Name of Sponsor/Company: Allergan Ltd	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use Only)***
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: AGN 201781	**Page:**	

Title of Study:
201781-504: A Pilot, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study with a 4-Week Treatment Period Followed by a 4-week Observation Period and an Optional 4 Month Observation Period of the Safety and Duration of Efficacy of AGN 201781 in Subjects with Neuropathic Pain. (EudraCT: 2007-003787-21; NCT00533351)

Investigators:
4 investigators in 2 countries enrolled subjects

Study Center(s):
Australia (1 study center) and Germany (3 study centers) enrolled subjects

Publication (reference):
None

Studied Period (years): Date of First Enrollment: 18 March 2008 Date of Last Completed: 27 June 2008 (study terminated 20 June 2008)	**Phase of Development:** 2

Objectives:
To assess the safety and explore the duration of analgesia with AGN 201781 in the treatment of pain associated with postherpetic neuralgia and post-traumatic peripheral neuralgia

Methodology:
Structure: Pilot, multi-center, double-blind, placebo-controlled, 3-period study followed by an optional 4-month observation period.

Visit Schedule: A minimum of 10 and a maximum of 15 scheduled visits over a minimum period of 9 weeks and a maximum of 30 weeks, incorporating up to a 4-week screening period (if washout of medication required), a baseline period of 1 to 2 weeks (note: if washout of medication was not required the screening visit was considered the baseline visit), 4 weeks on study medication (Period 1 for 2 weeks and Period 2 for 2 weeks) followed by a 4-week observation period (Period 3) and an optional further 4-month observation period (Period 4; note: 2 of the 4 scheduled monthly visits during Period 4 were to be telephone visits).

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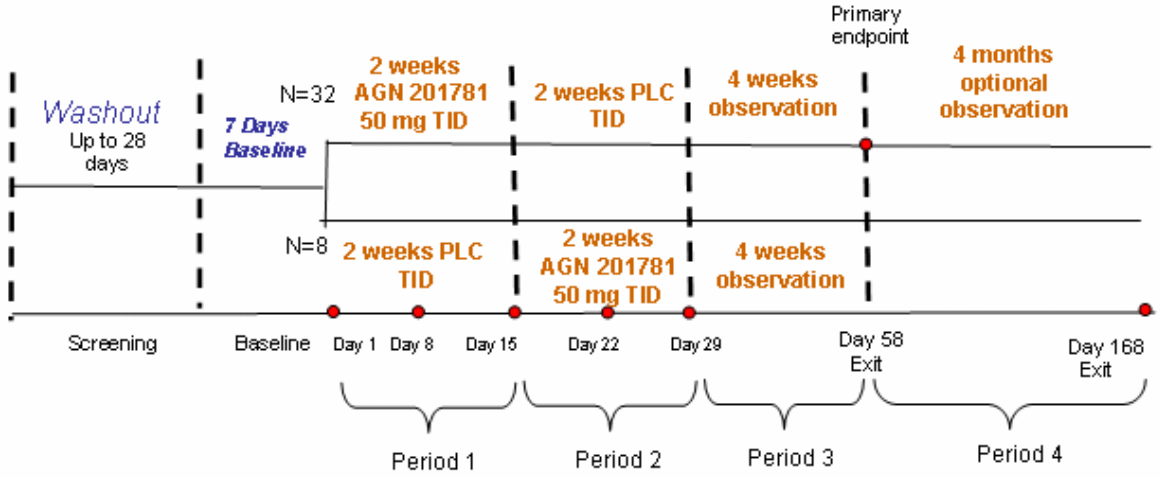

Randomization: Subjects were randomized to receive either AGN 201781 or placebo as their first treatment in different sequences during Period 1 and Period 2. Sequence 1 was treatment with AGN 201781 for 2 weeks (2 doses of 50 mg on day 1 and 50 mg TID on days 2 to 14) followed by placebo TID for 2 weeks (2 doses of placebo on day 15 and placebo TID on days 16 to 28) ; Sequence 2 was treatment with placebo (2 doses of placebo on day 1 and placebo TID on days 2 to 14) followed by 50 mg AGN 201781 TID for 2 weeks (2 doses of 50 mg on day 15 and 50 mg TID on days 16 to 28).

