SUPPLEMENTARY MATERIAL

Supplementary Material for:

Efficacy and safety of EMA401/olodanrigan, an orally administered selective angiotensin II type 2 receptor antagonist, in reducing peripheral neuropathic pain: results of two randomised, double-blind, placebo-controlled phase 2 studies in patients with postherpetic neuralgia and painful diabetic neuropathy

Andrew S.C. Rice, MD, Robert H. Dworkin, PhD, Nanna B. Finnerup, MD, Nadine Attal, MD, Praveen Anand, MD, Roy Freeman, MD, Francesca Callegari, PhD, Christie Doerr, PhD, Subhayan Mondal, PhD, Nisha Narayanan, M.Pharm , Laurent Ecochard, PhD, Yanina Flossbach, MD, Shaloo Pandhi, MD

Corresponding author: Shaloo Pandhi, Senior Global Program Clinical Head, Novartis Pharma AG, Forum 1, Novartis campus, CH-4056 Basel, Switzerland, tel: +41616960595, Fax: +41 61 6968073, Mobile: +41797888695, Email ID: shaloo.pandhi@novartis.com

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Appendix S1: Study design and participants

We recruited participants from 45 sites (EMPHENE) and 49 sites (EMPADINE) sites, in across 19 countries (Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Japan, Norway, Poland, Portugal, Slovakia, Spain and the United Kingdom). The Czech Republic and Italy had sites which recruited participants only for the EMPHENE study while Australia, Bulgaria and Finland recruited participants only for the EMPADINE study. The trial sites included pain and neurology clinics in hospitals and clinical trial facilities.

Concomitant medication in the studies were chosen because they are approved in most countries as first line treatment for neuropathic pain. Tapentadol, although approved in some countries for neuropathic pain treatment, was not selected as it is an opioid. TCAs although included as first line treatment options for PNP were not included as they are not recommended at a higher dose due to their anticholinergic and sedative side effects and they are also not approved in most countries for either of these conditions[1].

Appendix S2: Randomisation and masking

In the EMPHENE study, the initial cohort was planned to be randomised with approximately 135 patients in 1:1:1 ratio to either placebo b.i.d., EMA401 25 mg b.i.d., or EMA401 100 mg b.i.d treatment arms. There was a plan to randomise approximately 225 participants to a second cohort in a 1:1:1:2 ratio to treatment with placebo, EMA401 25 mg b.i.d., EMA401 100 mg b.i.d., or a higher dose of EMA401 300 mg b.i.d. following an unblinded safety review by an independent data monitoring committee (DMC). The second cohort was to be initiated after exposure of 50 participants with EMA401 up to 100 mg for at least 8 weeks (i.e. 25 participants each on EMA401 25 mg and 100 mg b.i.d.).

At baseline, all eligible participants were to be randomised via Novartis Interactive Response Technology (NIRT) to one of the treatment arms in the double-blind treatment epoch and to one of the treatment arms in the double-blind treatment withdrawal epoch as per the pre-specified randomisation scheme. The NIRT assigned a randomisation number to the patient, and specified a unique medication number for the first package of study drug to be dispensed to the participant. At Week 12, all participants who completed the 12-week double-blind treatment epoch entered the 1-week double-blind treatment withdrawal epoch. The NIRT system indicated the unique medication number (corresponding to the regimen assigned at baseline) for the package of study drug to be dispensed to the patient during the double-blind treatment withdrawal epoch. Using a validated system that automated the random assignment of participant numbers to randomisation numbers, the NIRT produced a patient randomisation list. These randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication list was to be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to packs containing the investigational drug(s). This procedure to generate randomisation numbers ensured that treatment assignment was unbiased and concealed from participants and investigator site staff. Randomisation was stratified by region and use of concomitant pain medication in order to achieve balance of treatment allocation within the stratification factors.

Appendix S3: Details of the USM for the EMPHENE and EMPADINE studies

For both the EMPHENE and EMPADINE studies, the following safety measures were taken as part of the USM and were communicated to all investigators via the Investigator Notification letter issued on February 25, 2019, and a follow-up Investigator Notification letter issued on April 5, 2019. The USM was implemented immediately, and all relevant IRB/IECs and Health Authorities were notified accordingly

- Participants in the treatment or the treatment withdrawal epoch were informed of the newly available preclinical safety information and instructed to stop the treatment immediately
- Participants in the treatment epoch had to return to the site as soon as possible and complete the treatment discontinuation visit as defined in the study protocol
- Participants in the treatment withdrawal epoch had to return to the site as soon as possible and complete the treatment withdrawal visit as defined in the study protocol
- Participants in the “Abbreviated Visit Schedule” had to come to the site for a visit as soon as possible

- Participants in the screening epoch had to return to the site and be classified as a screening failure. All planned screening visits for participants had to be cancelled

For all participants who received study treatment, laboratory assessments (full haematology, including coagulation and clinical chemistry panel) were to be performed, in addition to the protocol-specified assessments, via two unscheduled follow-up visits as follows:

- For all participants who discontinued the study treatment following the Investigator Notification letter dated February 25, 2019, additional laboratory assessments as aforementioned were to be performed within 4-8 weeks, and then within 12-16 weeks after discontinuation of study treatment
- For all participants who already completed the study or prematurely discontinued prior to the Investigator Notification letter dated February 25, 2019, investigators requested them to return to the site for the first follow-up visit within 8 weeks of the first USM notification but not earlier than 4 weeks after the last site visit. Participants were to also return to the site for the second follow-up visit at least 4 weeks after the first follow-up visit but not earlier than 12 weeks after the study treatment discontinuation following the Investigator Notification letter dated April 5, 2019. Participants had to return to the site for the additional laboratory assessments as aforementioned

All newly occurring or ongoing AEs (including liver laboratory triggers and liver events) were followed up until resolution. Investigators were asked to follow a standardised process for identification, monitoring, and evaluation of liver events. All newly occurring liver laboratory triggers and events (irrespective of investigator causality revealed in participants after their treatment discontinuation [serious or non-serious]) had to be reported to the Novartis local country Safety Desk (CO Patient Safety). If, for any reason, either of the safety follow-up visits could not be performed, this had to be documented in the source documents/participants' charts. All participants had to be informed of the newly available preclinical safety information and the investigators were instructed to document it in the patient's chart. The updated global informed consent form (ICF) was distributed and was to be signed by all participants taking into consideration local country regulations. If, for any reason, the ICF could not be signed, the site had to demonstrate due diligence and document it in the source documents/participants' charts.

Appendix S4: *eDiary device*

Participants recorded their pain intensity scores during the past 24 hours in the evening prior to sleep by touching the appropriate corresponding number between zero and ten on the eDiary device. The eDiary was completed daily for 7 consecutive days prior to randomisation and then every day through to the end of the study. To encourage compliance, participants were advised to record the information in the eDiary every day. Retroactive completion was allowed for pain scores up to 1 day in the past but entries more than a day old were not allowed.

Appendix S5: Details of the double-blind treatment withdrawal epoch

Participants receiving placebo treatment during the 12-week double-blind treatment epoch remained on placebo during the double-blind treatment withdrawal epoch. Participants receiving active treatment were randomised in a 1:1 ratio to either stop treatment (i.e. receive placebo) or to continue the active treatment assigned during the double-blind treatment epoch. Participants who discontinued the study drug during the 12-week double-blind treatment epoch were encouraged to stay in the study and continue to be followed with an abbreviated schedule of assessments until Week 12. This abbreviated schedule of assessments included a physical exam, daily pain diary (for NRS), Brief Pain Inventory Short Form (BPI-SF), NPSI, Patient Global Impression of Change (PGIC) and Columbia Suicide Severity Rating Scale (C-SSRS) scores.

