 2, 2004, the sponsor had further proposed that the extended-release formulation of Reminyl® be launched under a new proprietary name; based on the same communication, the sponsor appeared to planning to gradually phase out the immediate-release and oral solution formulations of Reminyl® (which was continue to be marketed under the current proprietary name, until all supplies were depleted) over 6 months. However, in subsequent contacts, the sponsor indicated that the immediate-release and oral solution would not be phased out, but would continue to be marketed under a new proprietary name. At the time of completion of this review, discussions between the Agency and sponsor regarding this transition were not complete. It was

agreed, however, that this application would be approved without a firm proprietary name being decided upon, but with the launch of the new formulation occurring only after a to-be-proposed new proprietary name was agreed on.

- The Division and sponsor have reached agreement on product labeling for extended-release galantamine, which is to be exclusive to that formulation. In that product labeling, the formulation to be approved is referred to as "TRADEMARK extended release capsules" pending Agency approval of a new proprietary name.

17. Recommendation

I continue to recommend that this application not be approved

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 12/14/04
cc:
HFD-120
NDA 21615

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ranjit Mani
12/14/04 03:08:52 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21615**
Sponsor:	**Johnson & Johnson**
Drug:	**Reminyl® ER**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Briefing Document**
Correspondence Date:	**9/3/04**
Date Received / Agency:	**9/3/04**
Date Review Completed	**11/10/04**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission contains a Briefing Package for a meeting between the Agency and sponsor to be held on 9/22/04. The purpose of the meeting, according to the sponsor, is to discuss what further steps need to be taken for the above application to be approved.

NDA 21615, originally submitted on 2/24/03, sought the approval of Reminyl® Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. The Division responded to that application with a Not-Approvable action letter on 12/23/03. Subsequently, the sponsor submitted a Complete Response to the Not-Approvable letter on 5/27/04, to which the Division responded with a further Not-Approvable action letter on 7/27/04; prior to the Complete Response being submitted, a meeting was held between the Division and sponsor on 2/17/04, to discuss the initial Not-Approvable action letter.

The original application under NDA 21615 was based mainly on the results of one Phase III randomized, double-blind, placebo-controlled efficacy study (GAL-INT-10), an uncontrolled, open-label extension to GAL-INT-10, and several pharmacokinetic trials.

Four-Month and Seven-Month Safety Updates to the original application under NDA 21615 were submitted on 6/19/03 and 10/3/03, respectively, and were reviewed with the original application.

Reminyl® Extended-Release capsules have been developed under Investigational New Drug Application (IND) 61703. The immediate-release tablet and oral solutions formulations of galantamine, Reminyl®, had earlier been developed by this sponsor for the treatment of Alzheimer's Disease under IND 51538. NDAs 21169 and 21224, for the use of the immediate-release tablet and oral solution forms, respectively, of galantamine in the treatment of mild-to-moderate dementia of the Alzheimer's type were approved in 2001. Later in 2001, a supplemental NDA (SCM-001) was approved for the use of immediate-release tablet and oral solution formulations of synthetic galantamine (for the treatment of mild-to-moderate dementia of the Alzheimer's type), instead of the plant-derived drug substance approved earlier.

The sponsor had earlier proposed that Reminyl® Extended-Release capsules be administered once daily, whereas it is recommended in the package insert for the currently approved immediate-release formulation of Reminyl® that that drug formulation be administered twice daily.

Please see my reviews of the original application under NDA 21615, the sponsor's Briefing Package for the meeting held on 2/17/04, and the Complete Response dated 5/27/04, for further details.

The extended-release formulation of Reminyl® is referred to in this review, interchangeably, as "Reminyl® ER", "GAL-ER", or "GAL-CR". The immediate-release formulation is referred to in this review, interchangeably, as "Reminyl® IR" or "GAL-IR". The terms "IR" and "ER" are used in this review as a substitute for "immediate-release" and "extended-release," respectively.

2. Contents Of Current Submission

The current submission contains the following

- Cover letter
- Briefing Package consisting of the following subheadings
  - Background
  - Current world-wide regulatory status
  - Efficacy of Galantamine ER
    - Efficacy in the co-primary endpoint ADAS-Cog/11
    - Reduced assay sensitivity of the CIBIC-Plus
    - Efficacy on clinically relevant endpoints
  - Conclusion

3. Contents Of Review

This review will address the following items in the same order as below

- Summary of Study GAL-INT-10
- Text of initial Not-Approvable Letter (dated 12/23/04)
- Summary of meeting with sponsor on February 17, 2004
- Summary of Complete Response to Not-Approvable Letter (dated 5/27/04)
- Text of second Not-Approvable Letter (dated 7/27/04)
- Contents of current submission

4. Summary Of Study GAL-INT-10

The following is an outline of the main features and key efficacy data for Study GAL-INT-10

4.1 Outline Of Study

The study is outlined in the following table

Protocol	GAL-INT-10
Objective	Efficacy and safety of Reminyl® ER in mild-to-moderate Alzheimer's Disease
Design	Randomized, double-blind, placebo-controlled, parallel-arm study
Key Inclusion Criteria	• Male or female • Probable Alzheimer's disease by NINCDS-ADRDA criteria • Mini-Mental Status Examination score 10-24 **and** ADAS-Cog score of at least 18
Dose Groups	▪ Placebo ▪ Reminyl® ER 16 to 24 mg q.d. ▪ Reminyl® IR 8 mg to 12 mg b.i.d
Duration	26 weeks
Randomized Population	Placebo → 324 patients Reminyl® ER 16 to 24 mg q.d. → 327 patients Reminyl® IR 8 mg to 12 mg b.i.d → 320 patients
Primary Efficacy Measures	▪ ADAS-Cog ▪ CIBIC-Plus
Secondary Efficacy Measures	▪ ADAS-Cog/13 ▪ ADAS-Cog/10 ▪ ADAS-Cog/mem ▪ Percentage of responders on standard ADAS-Cog using 0, 4, 7 and 10 points of improvement as cut-off ▪ Percentage of subjects with "improved" or "no change" on the CIBIC-Plus. ▪ Neuropsychiatry Inventory ▪ Alzheimer's Disease Cooperative Study-ADL
Primary Efficacy Analysis Methods	ADAS-Cog: ANOVA CIBIC-Plus: Cochran-Mantel-Haenszel Test Primary Dataset: Observed Cases Primary Comparison: Reminyl® ER vs Placebo

4.2 Results

4.2.1 Disposition

The disposition of all randomized patients is summarized in the following table, which I have taken from the original NDA submission

Trial Termination Reasons
(Study GAL-INT-10: All Randomized Subjects Analysis Set)

All Randomized Subjects Status Termination Reasons	PLACEBO (N=324) n (%)	GAL IR (N=327) n (%)	GAL CR (N=320) n (%)
Randomized and treated	320 (99)	326 (100)	319 (100)
Completed	266 (82)	251 (77)	251 (78)
Discontinued	54 (17)	75 (23)	68 (21)
Adverse event	15 (5)	24 (7)	28 (9)
Subject withdrew consent	21 (6)	23 (7)	18 (6)
Subject non-compliant	7 (2)	14 (4)	8 (3)
Other[a]	11 (3)	14 (4)	14 (4)

[a]Other reasons for discontinuation includes subject lost to follow-up, insufficient response, death, and subject violating protocol criteria. 8 subjects died during this trial. None of these deaths were related to study medication.

4.2.2 Primary Efficacy Measures

4.2.3 ADAS-Cog

The results of the primary analysis of the ADAS-Cog are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set - OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline	305	26.1 (0.54)	--	306	27.3 (0.55)	--	300	26.3 (0.54)	--	
Week 8	289	25.8 (0.63)	0.0 (0.30)	286	25.4 (0.58)	-1.7 (0.30)	284	24.6 (0.58)	-1.5 (0.30)	<0.001
Week 12	275	25.9 (0.66)	0.0 (0.32)	268	24.0 (0.57)	-2.6 (0.31)	269	23.9 (0.57)	-2.2 (0.32)	<0.001
Week 26	**248**	**26.4 (0.72)**	**1.3 (0.36)**	**227**	**24.7 (0.69)**	**-1.8 (0.42)**	**240**	**24.8 (0.69)**	**-1.4 (0.34)**	**<0.001**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS)
GAL-IR vs Placebo at Week 26 p< 0.001

4.2.4 CIBIC-Plus

The results of the primary analysis of the CIBIC-Plus are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)	(Cum %)	n (%)	(Cum %)	n (%)	(Cum %)	P value[a]
N at Week 26	259		240		246		
Markedly improved	3 (1.2)	(1.2)	3 (1.3)	(1.3)	3 (1.2)	(1.2)	
Moderately improved	9 (3.5)	(4.6)	14 (5.8)	(7.1)	14 (5.7)	(6.9)	
Mildly improved	41 (15.8)	(20.5)	36 (15.0)	(22.1)	43 (17.5)	(24.4)	
No change	94 (36.3)	(56.8)	93 (38.8)	(60.8)	90 (36.6)	(61.0)	
Mildly worse	70 (27.0)	(83.8)	67 (27.9)	(88.8)	69 (28.0)	(89.0)	
Moderately worse	36 (13.9)	(97.7)	25 (10.4)	(99.2)	23 (9.3)	(98.4)	
Markedly worse	6 (2.3)	(100.0)	2 (0.8)	(100.0)	4 (1.6)	(100.0)	0.086

[a] GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
Cum % cumulative percent
Note: Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at Week 26: p 0.223.

The results of the analysis of the CIBIC-Plus using the intent-to-treat (identical to classical intent-to-treat) dataset, and applying the last-observation-carried-forward (LOCF) method of imputation is in the following table, which I have copied from the original NDA submission

(Study GAL-INT-10: LOCF-CITT Data)

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)[b]	Cum %	n (%)[b]	Cum %	n (%)[b]	Cum %	P value[a]
LOCF CITT at Endpoint[b]	301		302		296		
Markedly improved	3 (1.0)	(1.0)	3 (1.0)	(1.0)	3 (1.0)	(1.0)	
Moderately improved	11 (3.7)	(4.7)	15 (5.0)	(6.0)	14 (4.7)	(5.7)	
Mildly improved	48 (15.9)	(20.6)	46 (15.2)	(21.2)	49 (16.6)	(22.3)	
No change	111 (36.9)	(57.5)	127 (42.1)	(63.2)	114 (38.5)	(60.8)	
Mildly worse	80 (26.6)	(84.1)	78 (25.8)	(89.1)	81 (27.4)	(88.2)	
Moderately worse	41 (13.6)	(97.7)	30 (9.9)	(99.0)	29 (9.8)	(98.0)	
Markedly worse	7 (2.3)	(100.0)	3 (1.0)	(100.0)	6 (2.0)	(100.0)	0.216

[a] GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
[b] The endpoint was defined as the last available observation up to 14 days after the last dose of study medication
Cum % cumulative percent.
Note Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at endpoint: p 0.144 (LOCF CITT)

4.2.5 Selected Secondary Efficacy Measures

4.2.6 ADCS-ADL

The results of the analysis of the ADCS-ADL, using the Observed Cases dataset, are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline	308	54.5 (0.87)	--	310	52.0 (0.90)	--	303	53.5 (0.88)	--	
Week 8	294	53.8 (0.98)	-0.7 (0.45)	292	52.6 (0.93)	0.9 (0.42)	290	54.5 (0.94)	0.8 (0.41)	0.013
Week 12	281	54.2 (0.99)	-0.3 (0.46)	279	52.8 (0.95)	1.1 (0.47)	276	54.1 (0.94)	0.4 (0.48)	0.321
Week 26	**258**	**52.4 (1.09)**	**-2.4 (0.60)**	**242**	**50.9 (1.12)**	**-1.0 (0.57)**	**245**	**53.9 (1.03)**	**0.0 (0.55)**	**0.003**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS)
GAL-IR vs. Placebo at Week 26: p=0.088.

4.2.7 Neuropsychiatry Inventory

The results of the analysis of the Neuropsychiatry Inventory, using the Observed Cases dataset, are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	P value[a]
Baseline	308	10.3 (0.69)	--	310	12.6 (0.76)	--	304	11.2 (0.79)	--	
Week 8	295	10.2 (0.70)	0.1 (0.48)	292	11.5 (0.68)	-1.2 (0.61)	291	10.4 (0.85)	-0.8 (0.53)	0.226
Week 12	281	9.5 (0.70)	-0.6 (0.56)	279	11.0 (0.75)	-1.9 (0.74)	276	9.6 (0.84)	-1.5 (0.62)	0.320
Week 26	**258**	**10.3 (0.82)**	**0.1 (0.66)**	**242**	**11.5 (0.83)**	**-1.2 (0.83)**	**245**	**10.0 (0.76)**	**-0.6 (0.69)**	**0.451**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p 0.203.

5. Text Of Initial Not-Approvable Letter

Key text from the Not Approvable action letter of 12/23/03 is reproduced verbatim below

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Lack of Substantial Evidence of Effectiveness:

The supporting clinical efficacy study GAL-INT-10 fails to provide evidence of effectiveness of extended-release galantamine.

As you know, the current regulatory standard for a demonstration of effectiveness for treatments of Alzheimer's Disease is the showing of statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure. Unfortunately, Reminyl ER was not shown to be superior to placebo on the CIBIC-Plus (for the intent-to-treat population on the last observation carried forward analysis, the between-treatment contrast yields p=0.22). Thus, based on the pre-specified primary efficacy analysis, this study must

be considered not to have shown substantial evidence of effectiveness of Reminyl® Extended-Release Capsules.

While the between-treatment comparison on the ADCS-ADL, a secondary efficacy measure that also can be acceptable as a co-primary measure of overall functioning (when so designated prospectively), was nominally significant ($p<0.001$), the negative finding on the protocol specified global measure (the CIBIC-Plus) makes relying on any analysis of further outcome variables inappropriate, because to do so inflates the overall Type I error for the study.

Before this application can be approved, you must submit a single adequate and well-controlled investigation that demonstrates superiority of Reminyl ER to placebo on two prospectively designated outcomes of the sort described above.

6. Summary Of Meeting With Sponsor: February 17, 2004

The following is an extract of the key elements of the meeting minutes

6.1.1 Discussion Points and Decisions (agreements) reached:

The meeting was requested by the sponsor to discuss the Division's December 23, 2003 Not Approvable letter for the controlled-release formulation of Reminyl®. The sponsor's and Division's viewpoints about the results of Study GAL-INT-10, and the next steps that the sponsor might take in obtaining approval of Reminyl® ER for the treatment of mild to moderate dementia of the Alzheimer's type, were discussed. The discussion included an outline of the sponsor's views as to why there was no evidence for the efficacy of either the extended-release or immediate-release formulations of Reminyl® on the CIBIC-Plus analysis in that study.

Based on that discussion, the following were the key agreements reached at the meeting

- The sponsor was advised to submit a detailed argument that addresses, on clinical and statistical grounds, why the results of the ADCS-ADL analysis for Study GAL-INT-10 should be considered in lieu of those for the CIBIC-Plus, in attempting to establish that that study is "positive".

- The sponsor proposed that another means of establishing the efficacy of the extended-release formulation of Reminyl® might be the demonstration of a correlation between exposure (based on AUC) and clinical effect, in a small study using the immediate-release formulation of Reminyl® alone, given the similarity in AUC between the 2 formulations of Reminyl®. The Division will comment more fully on such a proposal once more details are submitted. Such a proposal should clearly describe how a link between clinical effectiveness and pharmacokinetic exposure will be established.

- The sponsor proposed that a further efficacy study of the extended-release formulation of Reminyl® use the ADAS-Cog and ADCS-ADL as primary efficacy measures and be of 3 months duration. This proposal will in all likelihood be acceptable to the Division, although 3 months is the minimum duration for an efficacy study in Alzheimer's Disease.

- A submission comprising one or more of the above would be considered a response to the Division's Not-Approvable action letter.

The sponsor asked if the nomenclature to be used for the proposed new formulation in labeling – Reminyl® ER (galantamine hydrobromide) Extended Release Capsules had been agreed to by the Division of Medication Errors and Technical Support (DMETS). The Division stated that the final opinion of DMETS was pending, however, preliminarily it appeared to be acceptable.

7. Summary Of Complete Response To Initial Not-Approvable Letter

The following is my summary of the Complete Response to the initial Not-Approvable Letter. As noted earlier, the Complete Response was dated 5/27/04.

In that submission, the sponsor had performed a number of additional analyses of the CIBIC-Plus. The sponsor contended that the results of these additional analyses, together with the analyses of the ADAS-Cog and ADCS-ADL described in the original application, provided substantial evidence of the effectiveness of the Reminyl® Extended-Release formulation in mild to moderate dementia of the Alzheimer's type.

The new CIBIC-Plus analyses, which were all performed using the intent-to-treat, last-observation-carried-forward dataset (based on a Cochran-Mantel-Haenszel model using rank scores and stratified by study site) are further summarized below

- The sponsor now contended that the Cochran-Mantel-Haenszel test model used for the protocol-specified analysis of the CIBIC-Plus, which used modified ridit scores and was stratified by region (US vs. non-US), may not have been appropriate since, in that analysis, US and non-US centers were equally weighted, whereas US centers contributed 69% of those enrolled in the study. The sponsor was now of the view that, since randomization was stratified by study site, a more appropriate Cochran-Mantel-Haenszel test model for analysis of the CIBIC-Plus was one that used rank scores and was stratified by study site. The sponsor then used the latter model to demonstrate what appears to be a nominally statistically significant superiority of both the extended- and immediate-release formulations of Reminyl® over placebo on the CIBIC-Plus, with p-values of 0.030 and 0.027, respectively; these results were considered by the sponsor to more accurately reflect the overall treatment effects of both formulations of Reminyl® on that measure

- A number of baseline variables contributing to CIBIC-Plus outcome were identified by logistic regression analysis; these variables were screening Mini-Mental Status Examination score, baseline ADAS-Cog score, and prior cholinomimetic use. 3 separate analyses of the CIBIC-Plus were then performed using Cochran-Mantel-Haenszel test models; each was stratified for one of the variables considered of prognostic importance, and for country. In each of the 3 analyses the extended-release formulation of galantamine showed a nominally

statistically significant superiority to placebo; in each model, the immediate-release formulation showed either a nominally statistically significant superiority to placebo, or a superiority that approached nominal statistical significance

- Since US centers contributed about 69% of subjects to this study and since these subjects were considered by the sponsor to be more homogenous, a CIBIC-Plus analysis was performed confined to the US centers alone. This analysis, too, appeared to show a nominally statistically significant superiority of each Reminyl® formulation to placebo (p-values of 0.026 and 0.029 for the extended- and immediate-release formulations, respectively)

8. Text Of Second Not Approvable Letter

Key text from the Not Approvable action letter of 7/27/04 is reproduced verbatim below

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

You have presented numerous post hoc re-analyses of the CIBIC-Plus, all of which achieve nominal significance, and which you suggest establish that Reminyl ER is statistically significantly superior to placebo on this outcome measure. However, we believe that it is inappropriate to rely on the results of post hoc analyses unless a compelling argument can be made for disregarding the protocol-specified analyses (as we noted in our December 23, 2003 letter, relying on additional analyses in the face of a negative result on the primary analysis inflates the Type I error for the study). We do not believe that you have provided any convincing rationale for considering the protocol-specified analysis of the CIBIC-Plus to be inappropriate, and, therefore, replaceable by other analyses. Indeed, the protocol-specified analysis of this outcome measure was standard for this measure, and was reasonable in all fundamental aspects. The fact that you have identified numerous other analyses of this outcome measure that you believe, after the fact, are more appropriate, does not constitute, in our view, sufficient justification for rejecting the results of the original analysis. Therefore, given our view that the protocol-specified analysis was sound, we consider it inappropriate to accept as definitive analyses done retrospectively, after a non-significant finding on the original analysis.

Further, even if we were convinced that the protocol-specified analysis of the CIBIC-Plus was inappropriate, the alternative analyses you performed are not clearly appropriate on their own terms. For example, in the analysis in which you stratified by study site, you adopted a rule for pooling small centers that, in addition to being obviously unplanned (and therefore only one of many possible pooling schemes), was itself problematic, given that it resulted in a single "center" that was much larger than any other center in the study. The creation of this very large single "center" could have tended to obscure the effects of center in the analysis. Similarly, you have not adequately justified the appropriateness of the several other specific analyses you have performed, given the extraordinarily large number of analyses that could have been performed.

9. Summary Of Contents Of Current Briefing Package

I have summarized the contents of the current briefing package using the essentially the same headings as those used by the sponsor

9.1 Background

The sponsor states the following

- Galantamine extended-release capsules are a once-daily formulation consisting of 8, 16, and 24 mg of galantamine hydrobromide in each of 3 capsule sizes

- Each capsule shell contains [ ] sugar spheres coated in 3 layers, as follows

    - An inner layer containing [ ] of the total active ingredient (galantamine hydrobromide) content which is released over 24 hours

    - A [ ] membrane which provides for controlled release of galantamine via diffusion

    - An outer layer of immediate-release galantamine hydrobromide containing the remaining [ ] of the total active ingredient

- A single daily 8 mg dose of the extended-release capsule of galantamine is equivalent to 4 mg twice daily of the immediate-release tablet of galantamine, based on the AUC_{0-24}. [Reviewer's note: The bioequivalence of the 2 formulations was confirmed when the original submission under this application was reviewed]

- The efficacy of galantamine extended-release capsule was investigated in Study GAL-INT-10, a randomized, double-blind, placebo controlled study in patients with mild to moderate dementia of the Alzheimer's type. In this study,

    - The 2 co-primary efficacy endpoints were the ADAS-Cog, a cognitive measure, and the CIBIC-Plus, a functional/global instrument

    - An "acceptable alternative global/functional endpoint," the ADCS-ADL, was also included in the trial design as the key secondary endpoint (reviewer's note: there is no evidence from the study protocol that the ADCS-ADL was a pre-specified key secondary endpoint).

    - A positive control arm, immediate-release galantamine, was added after discussions with the Agency in June 1999

9.2 Current Worldwide Regulatory Status Of Galantamine ER

The sponsor states the following

- An application for authorization to market galantamine extended-release capsules was submitted in the first quarter of 2003 in the following countries: the United States, the European Union, Switzerland, Australia, Canada, [ ] Mexico, and Brazil. For all submissions
  - The formulation and composition of the drug product are identical
  - The site of manufacture for the active pharmaceutical ingredient, galantamine hydrochloride, is the same
  - The site of manufacture for the extended-release pellets is the same
- The Marketing Authorization Application in the European Union was submitted under a Mutual Recognition Procedure with Sweden as the Reference Member State (the Reference Member State is responsible for coordinating the approval process with the other Member State). Sweden approved the application in March 2004 for marketing and the application was then submitted to the remaining 16 European Concerned Member States in June 2004; the procedure is due to be completed on September 29, 2004.
- Galantamine extended-release capsules have so far been approved in the following countries: Australia, Sweden, Mexico, and Singapore. The product has been launched in Sweden and Mexico
- The approval of galantamine extended-release capsules is expected shortly in [ ] The sponsor states the following: "We are currently working with the healthy authorities in Canada, Switzerland and [ ] to resolve initial concerns."

9.3 Efficacy Of Galantamine ER

The following is stated by the sponsor

9.3.1 Overview

In Study GAL-INT-10

- A statistically significant difference in favor of GAL-ER and GAL-IR was observed, in comparison with placebo, for the ADAS-Cog
- For the CIBIC-Plus, the differences between the GAL-ER group and the placebo group, and between the GAL-IR group and placebo, did not reach statistical significance, using the protocol-specified method of analysis. In

this trial, the CIBIC-Plus demonstrated reduced assay sensitivity, as demonstrated by the "weaker" results for the GAL-IR group versus the placebo group, as compared with previous trials

- A statistically significant difference in favor of GAL-ER and GAL-IR compared with placebo was observed for the key secondary endpoint, a functional scale, the ADCS-ADL

The results described below are for the intent-to-treat analyses

9.3.2 Efficacy On The ADAS-Cog

Both the ER and IR arms of the GAL-INT-10 trial showed a clear superiority to placebo ($p < 0.001$)

9.3.3 Reduced Assay Sensitivity Of The CIBIC-Plus

- The results, when the GAL-ER and GAL-IR arms of this study were compared with placebo, on the CIBIC-Plus were similar; some analyses showed a statistically significant superiority for the galantamine arms, whereas others did not

- Evidence of reduced assay sensitivity is provided by the comparison of the GAL-IR group to placebo; whereas the immediate-release formulation of galantamine showed a statistically significant superiority to placebo on all 4 earlier trials, the same comparison did not reach statistical significance in GAL-INT-10 as indicated by the following table which I have copied from the submission

Study ITT/LOCF	Formulation	Cognition (ADAS-cog/11) P value vs Plac	Global (CIBIC-plus) P value vs Plac	Function (DAD or ADCS/ADL) P value vs Plac
Gal-INT-1 (6mths)	IR	<0.001	<0.05	NS (DAD)
Gal-USA-1 (6mths)	IR	<0.001	<0.05	NS (DAD)
Gal-INT-2 (3mths)	IR	<0.05	<0.05	<0.05 (DAD)
Gal-USA-10 (5mths)	IR	<0.001	<0.05	=0.002 (ADCS-ADL)
Gal-INT-10 (6mths)	IR	<0.001	NS (p=0.144)	=0.018 (ADCS-ADL)
	ER	<0.001	NS (p=0.216)	<0.001 (ADCS-ADL)

- Factors identified as potentially accounting for the reduced assay sensitivity of the CIBIC-Plus in Study GAL-INT-10 were as follows

- The inclusion of patients with milder dementia in Study GAL-INT-10 than in previous trials
- An imbalance between treatment groups in the severity of dementia at baseline
- Failure to properly weight data from individual centers in the protocol-specified analysis

- An analysis of the impact of these factors on the CIBIC-Plus results was provided in both the original application and in the Complete Response submitted May 27, 2004

- The additional post-hoc analyses of the CIBIC-Plus for GAL-INT-10 described above more accurately reflect the study results. To summarize these analyses

  - Screening Mini-Mental Status Examination scores for patients enrolled in GAL-INT-10 ranged from 10 to 24. When analyses of the CIBIC-Plus for GAL-INT-10 were confined to the subset with a screening Mini-Mental Status Examination score of 10 to 22 (the range for those enrolled in previous trials of immediate-release galantamine), both the GAL-ER and GAL-IR groups showed a statistically significant superiority to placebo
  - Baseline demographic data indicated that more of the mildly affected patients were randomized to the placebo group than to either of the galantamine groups. Additional post-hoc analyses were performed adjusting for baseline measures of disease severity that were found to be associated with response on the CIBIC-Plus. Each of these analyses yielded results that showed a statistically significant superiority for both galantamine arms over placebo
  - The protocol-specified analysis of the CIBIC-Plus used a method that did not reflect stratified randomization and used a method that resulted in greater weight being placed on data for a non-US subject than for a US subject. When a more design-based analysis, stratifying by center, was used, the analysis yielded results that showed a nominally statistically significant superiority on the CIBIC-Plus for both the GAL-ER and GAL-IR groups

- The sponsor acknowledges that, while, for the reasons already outlined, the statistical analyses which demonstrate a treatment effect on the CIBIC-Plus more accurately reflect the study results, these results are marginal and not as strong as for previous trials of the immediate-release formulation

9.3.4 Efficacy On Clinically Relevant Endpoints

- The current regulatory standard requires that the efficacy of drugs in the treatment of dementia of the Alzheimer's type be demonstrated by showing statistically significant results favoring the drug on each of 2 co-primary efficacy endpoints
    - A cognitive measure (the ADAS-Cog scale is generally recognized as an appropriate endpoint for assessing the effect on cognition)
    - A global or functional domain
- The ADAS-Cog scale is generally recognized as an appropriate endpoint for assessing the effect of a drug on cognition in dementia of the Alzheimer's type
- The 2 most commonly utilized global/functional scales are the CIBIC-Plus and ADCS-ADL. Further,
    - In GAL-INT-10, the choice of global/functional primary efficacy endpoint was arbitrary and the CIBIC-Plus was selected based on prior experience
    - The ADCS-ADL would have been equally acceptable as a co-primary endpoint, had it been specified prospectively
    - In this study, the ADCS-ADL demonstrated statistically significant evidence of efficacy for both the extended- and immediate-release formulations of galantamine ($p < 0.001$ and $p = 0.018$, respectively, at endpoint)

9.4 Sponsor's Conclusions

- The overall results of GAL-INT-10 support the effectiveness of GAL-ER in the treatment of mild to moderate dementia of the Alzheimer's type
- The CIBIC-Plus measure in this trial exhibited lowest assay sensitivity as demonstrated by the reduced effect of GAL-IR compared with previous trials. The reduced assay sensitivity is explicable by factors unique to the GAL-INT-10 trial
- Despite the reduced assay sensitivity, statistically significant positive results favoring the GAL-ER formulation over placebo were obtained on a cognitive endpoint (ADAS-Cog) and a functional outcome (ADCS-ADL), which are consistent with current regulatory standards required for the approval of such drugs

10. Comments

- This submission contains a Briefing Package for a scheduled meeting between the Agency and sponsor. The purpose of the meeting, according to the sponsor, is to discuss what further steps need to be taken for this New Drug Application to be approved

- This New Drug Application, originally submitted on 2/24/03, seeks the approval of Reminyl® Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. The Division responded to that application with a Not-Approvable action letter on 12/23/03. Subsequently, the sponsor submitted a Complete Response to the Not-Approvable letter on 5/27/04, to which the Division responded with a further Not-Approvable action letter on 7/27/04; prior to the Complete Response being submitted, a meeting was held between the Division and sponsor on 2/17/04, to discuss the initial Not-Approvable action letter.

- Reminyl® Extended-Release Capsules are intended for once-daily administration, in contrast to the currently-approved immediate-release tablet and oral solution formulations which are recommended as twice daily doses.

- The evidence in the original submission under this NDA, in support of the efficacy of Reminyl® Extended Release capsules, consisted of a single study, GAL-INT-10, the design and results of which are further described below

    - This was a randomized, double-blind, placebo-controlled, parallel-arm study.

    - The study had 3 treatment arms: Reminyl® Extended-Release capsules 16 to 24 mg once daily; immediate-release Reminyl® tablets 8 to 12 mg twice daily; and placebo. The period of double-blind, parallel-arm treatment in this study was 26 weeks

    - Key inclusion criteria were the diagnosis of probable Alzheimer's Disease; a Mini-Mental Status Examination score at screening of 10 -24; and an Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) score at screening of at least 18.

    - 971 patients were enrolled in the study and randomized in about equal proportions to the 3 treatment groups

    - The primary efficacy measures were the ADAS-Cog and the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). There were 10 secondary efficacy measures, including the Alzheimer's Disease Cooperative Study – Activities Of Daily Living (ADCS-ADL) scale.

- The primary efficacy analysis was performed, as specified in the protocol, on the observed cases dataset at Month 6, and the primary comparison was between the Reminyl® Extended-Release and placebo groups, again as specified in the protocol. The difference in this dataset, between the Reminyl® Extended-Release and placebo groups, for the mean change from baseline in the ADAS-Cog, was 2.7 points, and favored galantamine ($p \leq 0.001$). For the CIBIC-Plus, using the same dataset, 61% of those treated with extended-release galantamine, and 56.8% of those treated with placebo, either improved or showed no change ($p = 0.086$, when changes on the full 7-point scale were compared). Similar results were seen, on both primary efficacy parameters, when the Reminyl® Extended-Release and placebo groups were compared for the last-observation-carried-forward and classical intent-to-treat datasets; the results were also similar when the immediate-release Reminyl® and placebo groups were compared.

