# Vixotrigine (BIIB074; Nav1.7 inhibitor) for Small Fiber Neuropathy and Trigeminal Neuralgia

Patricia Wang, MD
Ruchi Sharma, MD

# Conflicts of Interest Statement

- I have no financial, business or personal Conflicts of interest to disclose.
- The phase 2 clinical trial of Vixotrigine for small fiber neuropathy and phase 3 study design for trigeminal neuralgia being presented, and information provided in the following studies were sponsored by Biogen
- The phase 2a clinical trial of Vixotrigine for trigeminal neuralgia presented, and information provided in the following study was funded by Convergence Pharmaceuticals

# Phase 2 Efficacy and Safety Study of BIIB074 in Participants With Small Fiber Neuropathy

# Role of Vixotrigine/BIIB074 in Small Fiber Neuropathy

- Small fiber neuropathy is a condition characterized by severe pain.
  - Described as burning, shooting, or prickling that typically begins in the feet or hands.
  - Associated with allodynia and hyperalgesia.
- Vixotrigine is a Nav1.7-selective, voltage and use-dependent sodium channel blocker.
  - Acts both centrally and peripherally.
  - Nav1.7 is preferentially expressed in peripheral neurons.
  - Loss of function mutations in Nav1.7 is associated with insensitivity to pain.[3]

# Inclusion Criteria

1. Subjects had a diagnosis of probable SFN
    1. ≥6 months and ≤10 years prior to screening.
    2. Defined as a history of the symptoms and clinical signs.
    3. Confirmed by intraepidermal nerve fiber density (IENFD).
2. Weekly mean average daily pain (ADP) score ≥5 and ≤9 on an PI-NRS
3. Diabetics required:
    1. HbA1c ≤11%
    2. Treated with oral hypoglycemics, subcutaneous insulin or diet.
    3. No evidence of ulcers, advanced retinopathy, severe nephropathy, clinically significant obstructive atherosclerotic disease, or current class IV heart failure.

# Exclusion Criteria

1. Previous exposure to BIIB074.
2. Capsaicin patch use within 3 months prior to Screening.
3. Use of concomitant medications for SFN.
4. Concomitant medication restrictions:
    1. UDP-glucuronosyltransferase (UGT) inducers and inhibitors, monoamine oxidase inhibitors (MAOIs), and Nav blockers.
    2. OTC medications, supplements, herbal remedies, or foods that affect UGTs.
    3. P-glycoprotein substrates with narrow therapeutic index (ie. digoxin).
5. History of hemophilia, Von Willebrand's disease, or use of anticoagulants that increase bleeding risk.
6. Contraindication to performing a skin biopsy for intraepidermal nerve fiber analysis.

# Study Design

- Randomized Double Blind Placebo Control Study.
- 265 Participants, 18 years and older.
- Masking of Participant, Care Provider, Investigator, Outcome Assessor.
- Primary objective to evaluate the efficacy of BIIB074 in treating pain with confirmed SFN (idiopathic or associated with diabetes).
- Secondary objectives was to evaluate the effect of BIIB074 on:
  - Worst pain
  - Neuropathic pain quality
  - Sleep interference
  - Patient global impression
  - Use of rescue medication
  - SFN symptoms
  - Safety and tolerability

# Study Arms

Taper -> Open-Label Run-In Period -> Double-blind Randomization (2 experimental, 1 placebo arm)

- Taper Period: If applicable, taper and washout from neuropathic pain medication.
- Open-Label Run-In Period: patients started on **350 mg** orally twice daily (BID).
- Double-Blind Treatment Period: Patients randomized into one of two possible experimental arms or the placebo arm.
    - Experimental arms:
        - BIIB074 **350 mg** tablets orally BID.
        - BIIB074 **200 mg** tablets orally BID.
    - Placebo Comparator:
        - BIIB074 **placebo-matching tablets** orally BID.
- Primary outcome measure was change in Weekly Mean Average Daily Pain (ADP) Scores.
    - ADP rated using an 11-point Numerical Rating Scale (NRS).
        - Compared between Baseline (prior to 1$^{st}$ dose in open-label period) and Week 12 in double-blind period
        - Randomization time (prior to 1$^{st}$ dose double-blind treatment) and Week 12 in double-blind period