Appendix S6: Sample size determination

A sample size of 90 participants per group in the EMPHENE yielded 77% power for the primary variable (NRS change from baseline to Week 12) assuming candidate shapes for the dose-response with a maximum effect in the dose range of 1·0 point for the 300 mg dose, and assuming a standard deviation of 2·6 points. The power was calculated based on the dose-response trend test to test the null hypothesis of a flat dose-response shape using MCP-Mod (Multiple Comparison Procedure – Modelling) methodology with the alpha equal to 0·025 (one-sided). For the EMPADINE a sample size of 200 participants per group yielded 85% power assuming a 0·8 point treatment difference (TD) between EMA401 100 mg and placebo and a standard deviation of 2·6 for the primary efficacy variable (NRS change from baseline to Week 12), and an effect size of 0·4 (100 mg) for the key secondary variable (NPSI change

from baseline to Week 12). The aim was to show that EMA401 100 mg is statistically significant over placebo for the primary efficacy variable, using a hierarchical testing procedure. The power for showing the statistical significance of EMA401 100 mg in terms of the key secondary variable was 84% under the same scenario. Therefore 360 (EMPHENE) and 400 (EMPADINE) participants were planned to be recruited.

Appendix S7: Handling of intercurrent events for primary estimand and supplementary estimand

The primary analysis for the primary estimand accounted for different intercurrent events (i.e. events which occurred post-randomisation) in alignment with the chosen primary estimand [20].These included changes in doses of the allowed concomitant medication, intake of paracetamol for incidental pain, intake of prohibited medications with potential confounding effect prior to treatment discontinuation, permanent discontinuation of treatment due to an AE, lack of efficacy, use of prohibited medication or other reasons (including for USM). A supplementary estimand was also evaluated.

The following definitions are used:

- Unfavourable event: An event after which the patient cannot plausibly continue to derive benefit from the study treatment
- Ignorable event: an event which is not unfavourable

Handling of intercurrent events for the primary estimand:

- Changes of dose of allowed concomitant medication for pain: ignorable event
- Data collected during and after the period of the intake of short-acting pain medications were included in the analysis.
- Intake of prohibited medications with potential confounding effect prior to treatment discontinuation: ignorable event
- Permanent discontinuation due to adverse events (AE), lack of efficacy, use of prohibited medication: unfavorable event for the active treatment arms, ignorable event for the placebo arms.
- Permanent discontinuation due other reasons: ignorable event

Events were handled as follows in the primary analysis:

- For unfavourable events: RDO (retrieved drop out) data were used if available, otherwise missing data after this event were handled via a jump-to-reference (J2R) missing data imputation mechanism.
- For ignorable events: RDO data, if available, were excluded, and missing data after this event were handled via a missing-at-random (MAR) data imputation mechanism.

Sensitivity and Supplementary analyses

A sensitivity analysis was also performed on the mFAS using the same ANCOVA model and the same rules for handling intercurrent events as for the primary analysis.

A supplementary analysis was performed on the FAS to quantify the treatment effect of EMA401 compared to placebo that would have been observed had all participants remained on their assigned treatment for 12 weeks (supplementary estimand).

Handling of intercurrent events for the supplementary estimand:

- Changes of dose of allowed concomitant medication for pain: ignorable event
- Data collected during and after the period of the intake of short-acting pain medications were included in the analysis.

- Intake of prohibited medications with potential confounding effect prior to treatment discontinuation: ignorable event
- Permanent discontinuation due to AE, lack of efficacy, use of prohibited medication: ignorable event for all treatment arms
- Permanent discontinuation due other reasons: ignorable event

Appendix S8: Statistical analysis methods of secondary efficacy measures

Responder analyses (based on at least a 30% or 50% improvement from baseline on the NRS) were performed in order to facilitate the interpretation of the results of the primary analyses from a clinical relevance perspective. The responder status for each patient was calculated based on the continuous weekly score measurements. From an analysis point of view, the resulting responder variables were analysed using a logistic regression model including all randomised participants and adjusting for the same covariates as the ANCOVA model for the primary analysis. Odds ratios were estimated along with their 95% CIs. For the NPSI total score the null hypothesis of superiority of EMA401 over placebo was tested. The estimations of treatment difference and intercurrent events were handled in a similar manner as the primary analysis. BPI-SF interference total score, the weekly mean of the 24-hour worst NRS pain score and the ISI score were summarised descriptively by treatment and visit, and PGIC at Week 12 was summarised descriptively by treatment.

Statistical analyses methods for paracetamol intake

The proportion of participants who needed paracetamol for incidental pain (at each visit and at least once during the study) was evaluated separately for the double-blind treatment epoch and treatment withdrawal epoch. The Kaplan-Meier estimates of the proportion of participants with paracetamol intake during the double-blind treatment epoch, along with the associated 95% CIs using Greenwood's formula were determined.

Appendix S9: Safety analyses methods

For the safety analyses, the Medical Dictionary for Regulatory Activities (MedDRA version 22·0) was used to code all AEs. AEs were summarised as the number of cases as a percentage of the number at risk by treatment arm separately for the treatment epoch and the treatment withdrawal epoch. An external independent DMC had access to unblinded data to conduct quarterly safety reviews. The DMC reviewed cumulative safety data, as well as patient narratives for deaths, SAEs, discontinuations due to AEs and cases of interest (allergic dermatitis, and clinically significant abnormal hepatic and haematology values).

Appendix S10: Supplementary and sensitivity analysis for NRS

In the EMPHENE, at Week 12, the TD between EMA401 25 mg and placebo was −0·5 (95% CI: −1·6, 0·7; p value: 0·408) while the TD between EMA401 100 mg and placebo was −0·6 (95% CI: −1·6, 0·5; p value: 0·308), numerically in favour of the EMA401 arms. Based on the sensitivity analysis performed at Week 12 no TD was observed between EMA401 25 mg and placebo in terms on LS means (95% CI: −1·2, 1·2; p value: 0·987), while the TD between EMA401 100 mg and placebo was −0·6 (95% CI: −1·8, 0·7; p value: 0·378).

In the supplementary analysis of the EMPADINE, at Week 12, the TD between EMA401 100 mg and placebo was −0·6 (95% CI: −1·4, 0·2; p value: 0·163). Based on the sensitivity analysis performed at Week 12, the LS mean TD between EMA401 100 mg and placebo was −0·4 (95% CI: −1·2, 0·5; p value: 0·400).

Appendix S11: NPSI Dimensional score discussion

In the EMPHENE, the reductions in NPSI dimensional score at Week 12, in the EMA401 treatment arms, were lower compared to placebo for all dimensions except for deep/pressing pain. While in the EMPADINE, in the EMA401 100 mg arm, the reduction in NPSI dimensional scores at Week 12 were higher as compared to the placebo arm for all of the dimensions. We agree that the total NPSI score is generally not more sensitive than a NRS; and in our studies also it was less sensitive. Recent studies have depicted the advantages of sensory phenotyping in chronic pain trials[2]. The results of our studies further support the importance of sensory profiles in NP conditions.

Appendix S12: Frequently reported treatment-emergent AEs (TEAEs) during the double-blind treatment epoch

The most frequently reported treatment-emergent AEs (TEAEs) during the double-blind treatment epoch in the EMPHENE across the three treatment arms were diarrhoea (7% with EMA401 25 mg, 4·7% with EMA401 100 mg and 7% with placebo) and nasopharyngitis (7% with EMA401 25 mg, 4·7% with EMA401 100 mg and 9·3% with placebo). Increased levels of amylase and lipase, increased blood triglycerides, increased blood creatinine, and muscle spasms were the TEAEs reported only in the EMA401 treatment arms; however, incidence of these was low. Specifically, increased level of amylase and lipase were isolated cases reported with both EMA401 25 mg (with a similar incidence of 2·3%) and EMA401 100 mg (4·7% and 7·0%, respectively).

The most frequently reported TEAEs during the double-blind treatment epoch in the EMPADINE study across both treatment arms were nasopharyngitis (5·8% [EMA401 100 mg] and 9·1% [placebo]) and headache (5·8% [EMA401 100mg] and 6·1% [placebo]). TEAEs of increased levels of lipase and upper abdominal pain were reported only in the EMA401 100 mg arm but with a low incidence (8·7% and 7·2%, respectively).

