Drug evaluation: VX-702, a MAP kinase inhibitor for rheumatoid arthritis and acute coronary syndrome

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Vertex Pharmaceuticals Inc, in collaboration with Kissei Pharmaceutical Co Ltd, is developing VX-702, one of a series of second-generation, orally active p38 MAP kinase inhibitors, for the potential treatment of inflammation, rheumatoid arthritis and cardiovascular diseases. In June 2005, a phase II clinical trial of VX-702 was initiated in rheumatoid arthritis. In July 2006, Vertex was planning to file an IND in the second half of 2006.

Originator Vertex Pharmaceuticals Inc

Licensee Kissei Pharmaceutical Co Ltd

Status Phase II Clinical

Indications Cardiovascular disease, Inflammation, Rheumatoid arthritis

Actions Anti-inflammatory, cardiovascular agent, p38 MAP kinase inhibitor

Synonyms and analogs KVK-702, p38 MAP kinase inhibitors (inflammation), VX-850, VX-954

Introduction

p38 MAP kinase (MAPK) is an intracellular, soluble proline-targeted serine-threonine kinase which belongs to a large family of proteins that include extracellular regulated kinases (ERKs) and c-Jun N-terminal kinases (JNKs) [688537], [688545], [688587]. Thus far, four p38 isoforms have been identified, namely p38α, p38β, p38β and p38δ. The ubiquitous p38α has been the most extensively studied and is believed to be the most physiologically relevant in the regulation of the inflammatory response. While the role of the three other isoforms is not currently well understood, their primary sites of expression are known. Similar to p38α, p38β is also ubiquitously expressed, while p38γ is expressed predominately in skeletal muscle and p38δ is expressed primarily in the lung, kidney, testis, small intestine and pancreas [478666], [608092], [688545], [688587]. Activation of p38 MAPK occurs by the phosphorylation of the Thr-Gly-Tyr (TGY) motif in the activation loop via MAPK kinase (MKK)-3 and MKK-6 in response to extracellular stimuli, such as environmental stress, cytokines, endotoxin (ie, lipopolysaccharide [LPS]), ultraviolet light and ischemia [478666], [608092], [688545], [688587]. The activation of p38 MAPKs leads to gene transcription and translation, followed by an increase in production of inflammatory mediators, such as TNFα, IL-1β, cyclooxygenase (COX)-2, IL-6, IL-12 and IFNγ [688537], [688545], all of which have been demonstrated to play important roles in autoimmune diseases such as rheumatoid arthritis (RA) and/or cardiovascular diseases.

The pathogenesis of RA requires cytokine-mediated communication between T-helper type-1 (Th1) lymphocytes, macrophages, neutrophils, endothelial cells and osteoclasts. The activation and infiltration of these cells, as well as the production of inflammatory cytokines in the synovium, have been revealed to be p38 MAPK-dependent [491004]. Patients with RA exhibited increased activation of p38 MAPK in the synovial lining layer and endothelial cells[547879]. In addition, the p38 MAPK pathway is rapidly activated in rheumatoid synovial fibroblasts by TNFα and IL-1β, resulting in over-production of IL-6 and IL-8 [688636]. Inhibition of p38 MAPK was shown to significantly improve clinical severity scores, reduce bone destruction and cartilage loss, and reduce mRNA levels and the production of inflammatory mediators in models of experimental arthritis [688770], [688772], suggesting that therapy involving the inhibition of p38 MAPK may constitute a new therapeutic strategy for RA.

Activation of p38 MAPK by pathological stressors, including ischemia, has been observed with cardiovascular diseases such as advanced heart failure [688631]. This leads to the activation of MAPK-activated protein kinase (MK)-2 followed by the over-production of inflammatory cytokines (ie, TNFα, IL-1β and IL-6), which play an important role in the pathogenesis of some cardiovascular diseases (ie, myocardial infarction [MI] and congestive heart failure) [688631]. TNFα can also induce p38 MAPK activity [688631]. p38 activity may be involved in many aspects of cardiac pathology, including gene regulation, interstitial remodeling, contractility, energy metabolism, cardiac COX-2 and prostaglandin biosynthesis, cardiac hypertrophy and endothelial dysfunction [505287], [688775]. Inhibition of p38 activation was shown to decrease cardiomyocyte apoptosis and improve cardiac function after myocardial ischemia and reperfusion [688777], reduce hypertrophy and left ventricular (LV) dilatation, and increase LV contractility in the cardiomyopathic hamster model [688778], all of which suggest that strategies to block p38 activation may have an application in ischemic diseases and heart failure, including acute coronary syndromes (ACS).

