NOVEL DOSAGE REGIMEN

REFERENCE TO RELATED APPLICATIONS

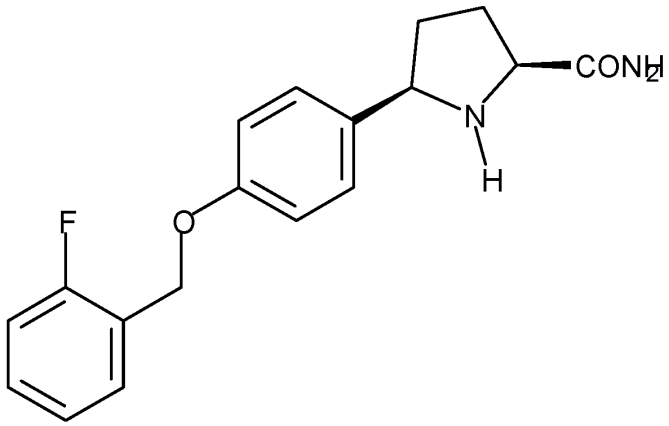
This application claims the benefit of U.S. Provisional Application No. 62/416,392, filed November 2, 2016, and U.S. Provisional Application No. 62/515,836, filed June 6, 2017, the contents of each of which are fully incorporated by reference herein in their entireties.

FIELD OF THE INVENTION

The present invention is directed to a novel method of treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channel subtypes, such as pain, in particular neuropathic pain, most particularly trigeminal neuralgia.

BACKGROUND OF THE INVENTION

The (2S, 5R)-5-(4-((2-fluorobenzyl)oxy)phenyl)pyrrolidine-2-carboxamide, herein referred to as the compound of formula (I):



(I)

is described in WO 2007/042239 as having utility in the treatment of diseases and conditions mediated by state-dependent modulation of Nav1.7 and other voltage-gated sodium channel subtypes.

However, there is a need for the development of improved dosage regimens to optimise the treatment of patients suffering from disorders such as trigeminal neuralgia and to minimise their debilitating symptoms.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channels in a patient in need thereof which comprises administering a therapeutically effective amount of a compound which is (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, characterised in that said compound, or a pharmaceutically acceptable salt thereof, is administered to a subject in need thereof at a dosage of either 150 mg or 250 mg three times per day (t.i.d.), such that said 150 mg dosage is administered only to a patient identified as a responder to treatment with said compound.

According to a second aspect of the invention there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channels in a patient in need thereof which comprises administering a therapeutically effective amount of a compound which is (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, characterised in that said compound, or a pharmaceutically acceptable salt thereof, is administered to a subject in need thereof at a dosage of either 300 mg or 400 mg two times per day (BID).

According to a further aspect of the invention there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 which comprises administering a therapeutically effective amount of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, to a subject in need thereof and avoiding the use or administration of a UGT inducer.

According to a further aspect of the invention there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 which comprises administering a therapeutically effective amount of a (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein the subject is using a UGT inducer.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: PK modelling plots: For all doses, the C_{Trough} is higher than efficacious doses in animal model of inflammation. FCA5 corresponds to an oral dose of 5mg/kg which fully reversed the hyperalgesia in the Freud Complete Adjuvant induced inflammation model. FCA1, an oral dose of 1mg/kg was the minimal effective dose in this model. TGN (trigeminal neuralgia), PLSR (painful lumbosacral radiculopathy).

Figure 2: Design of 300/400 MG BID Dosage study.

Figure 3: Change in Outpatient 24 h SBP (A) and DBP (B) from Baseline to Day 36.

Figure 4: Proportion of Observations with Changes in Outpatient 24 h SBP (A) or DBP (B) on Day 36 Compared to Baseline.

Figure 5: Change in Inpatient 12 h SBP (A) and DBP (B) from Baseline to Day 35.

Figure 6: PK/PD relationships between inpatient ABPM DBP and SBP and BIIB074 observed plasma concentration.

DETAILED DESCRIPTION OF THE INVENTION

According to a first aspect of the invention there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channels in a patient in need thereof which comprises administering a therapeutically effective amount of a compound which is (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, characterised in that said compound or a pharmaceutically acceptable salt thereof, is administered to a subject in need thereof at a dosage of either 200 mg two times per day (BID) or 150 mg or 250 mg three times per day (TID). In one embodiment, the 150 mg dosage is administered only to a patient identified as a responder to treatment with said compound. In one aspect, the compound is administered in the form of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide hydrochloride.

In one embodiment, said compound, or a pharmaceutically acceptable salt thereof, is administered at a dosage of 200 mg two times per day (BID), such as for treating painful lumbosacral radiculopathy (PLSR) in a patient in need thereof. In a further embodiment, the 200 mg BID dosage is administered only to a patient identified as a responder to treatment with said compound. In one aspect, the compound is administered in the form of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide hydrochloride.

In one embodiment, said compound, or a pharmaceutically acceptable salt thereof, is administered at a dosage of 150 mg three times per day (TID). In a further embodiment, the 150 mg dosage is administered only to a patient identified as a responder to treatment with said compound. In one aspect, the compound is administered in the form of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide hydrochloride.

In an alternative embodiment, said compound, or a pharmaceutically acceptable salt thereof, is administered at a dosage of 250 mg three times per day (TID) , such as for treating trigeminal neuralgia (TN) in a patient in need thereof. In one aspect, the compound is administered in the form of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide hydrochloride.

In a further embodiment, said 250 mg dosage is administered to a patient not previously treated with said compound. In an alternative embodiment, said 250 mg dosage is administered to a patient previously administered with a 150 mg dosage of said compound, or a pharmaceutically acceptable salt thereof, and wherein said patient has been identified as a non-responder to treatment with the 150 mg dosage of said compound. In one aspect, the compound is administered in the form of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide hydrochloride.

According to a second aspect of the invention there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channels in a patient in need thereof which comprises administering a therapeutically effective amount of a compound which is (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, characterised in that said compound, or a pharmaceutically acceptable salt thereof, is administered to a subject in need thereof at a dosage of either 300 mg or 400 mg two times per day (BID).

The dosage regimen of this second aspect of the invention provides the significant advantage of demonstrating a lack of clinically relevant change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) following dosage for 36 days (see the results of the study shown in Example 4).

In one embodiment of said second aspect of the invention, said 300mg BID dosage is administered to a female patient. In a further embodiment of said second aspect of the

invention, said 300 mg BID dosage is administered following a dosage of 400 mg BID for an initial period of time (such as approximately 1 week).

In one embodiment of said second aspect of the invention, said 400 mg BID dosage is administered to a male patient.

