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(54) Title: TREATMENT OF PAIN ASSOCIATED WITH PARKINSON'S DISEASE WITH OPICAPONE IN COMBINATION WITH LEVODOPA

(57) Abstract: This invention relates to methods for treating pain associated with Parkinson's disease (PD). In particular it relates to the use of opicapone for treating PD-associated pain, especially fluctuation-related pain.

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TREATMENT OF PAIN ASSOCIATED WITH PARKINSON'S DISEASE WITH OPICAPONE IN COMBINATION WITH LEVODOPA

FIELD OF THE INVENTION

This invention relates to methods for treating pain associated with Parkinson's disease (PD). In particular it relates to the use of opicapone for treating PD-associated pain, especially fluctuation-related pain.

BACKGROUND OF THE INVENTION

Although motor complications are the most well-known symptoms of PD, James Parkinson himself noted and described non-motor symptoms (NMS) of the disease which would come to bear his name. These symptoms included sleep problems, bowel dysfunction and pain. However, research into, and treatment of, PD has historically focused on controlling motor symptoms, and it is only relatively recently that the importance of NMS has become widely recognised [Martínez-Fernández et al, 2016].

Pain is one of the most frequent and burdensome NMS of PD, being a significant comorbidity in up to 85% of PD patients, and it may precede the motor symptoms of the disease. Pain has been shown to be associated with other NMS of PD such as sleep disruption and cardiovascular disturbances, indicating that pain, sleep disruption and dysautonomia may share a common pathophysiology that possibly involves non-dopaminergic pathways [Ghosh et al, 2020]. On the other hand, nociceptive pain accounts for the majority of reported pain in PD [Truini et al, 2013]. Dopamine can modulate pain and is known to have an anti-nociceptive role [Allen et al, 2015], and dopaminergic therapies have been shown to help alleviate pain in PD [Brefel-Courbon et al, 2005, 2013; Antonini et al, 2018; Rukavina et al, 2019. It is therefore possible that pain in PD may have, at least partially, a dopamine-associated aetiology [Antonini et al, 2018; Seppi et al, 2019]. Consequently, optimisation of dopaminergic therapy may help alleviate pain associated with PD [Jung et al, 2015; Antonini et al, 2018; Rukavina et al, 2019; Dafsari et al, 2019]. However, clinical evidence for the benefit of dopaminergic therapies in PD-associated pain is lacking [Seppi et al 2019], and previous studies in this setting have notable limitations.

The Phase II PANDA trial was the first randomised controlled trial to specifically assess treatment for PD-associated pain. Eligible patients were randomised to receive either prolonged-release oxycodone-naloxone or placebo. There was no significant difference between treatment arms in the average 24-h pain score at 16 weeks (primary endpoint). However, the measure used to assess pain was a general pain scale (the Likert scale) and

levodopa was used more frequently as a rescue treatment in the placebo arm, both of which factors might have affected the results [Trenkwalder et al, 2015].

The double-blind, exploratory DOLORES trial was the first to investigate the effect of a dopamine agonist (rotigotine; administered as a transdermal patch) on PD-associated pain as primary outcome. Although the findings suggested that rotigotine may improve PD-associated chronic pain in patients with advanced-stage PD, the trial was not powered to detect statistically significant treatment differences, due to the small sample size [Rascol et al, 2016].

Safinamide (an agent with multiple modes of action, including monoamine oxidase-B inhibition) was shown to significantly reduce the need for pain medication, and to significantly improve two out of three PDQ-39 pain-related items, in comparison with placebo, when added to existing levodopa-based therapy [Cattaneo et al, 2017]. The authors noted that safinamide is a state-dependent inhibitor of human voltage-gated sodium channels (VGSC) in the inactivated state and that it might regulate selective inhibition of glutamatergic hyperactivity, which may be an effective strategy for the treatment of some PD non-motor symptoms not responding to levodopa therapy, in particular pain and neuropsychiatric symptoms. Therefore, any effect might be independent of safinamide's effect on monoamine oxidase-B.

Levodopa is still the most effective symptomatic treatment for PD [Poewe et al, 2010]. However, following oral administration, levodopa is extensively metabolised in the periphery by dopa decarboxylase (DDC) and catechol-O-methyltransferase (COMT), with the result that only 1% of an oral dose of levodopa reaches the brain. Moreover, long-term treatment with levodopa is complicated by the development of "wearing off" periods (characterised by end-of-dose motor fluctuations) and drug-induced dyskinesia [Poewe et al, 2010]. PD associated pain often increases during such OFF periods and patients with dyskinesia often have increased pain sensitivity [Cheon et al, 2009; Sung et al, 2020].

Inhibitors of DDC (DDCIs) and COMT (COMTIs) are commonly used as an adjunct to levodopa in patients with PD in order to increase levodopa bioavailability and its delivery to the brain, and thereby ameliorate wearing-off symptoms, but potentially exasperating dyskinesia [Müller, 2015; Montioli et al, 2016]. According to WO01/68083, COMTIs may be used to treat or control pain of any origin, including acute and chronic pain. However, the evidence supporting this claim is limited to the use of nitecapone and entacapone in two animal models of inflammatory pain (i.e. a modified Randall-Sellitto test and the acetic acid induced writhing test). A third experiment in an animal model of centrally mediated analgesia

(the hot plate test) indicated that the analgesic effect of nitecapone and entacapone was not mediated through the CNS, but through some (unidentified) peripheral mechanism. The skilled person is aware that different sub-types of pain respond to different treatments and an effect on acute pain in animal models cannot indicate an effect in alternative pain paradigms.

