CLINICAL STUDY REPORT

Study title:	Prospective Research In Memory Clinics (PRIME)
Name of test drug/ investigational product:	Not applicable.
Indications studied:	Dementia and Mild Cognitive Impairment
Name of the sponsor:	Janssen-Cilag
Protocol version/date:	Protocol Version 5.0/ 3-Apr-2007
Development phase of study:	IV
Study initiation date (first participant enrolled):	15-Aug-2005
Date of early study termination, if any:	Not applicable.
Study completion date (last participant completed):	29-Jul-2011
Name and affiliation of principal or coordinating investigator(s) or sponsor's responsible medical officer:	Not applicable.
Name of company/sponsor signatory:	Janssen-Cilag 1-5 Khartoum Road North Ryde NSW 2113 AUSTRALIA Phone: +61 2 9815 3503 Fax: +61 2 9888 9346

Conduct and Monitoring of Study:

This study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Date of report: 4-Dec-2012

SYNOPSIS OF RESEARCH REPORT

COMPANY: Janssen-Cilag NAME OF FINISHED PRODUCT: Not applicable. NAME OF ACTIVE SUBSTANCE(S): Not applicable.	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / PROTOCOL VERSION No./ DATE OF REPORT	Clinical Study Report – Prospective Research In Memory Clinics (PRIME) Trial /Protocol Version 5.0/ 4-DEC-2012		
INVESTIGATORS / CENTERS AND COUNTRIES	Please see list of investigators appended.		
PUBLICATION (REFERENCE)	Please see Section 16.1.11		
PERIOD OF TRIAL	15-Aug-2005 (first participant enrolled) to 29-Jul-2011 (last participant completed)	CLINICAL PHASE	IV
OBJECTIVES	• To examine the current management and outcomes of participants with mild cognitive impairment (MCI) or dementia in Australia in order to identify the relationships among demographic variables, prognostic features, geographic region, treatment options and clinical, economic and health status (activities of daily living and caregiver impact) outcomes. • To provide the foundation for subsequent objective and prospective evaluation of evidence-based strategies for optimal treatment of MCI and dementia in Australia.		
STUDY DESIGN	Prospective, multiple-cohort study. Treatment and outcomes of participants with a diagnosis of MCI or dementia were monitored at 9 centres in Australia. All data were collected directly from the principal care site, using an internet-based Electronic Data Capture (EDC) system. Each participant was followed for up to 36 months, with scheduled visits at registration, and months 3, 6, 12, 24 and 36.		
NUMBER OF PARTICIPANTS	The study achieved an enrolment of n=964 participants.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion and exclusion criteria from Protocol Version 5.0 (3-Apr-2007): <u>Inclusion Criteria:</u> • Diagnosis of dementia under the DSM-IV criteria, or of Mild Cognitive Impairment, using the Petersen Criteria. • Living in the community (home, apartment or collective housing with nursing care available for less than 40 hours per week). • Competence of participant to provide written informed consent, or provision of written informed consent by a legal guardian/proxy. Availability of a caregiver willing to provide consent for required components of the study. • Fluency in English. • May be participating in a Phase IV or other post-marketing follow up study of an approved product for treatment of dementia or MCI. <u>Exclusion Criteria:</u> • Unwillingness of participant or legal guardian/proxy to provide written informed consent. • Unwillingness of caregiver to provide written informed consent. • Diagnosis of any concomitant life-threatening illness (a condition		

