Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pain 10 (2006) 567–571
www.EuropeanJournalPain.com

The NK_1-receptor antagonist TKA731 in painful diabetic neuropathy: A randomised, controlled trial

Søren H. Sindrup [a,*], Ana Graf [b], Nikolaos Sfikas [b]

[a] *Department of Neurology, Odense University Hospital, DK-5000 Odense C, Denmark*
[b] *Novartis Pharma AG, Basel, Switzerland*

Received 13 April 2005; received in revised form 4 August 2005; accepted 8 August 2005
Available online 30 September 2005

Abstract

Substance P is one of the neurotransmitters released by primary nociceptive neurons in the dorsal horn of the spinal cord and it binds postsynaptically to NK_1-receptors. This receptor is therefore an obvious target for analgesic drugs. The aim of this multicenter, randomised, double-blind, placebo-controlled and parallel-group study was to test if the non-peptide NK_1-receptor antagonist TKA731 would relieve painful diabetic polyneuropathy. Eighty-seven patients completed a treatment period of 2 weeks' duration with TKA731 (150 mg daily) or placebo preceded by one week for baseline observations. There was no significant difference between TKA731 and placebo in change in pain rating from baseline to study end neither for rating of total pain (mean −13.4 mm vs. −11.6 mm, $p = 0.664$) nor for change in ratings of different pain symptoms (touch- or pressure-evoked pain, pain paroxysms, steady burning or deep aching pain) ($p = 0.169$–0.834).
© 2005 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Ltd. All rights reserved.

Keywords: NK_1-receptor antagonist; Painful diabetic neuropathy; Treatment

1. Introduction

Painful polyneuropathy, one of the most common neuropathic pain condition, is usually treated with antidepressants or anticonvulsants (Sindrup and Jensen, 2000). Treatment with drugs from one of these groups will relieve one in every three or four patients. Although tramadol and oxycodone may also benefit patients with painful polyneuropathy, search for alternative drug treatments is needed.

The known mechanisms of neuropathic pain are, of course, obvious targets for drugs to be used to relieve this type of pain. Several mechanisms seems to be at play, e.g. ectopic activity in nociceptive C-fibres due to excessive expression of sodium channels, hyperexcitability in dorsal horn neurons mediated via NMDA-receptors, and maybe decreased segmental and suprasegmental inhibition (Woolf and Mannion, 1999). Under normal conditions, excitatory amino acids are responsible for transmission of signals in the nociceptive pathway, but with nerve injury causing barrages of action potentials to enter the dorsal horn peptide neurotransmitters such as substance P (SP) become increasingly important as changes in second order neurons may occur via its receptor NK_1. NK_1-receptor antagonists have shown efficacy in animal models of neuropathic pain, but it is disputed whether NK_1-receptor antagonists can be expected to relieve clinical pain (Hill, 2000; Urban and Fox, 2000).

TKA731 is an orally bioavailable, non-peptide NK_1-receptor antagonist (Novartis, Data on file). In a

* Corresponding author. Tel.: +45 65412471; fax: +45 65413389.
E-mail addresses: soeren.sindrup@ouh.fyns-amt.dk, s.sindrup@dadlnet.dk (S.H. Sindrup).

1090-3801/$32 © 2005 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejpain.2005.08.001

HELSINN EXHIBIT 2054
Azurity Pharmaceuticals, Inc. v. Helsinn Healthcare S.A.
IPR2025-00949

guinea-pig model of neuropathic pain (Campbell et al., 1998) oral administration of TKA731 reverses mechanical hyperalgesia established by partial ligation of one sciatic nerve (Novartis, Data on file). We have therefore tested the effect of TKA731 in painful diabetic neuropathy in a multicenter, randomised, placebo-controlled, parallel-group study to evaluate if it could be an alternative treatment for neuropathic pain in humans.

2. Methods

2.1. Patients

Male and female patients aged 18 years or older with painful diabetic polyneuropathy for 0.5–5 years and stable diabetes for at least 6 months were recruited from 12 centers in 5 European countries. A pain rating at a screening visit had to be at least 50 mm on a 100 mm VAS and the average of daily pain ratings during 7 days prior to randomisation had to be at least 40 mm. We excluded patients with causes of pain other than diabetic neuropathy, pain due to diabetic neuropathy refractory to two or more pharmacological treatments, any advanced, severe, or unstable disease that could put the patient or the evaluation at risk, amputation other than toes, body mass index >35 kg/m^2, clinically significant ECG abnormalities, creatinine clearance <30 ml/min, or alcohol or drug abuse.