Appendix S13: Serious Adverse Events

In the EMPHENE, three events (lower respiratory tract infection, traumatic haematoma and ECG ST segment elevation) were reported in the EMA401 100 mg arm and five events (non-cardiac chest pain, back pain, osteoarthritis, central nervous system lymphoma and lumbar radiculopathy) in the placebo arm. While in the EMPADINE, five events (product intolerance, cholelithiasis, two events of acute cholecystitis and localised infection) were reported in the EMA401 100 mg arm and three events (acute coronary syndrome, erysipelas, and chronic obstructive pulmonary disease) in the placebo arm. The severity of these events was moderate to severe.

Appendix S14: Treatment emergent adverse events reported in the treatment withdrawal epoch

During the treatment withdrawal epoch in the EMPHENE study, the majority of participants reported TEAEs with either mild (ranging between 7·0 and 13·0%) or moderate (ranging between 7·0 and 12·0%) severity and no severe TEAE was reported across all of the treatment arms. At least 7·0% of participants in all treatment arms experienced at least one TEAE during the treatment withdrawal epoch. In the EMPADINE study, four participants experienced at least one TEAE during the treatment withdrawal epoch but none of these were reported as serious. The severity of events was mild in one (3·8%) patient and moderate in three participants (7·1-16·7%) and no severe TEAE was reported in either treatment arm (Table S7).

Appendix S15: Additional safety results

EMPHENE study

- Respiratory tract infection, presyncope/dizziness, nausea, headache, allergic dermatitis, neutropenia, and elevation in hepatic enzymes were the AESIs. AESIs were reported in all three treatment arms with a similar incidence in the two active arms (25·6% with EMA401 25 mg and 23·3% with EMA401 100 mg) and a slightly higher incidence in the placebo arm (34·9%). The most frequently reported AESI was respiratory tract infection (14% each in the active treatment arms and 16·3% in the placebo arm)

- The search criterion for elevation in hepatic enzymes included "liver events and laboratory triggers" that used specific liver-related SMQs as well as predefined numerical cut-off values. No liver events, as defined in the protocol, were reported in the study. Newly occurring liver enzyme laboratory abnormalities identified according to predefined cut-off values in the statistical analysis plan were noted; however, they did not meet the criteria for liver events
- Liver function parameters were within the normal limits for most participants. One patient had elevated ALT (>3 times and <5 times ULN) in the EMA401 25 mg arm, one patient had elevated ALP (>1·5 times and <2 times ULN) in the placebo arm, and six participants – two participants in each treatment arm – had elevated TBL (>1 time and <1·5 times ULN). TBL was not >2 times ULN in any case. All of the events had either resolved or were resolving at the time of the last patient visit
- Ten participants reported drug abuse-related AEs across treatment arms, with low incidence (4·7% [EMA401 25 mg], 7% [EMA401 100 mg], and 11·6% [placebo]). Overall, two events (fatigue and dizziness) were reported in the EMA401 25 mg arm, three events (dizziness, somnolence, and sleep terror) in the EMA401 100 mg arm, and five events (two events of fatigue and three events of dizziness) in the placebo arm
- The incidence of clinically notable haematology abnormalities during the double-blind treatment epoch was low in most parameters and mostly balanced across all treatment arms
- The incidence of clinically notable biochemistry abnormalities during the double-blind treatment epoch was low in most parameters and mostly balanced across all treatment arms. The TEAEs of increased blood triglycerides and increased blood creatinine were reported only in the EMA401 100 mg arm (4·7%). The numbers of participants were similarly distributed between the treatment arms for increased triglyceride levels (47·6% [EMA401 25 mg], 51·2% [EMA401 100 mg], and 54·8% [placebo]) and increased creatinine levels (23·8%, 32·6%, and 16·7%, respectively) as per the laboratory assessment. The TEAEs of increased lipase levels (2·3% of participants in the EMA401 25 mg arm vs 4·7% of participants in the EMA401 100 mg arm) and increased amylase (2·3% vs 7%) were reported only in the EMA401 arms· The numbers of participants were similarly distributed between the treatment arms for increased lipase levels (14·3% [EMA401 25 mg], 18·6% [EMA401 100 mg], and 28·6% [placebo]) and increased amylase levels (21·4%, 25·6%, and 2·4%, respectively) as per the laboratory assessment
- Renal parameters were within the normal limits for most participants throughout the study. One patient was noted with new onset dipstick haematuria (urine event) in the placebo arm and two participants were noted with a serum creatinine increase (serum event) in the EMA401 100 mg arm. One patient was noted with serum creatinine increase (EMA401 100 mg, treatment epoch; EMA401 100 mg, treatment withdrawal epoch) during the treatment withdrawal epoch
- One patient each in the three treatment arms reported out-of-range values for vital signs. A lower than normal pulse rate was noted in one patient in the EMA401 100 mg arm, and high SBP was noted in one patient each in the EMA401 25 mg and placebo arms. Clinically notable ECG abnormalities were not observed in any of the participants during the study

EMPADINE study

- Respiratory tract infection, presyncope/dizziness, nausea, headache, allergic dermatitis, neutropenia, and elevation in hepatic enzymes were the AESIs. Some of the AESIs were reported in both treatment arms with a slightly higher incidence in the active arm (24·6% in the EMA401 100 mg arm and 19·7% in the placebo arm). The most frequently reported event in the AESI category was respiratory tract infection (11·6% of participants in the active arm and 10·6% of participants in the placebo arm)
- The search criterion for elevation in hepatic enzymes included "liver events and laboratory triggers" that used specific liver-related SMQs as well as pre-defined numerical cut-off values. Newly occurring liver enzyme laboratory abnormalities identified according to predefined cut-off values in the statistical analysis plan were noted. However, they did not meet the criteria for liver events. No liver event was reported in the EMA401 100 mg arm. A single liver event of hepatic steatosis was reported in a patient (1·5%) in the placebo arm, but was not considered serious. The severity of the event was mild and the patient had not recovered at the time of the last patient visit
- Liver function parameters were within the normal limits for most of the participants. A single patient had elevated ALT or AST (>3 times ULN and <5 times ULN), elevated TBL (>1 time ULN and <1·5 times ULN), and elevated ALP (>1·5 times ULN and <2 times ULN) in the EMA401 100 mg arm. One patient had elevated TBL (>1·5 times ULN and <2 times ULN) in the placebo arm. All events had resolved at the time of the last patient visit

- Renal parameters were within the normal limits for most participants throughout the study duration. Four participants (two each in the treatment arms) reported a serum creatinine increase during the double-blind treatment epoch
- Eight participants reported drug abuse-related AEs in both treatment arms, with low incidence (8·7% [EMA401 100 mg] and 3% [placebo])
- Overall, eight events (two events of fatigue; three events of dizziness; and one event each of lethargy, somnolence, and anxiety) were reported in the EMA401 100 mg arm and two events of dizziness were reported in the placebo arm. None of these events were reported as serious
- The incidence of clinically notable haematology abnormalities during the double-blind treatment epoch was low in most parameters and mostly balanced across the treatment arms. No clear trend in laboratory changes in the level of neutrophils was observed in the study, with abnormalities almost equally distributed across the two treatment arms
- The incidence of clinically notable biochemistry abnormalities during the double-blind treatment epoch was low in most parameters and mostly balanced across the treatment arms. Specifically, the increased laboratory values of some of the biochemistry parameters (lipase, GGT, and creatinine) were also reported as TEAEs. The TEAE of increased lipase was reported only in the EMA401 100 mg arm (8·7%); however, the proportion of participants with increased lipase levels as per the laboratory assessment were similarly distributed between the EMA401 100 mg arm (28·4%) and the placebo arm (26·2%). The overall incidence of the TEAE of increased GGT was low, but was higher in the EMA401 100 mg arm (5·8%) than in the placebo arm (1·5%). A similar trend was observed in the laboratory assessment in both treatment arms (23·5% of participants in the EMA401 100 mg arm vs 10·8% of participants in the placebo arm). A similar incidence (about 3%) of increased blood creatinine as a TEAE was reported in both treatment arms. Increased creatinine level was equally distributed across the treatment arms (28·4% with EMA401 100 mg vs 30·8% with placebo). The severity of most of these events was mild to moderate and most had either resolved or were resolving at the time of the last patient visit
- Clinically notable ECG abnormalities observed in the EMA401 100 mg arm were comparable to the placebo arm. An increase of >60 ms in the QTcF interval was noted in one (1·5%) patient in the EMA401 100 mg arm and in two (3·1%) patients in the placebo arm, while an increase of >500 ms was noted in one (1·6%) patient in the placebo arm