# Outcomes

- Statistical testing comparing each vixotrigine dose with placebo pre-defined at 10% significance level.
  - Without multiplicity adjustment.
- Vixotrigine 200 mg twice daily arm resulted in statistically significant reductions in:
  - Mean average daily pain (ADP) score (p=0.0501).
  - Mean worst daily pain score versus placebo (p=0.0455) at week 12.[2]
- Treatment effect noted in participants with diabetes mellitus based on subgroup analysis but was not evident in smaller subgroup of patients with idiopathic SFN.[2]
- Vixotrigine 350 mg twice daily arm did not meet primary endpoint of mean change in ADP at week 12.
  - Did show statistically significant increase in proportion of participants who reported “very much improved” or “much improved” when compared to baseline.
  - Using the Patient Global Impression of Change (PGIC) questionnaire (p=0.0580).[2]
- Open-label period common AEs (incidence ≥ 2.5%) were dizziness, headache, vertigo, and nausea.
- 5.3% of subjects discontinued the open-label part of the study due to adverse events.[2]

# Phase 2 Safety and Efficacy Trial of a Nav1.7 Selective Sodium Channel Blocker in Patients With Trigeminal Neuralgia

# Role of Vixotrigine in Trigeminal Neuralgia

- Trigeminal neuralgia is an orofacial disorder.
  - Characterized by unilateral recurrent, brief paroxysms of severe pain.
  - In the distribution of one or more branches innervated by the trigeminal nerve.
  - Usually unilateral and triggered by innocuous stimuli.
- Current standard of care for trigeminal neuralgia and the only FDA approved treatment is with voltage gated sodium channel blockers carbamazepine and its analogue oxcarbazepine.
  - Both raise the threshold of excitability, decreasing the increased frequency of neuronal firings thought to cause TN pain.[4]
- Limitations in these treatments include:
  - The necessity for titration.
  - Potential for pharmacological interactions.
  - Association with poor tolerability.
- Unpublished Phase 1 studies suggest that treatment with BIIB074:
  - Associated with lower rates of cognitive impairment (unlike carbamazepine).
  - Could be administered at therapeutic doses without the need for titration.[3]
- Electrophysiological studies shown that BIIB074 preferentially inhibits high frequencies of neuronal firing (such as those expected in trigeminal neuralgia attacks). [3]

# Study Design

- Double-blind, multicenter, placebo-controlled, randomized withdrawal phase 2a trial
- Study locations in 25 secondary care centers.
  - In Denmark, Estonia, France, Germany, Italy, Latvia, Lithuania, Romania, South Africa, Spain, Switzerland, and the UK.
- Patients, clinicians, and assessors were masked to treatment allocation.
- The randomization was stratified by whether or not the patient was taking existing pain medication.
- During double-blind phase, the study had 80% power to demonstrate a significant improvement with BIIB074 over placebo.
  - Using a one-sided test at a 5% level of significance.
- The modified intention-to-treat (mITT) population included all patients randomized into the double-blind phase who received ≥1 dose of double-blind medication.

# Inclusion and Exclusion Criteria

- Patients aged 18–80 years with confirmed trigeminal neuralgia.
  - Criteria for trigeminal neuralgia based on the International Classification of Headache Disorders (ICHD).
- Patients underwent imaging to ensure no secondary cause was present.
- Exclusion criteria included:
  - Any signs of dental causes, autonomic symptoms, or other neuropathic pain.
  - Not using other sodium channel blockers during the study.
  - Patients on medications that could adversely interact with MAO-B inhibitors.
  - QTcF <450 msec in two of three ECGs done at screening.
  - Known non-responders to sodium channel blockers at therapeutic doses.
- Other permitted concomitant medications for treatment of TN had to be stable for ≥3 weeks before the start of treatment and maintained at a stable dose.