- The protocol specified that evidence of the efficacy of extended-release galantamine was to be based on demonstrating a statistically significant ($p < 0.05$) treatment difference on both primary efficacy measures between that galantamine group and the placebo group.

- A comparison of the treatment groups on mean change from baseline to Week 26 scores for the ADCS-ADL using the observed cases dataset, revealed a mean difference between the Reminyl® Extended-Release and placebo groups of 2.4 points favoring galantamine ($p = 0.003$); a p-value of < 0.001 was seen in each instance when these groups were compared using the last-observed-carried-forward and classical intent-to-treat datasets

- The Agency's original Not Approvable action (12/23/03) on this application was based on the following

  - The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two prospectively-designated co-primary efficacy measures: a cognitive measure and a global/functional measure. In GAL-INT-10, Reminyl® Extended-Release capsules were not demonstrated to be superior to placebo on the CIBIC-Plus. Therefore this study could not be said to have shown substantial evidence of effectiveness

  - The comparison of the Reminyl® Extended-Release and placebo groups on the ADCS-ADL, a measure that could also be acceptable as a co-primary measure of efficacy, if prospectively designated, showed a nominally statistically significant treatment difference that favored the Reminyl® Extended-Release group. However, the negative finding on the protocol-specified global measure, the CIBIC-Plus, made relying on the results of any secondary efficacy measures inappropriate

- In the earlier Complete Response (5/27/04) to the initial Not-Approvable action, the sponsor had performed a number of additional analyses of the CIBIC-Plus. The sponsor contended that the results of these additional analyses, together with the analyses of the ADAS-Cog and ADCS-ADL described in the original application, provided substantial evidence of the effectiveness of the Reminyl® Extended-Release formulation in mild to moderate dementia of the Alzheimer's type.

  The new (post-hoc) CIBIC-Plus analyses, which were all performed using the intent-to-treat, last-observation-carried-forward dataset are briefly listed below, but are further described in Section 7. All analyses showed a nominally statistically significant superiority of both the ER and IR formulations of galantamine over placebo

  - An analysis in which protocol-specified Cochran-Mantel-Haenszel test model which was stratified by region (US vs. non-US) was modified to one stratified by study site.

  - Analyses in which 3 baseline variables (screening Mini-Mental Status Examination score, baseline ADAS-Cog score, and prior cholinomimetic use) contributing to CIBIC-Plus outcome were identified by logistic regression analysis and were then each used as stratification factors in the same Cochran-Mantel-Haenszel model.

  - An analysis confined to the US centers alone.

- The Agency's second Not-Approvable action, dated 7/27/04, was based on the following

  - The failure to provide a convincing argument for why the protocol-specified analysis of the CIBIC-Plus should be considered inappropriate, and, should, therefore be replaced by the post-hoc re-analyses of that measure, especially since the protocol-specified analysis of this outcome measure was standard for this measure, and was reasonable in all key aspects. In addition, as outlined in the earlier Not-Approvable action letter, the use of additional analyses after a negative primary analysis would inflate the Type I error for the study.

  - Concern that the alternative analyses proposed by the sponsor may not have been entirely appropriate in themselves

- The current submission does not present any <u>new</u> arguments favoring the approval of the extended-release formulation of Reminyl®. The sponsor does for the first time claim that, in Study GAL-INT-10, the ADCS-ADL was a key secondary efficacy measure, a claim that is not substantiated by review of the final study protocol.

- My overall view of this application remains as follows

- The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure.

- The protocol for the GAL-INT-10 study specified that the efficacy of the extended-release galantamine formulation in that study was to be based on demonstrating a statistically significant superiority to placebo on both primary efficacy measures, the ADAS-Cog and CIBIC-Plus.

- Since the treatment differences between extended-release galantamine and placebo on the CIBIC-Plus did not achieve or approach statistical significance using the protocol-specified analysis, this study has, according to the current regulatory standard, failed to establish evidence for the efficacy of extended-release Reminyl® in mild-to-moderate Alzheimer's Disease.

- The comparison of the Reminyl® Extended-Release and placebo groups on the ADCS-ADL showed a nominally statistically significant treatment difference favoring the Reminyl® Extended-Release group over placebo. While the ADCS-ADL would have been acceptable as a co-primary measure of efficacy in lieu of the CIBIC-Plus, if prospectively designated, it was one of 10 secondary efficacy measures in this study (albeit the only secondary efficacy measure other than the dichotomized CIBIC-Plus that could be considered a global or functional instrument), and these measures were subject to 90 separate analyses. Moreover, the lack of any evidence of efficacy on the protocol-specified global co-primary efficacy measure, the CIBIC-Plus, made relying on the results of any secondary efficacy measures inappropriate

- Since the extended-release formulation of galantamine is intended to be taken once daily and will therefore be more convenient to use than the immediate-release formulation, for which twice daily dosing is recommended, the former formulation is likely to be used much frequently than the latter, when marketed. It is therefore especially important that evidence for the efficacy of the extended-release formulation should be clearly demonstrated prior to marketing approval being granted; such evidence is currently lacking.

- While the sponsor has also performed further analyses of the CIBIC-Plus, using Cochran-Mantel-Haenszel test models different from those used for the primary efficacy analyses, which have shown nominally statistically significant differences favoring extended-release galantamine over placebo, the new analyses are post-hoc, and their results are model-dependent, confined to a subgroup, or otherwise deficient. For those results that are model-dependent, the sponsor has not provided convincing evidence that the models that show "positive" results are more appropriate to use than those that do not. These analyses cannot

therefore be considered to have met the "substantial evidence of effectiveness" standard

11. Addendum: November 10, 2004

The contents of this submission were discussed at an internal meeting held with Dr R. Temple on September 17, 2004.

Based on that meeting, the proposed meeting with the sponsor was cancelled

A Dispute Resolution Request package was then submitted directly to Dr R. Temple, which was received by his office on September 27, 2004; Dr Temple's response was provided to the sponsor on October 27, 2004 and concluded that the key deficiency in this application, the lack of substantial evidence of efficacy, had been adequately addressed in the original NDA and subsequent Amendments.

A Complete Response to the Not-Approvable Letters was then submitted on October 27, 2004 and is being reviewed separately

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 11/10/04
cc:
HFD-120
NDA 21615

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/s/

Ranjit Mani
11/10/04 11:31:46 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA	**21615 (B2)**
Sponsor:	**Johnson & Johnson**
Drug:	**Reminyl® Extended-Release**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Response To Agency Letter**
Correspondence Date:	**5/27/04**
Date Received / Agency:	**5/28/04**
Date Review Completed	**7/26/04**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission is a Complete Response to a Not Approvable letter issued by this Division for the original submission under New Drug Application (NDA) 21615. That application, originally submitted on 2/24/03, sought the approval of Reminyl® Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. The Not Approvable letter was issued on 12/23/03.

The original application under NDA 21615 was based mainly on the results of one Phase III randomized, double-blind, placebo-controlled efficacy study (GAL-INT-10), an uncontrolled, open-label extension to GAL-INT-10, and several pharmacokinetic trials. Four-Month and Seven-Month Safety Updates to that application were submitted on 6/19/03 and 10/3/03, respectively, and were reviewed with the original application.

Reminyl® Extended-Release capsules have been developed under Investigational New Drug Application (IND) 61703.

The immediate-release tablet and oral solutions formulations of galantamine, Reminyl®, had earlier been developed by this sponsor for the treatment of Alzheimer's Disease under IND 51538. NDAs 21169 and 21224, for the use of the immediate-release tablet and oral solution forms, respectively, of galantamine in the treatment of mild-to-moderate dementia of the Alzheimer's type were approved in 2001. Later in 2001, a supplemental NDA (SCM-001) was approved for the use of immediate-release tablet and oral solution formulations of synthetic galantamine (for the treatment of mild-to-moderate dementia of the Alzheimer's type), instead of the plant-derived drug substance approved earlier.

The sponsor has proposed that Reminyl® Extended-Release capsules be administered once daily, whereas it is recommended in the package insert for the currently approved immediate-release formulation of Reminyl® that that drug formulation be administered twice daily.

The Not Approvable action letter of 12/23/03 was discussed with the sponsor at a meeting held on 2/17/04. Please see my review of the Briefing Package for that meeting for further details. Please also see my review of the original submission under NDA 21615.

The extended-release formulation of Reminyl® is referred to in this review, interchangeably, as "Reminyl® ER", "Reminyl® CR", "GAL-ER", or "GAL-CR". The immediate-release formulation is referred to in this review, interchangeably, as "Reminyl® IR" or "GAL-IR". The terms "IR" and "ER" are used in this review as a substitute for "immediate-release" and "extended-release," respectively.

2. Contents Of Submission

This submission contains the following

- Cover letter
- Document entitled "Effectiveness of Reminyl ER, comprising 3 sections, entitled as follow
  - Executive summary
  - Use of CIBIC-Plus scale in galantamine studies
  - Overall conclusions

3. Contents Of Review

This review will address the following items in the same order as below

- Summary of Study GAL-INT-10
- Text of Not-Approvable Letter
- Summary of meeting with sponsor on February 17, 2004
- Contents of current submission
- Agency Biometrics review of current submission
- Consultation From Division Of Medical Errors And Technical Support

4. Summary Of Study GAL-INT-10

The following is an outline of the main features of the study and key efficacy data for Study GAL-INT-10

4.1 Outline Of Study

The study is outlined in the following table

Objective	Efficacy and safety of Reminyl® ER in mild-to-moderate Alzheimer's Disease
Design	Randomized, double-blind, placebo-controlled, parallel-arm study
Key Inclusion Criteria	• Male or female • Probable Alzheimer's disease by NINCDS-ADRDA criteria • Mini-Mental Status Examination score 10-24 **and** ADAS-Cog score of at least 18
Dose Groups	• Placebo • Reminyl® ER 16 to 24 mg q.d. • Reminyl® IR 8 mg to 12 mg b.i.d
Duration	26 weeks
Randomized Population	Placebo → 324 patients Reminyl® ER 16 to 24 mg q.d. → 327 patients Reminyl® IR 8 mg to 12 mg b.i.d → 320 patients
Primary Efficacy Measures	• ADAS-Cog • CIBIC-Plus
Secondary Efficacy Measures	• ADAS-Cog/13 • ADAS-Cog/10 • ADAS-Cog/mem • Percentage of responders on standard ADAS-Cog using 0, 4, 7 and 10 points of improvement as cut-off • Percentage of subjects with "improved" or "no change" on the CIBIC-Plus. • Neuropsychiatry Inventory • Alzheimer's Disease Cooperative Study-ADL
Primary Efficacy Analysis Methods	ADAS-Cog: ANOVA CIBIC-Plus: Cochran-Mantel-Haenszel Test Primary Dataset: Observed Cases Primary Comparison: Reminyl® ER vs Placebo

4.2 Results

4.2.1 Disposition

The disposition of all randomized patients is summarized in the following table, which I have taken from the original NDA submission

Trial Termination Reasons
(Study GAL-INT-10: All Randomized Subjects Analysis Set)

All Randomized Subjects	PLACEBO	GAL IR	GAL CR
Status	(N=324)	(N=327)	(N=320)
Termination Reasons	n (%)	n (%)	n (%)
Randomized and treated	320 (99)	326 (100)	319 (100)
Completed	266 (82)	251 (77)	251 (78)
Discontinued	54 (17)	75 (23)	68 (21)
Adverse event	15 (5)	24 (7)	28 (9)
Subject withdrew consent	21 (6)	23 (7)	18 (6)
Subject non-compliant	7 (2)	14 (4)	8 (3)
Other[a]	11 (3)	14 (4)	14 (4)

[a]Other reasons for discontinuation includes subject lost to follow-up, insufficient response, death, and subject violating protocol criteria. 8 subjects died during this trial. None of these deaths were related to study medication.

4.2.2 Primary Efficacy Measures

4.2.3 ADAS-Cog

The results of the primary analysis of the ADAS-Cog are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline	305	26.1 (0.54)	--	306	27.3 (0.55)	--	300	26.3 (0.54)	--	
Week 8	289	25.8 (0.63)	0.0 (0.30)	286	25.4 (0.58)	-1.7 (0.30)	284	24.6 (0.58)	-1.5 (0.30)	<0.001
Week 12	275	25.9 (0.66)	0.0 (0.32)	268	24.0 (0.57)	-2.6 (0.31)	269	23.9 (0.57)	-2.2 (0.32)	<0.001
Week 26	**248**	**26.4 (0.72)**	**1.3 (0.36)**	**227**	**24.7 (0.69)**	**-1.8 (0.42)**	**240**	**24.8 (0.69)**	**-1.4 (0.34)**	**<0.001**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs Placebo at Week 26: p<0.001.

4.2.4 CIBIC-Plus

The results of the primary analysis of the CIBIC-Plus are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)	(Cum %)	n (%)	(Cum %)	n (%)	(Cum %)	P value[a]
N at Week 26	259		240		246		
Markedly improved	3 (1.2)	(1.2)	3 (1.3)	(1.3)	3 (1.2)	(1.2)	
Moderately improved	9 (3.5)	(4.6)	14 (5.8)	(7.1)	14 (5.7)	(6.9)	
Mildly improved	41 (15.8)	(20.5)	36 (15.0)	(22.1)	43 (17.5)	(24.4)	
No change	94 (36.3)	(56.8)	93 (38.8)	(60.8)	90 (36.6)	(61.0)	
Mildly worse	70 (27.0)	(83.8)	67 (27.9)	(88.8)	69 (28.0)	(89.0)	
Moderately worse	36 (13.9)	(97.7)	25 (10.4)	(99.2)	23 (9.3)	(98.4)	
Markedly worse	6 (2.3)	(100.0)	2 (0.8)	(100.0)	4 (1.6)	(100.0)	0.086

[a]GAL-CR vs Placebo comparison using the Van Elteren test controlling for Pooled Country.
Cum % = cumulative percent
Note: Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at Week 26: p=0.223.

The results of the analysis of the CIBIC-Plus using the intent-to-treat (identical to classical intent-to-treat) dataset, and applying the last-observation-carried-forward (LOCF) method of imputation is in the following table, which I have copied from the original NDA submission

(Study GAL-INT-10: LOCF-CITT Data)

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)[b]	Cum %	n (%)[b]	Cum %	n (%)[b]	Cum %	P value[a]
LOCF-CITT at Endpoint[b]	301		302		296		
Markedly improved	3 (1.0)	(1.0)	3 (1.0)	(1.0)	3 (1.0)	(1.0)	
Moderately improved	11 (3.7)	(4.7)	15 (5.0)	(6.0)	14 (4.7)	(5.7)	
Mildly improved	48 (15.9)	(20.6)	46 (15.2)	(21.2)	49 (16.6)	(22.3)	
No change	111 (36.9)	(57.5)	127 (42.1)	(63.2)	114 (38.5)	(60.8)	
Mildly worse	80 (26.6)	(84.1)	78 (25.8)	(89.1)	81 (27.4)	(88.2)	
Moderately worse	41 (13.6)	(97.7)	30 (9.9)	(99.0)	29 (9.8)	(98.0)	
Markedly worse	7 (2.3)	(100.0)	3 (1.0)	(100.0)	6 (2.0)	(100.0)	0.216

[a]GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
[b]The endpoint was defined as the last available observation up to 14 days after the last dose of study medication
Cum % cumulative percent.
Note: Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at endpoint: p 0.144 (LOCF CITT).

4.2.5 Selected Secondary Efficacy Measures

4.2.6 ADCS-ADL

The results of the analysis of the ADCS-ADL, using the Observed Cases dataset, are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline	308	54.5 (0.87)	--	310	52.0 (0.90)	--	303	53.5 (0.88)	--	
Week 8	294	53.8 (0.98)	-0.7 (0.45)	292	52.6 (0.93)	0.9 (0.42)	290	54.5 (0.94)	0.8 (0.41)	0.013
Week 12	281	54.2 (0.99)	-0.3 (0.46)	279	52.8 (0.95)	1.1 (0.47)	276	54.1 (0.94)	0.4 (0.48)	0.321
Week 26	**258**	**52.4 (1.09)**	**-2.4 (0.60)**	**242**	**50.9 (1.12)**	**-1.0 (0.57)**	**245**	**53.9 (1.03)**	**0.0 (0.55)**	**0.003**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS)
GAL-IR vs. Placebo at Week 26: p=0.088.

4.2.7 Neuropsychiatry Inventory

The results of the analysis of the Neuropsychiatry Inventory, using the Observed Cases dataset, are summarized in the following table, which I have taken from the original NDA submission

(Study GAL-INT-10: ITT Analysis Set – OC Data)

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	P value[a]
Baseline	308	10.3 (0.69)	--	310	12.6 (0.76)	--	304	11.2 (0.79)	--	
Week 8	295	10.2 (0.70)	0.1 (0.48)	292	11.5 (0.68)	-1.2 (0.61)	291	10.4 (0.85)	-0.8 (0.53)	0.226
Week 12	281	9.5 (0.70)	-0.6 (0.56)	279	11.0 (0.75)	-1.9 (0.74)	276	9.6 (0.84)	-1.5 (0.62)	0.320
Week 26	**258**	**10.3 (0.82)**	**0.1 (0.66)**	**242**	**11.5 (0.83)**	**-1.2 (0.83)**	**245**	**10.0 (0.76)**	**-0.6 (0.69)**	**0.451**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p=0.203.

5. Text Of Not-Approvable Letter

Key text from the Not Approvable action letter of 12/23/03 is reproduced verbatim below

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Lack of Substantial Evidence of Effectiveness:

The supporting clinical efficacy study GAL-INT-10 fails to provide evidence of effectiveness of extended-release galantamine.

As you know, the current regulatory standard for a demonstration of effectiveness for treatments of Alzheimer's Disease is the showing of statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure. Unfortunately, Reminyl ER was not shown to be superior to placebo on the CIBIC-Plus (for the intent-to-treat population on the last observation carried forward analysis, the between-treatment contrast yields p=0.22). Thus, based on the pre-specified primary efficacy analysis, this study must be considered not to have shown substantial evidence of effectiveness of Reminyl® Extended-Release Capsules.

While the between-treatment comparison on the ADCS-ADL, a secondary efficacy measure that also can be acceptable as a co-primary measure of overall functioning (when so designated prospectively), was nominally significant (p<0.001), the negative finding on the protocol specified global measure (the CIBIC-Plus) makes relying on any analysis of further outcome variables inappropriate, because to do so inflates the overall Type I error for the study.

Before this application can be approved, you must submit a single adequate and well-controlled investigation that demonstrates superiority of Reminyl ER to placebo on two prospectively designated outcomes of the sort described above.

6. Summary Of Meeting With Sponsor Held On February 17, 2004

The sponsor's and Division's views about the results of Study GAL-INT-10, and the next steps that the sponsor might take in obtaining approval of Reminyl® ER for the treatment of mild to moderate dementia of the Alzheimer's type, were discussed. The discussion included an outline of the sponsor's views as to why there was no evidence for the efficacy of either the extended-release or immediate-release formulations of Reminyl® on the CIBIC-Plus analysis in that study.

[In the briefing package for the meeting, the sponsor had argued that the GAL-INT-10 study demonstrated clinical equivalence between the two galantamine formulations, based on their efficacy relative to placebo on both the ADAS-Cog and ADCS-ADL. The sponsor further believes that since both formulations were superior to placebo on the ADCS-ADL (on the last-observation-carried-forward dataset), those results are unlikely to have been due to chance.]

Based on that discussion, the following were the key agreements reached at the meeting

- The sponsor was advised to submit a detailed argument that addressed, on clinical and statistical grounds, why the results of the ADCS-ADL analysis for Study GAL-INT-10 should be considered in lieu of those for the CIBIC-Plus, in attempting to establish that that study was "positive"

- The sponsor proposed that another means of establishing the efficacy of the extended-release formulation of Reminyl® might be the demonstration of a correlation between exposure (based on AUC) and clinical effect in a small study using the immediate-release formulation of Reminyl® alone, given the similarity in AUC between the 2 formulations of Reminyl®. The Division agreed to comment more fully on such a proposal once more details were submitted. The sponsor was advised that such a proposal should clearly describe how a link between clinical effectiveness and pharmacokinetic exposure was to be established.

- The sponsor proposed that a further efficacy study of the extended-release formulation of Reminyl® use the ADAS-Cog and ADCS-ADL as primary efficacy measures and be of 3 months duration. The Division believed that that proposal would in all likelihood be acceptable, although 3 months is the minimum duration for an efficacy study in Alzheimer's Disease.

- A submission comprising one or more of the above would be considered a response to the Division's Not-Approvable action letter.

The sponsor asked if the nomenclature to be used for the proposed new formulation in labeling – Reminyl® ER (galantamine hydrobromide) Extended Release Capsules had been agreed to by the Division of Medication Errors and Technical Support (DMETS). The Division stated that the final opinion of DMETS was pending.

7. Response To Not Approvable Letter

The contents of this submission are summarized under the following headings

7.1 Overall CIBIC-Plus Results In Phase III Galantamine Studies In Alzheimer's Disease

The sponsor states the following.

- In Phase III placebo-controlled trials of the immediate-release formulation of galantamine in Alzheimer's Disease (GAL-INT-1, GAL-USA-1, and GAL-USA-10), evidence of efficacy was demonstrable on both the ADAS-Cog and CIBIC-Plus.

- In contrast, in GAL-INT-10, the immediate-release formulation of galantamine did not show a statistically significant superiority to placebo on the CIBIC-Plus, while such a superiority was seen for the ADAS-Cog and ADCS-ADL. This indicates, according to the sponsor that there was reduced "assay sensitivity" for the CIBIC-Plus in GAL-INT-10.

These results (and those comparing the extended-release preparation of galantamine with placebo in GAL-INT-10) are in the following table which I have copied from the submission.

Endpoint Results of Galantamine Phase III AD Studies (LOCF Data)[a]

Study	Formulation	Cognition (ADAS-cog/11)	Global (CIBIC-plus)	Functional (ADCS-ADL)
GAL-INT-1	IR	0.001	0.015	--
GAL-USA-1	IR	0.001	0.003	--
GAL-USA-10	IR	0.001	0.001	0.002
GAL-INT-10	IR	0.001	NS	0.018
	ER	0.001	NS	0.001

[a] p-values versus placebo; NS=not significant; LOCF = Last Observation Carried Forward. ADCS-ADL was not measured in GAL-INT-1 and GAL-USA-1.

7.2 Re-Analysis Of CIBIC-Plus Data

The sponsor indicates that a number of re-analyses of the CIBIC-Plus have been performed to "accurately reflect the study data."

All these re-analyses were performed using intent-to-treat, last-observation-carried-forward data, and 2-sided statistical tests. All Cochran-Mantel-Haenszel tests were performed using rank scores

These analyses are summarized under the following headings

7.2.1 Analysis Stratified By Study Site

The sponsor states the following

- The protocol-specified analysis of the CIBIC-Plus used a Cochran-Mantel-Haenszel model with modified ridit scores, stratified by region (US vs. non-US). The modified ridit score is defined as the rank score divided by the stratum sample size
- US centers comprised 69% of the study population
- The use of modified ridit scores and stratification by region (US vs. non-US) tends to underemphasize the contribution of US centers, by giving equal weight to the US and non-US centers.
- Since the randomization of subjects was stratified by study site, a design-based analysis which weighted each subject's overall contribution to the study results equally would be a Cochran-Mantel-Haenszel model using rank scores and stratified by study site; the results of the analysis based on that model are in the following table which I have copied from the submission (sites with 3 or fewer subjects were pooled). The sponsor considers the analysis to indicate a statistically significant superiority of both the immediate- and extended-release formulations of galantamine to placebo, and believes the results more accurately reflect the overall treatment effect of both formulations on the CIBIC-Plus

GAL-INT-10 Week 26 (LOCF) CIBIC-plus Results

	PLACEBO	GAL ER	GAL IR
All ITT Subjects	N 301	N 296	N 302
CIBIC-plus			
Markedly improved	1.0%	1.0%	1.0%
Moderately improved	3.7%	4.7%	5.0%
Mildly improved	15.9%	16.6%	15.2%
No change	36.9%	38.5%	42.1%
Mildly worse	26.6%	27.4%	25.8%
Moderately worse	13.6%	9.8%	9.9%
Markedly worse	2.3%	2.0%	1.0%
p-value[a] (vs Placebo)		**0.030**	**0.027**

[a] CMH model stratified by study site.

7.2.2 Analyses Stratified By Country And Prognostic Factors For CIBIC-Plus Outcome

7.2.2.1 Prognostic Factors

In order to identify factors associated with the CIBIC-Plus outcome, a logistic regression analysis was performed, using a cumulative logit model, on all baseline characteristics.

The results of this analysis are reproduced in the sponsor's table below. Three variables were found to be associated with CIBIC-Plus outcome: screening Mini-Mental Status Examination score, baseline ADAS-Cog score, and prior cholinomimetic use

Analysis of Potential Prognostic Factors Related To CIBIC-Plus Outcome

Candidate for Prognostic Factor	GAL-ER vs Placebo	GAL-IR vs. Placebo
MMSE score at screening (≤22, >22)	**0.017**	**0.011**
Baseline ADAS-cog 11 score (≤18, >18)	**<0.001**	**<0.001**
Age at onset of cognitive problems	0.339	0.774
Duration since diagnosis of cognitive problems	0.311	0.623
Age at diagnosis of probable AD	0.741	0.371
Duration since diagnosis of probable AD	0.589	0.535
Age	0.585	0.480
Height	0.477	0.937
Weight	0.229	0.897
Subject taken cholinommetics	**0.007**	**0.082**
First degree relatives with AD	0.874	0.539
Sex	0.577	0.869
Smoking	0.413	0.898

Based on these results, 3 separate analyses of CIBIC-Plus data, adjusting for each of the variables that were considered of prognostic importance, and country, were performed to examine the treatment effect on CIBIC-Plus [stratification by country rather than by site was used to prevent having too many strata with only a few subjects each]

- Analysis of CIBIC-Plus data stratified by baseline Mini-Mental Status Examination score (≤ 22 vs. > 22) and country

- Analysis of CIBIC-Plus data stratified by baseline ADAS-Cog score (≤ 18 vs. > 18) and country [an ADAS-Cog score of 18 was chosen as a cut-off

as it was considered to be equivalent to a Mini-Mental Status Examination cut-off score of 22].

- Analysis of CIBIC-Plus data stratified by prior use of cholinomimetic drugs (used vs. not used) and country.

7.2.2.2 Analysis Stratified By Screening Mini-Mental Status Examination Score (MMSE) And Country

The sponsor performed an analysis of the CIBIC-Plus data using a Cochran-Mantel-Haenszel model stratified by screening MMSE score (≤ 22 vs. > 22) and country

Based on that analysis, which is the following table that I have copied from the submission, the sponsor states the following

- In the sub-group consisting of those with screening MMSE ≤ 22, the CIBIC-Plus responder proportions were consistent with previous studies of immediate-release galantamine in Alzheimer's Disease

- In the subgroup of subjects with screening MMSE > 22, the CIBIC-Plus responder proportions in all treatment groups was higher than for the rest of the study population; the placebo responder proportion (77%) was notably high and greatly decreased the sensitivity of the CIBIC-Plus

- The comparison of the extended-release galantamine group with the placebo group was considered statistically significant, whereas the comparison of the immediate-release galantamine group with the placebo group closely approached statistical significance

Summary of CIBIC-Plus at Week 26 – LOCF Data by Screening MMSE Category (≤ 22 and > 22)

	PLACEBO	GAL ER	GAL IR
Subjects with MMSE ≤22	N=248	N=255	N=256
CIBIC-plus			
Markedly improved	0.8%	1.2%	0.8%
Moderately improved	2.0%	4.7%	4.3%
Mildly improved	14.5%	14.9%	15.2%
No change	35.9%	39.6%	40.6%
Mildly worse	28.2%	26.3%	27.3%
Moderately worse	15.7%	11.0%	10.6%
Markedly worse	2.8%	2.3%	1.2%
Subjects with MMSE >22	N=53	N=41	N=46
CIBIC-plus			
Markedly improved	1.9%	0.0%	2.2%
Moderately improved	11.3%	4.9%	8.7%
Mildly improved	22.6%	26.8%	15.2%
No change	41.5%	31.7%	50.0%
Mildly worse	18.9%	34.2%	17.4%
Moderately worse	3.8%	2.4%	6.5%
Markedly worse	0.0%	0.0%	0.0%
p-value[a] (vs Placebo)		**0.019**	**0.053**

[a] CMH model stratified by screening MMSE and country.

Additional similar analyses were performed using MMSE scores of 20, 21, and 23 as the cut-off; these yielded results that were similar to those using a cut-off MMSE score of 22, and, according to the sponsor, confirmed the robustness of the latter analysis. These analyses are in the following table, which I have copied from the submission.

GAL-INT-10 Week 26 (LOCF) CIBIC-Plus Results (p-values) from CMH Model Stratified by Screening MMSE Category and Country

Strata for CMH Model	GAL-ER vs. Placebo	GAL-IR vs Placebo
MMSE (10-20, 20), country	0.022	0.052
MMSE (10-21, 21), country	0.013	0.026
MMSE (10-22, 22), country	0.019	0.053
MMSE (10-23, 23), country	0.022	0.043

7.2.2.3 Analysis Stratified By Baseline ADAS-Cog And Country

The sponsor performed an analysis of the CIBIC-Plus data using a Cochran-Mantel-Haenszel model stratified by baseline ADAS-Cog score (≤ 18 vs. > 18) and country

Based on that analysis which is the following table that I have copied from the submission, the sponsor states the following

- In the sub-group consisting of those with baseline ADAS-Cog ≤ 18, the CIBIC-Plus responder proportions were consistent with previous studies of immediate-release galantamine in Alzheimer's Disease

- In the subgroup of subjects with baseline ADAS-Cog > 18 (milder subjects), the CIBIC-Plus responder proportions in all treatment groups was higher than for the rest of the study population; the placebo responder proportion (78%) was notably high and greatly decreased the sensitivity of the CIBIC-Plus

- The comparison of the extended-release and immediate-release galantamine groups with the placebo group were both considered statistically significant.

Summary of CIBIC-Plus at Week 26 – LOCF Data by Baseline ADAS-Cog Category

	PLACEBO	GAL ER	GAL IR
Subjects with Baseline ADAS-cog/11 >18	N 223	N 234	N 246
CIBIC-plus			
Markedly improved	0.5%	0.8%	0.8%
Moderately improved	2.2%	4.3%	4.1%
Mildly improved	15.3%	15.8%	14.6%
No change	32.7%	35.9%	42.3%
Mildly worse	29.2%	29.1%	25.2%
Moderately worse	17.0%	12.0%	11.8%
Markedly worse	3.1%	2.1%	1.2%
Subjects with Baseline ADAS-cog/11 ≤18	N 74	N 57	N 51
CIBIC-plus			
Markedly improved	2.7%	1.8%	2.0%
Moderately improved	8.1%	5.3%	9.8%
Mildly improved	18.9%	19.3%	17.6%
No change	48.6%	50.9%	45.1%
Mildly worse	17.6%	21.0%	23.5%
Moderately worse	4.1%	1.8%	2.0%
Markedly worse	0.0%	0.0%	0.0%
p-value[a] (vs Placebo)		**0.021**	**0.015**

[a] CMH model stratified by baseline ADAS-cog 11 score and country

Additional similar analyses were performed using ADAS-Cog scores of 16, 17, 19, and 20 as the cut-off; these yielded results that were similar to those using a cut-off ADAS-Cog score of 18, and, according to the sponsor, confirmed the robustness of the latter analysis. These analyses are in the following table, which I have copied from the submission.