Table S1. List of inclusion and exclusion criteria and concomitant medication

EMPHENE study
Inclusion Criteria • Written informed consent obtained before any assessment was performed • Males and females, 18 years of age and older • Documented diagnosis of PHN (ICD-10 code B02·29) at screening, defined as pain in the region of the rash persisting for more than 6 months after onset of a herpes zoster rash • Assessment of moderate to severe neuropathic pain across the screening epoch (NRS ≥4) • The assessment of moderate and severe pain was made using a proprietary screening algorithm • Documented past and/or ongoing inadequate treatment response (having insufficient pain relief with treatment or inability to tolerate) to at least two different prescribed therapies/analgesics commonly used to treat and considered effective for the treatment of PHN • Willingness to complete the daily eDiary
Exclusion Criteria • Use of other investigational drugs within five half-lives of enrollment, or within 30 days, whichever is longer • History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes • ECG abnormalities indicating significant risk of safety for participants participating in the study, such as: − Concomitant clinically significant cardiac arrhythmias e.g., sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular block without a pacemaker − History of familial long QT syndrome or known family history of Torsades de Pointes • Participants taking medications prohibited by the protocol • Skin conditions in the affected dermatome that in the investigator's opinion could alter sensation or active herpes zoster upon physical examination at screening • History of malignancy of any organ system (other than localised basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 2 years, regardless of whether there was evidence of local recurrence or metastases • Major depressive episode within 6 months prior to screening and/or a history of diagnosed recurrent major depressive disorder according to the Diagnostic and Statistical • Manual of Mental Disorders, 5th Edition (DSM-V) diagnostic criteria • Score of "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months; or "yes" on any item of the Suicidal Behaviour section, except for the "Non-Suicidal Self-Injurious Behaviour" (item also included in the Suicidal Behaviour section), if this behaviour occurred in the past 2 years • Pregnant or nursing (lactating) women • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using highly effective methods of contraception during dosing and for 3 days after discontinuing study medication. Highly effective contraception methods include: − Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal and post-ovulation methods) and withdrawal are not acceptable methods of contraception − Female sterilisation (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by a follow up hormone level assessment − Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomised male partner should be the sole partner of that patient − Placement of an intrauterine device or intrauterine system • Evidence of significant renal insufficiency indicated by an estimated glomerular filtration rate using the modification of diet in renal disease (MDRD) equation of <40 mL/min/1·73 m2 at screening (as calculated by the central laboratory). • Alcohol use disorder or other substance-use disorders (other than nicotine or caffeine) in accordance with DSM-V criteria within 12 months of screening • Positive urine drug screen at screening • Evidence of pre-existing liver condition as defined as any of the following: − AST or ALT ≥ 1·5 X ULN, or TBL or ALP > ULN from the central laboratory at screening − Known history of or active hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV − Hepatitis A or B vaccination within 3 months of screening − Active gallbladder or bile duct disease − Acute or chronic pancreatitis • Platelets ≤100 x 109/L, or neutrophil count <1·2 x 109/L (or equivalent), or hemoglobin ≤100 g/L for women or hemoglobin ≤110 g/L for men • Known diagnosis of diabetes and are stable on medication with a haemoglobin A1c >8% • Those who did not have a known diagnosis of diabetes with a haemoglobin A1c >7% • Other conditions: − Active, uncontrolled medical condition (e.g. neurological, gastrointestinal, renal, hepatic, cardiovascular, pulmonary, metabolic, endocrine, haematological, genitourinary or other major disorder), psychotic disorder or any other

uncontrolled psychiatric illness (participants who were not stable on medication for at least 2 months prior are excluded), or any other significant clinical disorder or laboratory finding
  - Clinically significant illness or operative procedure within 4 weeks of screening (e.g., influenza or myocardial infarction)
  - Any other pain in the region of the herpes zoster rash or any other moderate to severe pain that could be confused with the patient's PHN, or other chronic pain conditions (including osteoarthritis), that could confound evaluation of the treatment response
- Undergone neurolytic or neurosurgical therapy or used a neuro-stimulating device for PHN within 3 months of screening or were using/planned to use TENS

Concomitant treatment

- Participants were allowed to take only one of the following prescribed medications for managing their PHN, provided the dose level had been stable for at least 2 weeks prior to the Randomization Visit (i.e. Baseline visit) and remained at stable dose throughout the study (PRN (as needed) use was not allowed):
  - Pregabalin
  - Gabapentin
- In addition to other medications for non-pain related co-morbid conditions, participants were allowed to take throughout the study the following medications for other concomitant medical conditions. The dose level had to be stable at baseline and continued at stable doses throughout the study (PRN (as needed) use was not allowed):
  - Benzodiazepine, zolpidem, diphenhydramine or related drugs for insomnia.
  - SSRIs for depression.
  - Oral aspirin (≤ 325 mg/day) for cardio-protection.
- Participants had to notify the study site about any new medications taken after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study were recorded in the concomitant medications / significant non-drug therapies eCRF. Each concomitant drug was individually assessed against all exclusion criteria/ prohibited medication. If in doubt, the Investigator was to contact the Novartis medical monitor before randomising a patient or allowing a new medication to be started

EMPADINE study

Inclusion Criteria

- Written informed consent obtained before any assessment was performed
- Males and females, 18 years of age and older
- Documented diagnosis of Type I or Type II diabetes mellitus with painful distal symmetrical sensorimotor neuropathy (e.g. ICD-10 code G63·2) of more than 6 months in duration with any one or more of the following at screening:
  - Neuropathic symptoms (e.g. numbness, non-painful paraesthesias or tingling, and nonpainful sensory distortions or misinterpretations, etc)
  - Decreased distal sensation (e.g. decreased vibration, pinprick sensation, or light touch, etc)
- Assessment of moderate to severe neuropathic pain across the screening epoch (NRS ≥4)
- The assessment of moderate and severe pain was made using a proprietary screening algorithm
- Score of ≥4 on the Douleur Neuropathique en 4 Questions questionnaire at screening

Exclusion Criteria

- Use of other investigational drugs within five half-lives of enrolment or within 30 days, whichever is longer
- History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
- History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study, such as:
  - Concomitant clinically significant cardiac arrhythmias (e.g. sustained ventricular tachycardia) and clinically significant second- or third-degree atrioventricular block without a pacemaker
  - History of familial long QT syndrome or known family history of Torsades de Pointes
- Participants taking medications prohibited by the protocol
- History of malignancy of any organ system (other than localised basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases
- Major depressive episode within 6 months prior to screening and/or a history of diagnosed recurrent major depressive disorder according to the DSM-V diagnostic criteria
- Score of "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS if this ideation occurred in the past 6 months; or "yes" on any item of the Suicidal Behaviour section, except for the "Non-Suicidal Self-Injurious Behaviour" (item also included in the Suicidal Behaviour section), if this behaviour occurred in the past 2 years
- Pregnant or nursing (lactating) women
- Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after discontinuing study medication. Highly effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception
  - Female sterilisation (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by a follow up hormone level assessment
  - Male sterilisation (at least 6 months prior to screening). For female participants on the study, the vasectomised male partner should be the sole partner of that patient