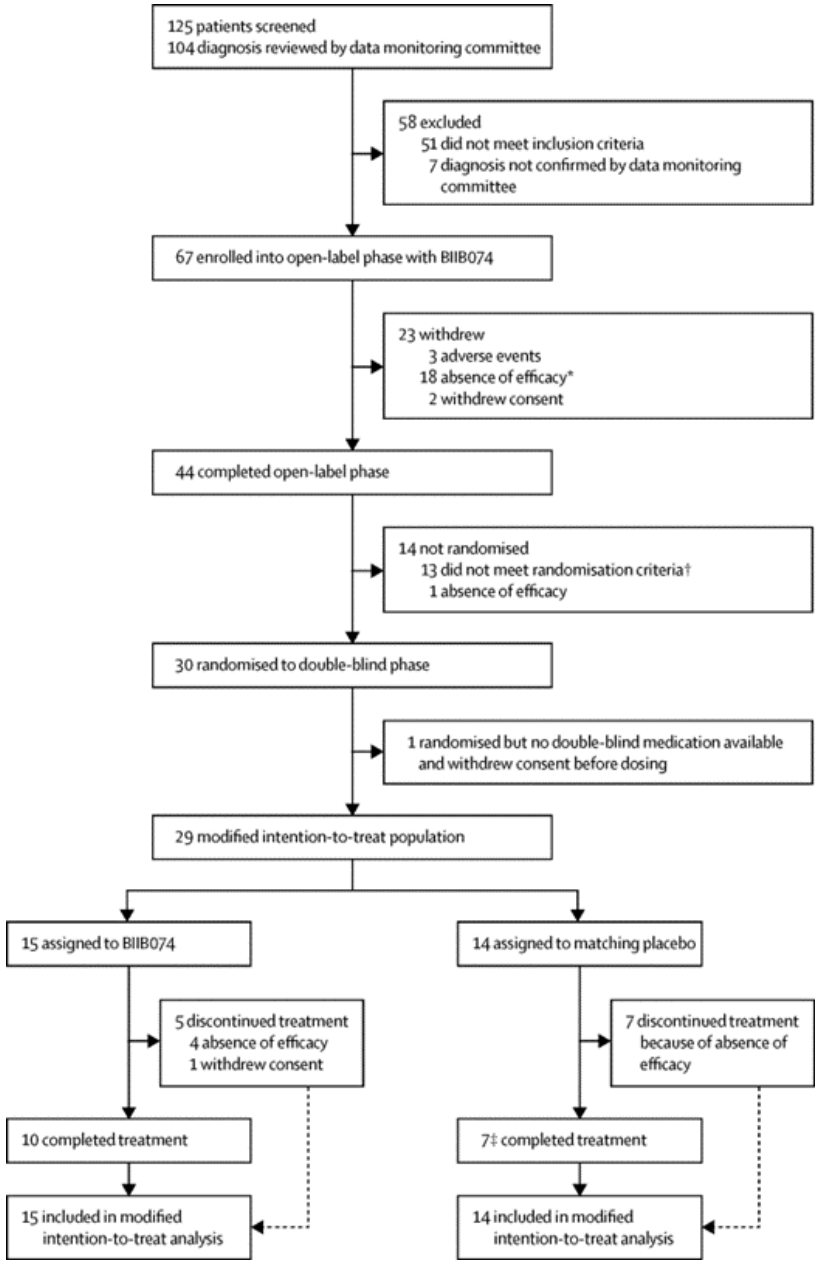
# Study Arms

7 Day Run-In -> Open-Label -> Randomization into Double-Blind (BIIB074 150 mg vs. placebo)

- 7-day run-in phase:
  - Patients recorded the number and severity of paroxysms of pain for eligibility.
    - Must rate each at intensity of ≥4 on a pain intensity numerical rating scale (PI-NRS).
    - On at least 4 days during this period.
  - Completed a washout of prohibited medications.
- Open-label phase patients received oral BIIB074 150 mg three times per day for 21 days.
- On Day 21, response criteria assessed to determine eligibility for double-blind phase.
- Meeting ≥1 of following criteria:
  - A decrease of at least 30% in the number of paroxysms of pain over the last 7 days of open-label compared with the 7-day run-in phase.
  - A reduction of at least 30% in the severity of paroxysms of pain in the same period.
  - A Patient Global Impression of Change (PGIC) rating of much improved or very much improved.
- Patients entering the double-blind phase were randomly assigned (1:1) to BIIB074 150 mg or matching oral placebo TID for up to 28 days.