Opicapone is a third-generation, once-daily COMTI [Kiss et al, 2010; Almeida et al, 2013; Scott, 2016; Fabbri et al 2018], which has been shown to be generally well tolerated and efficacious in reducing OFF-time in two pivotal studies in patients with PD and end-of-dose motor fluctuations (BIPARK-I and BIPARK-II) [Ferreira et al, 2016; Lees et al, 2017]. On the basis of these trials, opicapone is approved in the European Union, USA, Japan, Australia and other countries as adjunctive therapy to preparations of levodopa/DDCIs in patients with PD and end-of-dose motor fluctuations [Ongentys® EU Summary of Product Characteristics] or OFF episodes [Ongentys® USA Prescribing Information]. Although a positive signal for opicapone was observed on the Movement Disorder Society Non-Motor Symptoms Scale (NMSS) "Miscellaneous" domain, which includes pain as one aspect, in both the BIPARK-II trial [Oliveira et al, 2015] and the more recent OPTIPARK study [Reichmann et al, 2020], the effect was less than for that observed for placebo (in the BIPARK-II trial), and no specific effect on pain was identifiable. Placebo is known to activate dopamine receptors and to induce dopamine-like effects in PD [de la Fuente-Fernández et al, 2002; Benedetti, 2014; Colloca, 2019; Lou, 2020].

SUMMARY OF THE INVENTION

As a result of their detailed knowledge of the properties and effects of opicapone and their understanding of the problem of pain associated with PD, the present inventors elected to investigate the efficacy of opicapone in PD patients with end-of-dose motor fluctuations and associated pain, when administered as adjunctive therapy to existing treatment with levodopa/DDCI. Such insight has resulted in conception of the present invention as summarised below.

A first general embodiment relates to opicapone (or a pharmaceutically acceptable derivative thereof) in combination with levodopa (or a pharmaceutically acceptable derivative thereof) for use in the treatment of pain associated with Parkinson's disease.

A second general embodiment relates to the use of opicapone (or a pharmaceutically acceptable derivative thereof) in the manufacture of a medicament for use, in combination with levodopa (or a pharmaceutically acceptable derivative thereof) in the treatment of pain associated with Parkinson's disease.

A third general embodiment relates to a method of treating pain associated with Parkinson's disease comprising administering a therapeutically effect amount of opicapone (or a pharmaceutically acceptable derivative thereof) in combination with a therapeutically effect amount of levodopa (or a pharmaceutically acceptable derivative thereof) to a patient identified as suffering from pain associated with Parkinson's disease.

BRIEF DESCRIPTION OF THE DRAWINGS

Examples of the invention will be described in detail with reference to the accompanying drawings, in which:

Figure 1 shows the study design of a randomised, double-blind, placebo-controlled, parallel-group, interventional trial in PD patients with end-of-dose motor fluctuations and PD-associated pain. It is noted that V2 is divided in V2a and V2b. If ON/OFF diary entries are non-compliant at V2a, the patient will be re-trained on correct use of the diary and visit V2b will be postponed for 3-4 days. If diary completion is satisfactory at V2a, V2b is performed immediately on the same day. In Figure 1, AE = adverse event; DDCI = dopa decarboxylase inhibitor; L-dopa = levodopa; PD = Parkinson's disease; PSV = post-study visit; V = visit.

Figure 2 shows the timelines of study assessments. In Figure 2, CGI-C = Clinical Global Impression of Change; DDCI = dopa decarboxylase inhibitor; EMD = early morning dystonia; KPPS = King's Parkinson's Disease Pain Scale; L-dopa = levodopa; MDS-NMS = Movement Disorder Society-sponsored Non-Motor rating Scale; MDS-UPDRS = Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; PDQ-8 = 8-item Parkinson's Disease Questionnaire; PGI-C = Patient's Global Impression of Change; PSV = post-study visit; V = visit.

DETAILED DESCRIPTION OF THE EMBODIMENTS

In a first embodiment, the present invention provides opicapone (or a pharmaceutically acceptable derivative thereof) in combination with levodopa (or a pharmaceutically acceptable derivative thereof) for use in the treatment of pain associated with Parkinson's disease.

In a second embodiment, the present invention provides the use of opicapone (or a pharmaceutically acceptable derivative thereof) in the manufacture of a medicament for use, in combination with levodopa (or a pharmaceutically acceptable derivative thereof) in the treatment of pain associated with Parkinson's disease.

In a third embodiment, the present invention provides a method of treating pain associated with Parkinson's disease comprising administering a therapeutically effect amount of opicapone (or a pharmaceutically acceptable derivative thereof) in combination with a therapeutically effect amount of levodopa (or a pharmaceutically acceptable derivative thereof) to a patient identified as suffering from pain associated with Parkinson's disease. Thus, the method of the third embodiment involves the initial step of identifying patients who not only suffer from Parkinson's disease, but also pain associated therewith, and who will therefore benefit from the present invention.

For each of the three embodiments described above, the following paragraphs set out preferred aspects of the invention.

Primary indication

The primary goal of the present invention is the treatment of pain associated with Parkinson's disease. The severity of pain associated with Parkinson's disease may be measured using the King's Parkinson's Disease Pain Scale (KPPS). The KPPS evaluates the burden and characterises various phenotypes of pain in PD. It comprises seven domains including a total of 14 items. The domains are:

1. Musculoskeletal pain (pain around the joints (including arthritic pain));
2. Chronic pain (generalized or organ specific);
3. Fluctuation-related pain (dyskinetic pain, "OFF" dystonia or generalised "OFF" period pain);
4. Nocturnal pain (pain related to jerking leg movements or an unpleasant burning sensation in the legs which improves with movement, or pain related to difficulty turning in bed);
5. Orofacial pain (pain when chewing, pain due to teeth grinding at night, or burning mouth syndrome);
6. Discoloration, edema/swelling (burning pain in limbs (often associated with swelling or dopaminergic treatment) or generalised lower abdominal pain); and
7. Radicular pain (shooting pain/pins and needles down the limbs).

Each item is scored by severity (0, none to 3, very severe) multiplied by frequency (0, never to 4, all the time), resulting in subscores of 0–12. The total KPPS score (with a theoretical range of 0–168) represents the symptomatic burden by pain [Chaudhuri et al, 2015].