- Placement of an intrauterine device or intrauterine system. In case local regulations deviate from the contraception methods listed above, local regulations applied and were described in the ICF
- Evidence of significant renal insufficiency indicated by an estimated glomerular filtration rate using the modification of diet in renal disease (MDRD) equation of <40 mL/min/1·73 m2 at screening (as calculated by the central laboratory)
- Alcohol use disorder or other substance use disorders (other than nicotine or caffeine) in accordance with DSM-V criteria within 12 months of screening
- Positive urine drug screen at screening
- Evidence of a pre-existing liver condition as defined as any of the following:
  - AST or ALT ≥1·5 x ULN or TBL or ALP > ULN from the central laboratory at screening
  - Known history of active hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV
  - Hepatitis A or B vaccination within 3 months of screening
  - Known gallbladder or bile duct disease
  - Acute or chronic pancreatitis
- Platelets ≤100 x 109/L or neutrophil count <1·2 x 109/L (or equivalent), or haemoglobin ≤100 g/L for women or haemoglobin ≤ 110 g/L for men at screening
- Participants whose glycaemic control was unstable within 3 months immediately prior to screening (e.g. ketoacidosis requiring hospitalisation, any recent episode of hypoglycaemia requiring assistance through medical intervention, and uncontrolled hyperglycaemia)
- Participants with any differential diagnosis of PDN including, but not limited to, other neuropathies (e.g. vitamin B12 deficiency or chronic inflammatory demyelinating polyneuropathy), polyradiculopathies, central disorders (e.g. demyelinating disease), or rheumatological disease (e.g. foot arthritis or plantar fasciitis)
- Other than pain as a result of PDN:
  - An active, uncontrolled medical condition (e.g. neurological, gastrointestinal, renal, hepatic, cardiovascular, pulmonary, metabolic, endocrine, haematological, genitourinary, or other major disorder); psychotic disorder or any other uncontrolled psychiatric illness (participants who are not stable on medication for at least 2 months prior are excluded); any other significant clinical disorder or laboratory finding; or other chronic pain conditions (e.g. osteoarthritis or fibromyalgia) that, in the opinion of the investigator, precludes participation in the study or may interfere with the study objectives and assessment of change in neuropathic pain
  - Clinically significant illness or operative procedure within 4 weeks of screening (e.g. influenza or myocardial infarction)
- Undergone neurolytic or neurosurgical therapy or used a neurostimulating device for PDN within 3 months of screening or were using/planned to use TENS
- Unwillingness or inability to complete the daily eDiary

Concomitant treatment

- Participants were allowed to take only one of the following prescribed medications for managing their PDN, provided the dose level had been stable for at least 2 weeks prior to the Screening Visit and remained at stable doses throughout the study (PRN (as needed) use was not allowed):
  - Pregabalin
  - Duloxetine
- In addition to other medications for non-pain related co-morbid conditions, patients were allowed to take throughout the study the following medications for other concomitant medical conditions. The dose level had to be stable at baseline and continued at stable doses throughout the study (PRN use was not allowed):
  - Benzodiazepine, zolpidem, diphenhydramine or related drugs for insomnia.
  - SSRIs for depression.
  - Oral aspirin (≤ 325 mg/day) for cardio-protection.
- Participants had to notify the study site about any new medications taken after the patient was enrolled into the study. All medications (including antidiabetic medications), procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study were to be recorded in the concomitant medications/significant non-drug therapies eCRF. Each concomitant drug was individually assessed against all exclusion criteria/ prohibited medication. If in doubt, the Investigator was to contact the Novartis medical monitor before randomising a patient or allowing a new medication to be started

Table S2. Protocols

The protocol for EMPHENE study is available at: https://clinicaltrials.gov/ct2/show/study/NCT03094195?cond=Post-Herpetic+Neuralgia&draw=2&rank=10
The protocol for EMPADINE study is available at: https://clinicaltrials.gov/ct2/show/NCT03297294?cond=Painful+Diabetic+Neuropathy&draw=2&rank=2

Table S3. List of outcomes studied in the EMPHENE and EMPADINE studies

Outcome	EMPHENE study	EMPADINE study
Primary outcome	Change in weekly mean of the 24-houraverage pain score, using an 11-point NRS, from baseline to Week 12	Change in weekly mean of the 24-hour average pain score, using an 11-point NRS, from baseline to Week 12
Key secondary endpoint		NPSI score
Other secondary endpoint	NPSI score	
	Change from baseline to Week 12 in weekly mean 24-hour average pain score	Change from baseline to Week 12 in weekly mean 24-hour average pain score
	BPI-SF interference total score	BPI-SF interference total score
	ISI	ISI
	Responder criteria of at least 30% and 50% pain reduction in the weekly mean of the 24-hour average pain score	Responder criteria of at least 30% and 50% pain reduction in the weekly mean of the 24-hour average pain score
	PGIC	PGIC
	Exposure-response (decrease in pain intensity)	Exposure-response (decrease in pain intensity)
Additional secondary endpoints		Evaluation of the proportion of participants who needed paracetamol for incidental pain separately for the double-blind treatment epoch and treatment withdrawal epoch
		Time to first intake of paracetamol for incidental pain during the double-blind treatment epoch
Safety endpoints	AEs	AEs
	AESI	AESI
	AEs leading to discontinuation	AEs leading to discontinuation
	SAEs	SAEs
	Physical examination	Physical examination
	Vital signs and laboratory parameters	Vital signs and laboratory parameters
	ECG	ECG
	Withdrawal and rebound effects and suicidality evaluations	Withdrawal and rebound effects and suicidality evaluations

AEs, adverse events; AESI, AEs of special interest; BPI-SF, Brief Pain Inventory Short Form; ECG, electrocardiogram; ISI, Insomnia Severity Index; NPSI, Neuropathic Pain Symptom Inventory; NRS, Numeric Rating Scale; PGIC; Patient Global Impression of Change; SAEs, serious adverse events

Table S4. Study procedures and assessments for the EMPHENE and EMPADINE studies

Epoch	**Screening**	**Treatment**									**Treatment Withdrawal**
Visit	1	101	102	103	104	105	106	107	199		201
Week	-5 to -1	0 (BL)	1	2	4	6	8	10	12	TD visit	13
Day	-35 to -7	1	8	15	29	43	57	71	85		92
Informed consent	X										
Inclusion/exclusion criteria	X										
Demography	X										
Disease and medical history	X										
Smoking, alcohol, and liver History	X										
Surgical and medical Procedures concomitant medications/rescue medications	X	X	X	X	X	X	X	X	X	X	X

Complete physical exam	S	S							S	S	S
Brief physical exam			S	S	S	S	S	S			
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X							X	X	
Urine drug screen	X				X						
Serum pregnancy test[a,b]		X							X	X	
Urine pregnancy test	X				X		X				X
Haematology/blood chemistry	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[c]	X	X			X		X		X	X	X
Liver safety biomarkers[d]		X									
12-lead ECG[e, f]	X	X			X		X		X	X	X
Contact NIRT	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication		S	S	S	S	S	S	S	S[g]		
Dosage administration record		X	X	X	X	X	X	X	X		X
Treatment compliance		S	S	S	S	S	S	S	S		S
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X
Dispense ePRO eDiary device	S										
Complete pain diary daily (NRS)	X	X	X	X	X	X	X	X	X	X	X

Record VRS pain intensity		X									
Check electronic tablet for eligibility		S									
BPI-SF		X			X		X		X	X	
PGIC									X	X	
NPSI		X			X		X		X	X	X
ISI, HADS, EQ-5D,and SF-36		X							X	X	
QST		X									
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics		X[j]					X[i,j]		X[i,j]		
Pharmacogenetic sampling (optional)[k]		X									
Screening disposition	X										
Treatment epoch disposition									X	X	
Treatment withdrawal epoch disposition											X

[a]Collected as part of the blood chemistry.

[b]Required for all pre-menopausal women who are not surgically sterile.
[c]Urine dipstick performed at the site. If abnormalities are present, the urine sample is sent to the central laboratory for microscopy analysis.
[d]Blood sample collected at BL for all participants and stored for potential liver safety biomarker analysis only upon occurrence of a future liver event. Sample collection to be repeated upon liver event.
[e]Triplicate ECG and pharmacokinetics sample to be collected if abnormal ECG result (QTcF >500 ms).