# Study

- Enrolled 67 patients into the open-label phase.
  - 44 completed open-label treatment.
  - 29 randomly assigned to double-blind treatment (15 to BIIB074 and 14 to placebo).
- Primary endpoint was the difference in number of patients classified as treatment failure between groups during the double-blind phase.
  - Assessed as modified intention-to-treat population.
- During the double-blind phase;
  - Five (33%) patients assigned to BIIB074 versus nine (64%) assigned to placebo were classified as treatment failures (p=0·0974).
  - Patients meeting criteria for treatment failure were withdrawn from treatment.
- Treatment failure during double-blind phase determined on meeting ≥1 of the following criteria:
  - Compared with the final 7 days of open-label treatment.
  - >3 paroxysms in 7 days and either:
    - ≥50% increase in the frequency of paroxysms.
    - ≥50% in the severity of paroxysms.
  - PGIC rating of much worse or very much worse (relative to the end of the open-label phase).
  - Patient discontinued:
    - Because of absence of efficacy (as defined and reported by patient or clinician).
    - An adverse reaction or poor tolerability.

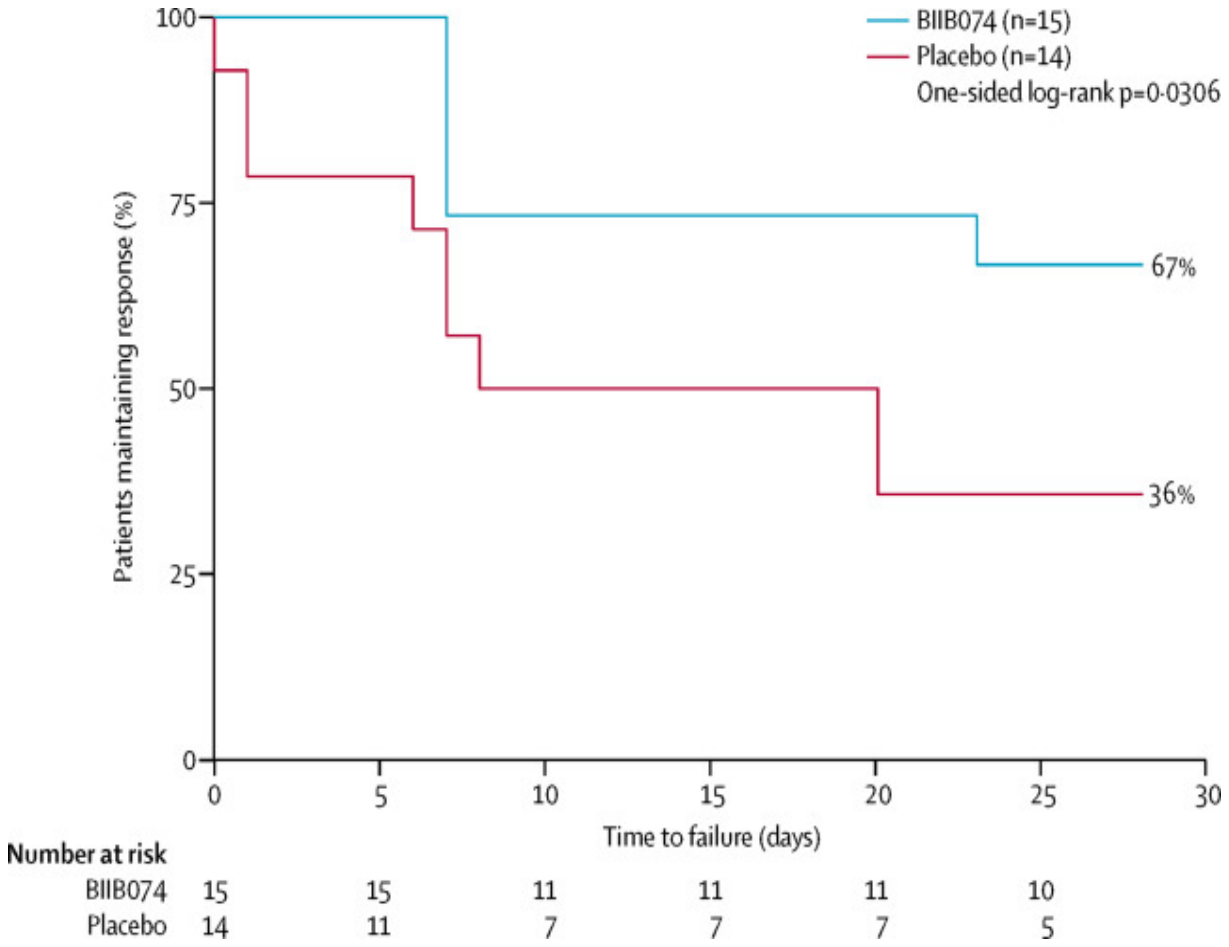


# Outcome Measures

- The number of spontaneous or evoked paroxysms of pain per 24h, and the severity of each paroxysm.
    - Rated on 11-point PI-NRS (0 no pain and 10 maximum pain imaginable).
- Patients rated pain intensity averaged over the last 24h before going to bed.
- Assessments of the change in overall status:
    - Using a 7-point NRS (1 very much improved and 7 very much worse).
        - Patient Global Impression of Change (PGIC) scales from patient.
        - Clinician Global Impression of Change (CGIC) scales from clinician.
    - Done at the end of open-label treatment.
    - At end of double-blind phase, or at premature discontinuation relative to end of open-label phase.
- Patients completed Brief Pain Inventory-Facial (BPI-F)
    - At the start and end of open-label treatment.
    - At the end of double-blind treatment or premature discontinuation.

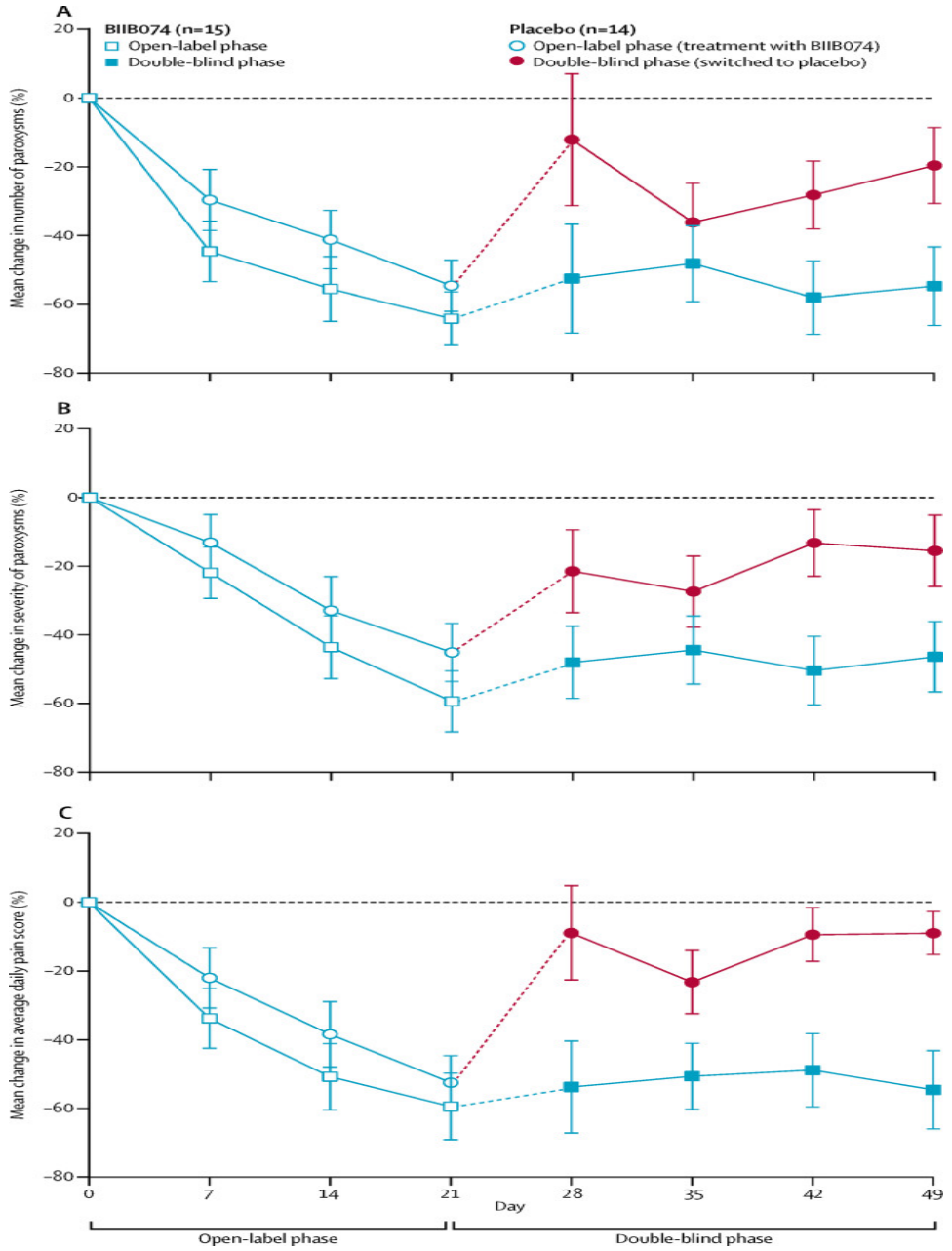
# Study Results: Time to Treatment Failure