Treatment according to the present invention results in a reduction in a patient's score in one or more of these seven domains. A particular population who will benefit from the present invention are patients having a total score greater than or equal to 40 in the KPPS. Preferably, treatment according to the present invention reduces the patient's total score in the KPPS, preferably to a score less than or equal to 8, more preferably to a score less than or equal to 10, most preferably to a score less than or equal to 12.

Whilst pain related to Parkinson's disease is not necessarily related to end-of-dose motor fluctuations and can occur at all stages of disease, it is preferable that the patient to be treated experiences end-of-dose motor fluctuations. End-of-dose motor fluctuations (also known as the "wearing off" phenomenon) are a well-known consequence of extended levodopa therapy. They relate to the predictable re-emergence or worsening of symptoms before administration of the next dose of levodopa. Typically, such re-emergence or worsening of symptoms starts 3 to 4 hours after the last dose of levodopa, as the therapeutic effect of the medication wears off. Symptoms then typically improve 15 to 45 minutes after the next levodopa dose is taken.

In patients experiencing end-of-dose motor fluctuations, the pain associated with Parkinson's disease is preferably pain associated with end-of-dose motor fluctuations, such as dyskinetic pain, "OFF" dystonia or generalised "OFF" period pain. The severity of this type of pain may be measured as fluctuation-related pain according to domain 3 of the KPPS. A particular population who will benefit from the present invention are patients having a score greater than or equal to 12 in domain 3 of the KPPS. Preferably, treatment according to the present invention reduces the patient's score in domain 3 of the KPPS, preferably to a score less than or equal to 2, more preferably to a score less than or equal to 3, most preferably to a score less than or equal to 4. The reduction may involve a reduction in one or more of the sub-domains – dyskinetic pain, "OFF" dystonia or generalised "OFF" period pain.

Alternatively, or additionally, the pain associated with Parkinson's disease is nocturnal pain. The severity of this type of pain may be measured as nocturnal pain according to domain 4 of the KPPS. A particular population who will benefit from the present invention are patients having a score greater than or equal to 8 in domain 4 of the KPPS. Preferably, treatment according to the present invention reduces the patient's score in domain 4 of the KPPS, preferably to a score less than or equal to 0.5, more preferably to a score less than or equal to 1, most preferably to a score less than or equal to 2.

Patient group

The patient is suffering from pain associated with Parkinson's disease, preferably the patient to be treated also experiences end-of-dose motor fluctuations. Such patients to be treated according to the invention may have been experiencing a mean daily OFF time of up to 8 hours prior to treatment according to the invention, preferably 0.5 to 8 hours, 1 to 8 hours, 2 to 8 hours, 4 to 8 hours, 5 to 8 hours per day. Patients experiencing end-of-dose motor fluctuations tend to have been treated for longer periods, for example, more than 1 year, preferably more than 2 years, more preferably more than 3 years, even more preferably more than 4 years, most preferably more than 5 years. The patients to be treated according to the invention may have been experiencing motor symptoms and/or motor complications such as motor fluctuations with or without dyskinesias prior to treatment according to the invention, for example more than 1 month, preferably more than 3 months, more preferably more than 6 months, even more preferably more than 1 year, most preferably more than 2 years.

Secondary indications

In addition to suffering from pain associated with Parkinson's disease, the patient to be treated may also experience one or more further non-motor symptoms and, preferably, the treatment reduces one or more of these symptoms too. The severity of non-motor symptoms may be assessed using the Movement Disorder Society Non-Motor Scale (MDS-NMS). The MDS-NMS comprises 13 domains covering a range of key PD- and treatment-related non-motor symptoms, and a subscale for non-motor fluctuations that assesses changes in non-motor symptoms in relation to timing of anti-PD medications across eight domains [Martinez-Martin et al, 2019; Chaudhuri et al, 2020]. Preferably, treatment according to the present invention reduces the patient's total score in the MDS-NMS.

A particular non-motor symptom which may be experienced in addition to pain associated with Parkinson's disease is anxiety and, preferably, the treatment reduces this symptom too. Preferably, the treatment reduces the patient's score in domain B of the MDS-NMS.

Another non-motor symptom which may be experienced in addition to pain associated with Parkinson's disease is depression and, preferably, the treatment reduces this symptom too. Preferably, the treatment reduces the patient's score in domain A of the MDS-NMS.

Another non-motor symptom which may be experienced in addition to pain associated with Parkinson's disease is sleep disorders and, preferably, the treatment reduces this symptom too. Preferably, the treatment reduces the patient's score in domain K of the MDS-NMS.

Treatment regimens

In the context of the present invention, the phrase "pharmaceutically acceptable derivative" of an active ingredient means a compound which is non-toxic and is converted to the active ingredient itself upon administration to the patient. It includes pharmaceutically acceptable salts, solvates and prodrugs (e.g. esters).

In the context of the present invention, wherein the active ingredient opicapone (or a pharmaceutically acceptable derivative thereof) is administered in combination with the active ingredient levodopa (or a pharmaceutically acceptable derivative thereof), the phrase "in combination with" does not mean the two active ingredients must be administered in the same dosage unit. Indeed, they need not even be given at the same point in time. Thus, the phrase "in combination with" simply means that the two active ingredients must exert their pharmacological effects on the patient at the same time. Thus, the two active ingredients may be administered concomitantly, separately or sequentially, in the same or different dosage unit(s), and with the same or different dosing frequency.

The particular dose amount and frequency for opicapone (or a pharmaceutically acceptable derivative thereof) may be determined by the skilled physician. Preferably, it is administered once daily. Preferably each dose is equivalent to 10 to 100 mg of opicapone, more preferably equivalent to 25 to 50 mg of opicapone and most preferably equivalent to 50 mg of opicapone. The most preferred dose amount and frequency is 50 mg, once daily. Opicapone can interact with food and with levodopa. Therefore, it is preferably administered at least 1 hour before or after a meal, and at least 1 hour before or after levodopa. A particularly suitable dosing point is at or near to bedtime, e.g. up to 1 hour before sleep.