	which was likely to interfere with the participant's ability to complete the study). • Perceived unwillingness or inability to complete the study. • Concurrent participation in a clinical trial of an investigational drug (phase I, II or III). • For participants with diagnosis of mild cognitive impairment; current or previous treatment with any cholinesterase inhibitor or with memantine.
TRIAL DRUG / STROKE (BATCH) No.	Not applicable.
DOSE / ROUTE / REGIMEN / DURATION	Not applicable.
REFERENCE DRUG / STROKE (BATCH) No.	Not applicable.
DOSE / ROUTE / REGIMEN / DURATION	Not applicable.
CRITERIA FOR EVALUATION	
EFFICACY:	This observational study aimed to identify the relationships among demographic variables, prognostic features, geographic region, treatment options and clinical, economic and health status outcomes. Specific study endpoints for the primary analysis, and secondary analyses are listed below: <u>Endpoint for primary analysis:</u> • Time to Institutionalization <u>Endpoints for secondary analyses:</u> • Clinical Dementia rating (CDR) Total Score and Overall Score. • Mini-Mental State Examination (MMSE) Total Score. • Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) Total Score. • Frontal Assessment Battery (FAB) Total Score. • Functional Autonomy Measurement System (SMAF) Total Score and subscores • Neuropsychiatric Inventory (NPI) Total (Frequency x Severity) Score, Total Distress to Caregiver Score, and total number of behaviours (number of features with frequency > 0). • Zarit Burden Interview (ZBI) Total Score. • Clock Drawing Total Score. • Direct and indirect Resource Utilization (RU) over the study period • Time to stopping driving • Reason for institutionalization
PHARMACODYNAMICS:	Not applicable.
PHARMACOKINETICS:	Not applicable.
SAFETY:	<u>Endpoints for safety assessment:</u> • Adverse events (AE) • Serious adverse events (SAEs) • Death
STATISTICAL METHODS	<u>Statistical Methods and Planned Sample Size:</u> Due to the observational nature of the study, all analyses were considered exploratory and subject to confirmation by follow-up randomized trials. No adjustments were made for multiple testing, and all p-values were to be interpreted descriptively. All statistical tests were two-sided and conducted at the α=0.05 significance level, except for the interaction

terms which were tested at the α=0.10 level.

The planned sample size was approximately 4500 participants. This target was based on adequate data availability to investigate the study objectives and was not based on statistical power considerations. However, due to the speed of recruitment, Janssen decided in November 2006 to lower the target number to 1000 participants to be realistically recruited from participating sites.

Several comparison groups were defined for the purpose of this study; the method for assigning participants to each comparison group is summarized below.

Diagnosis Groups:

Participants were categorised according to their baseline diagnosis, recorded in the Diagnosis eCRF, as follows:

- MCI: A participant was defined as a "MCI" participant if he/she had a diagnosis of MCI at baseline.
- Dementia: A participant was defined as a "Dementia" participant if he/she was not diagnosed with MCI at baseline.

Treatment Groups:

Though there were no protocol defined treatments, participants in the Dementia diagnosis group were further categorised according to the Anti-Dementia & Psychotropic medications reported on the eCRF at baseline as follows:

- Dementia Treated Group: A participant was defined as a "Dementia Treated" participant if he/she was not diagnosed with MCI at baseline and was treated with any cholinesterase inhibitor (donepezil, galantamine or rivastigmine), or with memantine within (+/-) 7 days of Baseline.
- Dementia Untreated Group: A participant was defined as a "Dementia Untreated" participant if he/she was not diagnosed with MCI at baseline and had not used any cholinesterase inhibitors within (+/- 7) days of Baseline.

Severity Grouping based on CDR:

Severity groups were assigned according to an intention-to-treat principle. Participants were categorised according to their CDR Overall Score calculated at baseline as follows:

- Very Mild: Baseline CDR of 0 or 0.5
- Mild: Baseline CDR of 1
- Moderate: Baseline CDR of 2
- Severe: Baseline CDR of 3

Statistical Analysis Plan is shown in Appendix 16.1.9.

METHODOLOGY:

This prospective, population-based pharmacoepidemiologic study was designed to monitor the treatment and outcomes of up to 4500 participants with a diagnosis of MCI or dementia at 9 centres in Australia, with enrolment distributed across all 9 sites. Informed consent was obtained from the participant or the participant's legal guardian/proxy as well as the participant's caregiver. Discontinued participants were not replaced.