- During the double-blind phase:
  - Five (33%) of 15 patients receiving BIIB074 were classified as treatment failures vs. nine (64%) of 14 receiving placebo
  - The difference between groups was not significant (p=0·0974).
- Median time to treatment failure during the double-blind phase was significantly longer with BIIB074 than placebo (p=0·0306).
- For BIIB074, <50% of patients had treatment failure.
  - Thus a median time to failure was not reached (95% CI).
- In the placebo group, the median time to treatment failure was 14 days (95% CI).



# Study Results: Number and Severity of Paroxysms, ADP

- Number of paroxysms was reduced by a mean of 53% from run-in to the end of double-blind treatment in BIIB074 group compared with 21% in placebo group.
  - Placebo-adjusted change −32%.
  - 95% CI −64 to 1.
- Severity of paroxysms reduced by a mean of 2.49 points with BIIB074 compared with 1.13 with placebo.
  - Placebo-adjusted change −1·35
  - 95% CI −3·06 to 0·35.
- Mean reduction in average daily pain score 3.05 in BIIB074 group and 0.74 in the placebo group.
  - Placebo-adjusted change −2.31.
  - 95% CI −3.78 to −0.83.



# Outcomes

- The primary endpoint of treatment failure was not significantly lower in the BIIB074 group than in the placebo group.
- BIIB074 was well tolerated, with similar adverse events (AE) in the double-blind phase to placebo:
  - The most common adverse event with BIIB074 in the open-label phase.
    - Headache in 13 [19%] of 67 patients.
    - Followed by dizziness in six [9%] patients.
  - The most frequent adverse events in patients assigned to BIIB074 in the double-blind phase:
    - Headache, pyrexia, nasopharyngitis, sleep disorder, and tremor.
    - In one [7%] of 15 patients for each event.
  - In patients assigned to placebo:
    - Headache, dizziness, diarrhea, and vomiting were the most frequent adverse events.
    - In one [7%] of 14 patients for each event.
- No severe or serious adverse events were reported in the BIIB074 group during double-blind phase.
- 1 patient assigned to placebo reported intestinal adhesions with obstruction as a serious AE.
  - This was considered unrelated to the study medication.