Evidence from X-ray crystallographic structures suggests that bound ATP directly interacts with the p38 hinge region residues His^{107} and Met^{109} to form a pair of hydrogen bonds with the adenine ring of ATP [688780]. Once p38 is activated, a gate uncovers the active site allowing optimum and efficient binding of ATP, thereby leading to the subsequent phosphorylation and activation of the enzyme

[688784]. To date, the development of p38 inhibitors has focused mainly on small-molecule ATP-competitive inhibitors. As a consequence, many inhibitors have been designed to take advantage of specific interactions that are located within or near the ATP binding site. So far, more than 150 patent applications from at least 30 pharmaceutical companies have claimed novel p38 inhibitors. The p38 inhibitors can be divided into six groups; pyridinyl- and pyrimidyl-imidazoles and related structures, bicyclic 6,6-heterocycles and related structures, *N*,*N'*-diaryl ureas and related compounds, substituted benzamides, diaryl ketones, and indole amides [688780].

More than 100 p38 MAPK inhibitors have been developed for the potential treatment of inflammatory and/or cardiovascular diseases, but the majority have been discontinued mainly due to undesirable side effects. VX-702, one of a series of second-generation, orally active p38 MAPK inhibitors, is under development by Vertex Pharmaceuticals Inc in collaboration with Kissei Pharmaceutical Co Ltd, for the potential treatment of inflammation, RA and cardiovascular diseases [435164], [512323], [688791]. Preliminary phase II results for the treatment of RA and ACS have been reported recently [592866], [654608].

Synthesis and SAR

Vertex developed the first generation of p38 inhibitors, including VX-745, which was suspended from further development due to CNS toxicity. VX-745 had a pyrimidopyridazinone bicycle which formed the hydrogen bond to the linker residue and was directly connected to a phenyl ring in the gatekeeper pocket by a single sulfur atom spacer. A 2,6-diCl phenyl was attached to the bicycle and this was predicted to occupy the hydrophobic pocket of the concave floor [688791]. The structure of VX-702 has not been disclosed, but a Vertex patent application [WO-00214281] suggests that it is an *N*-pyridinyl-*N*-phenyl urea-based inhibitor. The SAR for the urea class is in contrast with most of the other p38 inhibitors that rely more heavily on the hydrogen bonding interaction with Met^{109} for potent p38 activity. Additionally, because of their binding properties, this class of compounds tends to show high affinities and exhibit slow binding kinetics relative to other known p38 inhibitors [688780].

Preclinical development

In an *ex vivo* blood assay primed with LPS, VX-702 dose-dependently inhibited the production of IL-6, IL-1β and TNFα (IC_{50} = 59, 122 and 99 ng/ml, respectively) [592866]. To determine the effects, if any, of VX-702 on platelet function alone, or in conjunction with other commonly used anti-platelet therapies, gel-filtered platelets were prepared from healthy individuals (n = 6) for an *ex vivo* study [516895], [688796]. This activation was completely or partially inhibited by pre-incubation with 1 μM of VX-702 (IC_{50} = 4 to 20 nM). VX-702 had no effect on platelet aggregation induced by any of the p38 MAPK agonists, such as thrombin, SFLLRN, AYPGKF and collagen, in the presence or absence of platelet inhibitors, such as aspirin, heparin or apyrase. VX-702 did not directly cause platelet aggregation or induce Ca^{2+} mobilization, or affect basal aggregation induced by shear stress. In contrast, aspirin blocked thromboxane production, resulting in a significant inhibition of collagen-induced platelet aggregation. These results suggest that blocking p38 MAPK does not affect thromboxane production in human platelets. Unlike aspirin blockade of thromboxane production in platelets with aspirin, VX-702 does not significantly affect platelet function and would not be expected to contribute to an elevated risk of hematological side effects in treated patients [688796].

VX-702, at a dose of 0.1 mg/kg twice daily, was found to be equivalent to methotrexate (a commonly used disease-modifying antirheumatic drug [DMARD]; also at 0.1 mg/kg) in mouse collagen-induced arthritis. Furthermore, VX-702 (5 mg/kg, twice daily) was found to be equivalent to prednisolone (10 mg/kg, once daily) in the same model, as measured by the percentage inhibition of wrist joint erosion and an inflammation score [445056].