Number of Patients (Planned and Analyzed):
Approximately 40 subjects were to have been enrolled at approximately 8-10 sites in order to have an estimated 32 subjects complete the study through Period 3 (based on an anticipated 20% drop-out rate). The actual number of subjects enrolled on the study was 9 because the study was terminated early.

Diagnosis and Main Criteria for Inclusion:
Diagnosis: Male and female (non-childbearing potential) subjects with postherpetic neuralgia or post-traumatic peripheral neuralgia.

Key Inclusion Criteria:

- Male or female subjects between 18 and 80 years of age experiencing pain associated with postherpetic neuralgia or post-traumatic peripheral neuralgia for at least 6 months prior to the start of baseline; pain defined as a mean daily-average-pain score of at least 4 and no greater than 9 on the 11-point Likert Scale during the last 7 days of the baseline period, and the subject must record a daily average pain score on at least 6 days during the baseline period.
- Postherpetic neuralgia or post-traumatic peripheral neuralgia was the subject's predominant pain condition and he/she was able to distinguish between the neuropathic pain and other concurrent painful conditions.
- Subjects with a history of cancer (except basal cell carcinoma) had to be in complete remission for at least 12 months prior to baseline and throughout the baseline period.

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Key Exclusion Criteria:

- Subjects with pain resulting from injury to the spinal cord or central neuropathic pain.
- Evidence of an ongoing insult to the nerve (for those with post-traumatic peripheral neuralgia).
- Beck Depression Inventory (BDI) score >20 at baseline, or a score of ≥ 2 on question 9 (suicide) of the BDI at the baseline visit, or is deemed by the investigator to be at risk of significant self harm.
- Concurrent treatment or history of treatment within a specified period prior to the start of the baseline period and throughout the baseline period, ie, within 2 weeks: treatment with tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, alpha-adrenergic agonists or antagonists, monoamine oxidase inhibitors, opioids (including tramadol), topical analgesics, antiarrhythmics or N-methyl D-aspartate (NMDA) antagonists, benzodiazepines or muscle relaxants; within 4 weeks: use of topical capsaicin; within 24 hrs: treatment with acetaminophen; within the last 12 months: treatment for cancer, including radiation therapy, chemotherapy, etc., or treatment with methimazole/carbimazole or thiouracils.
- Treatment with an anti-convulsant (eg, gabapentin) and/or non-steroidal anti-inflammatory drugs (NSAIDs), and is not on a stable dose for at least 3 weeks prior to the start of the baseline period and throughout the baseline period; significant changes in the doses of current chronic medications except for the washout medication(s) within 4 weeks of baseline and throughout the baseline period; anti-coagulant therapy.
- Positive virology tests at the screening visit.
- Active herpes zoster infection.
- Previous neurolytic or neurosurgical therapy for neuropathic pain (eg, radiofrequency lesioning).
- Glucose-6-phosphate dehydrogenase deficiency.
- Diagnosis of hypothyroidism and on current hormone replacement therapy (thyroxine), or subject has received a thyroidectomy or radio-iodine therapy for hyperthyroidism within 12 months of baseline.

Test Product, Dose and Mode of Administration:
AGN 201781 50 mg oral capsule

Duration of Treatment:
Study medication (AGN 201781/placebo) was administered as two doses on day 1 and thereafter three times a day (TID) on days 2 to 14. On day 15 subjects crossed over to the opposite treatment, which was administered as two doses on day 15 and TID thereafter on days 16 to 28. The total duration of treatment with study medication was 4 weeks.

Reference Therapy, Dose and Mode of Administration:
AGN 201781 placebo oral capsule

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Criteria for Evaluation:

Efficacy:
Daily-average-pain score using the 11-point (0-10) Likert scale recorded on the electronic diary (the mean-daily-average pain score from baseline to week 2 as well as the change in the mean-daily- average pain score from baseline to week 8 were of primary interest).

First-dose assessments (captured every 30 min for the first 3 hrs then hourly during the 5 hr post-dose confinement session on day 1) included ordinal and visual analogue scales for pain intensity, an ordinal scale for pain relief, Subject Global Impression of Change (SGIC) Questionnaire (captured only at hour 5), and time to onset of meaningful pain relief (captured once based on subject's subjective impression).