The study was planned to include a maximum of 120 patients, i.e. 60 in each group. This sample size was based on the assumptions that the estimated change in average VAS score would be 19 units in the placebo group and 39 units in the TKA731 group, with SD 30 units. The study was powered to detect the efficacy of TKA731 compared with placebo with 90% power at the two-side significance level of 0.05.

2.2. Study design and randomisation

For patients already treated with drugs for their neuropathic pain, this treatment was slowly tapered during a pre-study period of at least 1 week, and no analgesic medication except paracetamol was allowed within 10 days prior to randomisation. After 1 week for baseline observations, the patients were randomised to enter a double-blind treatment period for 2 weeks with either TKA731 50 mg t.i.d. (150 mg/day) or matching placebos in a 1:1 ratio. TKA731 150 mg/day was the maximum dose allowed by toxicology and technical development. The patients were randomized in blocks of 4 and the randomization list was computer-generated. The study drugs were packed in boxes marked with patient number and after the baseline period, patients were numbered consecutively and treated with the study drugs with the corresponding randomisation number. Sealed envelopes with treatment sequence for each patient for emergency situations were present at the study sites. Up to 8 tablets of 500 mg paracetamol could be used daily as rescue medication during the pre-randomisation and the double-blind treatment phase.

2.3. Evaluations

The primary efficacy variable was the change in daily pain rating on a 100 mm VAS from baseline to treatment phases. Secondary efficacy variables were patients' global assessment of therapeutic effect on a 7 point scale (very much improved to very much deteriorated), use of rescue medication, sleep questionnaire (presence or absence of delayed onset of sleep and interruption of sleep), and pain VAS rating of different types of pain (lancinating, constant deep, constant superficial burning, touch- and pressure-evoked pain).

Safety was evaluated by recording of adverse effects reported spontaneously or on questioning at study visits after the first and second week of the double-blind treatment period.

Blood for determination of plasma drug concentration was drawn at study visits at the end of the first and second week of the double-blind treatment period. Drug concentrations were determined by liquid chromatography and mass spectrometry. The lower limit of quantification was 0.5 ng/ml.

2.4. Data analysis and statistics

A group sequential design based on truncated sequential probability ratio test design was used. After treatment was completed for a prespecified number of patients (50), an independent statistician would evaluate the primary efficacy data and enrollment should be stopped if active treatment was either shown to be statistically better than placebo, or not significantly different from placebo.

Statistical analysis of the primary efficacy variable (intention to treat population) was done by comparison of treatment group differences by analysis of covariance (ANCOVA with correction for baseline VAS rating, baseline rescue medication and center), using data sets with last observation carried forward imputation for missing and invalid values. The analysis was done in a naïve way, i.e. without corrections for the group sequential nature of the trial.

Exploratory analysis was performed for secondary efficacy variables. Summary descriptive statistics were used for the safety assessment results.

3. Results

At total of 123 patients were screened for participation. Thirtysix of these did not enter the study for var-

15322149, 2006, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1016/j.ejpain.2005.08.001 by Claudia Cohen , Wiley Online Library on [28/08/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ious reasons (some patients had more than one reason for not being randomized): 3 other diseases, 8 laboratory tests (drug abuse or glycated hemoglobin above 11%), 15 pain VAS score at baseline too low, 4 unacceptable medications, 5 consent withdrawn, and 7 end of recruitment. The first patient was recruited 9th April 2002 and the last patient completed 24th July 2002.

The first interim analysis was conducted after 50 patients had completed the trial and the efficacy results of this analysis asked for the recruitment to be stopped. An additional 37 patients were randomized, thus resulting in a total of 87 randomized patients. All enrolled patients were included in the safety analysis; 86 patients were included in the intention to treat (ITT) analysis (1 patient on placebo was excluded as he was unable to mark the VAS scales due to recent eye surgery), and 80 patients were included in the per protocol (PP) analysis (39 in the TKA731 group, and 41 in the placebo group). All 7 patients excluded from the PP population were excluded because of major protocol violations (2 low pain score at screening visit or during baseline, 1 less than 4 pain VAS scores during the second treatment week, 2 intake of prohibited medication within 2 weeks of randomization, 1 advanced unstable disease). Demographic details on patients in the ITT population group are given in Table 1. No significant difference between treatment groups was found.

The daily pain rating decreased on both TKA731 and placebo (Fig. 1), but there was no significant difference between the two treatments (Table 2). Among ratings of the different subtypes of pain, the touch- and pressure-evoked pain showed the greatest numerical difference between the treatment groups, which was however not statistically significant (Table 2). Global assessment of therapeutic effect, and sleep interference were also similar between TKA731 and placebo (Table 2) as was intake of rescue medication ($p = 0.101$).