As used herein, the phrase "is administered to a subject in need thereof at a dosage of" is meant to indicate that the free base form of the compound is delivered in the recited amount. For example, if the free base form of the compound is "administered at a dosage of 150 mg" in tablet form, the tablet would contain 150 mg of the free base of said compound. Furthermore, if the free base form of the compound is "administered at a dosage of 250 mg" in tablet form, the tablet would contain 250 mg of the free base of said compound. Furthermore, if the free base form of the compound is "administered at a dosage of 300 mg" in tablet form, the tablet would contain 300 mg of the free base of said compound. Furthermore, if the free base form of the compound is "administered at a dosage of 400 mg" in tablet form, the tablet would contain 400 mg of the free base of said compound. If the compound in the form of a hydrochloride salt is "administered at a dosage of 150 mg" in tablet form, the tablet would contain 167 mg of the hydrochloride salt of said compound. Furthermore, if the compound in the form of a hydrochloride salt is "administered at a dosage of 200 mg" in tablet form, the tablet would contain 223 mg of the hydrochloride salt of said compound. Furthermore, if the compound in the form of a hydrochloride salt is "administered at a dosage of 250 mg" in tablet form, the tablet would contain 279 mg of the hydrochloride salt of said compound. Furthermore, if the compound in the form of a hydrochloride salt is "administered at a dosage of 300 mg" in tablet form, the tablet would contain 334 mg of the hydrochloride salt of said compound. Furthermore, if the compound in the form of a hydrochloride salt is "administered at a dosage of 400 mg" in tablet form, the tablet would contain 446 mg of the hydrochloride salt of said compound.

According to a further aspect of the invention there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 which comprises administering a therapeutically effective amount of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, to a subject in need thereof and avoiding the use or administration of a UGT inducer.

In one embodiment, the subject is instructed to stop using the UGT inducer before beginning administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the subject is instructed to stop using the UGT inducer at least three weeks before beginning administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof. In a yet further embodiment, the subject is instructed to stop using the UGT inducer at least two weeks before beginning administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof. In a still yet further embodiment, the subject is instructed to stop using the UGT inducer at least one week before beginning administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof.

According to a further aspect of the invention, there is provided a method of treating a disease or condition mediated by modulation of Nav1.7 which comprises administering a therapeutically effective amount of a (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein the subject is using a UGT inducer.

In one embodiment, the subject's dosage of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, is increased at least 30% relative to what it would have been had the subject not been using a UGT inducer. In a further embodiment, the subject's dosage of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, is increased at least 50% relative to what it would have been had the subject not been using a UGT inducer. In a yet further embodiment, the subject's dosage of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, is increased to a dosage of 250 mg TID. In a still yet further embodiment, the subject is instructed to lower the dosage of the UGT inducer before beginning administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof. In a still yet further embodiment, the subject is instructed to lower the dosage of the UGT inducer at least three weeks before beginning administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof. In a still yet further embodiment, the subject is instructed to lower the dosage of the UGT inducer at least two weeks before beginning administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof. In a still yet further embodiment, the subject is instructed to lower the dosage of the UGT inducer at least one week before beginning

administration of (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof.

The phrase “using a UGT inducer” is intended to refer to a subject’s taking a UGT according to a prescribed dosage regimen.

Examples of suitable UGT inducers include but are not limited to: rifampin, ritonavir, ethinyl estradiol, methsuximide, phenytoin, phenobarbital, rifabutin, carbamazepine and oxcarbazepine. In one embodiment, the UGT inducer is carbamazepine.

In one embodiment, said disease or condition is selected from pain. For example said disease or condition may be chronic inflammatory pain (e.g. pain associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis); musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

In a further embodiment, said pain is selected from neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. In a yet further embodiment, said neuropathic pain is selected from: diabetic neuropathy; sciatica; non-specific lower back pain; painful lumbosacral radiculopathy; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; erythromelalgia; small fibre neuropathy; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and

dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

In a yet further embodiment, said neuropathic pain is selected from trigeminal neuralgia, painful lumbosacral radiculopathy, erythromelalgia and small fibre neuropathy.

In a still yet further embodiment, said neuropathic pain is selected from trigeminal neuralgia or painful lumbosacral radiculopathy.

In one embodiment, said disease or condition is inflammatory disorders, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases; lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, non-allergic rhinitis, cough, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. Crohn's disease, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease); other conditions with an inflammatory component such as migraine, multiple sclerosis, myocardial ischemia.

Without wishing to be bound by theory, other diseases or conditions that may be mediated by modulation of Nav1.7 and other voltage-gated sodium channels are selected from the list consisting of [the numbers in brackets after the listed diseases below refer to the classification code in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10)]:

i) Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes

With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90):

ii) Schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

iii) Anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00):

iv) Substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium,

Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9);

Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide:

v) Enhancement of cognition including the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease:

vi) Sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; sleep apnea and jet-lag syndrome:

vii) Eating disorders such as Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; Binge Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50):

viii) Autism Spectrum Disorders including Autistic Disorder (299.00), Asperger's Disorder (299.80), Rett's Disorder (299.80), Childhood Disintegrative Disorder (299.10) and Pervasive Disorder Not Otherwise Specified (299.80, including Atypical Autism).

ix) Attention-Deficit/Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23):

x) Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301,22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301,83), Histrionic Personality Disorder (301.50), Narcissistic Personality Disorder (301,81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9): and

xi) Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9);

gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

xii) Impulse control disorder" including: Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), Impulse-Control Disorders Not Otherwise Specified (312.3), Binge Eating, Compulsive Buying, Compulsive Sexual Behaviour and Compulsive Hoarding.

In another embodiment, diseases or conditions that may be mediated by modulation of Nav1.7 and other voltage-gated sodium channels are depression or mood disorders.

In another embodiment, diseases or conditions that may be mediated by modulation of Nav1.7 and other voltage-gated sodium channels are substance related disorders.

In a further embodiment, diseases or conditions that may be mediated by modulation of Nav1.7 and other voltage-gated sodium channels are Bipolar Disorders (including Bipolar I Disorder, Bipolar II Disorder (i.e. Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) or Bipolar Disorder Not Otherwise Specified (296.80)).

In a still further embodiment, diseases or conditions that may be mediated by modulation of Nav1.7 and other voltage-gated sodium channels are Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) or Nicotine-Related Disorder Not Otherwise Specified (292.9).

In one embodiment, said disease or condition is selected from epilepsy including post-traumatic epilepsy, obsessive compulsive disorders (OCD), sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), ataxias, muscular rigidity (spasticity), and temporomandibular joint dysfunction.

In one embodiment, said disease or condition is selected from bladder hyperrelexia following bladder inflammation.

In one embodiment, said disease or condition is selected from neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, motor neuron disease); The compound may also be useful for the treatment of amyotrophic lateral sclerosis (ALS) and neuroinflamation.