The particular dose amount and frequency for levodopa (or a pharmaceutically acceptable derivative thereof) may be determined by the skilled physician. Preferably, it is administered three to ten times daily. Preferably, each dose is equivalent to 50 to 200 mg of levodopa, more preferably equivalent to 75 to 125 mg of levodopa and most preferably equivalent to 100 mg of levodopa. Preferably, the total daily dose is equivalent to 300 to 2000 mg of levodopa, more preferably equivalent to 500 to 1000 mg of levodopa.

Levodopa therapy often benefits from the use of a DOPA decarboxylase inhibitor (DDCI). Therefore, treatment according to the present invention preferably involves administration of a DDCI, preferably selected from carbidopa or benserazide. The particular dose amount and frequency for the DDCI may be determined by the skilled physician. Preferably, it is administered three to ten times daily. Preferably, the total daily dose is equivalent to 25 to 500 mg of the DDCI, more preferably equivalent to 75 to 250 mg of the DDCI.

EXAMPLE

A clinical study to exemplify the present invention is described below.

Study design

A phase IV, randomised, double-blind, placebo-controlled, parallel-group, interventional trial in PD patients with end-of-dose motor fluctuations and PD-associated pain (experienced for ≥4 weeks prior to the start of the study, with a score of ≥12 on Domain 3 of the KPPS at screening and baseline). It consists of a 1-week screening period, 24-week double-blind treatment period and 2-week follow-up period (**Figure 1**). Following screening, at visit (V)2, eligible patients will be randomised 1:1 to opicapone 50 mg or placebo (PLC) once daily while continuing current treatment with levodopa/DDCI. Since opicapone enhances the effects of levodopa, it may be necessary to reduce the patient's levodopa/DDCI dosing within the first days or weeks of opicapone treatment; therefore, the investigator may decrease the daily dose of levodopa/DDCI as required until V4, while keeping the number of daily intakes unchanged. If necessary, dosing may be increased back to the baseline dose level. After V4, the levodopa/DDCI dose should not be changed until the end of the study. The anti-PD treatment regimen should be stable for at least 4 weeks prior to V1 (**Table 1**) and kept stable throughout the study (except for levodopa/DDCI during the adjustment period). No new anti-PD drugs should be started during the study.

Chronic pain treatment should be stable for at least 4 weeks prior to V1 (**Table 1**), and no new pain medication should be started during the study, except the allowed rescue medication (paracetamol or tramadol). The baseline dose of pain medication may be reduced throughout the study, if required due to pain medication-related adverse events (AEs), and increased again up to the baseline dose level if the investigator finds that the dose reduction was too much. Further visits will be performed on Day 85 ± 4 days (V5) and Day 169 ± 4 days (V6). The primary analysis will be performed on data collected at V6. A follow-up visit

will be performed on Day 183 ± 4 days (V7), approximately 2 weeks after the last intake of study medication (opicapone 50 mg or PLC). Patients who discontinue early will be requested to attend an early discontinuation visit. At V6 (or early discontinuation visit, if applicable), the investigator will arrange the patient's subsequent treatment (i.e. either prescribe further opicapone or switch to another treatment).

Study population

Inclusion and exclusion criteria are outlined in **Table 1** below.

Study assessments

An overview of study assessments is presented in **Table 2** below and the timing of these assessments is outlined in **Figure 2**.

Efficacy

The primary efficacy endpoint is change from baseline in Domain 3 (fluctuation-related pain) of the KPPS. The KPPS evaluates the burden and characterises various phenotypes of pain in PD. It comprises seven domains including a total of 14 items. Each item is scored by severity (0–3) multiplied by frequency (0–4), resulting in subscores of 0–12. The total KPPS score (0–168) represents the symptomatic burden by pain [Chaudhuri et al, 2015].

The key secondary efficacy endpoint is change from baseline in Domain B (anxiety) of the Movement Disorder Society-sponsored Non-Motor rating Scale (MDS-NMS). The MDS-NMS comprises 13 domains covering a range of key PD- and treatment-related non-motor symptoms, and a subscale for non-motor fluctuations that assesses changes in non-motor symptoms in relation to timing of anti-PD medications across eight domains [Martinez-Martin et al, 2019; Chaudhuri et al, 2020].

Additional secondary efficacy endpoints comprise other domains and total scores of KPPS and MDS-NMS, change from baseline in Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts III and IV, change from baseline in Parkinson's Disease Questionnaire (PDQ-8), Clinical Global Impression of Change (CGIC), Patient's Global Impression of Change (PGIC), change from baseline in functional status via Hauser's PD diary, changes from baseline in morning dystonia, and use of rescue medication (see **Table 2** below).

The MDS-UPDRS is a revision of the UPDRS originally developed in the 1980s, and evaluates various aspects of PD; it consists of four parts: Parts IA and IB, non-motor aspects of experiences of daily living; Part II, motor aspects of experiences of daily living; Part III, motor examination; and Part IV, motor complications. The PDQ-8 (a short form of the PDQ-39) is a patient-reported outcome that assesses eight aspects of functioning and well-being that are usually adversely affected by PD: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. It rates overall health status by providing a single score ranging from 0 (good health) to 100 (poor health). The CGIC and PGIC are, respectively, investigator and patient assessments of how much a patient's overall status has improved or worsened since the start of the study, comprising a 7-point scale: (1, 'very much improved'; 2, 'much improved'; 3, 'minimally improved'; 4, 'no change'; 5, 'minimally worse'; 6, 'much worse'; 7, 'very much worse'). The Hauser's PD diary is a patient record of their mobility during each 30-min period, categorised as: asleep; OFF time; ON time without dyskinesia; ON time with non-troublesome dyskinesia; or ON time with troublesome dyskinesia. When assessing changes from baseline in morning dystonia, the investigator will ask the patient if they experienced any morning dystonia within the last week (based on item 35 of the former UPDRS version). The amount and frequency of intake of rescue medication (paracetamol or tramadol) will be recorded by patients in a diary.