The steady state peak plasma concentration of TKA731 ranged from below detection limit of the drug assay to 1200 ng/ml and the mean value after exclusion of values from samples drawn more than 24 h after last dosing was 375 ng/ml. There was no relation between the changes in pain score and the plasma concentrations as determined from samples drawn within 24 h of last dosing ($R^2 = 0.0122$, $p = 0.487$).

Seventeen patients in the TKA731 group (38.6%) and 18 patients in the placebo group (41.9%) suffered at least one adverse event. The only adverse events

Table 1
Demographic and baseline characteristics by treatment group (ITT)

		TKA731 ($N = 44$)	Placebo ($N = 42$)
Age (years)	Mean ± SD	63.0 ± 9.3	61.1 ± 7.0
Sex	(male/female)	20/24	18/24
Body mass index (kg/m^2)	Mean ± SD	29.8 ± 4.1	29.6 ± 3.9
Duration of diabetes (years)	Mean ± SD	13.5 ± 9.3	14.9 ± 10.5
Type of diabetes	(type 1/type 2)	7/37	12/30
Duration of pain (years)	Mean ± SD	2.8 ± 1.8	2.8 ± 1.3
Screening pain rating (mm)	Mean ± SD	70.3 ± 13.4	66.4 ± 12.1
Average baseline pain rating (mm)	Mean ± SD	69.6 ± 11.2	66.8 ± 11.3

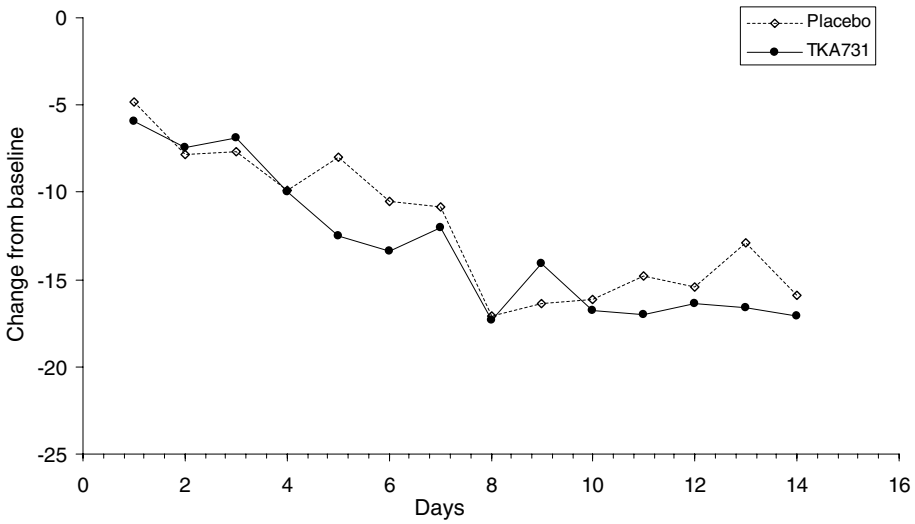

Fig. 1. Time course of pain ratings (VAS score) for the ITT patients with LOCF. ◇ = TKA731, ● = placebo.

15322149, 2006, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1016/j.ejpain.2005.08.001 by Claudia Cohen , Wiley Online Library on [28/08/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2
Treatment comparisons of change from baseline for the intention to treat population

	Mean (SD)	[a]*p*-Value
[b]*Total pain rating* (VAS, mm)		
Placebo	−11.6 (−19.5 to −3.7)	
TKA731	−13.4 (−20.2 to −6.6)	0.664
Global assessment		
Placebo	−0.7 (1.1)	
TKA731	−0.7 (1.3)	0.642
Delayed sleep onset (proportion of days)		
Placebo	−0.23 (0.37)	
TKA731	−0.19 (0.33)	0.710
Awaking from sleep (proportion of days)		
Placebo	−0.15 (0.30)	
TKA731	−0.23 (0.34)	0.417
Constant deep pain (VAS, mm)		
Placebo	−18.8 (29.0)	
TKA731	−19.9 (30.4)	0.796
Constant burning pain (VAS, mm)		
Placebo	−16.9 (23.0)	
TKA731	−18.1 (30.3)	0.803
Lancinating pain (VAS, mm)		
Placebo	−13.9 (24.2)	
TKA731	−12.5 (31.7)	0.834
Touch-evoked pain (VAS, mm)		
Placebo	1.6 (30.5)	
TKA731	−7.0 (26.6)	0.169
Pressure-evoked pain (VAS, mm)		
Placebo	−5.6 (23.5)	
TKA731	−12.7 (28.5)	0.364

[a] TKA731 vs. placebo.
[b] Least square means (95% CI intervals) adjusted for baseline VAS rating, baseline rescue medication and center.

observed in more than 2 patients in any group were headache (4 patients in the TKA731 group, 5 patients in the placebo group), blood glucose decrease (3 patients in the placebo group) and fatigue (3 patients in the TKA731 group). Blood glucose levels remained unaltered during the study.