Male Sprague Dawley rats (n = 30) with myocardial damage after ischemia-reperfusion injury were randomized to receive either vehicle or VX-702 (5 or 50 mg/kg) [514348]. The results suggested that phosphor MK2 was markedly increased in the ischemic zone tissue compared with the non-ischemic zone tissue in the vehicle group. This effect was dose-dependently reduced in the VX-702 groups. VX-702 selectively inhibited activation of p38 MAPK after ischemia, with no effects on ERKs and JNKs. There were no differences in hemodynamic data and area at risk (AAR)/LV ratio between the three groups. The MI/AAR ratio was significantly reduced in the 50-mg/kg group compared with the other two groups. This study concluded that oral administration of VX-702 reduces myocardial damage after ischemia-reperfusion injury, suggesting that selective p38 MAPK inhibition may play a therapeutic role in ACS.

Metabolism and pharmacokinetics

Healthy volunteers were administered VX-702 orally at doses of 2.5 to 80 mg (n = 5 to 8 per dose point) [592866]. The half-life was 16 to 20 h, with a median clearance of 3.75 l/h and a volume of distribution of 73 l/kg. Both the AUC and C_{max} were dose proportional for VX-702, which was found to be predominantly renally cleared.

Toxicity

No data are currently available.

Clinical development

Phase I

VX-702 was administered to 45 patients with ACS undergoing percutaneous coronary intervention (PCI) (5, 10, 20 and 40 mg, at 3 and 24 h prior to PCI) [592866]. There was a dose-dependent reduction in C-reactive protein (CRP), a predictor of coronary heart disease, 1 month after patient discharge. A significant but variable reduction in serum IL-6 was reported, and IL-1β production was inhibited in a pharmacodynamic assay. In addition there was a dose-dependent reduction in neutrophils and plasma monocytes at days 2, 3 and 4 of the study, and also after 1 month. There was no significant elevation of liver function tests.

Phase II

RA

A randomized, double-blind, multicenter, 12-week, phase II clinical study was conducted in patients with moderate to severe RA (n = 278) some of whom were receiving DMARDs but none were receiving methotrexate or anti-TNF therapies [654608]. Patients received either VX-702 (5 or 10 mg) or placebo once daily for 12 weeks. Patients were evaluated for improvement in clinical signs and symptoms according to the American College of Rheumatology (ACR)20 criteria, which assesses improvements in tender and swollen joint counts, plus three of the following: patient pain assessment, patient global assessment, physician global assessment, patient self-assessed disability and acute-phase reactant (erythrocyte sedimentation rate or CRP). VX-702 treatment significantly reduced signs and symptoms of RA in a dose-dependent manner, with 30, 38 and 40% of patients receiving placebo, 5 and 10 mg, respectively, achieving an ACR20 response at week 12 (p = 0.04). In addition, 32, 41 and 44% of patients receiving placebo, 5 and 10 mg, respectively, achieved a moderate or good European League Against Rheumatism response (p = 0.01), which has three categories (good, moderate and non-responders) based on the assessment of disease activity using the disease activity score. Dose-dependent significant effects were also seen on tender joint counts (p = 0.007), swollen joint counts (p = 0.003) and morning stiffness (p = 0.03).

In March 2006, Vertex expected to initiate clinical studies of VX-702 in combination with methotrexate for RA, including a 3-month, dose-ranging phase II study in more than 200 patients [654608].

ACS

A phase IIa double-blind, placebo-controlled, randomized study was designed to evaluate the safety and anti-inflammatory effect of VX-702 in 45 patients with unstable angina undergoing PCI [564973]. Patients received VX-702 (5, 10, 20 or 40 mg/day) 2 days prior to PCI and 3 days afterwards. CRP was lowered within 24 h of the first dose. A significant dose-dependent lowering was seen at 48 h after VX-702 treatment, with decreases of 37, 67, 71 and 63% in the 5-, 10-, 20- and 40-mg groups, respectively, compared with an increase of 98% in the placebo group. Decreased CRP was maintained for 4 weeks beyond the 5-day dosing schedule.