In one embodiment, said disease or condition is selected from neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

In one embodiment, said disease or condition is selected from tinnitus, and as local anaesthetics.

In one embodiment, the compound of the invention, or a pharmaceutically acceptable salt thereof, is administered in combination with one or more therapeutically effective medicaments.

In a further embodiment, the one or more therapeutically effective medicaments comprise analgesics. In a yet further embodiment, said analgesics include for example COX-2 (cyclooxygenase-2) inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib, COX-189 or 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (WO 99/012930); 5-lipoxygenase inhibitors; NSAIDs (non-steroidal anti-inflammatory drugs) such as diclofenac, indomethacin, nabumetone or ibuprofen; bisphosphonates, leukotriene receptor antagonists; DMARDs (disease modifying anti-rheumatic drugs) such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA (N-methyl-D-aspartate) receptor modulators, such as glycine receptor antagonists or memantine; ligands for the α2δ-subunit of voltage gated calcium channels, such as gabapentin, pregabalin and solzira; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; cholinesterase inhibitors such as galantamine; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; 5HT1 agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor modulators, for example modulators of the NR2B subtype; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 agonists and EP_2 agonists; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists;

cannabinoid receptor ligands; bradykinin receptor ligands; vanilloid receptor or Transient Receptor Potential (TRP) ligands; and purinergic receptor ligands, including antagonists at P2X3, P2X2/3, P2X4, P2X7 or P2X4/7; KCNQ/Kv7 channel openers, such as retigabine; additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995, US 5,633,272, US 5,466,823, US 6,310,099 and US 6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO 99/12930, WO 00/26216, WO 00/52008, WO 00/38311, WO 01/58881 and WO 02/18374.

In one embodiment, the present invention is directed to co-therapy, adjunctive therapy or combination therapy, comprising administration of the compound of the invention, or a pharmaceutically acceptable salt thereof, and one or more analgesics (e.g. tramadol or amitriptyline), anticonvulsant drugs (*e.g.* gabapentin, neurontin or pregabalin (*i.e.* Lyrica)) or antidepressant drugs (*e.g.* duloxetine (*i.e.* Cymbalta) or venlafaxine).

In this embodiment, therapeutically effective amount shall mean that amount of the combination of agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of co-therapy comprising administration of the compound of the invention, or a pharmaceutically acceptable salt thereof, and at least one suitable analgesic, anticonvulsant or antidepressant drug would be the amount of the compound of the invention, or a pharmaceutically acceptable salt thereof, and the amount of the suitable analgesic, anticonvulsant or antidepressant drugs that when taken together or sequentially have a combined effect that is therapeutically effective. Further, it will be recognized by one skilled in the art that in the case of co-therapy with a therapeutically effective amount, the amount of the compound of the invention, or a pharmaceutically acceptable salt thereof, and/or the amount of the suitable analgesic, anticonvulsant or antidepressant drugs individually may or may not be therapeutically effective.

As used herein, the terms "co-therapy", “adjunctive therapy” and "combination therapy" shall mean treatment of a subject in need thereof by administering one or more analgesic, anticonvulsant or antidepressant agent(s) and the compound of the invention, or a pharmaceutically acceptable salt thereof, wherein the compound of the invention or a pharmaceutically acceptable salt thereof, and the analgesic, anticonvulsant or antidepressant agent(s) are administered by any suitable means, simultaneously, sequentially, separately or in a single pharmaceutical formulation.

When administration is sequential, either the compound of the invention, or a pharmaceutically acceptable salt thereof, or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

Where the compound of the invention, or a pharmaceutically acceptable salt thereof, and the analgesic, anticonvulsant or antidepressant agent(s) are administered in separate dosage forms, the number of dosages administered per day for each compound may be the same or different. The compound of the invention, or a pharmaceutically acceptable salt thereof, and the analgesic, anticonvulsant or antidepressant agent(s) may be administered via the same or different routes of administration. Examples of suitable methods of administration include, but are not limited to, oral, intravenous (iv), intramuscular (im), subcutaneous (sc), intranasal, transdermal, and rectal. The compound of the invention, or a pharmaceutically acceptable salt thereof, may also be administered directly to the nervous system including, but not limited to, intracerebral, intraventricular, intracerebroventhcular, intrathecal, intracisternal, intraspinal and / or peri-spinal routes of administration by delivery via intracranial or intravertebral needles and / or catheters with or without pump devices. The compound of the invention, or a pharmaceutically acceptable salt thereof, and the analgesic, anticonvulsant or antidepressant agent(s) may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

In one embodiment, the compound of the invention, or a pharmaceutically acceptable salt thereof, is administered orally.

According to a further aspect of the invention, there is provided a compound which is (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, for use in treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channels in a patient in need thereof which comprises administering a therapeutically effective amount of characterised in that said compound, or a pharmaceutically acceptable salt thereof, is administered at a dosage of either 150 mg or

250 mg three times per day (t.i.d.), such that said 150 mg dosage is administered only to a patient identified as a responder to treatment with said compound.

According to a further aspect of the invention, there is provided the use of a compound which is (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channels in a patient in need thereof which comprises administering a therapeutically effective amount of characterised in that said compound, or a pharmaceutically acceptable salt thereof, is administered at a dosage of either 150 mg or 250 mg three times per day (t.i.d.), such that said 150 mg dosage is administered only to a patient identified as a responder to treatment with said compound.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound which is (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide, or a pharmaceutically acceptable salt thereof, for use in treating a disease or condition mediated by modulation of Nav1.7 and other voltage-gated sodium channels in a patient in need thereof which comprises administering a therapeutically effective amount of said compound, or a pharmaceutically acceptable salt thereof, characterised in that said compound, or a pharmaceutically acceptable salt thereof, is administered at a dosage of either 150 mg or 250 mg three times per day (t.i.d.), such that said 150 mg dosage is administered only to a patient identified as a responder to treatment with said compound.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human adult, child or infant, who has been the object of treatment, observation or experiment.

It will be appreciated that references herein to “treatment” extend to prophylaxis, prevention of recurrence and suppression or amelioration of symptoms (whether mild, moderate or severe) as well as the treatment of established conditions.

The term "therapeutically effective amount" as used herein, means that amount of active compound, or a pharmaceutically acceptable salt thereof, or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which

includes alleviation of one or more of the symptoms of the disease or disorder being treated; and / or reduction of the severity of one or more of the symptoms of the disease or disorder being treated.

The compound of the invention, or a pharmaceutically acceptable salt thereof, may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical composition. Thus, in one embodiment, said compound, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition comprising one or more pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s).