Safety assessments

Safety assessments include the incidence of treatment-emergent adverse events (TEAEs), and changes from baseline in vital signs, physical and neurological examinations and routine laboratory parameters (see **Table 2**; and **Figure 2**).

Sample size calculation

For the primary efficacy endpoint (change from baseline in Domain 3 of KPPS), a difference to PLC of 3.0 is regarded as clinically meaningful. From a former study [Rascol et al, 2016], a standard deviation (SD) of 5.8 can be assumed. With a two-sided significance α of 0.05, a power of 80%, a 1:1 treatment allocation ratio and with the above-mentioned assumptions, 2 x 60 = 120 evaluable patients are required. Assuming a drop-out rate of 15%, a total of 140 patients need to be randomised. Randomisation will follow a 1:1 allocation rate (opicapone 50 mg or PLC).

Statistical methodology

Efficacy assessments will be analysed for the Full Analysis Set, defined as all patients who are randomised and who have at least one measurement of the primary efficacy assessment. For sensitivity purposes, efficacy assessments will additionally be analysed for the Per-Protocol Set, defined as all patients included in the Full Analysis Set who have no major protocol deviations that could influence the primary efficacy assessment. The primary efficacy endpoint will be analysed using analysis of covariance (ANCOVA), with treatment as a fixed factor and baseline KPPS as a covariate, to demonstrate superiority of opicapone 50 mg against PLC. Secondary efficacy endpoints will be analysed in an exploratory manner by treatment arm using appropriate parametric and non-parametric statistical methods. Descriptive statistics, including 95% confidence intervals, will be presented per treatment arm.

Safety assessments will be analysed for the Safety Set, defined as all patients who take at least one dose of investigational product. TEAEs will be summarised in terms of the number and percentages of patients with TEAEs. Vital signs and laboratory parameters will be summarised using summary statistics of absolute values and changes from baseline. Summary statistics and shift tables will be presented for physical and neurological examinations. Demographic and baseline characteristics will be presented using descriptive statistics.

Discussion

The robust design of the above study addresses the current lack of reliable evidence for levodopa-based therapy in the treatment of PD-associated pain. The study features recent validated PD pain- and non-motor-specific scales (such as KPPS and MDS-NMS), which help to record dimensions of PD-associated pain that were not previously possible to assess. For instance, this may allow the detection of potential associations between pain and other non-motor symptoms, such as depression, anxiety and insomnia, and dysautonomic symptoms. The concomitant use of ON/OFF diaries with these scales may also allow a deeper understanding of pain during both the OFF and ON states. Placebo is known to activate dopamine receptors and to induce dopamine-like effects in PD [de la Fuente-Fernández et al, 2002; Benedetti, 2014; Colloca, 2019; Lou, 2020], which are often still apparent in studies at 3 months [Trenkwalder et al, 2015, Ferreira et al, 2016; Lees et al, 2017], tending to wane by the 6-month mark [Borgohain et al, 2014; Hattori et al, 2020]. The

6 months course of the study and its double-blind design may therefore help to disentangle the placebo effect from the true effect, especially when evaluating pain.

Table 1. Inclusion and exclusion criteria

Category of characteristic	Inclusion criteria	Exclusion criteria
Demographics	• Male or female • Age ≥30 years[a]	
Disease-related characteristics	• Disease severity Stages I–III at ON[b] • Signs of 'wearing-off' phenomena (end-of-dose fluctuations) with average total daily OFF time while awake ≥1.5 h (excluding early morning pre-first dose OFF period), despite optimal anti-PD therapy, according to the investigator's judgment at V1 • At least 1.5 OFF h/day (excluding early morning pre-first dose OFF period), as recorded in the self-rated diary, during at least 2 of the 3 days prior to V2	• Non-idiopathic PD[c] • Severe and/or unpredictable OFF periods (investigator's judgment)
Pain-related characteristics	• Experiencing PD-associated pain for ≥4 weeks prior to V1 • Domain 3 of KPPS ≥12 at V1 and V2 • No changes in chronic treatment regimen for pain within 4 weeks prior to V1[d]	• Major/prominent non-PD-related pain (e.g. due to malignant disease)
Anti-PD medication	• Treated with 3–8 intakes/day of levodopa/DDCI[e] and on a stable regimen for ≥4 weeks prior to V1 • Any other anti-PD medication regimen, if applicable, should remain stable for ≥4 weeks prior to	• Treatment with prohibited medication[f] within the 4 weeks prior to V1 • Treatment with apomorphine with 4 weeks prior to V1 or likely to be needed at any time until V6

	V1 and should not be likely to require any adjustment until V6	• Previous or planned (during the entire study duration) levodopa/carbidopa intestinal gel infusion, deep brain stimulation or stereotactic surgery (e.g. pallidotomy, thalamotomy) • Previous or current use of opicapone • Use of any other investigational product, currently or within 3 months (or five half-lives of the investigational product, whichever is longer) prior to V1
Compliance	• Adequate compliance with relevant PD and pain-related medication during the screening period (investigator's judgment) at V2 • Filled in the self-rating diary in accordance with the diary instructions and with ≤3 missing entries/day in the 3 days prior to V2	
Safety	• Acceptable results of screening laboratory tests (i.e. not clinically relevant for the well-being of the patient or for the purpose of the study according to investigator's judgment at V2 • *For female patients:* postmenopausal for ≥2 years before V1, surgically sterile for ≥6 months before V1, or practicing effective contraception until V6[g] • *For male patients:* use of condoms plus an approved	• Current or past (within previous year) history of suicidal ideation, suicide attempts or alcohol or substance abuse, excluding caffeine or nicotine • Pheochromocytoma, paraganglioma or other catecholamine-secreting neoplasms • Known hypersensitivity to the excipients of the investigation product[h] or rescue medication • History of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis

	method of highly effective contraception during the treatment period up to V6, if sexually active with a partner of childbearing potential	• History of severe hepatic impairment[i] • Previous history of psychosis or psychiatric disorders, including severe major depression • Any medical condition that might place the patient at increased risk or interfere with assessments • *For female patients:* pregnant or breastfeeding

[a]According to UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (2006) or Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease (2015).

