2. SYNOPSIS

Name of sponsor/company: **Convergence Pharmaceuticals Ltd.**	Individual study table referring to part of the dossier	(For National Authority use only)
Name of finished product: **CNV1014802**	Volume:	
Name of active ingredient: **CNV1014802**	Page:	

Title of study:

A randomized, double blind, cross-over study to evaluate the safety and efficacy of CNV1014802 in subjects with neuropathic pain from lumbosacral radiculopathy

Investigators:

Sweden: [redacted]
Czech Republic: [redacted]
France: [redacted]
Denmark: [redacted]

Study centres:

A full list of investigators and study sites is provided in Appendix 16.1.5.

Publication (reference): Not applicable

Studied period: First subject consented - 21 July 2011 Last subject completed - 04 June 2012	**Phase of development:** II

Objectives:

Primary:

- To investigate the effect of repeat oral dosing of CNV1014802 on neuropathic pain in subjects with lumbosacral radiculopathy

Secondary:

- To investigate the effects of repeat oral dosing of CNV1014802 on low back pain in subjects with lumbosacral radiculopathy in whom there is lower limb pain.
- To investigate the effects of repeat oral dosing of CNV1014802 on function in subjects with pain from lumbosacral radiculopathy.
- To investigate the safety and tolerability of CNV1014802 in subjects with lumbosacral radiculopathy.
- To assess the plasma concentrations and exposures of CNV1014802

Exploratory:

- Pharmacokinetic-pharmacodynamic relationships, if data permit

Methodology:

This was a multi-centre, double-blind, randomized, 2-period cross-over study of CNV1014802 versus placebo. Following a screening period, 137 subjects with a diagnosis of neuropathic pain due to lumbosacral radiculopathy (LSR) were enrolled into a run-in phase where they received single blind placebo medication for two weeks. On Day 15, 82 subjects were randomized to take part in two sequential 22-day dosing periods (AM dose only on day 22). Subjects were randomized in a 1:1 ratio to receive either 350mg CNV1014802 BID followed by placebo BID, or vice versa. The dosing periods were separated by a 13 day washout period and were followed by a 7 day run out, during which subjects received placebo.

Number of subjects:
Planned Randomized: 80
Enrolled: 137
Randomized: 82
Treated: 81 (CNV1014802 N=79; Placebo N=73)

Diagnosis and main criteria for inclusion:

Inclusion criteria: Male or female aged between 18 and 65 years, with a diagnosis of neuropathic pain due to lumbosacral radiculopathy (LSR). Female subjects were to be of non-child bearing potential or agree to use an approved form of contraception. Male subjects had to agree to use an approved form of contraception. Body weight ≥ 50 kg for men and ≥ 45 kg for women. Subjects had to be capable of giving written informed consent. Average QTcB or QTcF <450 msec; or QTc <480 msec in subjects with Bundle Branch Block at screening. AST and ALT <2xULN; alkaline phosphatase and bilirubin ≤ 1.5xULN. Approved concomitant medications must have been stable for at least 4 weeks prior to Day 1. Average baseline daily pain score for neuropathic pain due to LSR on the 11-point numerical rating scale of 4 or greater. *France only*: subjects had to be affiliated to a health social security system.

Exclusion criteria: Subjects who were unable to reliably delineate or assess their own pain by anatomical location/distribution. Subjects with lumbar canal stenosis in which the pain in the lower limbs occurred solely on walking and not at rest. Subjects with causes for their neuropathic pain other than LSR. Subjects who had received nerve blocks and/or steroid injections for neuropathic pain within 4 weeks prior to Day 1. Subjects who were indicated for surgical treatment of lumbosacral radiculopathy. Subjects with a positive pre-study drug screen, a positive history of HIV, a positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening. Subjects with history of any liver disease within the last 6 months, with the exception of known Gilbert's disease. Subjects with a history of excessive regular alcohol consumption within 6 months of the study. Subjects with a history or risk of seizures or a history of epilepsy, head injury or related neurological disorders. Subjects with a history of uncontrolled or poorly controlled hypertension, with systolic BP frequently exceeding 160mmHg and/or diastolic BP frequently exceeding 100mmHg, or subjects who had BP greater than or equal to 160mmHg systolic and/or greater than or equal to 100mmHg diastolic at screening after repeated measurements. Subjects with a history or presence of significant cardiovascular, gastro-intestinal, or renal disease or other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs. Subjects with conditions known to affect cardiac conduction or a personal or familial history of Brugada syndrome. Pregnant females or lactating females. Subjects with a history or presence of any clinically significant abnormality in vital signs / ECG / laboratory tests or have any medical or psychiatric condition, which, in the opinion of the Investigator may interfere with the study procedures or compromise subject safety. History of suicidal ideation and/or suicide attempts or clinical evidence of recent major depression. Subjects who were unable to maintain their same medications for the treatment of neuropathic pain at a stable dose during the study. Unable to refrain from excessive use of sedatives. Unable to comply with the prohibited concomitant medication restrictions as detailed in the protocol. Unable to stop and remain abstained from non-pharmacological treatments for their neuropathic pain during the study. History of hypersensitivity to CNV1014802. Subjects who had participated in a clinical trial and had received an investigational product within 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) prior to the start of this study. Exposure to more than four new chemical entities within 12 months prior to the first dosing day. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period. Subject was mentally or legally incapacitated. Subject who, in the clinical judgement of the investigator, may be malingering or be motivated by secondary gain from participation in the study. Unwillingness or inability to follow the procedures outlined in the protocol.