The compound the invention may be adminstered in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt of the compound of formula (I) may be, for example, a non-toxic acid addition salt formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. For reviews on suitable pharmaceutical salts see Berge *et al* (1977) J. Pharm Sci. 66, 1-19; P L Gould (1986) International Journal of Pharmaceutics, 33, 201-217; and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497.

In one aspect, the compound is administered in the form of a hydrochloride salt.

The carrier, diluent and/or excipient must be “acceptable” in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

Since the compound of the invention, or a pharmaceutically acceptable salt thereof, described herein is intended for use in pharmaceutical compositions it will readily be

understood that it is preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are given on a weight for weight basis). Impure preparations of the compound may be used for preparing the more pure forms used in the pharmaceutical compositions.

Pharmaceutical compositions containing the compound of the invention, or a pharmaceutically acceptable salt thereof, as the active ingredient can be prepared by intimately mixing the compound, or a pharmaceutically acceptable salt thereof, with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The compound of the invention or a pharmaceutically acceptable salt thereof may be administered in conventional dosage forms prepared by combining the compound of the invention, or a pharmaceutically acceptable salt thereof, with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The compound of the invention or a pharmaceutically acceptable salt thereof may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly, for administration to mammals including humans. In one embodiment, said compound is administered orally.

The compound of the invention or a pharmaceutically acceptable salt thereof which is active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatine, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatine, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile vehicle, water being preferred, or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration. The compound of the invention, or a pharmaceutically acceptable salt thereof, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound of the invention, or a pharmaceutically

acceptable salt thereof, can be dissolved in water for injection and filter-sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound, or a pharmaceutically acceptable salt thereof, is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound, or a pharmaceutically acceptable salt thereof, can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound, or a pharmaceutically acceptable salt thereof.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluoro-chloro-hydro-carbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

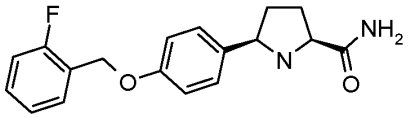
Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter. Compositions suitable for transdermal administration include ointments, gels and patches.

In one embodiment the composition is in unit dose form such as a tablet, capsule or ampoule.

EXAMPLES

The invention is illustrated by the following study described below:

Example 1: (5*R*)-5-(4-{[(2-Fluorophenyl)methyl]oxy}phenyl)-L-prolinamide hydrochloride (E1; also referred to herein as BIIB074, GSK1014802 and CNV1014802)



.HCl

The compound of Example 1 may be prepared as described in Example 2, Procedures 1 to 5 of WO 2007/042239.

EXAMPLE 2: DOSE SELECTION METHODOLOGY

Selection of the 150 and 250mg TID dose of the present invention was based on three different criteria: efficacy in preclinical models of pain, comparison with the 350mg BID dose which demonstrated clinical benefit in a painful lumbosacral radiculopathy Phase 2 study, and comparison with efficacious doses of marketed drugs in trigeminal neuralgia, using an *in vitro* assay to quantify activity at the primary target hNav1.7.

At steady state, the C_{Trough} exposure of Example 1 at the low dose of 150 mg TID and the high dose of 250mg TID (1099 ng/ml and 1750 ng/ml, respectively) is higher than the human scaled equivalent total plasma exposure of 786 ng/ml where a robust efficacy was observed in a rat model of inflammation (see Figure 1). In this model, inflammation was induced by intraplantar injection of Freud Complete Adjuvant.

Mechanical hypersensitivity was then assessed using weight bearing. The oral dose of 1mg/kg was identified as the minimal effective dose and 5mg/kg fully reversed the mechanical hypersensitivity.

From the PK modelling plots, the C_{Max} for 250mg TID was equivalent to that of another dose, 350mg BID (Table 1), which has demonstrated clinical benefit in a Phase 2 study in patients with lumbosacral radiculopathy (A novel proof of concept, randomized, double blind, cross-over study, demonstrating the safety and efficacy of CNV1014802 in subjects

with neuropathic pain from lumbosacral radiculopathy, American Pain Society meeting, Palm Springs, 2015).

Table 1

Comparison of activity of clinical anticonvulsants and Example 1 at several doses: The levels of inhibition (% inhibition) are extracted form the Example 1 dose-response plots at mid point inactivation for each Nav subtype. The exposures for Example 1 are extracted from dose modelling plots and the exposures / doses for marketed anticonvulsants have been found in various sources of literature below.

Cmax	Free fraction	Free plasma (μM)	Human Nav1.7 % Inhibition
[1, 2]Carbamazepine (TGN) 200mg qid (4-12μg/ml total plasma) EFFICACY OBSERVED	24%	4-12	11-38
Example 1 350mg bid (3.74 μg/ml total plasma) EFFICACY OBSERVED in PLSR	3.2%	0.37	**38**
Example 1 200mg bid (2.8 μg/ml total plasma) EFFICACY EXPECTED in PLSR	3.6%	0.29	**40**
Example 1 250mg tid (3.43μg/ml total plasma) EFFICACY EXPECTED in TN	3.2%	0.36	**38**
Example 1 150mg tid (2.06 μg/ml total plasma)	3.2%	0.21	**31**

EFFICACY OBSERVED in TN			
[3, 4] Lamotrigine (TN) 200mg bid (3.4µg/ml total plasma) NO EFFICACY OBSERVED	44%	5.8	6

[1]Wiffen *et al* (2014) Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews*, Issue 4.
[2] Prescribing information Carbamazepine, https://www.pharma.us.novartis.com/product/pi/pdf/tegretol.pdf, Sept 2015
[3] Wiffen *et al* (2013) Lamotrigine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews*, Issue 12.
[4] Rambeck B and Wolf P. (1993) Lamotrigine clinical pharmacokinetics. Clinical Pharmacokinetics, 25(6):433-43.

The C_{Trough} for 250mg TID is higher than that of the 350mg BID which is another reason for selection of this dose.

In Table 1, free plasma C_{Max} exposures of Example 1 obtained from modelling different dosing regimens were used to quantify the resulting amount of block at the primary target hNaV1.7. In the assay chosen for comparison purposes, at the doses of 250 mg TID, 350mg TID and 150 mg TID, the inhibitions at NaV1.7 are 38, 38% and 31%, respectively. Doses of marketed drugs used in trigeminal neuralgia were compared using the same paradigm. The amount of inhibition of hNaV1.7 obtained with Example 1 is in the range of activity obtained with the best exposures of carbamazepine used at 200 mg QID (11 to 38% inhibition), and much higher than exposures obtained with lamotrigine used at 200 mg bid (6% inhibition), which shows little or no efficacy in trigeminal, providing confidence on favourable outcome on efficacy.

The convergence of preclinical and clinical evidence on Example 1 provided the rationale to select the new dose of 250 mg TID for trigeminal neuralgia.