[b]Modified Hoehn and Yahn staging.

[c]Atypical parkinsonism, secondary (acquired or symptomatic) parkinsonism, Parkinson-plus syndrome.

[d]Includes medication (e.g. paracetamol, opioids, nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, corticosteroids) and non-medication therapies (e.g. transcutaneous electrical nerve stimulation, bioelectrical therapy).

[e]May include a slow-release formulation.

[f]Entacapone, tolcapone, monoamine oxidase inhibitors (except selegiline up to 10 mg/day [oral] or 1.25 mg/day [buccal], rasagiline up to 1 mg/day, safinamide up to 100 mg/day) or antiemetics with anti-dopaminergic action (except domperidone).

[g]Female patients requesting to continue with oral contraceptives must be willing to additionally use non-hormonal methods of contraception during the course of the study.

[h]Including lactose intolerance, galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

[i]Child-Pugh Class C.

DDCI, dopa decarboxylase inhibitor; KPPS, King's Parkinson's Disease, Pain Scale; PD, Parkinson's disease; V, visit.

Table 2. Overview of study assessments

Category	Assessment
Primary efficacy endpoint	Change from baseline in Domain 3 (fluctuation-related pain) of KPPS
Key secondary endpoint	Change from baseline in Domain B (anxiety) of MDS-NMS
Additional secondary endpoints	Change from baseline in Domain A (depression) of MDS-NMS
	Change from baseline in Domain K (sleep and wakefulness) of MDS-NMS
	Change from baseline in MDS-NMS total score
	Change from baseline in Domain 4 (nocturnal pain) of KPPS
	Change from baseline in KPPS total score
	Change from baseline in MDS-UPDRS Parts III and IV
	Change from baseline in PDQ-8
	CGIC
	PGIC
	Change from baseline in functional status via Hauser's PD diary
	Changes from baseline in morning dystonia
	Use of rescue medication[a]
Safety assessments	Incidence of TEAEs, including serious TEAEs
	Changes from baseline in vital signs
	Changes from baseline in physical and neurological examinations
	Changes from baseline in routine laboratory parameters[b]

[a]Paracetamol or tramadol; [b]haematology, serum biochemistry, pregnancy test.

CGIC, Clinical Global Impression of Change; KPPS, King's Parkinson's Disease Pain Scale; MDS-NMS, Movement Disorder Society-sponsored Non-Motor rating Scale; MDS-UPDRS, Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PDQ-8, 8-item Parkinson's Disease Questionnaire; PGIC, Patient's Global Impression of Change; TEAE, treatment-emergent adverse event.

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CLAIMS:

1. Opicapone, or a pharmaceutically acceptable derivative thereof, in combination with levodopa, or a pharmaceutically acceptable derivative thereof, for use in the treatment of pain associated with Parkinson's disease.

2. The combination for use according to claim 1, wherein the patient has a total score greater than or equal to 40 in the King's Parkinson's Disease Pain Scale (KPPS).

3. The combination for use according to claim 1 or claim 2, wherein the treatment reduces the patient's total score in the KPPS, preferably to a score less than or equal to 8, more preferably to a score less than or equal to 10, most preferably to a score less than or equal to 12.

4. The combination for use according to any one of claims 1 to 3, wherein the patient to be treated experiences end-of-dose motor fluctuations.

5. The combination for use according to claim 4, wherein the pain associated with Parkinson's disease is pain associated with end-of-dose motor fluctuations.

6. The combination for use according to claim 5, wherein the pain associated with end-of-dose motor fluctuations is fluctuation-related pain according to domain 3 of the KPPS.

7. The combination for use according to claim 6, wherein the patient to be treated has a score greater than or equal to 12 in domain 3 of the KPPS.

8. The combination for use according to claim 6 or claim 7, wherein the treatment reduces the patient's score in domain 3 of the KPPS, preferably to a score less than or equal to 2, more preferably to a score less than or equal to 3, most preferably to a score less than or equal to 4.

9. The combination for use according to any one of claims 1 to 4, wherein the pain associated with Parkinson's disease is nocturnal pain.

10. The combination for use according to claim 9, wherein the nocturnal pain is nocturnal pain according to domain 4 of the KPPS.

11. The combination for use according to claim 10, wherein the patient to be treated has a score greater than or equal to 8 in domain 4 of the KPPS.

12. The combination for use according to claim 10 or claim 11, wherein the treatment reduces the patient's score in domain 4 of the KPPS, preferably to a score less than or equal to 0.5, more preferably to a score less than or equal to 1, most preferably to a score less than or equal to 2.

13. The combination for use according to any one of the preceding claims, wherein the patient to be treated experiences one or more further non-motor symptoms and the treatment reduces one or more of those symptoms.

14. The combination for use according to claim 13, wherein the treatment reduces the patient's total score in the Movement Disorder Society Non-Motor Scale (MDS-NMS).

15. The combination for use according to claim 13 or claim 14, wherein the patient to be treated experiences anxiety and the treatment reduces the patient's score in domain B of the MDS-NMS.

16. The combination for use according to any one of claims 13 to 15, wherein the patient to be treated experiences depression and the treatment reduces the patient's score in domain A of the MDS-NMS.