[f]Blood sampling procedures, ECG, and vital signs assessments if required at the same visit, the blood sampling procedure to be started after completion of the ECG collection and haemodynamic assessments as per the sequence: 10-minute resting period and pre-dose single ECG, vital signs, re-dose pharmacokinetics and laboratory samples, study drug administration.
[g]Drug dispensation only for participants continuing into the treatment withdrawal epoch. Participants will take their last dose of the "treatment" study medication from their old bottle at the site visit in the morning, and will take their first dose of the "treatment withdrawal" study medication from their new bottle that evening.
[h]C-SSRS to be performed at unscheduled visits, except for visits that had an administrative purpose (e.g. visits related to eDiary device queries).
[i]Pharmacokinetic samples for all participants to be collected according to the schedule. Participants to be instructed not to take their morning dose of study medication prior to arriving at the site and completing the necessary assessments. Pharmacokinetics sample to be collected if abnormal ECG result (QTcF >500 ms).
[j]Additional pharmacokinetics sample collected for participants taking pregabalin, gabapentin, or duloxetine according to the schedule. Participants to be instructed not to take their morning dose of pregabalin/gabapentin/ duloxetine prior to arriving at the site and completing the necessary assessments. Participants to bring their pregabalin/gabapentin/duloxetine (if applicable) with them to the study visits where pharmacokinetics data were collected so it can be administered after the PK assessment, as required.
[k]Sampling to be performed only after a separate informed consent, which includes this assessment, to be obtained.

AEs, adverse events; BL, baseline; BPI-SF, Brief Pain Inventory-Short Form; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; eDiary, electronic diary; ePRO, electronic patient-reported outcomes; EQ-5D, EuroQol – 5 Dimensions; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; NIRT, Novartis Interactive Response Technology; NPSI, Neuropathic Pain Symptom Inventory; NRS, Numeric Rating Scale; PGIC; Patient Global Impression of Change; QST, quantitative sensory testing; S, assessment to be recorded on source documentation only; SF-36, Short-form 36; VRS, Verbal Rating Scale; TD, Study Treatment discontinuation; X, assessment to be recorded on clinical database

Table S5. Weekly mean of the 24-hour average pain score NRS: Summary statistics by visit - treatment withdrawal epoch

EMPHENE

Treatment Statistic	Baseline	Week 12	Week 13	Change from Week 12 to Week 13	Change from baseline to Week 13
EMA401 25 mg b.i.d. -> EMA401 25 mg b.i.d. (N=22)					
n	7	7	7	7	7
Mean (SD)	5·24 (1·04)	4·21 (1·77)	4·27 (1·73)	0·06 (0·37)	-0·97 (1·52)
EMA401 25 mg b.i.d. -> Placebo b.i.d. (N=21)					
n	13	13	13	13	13
Mean (SD)	5·41 (1.20)	4·.69 (1·80)	4·91 (1·85)	0·23 (1·06)	-0·50 (1·51)
EMA401 100 mg b.i.d. -> EMA401 100 mg b.i.d. (N=22)					
n	15	15	15	15	15
Mean (SD)	5·76 (0·75)	3·.97 (2·32)	3·99 (2·32)	0·.02 (0·44)	-1·77 (2·17)
EMA401 100 mg b.i.d. -> Placebo b.i.d. (N=21)					
n	7	6	7	6	7
Mean (SD)	5·53 (0·69)	2·36 (2·41)	3·.90 (2·5)	0·02 (0·05)	-1·63 (2·10)
Placebo b.i.d. -> Placebo b.i.d. (N=43)					
n	23	23	23	23	23
Mean (SD)	5·65 (1·12)	4·14 (2·04)	3·97 (2·16)	-0·17 (0·51)	-1·68 (2·.14)

EMPADINE

Treatment Statistic	Baseline	Week 12	Week 13	Change from Week 12 to Week 13	Change from baseline to Week 13
EMA401 100 mg b.i.d. -> EMA401 100 mg b.i.d. (N=35)					
n	13	13	13	13	13
Mean (SD)	5·37 (1·44)	3·02 (2·14)	3·04 (2·18)	0·01 (0·36)	-2·33 (1·93)
EMA401 100 mg b.i.d. -> Placebo b.i.d. (N=35)					
n	12	12	12	12	12
Mean (SD)	5·77 (1·31)	4·93 (2·08)	4·86 (2·07)	-0·07 (0·45)	-0·91 (1·09)
Placebo b.i.d. -> Placebo b.i.d. (N=67)					
n	26	26	26	26	26
Mean (SD)	5·41 (1·07)	4·28 (1·92)	4·41 (1·80)	0·14 (0·69)	-0·99 (1·34)

b.i.d., twice daily; N, total number of participants; n, participants per treatment arm; NRS, numeric rating scale; SD, standard deviation

Table S6. Reduction in NPSI dimensional score at Week 12

EMPHNE

NPSI dimensional score	EMA401 25 mg b.i.d. N=43 n=24	EMA401 100mg b.i.d. N=43 n=24	Placebo b.i.d. N=43 n=23
Burning pain	−0·75 (3·49)	−0·75 (2·64)	−1·96 (3·36)
Deep/pressing pain	−0·33 (2·08)	−1·33 (2·32)	−0·48 (2·05)
Paroxysmal pain	−0·44 (2·45)	−0·90 (2·04)	−1·43 (3·05)
Evoked pain	−0·76 (1·97)	−0·86 (2·34)	−1·09 (2·68)
Paraesthesia/dysesthesia	−0·67 (3·22)	−1·29 (2·30)	−1·46 (2·30)

EMPADINE

NPSI dimensional score	EMA401 100mg b.i.d. N=70 n=27	Placebo b.i.d. N=67 n=28
Burning pain	−1·85 (3·77)	−1·14 (2·73)
Deep/pressing pain	−0·93 (2·47)	−0·71 (2·61)
Paroxysmal pain	−2·13 (1·98)	−1·11 (2·22)
Evoked pain	−0·80 (2·15)	−0.76 (2·21)
Paraesthesia/dysesthesia	−1·44 (2·49)	−1·38 (2·27)

Data are mean (SD) unless otherwise stated

b.i.d., twice daily; N, total number of participants; n, participants per treatment arm; NP, neuropathic pain; NPSI, The Neuropathic Pain Symptom Inventory score; SD, standard deviation

Table S7. AEs during the treatment withdrawal epoch

EMPHENE

	EMA401 25 mg b.i.d. to EMA401 25 mg b.i.d. N=13 n (%)	EMA401 25 mg b.i.d. to placebo N=13 n (%)	EMA401 100 mg b.i.d. to EMA401 100 mg b.i.d. N=15 n (%)	EMA401 100 mg b.i.d. to placebo b.i.d. N=13 n (%)	Placebo b.i.d. to placebo b.i.d. N=26 n (%)
Participants with at least one AE	1 (7·7)	1 (7·7)	2 (13·3)	1 (7·7)	5 (19·2)
Mild	0	1 (7·7)	2 (13·3)	0	2 (7·7)
Moderate	1 (7·7)	0	0	1 (7·7)	3 (11·5)
Severe	0	0	0	0	0
TEAEs reported					
Cardiac disorders	1 (7·7)	0	0	0	0
Angina pectoris	1 (7·7)	0	0	0	0
Infections and infestations	0	0	0	0	1 (3·8)

Upper respiratory tract infection	0	0	0	0	1 (3·8)
Injury, poisoning, and procedural complications	0	0	1 (6·7)	0	1 (3·8)
Fall	0	0	0	0	1 (3·8)
Tongue injury	0	0	1 (6·7)	0	0
Investigations	0	0	1 (6·7)	1 (7·7)	0
Amylase increased	0	0	0	1 (7·7)	0
Blood creatinine increased	0	0	1 (6·7)	0	0
Lipase increased	0	0	0	1 (7·7)	0
Musculoskeletal and connective tissue disorders	0	0	0	0	2 (7·7)
Back pain	0	0	0	0	1 (3·8)
Musculoskeletal chest pain	0	0	0	0	1 (3·8)
Nervous system disorders	0	1 (7·7)	0	0	1 (3·8)
Postherpetic neuralgia	0	1 (7·7)	0	0	1 (3·8)
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	1 (3·8)
Hydrothorax	0	0	0	0	1 (3·8)