GAL-INT-10 Week 26 (LOCF) CIBIC-Plus Results (p-values) from CMH Model Stratified by Baseline ADAS-Cog Category and Country

Strata for CMH Model	GAL-ER vs. Placebo	GAL-IR vs. Placebo
ADAS-cog/11 (≤16, >16), Country	0.022	0.019
ADAS-cog/11 (≤17, >17), Country	0.019	0.016
ADAS-cog/11 (≤18, >18), Country	0.021	0.015
ADAS-cog/11 (≤19, >19), Country	0.025	0.020
ADAS-cog/11 (≤20, >20), Country	0.030	0.029

7.2.2.4 Analysis Stratified By Country And Prior Cholinomimetic Use

The sponsor performed a further analysis of the CIBIC-Plus data using a Cochran-Mantel-Haenszel model stratified by country and prior cholinomimetic use

Based on that analysis which is the following table that I have copied from the submission, the sponsor states the following

- In the sub-group consisting of those with prior cholinomimetic use, the CIBIC-Plus responder proportions were consistent with previous studies of immediate-release galantamine in Alzheimer's Disease
- In the subgroup of subjects without prior cholinomimetic use, the CIBIC-Plus responder proportions in all treatment groups was higher than for those who did not receive prior cholinomimetic treatment
- The comparison of the extended-release galantamine group with the placebo group was considered statistically significant, whereas the comparison of the immediate-release galantamine group with the placebo group closely approached statistical significance

Summary of CIBIC-Plus at Week 26 – LOCF Data by Prior Cholinomimetic Use

	PLACEBO	GAL ER	GAL IR
Subjects with Prior Cholinomimetics Use	N=137	N=142	N=145
CIBIC-plus			
Markedly improved	2.2%	0.7%	1.4%
Moderately improved	2.9%	4.9%	3.4%
Mildly improved	10.9%	10.6%	11.7%
No change	31.4%	40.1%	40.7%
Mildly worse	29.9%	27.5%	29.0%
Moderately worse	19.0%	12.7%	11.7%
Markedly worse	3.6%	3.5%	2.1%
Subjects without Prior Cholinomimetics Use	N=164	N=153	N=157
CIBIC-plus			
Markedly improved	0.0%	1.3%	0.6%
Moderately improved	4.3%	4.6%	6.4%
Mildly improved	20.1%	22.2%	18.5%
No change	41.5%	37.2%	43.3%
Mildly worse	23.8%	26.8%	22.9%
Moderately worse	9.1%	7.2%	8.3%
Markedly worse	1.2%	0.7%	0.0%
p-value[a] (vs Placebo)		**0.030**	**0.052**

[a] CMH model stratified by cholinomimetics status and country.

7.2.3 Analysis In US Population

The sponsor states the following

- The severity of dementia at baseline was higher in the US population enrolled in the study than in the non-US population
- Since the US population comprised 69% of those enrolled in the study and was therefore sufficiently large, and was also considered more homogenous than the non-US population, an analysis of the CIBIC-Plus results in the US alone, stratified by study site, was considered appropriate.
- The results of this analysis indicated that an about equal proportion (~ 65%) of those in the immediate- and extended-release galantamine groups were responders versus ~ 58% in the placebo group. While the responder proportion in the immediate-release galantamine group was similar to that seen in earlier Phase III studies, the responder rate in the placebo group was higher than that observed in earlier Alzheimer's Disease studies (~ 50%)

- The comparison of each of the galantamine groups with the placebo group was considered statistically significant. The results of this analysis are in the following table (sites with 3 or fewer subjects were pooled).

Summary of CIBIC-Plus at Week 26 – LOCF Data (Study GAL-INT-10: US Population)

	PLACEBO	GAL ER	GAL IR
U.S. Subjects	N=204	N=202	N=200
CIBIC-plus			
Markedly improved	1.5%	1.0%	0.5%
Moderately improved	2.0%	3.0%	5.5%
Mildly improved	11.8%	16.8%	12.5%
No change	42.6%	44.5%	47.0%
Mildly worse	26.0%	24.3%	23.0%
Moderately worse	13.2%	8.9%	10.0%
Markedly worse	2.9%	1.5%	1.5%
p-value[a] (vs Placebo)		**0.026**	**0.029**

[a] CMH model stratified by study site.

The sponsor concludes that for the US population, which comprised 69% of those enrolled in this study, the CIBIC-Plus performed as would have been expected. The sponsor believes that the large proportion of relatively mildly demented subjects at the non-US sites reduced the sensitivity of the CIBIC-Plus by inflating the placebo response

7.3 Sponsor's Overall Conclusions

The sponsor's overall conclusions may be summarized as follows (they are also partly summarized in the table below, which I have copied from the submission)

- The imbalance in mildly demented subjects among treatment groups contributed to the reduced CIBIC-Plus sensitivity in Study GAL-INT-10
- The CIBIC-Plus results from Study GAL-INT-10 comparing Reminyl® Extended-Release and Reminyl® Immediate-Release with placebo are positive under the following circumstances
  - When the analyses are stratified by study site
  - After adjusting for country and prognostic factors indicative of disease severity
  - When the analysis is based on the US population alone
- The efficacy of Reminyl® Extended-Release in a functional domain is confirmed by a statistically significant positive efficacy result for Reminyl®

Extended-Release based on the ADCS-ADL, a valid activities of daily living measure

Overall Efficacy Results In Study GAL-INT-10

Week 26 (LOCF) Endpoints	GAL-IR vs. Placebo	GAL-ER vs. Placebo
Cognitive: ADAS-cog/11		
Change from baseline to Week 26	0.001	-0.001
Functional: ADCS-ADL		
Change from baseline to Week 26	0.018	0.001
Global: CIBIC-plus		
Stratified by site	0.027	0.030
Stratified by country & MMSE at screening	0.053	0.019
Stratified by country & baseline ADAS-cog/11	0.015	0.021
Stratified by country & prior cholinomimetic use	0.052	0.030
U.S. population	0.029	0.026

The sponsor further believes that, when "properly analyzed," the results of Study GAL-INT-10 confirm the efficacy of the extended-release formulation of Reminyl®: statistically significant results have been seen on measures of cognition (ADAS-Cog), global performance (CIBIC-Plus), and function (ADCS-ADL). The results of Study GAL-INT-10 therefore confirm the efficacy of Reminyl® ER in a manner consistent with current regulatory guidelines

8. Agency Biometrics Review

The Agency Biometrics review of the current submission was performed by Dr Kun He.

Dr He's key comments about the sponsor's new analyses are as follows. Please see his review for full details.

8.1 Analysis Of CIBIC-Plus Stratified By Study Site

- In international studies, the CIBIC-Plus is commonly analyzed using a Cochran-Mantel-Haenszel test stratified by region or by country. When such analyses were applied to the current study data using rank scores

(rather than modified ridit scores, as specified in the protocol), the comparison of either galantamine group with placebo yield results that were not (nominally) statistically significant, as indicated by the following table

Stratification	GAL-ER vs placebo p-value	GAL-IR vs placebo p-value
None	0.2770	0.1512
By region (US vs. non-US)	0.0951	0.0958
By country	0.0582	0.0845

- The significance of the Cochran-Mantel-Haenszel analysis stratified by study site is questionable for the following reasons
    - There was no pre-specified plan for pooling subjects (in the post-hoc analysis, sites with ≤ 3 subjects were pooled)
    - It is unclear whether the nominally statistically significant result favoring extended-release galantamine over placebo in the sponsor's new Cochran-Mantel-Haenszel (stratified by study site) could have been "driven" by data from a single large pooled site (#995) with 177 patients [the p-value for the same comparison at that site was 0.0293]

8.2 Analyses Of CIBIC-Plus Stratified By Country And Prognostic Factors For CIBIC-Plus Outcome

- Cochran-Mantel-Haenszel test-based analyses stratified by each of the following did not show a (nominally) statistically significant superiority of the extended-release preparation of galantamine over placebo: country, baseline Mini-Mental Status Examination, baseline ADAS-Cog, and prior cholinomimetic use

Stratification	GAL-ER vs placebo p-value	GAL-IR vs placebo p-value
None	0.2770	0.1512
By country	0.0582	0.0845
By baseline Mini-Mental Status Examination score (> 22; ≤ 22)	0.0777	0.0477
By baseline ADAS-Cog score (> 18; ≤ 18)	0.1107	0.0251
By prior cholinomimetic use	0.2140	0.1192

Not that nominally statistically significant differences between extended-release galantamine and placebo were not seen even when other stratification cut-off points were used for the baseline Mini-Mental Status Examination and ADAS-Cog

- Thus the (nominally) statistically significant differences between extended-release galantamine seen when stratification by country was combined with stratification by one of the prognostic variables in Cochran-Mantel-Haenszel test-based analyses of the CIBIC-Plus may have been due to an interaction, rather than due to an effect of the individual variables themselves.

8.3 Analyses Of CIBIC-Plus Confined To US Centers

- Cochran-Mantel-Haenszel test-based analyses, limited to the US centers, did show a (nominally) statistically significant superiority of the extended-release preparation of galantamine over placebo, regardless of whether there was stratification by study site

Stratification	GAL-ER vs placebo p-value	GAL-IR vs placebo p-value
None	0.0478	0.0823
By site	0.026	0.029

- These results should be interpreted with caution since they are based on a sub-group analysis

8.4 Overall Conclusions

The post-hoc analyses of the CIBIC-Plus contained in this submission do not provide convincing evidence of a statistically significant difference between either the extended-release formulation of galantamine and placebo, or the immediate-release formulation of galantamine and placebo

9. Comments

- This submission is a Complete Response to a Not Approvable action letter that the Division issued on 12/23/03, for the original submission under NDA 21615. That application had sought the approval of Reminyl® (galantamine hydrobromide) Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. Reminyl® Extended-Release Capsules are intended for once-daily administration, in contrast to the currently-approved immediate-release tablet and oral solution formulations which are recommended as twice daily doses.

- The evidence in the original submission under NDA 21615, in support of the efficacy of Reminyl® Extended Release capsules, consisted of a single study, GAL-INT-10, the design and results of which are further described below

    - This was a randomized, double-blind, placebo-controlled, parallel-arm study.

    - The study had 3 treatment arms: Reminyl® Extended-Release capsules 16 to 24 mg once daily; immediate-release Reminyl® tablets 8 to 12 mg twice daily; and placebo. The period of double-blind, parallel-arm treatment in this study was 26 weeks

    - Key inclusion criteria were the diagnosis of probable Alzheimer's Disease; a Mini-Mental Status Examination score at screening of 10 -24; and an

Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) score at screening of at least 18.

- 971 patients were enrolled in the study and randomized in about equal proportions to the 3 treatment groups

- The primary efficacy measures were the ADAS-Cog and the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). There were 10 secondary efficacy measures, including the Alzheimer's Disease Cooperative Study – Activities Of Daily Living (ADCS-ADL) scale.

- The primary efficacy analysis was performed, as specified in the protocol, on the observed cases dataset at Month 6, and the primary comparison was between the Reminyl® Extended-Release and placebo groups, again as specified in the protocol. The difference in this dataset, between the Reminyl® Extended-Release and placebo groups, for the mean change from baseline in the ADAS-Cog, was 2.7 points, and favored galantamine ($p \leq 0.001$). For the CIBIC-Plus, using the same dataset, 61% of those treated with extended-release galantamine, and 56.8% of those treated with placebo, either improved or showed no change ($p = 0.086$, when changes on the full 7-point scale were compared). Similar results were seen, on both primary efficacy parameters, when the Reminyl® Extended-Release and placebo groups were compared for the last-observation-carried-forward and classical intent-to-treat datasets; the results were also similar when the immediate-release Reminyl® and placebo groups were compared.

- The protocol specified that evidence of the efficacy of extended-release galantamine was to be based on demonstrating a statistically significant ($p < 0.05$) treatment difference on both primary efficacy measures between that galantamine group and the placebo group.

- A comparison of the treatment groups on mean change from baseline to Week 26 scores for the ADCS-ADL using the observed cases dataset, revealed a mean difference between the Reminyl® Extended-Release and placebo groups of 2.4 points favoring galantamine ($p = 0.003$); a p-value of < 0.001 was seen in each instance when these groups were compared using the last-observed-carried-forward and classical intent-to-treat datasets

- The Agency's Not Approvable action on this application was based on the following

  - The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two prospectively-designated co-primary efficacy measures: a cognitive measure and a global/functional measure. In GAL-INT-10, Reminyl® Extended-Release capsules were not demonstrated to be superior to

placebo on the CIBIC-Plus. Therefore this study could not be said to have shown substantial evidence of effectiveness

- The comparison of the Reminyl® Extended-Release and placebo groups on the ADCS-ADL, a measure that could also be acceptable as a co-primary measure of efficacy, if prospectively designated, showed a nominally statistically significant treatment difference that favored the Reminyl® Extended-Release group. However, the negative finding on the protocol-specified global measure, the CIBIC-Plus, made relying on the results of any secondary efficacy measures inappropriate

- In the current application, the sponsor has performed a number of additional analyses of the CIBIC-Plus. The sponsor contends that the results of these additional analyses, together with the analyses of the ADAS-Cog and ADCS-ADL described in the original application, provided substantial evidence of the effectiveness of the Reminyl® Extended-Release formulation in mild to moderate dementia of the Alzheimer's type.

- The new CIBIC-Plus analyses, which were all performed using the intent-to-treat, last-observation-carried-forward dataset (based on a Cochran-Mantel-Haenszel model using rank scores and stratified by study site) are further summarized below

  - The sponsor now believes that the Cochran-Mantel-Haenszel test model used for the protocol-specified analysis of the CIBIC-Plus, which used modified ridit scores and was stratified by region (US vs. non-US), may not have been appropriate since, in that analysis, US and non-US centers were equally weighted, whereas US centers contributed 69% of those enrolled in the study. The sponsor is currently of the view that, since randomization was stratified by study site, a more appropriate Cochran-Mantel-Haenszel test model for analysis of the CIBIC-Plus was one that used rank scores and was stratified by study site. The sponsor has used the latter model to demonstrate what appears to be a nominally statistically significant superiority of both the extended- and immediate-release formulations of Reminyl® over placebo on the CIBIC-Plus, with p-values of 0.030 and 0.027, respectively; these results are considered by the sponsor to more accurately reflect the overall treatment effects of both formulations of Reminyl® on that measure

  - A number of baseline variables contributing to CIBIC-Plus outcome were identified by logistic regression analysis; these variables were screening Mini-Mental Status Examination score, baseline ADAS-Cog score, and prior cholinomimetic use. 3 separate analyses of the CIBIC-Plus were then performed using Cochran-Mantel-Haenszel test models; each was stratified for one of the variables considered of prognostic importance, and for country. In each of the 3 analyses the extended-release formulation of galantamine showed a nominally statistically significant superiority to placebo; in each model, the immediate-release formulation

showed either a nominally statistically significant superiority to placebo, or a superiority that approached nominal statistical significance

- Since US centers contributed about 69% of subjects to this study and since these subjects were considered by the sponsor to be more homogenous, a CIBIC-Plus analysis was performed confined to the US centers alone. This analysis, too, appeared to show a nominally statistically significant superiority of each Reminyl® formulation to placebo (p-values of 0.026 and 0.029 for the extended- and immediate-release formulations, respectively)

- The Agency Biometrics reviewer, Dr Kun He, has concluded the following about the sponsor's re-analyses of the CIBIC-Plus using the Cochran-Mantel-Haenszel test with rank scores

  - The significance of the analysis stratified by study site is questionable since there was no pre-specified plan for pooling subjects, and since the nominally statistically significant result favoring extended-release galantamine over placebo could have been driven mainly by data from a single large pooled site

  - The nominally statistically significant differences between extended-release galantamine and placebo that were seen when stratification by country was combined with stratification by one of the prognostic variables in Cochran-Mantel-Haenszel test-based analyses of the CIBIC-Plus may have been due to an interaction, since such differences were not seen when these variables were applied individually as stratification factors.

  - In the analysis confined to US centers, the nominally statistically significant difference between extended-release galantamine and placebo should be interpreted with caution since it was based on a subgroup

  - **The post-hoc analyses of the CIBIC-Plus presented in this submission do not provide convincing evidence of a statistically significant difference between extended-release galantamine and placebo**

- My overall view of this application is as follows

  - The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure.

  - The protocol for the GAL-INT-10 study specified that the efficacy of the extended-release galantamine formulation in that study was to be based on demonstrating a statistically significant superiority to placebo on both primary efficacy measures, the ADAS-Cog and CIBIC-Plus.

- Since the treatment differences between extended-release galantamine and placebo on the CIBIC-Plus did not achieve or approach statistical significance using the protocol-specified analysis, this study has, according to the current regulatory standard, failed to establish evidence for the efficacy of extended-release Reminyl® in mild-to-moderate Alzheimer's Disease.

- The comparison of the Reminyl® Extended-Release and placebo groups on the ADCS-ADL showed a nominally statistically significant treatment difference favoring the Reminyl® Extended-Release group over placebo. While the ADCS-ADL would have been acceptable as a co-primary measure of efficacy in lieu of the CIBIC-Plus, if prospectively designated, it was one of 10 secondary efficacy measures in this study (albeit the only secondary efficacy measure other than the dichotomized CIBIC-Plus that could be considered a global or functional instrument), and these measures were subject to 90 separate analyses. Moreover, the lack of any evidence of efficacy on the protocol-specified global co-primary efficacy measure, the CIBIC-Plus, made relying on the results of any secondary efficacy measures inappropriate

- Since the extended-release formulation of galantamine is intended to be taken once daily and will therefore be more convenient to use than the immediate-release formulation, for which twice daily dosing is recommended, the former formulation is likely to be used much frequently than the latter, when marketed. It is therefore especially important that evidence for the efficacy of the extended-release formulation should be clearly demonstrated prior to marketing approval being granted; such evidence is currently lacking.

- While the sponsor has now performed further analyses of the CIBIC-Plus, using Cochran-Mantel-Haenszel test models different from those used for the primary efficacy analyses, which have shown nominally statistically significant differences favoring extended-release galantamine over placebo, the new analyses are post-hoc, and their results are model-dependent, confined to a subgroup, or otherwise deficient. For those results that are model-dependent, the sponsor has not provided convincing evidence that the models that show "positive" results are more appropriate to use than those that do not. These analyses cannot therefore be considered to have met the "substantial evidence" of effectiveness standard

10. Conclusion And Recommendations

The sponsor has failed to provide substantial evidence of the effectiveness of the extended-release formulation of galantamine in the treatment of mild to moderate dementia of the Alzheimer's type.

I recommend that a further Not Approvable action letter be issued.

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 7/26/04
cc:
HFD-120
NDA 21615 (B2)

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/s/

Ranjit Mani
7/26/04 09:59:53 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21615**
Sponsor:	**Johnson & Johnson**
Drug:	**Reminyl® ER Capsules**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Briefing Package**
Correspondence Date:	**1/30/04**
Date Received / Agency:	**2/2/04**
Date Review Completed	**2/17/04**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission contains a briefing package for a meeting that is intended to discuss a recent Not Approvable letter issued by the Division for the original submission under New Drug Application (NDA) 21615. That application, originally submitted on 2/24/03, sought the approval of Reminyl® Extended-Release Capsules for the treatment of mild to moderate dementia of the Alzheimer's type. The Not Approvable letter was issued on 12/23/03.

The original application under NDA 21615 was based mainly on the results of one Phase III randomized, double-blind, placebo-controlled efficacy study (GAL-INT-10), an uncontrolled, open-label extension to GAL-INT-10, and several pharmacokinetic trials.

Four-Month and Seven-Month Safety Updates to the original application under NDA 21615 were submitted on 6/19/03 and 10/3/03, respectively, and were reviewed with the original application.

Reminyl® Extended-Release capsules have been developed under Investigational New Drug Application (IND) 61703. The immediate-release tablet and oral solutions formulations of galantamine, Reminyl®, had earlier been developed by this sponsor for the treatment of Alzheimer's Disease under IND 51538. NDAs 21169 and 21224, for the use of the immediate-release tablet and oral solution forms, respectively, of galantamine in the treatment of mild-to-moderate dementia of the Alzheimer's type were approved in 2001. Later in 2001, a supplemental NDA (SCM-001) was approved for the use of immediate-release tablet and oral solution formulations of synthetic galantamine (for the treatment of mild-to-moderate dementia of the Alzheimer's type), instead of the plant-derived drug substance approved earlier.

The sponsor had earlier proposed that Reminyl® Extended-Release capsules be administered once daily, whereas it is recommended in the package insert for the currently approved immediate-release formulation of Reminyl® that that drug formulation be administered twice daily.

Please see my review of NDA 21615 for further details.

2. Contents Of Submission And Review

2.1 Contents Of Submission

The submission contains the following

- Cover letter
- Briefing package containing the following
  - Summary of safety, efficacy, and biopharmaceutical information submitted earlier under IND 21615. This summary uses 3 headings:
    - Development History
    - Major Efficacy Results (GAL-INT-10)
    - Pharmacokinetic Comparison Between Extended-Release Capsules and Immediate-Release Tablets
  - Discussion Points (addressing items in the Not-Approvable Letter)
  - An additional question for the Division

2.2 Contents Of Review

In this review, I will address the following in the same order as below

- Text of Not Approvable Letter
- Development history for galantamine (as presented by sponsor)
- Major efficacy results for GAL-INT-10 (as presented by sponsor)
- Pharmacokinetic comparisons between extended-release capsules and approved immediate-release tablets of galantamine (as presented by sponsor)
- Discussion points (as presented by sponsor)

3. Text Of Not Approvable Letter

Key text from the Not Approvable action letter of 12/23/03 is reproduced verbatim below

> We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:
>
> **Lack of Substantial Evidence of Effectiveness:**
>
> The supporting clinical efficacy study GAL-INT-10 fails to provide evidence of effectiveness of extended-release galantamine.

As you know, the current regulatory standard for a demonstration of effectiveness for treatments of Alzheimer's Disease is the showing of statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure. Unfortunately, Reminyl ER was not shown to be superior to placebo on the CIBIC-Plus (for the intent-to-treat population on the last observation carried forward analysis, the between-treatment contrast yields p=0.22). Thus, based on the pre-specified primary efficacy analysis, this study must be considered not to have shown substantial evidence of effectiveness of Reminyl® Extended-Release Capsules.

While the between-treatment comparison on the ADCS-ADL, a secondary efficacy measure that also can be acceptable as a co-primary measure of overall functioning (when so designated prospectively), was nominally significant (p<0.001), the negative finding on the protocol specified global measure (the CIBIC-Plus) makes relying on any analysis of further outcome variables inappropriate, because to do so inflates the overall Type I error for the study.

Before this application can be approved, you must submit a single adequate and well-controlled investigation that demonstrates superiority of Reminyl ER to placebo on two prospectively designated outcomes of the sort described above.

4. Development History

The following is a summary of what is stated by the sponsor in the briefing document

- Galantamine is approved for the symptomatic treatment of mild to moderate Alzheimer's Disease

- The table below (which I have copied from the submission) compares the efficacy of galantamine in relation to placebo during the development of the immediate-release formulation.

Study ITT/LOCF	Formulation	Cognition (ADAS-cog/11) P value vs Plac	Global (CIBIC-plus) P value vs Plac	Function (DAD or ADCS/ADL) P value vs Plac
Gal-INT-1 (6mths)	IR	<0.001	<0.05	NS (DAD)
Gal-USA-1 (6mths)	IR	<0.001	<0.05	NS (DAD)
Gal-INT-2 (3mths)	IR	<0.05	<0.05	<0.05 (DAD)
Gal-USA-10 (5mths)	IR	<0.001	<0.05	=0.002 (ADCS-ADL)
Gal-INT-10 (6mths)	IR	<0.001	NS	=0.018 (ADCS-ADL)
	ER	<0.001	NS	<0.001 (ADCS-ADL)

- In regard to the studies depicted in the table
    - Studies GAL-INT-1, GAL-USA-1, and GAL-USA-10 were considered pivotal and met the regulatory requirement of showing statistically significant benefits on 2 co-primary efficacy measures. GAL-INT-2 was a shorter supportive trial of 3 months duration and corroborated the results of the pivotal trials
    - The ADCS-ADL was used an outcome measure in GAL-USA-10 and a statistically significant effect favoring galantamine was observed on that measure in that study
    - The once-daily dosage form (i.e., the extended-release capsule form) was bioequivalent to the immediate-release formulation in regard to AUC and C_{min}, but had a lower C_{max}(estimated ration of means = 0.76). On account of a paucity of information about the role of the C_{max} in the efficacy of this class of compounds, "the Agency mandated an efficacy study."
    - The efficacy study (GAL-INT-10) for the once-daily formulation of galantamine, which was discussed with the Division, had the following features
        - It included not only a placebo arm but also the immediate-release formulation as an active control
        - In accordance with a draft Agency guidance, the criterion for a "positive" study was the demonstration of a statistically significant superiority of the extended-release formulation of galantamine over placebo on the same co-primary efficacy endpoints (ADAS-Cog and CIBIC-Plus) that were used in the development of the immediate-release formulation of galantamine
        - The inclusion criteria and dosing regimen used in GAL-INT-10 were the same as those used for GAL-USA-10, except that the upper limit of the Mini-Mental Status Examination score range for inclusion was increased from 22 to 24, so that patients with milder disease could be enrolled.

5. Major Efficacy Results For Study GAL-INT-10

The following is a summary of what is stated by the sponsor in the briefing document

- Study GAL-INT-10 was used to assess the efficacy of extended-release galantamine versus placebo. This was a 26-week randomized, double-blind, placebo-controlled, parallel-arm flexible-dose in patients
- The study which was carried out in 93 centers randomized 971 patients to 3 treatment groups: placebo, extended-release galantamine, and immediate-release galantamine

- The primary efficacy measures were the ADAS-Cog and CIBIC-Plus. The secondary efficacy measures were the ADCS-ADL and Neuropsychiatry Inventory.

- The results for the intent-to-treat population, and for the ADAS-Cog, CIBIC-Plus and ADCS-ADL are summarized in the following table (which I have copied from the submission

Summary of efficacy measures between galantamine ER and IR based on change from baseline in comparison with placebo			
	ADAS-cog/11 Mean change (95%CI) p-value	*CIBIC-plus* % of no change and improved p-value*	*ADCS-ADL* Mean change (95%CI) p-value
Pivotal AD clinical study for ER: GAL-INT-10			
Intent-to-Treat:			
Endpoint *LOCF*			
ER vs. Placebo	-2.4 (-3 34 ~ -1.49) p<0 001	60 8% vs. 57.5% p=0.216	2 7 (1 24 ~ 4.10) p<0.001
IR vs. Placebo	-2.8 (-3.70 ~ -1.86) p<0.001	63.2% vs. 57.5% p=0.144	1 7 (0.29 ~ 3.13) p=0 018
ER vs. IR	0.4 (-0 56 ~ 1 29) p=0 438	60 8% vs. 63.2% p=0 752	1 0 (-0.47 ~ 2 39) p=0.188

*p value based on the entire 7-point scale

6. Pharmacokinetic Comparison Between Extended-Release Capsules And Approved Immediate-Release Tablets Of Reminyl®

The following is a summary of what is stated by the sponsor in the briefing document

- The pharmacokinetic properties of the extended-release capsules of galantamine were compared with the immediate-release tablets in the single-center, randomized, open-label, 3-way crossover Phase I study GAL-NED-8.

- Based on the comparison of 24 mg doses, the exposure was somewhat (approximately 10%) less with the extended-release capsule. AUC and C_{min} were within the bioequivalence limits of 80 to 125%, while the estimated ratio of means for C_{max} was 76%

- The results of the study are in the following table (which I have copied from the submission)

Summary of PK bioequivalence between galantamine ER and IR			
ER vs. IR Bioequivalent Study: GAL-NED-8 (at 24 mg dose level)			
Mean treatment ratio (90% CI)	AUC_{24h}	Cmin	Cmax
ER (fasted) / IR (fasted)	93 (90 - 96)	89 (83 - 96)	76 (71 - 80)

7. Discussion Points

The sponsor has highlighted two sections of the Not Approvable letter of December 23, 2003 for further discussion. These sections are highlighted in bold italics for further discussion with the sponsor's response below each item

The text highlighted below by me is taken from the actual text of the letter. The text used by the sponsor for the first item is different from the actual text of the letter, although the meaning conveyed is the same.

As you know, the current regulatory standard for a demonstration of effectiveness for treatments of Alzheimer's Disease is the showing of statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure. Unfortunately, Reminyl ER was not shown to be superior to placebo on the CIBIC-Plus (for the intent-to-treat population on the last observation carried forward analysis, the between-treatment contrast yields p=0.22). Thus, based on the pre-specified primary efficacy analysis, this study must be considered not to have shown substantial evidence of effectiveness of Reminyl® Extended-Release Capsules.

While the between-treatment comparison on the ADCS-ADL, a secondary efficacy measure that also can be acceptable as a co-primary measure of overall functioning (when so designated prospectively), was nominally significant (p<0.001), the negative finding on the protocol specified global measure (the CIBIC-Plus) makes relying on any analysis of further outcome variables inappropriate, because to do so inflates the overall Type I error for the study.

- The sponsor's view is that GAL-INT-10 demonstrated clinical equivalence between the extended- and immediate-release formulations of galantamine, in relation to placebo, based on similarly positive findings on both a cognitive and a functional measure

- The sponsor has the following questions for the Division in relation to GAL-INT-10

    - How did the Division interpret the data for the effect of the immediate-release formulation of galantamine on the CIBIC-Plus?

- How did the Division interpret the positive results for effects of both formulations on the ADCS-ADL (consistent with the results of previous studies) on the last-observation-carried-forward analysis given that these results are unlikely to have occurred by chance

Before this application can be approved, you must submit a single adequate and well-controlled investigation that demonstrates superiority of Reminyl ER to placebo on two prospectively designated outcomes of the sort described above.

The sponsor's response is as follows

- While Study GAL-INT-10 was being conducted , the American Academy of Neurology published (in May 2001) its clinical practice guideline in which it is recommended that acetylcholinesterase inhibitors should be considered for the treatment of mild to moderate Alzheimer's Disease. The guidance issued by the National Institute of Clinical Excellence (UK) in 2001 has a similar suggestion. As a consequence of the latter guidance a central Institutional Review Board in the UK failed to approved GAL-INT-10 which, in turn, resulted in the UK being removed as a participating region for that study

- Given current clinical practice standards for treating Alzheimer's Disease, and "emerging" data suggesting that untreated patients who initiate treatment late may not reach the same level of function as patients treated earlier in their clinical course, the sponsor is concerned that placebo-controlled trials in Alzheimer's Disease may no longer be justifiable or practical

- The sponsor wishes to discuss an alternative approach (i.e., an approach other than a further clinical trial) to secure the approval of the extended-release formulation of galantamine. This approach will consist of the demonstration of a link between the pharmacokinetic profile and pharmacological response. The basis for this approach is as follows

    - The pharmacokinetic profiles of the extended- and immediate-release formulations of galantamine differ in plasma C_{max}, but not in AUC or C_{min}.