Side effects and contraindications

A 12-week study in patients with moderate to severe RA (n = 315) indicated that VX-702 (5 or 10 mg) was well tolerated [654608]. Premature discontinuations for adverse events were low (2, 5 and 10% in the placebo, 5- and 10-mg groups, respectively). No significant effects were observed from liver function tests. Gastroenteritis, nausea/vomiting, rash and renal impairment (increased serum creatinine levels to 1.2- to 1.5-fold of upper limit of normal) associated with VX-702 treatment led to discontinuation in two patients. The most common adverse events were generally mild or moderate, and included infection (5 and 10% of placebo and VX-702 patients, respectively), gastrointestinal disorders (6 and 8%, respectively), and skin disorders (0 and 9%, respectively). Ambulatory and 12-lead electrocardiographic monitoring revealed no differences in ventricular ectopic activity or cardiac arrhythmias between placebo and treated patients. A minimal (~ 1.5%) dose-dependent increase on digital electrocardiograms in the Fridericia rate-corrected QT interval (QTcF) was observed in the VX-702 treatment groups, from baseline to the end of treatment. No patient experienced a clinically significant increase in QTcF (defined as 60 ms, or ~ 15%) at any time in the study.

VX-702 (5, 10, 20 or 40 mg) was well tolerated in 45 patients with unstable angina undergoing PCI [564973]. The frequency of adverse events, including bleeding, arrhythmia and liver enzyme abnormalities, were similar in the VX-702 and placebo groups over a 4-week period.

Patent summary

As of October 2006, the structure of VX-702 had not been disclosed; however, Vertex had previously stated that VX-702 was structurally distinct from the earlier p38 inhibitor, VX-745 [445056], [450049]. The product case for VX-745 is WO-09827098, the first of ten PCT applications from Vertex claiming new compounds as p38 kinase inhibitors; the other applications being WO-09900357, WO-09958502, WO-09964400, WO-00017204, WO-00017175, WO-00170695, WO-00214281, WO-02092087 and WO-02100405. As VX-702 has been disclosed to be structurally distinct from VX-745, it is probable that it is not disclosed in WO-09827098, but rather in one of the subsequent PCT applications. In August 2004, the process case WO-2004072038 was published, claiming methods for preparing p38 inhibitors, in particular, compounds disclosed in WO-09958502 and WO-00017175. If WO-2004072038 covers the preparation of VX-702, the product case for VX-702 is likely to be WO-09958502 or WO-00017175.

Current opinion

Activation of p38 MAPK is associated with the over-production of proinflammatory mediators, including TNFα, IL-1β, COX-2, IL-6, IL-12 and IFNγ. Therefore, inhibition of p38 MAPK activity by VX-702 has the potential for the treatment of disorders, including a variety of inflammatory diseases such as RA, Crohn's disease and psoriasis, as well as cardiovascular diseases such as ACS. Preliminary clinical studies have shown promising results; VX-702 significantly reduced the signs and symptoms of RA over 12 weeks, and decreased CRP levels in patients with ACS. It was well tolerated with no observed liver function abnormalities. VX-702 was unable to cross the blood-brain barrier [422880], thus it may have little neurological adverse effects. It did not affect platelet function, and therefore may not cause the side effects of bleeding in treated patients [688796].

Of note, p38 MAPK has been involved in many mammalian cell processes including cell-cycle regulation, death, development and differentiation [688537]. As a consequence of the wide-ranging regulatory role of p38 MAPK in these diverse cellular processes, the possibility of adverse effects resulting from undesired pharmacological activity is the major concern for the p38 MAPK inhibitors. Many of these inhibitors have been reported to equally inhibit both the

p38α and p38β isoforms, and p38β inhibition may induce more unwanted off-target effects due to the divergent physiological roles of p38β.