EMPADINE

	EMA401 100 mg b.i.d. to EMA401 100 mg b.i.d. **N=14** **n (%)**	**EMA401 100 mg b.i.d. to placebo b.i.d.** **N=12** **n (%)**	**Placebo b.i.d. to placebo b.i.d.** **N=26** **n (%)**
Participants with at least one AE	1 (7·1)	2 (16·7)	1 (3·8)
Mild	0	0	1 (3·8)
Moderate	1 (7·1)	2 (16·7)	0
Severe	0	0	0
TEAEs reported			
Cardiac disorders	0	1 (8·3)	0
Palpitations	0	1 (8·3)	0

Investigations	1 (7·1)	0	1 (3·8)
Blood creatinine increased	0	0	1 (3·8)
Lipase increased	1 (7·1)	0	0
Vascular disorders	0	1 (8·3)	0
Hypertension	0	1 (8·3)	0

Only AEs reported during the treatment withdrawal epoch and within 21 days after the end of study date are included. MedDRA Version 22·0 has been used for the reporting of AEs. AEs starting after the date of the Week 12 visit are assigned to the treatment withdrawal epoch and included in this table
AE, adverse event; b.i.d., twice daily; N, total number of participants; n, participants per treatment arm; TEAE, treatment-emergent adverse event

Table S8: AEs during the USM safety follow-up

EMPHENE

	EMA401 25 mg b.i.d. to EMA401 25 mg b.i.d. **N=22** **n (%)**	**EMA401 25 mg b.i.d. to placebo b.i.d.** **N=21** **n (%)**	**EMA401 100 mg b.i.d. to EMA401 100 mg b.i.d.** **N=22** **n (%)**	**EMA401 100 mg b.i.d. to placebo b.i.d.** **N=21** **n (%)**	**Placebo b.i.d. to placebo b.i.d.** **N=43** **n (%)**
Participants with at least one AE	0	1 (4·8)	1 (4·5)	3 (14·3)	0
TEAEs reported					
Blood creatinine increased	0	1 (4·8)	0	0	0
Blood potassium increased	0	1 (4·8)	0	0	0
Glomerular filtration rate decreased	0	1 (4·8)	0	1 (4·8)	0
Alanine aminotransferase increased	0	0	0	1 (4·8)	0
Blood creatinine phosphokinase increased	0	0	0	1 (4·8)	0
Blood glucose increased	0	0	1 (4·5)	0	0

EMPADINE

	EMA401 100 mg b.i.d. to EMA401 100 mg b.i.d. **N=34** **n (%)**	**EMA401 100 mg b.i.d. to placebo b.i.d.** **N=35** **n (%)**	**Placebo b.i.d. to placebo b.i.d.** **N=66** **n (%)**
Participants with at least one AE	1 (2·9)	0	1 (1·5)
TEAEs reported			
Gastrointestinal disorders	1 (2·9)	0	0
Peritoneal adhesions	1 (2·9)	0	0
Hepatobiliary disorders	1 (2·9)	0	0
Cholelithiasis	1 (2·9)	0	0
Infections and infestations	1 (2·9)	0	0
Liver abscess	1 (2·9)	0	0
Investigations	0	0	1 (1·5)

Blood creatinine increased	0	0	1 (1·5)

Only AEs reported during the USM follow-up are included. MedDRA Version 22·0 was used for the reporting of AEs

AE, adverse event; b.i.d., twice daily; N, total number of participants; n, participants per treatment arm; TEAE, treatment-emergent adverse event; USM, urgent safety measure

Figure S1· LS means and associated 95% CI of change from baseline in weekly mean of the 24-hour average pain score using the NRS over post-baseline visits during double-blind treatment epoch – Supplementary analysis (FAS)