Example 3: 150 MG TID DOSAGE STUDY

A clinical trial was conducted to evaluate certain pharmacokinetic parameters of the compound of Example 1 when dosed at 150 mg TID for seven days. 15 young males and females aged 18 to 45 were scheduled to received ether the compound of Example 1 at 150 mg TID during a first period of 8 days followed by placebo during a second period of 8

days; or placebo during the first period and the compound of Example 1 during the second period.

The subjects were exhibited the following pharmacokinetic parameters on day 8 of the period during which they received the compound of Example 1: AUC_{0-8} (h•ng/mL) = 15319 (20.6); C_{max} (ng/mL) = 2711 (21.0); C_{min} = 1313 (25.7).

EXAMPLE 4: 300/400 MG BID DOSAGE STUDY

This study reports the results of a Phase 1, randomized cross-over trial designed to assess inpatient and outpatient ambulatory blood pressure monitoring (ABPM) in healthy volunteers treated with the compound of Example 1 (BIIB074) for 36 days.

Methods

Study design

This was a Phase 1, randomized, double-blind, placebo-controlled, repeat dose, 2-period cross-over study to investigate the effect of BIIB074 300-400 mg bid on ambulatory blood pressure (ABP) in healthy participants (**Figure 2**). The study comprised: screening (to occur a maximum of 30 days before the first baseline assessment); two 36-day treatment periods, each preceded by a baseline visit and separated by a 7-day washout (to minimize possible carry over effects); and a follow-up period of 7–14 days after last dose. Prior to this study, no females had received BIIB074; for this reason, a single dose BIIB074 session at the dose level of 400 mg was also conducted in female participants one week prior to the period 1 baseline visit. Following this session, some participants were predicted to exceed the predefined PK limit (area under the plasma concentration-time curve [AUC] 97 µg.h/mL) when receiving 400 mg bid at steady state. Therefore, in the subsequent phases of the study, all female participants received a lower dose of 300 mg bid (males received 400 mg bid).

The study was conducted at one clinical site (Buffalo Clinical Research Center) in the United States. All participants provided written informed consent. The study protocol, participant information and informed consent forms were reviewed and approved by relevant independent ethics committees or institutional review boards, and the study was conducted in accordance with the International Conference on Harmonization principles of Good Clinical Practice and principles of the Declaration of Helsinki.

Study population

Eligible participants were healthy males or females between the ages of 18–65 years. The following additional criteria applied for eligibility: body weight ≥50 kg; body mass index (BMI) within the range 19–40.0 kg/m^2; no significant abnormalities on clinical examination, clinical chemistry, or hematology parameters; non-child bearing potential or willing to use agreed methods of contraception.

Volunteers had to abstain from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives, whichever was longer, prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the investigator and sponsor the medication would not interfere with the study.

Randomization and masking

Participants were assigned to treatment sequences in accordance with a randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated software. Study treatment was BIIB074 400 mg bid for males/300 mg bid for females, or placebo, for 36 days. Prior to dosing, volunteers were randomized into one of the following treatment sequences, BIIB074 (period 1):placebo (period 2) or placebo (period 1):BIIB074 (period 2), and more specifically AB and BA if male and CAB and CBA if female, where A = placebo, B = BIIB074 400 mg bid in males and 300 mg bid in females, C = BIIB074 400 mg single dose in females. Randomization numbers were assigned by the site ensuring there was a balance of sequences (AB/BA and CAB/CBA) in each group. Periods 1 and 2 were double-masked to patients and study personnel.

Study medication

BIIB074 was supplied as film-coated, brownish yellow, oblong, biconvex tablets in two strengths: 150 mg and 200 mg. Placebo tablets visually matched the active tablets. All tablets were taken orally with 240 mL of water.

Outcomes

The primary endpoint was change in 24 h average SBP and DBP from baseline to day 36 as determined by ABPM. Secondary outcome measures included: change in 24 h average SBP and DBP from baseline to days 4 and 15; change in average SBP and DBP within a 12 h dosing interval from baseline to days 14 and 35 (inpatient); change in 24 h average ambulatory heart rate from baseline to days 4, 15 and 36; proportion of participants whose

24 h SBP and DBP increased by <5, 5–9, 10–14, 15–19, and >20 mm Hg compared with baseline; PK parameters of BIIB074 following a single oral dose in healthy female participants, and following repeated oral doses given twice daily to healthy male and female participants; PK/pharmacodynamic (PD) analyses to examine the correlation between ABP and plasma levels and/or metrics of the systemic exposure of BIIB074.

ABP was collected over 24 hours on an outpatient basis at baseline and at days 4, 15 and 36, and over 12 hours on an inpatient basis at baseline, and at days 14 and 35. The ABPM device was placed on the non-dominant arm (except in clinical situations that prohibited measuring BP in the non-dominant arm). BP and heart rate were measured every 15 minutes.

Safety was assessed through monitoring of adverse events (AEs), vital signs, electrocardiogram (ECG), and laboratory safety tests (including clinical chemistry).

Statistical analysis

Non-inferiority was based on the one-sided 95% confidence interval (CI) for BIIB074-placebo excluding an effect of ≥5 mmHg in SBP or DBP. It was planned to recruit approximately 60 participants in order to obtain a minimum of 48 evaluable for ABPM during the repeat dose phase, for at least 90% power, assuming a within-subject standard deviation (SDw) of 8.21 mmHg.

ABPM data were analyzed using a repeated measures mixed effects model, whereby fixed effects were treatment, day, treatment*day, period, average baseline*day, period adjusted baseline*day, sex and treatment*sex; random effect was subject; and repeated effect was day. All summary statistics were carried out using SAS 8.02 for UNIX running under the Harmonisation of Analysis and Reporting Program (HARP) environment. PK parameters were calculated by standard non-compartmental analysis according to working practices and using Win Nonlin Pro v. 5.2.

The safety population was the primary analysis population for this study and included all participants who received one or more doses of BIIB074. The PK population was defined as participants in the safety population for whom a PK sample was obtained and analysed.

Results

The first participant was enrolled in the study on July 13, 2009 and the last participant completed on December 21, 2009. Overall, 60 participants were enrolled, of whom 10 withdrew prematurely (7 due to an AE, 2 at the investigator's discretion, and 1 withdrew consent).

The mean age of the overall population (n=60) was 34.3 years and 40% were female. Participants' baseline demographics are summarized in **Table 2**. Mean duration of treatment with BIIB074 (300-400 mg bid repeat dosing) was 35.4 days, and mean dose of BIIB074 was 361.1 mg. Mean duration of treatment with placebo was 34.4 days.