    - The similarity in efficacy on the cognitive and functional domains between the immediate- and extended-release formulations of galantamine suggests that efficacy is not driven by C_{max}, although that hypothesis has not been tested.

  The sponsor wishes to know if the Division will be amenable to such an approach

8. Additional Question

The sponsor has asked if the nomenclature to be used for the proposed new formulation in labeling – Reminyl® ER (galantamine hydrobromide) Extended Release Capsules has been agreed to by the Division of Medication Errors and Technical Support.

9. Comments

- This submission is a briefing package for a meeting that the sponsor has sought discuss a Not Approvable action letter that the Division issued, on 12/23/03, for NDA 21615. That application sought the approval of Reminyl® (galantamine hydrobromide) Extended-Release Capsules for the treatment of mild-to-moderate dementia of the Alzheimer's type. Reminyl® Extended-Release Capsules are intended for once-daily administration.

- The evidence submitted in that application in support of the efficacy of Reminyl® Extended Release capsules consisted of a single study, GAL-INT-10, the design and results of which are further described below

    - This was a randomized, double-blind, placebo-controlled, parallel-arm study.

    - The study had 3 treatment arms: Reminyl® Extended-Release capsules 16 to 24 mg once daily; immediate-release Reminyl® tablets 8 to 12 mg twice daily; and placebo. The period of double-blind, parallel-arm treatment in this study was 26 weeks

    - Key inclusion criteria were the diagnosis of probable Alzheimer's Disease; a Mini-Mental Status Examination score at screening of 10 -24, and an Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) score at screening of at least 18.

    - 971 patients were enrolled in the study and randomized in about equal proportions to the 3 treatment groups

    - The primary efficacy measures were the ADAS-Cog, and the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). There were 10 secondary efficacy measures, including the Alzheimer's Disease Cooperative Study – Activities Of Daily Living (ADCS-ADL) scale.

    - The primary efficacy analysis was performed, as specified in the protocol, on the observed cases dataset at Month 6, and the primary comparison was between the Reminyl® Extended-Release and placebo groups, again as specified in the protocol. The difference in this dataset, between the Reminyl® Extended-Release and placebo groups for the mean change from baseline in the ADAS-Cog was 2.7 points, and favored galantamine ($p \leq 0.001$). For the CIBIC-Plus, using the same dataset, 61% of those

treated with extended-release galantamine, and 56.8% of those treated with placebo improved or showed no change ($p = 0.086$, when changes on the full 7-point scale were compared). Similar results were seen, on both primary efficacy parameters, when the Reminyl® Extended-Release and placebo groups were compared for the last-observation-carried-forward and classical intent-to-treat datasets; the results were also similar when the immediate-release Reminyl® and placebo groups were compared.

- The protocol specified that evidence of the efficacy of extended-release galantamine was to be based on demonstrating a statistically significant ($p < 0.05$) treatment difference on both primary efficacy measures between that galantamine group and the placebo group.

- A comparison of the treatment groups on mean change from baseline to Week 26 scores for the ADCS-ADL using the observed cases dataset, revealed a mean difference between the Reminyl® Extended-Release and placebo groups of 2.4 points favoring galantamine ($p = 0.003$); a p-value of < 0.001 was seen in each instance when these groups were compared using the last-observed-carried-forward and classical intent-to-treat datasets

- The Agency's Not Approvable action on this application was based on the following

  - The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two prospectively-designated co-primary efficacy measures: a cognitive measure and a global/functional measure. In GAL-INT-10, Reminyl® Extended-Release capsules were not demonstrated to be superior to placebo on the CIBIC-Plus. Therefore this study could not be said to have shown substantial evidence of effectiveness

  - The comparison of the Reminyl® Extended-Release and placebo groups on the ADCS-ADL, a measure that could also be acceptable as a co-primary measure of efficacy if prospectively designated, showed a nominally statistically significant treatment difference that favored the Reminyl® Extended-Release group. However, the negative finding on the protocol-specified global measure, the CIBIC-Plus, made relying on the results of any secondary efficacy measures inappropriate

- In the current submission, the sponsor has argued that the GAL-INT-10 study demonstrated clinical equivalence between the two galantamine formulations, based on their efficacy relative to placebo on both the ADAS-Cog and ADCS-ADL. The sponsor further believes that since both formulations were superior to placebo on the ADCS-ADL (on the last-observation-carried-forward dataset), those results are unlikely to have

been due to chance. The sponsor has also drawn attention to the lack of efficacy on the CIBIC-Plus for both formulations.

- The sponsor believes that the conduct of a further placebo-controlled trial of Reminyl® may not be justifiable or practical. Accordingly, the sponsor proposes that an alternative route to approval of this formulation may be the demonstration of a link between pharmacokinetic profile and pharmacological activity; further details of this proposal are not provided.

- This reviewer's opinion continues to be as follows

    - The efficacy of Reminyl® Extended-Release capsules in treating mild to moderate dementia of the Alzheimer's type has not been clearly established. Study GAL-INT-10 must be considered negative, based on the results of the prospectively-defined statistical analysis. The similarity in effect between the two formulations of Reminyl® in this study does not by itself establish that the extended-release formulation is effective, just because the immediate-release formulation is approved; the similarity in effect of both formulations could be explained on the basis that both formulations were ineffective in this study.

    - The sponsor has not provided any details of the proposal to establish a link between pharmacokinetic profile and pharmacological activity of galantamine and thereby seek approval

10. Meeting With Sponsor: February 17, 2004

A meeting was held with the sponsor today, chaired by Dr R. Katz.

The sponsor's and Division's viewpoints about the results of Study GAL-INT-10, and the next steps that the sponsor might take in obtaining approval of Reminyl® ER for the treatment of mild to moderate dementia of the Alzheimer's type, were discussed. The discussion included an outline of the sponsor's views as to why there was no evidence for the efficacy of either the extended-release or immediate-release formulations of Reminyl® on the CIBIC-Plus analysis in that study.

Based on that discussion, the following were the key agreements reached at the meeting

- The sponsor was advised to submit a detailed argument that addresses, on clinical and statistical grounds, why the results of the ADCS-ADL analysis for Study GAL-INT-10 should be considered in lieu of those for the CIBIC-Plus, in attempting to establish that that study is "positive"

- The sponsor proposed that another means of establishing the efficacy of the extended-release formulation of Reminyl® might be the demonstration

of a correlation between exposure (based on AUC) and clinical effect, in a small study using the immediate-release formulation of Reminyl® alone, given the similarity in AUC between the 2 formulations of Reminyl®. The Division will comment more fully on such a proposal once more details are submitted. Such a proposal should clearly describe how a link between clinical effectiveness and pharmacokinetic exposure will be established.

- The sponsor proposed that a further efficacy study of the extended-release formulation of Reminyl® use the ADAS-Cog and ADCS-ADL as primary efficacy measures and be of 3 months duration. This proposal will in all likelihood be acceptable to the Division, although 3 months is the minimum duration for an efficacy study in Alzheimer's Disease .

- A submission comprising one or more of the above would be considered a response to the Division's Not-Approvable action letter.

The sponsor asked if the nomenclature to be used for the proposed new formulation in labeling – Reminyl® ER (galantamine hydrobromide) Extended Release Capsules had been agreed to by the Division of Medication Errors and Technical Support (DMETS). The Division stated that the final opinion of DMETS was pending.

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 2/17/04
cc:
HFD-120
NDA 21615

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ranjit Mani
2/17/04 05:01:48 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21615 (000)**
Sponsor:	**Johnson & Johnson**
Drug:	**Reminyl® ER**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**New Drug Application**
Correspondence Date:	**2/24/03**
Date Received / Agency:	**2/26/03**
Date Review Completed	**12/21/03**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Table Of Contents

2. Executive Summary

2.1 Recommendations

I recommend against approval of this application, and propose that a Non-Approval letter be issued.

2.2 Proposed Indication

This application seeks the approval of Reminyl® (galantamine hydrobromide) Extended-Release Capsules **for the treatment of mild-to-moderate dementia of the Alzheimer's type.**

Reminyl® Extended-Release Capsules are intended for once-daily administration.

Currently, an immediate-release tablet formulation of Reminyl® is approved for the treatment of mild-to-moderate dementia of the Alzheimer's type, but as a twice-daily dose.

2.3 List Of Studies Included In Submission

This application is based mainly on the following clinical studies

- GAL-INT-10, a randomized, double-blind, placebo-controlled, parallel-arm efficacy study
- GAL-INT-21, an open-label, uncontrolled, extension to GAL-INT-10 (this study is still ongoing).
- 5 clinical pharmacology studies: GAL-BEL-19; GAL-BEL-20; GAL-NED-8; GAL-NED-9; and GAL-NED-12.

2.4 Results Of Key Efficacy And Safety Studies

2.4.1 GAL-INT-10

This was a randomized, double-blind, placebo-controlled, parallel- and three-arm study, whose objective was to evaluate the efficacy and safety of Reminyl® Extended-Release capsules in mild-to-moderate Alzheimer's Disease. The 3 treatment arms for this study were: Reminyl® Extended-Release capsules 16 to 24 mg once daily; immediate-release Reminyl® tablets 8 to 12 mg twice daily; and placebo. The period of double-blind, parallel-arm treatment in this study was 26 weeks

Key inclusion criteria were the diagnosis of probable Alzheimer's Disease; a Mini-Mental Status Examination score at screening of 10 -24, and an Alzheimer's

Disease Assessment Scale – Cognitive (ADAS-Cog) score at screening of at least 18.

971 patients were enrolled in the study. The number of patients randomized to, and the number completing the study in each of the 3 treatment groups is summarized in the following table.

Treatment group	Number randomized	Number completing study
Reminyl® Extended-Release Capsules	327	251
Reminyl® Immediate-Release Tablets	320	251
Placebo	324	266

The primary efficacy measures were the ADAS-Cog, and the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). There were 10 secondary efficacy measures, including the Alzheimer's Disease Cooperative Study – Activities Of Daily Living (ADCS-ADL) scale. Safety measures included vital signs, safety laboratory tests, physical examinations, adverse events, and body weight.

The primary efficacy analysis was performed, as specified in the protocol, on the observed cases dataset at Month 6, and the primary comparison was between the Reminyl® Extended-Release and placebo groups, again as specified in the protocol. The difference in this dataset, between the Reminyl® Extended-Release and placebo groups for the mean change from baseline in the ADAS-Cog was 2.7 points, and favored galantamine ($p \leq 0.001$). For the CIBIC-Plus, using the same dataset, 61% of those treated with extended-release galantamine, and 56.8% of those treated with placebo improved or showed no change ($p = 0.086$, when changes on the full 7-point scale were compared). Similar results were seen, on both primary efficacy parameters, when the Reminyl® Extended-Release and placebo groups were compared for the last-observation-carried-forward and classical intent-to-treat datasets; the results were also similar when the immediate-release Reminyl® and placebo groups were compared.

The protocol specified that evidence of the efficacy of extended-release galantamine was to be based on demonstrating a statistically significant ($p < 0.05$) treatment difference on both primary efficacy measures.

A comparison of the treatment groups on mean change from baseline to Week 26 scores for the ADCS-ADL using the observed cases dataset, revealed a mean difference between the Reminyl® Extended-Release and placebo groups of 2.4 points favoring galantamine ($p = 0.003$); a p-value of < 0.001 was seen in each instance when these groups were compared using the last-observed-carried-forward and classical intent-to-treat datasets. However, the analyses performed on all the secondary efficacy measures involved 90 comparisons of extended-release galantamine with placebo, rendering questionable the

significance of the p-values obtained for those comparisons that evaluated changes on the ADCS-ADL alone.

The safety profile of the extended-release galantamine formulation was broadly similar to that of the immediate-release formulation. There were no safety concerns specific to the extended-release formulation.

2.4.2 GAL-INT-21

This study is an open-label uncontrolled extension to Study GAL-INT-10, and remains ongoing. To be enrolled in this study, a patient should have completed Study GAL-INT-10.

All patients enrolled in this study were to be titrated to a dose of Reminyl® ER of 16 to 24 mg once daily. The study is of 12 months' duration.

Safety outcome measures include vital signs, safety laboratory tests, physical examinations, adverse events, and body weight.

Based on the Seven-Month Safety Update to this application which had a data cut-off date of 5/31/03, 722 patients have been enrolled in, and 393 patients have completed, this study. Interim safety data summaries have been included in the original application and in the Four-Month and Seven-Month Safety Updates; they contain information about deaths, other serious adverse events, and discontinuations due to adverse events for the 536 enrolled patients for whom such information is available. The spectrum of such events is similar to that seen in patients treated with immediate-release galantamine, and does not indicate the presence of any special safety concern that can be linked to the use of the extended-release capsule formulation of galantamine

2.5 Safety Data From Clinical Pharmacology Studies In Original Application

A total of 109 unique healthy subjects received at least one dose of study drug in these trials; of these subjects, all received the extended-release formulation of galantamine and 50 received the immediate-release formulation.

The spectrum of adverse events seen in these studies was similar to that of immediate-release galantamine and did not raise any special concerns

2.6 Conclusions

2.6.1 Efficacy

The protocol for the GAL-INT-10 study specified that the efficacy of the extended-release galantamine formulation in this study was to be based on demonstrating a statistically significant superiority to placebo on both primary efficacy measures, the ADAS-Cog and CIBIC-Plus.

Since the treatment differences between extended-release galantamine and placebo on the CIBIC-Plus did not achieve statistical significance, this study has failed to establish evidence for the efficacy of extended-release Reminyl® in mild-to-moderate Alzheimer's Disease.

2.6.2 Safety

Safety data contained in this submission did not indicate any areas of concern specific to Reminyl® Extended-Release Capsules, with the overall safety profile of that formulation being similar to that of the approved immediate-release tablet formulation of Reminyl®.

3. Introduction

This submission contains a New Drug Application (NDA) for Reminyl® Extended-Release capsules (modified-release galantamine hydrobromide capsules), which the sponsor is seeking to market for the treatment of mild-to-moderate dementia of the Alzheimer's type.

This application is based mainly on the results of one Phase III randomized, double-blind, placebo-controlled efficacy study, an uncontrolled, open-label extension study, and several pharmacokinetic trials.

Four-Month and Seven-Month Safety Updates to this application were submitted on 6/19/03 and 10/3/03, respectively. These Safety Updates are also reviewed here.

Reminyl® Extended-Release capsules have been developed under Investigational New Drug Application (IND) 61703. The immediate-release formulation of galantamine, Reminyl® had earlier been developed by this sponsor for the treatment of Alzheimer's Disease under IND 51538. NDAs 21169 and 21224 for the use of the immediate-release tablet and oral solution forms, respectively, of galantamine in the treatment of mild-to-moderate dementia of the Alzheimer's type were approved in 2001. Later in 2001, a supplemental NDA (SCM-001) was approved for the use of a synthetic formulation of galantamine (for the treatment of mild-to-moderate dementia of the Alzheimer's type), instead of the plant-derived formulation approved earlier.

The sponsor proposes that Reminyl® Extended-Release capsules be administered once daily, whereas it is recommended in the package insert for the currently approved immediate-release formulation of Reminyl® that that drug formulation be administered twice daily.

This application has been the subject of two pre-NDA discussions with the sponsor, at a formal meeting held on 9/19/02, and a teleconference held on 11/26/02.

The statistical, clinical pharmacology and biopharmaceutics, and chemistry reviewers of this submission are Drs Kun He, Ronald Kavanagh, and Janusz Rzeszotarski, respectively.

4. Terminology

In this submission, Reminyl® Extended-Release capsules have also been referred to as the "controlled-release" or "extended-release" formulation of Reminyl® or galantamine, and as "galantamine CR" or "GAL-CR." The approved

immediate-release formulation of Reminyl®/galantamine has also been referred to as "galantamine IR" or "GAL-IR."

In addition to using the above terminology, I will, in this review also refer to the extended-release and immediate-release formulations of Reminyl®, as Reminyl® ER and Reminyl® IR, respectively.

5. Studies Contained In Submission

This application is mainly based on the following clinical studies

- GAL-INT-10, a randomized, double-blind, placebo-controlled, parallel-arm efficacy study.
- GAL-INT-21, an open-label, uncontrolled, extension to GAL-INT-10 (this study is still ongoing).
- 5 clinical pharmacology studies: GAL-BEL-19; GAL-BEL-20; GAL-NED-8; GAL-NED-9; and GAL-NED-12.

Limited safety data from 2 additional studies of Reminyl® Extended-Release capsules have been included in the 7-Month Safety Update for this application.

6. Outline Of Review

The rest of this review will consist of the following in the same order as below:

- Tabular summary of key efficacy study, GAL-INT-10
- Efficacy rating scales and outcome measures used in key efficacy study, GAL-INT-10
- Protocol for Study GAL-INT-10
- Efficacy results of Study GAL-INT-10
- Safety results of Study GAL-INT-10
- Protocol for Study GAL-INT-21
- Safety summary of Study GAL-INT-21
- Four-Month Safety Update
- Seven-Month Safety Update

- Safety data from clinical pharmacology studies
- Summary of clinical pharmacology and biopharmaceutics review
- Pre-NDA discussions with sponsor
- Overall comments on efficacy and safety
- Review of draft labeling
- Financial disclosure certification
- Recommendations

7. Summary Of Efficacy Study

The protocol and the results of the primary efficacy analysis are summarily outlined below.

7.1 Protocol

Full details of the rating scales that are listed in abbreviated form in this summary, are contained in Section 8

Protocol#:	GAL-INT-10
Objective:	Efficacy and safety of Reminyl® CR in mild-to-moderate Alzheimer's Disease
Design:	Randomized, double-blind, placebo-controlled, parallel-arm study
Key Inclusion Criteria:	• Male or female • Probable Alzheimer's disease by NINCDS-ADRDA criteria • Mini-Mental Status Examination score 10-24 and ADAS-Cog score of at least 18
Dose Groups:	Placebo Reminyl® ER 16 to 24 mg q.d. Reminyl® IR 8 mg to 12 mg b.i.d
Duration:	26 weeks
Randomized Population:	Placebo → 324 patients Reminyl® ER 16 to 24 mg q.d. → 327 patients Reminyl® IR 8 mg to 12 mg b.i.d → 320 patients
Primary Efficacy Measures:	• ADAS-Cog • CIBIC-Plus
Secondary Efficacy Measures:	• ADAS-Cog/13 • ADAS-Cog/10 • ADAS-Cog/mem • Percentage of responders on standard ADAS-Cog using 0, 4, 7 and 10 points of improvement as cut-off • Percentage of subjects with "improved" or "no change" on the CIBIC-Plus. • Neuropsychiatry Inventory • Alzheimer's Disease Cooperative Study-ADL

Primary Efficacy Analysis: ADAS-Cog: ANOVA
(Observed Cases Dataset) CIBIC-Plus: Cochran-Mantel-Haenszel Test

Primary Comparison: Reminyl® ER vs Placebo

7.2 Results Of Primary Efficacy Analyses

7.2.1 Alzheimer's Disease Assessment Scale-Cog (ADAS-Cog)

The results of the analysis comparing the 2 treatment groups on the primary observed cases dataset is in the following table, which I have copied from the submission. The primary efficacy analysis is that at Week 26 (bolded).

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[1]
Baseline	305	26.1 (0.54)	--	306	27.3 (0.55)	--	300	26.3 (0.54)	--	
Week 8	289	25.8 (0.63)	0.0 (0.30)	286	25.4 (0.58)	-1.7 (0.30)	284	24.6 (0.58)	-1.5 (0.30)	<0.001
Week 12	275	25.9 (0.66)	0.0 (0.32)	268	24.0 (0.57)	-2.6 (0.31)	269	23.9 (0.57)	-2.2 (0.32)	<0.001
Week 26	**248**	**26.4 (0.72)**	**1.3 (0.36)**	**227**	**24.7 (0.69)**	**-1.8 (0.42)**	**240**	**24.8 (0.69)**	**-1.4 (0.34)**	**<0.001**

[1]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p<0.001.

7.2.2 Clinician Interview Based Impression of Change-Plus (CIBIC-Plus)

The results of the analysis comparing the 2 treatment groups on the observed cases dataset at Week 26 is in the following table, which I have copied from the submission.

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)	(Cum %)	n (%)	(Cum %)	n (%)	(Cum %)	P value[1]
N at Week 26	259		240		246		
Markedly improved	3 (1.2)	(1.2)	3 (1.3)	(1.3)	3 (1.2)	(1.2)	
Moderately improved	9 (3.5)	(4.6)	14 (5.8)	(7.1)	14 (5.7)	(6.9)	
Mildly improved	41 (15.8)	(20.5)	36 (15.0)	(22.1)	43 (17.5)	(24.4)	
No change	94 (36.3)	(56.8)	93 (38.8)	(60.8)	90 (36.6)	(61.0)	
Mildly worse	70 (27.0)	(83.8)	67 (27.9)	(88.8)	69 (28.0)	(89.0)	
Moderately worse	36 (13.9)	(97.7)	25 (10.4)	(99.2)	23 (9.3)	(98.4)	
Markedly worse	6 (2.3)	(100.0)	2 (0.8)	(100.0)	4 (1.6)	(100.0)	0.086

[1]GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
Cum % = cumulative percent
Note: Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at Week 26: p=0.223.

8. Efficacy Rating Scales/Outcome Measures Used In Study GAL-INT-10

8.1 Primary Efficacy Variables

8.1.1 Alzheimer's Disease Assessment Scale-Cog (ADAS-Cog)

This is a validated instrument consisting of the following 11 items: Word Recall Task, Naming Fingers and Objects, Orientation Questions, Constructional Praxis Task, Following Commands, Ideational Praxis Task, Word Recognition Task, Rating of Spoken Language, Rating of Language Comprehension, Rating of Word Finding Difficulty and Rating of Ability to Recall Test Instructions. The total

scores range from 0-70 with higher scores indicating greater cognitive impairment.

Note that extended forms and subsets of the ADAS-Cog are used as secondary efficacy measures in this protocol. These include:
ADAS-Cog/13 consisting of the standard ADAS-Cog and 2 additional items: Concentration and Distractibility and Delayed Word Recall
ADAS-Cog/10 consisting of the non-memory section of the ADAS-Cog
ADAS-Cog/mem comprising the memory items of the ADAS-Cog: Word Recall, Delayed Word Recall and Word Recognition

8.1.2 Clinician Interview Based Impression of Change-Plus (CIBIC-Plus)

The format for this instrument, as used in the galantamine efficacy studies, consists of the assessment of an independent clinician, with experience in Alzheimer's Disease. At the randomization visit this investigator assesses the patient's clinical status, audiotaping or videotaping that interview if needed. Subsequently this rater is denied access to any information about the patient's condition other than that derived from personal observation of the patient at an interview, and information provided directly to the rater by the caregiver. The caregiver can be asked to provide factual information only about the patient, such as information about recent events, but the clinician will avoid obtaining the caregiver's opinion about the patient's condition

A 7-point categorical rating scale was used as follows
1 = markedly improved relative to baseline
2 = moderately improved relative to baseline
3 = minimally improved relative to baseline
4 = no change relative to baseline
5 = minimally worse relative to baseline
6 = moderately worse relative to baseline
7 = markedly worse relative to baseline

8.2 Secondary Efficacy Variables

8.2.1 Neuropsychiatry Inventory

This is an instrument that assesses the following 10 domains (subscales): delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior. Each item is rated according to its frequency and severity; rating is based on interviewing a caregiver. The maximum total score (the sum of the subscale scores) is 120 with a higher score indicating greater behavioral abnormality.

8.2.2 Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)

This is a rating scale used to assess basic and instrumental activities of daily living. 23 items are rated by the investigator using information supplied by the caregiver. Each item has a score range varying from 0-3 to 0-7. The maximum possible total score is 78 with a higher score indicating better function.

8.2.3 ADAS-Cog Subsets

Subsets of the ADAS-Cog/11 have been used as secondary efficacy measures in this study. These include:

- ADAS-Cog/13 consisting of the standard ADAS-Cog and 2 additional items: Concentration and Distractibility and Delayed Word Recall
- ADAS-Cog/10 consisting of the non-memory section of the ADAS-Cog
- ADAS-Cog/mem comprising the memory items of the ADAS-Cog: Word Recall, Delayed Word Recall and Word Recognition

8.2.4 ADAS-Cog Responders

Additional secondary efficacy measures used in this study include the percentage of patients with changes in ADAS-Cog from baseline, exceeding each of the following

- 0 points
- - 4 points
- - 7 points
- - 10 points

8.2.5 Dichotomized CIBIC-Plus

The 7-point CIBIC-Plus has been dichotomized as follows

- "Improved" or "no change" (CIBIC-Plus score of 1 to 4)
- "Worse" (CIBIC-Plus Score of 5 to 7)

The proportion of those in the "improved" or "no change" category was a secondary efficacy measure.

9. Protocol For Efficacy Study GAL-INT-10

9.1 Title

Placebo-Controlled Evaluation Of Galantamine In The Treatment Of Alzheimer's Disease: Safety Of A Controlled-Release Formulation

9.2 Objectives

9.2.1 Primary

To evaluate the efficacy of controlled-release galantamine 16 mg/day and 24 mg/day compared to placebo in the treatment of Alzheimer's Disease as measured by the ADAS-Cog and CIBIC-Plus

9.2.2 Secondary

- To evaluate the effect of controlled-release galantamine on non-cognitive behaviors and activities of daily living using the Neuropsychiatry Inventory and ADCS-ADL
- To estimate the difference in effect between the controlled-release (Reminyl® ER) and immediate-release (Reminyl® IR) preparations of galantamine
- To evaluate the efficacy of controlled-release galantamine 16-24 mg/day compared with placebo on scores for additional versions of the ADAS-Cog: ADAS-Cog-13, ADAS-Cog-11 and ADAS-Cog-mem.
- To evaluate the safety and tolerability of controlled-release galantamine 16 mg/day and 24 mg/day compared to that of placebo and immediate-release galantamine 8 to 12 mg b.i.d by means of adverse event reports, physical examinations, electrocardiograms and laboratory tests

9.3 Design

Randomized (1:1:1), double-blind, placebo-controlled, parallel-arm, flexible-dose study

The study will be conducted at about 120-140 study sites in 8 countries.

3 study arms
Placebo
Galantamine CR 16-24 mg/day (as a single daily dose)
Galantamine IR 16-24 mg/day (as a twice daily dose)

9.4 Duration

6 months of double-blind treatment preceded by a placebo run-in period of one month

9.5 Sample Size

1020 patients randomized equally to the 3 treatment groups (340 patients in each group)

9.6 Key Inclusion Criteria

- Male or female
- If living in a residential home for the elderly, must be independent and approved by sponsor
- Probable Alzheimer's Disease by NINCDS-ADRDA criteria
- Mini-Mental Status Examination score 10-24 **and** ADAS-Cog score of at least 18
- Cognitive decline that was gradual in onset, progressive over a period of at least 6 months, and with evidence of sustained memory deterioration in an otherwise alert subject plus additional involvement in at least one of the following 5 areas: orientation, judgement and problem solving, functioning in

community affairs, functioning in home and hobbies, and functioning in personal care
- Reliable caregiver (criteria specified)
- Signed informed consent from patient or legal representative **and** caregiver

9.7 Key Exclusion Criteria

- Neurodegenerative disorders such as Parkinson's disease, Pick's disease, and other entities; mild extrapyramidal signs for which no treatment is needed were not criteria for exclusion
- Cognitive impairment due to head trauma, hypoxia, vitamin deficiency (patients taking regular B12 and/or folate are allowed if their dose has been stable and ongoing for at least 4 weeks prior to screening), infection, neoplasm, endocrine or metabolic disease, and mental retardation
- Multi-infarct dementia or clinically active cerebrovascular disease, for which the sponsor had specified certain ad hoc criteria listed below (and copied from the submission). There should have been evidence of :

a. A history of a significant cerebro-vascular event yielding a physical or neurological deficit likely to confound the assessment of the subject's intellectual function.
b. Multiple focal signs on neurological examination indicative of multiple ischemic attacks.
c. One or more of the following findings on a CT or MRI scan (taken within the last 12 months):
   - Multiple (2 or more) infarcts or white matter lacunes
   - A single strategically placed infarct in the angular gyrus, the thalamus, the basal forebrain, the Posterior Cerebral Artery (PCA) or Anterior Cerebral Artery (ACA) territory.
   - Extensive periventricular white matter lesions. Leukoaraiosis (periventricular white matter, low attenuation) is to be distinguished from multiple infarction. Leukoaraiosis is common in normal elderly individuals and persons with Alzheimer's disease. White matter deterioration should not result in exclusion unless it is abnormal and widespread (e.g., Binswanger's disease).

Note: subjects with an isolated cerebral infarct confirmed by appropriate imaging techniques, e.g., CT or MRI (both within the last year), can be included if the infarct is not strategically placed, as defined above. A CT or MRI must be repeated before inclusion if the subject has experienced significant loss of consciousness or other neurological signs or symptoms, stepwise deterioration, or has sustained head injury since the last scan. Subjects with an isolated loss of consciousness, transient ischemic attack or 'drop attacks', may be considered for inclusion providing that these did not occur in the previous 12 months.

At inclusion a CT or MRI scan not older than 12 month has to be available.

- Any of the following coexisting medical conditions: history of epilepsy or convulsions (other than febrile convulsions), clinically significant psychiatric disease, active peptic ulcer (criteria specified), clinically significant urinary

outflow obstruction, and clinically significant cardiovascular (criteria specified), hepatic, renal, pulmonary, metabolic or endocrine disease

- Any agent being used for the treatment of dementia such as nootropics, cholinomimetic drugs, estrogens without medical need, non-steroidal anti-inflammatory drugs or cyclo-oxygenase 2 inhibitors for > 30 days, Vitamin E (unless a stable dose had been taken for at least 6 months prior to trial initiation), and deprenyl. Subjects who had previously received cholinesterase inhibitors or M_1 agonists, whether approved or experimental, could be included in the trial, provided there was a washout period of at least 30 days prior to dispensing of study medication
- Drug or alcohol abuse within the previous year or prior prolonged history
- Female subjects who were not surgically sterile or post-menopausal
- History of severe drug allergy or hypersensitivity including to cholinomimetic agents or bromide
- Enrollment in other galantamine trials
- Enrollment in other clinical trials except with approval of sponsor
- Conditions that could interfere with absorption of compound or evaluation of disease
- Use of any other investigational medication within 30 days prior to enrollment
- Unsuitability for a trial of this type as per the investigator

9.8 Concomitant Medications

9.8.1 Prohibited Medications

These are listed above in Section 9.7.

9.8.2 Permitted Medications

These included the following

- sedative/hypnotics, if used when essential, not more than twice a week, and, if possible, not less than 48 hours prior to cognitive testing (if benzodiazepines are used, short acting ones are preferred)
- antidepressants if they did not have anticholinergic effects
- antipsychotics, provided those with a high tendency to anticholinergic effects and extrapyramidal adverse effects were avoided
- cough and cold remedies provided sedating drugs were discontinued where possible at least 48 hours before cognitive testing is carried out
- cholinergic agents, except for cholinomimetic drugs intended to treat dementia
- peripherally-acting anticholinergics if gastrointestinal adverse effects of galantamine were troublesome
- anti-emetics provided these were used for short periods of time
- antihypertensives except that methyldopa, clonidine and beta-blockers were to be prescribed with caution.