All data were collected directly from the principal care site, using an internet-based Electronic Data Capture system. Each participant was followed for up to 36 months, with scheduled visits at registration (baseline), and months 3, 6, 12, 24 and 36. The data collected at each visit is outlined in the following table:

	Baseline	Month 3 ± 30 days	Month 6 ± 30 days	Month 12 ± 60 days	Month 24 ± 60 days	Month 36 ± 60 days
Participant and Caregiver Informed Consent *	X					
Participant Information	X					
Diagnosis and Family History	X					
Previous Anti-dementia Medications	X					
Miscellaneous Items	X	X	X	X	X	X
Other Medications	X	X	X	X	X	X
Clinical Dementia Rating	X	X	X	X	X	X
Mini-Mental State Examination	X	X	X	X	X	X
Alzheimer's Disease Assessment Scale – Cognitive **	X	X	X	X	X	X
Clock Drawing Test	X	X	X	X	X	X
Frontal Assessment Battery	X	X	X	X	X	X
Functional Autonomy Measurement System	X	X	X	X	X	X
Neuropsychiatric Inventory	X	X	X	X	X	X
Zarit Burden Interview	X	X	X	X	X	X
Resource Utilization Forms §	Completed at the end of each calendar month by participant/caregiver and mailed to clinic					

** Participant and caregiver read and signed the information and consent form before beginning the study. If the participant was not competent to provide consent, consent could be obtained from the legal guardian/proxy, in accordance with the local regulations.*
§ For resources used each month
***ADAS-Cog was recommended for AD participants with a MMSE of 25 and over*

The following information was recorded during unscheduled visits:

- Adverse Events
- Changes to existing Adverse Events
- Changes to medications
- MMSE score
- Reason for the unscheduled visit

Data shown in the following table were collected as events occurred using event-based forms:

Concomitant Medications	At baseline and as changes occurred
Co-morbid Conditions & Risk Factors	Baseline history and as events changed / stopped
Adverse Events	As events occurred / changed / stopped
Change in diagnosis	As events occurred
Institutionalization	If required
Study Completion	At month 36 or earlier if discontinued
Serious Adverse Events (paper only)	As events occurred

EFFICACY RESULTS:

A total of 964 participants were enrolled in the study. Participants were categorised according to whether their baseline diagnosis was mild cognitive impairment (MCI Diagnosis Group) or not (Dementia Diagnosis Group). Of the enrolled participants, 185 were categorised as MCI and 779 were categorised as Dementia. This definition of diagnosis groups did not account for any changes to participants' diagnosis subsequent to their baseline diagnosis. Dementia participants were further classified into Dementia Treated (N=605) and Dementia Untreated (N=174) groups based on whether participants were treated with anti-dementia medications at baseline.

Demographic characteristics of the three diagnosis/treatment groups (MCI, Dementia Treated, and Dementia Untreated) were broadly similar. Only one small difference between groups was noted. Education levels were slightly higher in the MCI group compared to the Dementia Treated and Dementia Untreated groups. A slightly higher proportion of MCI participants received some post-secondary education or a college/university degree (42.7%) compared with the Dementia Treated (30.9%) and Dementia Untreated (29.9%) groups.

At baseline 19.2% of all participants were diagnosed with mild cognitive impairment, and 54.0% were diagnosed with early or late onset dementia of the Alzheimer's type; the remaining 26.8% of participants were diagnosed with other forms of dementia. One difference between the two Dementia groups was observed with regard to participant diagnosis; a larger proportion of participants in the Dementia Treated group were diagnosed with early or late onset dementia of the Alzheimer's type compared with the Dementia Untreated group (72.7% vs. 46.6%).

With regard to other baseline characteristics, a higher proportion of MCI participants were still driving (77.8%) compared with Dementia Treated (29.1%) and Dementia Untreated (40.8%) participants. In addition, a larger proportion of the Dementia Treated group (23.8%) was treated with anti-dementia medications prior to the study compared with the MCI group (2.7%) or the Dementia Untreated group (7.4%).