More than 100 p38 MAPK inhibitors have been investigated over the past decade, but the majority have not entered into clinical trials or have been withdrawn after initial clinical trials mainly due to undesirable side effects. For example, BIRB-796 (Doramapimod), an *N*-pyrazole urea derivative, was being developed by Boehringer Ingelheim GmbH. In a phase I clinical trial, BIRB-796 (20, 50 and 150 mg for 7 days) demonstrated a symptomatic dose-related rise in alanine transaminase and aspartate transaminase levels, primarily with the 150-mg dose [472871]. In a 14-day study with oral doses of 15 and 30 mg twice daily, 9 of 48 individuals had alanine transaminase values above the upper limit of normal [472871]. Although phase II studies in RA, Crohn's disease and psoriasis were completed, BIRB-796 was discontinued from further development, perhaps due to the observed liver function abnormalities [608092], [688791]. AMG-548, a pyrimidinone compound that was being developed by Amgen Inc, was the most potent and efficacious p38 inhibitor reported to progress to phase I studies. However, random liver enzyme elevations in a multidose study prevented further development of this drug [608092], [688791]. VX-745, the first generation p38 MAPK inhibitor developed by Vertex, had entered phase II trials for the treatment of RA [688784], but was discontinued in 2001 after the compound was shown to cross the blood-brain barrier and exhibit toxicity at high doses in animal studies [422880]. SCIO-469 (Scios Inc), a potent p38α inhibitor possibly derived from the indole amide class [688780], is currently undergoing phase II clinical trials for the treatment of pain, multiple myeloma and RA [608092]. Although results from phase I trials suggested that SCIO-469 was well-tolerated, there was a transient and mild light-headedness associated with the highest doses, suggesting that it may cross the blood-brain barrier. In contrast to these p38 inhibitors, VX-702 may have a superior safety profile because of its inability to cross the blood-brain barrier and no reports of liver dysfunction, even though it has a similar urea structure to BIRB-796. However, the undesired common effects of p38 inhibitors on liver, central nervous, immune (resulting in infection), cardiovascular and gastrointestinal systems should be kept in mind for future clinical trials of VX-702.

With regard to efficacy, VX-702 effectively relieved signs and symptoms of RA but only showed modest improvement in the ACR20 response rate compared with placebo during the phase II clinical trial. This is possibly due to the ability of p38 MAPK inhibitors to not only inhibit the Th1 response (useful for the treatment of chronic inflammatory diseases), but also to decrease Th2 function which reduces the production of IL-4 and IL-10 (resulting in enhancement rather than amelioration of the underlying inflammatory response in Th1-driven diseases such as RA) [688537]. Furthermore, other members of the MAPK family (such as JNK) also play an important role in the pathogenesis of RA [688798], thus while the selective inhibition of p38 MAPK can diminish side effects, it may consequently compromise the efficacy for the treatment of RA. Inhibition of spinal p38 may regulate peripheral inflammation [693122], and therefore the inability of VX-702 to cross the blood-brain barrier could decrease the anti-inflammatory effects. The efficacy of VX-702 on ACS is unclear; however, it has been reported to reduce CRP level in patients with ACS.

There are currently limited published data available on VX-702 and reasons for this are unknown. It may reflect business consideration by the developer, as there is fierce competition for p38 inhibitor development between different pharmaceutical companies.

In summary, VX-702 is well tolerated and significantly reduces inflammatory responses in the treatment of RA and ACS, but its clinical efficacy and safety remain to be further demonstrated.

Commercial opinion

Analysts from Wachovia Securities ascribed a low probability of success to the VX-702 program based on what they believe to be low results from the rheumatoid arthritis phase II study in combination with Vertex's announced delay on the start of a phase IIb trial until the second half of 2007 [728603]. However, if launched in 2011, Wachovia estimated initial worldwide sales of US $221.4 million, to peak at US $750 million by 2013.

Licensing

Kissei Pharmaceutical Co Ltd

By September 1997, Kissei had exercised an option for the development of p38 MAP kinase inhibitors and had entered into a three-year agreement with Vertex to develop these inhibitors, including VX-702 [386727]. Under the agreement, Kissei was to pay a license fee, research support and milestone payments up to US $22 million; Kissei gained exclusive rights in Japan and certain rights in south east Asia, and semi-exclusive rights in China, Taiwan and South Korea. Vertex retained US and European rights [386727], [399818]. In the fourth quarter of 2000, Kissei paid Vertex a US $1 million milestone payment for the advancement of VX-702 into preclinical studies [399818], [475831].