9.9 Dosage

As noted above, the 3 dose groups for this study were:

Placebo
Galantamine CR 16-24 mg/day (as a single daily dose)
Galantamine IR 16-24 mg/day (as a twice daily dose)

The dose titration schedule to be used for this study was as follows

	Galantamine CR	Galantamine IR
Weeks 1-4	8 mg q.d.	4 mg b.i.d
Weeks 5-8	16 mg q.d.	8 mg b.i.d
Weeks 9-12	16 or 24 mg q.d.	8 mg b.i.d or 12 mg b.i.d
Weeks 13-26	16 or 24 mg q.d.	8 mg b.i.d or 12 mg b.i.d

Note:

- Patients in the placebo group were to receive placebo throughout the study
- In both the galantamine CR and galantamine IR groups the dose was to be increased at the end of Week 8 to 24 mg/day based on efficacy and tolerability
- In both the galantamine CR and galantamine IR groups, at the end of Week 12, the dose could be reduced to 16 mg/day based on tolerability. The dose reduction was to be permitted only at the end of Week 12
- From Weeks 13-26, the dose used in both the galantamine CR and galantamine IR groups was to be fixed at the dose chosen at the end of Week 12

9.10 Schedule

The study visit schedule is summarized in the following table, which I have copied from the submission

	V1	V2	V3	V4	V5	V6	V7
Assessments	Screen[1]	Eligibility confirmation (End screen)[2]	Baseline Day 0	End Week 4	End Week 8	End Week 12	Final Visit Week 26 or premature discontinuation
Informed consent	X						
MMSE	X						
Medical History	X						
Neurol. Exam.	X						
CT Scan / MRI[3]	X						
Physical Exam	X		X			X	X
Vital Signs	X		X	X	X	X	X
Weight	X		X	X	X	X	X
ECG	X		X		X	X	X
Safety Lab[4]	X		X		X	X	X
DNA Sample (optional)			X				
Adverse Events		X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X
ADAS	X		X		X	X	X
CIBIC-plus			X		X	X	X
ADCS-ADL inventory			X		X	X	X
NPI			X		X	X	X
Dispense Trial Medication		X	X	X	X	X	
Collect previous Medication			X	X	X	X	X

1 A maximum of 10 days is allowed to obtain all screening assessments.
2 All results from the screening visit (Visit 1), should be checked. Note: If the patient discontinues the trial between Visits 2 and 3, then safety evaluations (ECG, clinical laboratory, vital signs, weight, physical examination,) alone need to be performed for this Premature Trial Discontinuation Visit.
3 Obtain CT or MRI scan of brain if one has not been performed within the last 12 months.
4. TSH and B12 will be assayed at the screening visit only.

9.11 Outcome Measures

9.11.1 Primary Efficacy Measures

- ADAS-Cog (ADAS-Cog/11; standard ADAS-Cog)
- CIBIC-Plus.

9.11.2 Secondary Efficacy Measures

- ADAS-Cog/13 consisting of the standard ADAS-Cog and 2 additional items: Concentration and Distractibility and Delayed Word Recall
- ADAS-Cog/10 consisting of the non-memory section of the ADAS-Cog
- ADAS-Cog/mem comprising the memory items of the ADAS-Cog: Word Recall, Delayed Word Recall and Word Recognition

- Percentage of responders on standard ADAS-Cog using 0, 4, 7 and 10 points of improvement as cut-off
- Percentage of subjects with "improved" or "no change" on the CIBIC-Plus.
- Neuropsychiatry Inventory
- Alzheimer's Disease Cooperative Study-ADL

9.11.3 Safety Outcome Measures

Vital signs, safety laboratory tests, physical examinations, adverse events, body weight

9.12 Analysis Plan

9.12.1 General

All p-values were to be rounded to 3 decimal places and were to be based on 2-sided tests with a significance level of 0.05

9.12.2 Demographic And Other Baseline Parameters

- This analysis was to be done on all patients who received at least one dose of double-blind study medication.
- A 2-way ANOVA with treatment and country as factors was to be used comparing continuous variables between the treatment groups
- A Cochran-Mantel-Haenszel test for general association, controlling for country effect, was to be used for comparing categorical variables between the treatment groups.

9.12.3 Primary Efficacy Parameters

- The primary efficacy parameters were the change from baseline in ADAS-Cog at Week 26 and the CIBIC-Plus at Week 26.
- The primary comparisons were to be between the galantamine CR and placebo groups
- The primary hypotheses were as follows
  - Null hypothesis: No difference in treatment effects between galantamine CR and placebo as measured by change from baseline in ADAS-Cog at Week 26 and CIBIC-Plus at Week 26.
  - Alternative hypothesis: Treatment with galantamine CR improves change from baseline in ADAS-Cog and CIBIC-Plus
- The population that consisted of all randomized subjects who received at least one dose of study medication and provided baseline efficacy assessments was to be used in all efficacy analyses, except the classical intent-to-treat analysis
- 3 imputation schemes put forward by this Division were to be used for the primary efficacy analysis: classical intention-to-treat (CITT), traditional DNDP-last-observation-carried-forward (LOCF), and traditional observed cases (OC).

These schemes are defined further as follows:

Classical Intent-To-Treat:	The last observation available for each subject (during the trial) is used regardless of whether this data is obtained from baseline or during the double-blind period
Traditional DNDP-LOCF:	The last observation available for each subject during the double-blind period prior to the designated assessment time is used (exclude baseline)
Traditional Observed Cases:	No imputation occurs. This subset includes double-blind data only from subjects randomized who did not discontinue prematurely and are available for evaluation at the designated time point

- The primary analysis dataset was to be traditional observed cases
- For the ADAS-Cog, least squares means were to be used to compare treatment groups
- In addition to treatment group comparisons at Week 26, additional ADAS-Cog analyses were to be performed at Weeks 8 and 12
- For the ADAS-Cog the statistical model to be used was to be as follows
  - A parametric 2-way ANOVA model was to be used, with treatment and country as factors, to compare treatment groups
  - The country variable might be dichotomized, i.e., "US" and "non-US," since 70% of study sites were in the US.
  - The interaction of treatment with country was to be examined and removed from the model if it was found not to be significant at the 10% level or primarily quantitative in nature (i.e., differences among treatment consistent within each country, but varying in magnitude).
  - The linear contrasts on the least squares means of the treatment effects was to be used to perform the between-groups comparisons
  - Parametric model assumptions were to be tested using the Shapiro-Wilk test on residuals for verification of normality, and Levene's test on the variances of residuals for testing the homogeneity of variances.
- For the ADAS-Cog, a paired t-test was to be used for the within-group treatment comparisons of change from baseline at each timepoint. A mixed effects model including treatment, country, time and treatment-by-time interaction as factors was to be performed to assess the effects of treatment over time
- For the CIBIC-Plus the primary analysis was to be based on scores that used the original 7-point scale as follows: The Cochran-Mantel-Haenszel statistic using modified ridit scores, derived from rank scores (the Van Elteren test), controlling for country effect, was to be applied to compare the distribution between each pair of treatments.

9.12.4 Secondary Efficacy Parameters And Additional Analyses

- The secondary efficacy parameters were as follows
  Continuous Measures
  - ADAS-Cog/13 change from baseline scores at Weeks 8, 12 and 26
  - ADAS-Cog/10 change from baseline scores at Weeks 8, 12 and 26

- ADAS-Cog/mem change from baseline scores at Weeks 8, 12 and 26
- Neuropsychiatry Inventory change from baseline scores at Weeks 8, 12 and 26
- Alzheimer's Disease Cooperative Study-ADL change from baseline scores at Weeks 8, 12 and 26

Categorical Measures

- Percentage of responders on standard ADAS-Cog using ≤ 0, ≤ 4, ≤ 7 and ≤ 10 points of improvement as cut-off scores and measuring the change from baseline to Week 26
- Percentage of subjects with "improved" or "no change" on the CIBIC-Plus at Week 26.

- The continuous measures above were be analyzed in a manner identical to the analysis of the standard ADAS-Cog
- The categorical measures above were to be analyzed using the Cochran-Mantel-Haenszel test for general association, controlling for country effect. The differences in percentage between each pair of treatments were to be estimated and the 95% confidence intervals calculated.
- Sub-group analyses were to be done as follows
  - These analyses were to be done on the change from baseline at Week 26 in the ADAS-Cog, and the percentage of subjects with "improved" or "no change" in CIBIC-Plus scores at Week 26
  - These analyses were to be primarily exploratory and were to be done to assess the consistency in treatment effects across sub-groups
  - The analyses were to be done on the traditional observed cases dataset
  - The statistical models used were to be identical to those described above
  - 95% confidence intervals for the differences in LS means (for the ADAS-Cog) and percentages (for the CIBIC-Plus) between each pair of treatments for each sub-group were to be estimated
  - Subgroup variables were to include gender, race, age group, weight at screening, ApoE genotype, baseline ADAS-Cog, baseline Mini-Mental Status Examination, extrapyramidal signs, smoker, first-degree relatives with Alzheimer's Disease, years since onset of cognitive problems, years since diagnosis of Alzheimer's Disease and prior exposure to cholinesterase inhibitors.

9.12.5 Safety Parameters

- The safety analyses were to include all subjects who receive at least one dose of double-blind study medication
- Vital signs and electrocardiogram results were to be addressed by descriptive statistics at each timepoint. Within group comparisons were to be made by using the paired t-test; between group comparisons will be made using 2-way ANOVA, including treatment and country as factors.
- Physical examination results were to be summarized by the number and percentage of abnormality in each body system at each timepoint.
- Adverse events were to be coded using WHO preferred terms; the incidence rates for each treatment group during the double-blind phase were to be summarized
- With regard to laboratory parameters: descriptive statistics were to be calculated for each parameter at baseline and each scheduled timepoint; changes from baseline results were to be presented in shift tables; a listing of subjects with laboratory results outside the reference range was to be

provided; individual subject listings would also contain the results for laboratory parameters not specified in the protocol.

9.12.6 Sample Size Rationale

- The sample size calculation was based on the primary hypotheses
- Assumptions
  - For mean change in ADAS-Cog at Week 26 a drug-placebo difference of 2.5 ("clinically meaningful difference") and standard deviation of 6.2 (upper end of pooled range of standard deviations from completed trials GAL-USA-1, GAL-INT-1 and GAL-USA-10 that used the immediate-release formulation)
  - For CIBIC-Plus an increase of 15% ("clinically meaningful difference") in subjects with "no change" or "improved" scores at Week 26 in drug group as compared with placebo; 55% of subjects in placebo group with "no change" or "improved" scores at Week 26 (upper end of pooled percentages from completed trials GAL-USA-1, GAL-INT-1 and GAL-USA-10)
  - Type I error = 0.05 (2-sided) for each primary endpoint. No adjustment for multiple comparisons was planned
- Based on the above assumptions for the CIBIC-Plus, at 95% power, 265 subjects would need to complete the trial in each treatment group.
- Based on the above assumptions for the ADAS-Cog, at >95% power, 265 subjects would need to complete the trial in each treatment group.
- The overall global (i.e., dual outcome) power for testing these hypotheses was about 95% with 265 patients completing the study in each treatment group (total=795 patients)
- The dropout rate was assumed to be 22% based on GAL-USA-10.
- The trial would therefore need to randomize 340 patients to each of the 3 treatment groups (total=1020 patients).

9.12.6.1 Amendment To Sample Size Calculation

The sample size calculation was amended, prospectively, as follows

- The assumed power for each primary efficacy endpoint was reduced to 90%.
- The other assumptions were not changed
- Based on the revised power assumption, 230 patients in each group would be required to complete the trial
- Based on a dropout rate of 22%, 295 patients would need to be randomized to each of the 3 treatment groups (total = 885 patients)

9.13 Safety Monitoring

Vital signs, safety laboratory tests, physical examinations, adverse events

9.14 Amendments To Protocol

The final protocol is outlined above

10. Efficacy Results Of Study GAL-INT-10

93 centers in 5 countries participated in the study and were distributed as follows:

United States:	64 centers
Australia:	11 centers
Canada:	10 centers
South Africa:	7 centers
New Zealand:	1 center

10.1 Patient Disposition

Patient disposition is summarized in the following self-explanatory table which I have copied from the submission

All Randomized Subjects Status Termination Reasons	PLACEBO (N=324) n (%)	GAL-IR (N=327) n (%)	GAL-CR (N=320) n (%)	Total (N=971) n (%)
Randomized and treated	320 (99)	326 (100)	319 (100)	965 (99)
Completed	266 (82)	251 (77)	251 (78)	768 (79)
Discontinued	54 (17)	75 (23)	68 (21)	197 (20)
Adverse event	15 (5)	24 (7)	28 (9)	67 (7)
Subject withdrew consent	21 (6)	23 (7)	18 (6)	62 (6)
Subject non-compliant	7 (2)	14 (4)	8 (3)	29 (3)
Subject lost to follow-up	2 (1)	7 (2)	2 (1)	11 (1)
Insufficient response	6 (2)	1 (<1)	3 (1)	10 (1)
Death	1 (<1)	1 (<1)	3 (1)	5 (1)
Subject ineligible to continue the study	0	0	4 (1)	4 (<1)
Other	2 (1)	5 (2)	2 (1)	9 (1)
Randomized and not treated	4 (1)	1 (<1)	1 (<1)	6 (1)
Discontinued	4 (1)	1 (<1)	1 (<1)	6 (1)
Adverse event	1 (<1)	0	1 (<1)	2 (<1)
Subject withdrew consent	2 (1)	0	0	2 (<1)
Subject ineligible to continue the study	1 (<1)	0	0	1 (<1)
Subject non-compliant	0	1 (<1)	0	1 (<1)

Percentages for each category in a group was calculated based on all randomized subjects for that group as denominator.

10.2 Demographic And Other Baseline Characteristics

These are summarized in the following table which I have copied from the submission. The treatment groups appear to have been comparable at baseline.

	PLACEBO (N=320)	GAL-IR (N=326)	GAL-CR (N=319)	Total (N=965)
Sex, n (%)				
N	320	326	319	965
Male	115 (36)	118 (36)	114 (36)	347 (36)
Female	205 (64)	208 (64)	205 (64)	618 (64)
Race, n (%)				
N	320	326	319	965
Black	12 (4)	12 (4)	9 (3)	33 (3)
Caucasian	289 (90)	293 (90)	297 (93)	879 (91)
Hispanic	6 (2)	6 (2)	2 (1)	14 (1)
Oriental	7 (2)	5 (2)	9 (3)	21 (2)
Other	6 (2)	10 (3)	2 (1)	18 (2)
Smoking, n (%)				
N	319	325	318	962
Yes	24 (8)	22 (7)	19 (6)	65 (7)
No	295 (92)	303 (93)	299 (94)	897 (93)
Age, years				
N	320	326	319	965
Category, n (%)				
<65	27 (8)	30 (9)	22 (7)	79 (8)
65-85	254 (79)	268 (82)	265 (83)	787 (82)
>85	39 (12)	28 (9)	32 (10)	99 (10)
Mean (SD)	76.3 (8.03)	76.5 (7.77)	76.6 (7.64)	76.5 (7.81)
Median	77.0	78.0	77.0	77.0
Range	48 - 92	49 - 92	55 - 93	48 - 93
Weight at baseline, kg				
N	319	325	319	963
Mean (SD)	67.78 (14.591)	68.29 (15.857)	68.68 (14.159)	68.23 (14.881)
Median	66.00	67.30	67.30	67.00
Range	37.4 - 119.5	37.0 - 136.4	35.8 - 120.9	35.8 - 136.4
Height, cm				
N	320	326	318	964
Mean (SD)	162.7 (10.03)	162.7 (10.85)	164.1 (10.23)	163.2 (10.39)
Median	162.6	161.0	162.6	162.0
Range	132 - 189	122 - 207	142 - 191	122 - 207
Sum of MMSE at screening				
N	320	326	319	965
Category, n (%)				
10-22	265 (83)	276 (85)	276 (87)	817 (85)
>22	55 (17)	50 (15)	43 (13)	148 (15)
Mean (SD)	18.08 (4.082)	17.89 (4.138)	17.96 (3.966)	17.95 (4.061)
Median	19.00	18.00	18.00	18.00
Range	10 - 24	10 - 24	10 - 24	10 - 24
ADAS-cog/11 score at screening				
N	317	323	315	955
Category, n (%)				
<18	3 (1)	3 (1)	8 (3)	14 (1)
≥18	314 (99)	320 (99)	307 (97)	941 (99)
Mean (SD)	26.97 (8.300)	27.80 (8.486)	26.73 (8.036)	27.17 (8.282)
Median	25.00	26.80	25.00	25.00
Range	13 - 57	13 - 55	12 - 52	12 - 57

Note: Percentages calculated with the number of subjects by parameter as denominator. (continued)

	PLACEBO (N=320)	GAL-IR (N=326)	GAL-CR (N=319)	Total (N=965)
ADAS-cog/11 score at baseline				
N	316	320	314	950
Category, n (%)				
<18	58 (18)	44 (14)	52 (17)	154 (16)
≥18	258 (82)	276 (86)	262 (83)	796 (84)
Mean (SD)	26.23 (9.588)	27.47 (9.935)	26.43 (9.303)	26.71 (9.620)
Median	25.00	26.00	25.00	25.00
Range	9 - 62	9 - 58	7 - 55	7 - 62

Note: Percentages calculated with the number of subjects by parameter as denominator.

Alzheimer's Disease history characteristics were also compared between treatment groups as in the following table. These characteristics were comparable between treatment groups at baseline

	PLACEBO (N=320)	GAL IR (N=326)	GAL CR (N=319)	Total (N=965)
Age at onset of cognitive problems				
N	319	326	319	964
Mean (SD)	72.3 (8.30)	72.0 (8.30)	72.6 (8.12)	72.3 (8.24)
Median	73.0	73.0	74.0	73.0
Range	44 - 89	45 - 89	49 - 91	44 - 91
Duration (yrs) since diagnosis of cognitive problems				
N	319	326	319	964
Mean (SD)	4.00 (2.439)	4.48 (2.674)	4.07 (2.501)	4.18 (2.547)
Median	3.40	3.90	3.40	3.50
Range	0.5 - 15	0.7 - 16	0.5 - 15	0.5 - 16
Age at diagnosis of probable Alzheimer's disease				
N	320	326	319	965
Mean (SD)	75.0 (8.32)	75.2 (7.97)	75.4 (7.85)	75.2 (8.04)
Median	76.0	76.0	76.0	76.0
Range	48 - 92	48 - 91	51 - 93	48 - 93
Duration (yrs) since diagnosis of probable Alzheimer's disease				
N	320	326	319	965
Mean (SD)	1.28 (1.584)	1.24 (1.474)	1.23 (1.573)	1.25 (1.542)
Median	0.60	0.65	0.60	0.60
Range	0.0 - 7.5	0.0 - 6.3	0.0 - 9.2	0.0 - 9.2
First-degree relatives with Alzheimer's disease, n (%)				
N	318	325	317	960
Yes	96 (30)	86 (26)	90 (28)	272 (28)
No	222 (70)	239 (74)	227 (72)	688 (72)
Subject taken cholinomimetics, n (%)				
N	320	326	318	964
Yes	150 (47)	157 (48)	153 (48)	460 (48)
No	170 (53)	169 (52)	165 (52)	504 (52)

10.3 Protocol Violations

4% of all subjects enrolled in the trial had 1 or more major protocol violations. The incidence of these were comparable across treatment groups

10.4 Treatment Compliance

12 patients had treatment interruptions that were considered too long (> 3 days). Non-compliance with study requirements was seen in 6 patients

10.5 Primary Efficacy Analysis

10.5.1 ADAS-Cog

10.5.1.1 Observed Cases

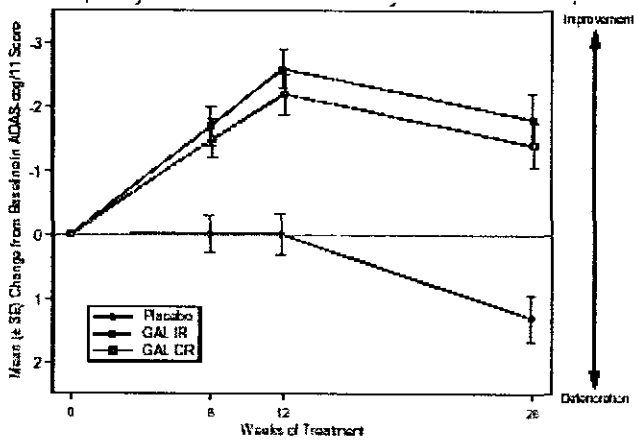
The table below, copied from the submission, summarizes change from baseline scores on this measure for the observed cases dataset at each study timepoint

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[1]
Baseline	305	26.1 (0.54)	--	306	27.3 (0.55)	--	300	26.3 (0.54)	--	
Week 8	289	25.8 (0.63)	0.0 (0.30)	286	25.4 (0.58)	-1.7 (0.30)	284	24.6 (0.58)	-1.5 (0.30)	<0.001
Week 12	275	25.9 (0.66)	0.0 (0.32)	268	24.0 (0.57)	-2.6 (0.31)	269	23.9 (0.57)	-2.2 (0.32)	<0.001
Week 26	**248**	**26.4 (0.72)**	**1.3 (0.36)**	**227**	**24.7 (0.69)**	**-1.8 (0.42)**	**240**	**24.8 (0.69)**	**-1.4 (0.34)**	**<0.001**

[1]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p<0.001.

For the observed cases dataset at Week 26, the dataset pre-specified for the primary efficacy analysis, a statistically significant superiority for the controlled-release galantamine group was seen in comparison with placebo, for an effect size of 2.7.

As indicated in the table above, and in the figure below, the galantamine groups showed a mean improvement compared with baseline, whereas the placebo group worsened over the course of the study. However, the effect size, in comparison with placebo was slightly higher for the immediate-release galantamine group than for the controlled-release group



10.5.1.2 Last-Observation-Carried-Forward And Classical Intent-To-Treat

The analysis of these datasets, neither of which was the protocol-specified primary efficacy analysis, yielded results similar to the primary efficacy analysis proper.

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline										
LOCF	305	26.1 (0.54)	--	306	27.3 (0.55)	--	300	26.3 (0.54)	--	
CITT	316	26.1 (0.54)	--	319	27.5 (0.55)	--	313	26.4 (0.53)	--	
Week 8										
LOCF	293	25.9 (0.63)	0.0 (0.30)	294	25.4 (0.57)	-1.7 (0.29)	287	24.7 (0.57)	-1.5 (0.30)	<0.001
CITT	316	26.2 (0.61)	0.0 (0.30)	319	25.9 (0.57)	-1.7 (0.29)	313	25.0 (0.56)	-1.5 (0.30)	<0.001
Week 12										
LOCF	296	26.0 (0.64)	0.2 (0.31)	296	24.5 (0.56)	-2.5 (0.30)	290	24.2 (0.56)	-2.0 (0.31)	<0.001
CITT	316	26.3 (0.62)	0.2 (0.31)	319	25.2 (0.56)	-2.5 (0.30)	313	24.6 (0.55)	-2.0 (0.31)	<0.001
Endpoint[b]										
LOCF	296	27.0 (0.67)	1.2 (0.33)	296	25.4 (0.62)	-1.6 (0.36)	291	24.9 (0.62)	-1.3 (0.31)	<0.001
CITT	316	27.2 (0.65)	1.2 (0.33)	319	26.0 (0.62)	-1.6 (0.36)	313	25.3 (0.60)	-1.3 (0.31)	<0.001

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
[b]The endpoint was defined as the last available observation up to 14 days after the last dose of study medication.
GAL-IR vs. Placebo at endpoint: p<0.001 (LOCF/CITT)

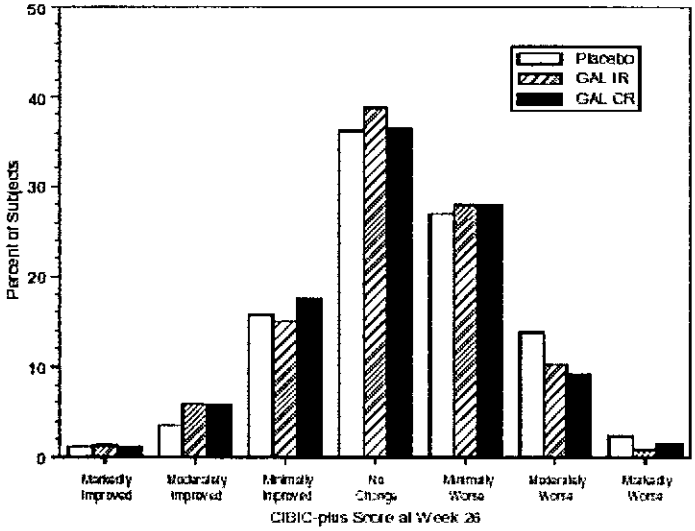
10.5.2 CIBIC-Plus

10.5.2.1 Observed Cases

The results for the primary efficacy analysis for this parameter (Month 6, observed cases) are summarized in the following table and figure which I have copied from the submission.

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)	(Cum %)	n (%)	(Cum %)	n (%)	(Cum %)	P value[a]
N at Week 26	259		240		246		
Markedly improved	3 (1.2)	(1.2)	3 (1.3)	(1.3)	3 (1.2)	(1.2)	
Moderately improved	9 (3.5)	(4.6)	14 (5.8)	(7.1)	14 (5.7)	(6.9)	
Mildly improved	41 (15.8)	(20.5)	36 (15.0)	(22.1)	43 (17.5)	(24.4)	
No change	94 (36.3)	(56.8)	93 (38.8)	(60.8)	90 (36.6)	(61.0)	
Mildly worse	70 (27.0)	(83.8)	67 (27.9)	(88.8)	69 (28.0)	(89.0)	
Moderately worse	36 (13.9)	(97.7)	25 (10.4)	(99.2)	23 (9.3)	(98.4)	
Markedly worse	6 (2.3)	(100.0)	2 (0.8)	(100.0)	4 (1.6)	(100.0)	0.086

[a] GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
Cum % = cumulative percent
Note: Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at Week 26: p=0.223.



As the above results indicate, neither galantamine group showed a statistically significant superiority to placebo; only a minimal trend in that direction was seen for the Reminyl® ER group, albeit inconsistently, across the 4 improvement categories. The sponsor has noted that there was a higher proportion of placebo responders in this study, as compared with the pre-approval studies with immediate-release galantamine.

10.5.2.2 Last-Observation-Carried-Forward And Classical Intent-To-Treat

The analyses of these datasets (which were identical) revealed no statistically significant differences between either galantamine group and placebo group

	PLACEBO		GAL-IR		GAL-CR		
7-Point Category	n (%)[b]	Cum %	n (%)[b]	Cum %	n (%)[b]	Cum %	P value[a]
LOCF/CITT at Endpoint[b]	301		302		296		
Markedly improved	3 (1.0)	(1.0)	3 (1.0)	(1.0)	3 (1.0)	(1.0)	
Moderately improved	11 (3.7)	(4.7)	15 (5.0)	(6.0)	14 (4.7)	(5.7)	
Mildly improved	48 (15.9)	(20.6)	46 (15.2)	(21.2)	49 (16.6)	(22.3)	
No change	111 (36.9)	(57.5)	127 (42.1)	(63.2)	114 (38.5)	(60.8)	
Mildly worse	80 (26.6)	(84.1)	78 (25.8)	(89.1)	81 (27.4)	(88.2)	
Moderately worse	41 (13.6)	(97.7)	30 (9.9)	(99.0)	29 (9.8)	(98.0)	
Markedly worse	7 (2.3)	(100.0)	3 (1.0)	(100.0)	6 (2.0)	(100.0)	0.216

[a]GAL-CR vs. Placebo comparison using the Van Elteren test controlling for Pooled Country.
[b]The endpoint was defined as the last available observation up to 14 days after the last dose of study medication
Cum % = cumulative percent.
Note: Percentages calculated with the number of subjects at Week 26 as denominator.
GAL-IR vs. Placebo at endpoint: p=0.144 (LOCF/CITT).

10.6 Secondary Efficacy Analyses

Note again that the secondary efficacy parameters were as follows

Continuous Measures

- ADAS-Cog/13 change from baseline scores at Weeks 8, 12 and 26
- ADAS-Cog/10 change from baseline scores at Weeks 8, 12 and 26
- ADAS-Cog/mem change from baseline scores at Weeks 8, 12 and 26
- Neuropsychiatry Inventory change from baseline scores at Weeks 8, 12 and 26
- Alzheimer's Disease Cooperative Study-ADL change from baseline scores at Weeks 8, 12 and 26

Categorical Measures

- Percentage of responders on standard ADAS-Cog using ≤ 0, ≤ 4, ≤ 7 and ≤ 10 points of improvement as cut-off scores and measuring the change from baseline to Week 26
- Percentage of subjects with "improved" or "no change" on the CIBIC-Plus at Week 26.

Based on the above, and the actual analyses performed

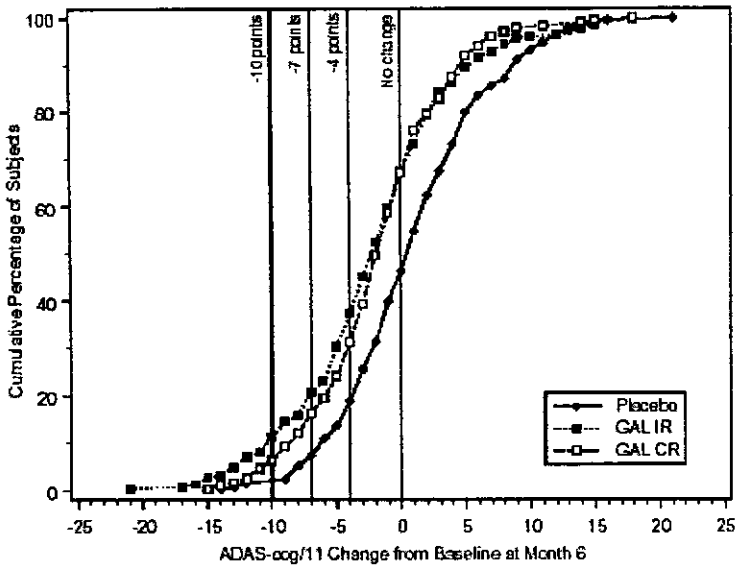
- There were a total of 10 secondary efficacy measures
- Analyses on each of these measures was performed at Weeks 8, 12, and 26
- Each of the analyses were performed on 3 different datasets (observed cases, classical intent-to-treat, and last-observation-carried-forward)

Thus, the analyses of the secondary efficacy measures involved 90 comparisons of controlled-release galantamine with placebo. For each secondary efficacy measure at each timepoint and for each dataset, comparisons of the immediate-release galantamine group with placebo, and of the 2 galantamine groups were also performed.

The protocol did not specify that any of the secondary efficacy measures would be weighted more importantly than the others.

10.6.1 Percentage of responders on standard ADAS-Cog using 0, 4, 7 and 10 points of improvement as cut-off

These results for the Week 26 observed cases dataset are summarized in the following figure, a cumulative distribution graph taken from the submission



The changes seen on these measures correlate with those seen on the ADAS-Cog/11. p-values for the comparison of each galantamine group with the placebo group for the observed cases dataset at Month 6 are in the following table.