Baseline scores for all assessments examining cognitive and non-cognitive function and caregiver burden (CDR, MMSE, ADAS-Cog if administered, ZBI, FAB, SMAF, NPI, and Clock Drawing) indicated that participants in the MCI group had a higher level of cognitive function and less impairment compared with the Dementia Treated and Dementia Untreated groups. Mean assessment scores for Dementia Treated and Untreated groups were generally similar, although small differences in mean scores between the two Dementia groups were noted. On many assessments Dementia Untreated participants displayed a slightly higher level of function compared to Dementia Treated participants; however, the variability around mean assessment scores was too high to draw meaningful conclusions.

Approximately one-fifth (21.4%) of all participants were institutionalized during the study. The risk of institutionalization increased with increasing age (P=0.0239) and increasing CDR Overall Score (P=0.0003); risk of institutionalization decreased with increasing MMSE score (P=0.0005). An increase in CDR Overall score and a decrease in MMSE score indicate a higher level of cognitive impairment, which could lead to an increase in the level of care required by the participant. During the study the rate of institutionalization was highest for participants categorized in the severe dementia group, and rates decreased with decreasing severity (severe > moderate > mild > very mild). Also, rates of institutionalization were highest in the Dementia Treated group, lower in the Dementia Untreated group, and lowest for the MCI group.

Mean assessment scores recorded at Months 3, 6, 12, 24 and 36 showed that the level of cognitive and non-cognitive function declined for all diagnosis/treatment groups from baseline to Month 36. Mean changes in CDR, MMSE, and NPI scores were lowest for MCI participants during the study suggesting these participants may have declined at a slightly slower rate than Dementia participants.

Dementia and MCI participants reported generally similar resource utilization in many areas examined in the study. Differences between groups were observed in the number of days participants and caregivers were prevented from activities per month. The mean number of days was higher for the Dementia group compared with the MCI group for all time periods assessed during the study; however, the variability associated with mean values was high. In addition, a greater proportion of Dementia caregivers reported using caregiver support group outpatient services compared to MCI caregivers during the study; again however, the variability associated with resource utilization measurements was very high.

Consistent with a lower level of function for the participants diagnosed with Dementia, the rate at which participants stopped driving after baseline (among those still driving at baseline) was higher for Dementia participants compared to MCI participants.

PHARMACODYNAMIC RESULTS:
Not applicable.

PHARMACOKINETIC RESULTS:
Not applicable.

SAFETY RESULTS:
At baseline MCI and Dementia Untreated participants were not receiving treatment with any cholinesterase inhibitor or memantine, and Dementia Treated participants were receiving treatment with one or more of these medications. During the study a considerable proportion of participants in each group switched to or from receiving anti-dementia medication. From Month 30 to 36 the estimated proportion of Dementia Untreated participants switching from no anti-dementia medication to receiving medication was higher than the estimated proportion of Dementia Treated participants switching to no anti-dementia medication during the study (0.485 vs. 0.339, respectively). In addition, during the study 25.4% of MCI participants began receiving a cholinesterase inhibitor or memantine.

During the study a higher proportion of Dementia participants (95.8%) were treated with anti-dementia and other medications compared with MCI participants (73.0%) possibly due to the higher level of impairment of Dementia participants compared to MCI participants.

A total of 111 participants died during the study (11.5% of all enrolled participants). Rates of death were highest for Dementia Treated participants, lower for Dementia Untreated participants, and lowest for MCI participants. From Month 30 to 36 the estimated proportions of participants who died during the study were 0.187, 0.122, and 0.031 for the Dementia Treated, Dementia Untreated and MCI groups, respectively. Analysis of the rate of death by severity group showed the highest rates of death for participants classified with severe or moderate dementia and lower rates of death for participants classified with mild or very mild dementia.

A total of 685 of 964 participants experienced one or more AEs during the study. The majority of participants in the Dementia Treated (74.7%) and the MCI (59.5%) groups reported AEs in any class, and one-fifth (20.3%) of participants in the Dementia Untreated group reported AEs. Overall, the most common Adverse Events were infections and infestations (26.2%); injury, poisonings, and procedural complications (22.4%), and gastrointestinal disorders (18.4%). Of the 529 AEs that were reported while participants were treated with anti-dementia therapy, 315 events were classified as Not related to therapy.