# Future Avenues

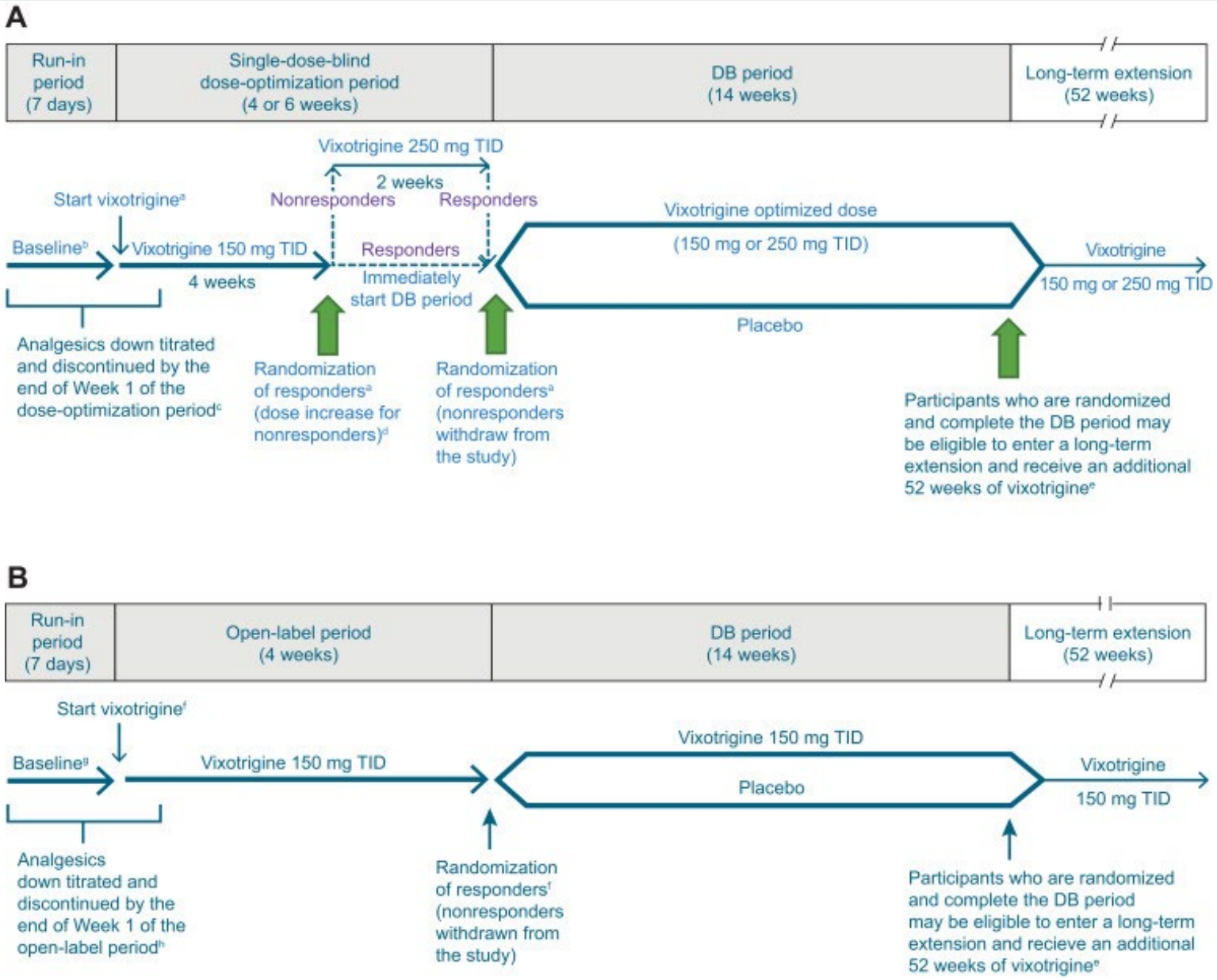
# Design of Phase 3 Studies Evaluating Vixotrigine for Treatment of Trigeminal Neuralgia

# Study Design

- Two double-blind randomized withdrawal studies planned to evaluate the efficacy and safety of vixotrigine compared with placebo in participants with TN.
- Participant criteria include:
  - ≥18 years old.
  - Have classical, purely paroxysmal TN diagnosed ≥3 months prior to study entry.
  - Experience ≥3 paroxysms of pain/day.
- Primary endpoint of both studies is the proportion of participants classified as responders at Week 12 of the double-blind period.
- Secondary endpoints include:
  - Safety measures
  - Quality of life
  - Evaluation of population pharmacokinetics

# Study Arms

- The two studies will include:
  - Screening period
  - 7-day run-in period
  - Dose optimization Period vs. Open label period
  - 14-week double-blind period
- Study A: 4- or 6-week single-dose-blind dose-optimization period.
  - Responders randomized to optimized dose or placebo.
  - Responders are defined as participants with ≥30% reduction in mean pain score from run-in period baseline to the last week of the dose-optimization period.
- Study B: 4-week open label period.
- Participants receive oral vixotrigine 150 mg TID in the dose-optimization and open-label periods.



# Discussion & Questions

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