Development history

Developer	Country	Status	Indication	Date	Reference
Vertex Pharmaceuticals Inc	Europe	Phase II	Rheumatoid arthritis	12-JUN-05	606796
Vertex Pharmaceuticals Inc	US	Phase II	Cardiovascular disease	21-MAY-03	490502
Kissei Pharmaceutical Co Ltd	Japan	Phase I	Cardiovascular disease	31-DEC-05	649069
Kissei Pharmaceutical Co Ltd	Japan	Phase I	Inflammation	31-DEC-05	649069
Vertex Pharmaceuticals Inc	US	Discovery	Inflammation	24-OCT-00	386727

Literature classifications

Biology

Study type	Effect studied	Model	Result	Reference
Ex vivo	Activity	Blood assay primed with LPS.	VX-702 dose-dependently inhibited the production of IL-6, IL-1β and TNFα (IC_{50} = 59, 122 and 99 ng/ml, respectively).	592866
In vivo	Efficacy	Mouse collagen-induced arthritis.	VX-702 (at a dose of 0.1 mg/kg twice daily) had an equivalent effect as methotrexate (0.1 mg/kg). In addition, VX-702 (5 mg/kg twice daily) had an equivalent effect as prednisolone (10 mg/kg once daily), as measured by percentage inhibition of wrist joint erosion and inflammation score.	445056
In vivo	Efficacy	Ischemia-reperfusion injury model in male Sprague Dawley rats (n = 30) randomized to receive vehicle or VX-702 (5 or 50 mg/kg).	VX-702 selectively inhibited activation of p38 MAPK after ischemia with no effects on ERKs and JNKs. The MI/AAR ratio was significantly reduced in the 50-mg/kg group compared with the vehicle and 5-mg/kg groups.	514348
In vitro	Activity	Gel-filtered platelets prepared from healthy individuals (n = 6).	Pre-incubation of platelets with VX-702 (1 μM) completely or partially inhibited platelet agonist-induced p38 activation (IC_{50} = 4 to 20 nM). No effect of VX-702 on platelet aggregation induced by any of the p38 MAPK agonists in the presence or absence of anti-platelet therapies occurred.	688796

Metabolism

Study type	Effect studied	Model	Result	Reference
In vivo	Pharmacokinetics	Volunteers administered VX-702 orally at doses of 2.5 to 80 mg (n = 5 to 8 per dose point).	The half-life of VX-702 was 16 to 20 h, with a median clearance of 3.75 l/h and a volume of distribution of 73 l/kg. Both AUC and C_{max} values were dose proportional for VX-702, which was predominantly renally cleared.	592866

Clinical

Effect studied	Model	Result	Reference
Safety and efficacy	A phase I, 5-day study of VX-702 (5, 10, 20 and 40 mg, at 3- and 24-h prior to PCI) administered to 45 patients with ACS undergoing PCI.	There was a dose-dependent reduction in CRP 1 month after patient discharge. A significant but variable reduction in serum IL-6 was reported, as well as a dose-dependent reduction in neutrophils and plasma monocytes.	592866
Safety and efficacy	A phase II, randomized, double-blind, 12-week clinical trial in patients with moderate to severe RA (n = 278). Patients received either VX-702 (5 or 10 mg) or placebo once daily for 12 weeks.	VX-702 significantly reduced signs and symptoms of RA in a dose-dependent manner, with 30, 38 and 40% of patients receiving placebo, and 5 and 10 mg of VX-702, respectively, achieving an ACR20 response at week 12. In addition, 32, 41 and 44% of patients, respectively, achieved a moderate or good European League Against Rheumatism score. Dose-dependent, significant effects were also seen on tender joint counts (p = 0.007), swollen joint counts (p = 0.003) and morning stiffness (p = 0.03).	654608
Safety, tolerability and efficacy	A phase IIa, double-blind, placebo-controlled, randomized study of VX-702 (5, 10, 20 or 45 mg/day) administered for 2 days prior to PCI and 3 days afterwards in 45 patients with unstable angina undergoing PCI.	CRP was lowered within 24 h of the first dose of VX-702. A significant dose-dependent lowering was observed at 48 h with decreases of 37, 67, 71 and 63% in the 5-, 10-, 20- and 40-mg VX-702 groups, respectively, compared with an increase of 98% in the placebo group. Decreased CRP remained at 4 weeks beyond the 5-day dosing schedule. VX-702 was well tolerated, and adverse events, including bleeding, arrhythmias and liver enzyme abnormalities, were similar in the drug and placebo groups in a 4-week period.	564973

Associated patent

Title Inhibitors of p38.

Assignee Individual

Publication WO-00214281 21-FEB-02

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Inventors Cochran J, Galullo V, Bemis G.

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