Table 2

Baseline demographics

	All participants		
Demographics	N=60		
Age in years, mean (SD)	34.3 (11.63)		
Sex, n (%)			
Female	24 (40)		
Male	36 (60)		
BMI in kg/m^2, mean (SD)	27.07 (4.009)		
Height in cm, mean (SD)	169.9 (9.23)		
Weight in kg, mean (SD)	78.35 (13.679)		
Baseline vital signs at Day 1, predose*	Placebo N=54	BIIB074 300-400 mg repeat dose N=54	BIIB074 400 mg single dose N=22
SBP in mmHg, mean (SD)	116.9 (11.78)	117.1 (11.03)	114.8 (10.66)
DBP in mmHg, mean (SD)	78.6 (7.77)	77.5 (7.85)	78.5 (4.56)
Heart rate in beats/min, mean (SD)	79.5 (13.00)	78.3 (12.20)	81.9 (12.50)

N, number of participants; BMI, body mass index; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Vital signs were recorded on Day 1 of each treatment period, predose time and standing position. Data should be interpreted with caution given the cross-over design and potential for carryover between treatment periods despite washouts.

Ambulatory blood pressure monitoring

No participant had changes of BP or heart rate meeting the flagging criteria defined in the protocol or that were considered clinically significant by the investigator.

Outpatient ABPM

Changes from baseline in hourly BPs over 24 hours at the end of the 36 day period are shown in **Figure 3**. These data demonstrate that BIIB074 had similar effects on 24 h BP to placebo.

In addition to assessment of the mean changes from baseline in 24 h BP, it is relevant to study the range of individual changes on drug versus placebo to determine if there may be a small percentage of substantial outliers. Examination of change from baseline in outpatient 24 h SBP and DBP revealed a normal distribution (**Figure 4**), with the majority of SBP and DBP measurements at day 36 within 0–10 mmHg of their associated time-matched baseline for both treatments. There was no evidence to suggest a significant increase in SBP or DBP for BIIB074.

Additionally, a clinically relevant effect was considered to be >20% of participants on BIIB074 having an average 24 h increase from baseline in SBP >30 mmHg or DBP >20 mmHg versus placebo. 4/1249 observations (0%) fell in the category SBP >30 mmHg at day 36 for BIIB074 (versus 4/1072 observations [0%] for placebo) (**Figure 4**). Also, 35/1249 observations (3%) fell in the category DBP >20 mmHg at day 36 for BIIB074 (versus 19/1072 observations [2%] for placebo) (**Figure 4**).

Summaries and mixed model repeated measures outputs of the analyses of outpatient 24 h SBP and DBP on days 4, 15 and 36, over 24 h are provided in **Table 3**. Mean change in average SBP from baseline to day 36 was -0.327. Non-inferiority of BIIB074 compared to placebo was demonstrated for outpatient 24 h SBP and DBP since the one-sided 95% CI for BIIB074-placebo excluded an effect ≥5 mmHg. In fact, due to very low within-subject variability observed in these normal healthy participants (SDw=3.8 mmHg for SBP and

SDw=2.9 mmHg for DBP), the power of the study was larger than planned and a smaller effect size than 5 mmHg could be ruled out. The upper bound of the one-sided 95% CI also was <2 mmHg for the majority of SBP and DBP comparisons on days 4, 15, and 36 with the exception of SBP on day 4 (~2.2 mmHg).

Table 3

Summary of the Analysis of Change in 24 h Average SBP and DBP from Baseline to Days 4, 15 and 36 (Outpatient)

Parameter	Visit (Day)	LS Mean BIIB074 300-400mg	LS Mean Placebo	BIIB074-Placebo	90% CI for Difference*
SBP (mmHg)	4	2.372	1.366	1.006	(-0.226, 2.238)
	15	0.915	0.621	0.294	(-0.929, 1.516)
	36	-0.327	0.180	-0.507	(-1.755, 0.741)
DBP (mmHg)	4	1.856	1.066	0.789	(-0.258, 1.837)
	15	0.907	0.262	0.645	(-0.395, 1.685)
	36	0.201	-0.086	0.287	(-0.776, 1.350)

LS, least square; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

*Two-sided 90% CI equates to a one-sided 95% CI.

To further explore the potential occurrence of clinically relevant changes in BP, the proportions of participants whose BP increased by more than 10 mmHg from baseline and who had a resultant absolute value >130 mmHg for SBP or >80 mmHg for DBP were calculated. On day 36, 6.0% of BP values on placebo and 5.0% of observations on BIIB074 fell into this category for SBP, while 6.3% of observations on placebo and 6.9% of observations on BIIB074 fell into this category for DBP (**Table 4**).

Table 4

Proportion of Observations with Changes in SBP >10mmHg that Caused Shift into Hypertensive Range (SBP >130mmHg and DBP >80mmHg) over 24 h for Days 4, 15 and 36 (Outpatient)

Visit (Day)		Placebo (N=54)	BIIB074 300-400mg repeat dose (N=54)
4	n	1197	1294
	SBP: Change >10 and absolute value >130mmHg	92 (7.7%)	116 (9.0%)
	DBP: Change >10 and absolute value >80mmHg	103 (8.6%)	137 (10.6%)
15	n	1199	1322
	SBP: Change >10 and absolute value >130mmHg	72 (6.0%)	95 (7.2%)
	DBP: Change >10 and absolute value >80mmHg	77 (6.4%)	109 (8.3%)
36	n	1072	1249
	SBP: Change >10 and absolute value >130mmHg	64 (6.0%)	63 (5.0%)
	DBP: Change >10 and absolute value >80mmHg	67 (6.3%)	86 (6.9%)

N, number of participants; n, number of observations; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Inpatient ABPM

Analysis of the inpatient 12 h ABPM showed very similar findings to the ABPM data captured over 24 hours as an outpatient (**Figure 5**). There were no significant differences between BIIB074 and placebo after 36 days of therapy. Similar to the outpatient ABPM results, the majority of inpatient 12 h SBP and DBP measurements at day 35 were within 0–10 mmHg of their associated time-matched baseline for both treatments. No observations showed an increase of ≥30 mmHg for SBP and only a few observations showed an increase of ≥20 mmHg for DBP.

In contrast to the outpatient ABPM readings, the inpatient ABPM measurements demonstrated a slight increase in change from baseline (2.0–2.5 mmHg/bpm) at days 14 and 35 for SBP, DBP, and heart rate; however, this was not considered clinically meaningful and non-inferiority of BIIB074 compared with placebo was demonstrated, since the one-sided 95% CI for the difference BIIB074-placebo excluded an effect ≥5 mmHg.