A total of 373 of 964 participants experienced one or more SAEs during the study. The Dementia Treated group had the highest proportion of participants who reported SAEs (44.1%); one-quarter of the MCI participants (25.4%) and one-tenth of the Dementia Untreated participants (9.8%) experienced SAEs. Of the 279 SAEs that were reported while participants were treated with anti-dementia therapy, 221 events were classified as Not related to therapy.

CONCLUSIONS:
This study examined the current management strategies and outcomes of 964 participants with mild cognitive impairment or dementia in Australia. Participants were assigned to diagnosis, treatment, and severity groups for analysis according to their baseline characteristics. Participants in the MCI group (N=185) were diagnosed with mild cognitive impairment and were not treated with any cholinesterase inhibitor or with memantine at baseline. Participants in the Dementia group (N=779) were not diagnosed with mild cognitive impairment at baseline. Dementia participants were further categorized as Dementia Treated (N=605) if they were treated with any cholinesterase inhibitor (donepezil, galantamine or rivastigmine) or with memantine within 7 days of Baseline or as Dementia Untreated (N=174) if they were not. Participants were also categorized by dementia severity group (severe, moderate, mild, and very mild) according to CDR Overall Score. These groups were defined at baseline, and participants remained in their groups regardless of changes in diagnosis, treatment or CDR score during the 36 month course of the study.

The diagnosis/treatment groups were broadly similar in terms of demographic features, although slight differences in education levels were noted between the MCI and Dementia groups with MCI participants attaining higher levels of education compared to the Dementia group. Furthermore, baseline diagnoses differed between participants in the

Dementia Treated and Dementia Untreated groups; a higher proportion of participants in the Dementia Treated group (72.7%) were diagnosed with early or late onset dementia of the Alzheimer's type compared with the Dementia Untreated group (46.6%).

Baseline scores for assessments measuring cognitive and non-cognitive function and caregiver burden (CDR, MMSE, ADAS-Cog, FAB, SMAF, ZBI, NPI, and Clock Drawing) indicated that participants in the MCI group were functioning at a higher level compared with participants in the Dementia group. Assessment scores recorded throughout the study showed that cognitive and non-cognitive function declined for all groups from baseline to Month 36. CDR, MMSE, and NPI scores measured during the study suggesting MCI participants may have declined at a slightly slower rate than Dementia participants.

Approximately one-fifth of all participants were institutionalized during the study; the most important reasons given for institutionalization in all groups were caregivers being overwhelmed (61.7%) and recommendation by doctors (51.5%). The risk of institutionalization increased with increasing age and increasing cognitive impairment as measured by CDR and MMSE scores. During the study the rate of institutionalization, rate of death, and incidence of AEs and SAEs were highest in the Dementia Treated group compared with both the Dementia Untreated and MCI groups.

Previous randomized, placebo-controlled trials have shown that cholinesterase inhibitors and memantine may improve or reduce declines in cognitive function in participants with dementia. However, in this study the rates of institutionalization and death were higher for the Dementia Treated group compared to the Dementia Untreated group. Due to the non-randomized, observational nature of the study, the results should be treated with caution. For example, a substantial fraction participants in the Dementia Untreated group received treatment with cholinesterase inhibitors during the study, and a substantial fraction of participants in the Dementia Treated group stopped treatment with anti-dementia medications. During the last six months of the study the estimated proportion of Dementia Untreated participants who began treatment with anti-dementia medication was 0.49, and the estimated proportion of Dementia Treated participants who ceased treatment with medication was 0.34. Thus, the categorisation of participants for analysis based on treatments at baseline was in essence an 'intention-to-treat' categorisation, which was not intended as a marker of the ongoing treatment status.

Despite the well-known challenges drawing strong conclusions about treatment efficacy or safety in observational studies of this nature, the results of some analyses generated by this study have been included in publications, which are included in the appendix.

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