Test product, dose and mode of administration, batch number:

CNV1014802, oblong shape, film-coated, immediate release tablets.

Excipients: Mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, titanium dioxide (E171), hypromellose, polyethylene glycol 400, iron oxide yellow (E172) and iron oxide black (E172)

Batch number: [redacted]

Study medication was to be taken at a dose of 350 mg BID at the same time each day (plus or minus 1

hour) and one hour before or after food.

Duration of treatment:

Subjects took part in two treatment periods of 22 days with randomized CNV1014802 350 mg BID or placebo BID. In addition, placebo was administered during the run-in, wash-out and run-out phases.

Reference therapy, dose and mode of administration, batch number:

Placebo was identical in appearance to the active drug but without CNV1014802.

Excipients: Mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, titanium dioxide (E171), hypromellose, polyethylene glycol 400, iron oxide yellow (E172) and iron oxide black (E172)

Batch number: [redacted]

This study was a double blind study and consequently the route of administration and dosing requirements were identical to those for CNV1014802 (as above).

Criteria for evaluation:

Efficacy:

- Change in average daily neuropathic pain score from baseline to Week 3 based on the 11 point Pain Intensity Numerical Rating Scale (PI-NRS).
- Change in average daily pain score from baseline to Week 1, 2 and 3 of treatment and 1 week following the end of randomized treatment, based on the 11 point PI-NRS. Pain intensity for neuropathic pain associated with lumbosacral radiculopathy and that for low back pain in the lumbosacral spine was to be scored separately.
- Proportion of subjects who had ≥30% and ≥50% reduction in average daily pain score for neuropathic pain from LSR and low back pain (each separately) relative to baseline during Weeks 1, 2 and 3 of treatment and 1 week following the end of randomized treatment.
- Change in the amount of rescue medication used from baseline to Week 3 of treatment
- Change in Galer Neuropathic Pain Scale from baseline to Week 3 of treatment.
- Change in average disability score from baseline to Week 3 of treatment based on Oswestry Disability Index.
- Proportion of subjects who had "improved", "much improved" or "very much improved" relative to baseline on each of the Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) on Week 3 of treatment.
- Change in pain (11-point NRS) from baseline on straight leg raise.
- Change in angle of extension of leg from baseline during straight leg raise.

Pharmacokinetics:

- Pre-dose and post-dose plasma CNV1014802 concentrations – AUC(0-24)-ss, Cmin-ss and Cmax-ss

Safety:

- Adverse events
- Vital signs
- ECG parameters
- Laboratory safety tests (clinical chemistry, haematology, urinalysis)

Exploratory:

- PK-PD relationship, if data permit

Statistical methods:

Efficacy Analysis:

The intent-to-treat population, defined as all randomized subjects who received at least one dose of randomized study medication, was used for all efficacy analyses.

In general, continuous data was summarized using descriptive statistics. The primary efficacy analysis was performed using a mixed effect model including subject as a random effect. For statistical analyses, all tests were two-sided with significance interpreted at the 5% level.

Subjects randomized into this study either had radiculopathic pain in one or both lower limbs only, or one or both lower limbs and back pain together. If subjects only had pain in one or both lower limbs then the

primary endpoint was the PI-NRS score associated with the pain in their worst affected lower limb (most painful lower limb determined at Screening). If the subject had pain in one or both lower limbs and back pain then the PI-NRS score for the worst affected lower limb was used as the primary endpoint for that subject, but the PI-NRS score for the back was also recorded and analysed separately as a secondary endpoint.

Post Hoc Analyses

Post hoc analyses were conducted on the primary endpoint and responder rates to explore the treatment effect in different subpopulations.

In addition to the model described by the SAP (period level baseline), analyses of the primary endpoint and responder rates were also conducted using a mixed effects model that included both a period and subject level (mean of baseline 1 & 2) baseline as fixed effects.

Pharmacokinetics Analysis:

The PK analysis population consisted of 78 subjects (43 males, 35 females). Each subject had 11 PK samples taken, of which four at steady state on active treatment (two pre-dose and two 2 hrs post-dose). The total number of concentration records (on active treatment only) in the final datafile was 287. The observations were visually compared to the study specific (regimen and population) predictions (median and 90% prediction interval) from a historical popPK model based on healthy volunteer phase I data. Subsequently, non-linear mixed effect modelling was used, applying the historical popPK model, to estimate the PK parameters for each individual. For the final model all PK parameters were fixed to the healthy volunteer values except for the between subject variability on CL/F. The data did not allow other parameters to be estimated with sufficient confidence. The final model described the observations well and neither obvious biases, nor evidence of non-compliance were observed. The individual PK parameters were then used to derive (through simulation and calculation) the individual exposures at steady state, assuming full compliance.