Response Criterion (Improvement in ADAS-Cog score compared with baseline at Week 26)	% responders (Observed Cases)		p-value Gal-CR vs placebo	p-value Gal-IR vs placebo
≤ 10	Placebo	1.6	0.008	< 0.001
	Gal-IR	11.5		
	Gal-CR	6.3		
≤ 7	Placebo	7.3	0.002	< 0.001
	Gal-IR	20.7		
	Gal-CR	16.3		
≤ 4	Placebo	19.0	0.002	< 0.001
	Gal-IR	37.4		
	Gal-CR	31.3		
≤ 0	Placebo	46.0	< 0.001	< 0.001
	Gal-IR	67.8		
	Gal-CR	67.1		

The p-values for the last-observation-carried-forward dataset for Week 26 were similar.

Similar analyses were also performed at Weeks 8 and 12.

10.6.2 Percentage Of Subjects With "Improved" Or "No Change" On The CIBIC-Plus.

These results are summarized in the following table for the observed cases, last-observation-carried forward and classical intent-to-treat datasets

Timepoint	PLACEBO n/N (%)	GAL-IR n/N (%)	GAL-CR n/N (%)	P value[a]
Week 8				
OC	222/294 (75.5)	230/293 (78.5)	225/288 (78.1)	0.466
LOCF	225/299 (75.3)	235/301 (78.1)	227/293 (77.5)	0.529
CITT	225/299 (75.3)	235/301 (78.1)	227/293 (77.5)	0.529
Week 12				
OC	198/279 (71.0)	202/278 (72.7)	215/275 (78.2)	0.053
LOCF	215/301 (71.4)	219/302 (72.5)	226/296 (76.4)	0.172
CITT	215/301 (71.4)	219/302 (72.5)	226/296 (76.4)	0.172
Week 26/Endpoint[b]				
OC	147/259 (56.8)	146/240 (60.8)	150/246 (61.0)	0.361
LOCF[b]	173/301 (57.5)	191/302 (63.2)	180/296 (60.8)	0.412
CITT[b]	173/301 (57.5)	191/302 (63.2)	180/296 (60.8)	0.412

[a] Pairwise comparison for no differences between GAL-CR and Placebo from CMH test for general association controlling for pooled country.
[b]The endpoint was defined as the last available observation up to 14 days after the last dose of study medication. Responder: improved or no change (1-4); nonresponder: worsened (5-7).

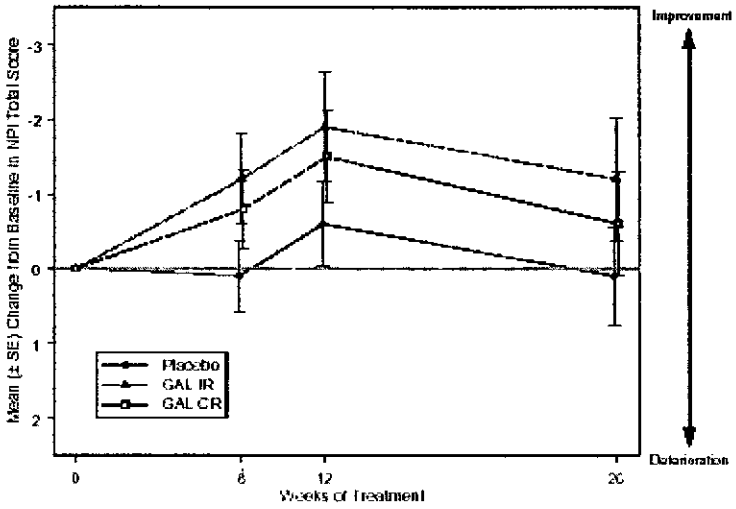
As the above table indicates, the proportion of responders was slightly higher in both galantamine groups as compared with the placebo group.

10.6.3 Neuropsychiatry Inventory

The results of the analysis of change-from-baseline scores at Month 6 (observed cases) are summarized in the following table and figure, both copied from the submission

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	N	Mean (SE)	Mean Change SE)	P value[a]
Baseline	308	10.3 (0.69)	--	310	12.6 (0.76)	--	304	11.2 (0.79)	--	
Week 8	295	10.2 (0.70)	0.1 (0.48)	292	11.5 (0.68)	-1.2 (0.61)	291	10.4 (0.85)	-0.8 (0.53)	0.226
Week 12	281	9.5 (0.70)	-0.6 (0.56)	279	11.0 (0.75)	-1.9 (0.74)	276	9.6 (0.84)	-1.5 (0.62)	0.320
Week 26	**258**	**10.3 (0.82)**	**0.1 (0.66)**	**242**	**11.5 (0.83)**	**-1.2 (0.83)**	**245**	**10.0 (0.76)**	**-0.6 (0.69)**	**0.451**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p=0.203.



As the data indicate, neither Reminyl® group showed even a nominally statistically significant superiority to placebo. Very minor treatment effects, if any, were seen with both galantamine groups.

The results for the last-observation-carried-forward and classical intent-to-treat datasets were similar.

Similar analyses were also performed at Weeks 8 and 12.

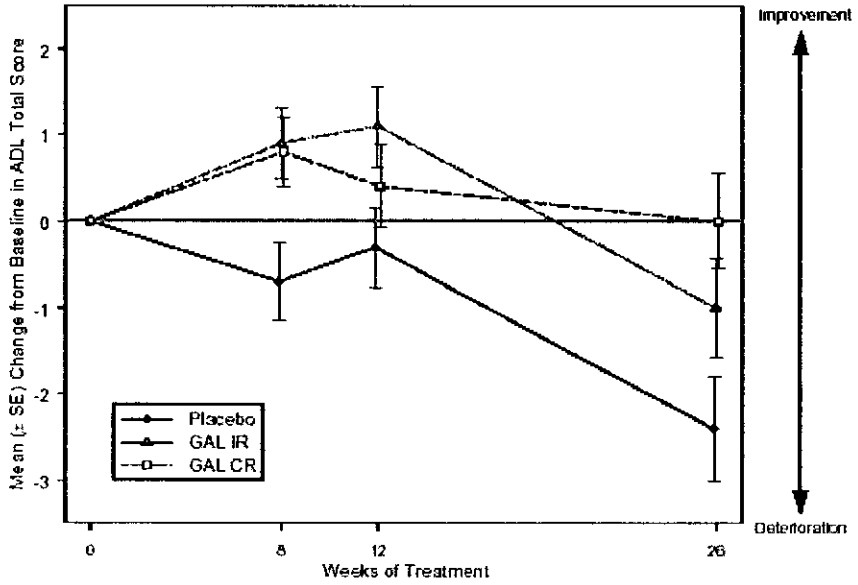
10.6.4 Alzheimer's Disease Cooperative Study-ADL

10.6.4.1 Observed Cases

The results of the analysis of change-from-baseline scores at Month 6 (observed cases) are summarized in the following table and figure, both copied from the submission

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	P value[a]
Baseline	308	54.5 (0.87)	--	310	52.0 (0.90)	--	303	53.5 (0.88)	--	
Week 8	294	53.8 (0.98)	-0.7 (0.45)	292	52.6 (0.93)	0.9 (0.42)	290	54.5 (0.94)	0.8 (0.41)	0.013
Week 12	281	54.2 (0.99)	-0.3 (0.46)	279	52.8 (0.95)	1.1 (0.47)	276	54.1 (0.94)	0.4 (0.48)	0.321
Week 26	**258**	**52.4 (1.09)**	**-2.4 (0.60)**	**242**	**50.9 (1.12)**	**-1.0 (0.57)**	**245**	**53.9 (1.03)**	**0.0 (0.55)**	**0.003**

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
GAL-IR vs. Placebo at Week 26: p=0.088.



As the table and figure above indicate, a nominally statistically significant difference (p = 0.003) between the Reminyl® ER and placebo groups was seen on the measure at Week 26. Note that this analysis was one of 90 planned

comparisons between the controlled-release galantamine and placebo groups on the secondary efficacy measures, and that this nominally statistically significant comparison was not as clearly statistically significant ($p < 0.05$) after the Type I error was adjusted for multiple comparisons.

10.6.4.2 Last-Observation-Carried-Forward And Classical Intent-To-Treat

The results of analyses of these datasets yielded results similar to analysis of the observed cases dataset at endpoint.

	PLACEBO			GAL-IR			GAL-CR			
Timepoint	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change (SE)	N	Mean (SE)	Mean Change SE)	P value[a]
Baseline										
LOCF	308	54.5 (0.87)	--	310	52.0 (0.90)	--	303	53.5 (0.88)	--	
CITT	319	54.3 (0.87)	--	323	51.9 (0.88)	--	316	53.3 (0.86))	--	
Week 8										
LOCF	299	53.8 (0.96)	- 0.8 (0.45)	300	52.7 (0.91)	0.8 (0.41)	295	54.2 (0.94)	0.8 (0.40)	0.007
CITT	319	53.5 (0.93)	-0.8 (0.45)	323	52.6 (0.87)	0.8 (0.41)	316	54.0 (0.91)	0.8 (0.40)	0.007
Week 12										
LOCF	301	54.0 (0.95)	-0.6 (0.45)	301	52.9 (0.91)	0.9 (0.45)	296	53.7 (0.94)	0.3 (0.46)	0.146
CITT	319	53.7 (0.93)	-0.6 (0.45)	323	52.7 (0.87)	0.9 (0.45)	316	53.6 (0.91)	0.3 (0.46)	0.146
Endpoint[b]										
LOCF	301	52.0 (1.02)	-2.7 (0.56)	301	51.0 (0.98)	-1.0 (0.50)	296	53.3 (0.96)	0.0 (0.48)	<0.001
CITT	319	51.7 (0.99)	-2.7 (0.56)	323	51.0 (0.94)	-1.0 (0.50)	316	53.2 (0.93)	0.0 (0.48)	<0.001

[a]Pairwise comparison for no difference between GAL-CR and Placebo from ANOVA model with factors Treatment and Pooled Country (type III SS).
[b]The endpoint was defined as the last available observation up to 14 days after the last dose of study medication GAL-IR vs. Placebo at endpoint: p=0.018 (LOCF/CITT).

10.6.5 ADAS-Cog Subsets (Subscales)

The treatment groups were compared on the change from baseline to Week 26 scores for each of the following ADAS-Cog subsets: ADAS-Cog/13, ADAS-Cog/10, and ADAS-Cog/mem. For each of these subsets, the Reminyl® ER group had a nominally statistically significant ($p \leq 0.002$) superiority to placebo on both the observed cases, intent-to-treat-last-observation-carried-forward, and classical intent-to-treat datasets.

10.7 Subgroup Efficacy Analyses

The treatment groups were compared on the change from baseline in ADAS-Cog score at Week 26, and the CIBIC-Plus score at Week 26 on subgroups based on sex, body weight, baseline ADAS-Cog and Mini-Mental Status Examination scores, smoking status, presence of a first-degree relative with Alzheimer's Disease, years since onset of cognitive difficulty, years since diagnosis of probable Alzheimer's Disease, and previous exposure to cholinomimetic drugs. The results of these analyses were interpreted by the sponsor as being consistent with the primary efficacy analysis.

10.8 Additional Efficacy Analyses

Additional post-hoc efficacy analyses were conducted by the sponsor to determine the extent to which the protocol-specified efficacy analyses were reproducible. These analyses were conducted on each of the following efficacy parameters: ADAS-Cog, CIBIC-Plus, and ADCS-ADL. In addition, composite responder analyses were also performed.

The additional efficacy analyses are summarized below

10.8.1 Analyses For Subjects With Screening Mini-Mental Status Examination Score Of 10 to 22

Analyses were performed on the subset of those with a screening Mini-Mental Status Examination score of 10 to 22 comparing the treatment groups on the change from baseline in ADAS-Cog and ADCS-ADL at Week 26, and the CIBIC-Plus score at Week 26. The p-values for the comparison between the Reminyl® ER and placebo groups on the observed cases and intent-to-treat-LOCF datasets is in the following table

Parameter	p-value	
	Observed Cases	LOCF
ADAS-Cog	< 0.001	< 0.001
CIBIC-Plus	0.024	0.049
ADCS-ADL	0.004	< 0.001

Nominally statistically significant p-values were seen for all the comparisons as indicated in the table above.

The results of the entire analysis (i.e., comparisons of both the extended- and immediate-release preparations of Reminyl® with placebo) of the CIBIC-Plus for this subset, as defined by a screening Mini-Mental Status Examination score of 10 to 22, are in the following table which I have copied from the submission. The table represents the observed cases dataset

	PLACEBO		GAL-IR		GAL-CR	
7-Point Category	n (%)	Cum %	n (%)	Cum %	n (%)	Cum %
n at Week 26	212		202		209	
Markedly improved	2 (0.9)	(0.9)	2 (1.0)	(1.0)	3 (1.4)	(1.4)
Moderately improved	3 (1.4)	(2.4)	10 (5.0)	(5.9)	12 (5.7)	(7.2)
Mildly improved	32 (15.1)	(17.5)	31 (15.3)	(21.3)	32 (15.3)	(22.5)
No change	74 (34.9)	(52.4)	76 (37.6)	(58.9)	79 (37.8)	(60.3)
Mildly worse	61 (28.8)	(81.1)	59 (29.2)	(88.1)	57 (27.3)	(87.6)
Moderately worse	34 (16.0)	(97.2)	22 (10.9)	(99.0)	22 (10.5)	(98.1)
Markedly worse	6 (2.8)	(100.0)	2 (1.0)	(100.0)	4 (1.9)	(100.0)
Pairwise p-value (vs. placebo)[a]	---		0.062		0.024	

[a]Van Elteren test controlling for pooled country.
Cum % cumulative percent
Note: Percentages calculated with the number of subjects with CIBIC-plus scores in each treatment group as denominator.

10.8.2 Analysis For Subjects With Screening Mini-Mental Status Examination Score Of 10 to 22 For US Centers

Analyses were performed on the subset of those with a screening Mini-Mental Status Examination score of 10 to 22, at US centers only, comparing the treatment groups on the change from baseline in ADAS-Cog and ADCS-ADL at Week 26, and the CIBIC-Plus score at Week 26. The p-values for the comparison between the Reminyl® ER and placebo groups on the observed cases and intent-to-treat-LOCF datasets, for this subset, are in the following table

Parameter	p-value	
	Observed Cases	LOCF
ADAS-Cog	< 0.001	< 0.001
CIBIC-Plus	0.007	0.009
ADCS-ADL	0.001	< 0.001

Nominally statistically significant p-values were seen for all the comparisons as indicated in the table above.

The results of the entire analysis (i.e., comparisons of both the extended- and immediate-release preparations of Reminyl® with placebo) of the CIBIC-Plus for this subset (US centers only), as defined by a screening Mini-Mental Status Examination score of 10 to 22, are in the following table which I have copied from the submission. The table represents the observed cases dataset

	PLACEBO		GAL-IR		GAL-CR	
7-Point Category	n (%)	Cum %	n (%)	Cum %	n (%)	Cum %
n at Week 26	137		129		141	
Markedly improved	2 (1.5)	(1.5)	1 (1)	(0.8)	2 (1.4)	(1.4)
Moderately improved	0 (0.0)	(1.5)	6 (5)	(5.4)	5 (3.5)	(5.0)
Mildly improved	15 (10.9)	(12.4)	16 (12)	(17.8)	20 (14.2)	(19.1)
No change	56 (40.9)	(53.3)	54 (42)	(59.7)	67 (47.5)	(66.7)
Mildly worse	38 (27.7)	(81.0)	35 (27)	(86.8)	31 (22.0)	(88.7)
Moderately worse	21 (15.3)	(96.4)	15 (12)	(98.4)	14 (9.9)	(98.6)
Markedly worse	5 (3.6)	(100.0)	2 (2)	(100.0)	2 (1.4)	(100.0)
Pairwise p-value (vs. placebo)[4]	---		0.035		0.007	

[4]Van Elteren test controlling for pooled centers (Section 3.11.2.3)..
Cum % = cumulative percent.
Note: Percentages calculated with the number of subjects with CIBIC-plus scores in each treatment group as denominator.

10.8.3 Composite Responder Analyses

10.8.3.1 ADAS-Cog And CIBIC-Plus Composite Responders

This category of composite responder was defined by having a combination of a reduction in ADAS-Cog score of at least 4 points, and a CIBIC-Plus result of improved or no change at endpoint

The treatment group comparison for this measure, on the observed cases dataset, is in the following table which I have copied from the submission.

	PLACEBO (N=247)	GAL-IR (N=225)	GAL-CR (N=239)	P value[a]
Composite responders (%)	33 (13.4)	57 (25.3)	51 (21.3)	0.020

[a] Pairwise comparison for no difference between GAL-CR and Placebo from CMH test for general association controlling for pooled country.
GAL-IR vs. Placebo: p=0.001.
Note: Percentages calculated with the number of subjects in each treatment group as denominator

As the table indicates, the proportion of composite responders in both the Reminyl® IR and Reminyl® ER groups was higher, at a nominally statistically significant level, than in the placebo group.

10.8.3.2 ADAS-Cog, CIBIC-Plus, And ADCS-ADL Composite Responders

This category of composite responder was defined by having a combination of a reduction in ADAS-Cog score of at least 4 points, a CIBIC-Plus result of improved or no change at endpoint, and a change in ADCS-ADL ≥ 0

The treatment group comparison for this measure, on the Observed Cases dataset, is in the following table which I have copied from the submission.

	PLACEBO (N=245)	GAL-IR (N=225)	GAL-CR (N=238)	P value[a]
Composite responders (%)	20 (8.2)	43 (19.1)	38 (16.0)	0.008

[a] Pairwise comparison for no differences between GAL-CR and Placebo from CMH test for general association controlling for pooled country.
GAL-IR vs. Placebo: p<0.001.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.

As the table indicates, the proportion of composite responders of this category too in both the Reminyl® IR and Reminyl® ER groups was higher, and at a nominally statistically significant level, than in the placebo group

10.9 Sponsor's Conclusions

- Both galantamine treatments showed a statistically significant superiority to placebo on the change from baseline in ADAS-Cog score at Week 26 on the primary observed cases dataset.

- On the CIBIC-Plus, both galantamine treatments showed a numerical superiority to placebo, that was not, however, statistically significant (on the primary observed cases dataset). The lack of a statistically significant superiority for both galantamine treatments, over placebo, is mainly due to the high placebo response rate in this study.

- Repeating the above analyses of the ADAS-Cog and CIBIC-Plus on the intent-to-treat-LOCF and classical intent-to-treat datasets yielded results that were similar to those seen when the observed cases dataset was analyzed.

- The protocol specified that for this study to be declared positive, Reminyl® ER should be shown to be superior at a statistically significant level on both primary efficacy measures; that objective was not achieved in this study

- For the "key" secondary efficacy endpoint, the ADCS-ADL, the analyses yielded results that were consistent with those of the primary efficacy analysis. A statistically significant superiority over placebo was seen for the Reminyl® ER group, but not for the Reminyl® IR group.

- Composite responder analyses supported the results of the primary efficacy analysis.

10.10 Agency Statistical Reviewer's Comments

- Dr Kun He has performed the Agency statistical review of this submission.
- He has confirmed the results of the sponsor's analysis of the primary efficacy parameters and ADCS-ADL.
- He has concluded that the results of the study do not support the proposed claim for the use of extended-release Reminyl® in the treatment of mild-to-moderate dementia of the Alzheimer's type, given the sponsor's pre-specified criteria for declaring this study positive.
- He has also expressed the view that the p-values derived from the analysis of the ADCS-ADL using the observed cases and last observation carried forward datasets, although nominally statistically significant, should be interpreted with caution as the primary efficacy analysis was "negative" overall and the Type I error, therefore, "spent" even prior to the analysis of the secondary efficacy measures being performed.
- Please refer to his review for full details.

10.11 Reviewer's Comments

- Using the criteria specified a priori in the analysis plan, Study GAL-INT-10 must be considered "negative" in demonstrating the superiority of the extended-release formulation of galantamine over placebo: the difference at endpoint between the extended-release galantamine and placebo groups on the CIBIC-Plus, although showing a numerical trend in favor of galantamine; was not statistically significant, with a p-value of 0.086 when the analysis was performed on the observed cases dataset. For the last-observation-carried-forward and classical intent-to-treat datasets (these 2 datasets were identical), the p-value for this comparison was 0.216.

- The purpose of using the CIBIC-Plus, a global instrument, as a primary efficacy measure in Phase III studies of drugs for Alzheimer's Disease, is to establish that any drug effect seen on the cognitive primary efficacy measure is clinically meaningful.

- A measure of activities of daily living is an acceptable alternative to a global primary efficacy measure in clinical drug trials in Alzheimer's Disease. In Study GAL-INT-10, the (modified) ADCS-ADL, a secondary efficacy measure, evaluated functional abilities. On the change from baseline score for this measure, the difference between the extended-release galantamine and placebo groups at endpoint on the observed cases dataset was at least nominally statistically significant ($p = 0.003$); nominally statistically significant differences ($p < 0.001$) were also seen on the last-observation-carried-forward and classical intent-to-treat datasets.

  However, whether the "positive" result on the ADCS-ADL can be used to offset the "negative" result on the CIBIC-Plus, so as to render the overall study "positive" is questionable, for the following reasons.

  - The ADCS-ADL was one of 10 secondary efficacy measures and it was not specified a priori that the ADCS-ADL would be a key secondary efficacy measure; nor was the primary method of analysis for this measure specified a priori

  - About 90 analytical comparisons of the extended-release galantamine and placebo groups were performed on the secondary efficacy measures. Thus, if adjusted for multiple comparisons the difference between the these groups on the ADCS-ADL can no longer be considered statistically significant in relation to a p-value ≤ 0.05

- It is noteworthy that there was no evidence that the 16-24 mg/day (8 mg BID to 12 mg BID) dose of immediate-release Reminyl® was superior to placebo on the CIBIC-Plus in this trial; this is in contrast to the clear evidence of efficacy on that measure that was seen at doses of both 16 mg/day and 24 mg/day (8 mg BID and 12 mg BID, respectively) in GAL-USA-10, which was a key study done prior to the approval of the immediate-release formulation of Reminyl®.

- The sponsor has suggested that both the immediate-release and extended-release formulations of Reminyl® may have failed to show a statistically significant superiority to placebo on the CIBIC-Plus, because of an unexpectedly high response rate to placebo. Notwithstanding that explanation, this study must still be considered to be "negative", based on the a priori criteria for success.

11. Safety Results Of Study GAL-INT-10

11.1 Datasets Analyzed

The safety results are based on 965 patients who were randomized, received at least one dose of study medication and had any safety data after the start of study treatment.

11.2 Adverse Events

This was a flexible dose study; the dose could be increased to the highest dose level 24 mg/day based on safety and tolerability

A larger proportion of patients (66%) in the Reminyl® ER group reached a dose of 24 mg/day in comparison with the Reminyl® IR group (61%).

11.2.1 All Adverse Events

While adverse events were more frequent in the Reminyl® groups than in the placebo group, the adverse event profile in the 2 Reminyl® groups was similar as indicated by the following table (copied from the submission) which indicates the incidence of adverse events occurring in ≥ 2% of patients in each treatment group. Nausea was the most common adverse event in the Reminyl® ER group, and more common than in the placebo, and Reminyl® IR groups.

System Organ Class Preferred Term	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Total no. subjects with adverse events	224 (70)	235 (72)	253 (79)	712 (74)
Gastrointestinal system disorders	72 (23)	92 (28)	92 (29)	256 (27)
Nausea	16 (5)	45 (14)	54 (17)	115 (12)
Diarrhea	22 (7)	22 (7)	15 (5)	59 (6)
Vomiting	7 (2)	28 (9)	21 (7)	56 (6)
Constipation	10 (3)	8 (2)	9 (3)	27 (3)
Abdominal pain	7 (2)	11 (3)	7 (2)	25 (3)
Dyspepsia	7 (2)	9 (3)	6 (2)	22 (2)
Psychiatric disorders	74 (23)	80 (25)	92 (29)	246 (25)
Agitation	21 (7)	20 (6)	22 (7)	63 (7)
Anorexia	8 (3)	22 (7)	19 (6)	49 (5)
Depression	8 (3)	16 (5)	18 (6)	42 (4)
Insomnia	12 (4)	12 (4)	11 (3)	35 (4)
Confusion	9 (3)	8 (2)	7 (2)	24 (2)
Anxiety	8 (3)	2 (1)	13 (4)	23 (2)
Somnolence	6 (2)	6 (2)	9 (3)	21 (2)
Depression aggravated	4 (1)	8 (2)	6 (2)	18 (2)
Aggressive reaction	4 (1)	6 (2)	7 (2)	17 (2)
Psychosis	6 (2)	5 (2)	4 (1)	15 (2)
Hallucination	5 (2)	5 (2)	2 (1)	12 (1)
Nervousness	2 (1)	5 (2)	4 (1)	11 (1)
Body as a whole - general disorders	60 (19)	62 (19)	76 (24)	198 (21)
Injury	18 (6)	12 (4)	24 (8)	54 (6)
Edema peripheral	9 (3)	8 (2)	14 (4)	31 (3)
Fatigue	2 (1)	12 (4)	12 (4)	26 (3)
Back pain	10 (3)	5 (2)	10 (3)	25 (3)
Chest pain	5 (2)	8 (2)	4 (1)	17 (2)
Pain	8 (3)	3 (1)	4 (1)	15 (2)
Syncope	3 (1)	4 (1)	7 (2)	14 (1)
Fever	2 (1)	7 (2)	2 (1)	11 (1)
Leg pain	3 (1)	5 (2)	1 (<1)	9 (1)
Centr & periph nervous system disorders	52 (16)	69 (21)	77 (24)	198 (21)
Dizziness	14 (4)	24 (7)	33 (10)	71 (7)
Headache	18 (6)	18 (6)	27 (8)	63 (7)
Gait abnormal	5 (2)	6 (2)	7 (2)	18 (2)
Tremor	0	4 (1)	5 (2)	9 (1)
Respiratory system disorders	43 (13)	41 (13)	45 (14)	129 (13)
Upper respiratory tract infection	16 (5)	12 (4)	15 (5)	43 (4)
Rhinitis	10 (3)	13 (4)	13 (4)	36 (4)
Dyspnea	8 (3)	5 (2)	7 (2)	20 (2)
Coughing	7 (2)	5 (2)	2 (1)	14 (1)
Pneumonia	2 (1)	6 (2)	6 (2)	14 (1)
Bronchitis	5 (2)	2 (1)	1 (<1)	8 (1)
Metabolic and nutritional disorders	36 (11)	43 (13)	42 (13)	121 (13)
Weight decrease	4 (1)	17 (5)	14 (4)	35 (4)
Hyperglycemia	4 (1)	5 (2)	7 (2)	16 (2)
Creatine phosphokinase increased	5 (2)	4 (1)	2 (1)	11 (1)

(continued)

System Organ Class Preferred Term	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Urinary system disorders	38 (12)	39 (12)	40 (13)	117 (12)
Urinary tract infection	26 (8)	22 (7)	22 (7)	70 (7)
Urinary incontinence	5 (2)	3 (1)	7 (2)	15 (2)
Hematuria	4 (1)	4 (1)	5 (2)	13 (1)
Micturition frequency	2 (1)	5 (2)	4 (1)	11 (1)
Secondary terms	39 (12)	30 (9)	28 (9)	97 (10)
Fall	19 (6)	20 (6)	20 (6)	59 (6)
Surgical intervention	10 (3)	7 (2)	4 (1)	21 (2)
Abrasion nos[a]	2 (1)	3 (1)	5 (2)	10 (1)
Musculoskeletal system disorders	21 (7)	27 (8)	31 (10)	79 (8)
Arthralgia	6 (2)	6 (2)	10 (3)	22 (2)
Skeletal pain	4 (1)	10 (3)	5 (2)	19 (2)
Arthritis	4 (1)	3 (1)	5 (2)	12 (1)
Myalgia	3 (1)	3 (1)	5 (2)	11 (1)
Cardiovascular disorders, general	24 (8)	27 (8)	27 (8)	78 (8)
Hypertension	9 (3)	8 (2)	9 (3)	26 (3)
Heart rate and rhythm disorders	16 (5)	19 (6)	19 (6)	54 (6)
Bradycardia	5 (2)	5 (2)	9 (3)	19 (2)
Skin and appendages disorders	24 (8)	5 (2)	25 (8)	54 (6)
Rash	2 (1)	1 (<1)	8 (3)	11 (1)
Platelet, bleeding & clotting disorders	15 (5)	13 (4)	15 (5)	43 (4)
Purpura	10 (3)	11 (3)	9 (3)	30 (3)
Neoplasm	15 (5)	13 (4)	10 (3)	38 (4)
Neoplasm nos[a]	5 (2)	3 (1)	2 (1)	10 (1)
Vision disorders	10 (3)	10 (3)	13 (4)	33 (3)
Cataract	3 (1)	4 (1)	6 (2)	13 (1)
Red blood cell disorders	9 (3)	9 (3)	3 (1)	21 (2)
Anemia	9 (3)	9 (3)	3 (1)	21 (2)

[a]nos = not otherwise specified.

The sponsor has performed a further analysis of adverse events, based on actual total daily dose at the time the adverse event occurred. The incidence of such events was comparable at given doses between the two galantamine groups.

11.2.2 Deaths, Other Serious Adverse Events, And Adverse Event Discontinuations

The incidence of deaths, other serious adverse events, and adverse event discontinuations in the 3 treatment groups are summarized in the following table which I have copied from the submission

Categories	PLACEBO (N=320) n (%)	GAL-IR N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Death	2 (1)	1 (<1)	5 (2)	8 (1)
Subjects with 1 or more serious adverse events	35 (11)	49 (15)	36 (11)	120 (12)
Adverse events leading to subject discontinuation	15 (5)	22 (7)	29 (9)	66 (7)

Note: Percentages calculated with the number of subjects in each group as denominator.

As the above table indicates, the overall incidence of deaths and adverse event discontinuations was slightly higher in the controlled-release galantamine group than in the immediate-release galantamine group.

Further details about these events are summarized below.

11.2.2.1 Deaths

These are summarized in the following table, taken from the submission. The deaths listed are those which occurred during treatment or within 30 days of study termination

Subject No.	Age (Yrs)/ Sex	Day of Death	Precipitative Adverse Event	Relationship of AE to Study Drug	Treatment Duration (Days)
Treatment Group: GAL-CR					
A31307	82/F	58	Cardiac arrest	Doubtful	31
A31978	92/F	56	Pneumonia	None	53
A32233	75/M	116	GI hemorrhage	None	111
			Neoplasm nos[a]	None	111
A33063	80/F	169	Cardiac arrest	Doubtful	153
A35105	85/F	157	Bronchospasm	None	148
			Cerebrovascular disorder	Doubtful	148
			Pneumonia	None	148
Treatment Group: GAL-IR					
A31287	78/F	139	Cardiac failure	Doubtful	133
Treatment Group: Placebo					
A31274	84/M	26	Asthenia	None	25
			Hypotension	None	25
			Postoperative hemorrhage	None	25
A32034	86/F	99	Pneumonitis	None	26

[a] nos = not otherwise specified.

I have read the narratives for these deaths; a further description of individual events is not warranted. Although the incidence of deaths in the Reminyl® ER group is higher than in the placebo group, the narratives for individual deaths suggest that they were more likely to be related to intercurrent illnesses than to galantamine.