Multiple dose assessments (captured daily on the electronic diary and during the weekly clinic visits) included daily-average-pain score, daily-worst-pain score and daily sleep interference score (as recorded by electronic diary), Short Form McGill Pain Questionnaire (SF-MPQ), Short Form Brief Pain Inventory (SF-BPI), Profile of Mood State (POMS) Standard Form, Beck Depression Inventory (BDI), SGIC Questionnaire. In addition, Quantitative Sensory Testing (QST) was to be done. The incidences of responders with various percentage reductions from baseline in mean-daily-average and mean-daily worst pain score from baseline were to be calculated.

Safety:
Adverse events.

Statistical Methods:
As the study was terminated early, the statistical analyses of the protocol were not performed. As just 9 subjects were enrolled, only by-subject listings were produced.

Summary – Conclusions:

Efficacy:
A summary of available efficacy data for the 9 subjects who participated in the study is presented below.

Mean-Daily-Average Pain Score
Of the 6 subjects who completed Periods 1 and 2 (through day 29/week 4), 3 in Sequence 1 had experienced either a slight decrease (Subject 1002), a slight increase (Subject 1006) or no change (Subject 1013) in mean-daily-average pain score compared to baseline during the 4 weeks; 1 subject in Sequence 1 (Subject 1004) had experienced a decrease in mean-daily-average pain score from 6.17 at baseline to 3.43 at week 2 (while receiving AGN 201781), returning to values that were close to baseline by week 4 (5.29) while receiving placebo; 1 subject in Sequence 1 (Subject 1010) experienced a decrease in mean-daily-average pain score compared to baseline from week 1 that reached a maximum by week 2 (baseline, 4.00; week 2, 0.17) while receiving AGN 201781 and was still markedly lower than baseline at week 4 (0.86) after receiving placebo for 2 weeks. The 1 subject in Sequence 2 who completed Periods 1 and 2 (Subject 1014) experienced a slight increase in mean-daily-average pain score during the first 2 weeks (while receiving placebo) and a decrease in mean-daily-average pain score during the second 2 weeks (while receiving AGN 201781), from 5.14 at week 2 to 2.67 at week 4 (baseline, 4.71).

Of the 3 subjects (all in Sequence 1) who completed the study through to week 8 (day 58), 1 (Subject 1010) continued to experience markedly lower mean-daily-average pain scores than at baseline (baseline, 4.00; week 8, 0.50). The 2 other subjects (Subjects 1004 and 1006) had slightly lower or slightly higher mean-

daily-average pain scores, respectively, as compared to their week 4 values.

Subject Global Impression of Change

On day 1, approximately 5 hrs post-dose, 4 of the 7 subjects allocated to Sequence 1 reported a minimally or much improved relief from symptoms of neuropathic pain after taking AGN 201781 and the other 3 reported no change. Both subjects in Sequence 2 reported no change after receiving placebo 5 hrs post-dose on day 1.

Of the subjects remaining in the study at the end of Period 1 (day 15), the 2 subjects in Sequence 1 who had initially reported their relief of symptoms as much improved were either still much improved (Subject 1004) or very much improved (Subject 1010), 2 continued to be unchanged (Subjects 1002 and 1013) and one who was originally minimally improved was now reporting no change (comparisons at day 15 were subject assessments of their condition relative to prior to staking study drug). The 1 subject in Sequence 2 remaining in the study at the end of Period 1 reported their condition as minimally worse.

At day 29 (14 days after the last dose of AGN 201781) 3 of the 4 remaining subjects in Sequence 1 reported no change in their condition whereas 1 subject (Subject 1010) continued to report their condition as very much improved. Neither of the 2 subjects in Sequence 2 completed the SGIC questionnaire at day 29.

Short Form McGill Pain Questionnaire

For the 5 subjects in Sequence 1 that completed the McGill Pain questionnaire at the end of Period 1 (day 15), the mean change from baseline in the Total McGill Pain Score was -5.8 (due primarily to the very large change from baseline of -24 points for Subject 1010). Similarly, the mean VAS pain scores for these 5 subjects decreased by 13.6 points (on a 100-point scale) compared to baseline (but this again was due primarily to the very large change from baseline of -66 points for Subject 1010). The one subject in Sequence 2 that completed the questionnaire at day 15 recorded a Total McGill Pain Score that had increased by 3 points compared to baseline, and a VAS pain score that had increased by 27 points compared to baseline.