No exploratory PKPD analysis was performed.

Safety Analysis:

The safety population, defined as all subjects who had received any amount of study medication, was used for safety analyses. Safety data was presented in tabular and/or graphical format and summarized descriptively.

SUMMARY: RESULTS

Efficacy:

- CNV1014802 significantly improved neuropathic pain in LSR patients. On the primary endpoint, there was a difference in the average change in PI-NRS for neuropathic pain from baseline to Week 3 of -0.43 (p= 0.0255) for CNV1014802 compared to placebo.
- A statistically significant effect on neuropathic pain levels was seen from Week 2 onwards.
- There were no statistically significant effects of CNV1014802 on PI-NRS assessments of lower back pain – non-neuropathic.
- The effect of CNV1014802 on neuropathic pain was most pronounced in monotherapy patients. There was a difference in the average change in PI-NRS for neuropathic pain from baseline to Week 3 of -0.73 (p= 0.0038) for CNV1014802 compared to placebo in monotherapy patients.
- There was no evidence that patients with no prior surgery responded any differently to CNV1014802 than those with a history of surgery.
- There were no statistically significant differences between CNV1014802 and placebo on any of the other secondary efficacy endpoints as analysed using the period 1 baseline only.
- Sensitivity analyses conducted analysing the first period only in a between subject analysis showed a similar magnitude of effect of PI-NRS in Week 3 compared to baseline, in both the all subject ITT population (-0.43, p= 0.1858) and the Monotherapy subjects (-0.81, p=0.0555).

Pharmacokinetics:

- CNV1014802 plasma concentrations and exposures were as expected from the healthy volunteer

Phase I PK data.

- Individual PK exposures could be estimated in 78/79 subjects that received active treatment 350 BID.
- The median (90% percentile range) derived exposures were AUC(0-24)-ss 55 (40 - 78) [µg*hr/ml], Cmax-ss 3.7 (2.7 - 5.0) [µg/ml], Cmin-ss 1.4 (0.9 - 2.0) [µg/ml].
- The PK data suggested no evidence of major non-compliance.

Safety:

- CNV1014802 was well tolerated; 58% subjects dosed with CNV1014802 reported TEAE's compared to 49% dosed with placebo.
- The most common treatment emergent adverse events occurring in this study were headache (CNV1014802: 12 subjects (15.2%); placebo: 5 subjects (6.8%)) and dizziness (CNV1014802: 9 subjects (11.4%); placebo: 3 subjects (4.1%)). The majority of all TEAE's were mild in severity.
- A total of 8 (10.1%) CNV1014802 and 1 (1.4%) placebo treated subjects were discontinued due to TEAE's. One CNV1014802 subject was discontinued due to a rash which was considered to be related to study drug.
- ALT increases of >3xULN were observed in two subjects dosed with CNV1014802. One subject was discontinued from the study; this subject also had significant elevations of AST, GGT and alkaline phosphatase. Serum bilirubin was normal in both subjects. The abnormal laboratory parameters in both subjects rapidly fell once CNV1014802 was withdrawn.
- No other clinically significant changes in laboratory test parameters, were reported.
- There were no clinically significant changes in BP, heart rate or ECG parameters associated with CNV1014802

SUMMARY: CONCLUSION

The primary objective of this study was to investigate the efficacy of repeat oral dosing of CNV1014802 on neuropathic pain in subjects with lumbosacral radiculopathy. There was a small but statistically significant effect of CNV1014802 compared to placebo at Week 3 on the change in neuropathic pain associated with LSR, but not with low back pain. The improvement in the monotherapy subset was greater than in the overall ITT population. No significant changes in the secondary endpoints were observed. Whilst improvements in pain ratings were seen, there were no statistically significant differences between CNV1014802 and placebo on any of the other secondary efficacy endpoints. However, these were analysed using the period 1 baseline only for both treatment periods baseline. CNV1014802 plasma concentrations and exposures were as expected from phase I healthy volunteer data and there was no evidence of major non-compliance.

CNV1014802 was generally well tolerated with the most common adverse events being headache and dizziness. No serious adverse events were reported and only 2 subjects experienced severe treatment emergent adverse events (headache and liver function test abnormal) which both resolved without sequelae. Two subjects treated with CNV1014802 reported rises in ALT greater than 3x ULN which fell rapidly once CNV1014802 was terminated. One subject was discontinued with a rash which was related to CNV1014802. No other clinically significant changes in laboratory test parameters, vital signs or ECG changes were reported.

Date of Report: 04 September 2014