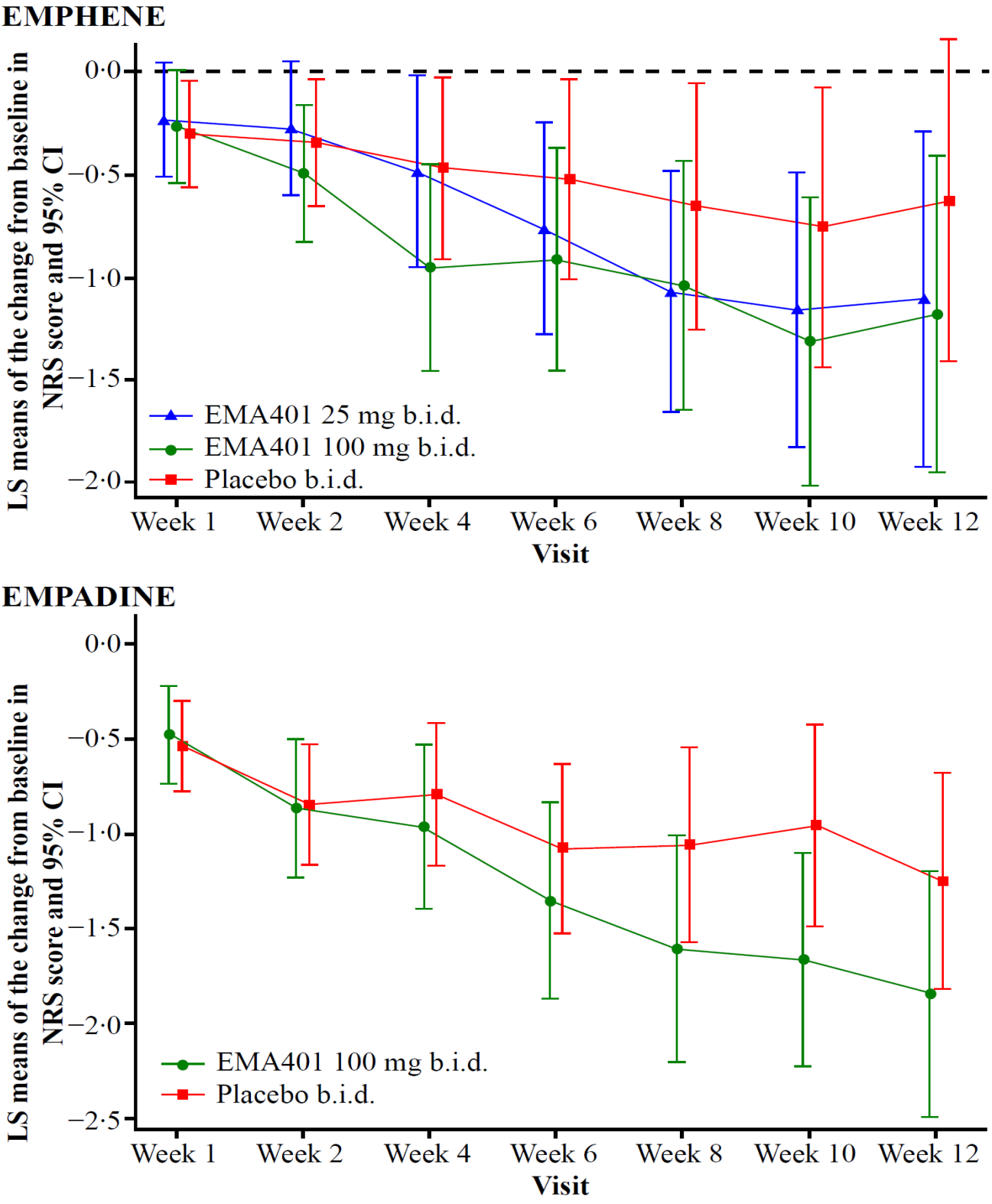
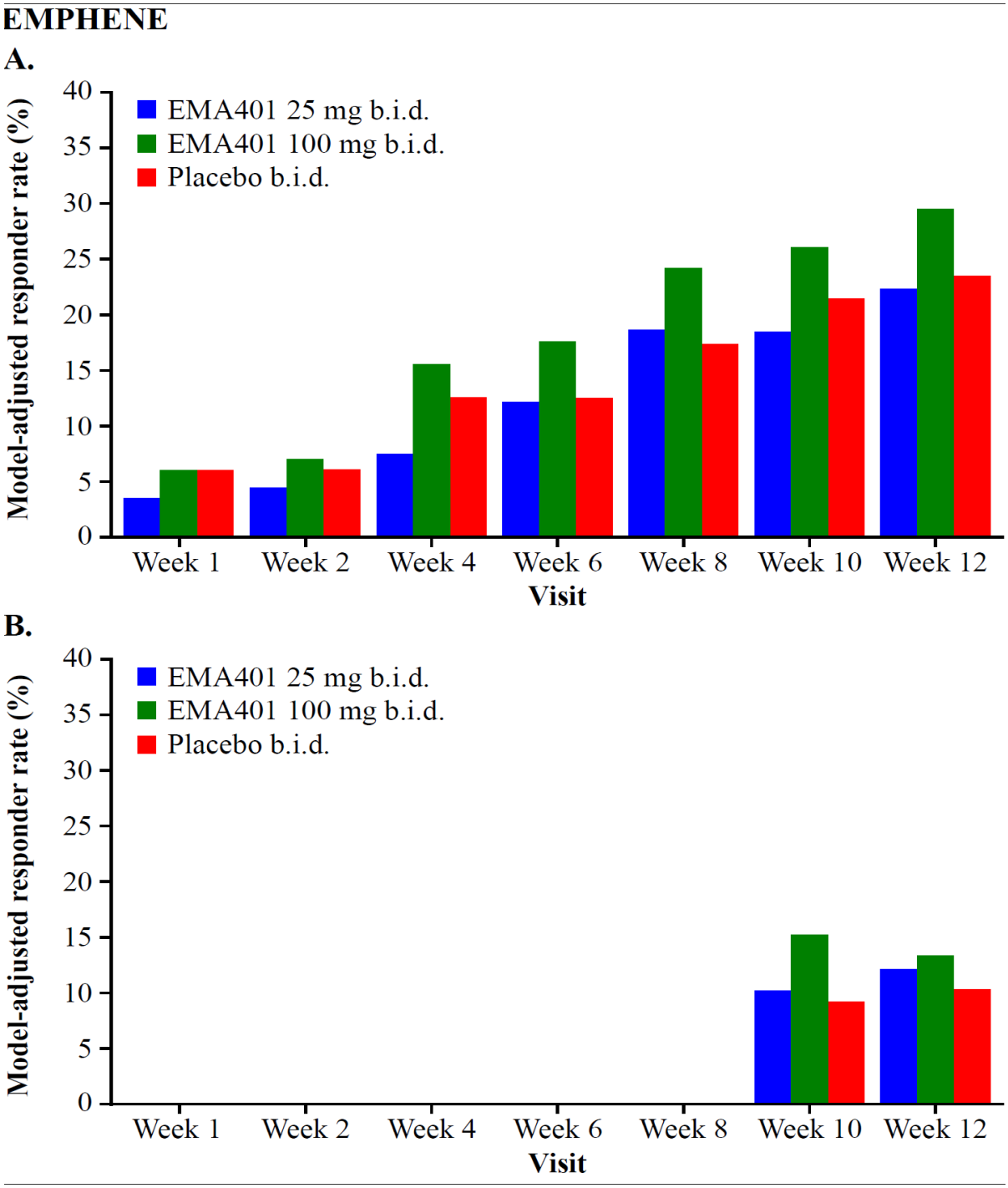
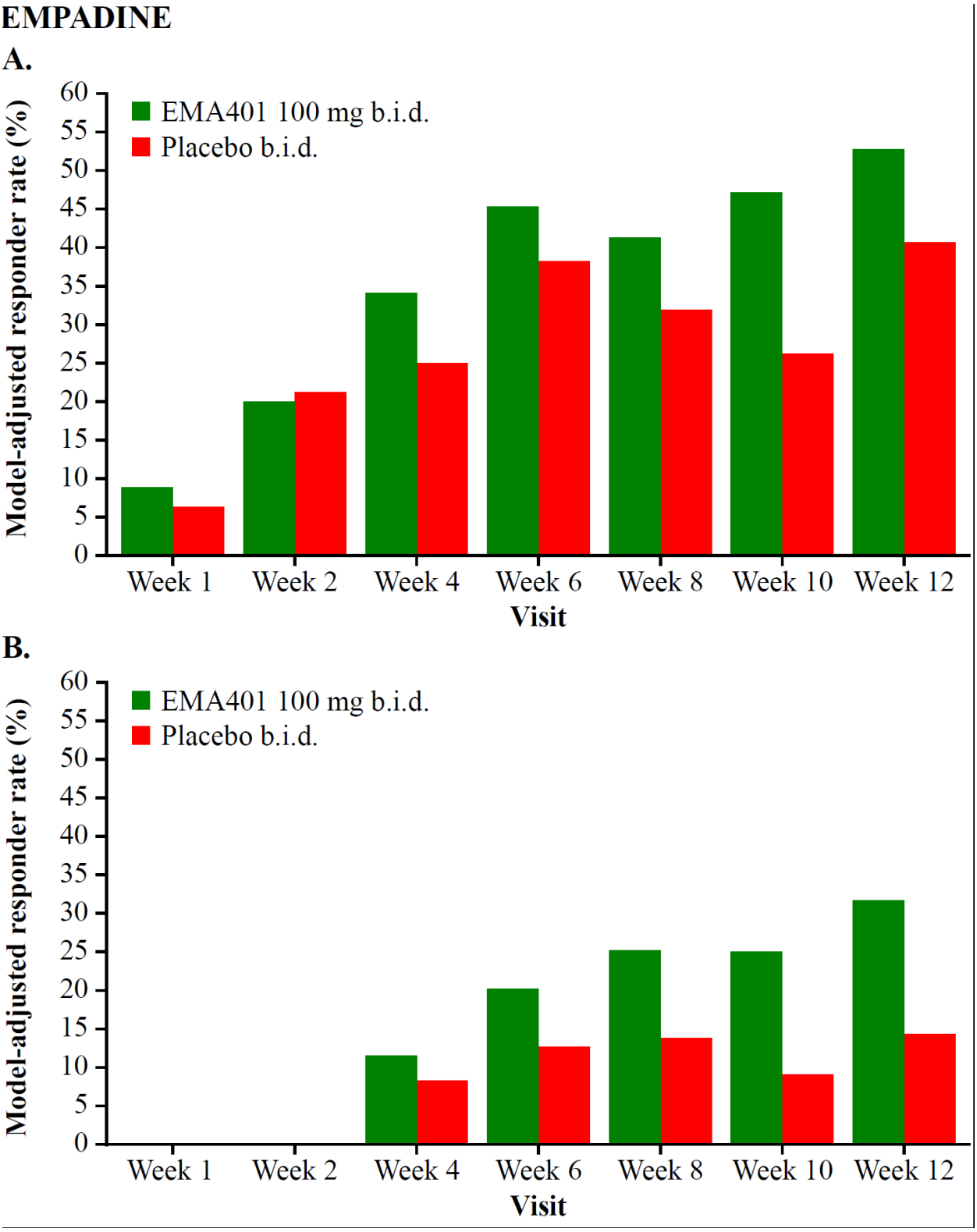


Figure S2: Responder plots

A) Responder rates of participants with at least 30% reduction in the weekly mean of the 24-hour average pain score (NRS) during the double-blind treatment epoch

B) Responder rates of participants with at least 50% reduction in the weekly mean of the 24-hour average pain score (NRS) during the double-blind treatment epoch




EMPADINE
A.
Model-adjusted responder rate (%)
EMA401 100 mg b.i.d.
Placebo b.i.d.
0
5
10
15
20
25
30
35
40
45
50
55
60
Week 1
Week 2
Week 4
Week 6
Week 8
Week 10
Week 12
Visit
B.
Model-adjusted responder rate (%)
EMA401 100 mg b.i.d.
Placebo b.i.d.
0
5
10
15
20
25
30
35
40
45
50
55
60
Week 1
Week 2
Week 4
Week 6
Week 8
Week 10
Week 12
Visit

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