With regard to the current pain status reported by subjects on the McGill Pain Questionnaire, it is most notable that Subject 1010, who initially recorded their pain as ‘discomforting’, recorded ‘no pain’ from day 8 through day 58.

Meaningful Pain Relief Following First Dose of Study Drug

Of the 9 subjects who participated in the study, 2 experienced meaningful pain relief after treatment with AGN 201781 (Subjects 1004 and 1010 [Sequence 1] at 38 min and 35 min post-dose, respectively).

Safety:

Of the 9 subjects randomized, 8 received active treatment (AGN 201781 50 mg TID). All 7 subjects in Sequence 1 received AGN 201781 in Period 1, and of these, 5 also received placebo in Period 2. The 2 subjects who had been allocated to Sequence 2 both received placebo in Period 1, and one of these also received AGN 201781 in Period 2.

Overall, 5 of the 9 subjects (55.6%) experienced one or more adverse events during the study. Of the 7 subjects randomized to Sequence 1 (AGN201781-placebo), 2 receiving AGN 201781 in Period 1 experienced adverse events that were considered by the investigator to be related to study treatment (Subject 1004 experienced moderate headache and fatigue both with onset 3 days after the first dose of AGN 201781 and Subject 1010 with a mild increase in alanine aminotransferase [ALT] 7 days after the first dose of AGN 201781). In addition, 2 subjects receiving placebo in Period 2 also reported adverse events considered

study treatment-related by the investigator (Subject 1004 reported moderate somnolence with onset 1 day after the last dose of AGN 201781, and Subject 1006 experienced moderate pityriasis rosea 15 days after the last dose of AGN 201781).

Neither of the 2 subjects in Sequence 2 (placebo - AGN 201781) reported treatment-related adverse events during treatment with placebo in Period 1. One of the 2 subjects in Sequence 2 (Subject 1014) reported a treatment-related adverse event of elevated reverse tri-iodo-thyronine (rT3) during treatment with AGN 201781 50 mg TID in Period 2 that was incorrectly recorded as hypothyroidism.

Other adverse events that were reported during Periods 1 and 2 but were not considered treatment-related included blood creatinine increased, hypertension, dyspnoea and leukocyturia. In addition, one subject with an ongoing history of renal failure (compensated) (Subject 1014) reported an unrelated adverse event of renal pain during no treatment in Period 3.

One subject (Subject 1002) was discontinued prematurely from the study 14 days after the last dose of AGN 201781 due to adverse events of hypertension and dyspnoea. Hypertension was first noted 7 days after the start of AGN 201781; the subject subsequently developed dyspnoea on the fourth day of placebo treatment (day 18). The subject had a medical history of increased blood pressure, bronchitis, hepatic steatosis (ongoing), renal cell carcinoma, nephrectomy and obesity (body mass index = 37.43) prior to study entry. During the baseline period, borderline high blood pressure readings were recorded (145/90 in the standing position). It was thought that these two events may have been due to ibuprofen, the only permissible pain relief in the study, and the subject should exit the study in order to use alternative treatment. Study medication (placebo) was stopped on day 21 and the subject's dyspnoea resolved 4 days after onset without sequelae; hypertension is recorded as ongoing. Both of these adverse events were considered not related to study treatment by the investigator.

None of the adverse events recorded during the study was reported as severe or serious and there were no deaths.

Conclusion:
No overall conclusions could be made regarding the effectiveness of orally administered AGN 201781 50 mg TID in the treatment of pain associated with postherpetic neuralgia or post-traumatic peripheral neuralgia due to the enrolment of only 9 subjects. Nonetheless, there was some evidence of pain relief in a number of subjects after daily oral dosing with AGN 201781 50 mg TID.

Although relatively small numbers of subjects were recruited, the safety profile observed in this study was acceptable. No subject discontinued due to any treatment-related adverse events. AGN 201781 was well tolerated at an oral dose of 50 mg TID.

Date of the Report:
27 January 2009