Safety

The most common AEs during BIIB074 treatment were nervous system disorders such as headache and dizziness, followed by nasopharyngitis, nausea and vomiting. The rate of AEs was generally very similar to placebo, particularly for the most common AE of headache (n=11 [20%] for BIIB074 300-400 mg bid repeat dose versus n=10 [19%] for placebo). The majority of AEs associated with BIIB074 300-400 mg bid repeat dose were mild in nature, apart from 9 AEs of moderate intensity (headache, dizziness, 2 x oropharyngeal pain, nasal congestion, ulcer hemorrhage [verbatim: “hemorrhagic ulcerations on lips”], neck pain, eye pain, abnormal liver function test) and 2 AEs of severe intensity (headache, oral disorder [verbatim: “oral lesions”]). All AEs associated with BIIB074 400 mg single dose in females were mild in nature. **Table 6** summarizes AEs that occurred in ≥2 participants in any treatment group.

Out of the ten (17%) participants who were withdrawn from the study, 7 (12%) were due to AEs (2 were on placebo and 5 on BIIB074 at the time of withdrawal). For 1 participant on placebo, the AE started prior to dosing. One of the withdrawals was due to erythema multiforme (with hemorrhagic mouth ulcers) in a participant who had received BIIB074. No serious AEs were reported in this study. There were no clinically significant ECG changes in either treatment group, and the majority of ECGs from day 1–35 were normal. There were no changes in clinical laboratory values that were considered to be of clinical importance.

Table 6

Adverse events occurring in ≥2 participants in any treatment group

Preferred Term	Placebo N=54	BIIB074 300-400 mg bid repeat dosing N=54	BIIB074 400 mg single dose N=22
	n (%)	n (%)	n (%)
Participants with any AE	26 (48)	25 (46)	12 (55)
Headache	10 (19)	11 (20)	6 (27)
Dizziness	3 (6)	6 (11)	5 (23)
Nausea	2 (4)	4 (7)	3 (14)
Vomiting	2 (4)	3 (6)	1 (5)
Diarrhoea	3 (6)	1 (2)	0
Nasopharyngitis	5 (9)	6 (11)	0
Oropharyngeal pain	1 (2)	2 (4)	0
Pyrexia	1 (2)	2 (4)	0
Fatigue	0	2 (4)	0
Pain in extremity	2 (4)	0	0
Rash	3 (6)	1 (2)	0
Hypersensitivity*	0	2 (4)	0

AE, adverse event; bid, twice daily. *Verbatim text: allergy symptoms.

Pharmacokinetics

Following single dose administration to female participants, BIIB074 was characterized by rapid and extensive absorption (plasma concentrations were measurable in all female participants between 0.5 and 24 h). Peak levels were achieved within 1.5 h post-dosing and, afterwards, plasma levels declined with a median terminal half-life ($t_{1/2}$) of ~9 h (**Table 7**). AUC over the 24 h dosing interval [$AUC_{(0-24)}$] were characterized by a small between-subject variability (coefficient of variation between subjects [CV%] 20–25%). $AUC_{(0-24)}$ in males receiving BIIB074 repeat dose at a dose level of 400 mg bid was on average 10% higher than in females receiving the same compound at a dose level of 300 mg bid, on

days 14 and 35. In the same conditions, maximum observed concentration (C_{max}) in males was on average 11–19% higher than in females. Following repeat dosing (days 14 and 35), dose-normalized AUC and C_{max} were, on average, 17–18% and 11–17% lower in male than in female participants (**Table 7**), likely due to a dependency of BIIB074 exposure on body size.

Table 7

BIIB074 Pharmacokinetic Parameters

PK Parameter*	Single Dose (400 mg)	Repeat dose (females: 300 mg bid; males: 400 mg bid)					
		Day 1		Day 14		Day 35	
	Female (N=22)	Female (N=21)	Male (N=33)	Female (N=21)	Male (N=33)	Female (N=21)	Male (N=33)
$AUC_{(0-12)}$ (ng.h/mL)*	24200 (20.9)	16200 (20.4)	19100 (19.9)	29200 (24.7)	32100 (23.5)	27400 (23.4)	30100 (21.8)
$AUC_{(0-24)}$ (ng.h/mL)*	48300 (20.9)	32400 (20.4)	38300 (19.9)	58300 (24.7)	64100 (23.5)	54800 (23.4)	60100 (21.8)
C_{max} (ng/mL)*	3780 (20.4)	2570 (22.2)	3210 (22.1)	4030 (21.2)	4790 (24.1)	3990 (26.6)	4410 (21.6)
t_{max} (h)†	1.50 (0.50, 3.0)	1.50 (0.50, 3.0)	1.00 (0.50, 3.0)	1.50 (1.00, 3.0)	1.00 (0.50, 2.5)	1.00 (0.50, 2.5)	1.00 (0.50, 3.0)
C_{12h} (ng/mL)*	ND	746 (20.8)	889 (23.6)	1440 (29.9)	1590 (28.3)	1310 (24.0)	1460 (26.4)
$AUC_{(0-t)}$ (ng.h/mL)*	32800 (21.9)	ND	ND	ND	ND	ND	ND
$AUC_{(0-\infty)}$ (ng.h/mL)*	38700 (24.1)	ND	ND	ND	ND	ND	ND
AUC_{ex} (%)†	15.2 (8.70, 26.6)	ND	ND	ND	ND	ND	ND
$t_{1/2}$ (h)	8.91 (13.7)	ND	ND	ND	ND	ND	ND

PK/PD analyses of ABPM inpatient data (for which observed plasma concentrations were available) indicated a statistically significant but minimal linear increase of DBP and SBP with increasing BIIB074 observed plasma concentrations (**Figure 6**). The slopes of the linear relationships were small (approximately 0.00077±0.00012 and 0.00056±0.00013 mmHg/(ng/mL)), indicating, on average, an increase of DBP and SBP of less than 3 and 2 mmHg, respectively, over the 24 h interval.

Discussion

Based on the overall results of this study, it was concluded that outpatient and inpatient ABPM were consistent in demonstrating a lack of clinically relevant change in SBP and DBP following repeat doses of BIIB074 for 36 days. Non-inferiority was demonstrated since the 2-sided 90% CI (1-sided 95% CI) for BIIB074-placebo excluded an effect of 5 mmHg for outpatient and inpatient systolic and diastolic BP. PK/PD analyses of ABPM inpatient data indicated a small increase of DBP and SBP with increasing BIIB074 observed plasma concentrations. However, this analysis suggested that the increase was lower than 3 and 2 mmHg for DBP and SBP, respectively, and was not considered clinically relevant.