11.2.2.2 Serious Adverse Events

The following table lists the incidence of individual non-fatal serious adverse events which occurred in ≥ 1% of patients in any treatment group during treatment or within 30 days of study termination. The table is taken from the submission

System Organ Class Preferred Term	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Total no. subjects with serious adverse events	35 (11)	40 (12)	36 (11)	111 (12)
Body as a whole - general disorders	14 (4)	11 (3)	8 (3)	33 (3)
Injury	6 (2)	3 (1)	5 (2)	14 (1)
Syncope	2 (1)	3 (1)	3 (1)	8 (1)
Fever	2 (1)	2 (1)	1 (<1)	5 (1)
Chest pain	2 (1)	2 (1)	0	4 (<1)
Secondary terms	10 (3)	9 (3)	6 (2)	25 (3)
Surgical intervention	5 (2)	4 (1)	3 (1)	12 (1)
Fall	4 (1)	4 (1)	3 (1)	11 (1)
Respiratory system disorders	2 (1)	5 (2)	9 (3)	16 (2)
Pneumonia	0	4 (1)	5 (2)	9 (1)
Dyspnea	0	1 (<1)	3 (1)	4 (<1)
Neoplasm	5 (2)	8 (2)	2 (1)	15 (2)
Neoplasm nos[a]	2 (1)	1 (<1)	1 (<1)	4 (<1)
Gastrointestinal system disorders	2 (1)	7 (2)	3 (1)	12 (1)
GI hemorrhage	0	1 (<1)	2 (1)	3 (<1)
Abdominal pain	0	2 (1)	0	2 (<1)
Gastritis	0	2 (1)	0	2 (<1)
Psychiatric disorders	4 (1)	5 (2)	2 (1)	11 (1)
Agitation	2 (1)	1 (<1)	1 (<1)	4 (<1)
Confusion	0	3 (1)	0	3 (<1)
Psychosis	2 (1)	0	0	2 (<1)
Vascular (extracardiac) disorders	2 (1)	4 (1)	5 (2)	11 (1)
Cerebrovascular disorder	2 (1)	1 (<1)	3 (1)	6 (1)
Hemorrhage intracranial	0	2 (1)	1 (<1)	3 (<1)
Transient ischemic attack	0	1 (<1)	2 (1)	3 (<1)

[a]nos = not otherwise specified.

(continued)

System Organ Class Preferred Term	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Centr & periph nervous system disorders	2 (1)	5 (2)	3 (1)	10 (1)
Convulsions	0	3 (1)	1 (<1)	4 (<1)
Gait abnormal	2 (1)	1 (<1)	0	3 (<1)
Heart rate and rhythm disorders	2 (1)	3 (1)	4 (1)	9 (1)
Cardiac arrest	0	0	2 (1)	2 (<1)
Cardiovascular disorders, general	3 (1)	2 (1)	2 (1)	7 (1)
Cardiac failure	1 (<1)	2 (1)	1 (<1)	4 (<1)
Hypotension	2 (1)	0	0	2 (<1)
Urinary system disorders	1 (<1)	5 (2)	0	6 (1)
Urinary tract infection	0	2 (1)	0	2 (<1)
Metabolic and nutritional disorders	4 (1)	0	1 (<1)	5 (1)
Dehydration	2 (1)	0	0	2 (<1)
Liver and biliary system disorders	1 (<1)	1 (<1)	2 (1)	4 (<1)
Cholecystitis	0	1 (<1)	2 (1)	3 (<1)

As the table indicates there were no striking differences in the incidence of individual serious adverse events between the galantamine groups. Pneumonia was, however, more common in the galantamine groups than in the placebo group.

The sponsor has performed a further analysis of serious adverse events, based on actual total daily dose at the time the adverse event occurred. The incidence of such events was comparable between the 2 galantamine groups at specific doses.

I have read the narratives for all these events and believe a more detailed description is not warranted.

11.2.2.3 Adverse Event Discontinuations

The following table lists the incidence of individual discontinuations for adverse events which occurred in ≥ 1% of patients in any treatment group during treatment or within 30 days of study termination. The table is taken from the submission

System Organ Class Preferred Term	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Total no. subjects with permanent stop	15 (5)	22 (7)	29 (9)	66 (7)
Gastrointestinal system disorders	4 (1)	8 (2)	14 (4)	26 (3)
Nausea	2 (1)	5 (2)	10 (3)	17 (2)
Vomiting	0	2 (1)	3 (1)	5 (1)
Psychiatric disorders	6 (2)	4 (1)	10 (3)	20 (2)
Anorexia	1 (<1)	2 (1)	4 (1)	7 (1)
Agitation	2 (1)	0	4 (1)	6 (1)
Somnolence	2 (1)	0	1 (<1)	3 (<1)
Hallucination	2 (1)	0	0	2 (<1)
Centr & periph nervous system disorders	3 (1)	5 (2)	4 (1)	12 (1)
Dizziness	0	2 (1)	3 (1)	5 (1)
Gait abnormal	2 (1)	0	1 (<1)	3 (<1)
Convulsions	0	2 (1)	0	2 (<1)
Vascular (extracardiac) disorders	1 (<1)	1 (<1)	3 (1)	5 (1)
Cerebrovascular disorder	1 (<1)	0	2 (1)	3 (<1)
Metabolic and nutritional disorders	0	1 (<1)	2 (1)	3 (<1)
Weight decrease	0	1 (<1)	2 (1)	3 (<1)
Secondary term	1 (<1)	2 (1)	0	3 (<1)
Fall	0	2 (1)	0	2 (<1)

As the table above indicates, there were no prominent differences in the incidence of individual events between the galantamine treatment groups, although the incidence of nausea was slightly higher in the controlled-release galantamine group than in the immediate-release group.

I have read all the sponsor-supplied narratives for these events and do not feel that a more detailed description of individual events is warranted.

11.2.3 Incidence Of Nausea And Vomiting During Dose-Titration

An analysis was conducted to compare the incidence of nausea and vomiting, the most common adverse seen with acetylcholinesterase inhibitors between the treatment groups during the dose-titration period. The results of the analysis are displayed in the following table, copied from the submission

	PLACEBO (N=320)			GAL-IR (N=326)			GAL-CR (N=319)		
Onset Time Interval	Nausea n (%)	Vomiting n (%)	Nausea or Vomiting n (%)	Nausea n (%)	Vomiting n (%)	Nausea or Vomiting n (%)	Nausea n (%)	Vomiting n (%)	Nausea or Vomiting n (%)
Week 1	4 (1)	0	4 (1)	7 (2)	3 (1)	8 (2)	7 (2)	2 (1)	7 (2)
Week 2	1 (0)	1 (0)	2 (1)	1 (<1)	0	1 (<1)	2 (1)	1 (<1)	2 (1)
Week 3	0	0	0	3 (1)	0	3 (1)	2 (1)	0	2 (1)
Week 4	0	2 (1)	2 (1)	3 (1)	3 (1)	5 (2)	1 (<1)	0	1 (<1)
Week 5	3 (1)	1 (0)	3 (1)	12 (4)	7 (2)	15 (5)	9 (3)	3 (1)	11 (3)
Week 6	0	0	0	6 (2)	1 (<1)	6 (2)	4 (1)	2 (1)	5 (2)
Week 7	1 (0)	1 (0)	2 (1)	4 (1)	6 (2)	8 (2)	0	2 (1)	2 (1)
Week 8	2 (1)	1 (0)	3 (1)	4 (1)	2 (1)	4 (1)	3 (1)	2 (1)	4 (1)
Week 9	1 (<1)	1 (<1)	1 (<1)	7 (2)	4 (1)	11 (3)	10 (3)	2 (1)	11 (3)
Week 10	1 (0)	0	1 (0)	9 (2)	5 (2)	7 (2)	7 (2)	3 (1)	9 (3)
Week 11	1 (0)	0	1 (0)	2 (1)	1 (<1)	2 (1)	7 (2)	4 (1)	8 (3)
Week 12	0	0	0	0	1 (<1)	1 (<1)	2 (1)	2 (1)	4 (1)

As the table above indicates, the overall incidence of nausea and vomiting was slightly lower in the controlled-release galantamine group than in the immediate-release galantamine group. The incidence of both adverse events was higher in the galantamine groups at Weeks 5 and 9, compared with the placebo group.

11.2.4 Muscle Weakness Related Adverse Events

The incidence of adverse events considered potentially related to muscle weakness (a prominent adverse event for a previously-reviewed acetylcholinesterase inhibitor drug) was compared between treatment groups without any clear differences between the two galantamine groups, although fatigue was more frequent in the galantamine groups than in the placebo. These results are summarized in the sponsor table below

Preferred Term	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Total no. subjects with muscle weakness	39 (12)	52 (16)	52 (16)	143 (15)
Fall	19 (6)	20 (6)	20 (6)	59 (6)
Fatigue	2 (1)	12 (4)	12 (4)	26 (3)
Dyspnea	8 (3)	5 (2)	7 (2)	20 (2)
Gait abnormal	5 (2)	6 (2)	7 (2)	18 (2)
Myalgia	3 (1)	3 (1)	5 (2)	11 (1)
Asthenia	3 (1)	4 (1)	3 (1)	10 (1)
Muscle contractions involuntary	2 (1)	3 (1)	3 (1)	8 (1)
Ataxia	0	3 (1)	2 (1)	5 (1)
Dysphagia	2 (1)	2 (1)	1 (<1)	5 (1)
Muscle weakness	1 (<1)	3 (1)	1 (<1)	5 (1)
Dysphonia	0	1 (<1)	2 (1)	3 (<1)
Malaise	0	3 (1)	0	3 (<1)
Hypokinesia	0	0	1 (<1)	1 (<1)
Paralysis	1 (<1)	0	0	1 (<1)
Speech disorder	0	0	1 (<1)	1 (<1)

Note: Percentages calculated with the no. of subjects in each group as denominator.
Note: Selected adverse events during double-blind treatment phase and all serious adverse events during treatment or within 30 days after stop of double-blind medication

11.3 Safety Laboratory Tests

11.3.1 Changes In Laboratory Values Over Time

There were no changes in mean values for hematology or clinical chemistry variables that could be considered clinically important, based on tables contained in the submission.

11.3.2 Changes From Baseline In Individual Subjects

The incidence of changes in individual laboratory values from within normal limits at baseline, to pathological during the study, are summarized in the following table, contained in the submission. With the exception of increases in random blood glucose and serum triglycerides, these changes were very infrequent. For blood glucose and serum triglycerides, these changes were similar in the placebo and galantamine groups

Laboratory Class Laboratory Test Abnormalities	PLACEBO (N=320) N (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Clinical chemistry	289	292	291	872
Albumin	287	291	291	869
Low	0	4 (1)	1 (<1)	5 (1)
High	0	0	0	0
Alkaline phosphatase	287	292	291	870
Low	0	0	0	0
High	0	0	0	0
ALT (SGPT)	284	290	289	863
Low	0	0	0	0
High	1 (<1)	1 (<1)	3 (1)	5 (1)
AST (SGOT)	283	286	289	858
Low	0	0	0	0
High	1 (<1)	1 (<1)	1 (<1)	3 (<1)
BUN	279	285	284	848
Low	0	0	0	0
High	13 (5)	8 (3)	14 (5)	35 (4)
Calcium	287	291	291	869
Low	3 (1)	1 (<1)	0	4 (<1)
High	2 (1)	0	0	2 (<1)
Chloride	282	289	290	861
Low	3 (1)	2 (1)	0	5 (1)
High	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Cholesterol	286	290	291	867
Low	1 (<1)	2 (1)	0	3 (<1)
High	3 (1)	2 (1)	0	5 (1)
Creatine phosphokinase	284	286	285	855
Low	0	0	0	0
High	3 (1)	5 (2)	7 (2)	15 (2)
Creatinine	288	292	291	871
Low	0	0	1 (<1)	1 (<1)
High	1 (<1)	3 (1)	1 (<1)	5 (1)
GGT	286	290	288	864
Low	0	0	0	0
High	3 (1)	2 (1)	3 (1)	8 (1)
Glucose	239	243	244	726
Low	1 (<1)	1 (<1)	0	2 (<1)
High	49 (21)	66 (27)	57 (23)	172 (24)
Phosphorus	285	290	290	865
Low	2 (1)	0	1 (<1)	3 (<1)
High	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Potassium	282	287	290	859
Low	3 (1)	1 (<1)	3 (1)	7 (1)
High	6 (2)	8 (3)	6 (2)	20 (2)
Sodium	288	292	291	871
Low	0	0	0	0
High	1 (<1)	1 (<1)	0	2 (<1)

Note: Percentages calculated with the number of subjects per laboratory test as denominator.
A subject may be in more than one category (Low/High).
Abnormality defined as clinically significant abnormal assessment during the double-blind period.

Laboratory Class Laboratory Test Abnormalities	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Clinical chemistry (continued)				
Total bilirubin	281	284	285	850
Low	0	0	0	0
High	3 (1)	3 (1)	5 (2)	11 (1)
Total protein	286	289	290	865
Low	6 (2)	2 (1)	2 (1)	10 (1)
High	2 (1)	1 (<1)	0	3 (<1)
Triglycerides	232	246	237	715
Low	0	0	0	0
High	40 (17)	32 (13)	32 (14)	104 (15)
Uric acid	279	289	287	855
Low	0	0	0	0
High	12 (4)	8 (3)	5 (2)	25 (3)
Hematology	285	292	290	867
Hematocrit	275	284	278	837
Low	15 (5)	17 (6)	9 (3)	41 (5)
High	0	0	0	0
Hemoglobin	266	277	277	820
Low	18 (7)	13 (5)	9 (3)	40 (5)
High	0	0	0	0
Platelet count	270	276	271	817
Low	2 (1)	3 (1)	3 (1)	8 (1)
High	15 (6)	14 (5)	14 (5)	43 (5)
RBC	277	286	284	847
Low	4 (1)	10 (3)	4 (1)	18 (2)
High	0	0	0	0
WBC	276	286	279	841
Low	2 (1)	0	0	2 (<1)
High	11 (4)	15 (5)	19 (7)	45 (5)

Note: Percentages calculated with the number of subjects per laboratory test as denominator.
A subject may be in more than one category (Low/High).
Abnormality defined as clinically significant abnormal assessment during the double-blind period.

11.3.3 Individual Clinically Significant Abnormalities

The frequencies of individual laboratory abnormalities reported as adverse events was similar across treatment groups. The most frequent of these was hyperglycemia (2%)

11.4 Vital Signs

The incidence of changes in vital signs from within normal limits at baseline to pathological during the study are summarized in the following table, contained in the submission.

Vital Signs Abnormalities	PLACEBO (N=320) N (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Systolic BP	302	313	307	922
Low	1 (<1)	1 (<1)	1 (<1)	3 (<1)
High	3 (1)	4 (1)	6 (2)	13 (1)
Diastolic BP	305	314	308	927
Low	4 (1)	5 (2)	6 (2)	15 (2)
High	2 (1)	0	0	2 (<1)
Pulse rate	309	318	309	936
Low	3 (1)	0	2 (1)	5 (1)
High	1 (<1)	0	0	1 (<1)

Note: Percentages calculated with the number of subjects per parameter as denominator.

Note that the incidence of these changes was small and without prominent differences between treatment groups.

None of the individual changes in vital signs was considered clinically important.

11.5 Physical Examinations

Changes in physical examination findings were similar across treatment groups with none being considered clinically significant.

11.6 Electrocardiograms

11.6.1 Mean Changes From Baseline

Mean changes from baseline in electrocardiogram parameters are summarized in the following table taken from the submission

	PLACEBO			GAL-IR			GAL-CR		
	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
PR interval (ms)									
Baseline	304	165.1 (34.52)		315	163.6 (34.22)		311	164.2 (32.40)	
Week 12	272	166.1 (33.27)	1.0 (16.98)	268	165.3 (36.50)	0.1 (16.16)	264	165.3 (32.53)	0.8 (20.84)
Week 26	242	164.8 (31.98)	0.2 (16.03)	233	165.0 (33.70)	0.5 (17.26)	233	165.6 (32.17)	0.9 (18.60)
QRS interval (ms)									
Baseline	315	92.9 (22.50)		320	93.1 (21.41)		316	94.7 (22.06)	
Week 12	279	90.7 (20.61)	-0.6 (14.68)	270	92.7 (21.25)	-0.5 (11.91)	269	95.5 (23.57)	0.8 (12.00)
Week 26	250	90.5 (20.89)	-1.1 (13.68)	235	94.2 (21.69)	0.6 (12.74)	235	96.2 (23.75)	1.6 (13.67)
QT interval (ms)									
Baseline	312	407.6 (33.42)		318	403.7 (32.17)		310	409.2 (29.83)	
Week 12	273	409.3 (34.43)	1.7 (23.80)	262	413.3 (31.97)	8.8 (26.74)	257	415.9 (31.73)	6.0 (28.07)
Week 26	244	405.9 (31.95)	-1.8 (28.12)	229	413.0 (33.28)	8.8 (27.67)	226	414.3 (32.77)	4.3 (27.34)
QTc linear (ms)									
Baseline	312	419.6 (23.91)		318	418.1 (20.54)		310	420.8 (21.18)	
Week 12	273	419.5 (22.69)	0.7 (18.75)	262	420.9 (23.80)	3.1 (21.31)	257	422.0 (22.16)	1.3 (19.89)
Week 26	244	417.8 (21.63)	-0.8 (20.30)	229	421.1 (22.89)	3.8 (20.14)	226	421.4 (21.88)	0.4 (20.25)
QTc linear derived (ms)									
Baseline	312	420.5 (23.84)		318	419.2 (20.56)		310	421.7 (21.25)	
Week 12	273	420.3 (22.51)	0.6 (18.83)	262	421.5 (24.00)	2.6 (21.35)	257	422.4 (22.15)	0.9 (19.84)
Week 26	244	418.7 (21.75)	-0.7 (20.30)	229	421.7 (22.91)	3.4 (20.07)	226	422.0 (21.73)	0.2 (20.12)
QTc Bazett (ms)									
Baseline	312	426.2 (25.40)		318	426.2 (23.16)		310	427.4 (23.57)	
Week 12	273	425.5 (24.07)	0.3 (20.27)	262	426.1 (26.99)	0.7 (23.00)	257	425.9 (23.41)	-0.9 (21.16)
Week 26	244	424.7 (24.28)	0.0 (21.40)	229	426.4 (25.14)	1.7 (21.09)	226	426.0 (22.83)	-1.3 (21.20)
QTc Fridericia (ms)									
Baseline	312	419.6 (24.32)		318	418.3 (20.90)		310	421.0 (21.46)	
Week 12	273	419.8 (23.25)	0.8 (18.79)	262	421.5 (24.18)	3.5 (21.77)	257	422.3 (22.24)	1.5 (20.07)
Week 26	244	417.9 (22.00)	-0.7 (20.27)	229	421.6 (23.33)	4.1 (20.53)	226	421.7 (22.16)	0.5 (20.27)
Heart rate (bpm)									
Baseline	315	66.6 (10.46)		320	68.2 (12.32)		316	66.4 (9.92)	
Week 12	279	66.0 (10.76)	-0.4 (7.28)	270	64.8 (10.31)	-2.9 (8.11)	269	63.9 (9.73)	-2.0 (8.29)
Week 26	250	66.7 (11.12)	0.7 (9.40)	235	65.2 (10.86)	-2.2 (8.42)	235	64.2 (10.19)	-1.8 (8.33)

The data appear to indicate the following

- Mean changes in PR and QRS intervals were very small across treatment groups
- Small mean increases in the absolute QT interval were observed in both galantamine groups compared with placebo
- Mean changes in several QT_c parameters were small in all 3 treatment groups. Small mean increases were seen in the immediate-release galantamine group only
- Small mean decreases in heart rate were seen in both galantamine groups.

11.6.2 Individual Subject Changes

The incidence of changes in individual electrocardiogram parameters from within normal limits at baseline to potentially clinically significant during the study are summarized in the following table, contained in the submission. The table indicates the number and proportion of patients in each treatment group with potentially clinically significant changes in each parameter

ECG Parameters Abnormalities	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
PR interval	258	267	261	786
Low	0	0	0	0
High	12 (5)	10 (4)	16 (6)	38 (5)
QRS interval	278	288	278	844
Low	1 (<1)	4 (1)	4 (1)	9 (1)
High	3 (1)	11 (4)	8 (3)	22 (3)
QT interval	288	292	281	861
Low	0	0	0	0
High	1 (<1)	2 (1)	5 (2)	8 (1)
QTc Linear	275	281	274	830
Low	0	0	0	0
High	13 (5)	23 (8)	26 (9)	62 (7)
QTc Linear derived	275	281	274	830
Low	0	0	0	0
High	14 (5)	25 (9)	27 (10)	66 (8)
QTc Bazett	269	269	259	797
Low	0	0	0	0
High	24 (9)	29 (11)	22 (8)	75 (9)
QTc Fridericia	275	281	274	830
Low	0	0	0	0
High	14 (5)	24 (9)	24 (9)	62 (7)
Heart rate	289	285	287	861
Low	4 (1)	1 (<1)	7 (2)	12 (1)
High	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
A subject may be in more than one category (Low/High).
Abnormality defined as clinically significant abnormal assessment during the double-blind period.

As the table above indicates

- The proportion of subjects with potentially clinically significant increases in PR interval, increases in QT_cB interval, and in decreases in heart rate was similar across treatment groups
- For QT_c intervals calculated by other methods, a slightly higher proportion of subjects in the galantamine groups had abnormalities as compared with the placebo group

QT interval prolongation as an adverse event was reported for only 1 patient in the study who received placebo. The maximum post-baseline QT_cB and QT_cLD intervals were 466 msec and 451 msec, respectively.

11.6.3 Maximum QT_c And Maximum Changes In QT_c

The distribution of maximum post-baseline QT_cB intervals by treatment group and gender, stratified by QT_c interval range, is in the following table, taken from the submission

	PLACEBO (N=320)			GAL-IR (N=326)			GAL-CR (N=319)		
Maximum QTcB Interval (ms)	All Subjects	Male	Female	All Subjects	Male	Female	All Subjects	Male	Female
No. of Subjects[a]	297	103	194	300	111	189	290	103	187
≤430	110 (37)	44 (43)	66 (34)	126 (42)	47 (42)	79 (42)	107 (37)	36 (35)	71 (38)
431-450	122 (41)	31 (30)	91 (47)	100 (33)	34 (31)	66 (35)	120 (41)	42 (41)	78 (42)
451-470	44 (15)	16 (16)	28 (14)	47 (16)	16 (14)	31 (16)	48 (17)	21 (20)	27 (14)
471-500	16 (5)	9 (9)	7 (4)	20 (7)	10 (9)	10 (5)	14 (5)	3 (3)	11 (6)
>500	5 (2)	3 (3)	2 (1)	7 (2)	4 (4)	3 (2)	1 (<1)	1 (1)	0

[a]Subjects with at least one postbaseline QTcB interval value.

The distribution of post-baseline maximum QT_c values > 450 msec was similar across treatment groups, regardless of the correction method used.

The distribution of maximum increases from baseline in QT_cB intervals by treatment group and gender, stratified by change in QT_c interval range, is in the following table, copied from the submission

	PLACEBO (N=320)			GAL-IR (N=326)			GAL-CR (N=319)		
Maximum QTcB Increase from Baseline (ms)	All Subjects	Male	Female	All Subjects	Male	Female	All Subjects	Male	Female
No. of Subjects[a]	222	78	144	203	77	126	193	76	117
<30	175 (79)	59 (76)	116 (81)	155 (76)	55 (71)	100 (79)	150 (78)	61 (80)	89 (76)
30 – 60	44 (20)	18 (23)	26 (18)	44 (22)	18 (23)	26 (21)	40 (21)	15 (20)	25 (21)
>60	3 (1)	1 (1)	2 (1)	4 (2)	4 (5)	0	3 (2)	0	3 (3)

[a]Subjects with a baseline and at least one postbaseline QTcB interval value. Percentages for males and females are based on total males and females who had a baseline and at least one postbaseline QTcB interval value.

The distribution of these changes was similar across treatment groups as indicated in the above table.

11.7 Body Weight

Mean changes in body weight in the 3 treatment groups are in the following table, taken from the submission

	PLACEBO		GAL-IR		GAL-CR	
	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Baseline	319	67.8 (14.59)		325	68.3 (15.86)		319	68.6 (14.16)	
Week 12	281	68.0 (14.74)	-0.0 (2.15)	274	68.4 (15.66)	-0.6 (2.66)	270	68.6 (14.27)	-0.7 (2.17)
Week 26	252	68.3 (14.66)	-0.0 (2.74)	239	67.6 (15.45)	-1.3 (3.15)	238	68.7 (14.34)	-1.0 (3.47)

As the table indicates, mean changes (decreases) in each treatment group were small

A higher proportion of subjects in both galantamine groups than in the placebo group had at least a 7% decrease in body weight from baseline at Week 26. The number and proportion of patients who had specific levels of weight change are in the following table, which I have copied from the submission

Parameter Time Interval Categories	PLACEBO (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Total no. subjects	308 (96)	317 (97)	311 (97)	936 (97)
Percent change from baseline weight				
Week 4	306	316	310	932
Decrease: >= 21%	0	0	0	0
Decrease: 15% to <21%	0	0	1 (<1)	1 (<1)
Decrease: 7% to <15%	3 (1)	3 (1)	4 (1)	10 (1)
Decrease: >0% to <7%	106 (35)	110 (35)	105 (34)	321 (34)
No change or gain	197 (64)	203 (64)	200 (65)	600 (64)
Week 8	293	295	289	877
Decrease: >= 21%	0	0	0	0
Decrease: 15% to <21%	0	0	1 (<1)	1 (<1)
Decrease: 7% to <15%	2 (1)	6 (2)	1 (<1)	9 (1)
Decrease: >0% to <7%	113 (39)	150 (51)	142 (49)	405 (46)
No change or gain	178 (61)	139 (47)	145 (50)	462 (53)
Week 12	281	274	270	825
Decrease: >= 21%	0	1 (<1)	0	1 (<1)
Decrease: 15% to <21%	0	0	1 (<1)	1 (<1)
Decrease: 7% to <15%	6 (2)	14 (5)	7 (3)	27 (3)
Decrease: >0% to <7%	112 (40)	142 (52)	141 (52)	395 (48)
No change or gain	163 (58)	117 (43)	121 (45)	401 (49)
Week 26	252	239	238	729
Decrease: >= 21%	0	0	1 (<1)	1 (<1)
Decrease: 15% to <21%	1 (<1)	3 (1)	0	4 (1)
Decrease: 7% to <15%	9 (4)	27 (11)	29 (12)	65 (9)
Decrease: >0% to <7%	94 (37)	128 (54)	103 (43)	325 (45)
No change or gain	148 (59)	81 (34)	105 (44)	334 (46)

Note: Percentages calculated with the number of subjects observed at each time point as denominator.

11.8 Sponsor's Conclusions

- The controlled-release formulation of galantamine, administered in a flexible dose regime of 16 to 24 mg/day was well-tolerated
- The safety and tolerability profile of controlled-release galantamine was comparable to that of the approved immediate-release product

11.9 Reviewer's Comments

The safety profile of the extended-release galantamine formulation was broadly similar to that of the immediate-release formulation, based on the head-to-head comparison that was possible in this study. There were no safety concerns specific to the extended-release formulation.

12. Summary Of Protocol For Open-Label Extension Study GAL-INT-21

The protocol for this study, dosing regime, and the schedule for study assessments is summarized below.

12.1 Summary Of Protocol

This study protocol is summarized below; the study is currently ongoing

Protocol:	GAL-INT-21
Primary Objective:	To evaluate the long-term safety of controlled-release galantamine in Alzheimer's Disease
Design:	Open-label uncontrolled trial
Key Inclusion Criteria:	Completion of Study GAL-INT-10
Dosage:	Reminyl® ER 16 to 24 mg q.d.
Duration:	12 months
Original Projected Sample Size:	700 patients
Safety Outcome Measures:	Adverse events, vital signs, safety laboratory tests, electrocardiograms, and physical examinations
Efficacy Outcome Measures:	ADAS-Cog, Neuropsychiatry Inventory, ADCS-ADL
Status	Ongoing

12.2 Dosing Regime

The dosing regimen for this study was as follows

- Patients enrolled in this study were to be titrated to a dose of Reminyl® ER of either 16 mg q.d. or 24 mg q.d.
- All patients were to initially receive Reminyl® ER in a dose of 8 mg q.d. for 4 weeks, followed by a dose of 16 mg q.d. for at least 8 weeks.
- Subsequently (i.e., at Visit 2 or thereafter; see study schedule below) the dose could be increased to 24 mg q.d., based on safety and tolerability
- At or beyond Visit 2, dose adjustments could be made only twice (including the initial increase to 24 mg q.d.). A decrease to 16 mg q.d. could be made based on safety and tolerability, but once such a decrease was made, the dose would have to remain unchanged for the remainder of the trial.

12.3 Schedule For Assessments

The schedule for safety and other assessments is summarized in the following table copied from the submission

Visit	V1[a) b)]	V2[b) c)]	Phone Call[b) d)]	V3[b)]	V4[b)]
Assessment	Initial	End of Month 3	End of Month 4	End of Month 6	End of Month 12
Informed Consent	X				
Eligibility Criteria	X				
Medical History	X				
ADAS	X			X	X
NPI	X			X	X
ADCS-ADL Inventory	X			X	X
Physical Examination	X	X		X	X
Body Weight	X		X[b)]		X
Vital Signs	X	X	X[b)]	X	X
ECG	X	X	X[b) e)]	X	X
Laboratory Safety	X	X	X[b) e)]	X	X
Adverse Events	X	X	X[b)]	X	X
Dose Tolerability			X		
Concomitant Therapy	X	X	X[b)]	X	X
Dispense Trial Medication	X	X	X[b)]	X	
Collect Trial Medication		X	X[b)]	X	X

a) The initial visit (Visit 1) of GAL-INT-21 should occur the same day as the final visit (Visit 7) of the preceding double-blind trial (GAL-INT-18). Therefore, information obtained at the final visit (Visit 7) of the double-blind trial can be used for the initial visit (Visit 1) of the present trial. If there is a delay >7 days, the physical examination, weight, vital signs, and adverse events must be reassessed at Visit 1. If the delay is >30 days, the subject is not eligible.

b) If a subject misses 4 or more consecutive days of trial medication he/she must repeat the full dose titration sequence, starting with 8 mg CR o.d. The subject must return to the clinic for assessment of body weight, vital signs, adverse events, and concomitant therapy. Laboratory samples may be taken and/or an ECG performed at the discretion of the investigator. Trial medication dispensed at the previous visit will be collected and new trial medication dispensed.

c) Based on safety and tolerability, the investigator may increase the dose to 24 mg CR o.d.

d) Subjects or caregivers are to be contacted by telephone at the end of Month 4 (Week 16). Based on safety and tolerability, the investigator may increase the dose to 24 mg CR o.d. or reduce the dose to 16 mg CR o.d. If a dose adjustment is required, the subject must return to the clinic for new trial medication and safety assessments (as noted in the flowchart).

e) At the discretion of the investigator

13. Safety Summary Of Study GAL-INT-21

GAL-INT-21 is an ongoing study. The safety summary for this study contained in the original application provides information for deaths, other serious adverse events, and adverse event discontinuations only.

In addition to a very brief overall narrative summary, the sponsor has provided appendices containing adverse event reports for these events.

The cut-off date for data included in this submission is September 30, 2002.

The key data included in the safety summary are summarized below.