17. The combination for use according to any one of claims 13 to 16, wherein the patient to be treated experiences sleep disorders and the treatment reduces the patient's score in domain K of the MDS-NMS.

18. The combination for use according to any one of the preceding claims, wherein said combination further comprises a DOPA decarboxylase inhibitor (DDCI), preferably selected from carbidopa or benserazide.

19. The combination for use according to any one of the preceding claims, wherein the opicapone, or a pharmaceutically acceptable derivative thereof, is administered once daily, preferably at a dose equivalent to 10 to 100 mg of opicapone, more preferably at a dose equivalent to 25 to 50 mg of opicapone and most preferably at a dose equivalent to 50 mg of opicapone.

20. A method of treating pain associated with Parkinson's disease comprising administering a therapeutically effect amount of opicapone, or a pharmaceutically acceptable derivative thereof, in combination with a therapeutically effect amount of levodopa, or a pharmaceutically acceptable derivative thereof, to a patient identified as suffering from pain associated with Parkinson's disease.

21. Use of opicapone, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use, in combination with levodopa, or a pharmaceutically acceptable derivative thereof, in the treatment of pain associated with Parkinson's disease.

1/2

FIGURE 1

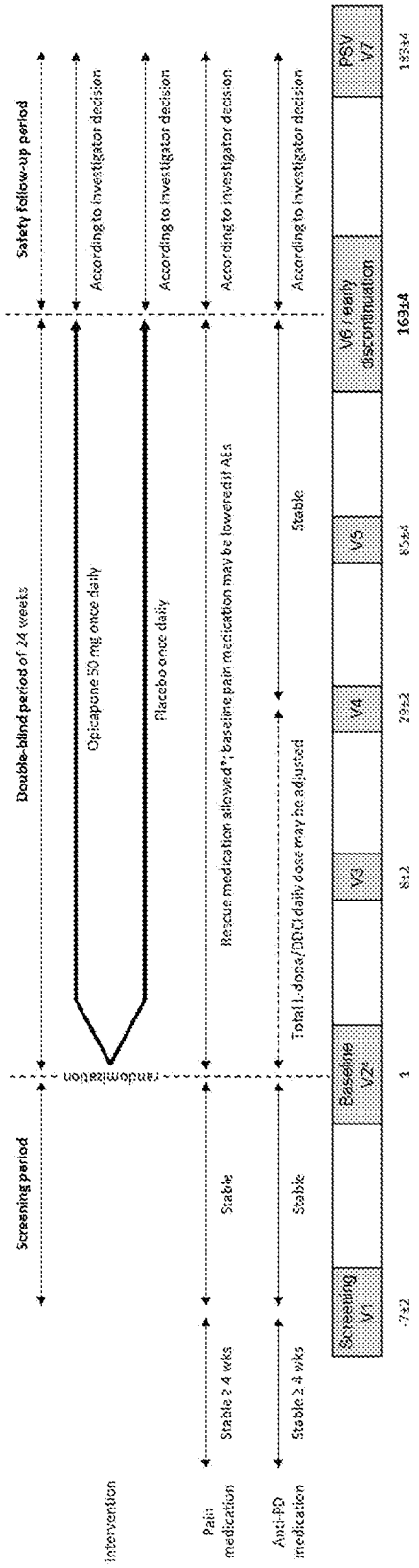
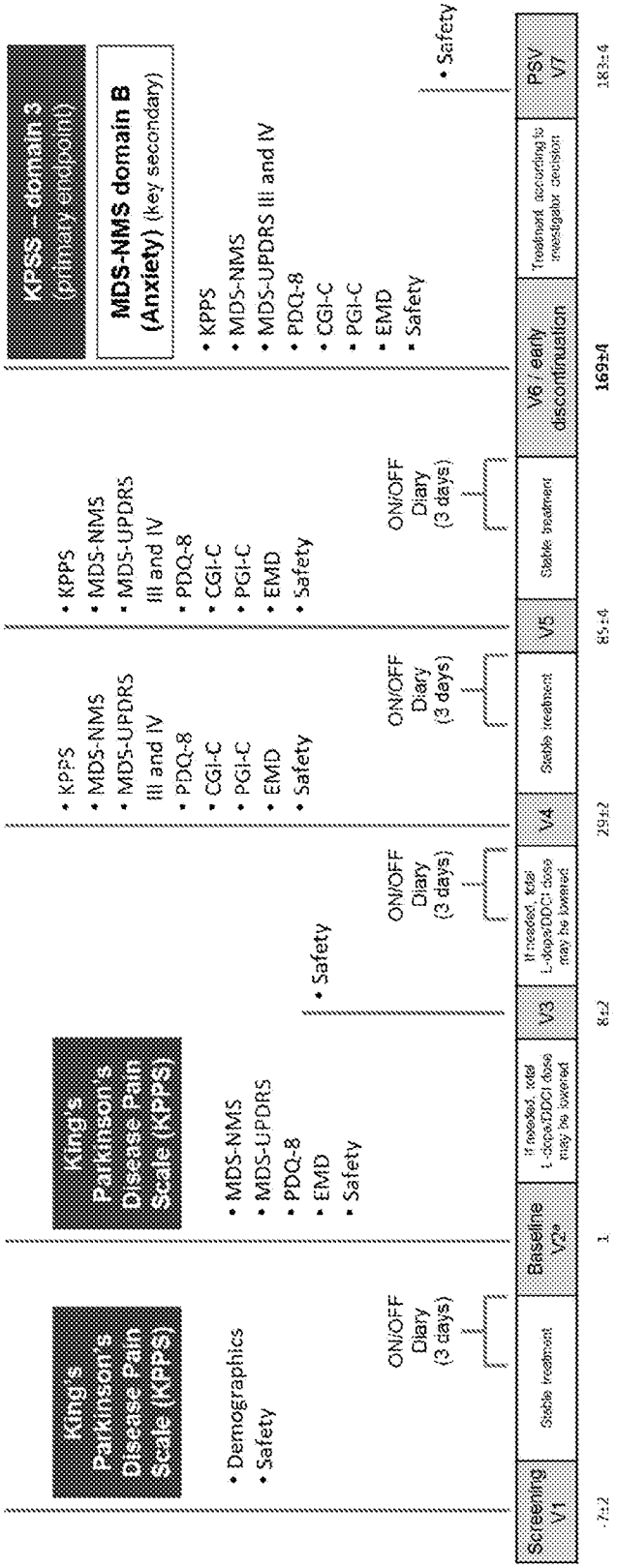