BIIB074 was well tolerated in this study, with most AEs mild to moderate. The most common AEs during BIIB074 treatment were headache and dizziness, occurring with a rate similar to placebo. AEs were also consistent with earlier Phase 1 studies (single and multiple ascending dose) in healthy male volunteers (Data on File), and Phase 2 studies in TN (Tate *et al.* (2015) American Pain Society - 34th Annual Scientific Meeting. **16**(4): S72[386]) and PLSR (Tate *et al.* (2015) American Pain Society - 34th Annual Scientific Meeting. **16**(4): S72[387]). One participant reported skin rash of erythema multiforme, which was considered to be related to BIIB074. Because allergic skin reactions have been observed with other sodium channel blockers (e.g., lamotrigine), future studies will continue to closely monitor for occurrence of serious rash.

Ambulatory BP monitoring is a more robust means than clinic measurements to evaluate destabilization of BP values on a non-cardiac drug (White *et al.* (2002) Hypertension **39**(4): 929-934). The use of ABPM in this study has the advantage of providing BP readings when subjects are in their own environment (outpatient), which is regarded in the field as more representative of change as opposed to a clinic setting. Additional benefits of ABPM include: 1) non-invasiveness for the

monitored subjects; 2) superior reliability (over 24 h) compared with a one-off measurement; 3) higher value (more accurate) in the overall assessment of cardiovascular risk and severity of hypertension (Mancia and Verdecchia (2015) Circulation Research **116**(6): 1034-1045). Hence, it is believed that the results seen in the 54 participants who completed this trial outweigh those from the earlier Phase 1 studies that indicated possible BP effects (data not shown).

The 36 day treatment duration in this study was rationally designed to determine whether tolerance developed for any potential effects of BIIB074 on SBP or DBP, since BP effects resolved by day 28 in the earlier phase 1 trial. The data from this study show a slight trend towards a decrease in the BP difference between BIIB074 and placebo between day 4 and day 35, although differences were minimal at all time points. An additional point of note is that, in preclinical safety/pharmacology studies, there were no effects of BIIB074 on cardiovascular parameters in dogs, and no effects on tyramine-induced hypertension in rats (data not shown). Thus, the body of evidence, encompassing clinical and preclinical studies, supports safety and minimal effects of BIIB074 on BP/cardiovascular parameters.

Limitations of the current study were the relatively small population and the short-term duration of treatment and BP assessment (36 days). It should also be considered that the investigation was carried out among healthy individuals rather than the intended patient population with neuropathic pain and associated comorbidities. The current study population was also younger (mean age 34.3 years) than the intended patient population; for instance, peak onset age of TN is between 50–60 years (Cruccu *et al*. (2008) Eur J Neurol **15**(10): 1013-1028); and for PLSR, individuals are most likely to develop symptoms between 40–60 years of age (Tarulli and Raynor (2007) Neurol Clin **25**(2): 387-405). There are additionally some inherent limitations with current ABPM devices, which only record intermittent BP readings (every 15 minutes) of the entire 24-h BP profile, compared to an ideal futuristic beat-to-beat ambulatory BP device (Mancia and Verdecchia (2015) Circulation Research **116**(6): 1034-1045).

Overall, despite these limitations, the results from this study confirm that it is unlikely that a clinically important hypertensive signal will be observed for BIIB074 in normotensive subjects, and it is believed that monitoring of the in-clinic BP does not need to be carried out in larger studies.

EXAMPLE 5: CARBAMAZEPINE DOSAGE STUDY

The interaction between BIIB074 and carbamazepine (CBZ) was investigated in a double-blind, randomized, placebo-controlled, 3-period, phase-1 study. Healthy subjects were randomized by sex to either CBZ (100 mg twice daily [BID] days 1–3, 200 mg BID days 4–21) or placebo (BID days 1–21). During days 16–21, subjects in both groups also received BIIB074 150 mg 3-times daily (TID). Thereafter, treatment with CBZ or placebo was discontinued, while dosing with BIIB074 was continued for another 7 days (days 22–28). The primary objective was to evaluate the effect of CBZ on BIIB074 steady-state PK; a secondary objective was to observe BIIB074 PK recovery following CBZ discontinuation.

A total of 36 subjects were randomized, of whom 33 were included in the analysis (3 subjects withdrew prior to receiving BIIB074). BIIB074 absorption following oral administration with CBZ or placebo was rapid; median time to maximum concentration (C_{max}) was 1–1.5 h postdose. CBZ co-administration with BIIB074 reduced BIIB074 systemic exposure (area under the concentration-time curve within a dosing interval, $AUC_{(0\text{-}tau)}$) by ~31.6%, and reduced BIIB074 C_{max} by ~26.3%, vs BIIB074 co-administration with placebo (see Table 8). CBZ discontinuation for 7 days resulted in incomplete recovery of BIIB074 exposure at day 28; $AUC_{(0\text{-}tau)}$ and C_{max} remained ~24.5%, and ~21.4%, lower than in the placebo group, respectively (see Table 8). BIIB074 150 mg TID appeared well tolerated when co-administered with CBZ, and no safety concerns were raised.

CBZ has a significant effect on BIIB074 exposure, which was reduced by ~31.6% during co-administration; recovery is also incomplete following CBZ discontinuation for 7 days. These results suggest that if BIIB074 is to be administered to a patient using a glucuronosyltransferase inducer (UGT), the dosage of BIIB074 and/or the UGT should be modified. If the drugs are to be used simultaneously, the dosage of BIIB074 can be increased, and/or the dosage of the UGT can be decreased. In another aspect, the dosage of the UGT can be stopped entirely before administration of BIIB074.

Table 8. Treatment comparison at day 21 (effect of CBZ on BIIB074 steady-state PK) and at day 28 (effect of discontinuation of CBZ on recovery of BIIB074 PK)

	Parameter	Carbamazepine (Group 1)		Placebo (Group 2)		Ratio (%)	90% CI	
		N	Adj Geo Mean	N	Adj Geo Mean		Lower	Upper
BIIB074, day 21	$AUC_{(0\text{-}tau)}$	17	11986	16	17523	68.4	62.6	74.8
	C_{max}	17	2156	16	2926	73.7	66.9	81.2
BIIB074, day 28	$AUC_{(0\text{-}tau)}$	16	12068	15	15986	75.5	69.4	82.1
	C_{max}	16	2148	15	2734	78.6	71.7	86.1

Adj Geo Mean, adjusted geometric mean from the statistical model; $AUC_{(0\text{-}tau)}$, area under the concentration-time curve within a dosing interval; BID, twice daily; C_{max}, maximum observed concentration; CBZ, carbamazepine; CI, confidence interval; PK, pharmacokinetics; ratio, ratio of the Adj Geo Mean for Group 1/Group 2; TID, 3-times daily.

Note: Group 1 consisted of subjects who received 100 mg CBZ BID on Days 1 to 3 and 200 mg CBZ BID on Days 4 to 21; Group 2 consisted of subjects who received matching placebo on Days 1 to 21. All subjects received 150 mg BIIB074 TID on Days 16 to 28.