13.1 Disposition

Key information on patient disposition is as summarized below; the first patient to enter this study did so on 9/20/01

Category	n (%)
Enrolled	719 (100)
Completed	130 (18)
Ongoing	487 (68)
Prematurely discontinued	102 (14)

The most common reasons for discontinuation was adverse events.

13.2 Deaths

18 patients died during the study. They are listed in the table below. The medical conditions listed do not appear to have been consistently based on preferred terms

Initials	Age	Sex	Listed Conditions
[redacted]	88	F	Hematemesis, respiratory failure, cardiac arrest, shock, sepsis
	39	F	Septicemia, intestinal stenosis, bowel perforation, malignant colonic neoplasm
	81	M	Myocardial infarction
	76	M	Heart attack
	79	M	Sudden death
	79	F	Accidental injury, cerebral hemorrhage, respiratory failure
	69	F	Stroke, hemiparesis, hypertension, atrial flutter-fibrillation
	83	M	Sudden death (earlier had surgery for a volvulus)
	78	M	Accident, multiple organ failure, myocardial infarction, intra-abdominal hemorrhage, respiratory failure
	91	F	Cardiac arrest, aspiration pneumonitis, injury, fall
	79	F	Cushing's syndrome, atrial fibrillation, hypoxia, agitation, and urinary tract infection
	80	M	Non-Hodgkins lymphoma
	91	M	Pneumonia
	75	M	Cerebral hemorrhage
	83	F	Stroke, heart attack, acute renal failure, gangrene
	91	F	Fall, subdural hematoma, coma
	85	F	Myocardial infarction, congestive heart failure
[redacted]	73	F	Failure to thrive

I have read the adverse event reports for all these events. None of the events above warrant further description; most are events that are common in this population.

13.3 Serious Adverse Events

103 patients experienced serious adverse events (including fatal ones) during the study.

The most common serious adverse events were fall, injury, myocardial infarction, urinary tract infection, syncope, and pathological fracture.

I have read the adverse event reports for all these events. None of the events above warrant further description; most were events that are common in this population or attributable to the pharmacological effects of galantamine.

13.4 Adverse Event Discontinuations

25 patients withdrew from this study on account of adverse events.

The most common such adverse events were nausea, vomiting, and decreased weight.

I have read the adverse event reports for all these events. None of the events above warrant further description; all were events that are either common in this population or attributable to the pharmacological effects of galantamine.

13.5 Reviewer's Comments

The interim data for deaths, other serious adverse events, and adverse event discontinuations in this study do not raise any safety concerns that have not already been evident with the approved immediate-release formulation of galantamine.

14. Four-Month Safety Update

The 4-Month Safety Update was submitted on 6/19/03. It had a cut-off date of 2/28/03. The Safety Update contained data from GAL-INT-21 only (this is the only study with Reminyl® ER that was ongoing at the time of submission of that update).

The safety summary for the GAL-INT-21 study that was contained in the original application provided information for deaths, other serious adverse events, and adverse event discontinuations only. The 4-Month Safety Update continued to provide information about the same types of events only.

In the 4-Month Safety Update, in addition to a very brief overall narrative summary, the sponsor had provided appendices containing full reports for deaths, serious adverse events, and adverse event discontinuations.

The key data included in the Safety Update are summarized below.

14.1 Patient Disposition

Key information on patient disposition (for the entire population included in this study) was as summarized below.

Category	n (%)
Enrolled	720 (100)
Completed	378 (53)
Ongoing	198 (28)
Prematurely discontinued	144 (20)

A total 46 subjects had discontinued this study on account of adverse events, through the cut-off date of 2/28/03.

14.2 Deaths

13 additional deaths had occurred during the GAL-INT-21 study at the time of the 4-Month Safety Update (through the cut-off date of 2/28/03)

Initi?s	Age	Sex	Listed Conditions
	88	M	Pneumonia, fall, accidental injury
	70	F	Pneumonia, cardiac arrest
	88	F	Myocardial infarction
	85	M	Rhabdomyolysis, dehydration, aggression, pneumonia, exacerbation of Alzheimer's Disease
	90	F	Cardiac arrest, pulmonary embolism, deep vein thrombosis, injury, congestive heart failure
	81	M	Failure to thrive, fall, anorexia, injury, aggravation of Alzheimer's Disease
	89	F	Death (further details unavailable)
	75	M	Accidental injury
	82	M	Malignant lymphoma
	91	F	Congestive heart failure, chest pain, leukocytosis, hypotension, unconsciousness, urinary tract infection, decubiti
	78	M	Heart attack
	79	F	Respiratory failure, septic shock, pneumonia, dehydration
	77	F	Pneumonia, acute renal failure

I have read the adverse event reports for all these events. None of the events above warrant further description; most are events that are common in this population.

14.3 Serious Adverse Events

52 patients had new serious adverse events during the GAL-INT-21 study at the time of the 4-Month Safety Update (through the cut-off date of 2/28/03); 12 of these patients had other serious adverse events reported in the original submission of this application. The most commonly reported new adverse events included pneumonia, injury, cardiac arrest/failure, falls, chest pain, neoplasm, urinary tract infection, worsening of Alzheimer's Disease, coronary artery disease, dehydration, myocardial infarction, and syncope.

I have read the adverse event reports for all these events. None of the events above warrant further description; most were events that are common in this population or attributable to the pharmacological effects of galantamine.

14.4 Adverse Event Discontinuations

An additional 22 subjects withdrew from the GAL-INT-21 study on account of adverse events at the time of the 4-Month Safety Update (through the cut-off date of 2/28/03). Several of these were also classed as serious adverse events and were subsumed as such under the original submission or the 4-Month Safety Update.

The most common adverse events that led to premature discontinuation included nausea, cardiac arrest/failure, myocardial infarction, asthenia, cerebrovascular disorder, falls, injury, pneumonia, and vomiting.

I have read the adverse event reports for all these events. None of the events above warrant further description; most were events that are common in this population or attributable to the pharmacological effects of galantamine.

14.5 Reviewer's Comments

The interim data for deaths, other serious adverse events, and adverse event discontinuations in the GAL-INT-21 study, as contained in the 4-Month Safety Update, do not raise any safety concerns that have not already been evident with the approved immediate-release formulation of galantamine.

15. Seven-Month Safety Update

The 7-Month Safety Update was submitted on 10/3/03. It has a cut-off date of 5/31/03.

The safety summaries for this study contained in the original application, and the Four-Month Safety Update provided information for deaths, other serious adverse events, and adverse event discontinuations only. The current summary provides information about the same types of events only.

In the current submission, in addition to a very brief overall narrative summary, the sponsor has provided appendices containing reports for deaths, serious adverse events and adverse event discontinuations, only

Data from the following 3 ongoing studies are included in this Safety Update

- GAL-INT-21, which was the only study for which data were submitted in the 4-Month Safety Update
- GAL-SCH-210, a study of Reminyl® ER as an adjunct to risperidone in the treatment of outpatients with schizophrenia associated with cognitive deficits
- GAL-NPH-101 is a pharmacokinetic study that is intended to evaluate 4 different formulations of controlled-release galantamine, in comparison with the immediate-release formulation

GAL-SCH-210 and GAL-NPH-101 are summarized in the table below

Study	GAL-SCH-210	GAL-NPH-101
Objective	Efficacy of Reminyl® Extended-Release as an adjunct to risperidone in schizophrenia associated with cognitive deficits	Pharmacokinetics of 4 different formulations of controlled-release galantamine compared with the immediate release formulation
Design	Randomized, double-blind, placebo-controlled, parallel-arm study	Randomized, open-label, single-dose, cross-over study
Key Inclusion Criteria	• Male • Age: 18 to 50 years • Schizophrenia • Taking stable doses of risperidone • Using tobacco products	• Male or female • Age: 18 to 55 years • Healthy • Body Mass Index: 19 to 28 kg/m^2
Duration	8 weeks of double-blind, parallel-arm treatment	Single doses at 1-week intervals (5 doses)

Dose Groups	3 dose groups • Placebo • Reminyl® ER 8 mg daily • Reminyl® ER 16 mg daily	8 mg single doses of each formulation
Sample Size	90 patients randomized equally to the 3 treatment groups	16 healthy subjects
Safety Monitoring	Adverse events, vital signs, standard safety laboratory tests, electrocardiograms, physical examinations, serum prolactin, Simpson-Angus Extrapyramidal Side Effects Scale – Abbreviated, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movements Scale	Adverse events, vital signs, standard safety laboratory tests, electrocardiograms, physical examinations

The key data included in the Safety Update are summarized below.

15.1 Patient Disposition

Patient disposition for each study, as of 5/31/03 is summarized below.

15.1.1 GAL-INT-21

722 patients have been enrolled in this study, but information is available for only 536 patients. The disposition of these 536 patients is summarized in the following table.

Category	n
Information available	536 (100)
Completed	393 (73)
Discontinuation prematurely	143 (27)
Discontinuation prematurely on account of adverse events	52 (10)

The age range for enrolled patients for whom information was available was between 50 and 93 years; the median age was 78 years.

15.1.2 GAL-SCH-201

5 patients have enrolled in this study; none have completed the study or prematurely discontinued. The median age for these patients was 40 years (range: 22 to 55 years).

15.1.3 GAL-NPH-101

Patient disposition is summarized in the following table

Category	n
Enrolled	17
Completed	16
Consent withdrawn	1

Of those enrolled

- 9 were male and 8 female
- The median age was 40 (range: 22 to 48)

15.2 Deaths, Other Serious Adverse Events, And Adverse Event Discontinuations

Only those events not listed in the original NDA and in the 4-Month Safety Update are below. All events listed below were in Study GAL-INT-21.

15.2.1 Deaths

A single new death occurred, in Study GAL-INT-21: a 92 year old man (initials — sustained a cardiac arrest against a background of pre-existing atrial fibrillation

Another patient, initials — (see Section 14.2) previously reported to have died of malignant lymphoma, also had hypothermia, renal failure and cardiac failure

I have read the adverse event reports for both the above events. None of the events above warrant further description; most are events that are common in this population.

15.2.2 Other Serious Adverse Events

12 patients, all from Study GAL-INT-21, had newly reported serious adverse events other than death at the time of the 7-Month Safety Update. Among the events newly reported were the following: pneumonia, injury, cardiac failure, myocardial infarction, atrial fibrillation, abdominal aortic aneurysm, fall with injury, urinary incontinence, depression, ataxia, grand mal convulsions, and lymphocytic leukemia.

I have read the adverse event reports for all these events. None of the events above warrant further description; these were events that are common in this population or attributable to the pharmacological effects of galantamine.

15.2.3 Adverse Event Discontinuations

5 more patients withdrew during the new reporting period for the following adverse events: diarrhea, headache, purpura, anorexia, and somnolence. All discontinuations were from Study GAL-INT-21

I have read the adverse event reports for these events. None of the events above need further description or raise any new safety concerns.

15.3 Reviewer's Comments

The interim data for deaths, other serious adverse events, and adverse event discontinuations in this 7-Month Safety Update do not raise any safety concerns that have not already been evident with the approved immediate-release formulation of galantamine.

16. Safety Data From Clinical Pharmacology Studies

A total of 5 clinical pharmacology studies are part of the development program for the controlled-release preparation of galantamine: GAL-BEL-19; GAL-BEL-20; GAL-NED-8; GAL-NED-9; and GAL-NED-12.

16.1 Summary Of Clinical Pharmacology Studies

These studies are summarized in the following table, which I have copied from the submission

	GAL-BEL-19	GAL-BEL-20	GAL-NED-8	GAL-NED-9	GAL-NED-12
Subjects	Healthy males or females aged 18–55 years	Healthy males or females aged 18–55 years	Healthy males or females aged 18–45 years	Healthy young (18–55 years) and elderly (≥65 years) males or females	Healthy males or females aged 18–55 years
Country	The Netherlands	The Netherlands	The Netherlands	The Netherlands	The Netherlands
Study design	Randomized, open-label, single-dose, 3-way crossover	Randomized, open-label, repeated-dose, 2-way crossover	Randomized, open-label, repeated-dose, 3-way crossover	Open-label, repeated-dose, parallel-group	Randomized, open-label, repeated-dose, 2-way crossover
Study drug (GAL)					
Dosage escalation	Not applicable				
Week 1		CR 8 mg q.d.	CR 8 mg q.d.	CR 8 mg q.d.	CR 8 mg q.d. [b]
Week 2		CR 16 mg q.d.	CR 16 mg q.d.	CR 16 mg q.d.	CR 16 mg q.d. [b]
Study drugs at final dosage	CR 8 mg 1 dose [a] CR 8 mg 1 dose [a] IR 4 mg 2 doses [a]	CR 24 mg q.d. [a] IR 12 mg b.i.d. [a]	CR 24 mg q.d (fed) [a] CR 24 mg q.d (fasted) [a] IR 12 mg b.i.d. (fasted) [a]	CR 24 mg q.d.	CR 24 mg q.d. [a,b] CR 24 mg q.d. [a]
Total planned duration of GAL-CR treatment [c]	Single dose	4 weeks	5 weeks	3 weeks	4 weeks
Total planned number of subjects	12	16	24	32	25

Note: b.i.d. = twice daily; q.d. = once daily.
[a] Randomized crossover design: all subjects were to receive all treatments.
[b] This batch of galantamine CR was intended for marketing and was used in the Phase 3 study
[c] Planned duration of treatment includes period of dosage escalation (repeated-dose studies) and the period of treatment with all formulations of galantamine CR and or galantamine IR.

16.2 Exposure

A total of 109 unique healthy subjects received at least one dose of study drug in these trials; of these subjects, all received Reminyl® ER and 50 received Reminyl® IR.

Further data regarding the duration of exposure to study drug in these 5 trials combined is in the following table, which I have copied from the submission

Treatment duration, days	Placebo	GAL IR	GAL CR
Phase I studies: NED-8+NED-9+NED-12+BEL-20+BEL-19 Analysis Set			
N	–	50	109
Mean (SD)	–	5.4 (2.63)	21.4 (8.08)
Median	–	7.0	21.0
Range	–	1 - 7	1 - 28

16.3 Reasons For Study Termination

These are in the following table. The overall discontinuation rate was small

Status Termination Reasons	Galantamine (N=97) n (%)
Completed	91 (94)
Discontinued	6 (6)
Adverse event	4 (4)
Subject non-compliant	1 (1)
Ineligible	1 (1)

16.4 Deaths And Other Serious Adverse Events

No deaths or other serious adverse events occurred in these studies

16.5 Adverse Events Leading To Discontinuation

4 patients permanently discontinued study drug on account of adverse events in these 5 studies. These discontinuations are summarized in the following table, which I have copied from the submission.

System Organ Class Preferred Term	GAL CR 8 mg (N=97) n (%)	GAL CR 16 mg (N=96) n (%)	GAL CR 24 mg (N=94) n (%)	GAL IR 24 mg (N=38) n (%)	Total (N=97) n (%)
Total no. subjects with permanent stop	1 (1)	0	2 (2)	1 (3)	4 (4)
Gastrointestinal system disorders	1 (1)	0	2 (2)	1 (3)	4 (4)
Nausea	1 (1)	0	2 (2)	1 (3)	4 (4)
Vomiting	1 (1)	0	0	0	1 (1)

Note: Percentages calculated using the number of subjects in each group as denominator.
One subject could be counted in more than 1 column.

As the table indicates, these adverse events were all gastrointestinal in type.

16.6 All Adverse Events

These are summarized in the following table, taken from the submission, which provides the incidence of treatment-emergent adverse events that occurred in ≥ 5% of patients in any dose category.

System Organ Class Preferred Term	GAL CR 8 mg (N=97) n (%)	GAL CR 16 mg (N=96) n (%)	GAL CR 24 mg (N=94) n (%)	GAL IR 24 mg (N=38) n (%)	Total (N=97) n (%)
Total no. subjects with adverse events	52 (54)	55 (57)	62 (66)	24 (63)	86 (89)
Gastrointestinal system disorders	27 (28)	37 (39)	35 (37)	18 (47)	63 (65)
Nausea	14 (14)	28 (29)	22 (23)	16 (42)	46 (47)
Diarrhea	8 (8)	3 (3)	10 (11)	0	19 (20)
Vomiting	4 (4)	7 (7)	9 (10)	2 (5)	17 (18)
Flatulence	6 (6)	1 (1)	5 (5)	0	11 (11)
Centr & periph nervous system disorders	24 (25)	29 (30)	32 (34)	16 (42)	58 (60)
Headache	20 (21)	18 (19)	22 (23)	5 (13)	44 (45)
Dizziness	4 (4)	13 (14)	15 (16)	15 (39)	33 (34)
Muscle contractions involuntary	0	2 (2)	2 (2)	2 (5)	6 (6)
Body as a whole - general disorders	7 (7)	7 (7)	13 (14)	1 (3)	22 (23)
Fatigue	3 (3)	6 (6)	9 (10)	0	14 (14)
Psychiatric disorders	10 (10)	8 (8)	10 (11)	4 (11)	23 (24)
Somnolence	2 (2)	5 (5)	4 (4)	2 (5)	9 (9)
Concentration impaired	0	2 (2)	3 (3)	2 (5)	5 (5)
Red blood cell disorders	1 (1)	0	5 (5)	0	6 (6)
Anemia	1 (1)	0	5 (5)	0	6 (6)
Vision disorders	0	1 (1)	2 (2)	3 (8)	5 (5)
Vision abnormal	0	0	1 (1)	2 (5)	3 (3)

Note: Percentages calculated using the number of subjects in each group as denominator.
One subject could be counted in more than 1 column.

16.7 Laboratory Data

No changes in laboratory data were noted that could be considered clinically important; the most common abnormalities were decreases in hemoglobin and hematocrit, which the sponsor attributes to the high volume of blood sampled.

16.8 Vital Signs And Physical Examinations

None of the changes in these parameters appeared clinically significant.

16.9 Electrocardiograms

Again, no changes were seen that were considered clinically important.

7 subjects had prolonged QT_c intervals described as an adverse event. In these 7 subjects:

- The maximum QT_cB interval was 456 msec (range: 420 to 456 msec) and the maximum QT_cLD interval was 460 msec (range: 391 to 460 msec)
- The maximum increase from baseline, in both QT_cB and QT_cLD, was ≤ 60 msec in 6 subjects and > 60 msec in one subject (the latter subject had a maximum QT_cB of < 450 msec.

Mean QT_cB decreases from baseline in galantamine-treated subjects in the 4 repeated-dose trials were < 6 msec.

16.10 Reviewer's Comments

The spectrum of adverse events and other safety abnormalities seen in these studies was similar to that of immediate-release galantamine.

17. Summary Of Clinical Pharmacology And Biopharmaceutics Review

Dr Ronald Kavanagh is the Clinical Pharmacology and Biopharmaceutics reviewer of this submission.

The capsule strengths of Reminyl® ER that are proposed for use are 8, 16, and 24 mg.

17.1 Key Issues Addressed In Review

Key items in Dr Kavanagh's review are below

- The structure and composition of the proposed modified-release formulation is described
- The extent of absorption is similar between the modified- and immediate-release formulations after both single doses and at steady-state after repeated dosing. C_{max} is 15 to 30% lower and t_{max} longer (median of 3.5 to 5 hours versus 1 hour) for the modified-release capsules
- There are no consistent differences in half-life between the modified- and immediate-release preparations that could be attributed to flip-flop kinetics.
- With multiple dosing with the modified-release formulation, dose proportionality is observed from 8 to 24 mg/day
- While the extent of absorption of the Reminyl® ER capsule at the highest to-be-marketed strength (24 mg) is not altered in the presence of food, the t_{max} is delayed by about an hour, and the C_{max} about 12% higher in the presence of food.
- The pharmacokinetics of the modified-release formulation of Reminyl® are comparable between healthy older and younger adults.

- A gender effect was not examined with the modified-release capsule of Reminyl® and there were too few subjects to examine the effect of race or ethnicity

- The commercial batches of the modified-release capsule were bioequivalent to the pivotal clinical trial batches

- The proposed dissolution method is acceptable; modifications to the dissolution specifications have been recommended (interim dissolution methods and specifications for all strengths of the modified-release capsules have been specified)

17.2 Office Of Clinical Pharmacology And Biopharmaceutics Recommendations

- This application is acceptable

- This sponsor should be requested to provide additional dissolution data (details are in Dr Kavanagh's review) within 6 months of approval to set final dissolution specifications

- Changes to the sponsor's proposed labeling for the Clinical Pharmacology, Precautions, and Dosage and Administration sections have also been recommended (see Dr Kavanagh's review).

18. Summary Of Chemistry, Manufacturing, And Controls Review

The Chemistry review of this submission was performed by Dr Janusz Rzeszotarski. Please see his review for full details.

He has recommended Approvable status for this application, subject to the recommendations made in the Establishment Evaluation Report (EER).

Subsequently this Center's Office of Compliance issued an overall Acceptable recommendation.

Based on the above, the Office of New Drug Chemistry has recommended that this application be approved.

19. Pre-NDA Discussions With Sponsor

As mentioned earlier in this review, a pre-NDA meeting concerning this application was held with the sponsor on 9/19/02, and a further teleconference on 11/26/02. A summary of the results of Study GAL-INT-10 were presented in

the briefing package for the latter discussion. Please see the minutes of both discussions for further details.

At the teleconference held on 11/26/02, the Division conveyed the following to the sponsor, in regard to Study GAL-INT-10, and the proposed supplemental NDA for the extended-release formulation of Reminyl®.

- Based on the contents of the briefing package, the Division would not refuse to file the proposed NDA
- The Division noted that the GAL-INT-10 study results on the Observed Cases dataset, as contained in this submission, showed evidence of the following
  - That Reminyl® ER had a statistically significant superiority to placebo on the ADAS-Cog ($p < 0.001$), similar with what was seen with the immediate-release preparation of Reminyl® in the current study, and in the pre-approval studies of that formulation
  - That the difference between the Reminyl® ER and placebo groups on the CIBIC-Plus was not statistically significant ($p = 0.086$)
  - That a nominally statistically significant ($p = 0.003$) difference was seen between the Reminyl® CR group and placebo group on the ADCS-ADL*.
- In the proposed application, a detailed argument should be provided as to why the study might still be considered to show evidence for the efficacy of Reminyl® ER in mild-to-moderate dementia of the Alzheimer's type.
- The results of analyzing the CIBIC-Plus data using datasets other than Observed Cases (e.g., intent-to-treat-LOCF) should be provided

*The Type I error for the secondary efficacy analyses had, in the view of our statisticians been "forfeited" since the results of the primary efficacy analysis for the CIBIC-Plus was negative; thus a Bonferroni correction of the Type I error could not, strictly speaking, be applied to the analysis of the ADCS-ADL.

20. Overall Comments

20.1 Efficacy

- In this application, the efficacy of the extended-release formulation of galantamine is intended to be based on the results of the GAL-INT-10 study. This was a randomized, double-blind, placebo-controlled, parallel- and three-arm study whose main objective was to evaluate the efficacy and safety of Reminyl® Extended-Release capsules in mild-to-moderate probable Alzheimer's Disease. The 3 treatment arms for this study were: Reminyl® Extended-Release capsules 16 to 24 mg once daily; immediate-release Reminyl® tablets 8 to 12 mg twice daily; and placebo. The period

of double-blind, parallel-arm treatment in this study was 26 weeks, including the period of dose-titration.

- The primary efficacy measures for this study were the ADAS-Cog, and the CIBIC-Plus. There were 10 secondary efficacy measures, including the ADCS-ADL scale which measures activities of daily living; however, neither the ADCS-ADL nor any other secondary efficacy measure was designated as a key instrument.

- The primary efficacy analysis was performed, as specified in the protocol, on the observed cases dataset at Month 6, and the primary comparison was between the Reminyl® Extended-Release and placebo groups, as again specified in the protocol. The difference in this dataset, between the Reminyl® Extended-Release and placebo groups for the mean change from baseline in the ADAS-Cog was 2.7 points, and favored galantamine ($p \leq 0.001$). For the CIBIC-Plus in the same dataset, 61% of those treated with extended-release galantamine, and 56.8% of those treated with placebo improved or showed no change ($p = 0.086$, when changes on the full 7-point scale were compared); on the last-observation-carried-forward and classical intent-to-treat datasets (these 2 datasets were identical), the p-value for this comparison was even less robust at 0.216.

  Similar results were seen, on both primary efficacy measures, when the immediate-release Reminyl® and placebo groups were compared.

- The protocol specified that evidence of the efficacy of extended-release galantamine was to be based on demonstrating a statistically significant ($p < 0.05$) treatment difference on both primary efficacy measures.

- Thus, based on the pre-specified primary efficacy analysis, this study must be considered not to have shown evidence for the efficacy of Reminyl® Extended-Release over placebo

- A comparison of the treatment groups on mean change from baseline to Week 26 scores for the ADCS-ADL, a secondary efficacy measure, using the observed cases dataset, revealed a mean difference between the Reminyl® Extended-Release and placebo groups of 2.4 points favoring galantamine ($p = 0.003$); nominally statistically significant differences ($p < 0.001$) were seen on the last-observation-carried-forward and classical intent-to-treat datasets as well.

- The analyses performed on all 10 secondary efficacy measures involved 90 comparisons of extended-release galantamine with placebo. None of these analyses was designated a priori as being more critical to the outcome of the study than the others. When adjusted for multiple comparisons, the p-value for the comparison of the extended-release

galantamine and placebo groups on the ADCS-ADL is no longer even nominally statistically significant.

- At a pre-NDA meeting, at which the preliminary results of this study were discussed, the sponsor was asked to provide, in this application, a detailed argument as to why the study might still be considered to show evidence for the efficacy of Reminyl® ER in mild-to-moderate dementia of the Alzheimer's type. The sponsor was also asked to provide the results of analyzing the CIBIC-Plus data for this study using datasets other than observed cases (as noted earlier in this review, the subsequent analysis of the last-observation-carried-forward and classical intent-to-treat datasets on this measure yielded results that were even less robust than for the observed cases dataset)

  In this application, the sponsor has conceded that according to the criteria specified in the protocol, this study cannot be considered "positive." The sponsor has, however pointed out that, in this study

  - Both galantamine treatments showed a numerical superiority to placebo
  - The effects of extended-release galantamine on the ADCS-ADL, and in a composite responder analysis tended to mirror those of the primary efficacy

- The current regulatory standard requires that evidence for the efficacy of drugs approved for the treatment of Alzheimer's Disease be based on demonstrating a statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure.

- In this study, evidence of the superiority of extended-release galantamine over placebo at endpoint was seen only on the cognitive primary efficacy measure (ADAS-Cog), and not on the global primary efficacy measure, (CIBIC-Plus). Nominally statistically significant treatment differences favoring galantamine on the ADCS-ADL, a measure of activities of daily living, are insufficient to substitute for the lack of an effect on the CIBIC-Plus, for the reasons already stated above.

- Thus, it must be concluded that evidence for the efficacy of the extended-release preparation of galantamine, Reminyl® ER, has not been demonstrated by the usual regulatory standard.

- Since the extended-release formulation of galantamine is intended to be taken once daily and will therefore be more convenient to use than the immediate-release formulation, which needs to be taken twice daily, the former formulation is likely to be used much frequently than the latter, when marketed. It is therefore especially important that evidence for the

efficacy of Reminyl® ER be clearly demonstrated prior to marketing approval being granted; such evidence is currently lacking.

20.2 Safety

- In this application, safety data for the extended-release formulation of Reminyl® was mainly derived from the GAL-INT-10 study, its open-label, uncontrolled extension, GAL-INT-21, and clinical pharmacology studies

- The submitted safety data for the Reminyl® Extended-Release formulation show a spectrum of findings that are not meaningfully different from those seen with immediate-release galantamine, both in a head-to-head comparison in Study GAL-INT-10 and using pre-approval and post-marketing safety data for the immediate-release formulation for Reminyl®.

20.3 Clinical Pharmacology And Biopharmaceutics

Based on a review performed by the Office of Clinical Pharmacology and Biopharmaceutics

- This application is acceptable
- Additional dissolution data are to be requested as part of a post-marketing commitment

20.4 Chemistry, Manufacturing, And Controls

The Office of New Drug Chemistry has recommended that this application be approved.

21. Review Of Draft Labeling

This section contains the following

- Changes (additions) to labeling proposed by the sponsor
- Comments

21.1 Changes Proposed To Labeling

Changes have been proposed to the following sections of the approved labeling for Reminyl®

- Description
- Clinical Pharmacology: Metabolism and Elimination
- Clinical Pharmacology: Clinical Trials
- Precautions
- Adverse Reactions
- Dosage and Administration
- How Supplied
- Storage and Handling

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

21.2 Comments

Since, in this reviewer's opinion, the GAL-INT-10 study has failed to establish the efficacy of extended-release galantamine and this application should therefore not be approved, the labeling has not been further edited by me.

22. Site Inspections

22.1 Site Inspection Report

The Clinical Inspection Summary for study sites has been completed by Ni A. Khin, MD, of the Division of Scientific Investigations.

The sites inspected and their classification following inspection are in the following table, which I have copied from Dr Khin's report

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Dr. Aronson	Farmington Hills	MI	04-23-2003	08-14-2003	VAI
Dr. Goldstein	San Francisco	CA	04-23-2003	08-13-2003	NAI

VAI: Voluntary action indicated, data acceptable. NAI: No action indicated

Dr Khin's overall assessment was that the data from the two inspected sites appeared acceptable for use in support of this NDA.

Please see Dr Khin's report for full details.

22.2 Reviewer's Comments

The site inspection summary did not yield any findings that would preclude the use of data from those sites in support of this application.

23. Financial Disclosure Certification

23.1 Components Of Certification

This certification provided by the sponsor has 3 components.

23.1.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in Studies GAL-INT-10, GAL-BEL-18, GAL-BEL-19, GAL-BEL-20, GAL-NED-8, GAL-NED-9, and GAL-NED-12. In regard to this list, the sponsor has:

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application whereby the compensation to the

investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)

- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

This certification has been provided on FDA Form 3454.

23.1.2 Certification Pertinent To Investigators/Sub-Investigators From Whom Financial Information Could Not Be Obtained

The sponsor has stated listed a number of investigators and sub-investigators who were involved in Studies GAL-INT-10, GAL-BEL-19, GAL-NED-9, and GAL-NED-12, for whom financial information could not be obtained. For these the sponsor states that the steps for due diligence were performed; these steps are described.

This certification has been provided on FDA Form 3454.

23.1.3 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests

The sponsor has provided a list of investigators and sub-investigators who were involved in Studies GAL-INT-10 and GAL-BEL-18 who had a significant equity interest [as defined in 21 CFR 54.2 (b)] held by the clinical investigator in the sponsor. The specific disclosable financial interests that these investigators and sub-investigators had in the sponsor have also been stated.

This certification has been provided on FDA Form 3455.

The financial interests listed include the following:

- Being an employee of the sponsor
- Becoming an employee of the sponsor, subsequent to participation in the clinical trial
- Payments from the sponsor, covering educational and research grants, speaking, and consulting.
- Equity interest in the sponsor

23.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of studies carried out with controlled-release Reminyl®, and submitted with this application.

24. Recommendation

I recommend that this application NOT be approved, on the grounds that the efficacy of the extended-release formulation of Reminyl® has not been established.

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 12/21/03
cc:
HFD-120
NDA 21615 (000)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ranjit Mani
12/22/03 07:27:14 AM
MEDICAL OFFICER