Safety follow-up period
According to investigator decision
According to investigator decision
According to investigator decision
According to investigator decision
Double-blind period of 24 weeks
Opicapone 50 mg once daily
Placebo once daily
Rescue medication allowed*; baseline pain medication may be lowered if AEs
Total 1-dose/DDD daily dose may be adjusted
Stable
Randomisation
Screening period
Stable
Stable
Intervention
Pain medication
Stable ≥ 4 wks
Anti-PD medication
Stable ≥ 4 wks
Screening V1
Baseline V2*
V3
V4
V5
V6 / early discontinuation
PSV V7
-7±2
1
8±2
29±2
85±4
16±4
18±4

FIGURE 2


King's Parkinson's Disease Pain Scale (KPPS)
• Demographics
• Safety
ON/OFF Diary (3 days)
King's Parkinson's Disease Pain Scale (KPPS)
• MDS-NMS
• MDS-UPDRS
• PDQ-8
• EMD
• Safety
• Safety
ON/OFF Diary (3 days)
• KPPS
• MDS-NMS
• MDS-UPDRS III and IV
• PDQ-8
• CGI-C
• PGI-C
• EMD
• Safety
ON/OFF Diary (3 days)
• KPPS
• MDS-NMS
• MDS-UPDRS III and IV
• PDQ-8
• CGI-C
• PGI-C
• EMD
• Safety
KPSS – domain 3 (primary endpoint)
MDS-NMS domain B (Anxiety) (key secondary)
• KPPS
• MDS-NMS
• MDS-UPDRS III and IV
• PDQ-8
• CGI-C
• PGI-C
• EMD
• Safety
• Safety
Screening V1
Stable treatment
Baseline V2*
If needed, total L-dopa/DDCI dose may be lowered
V3
If needed, total L-dopa/DDCI dose may be lowered
V4
Stable treatment
V5
Stable treatment
V6 / early discontinuation
Treatment according to investigator decision
PSV V7
-7±2
1
8±2
29±2
85±4
169±4
183±4

INTERNATIONAL SEARCH REPORT

International application No
PCT/PT2021/050001

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/165 A61K31/198 A61K31/4439 A61P25/06 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ROMMEL O ET AL: "Lumbar back pain in patients with Parkinson's disease", DER NERVENARZT, SPRINGER VERLAG, BERLIN, DE, vol. 87, no. 4, 3 February 2016 (2016-02-03), pages 418-425, XP035803990, ISSN: 0028-2804, DOI: 10.1007/S00115-015-0060-2 [retrieved on 2016-02-03] page 420 - page 421	1-21
Y	WO 01/68083 A1 (ORION CORP [FI]; AHO PAEIVI [FI]; LINDEN INGE BRITT [FI]) 20 September 2001 (2001-09-20) cited in the application claims; examples	1-21

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2021	13/10/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pacreu Largo, Marta

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HEINZ REICHMANN ET AL: "Effectiveness and safety of opicapone in Parkinson's disease patients with motor fluctuations: the OPTIPARK open-label study", TRANSLATIONAL NEURODEGENERATION, BIOMED CENTRAL LTD, LONDON, UK, vol. 9, no. 1, 4 March 2020 (2020-03-04), pages 1-9, XP021274441, DOI: 10.1186/S40035-020-00187-1 cited in the application abstract	1-21
A	FERREIRA JOAQUIM J ET AL: "Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial", LANCET NEUROLOGY, LANCET PUBLISHING GROUP, LONDON, GB, vol. 15, no. 2, 23 December 2015 (2015-12-23), pages 154-165, XP029384199, ISSN: 1474-4422, DOI: 10.1016/S1474-4422(15)00336-1 cited in the application abstract; table 3	1-21
A	RODRÍGUEZ-VIOLANTE MAYELA ET AL: "Clinical Determinants of Parkinson's Disease-associated Pain Using the King's Parkinson's Disease Pain Scale", MOVEMENT DISORDERS CLINICAL PRACTICE, vol. 4, no. 4, 1 July 2017 (2017-07-01), pages 545-551, XP055843987, ISSN: 2330-1619, DOI: 10.1002/mdc3.12469 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6174437/pdf/MDC3-4-545.pdf> the whole document	1-21
A	SEPPI KLAUS ET AL: "Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review", MOVEMENT DISORDERS, vol. 34, no. 2, 1 February 2019 (2019-02-01), pages 180-198, XP055843967, US ISSN: 0885-3185, DOI: 10.1002/mds.27602 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6916382/pdf/MDS-34-180.pdf> cited in the application page 190; table 10	1-21

2 -/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GEROIN CHRISTIAN ET AL: "Effects of safinamide on pain in Parkinson's disease with motor fluctuations: an exploratory study", JOURNAL OF NEURAL TRANSMISSION, SPRINGER WIEN, VIENNA, vol. 127, no. 8, 22 June 2020 (2020-06-22) , pages 1143-1152, XP037186648, ISSN: 0300-9564, DOI: 10.1007/S00702-020-02218-7 [retrieved on 2020-06-22] abstract -----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PT2021/050001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0168083 A1	20-09-2001	AT 256461 T	15-01-2004
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		DE 60101559 T2	16-09-2004
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		JP 2003526663 A	09-09-2003
		US 2003069316 A1	10-04-2003
		WO 0168083 A1	20-09-2001