4. Discussion

This study did not find any analgesic effect of the non-peptide NK_1-receptor antagonist TKA731 in painful diabetic polyneuropathy. The study included an adequate sample size and the patients are supposed to have been the best possible candidates for an analgesic drug trial, since they had a well defined pain condition, were on no other pain medication and had not failed on multiple previous treatments. Therefore the results probably reflect that this NK_1-receptor antagonist has no analgesic effect on painful diabetic neuropathy. However, it cannot be excluded that the lack of effect on neuropathic pain in this study was caused by use of subtherapeutic doses although different lines of evidence indicate that this is not the case. The plasma TKA731 concentrations ranged from very low levels to high level. Therefore, the analysis of a relation between pharmacokinetics and pharmacodynamics is expected to have been able to detect an interaction in case of therapeutic efficacy. Further, the plasma concentrations were within a range which is relevant for binding of TKA731 to the NK_1-receptor. TKA731 has a high affinity for the human NK_1-receptor, with a K_i of 0.09 nM corresponding to 0.051 ng/ml for displacing substance P from the receptor (TKA731A Investigators Brochure, Novartis Pharma AG, Basel). Binding of TKA731 to plasma proteins may though have prevented sufficient concentrations to reach the receptors, in particular in the brain. In rats, there is a poor blood/brain barrier penetration, whereas in guinea pigs the penetration is significant with a brain/blood ratio of 0.2–0.4 (TKA731A Investigators Brochure, Novartis Pharma AG, Basel).

Previous clinical trials of the NK1-receptor antagonists Lanepitant and MK-0869 in chronic neuropathic pain have also been negative (Block et al., 1998; Goldstein and Wang, 1999). For Lanepitant, this may be explained by a relatively poor effect in the relevant animal models and poor penetration of the blood brain barrier and MK-0869 had not been tested in the relevant animal model, i.e. models of neuropathic pain in guinea pigs and not models in rats (Urban and Fox, 2000). The issue of guinea pig versus rat models of neuropathic pain relates to the fact that drug substance affinities for human and guinea pig NK_1-receptors are quite similar, whereas the affinities are different between humans and rats. TKA731 had in fact been found to have analgesic effect in a guinea pig model of neuropathic pain. The present clinical data for TKA731 thus further indicate that NK_1-receptor antagonists may not have a potential for relieving clinical pain and TKA731 is not being developed further by Novartis.

Why are then NK_1-receptor antagonists not analgesic in clinical pain in humans? It has been speculated that the lack of effect in clinical pain in spite of obvious effect in animal experimental pain models may be related to differences in physiology of SP between humans and experimental animals which species differences in supraspinal distribution of NK_1-receptors may indicate (Ma and Hill, 1999; Hill, 2000). Another explanation could be the timing of NK_1-receptor antagonist treatment. Possibly SP and NK_1-receptors are only involved during a narrow time window relatively early during development of neuropathic pain and may have lost its importance later during the chronic phase where the drug trial is performed.

References

Block GA, Rue D, Panebianco D, Reines SAthe L-754-030 Study Group. The substance P receptor antagonist L-754-030 (MK-0869)

15322149, 2006, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1016/j.ejpain.2005.08.001 by Claudia Cohen , Wiley Online Library on [28/08/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

is ineffective in the treatment of post-therapeutic neuralgia. Neurology 1998;50:A225.

Campbell EA, Gentry C, Patel S, Panesar MS, Walspole CSJ, Urban L. Selective neurokinin-1 receptor antagonists are antihyperalgesic in a model of neuropathic pain in guinea-pig. Neuroscience 1998;87:527–32.

Goldstein DJ, Wang O. Lanepitant, an NK_1 antagonist, in painful diabetic neuropathy. Clin Pharmacol Ther 1999;65:119.

Hill R. NK_1 (substance P) receptor antagonists – why are they not analgesic in human? TiPS 2000;21:244–6.

Ma O-P, Hill RG. Neurokinin antagonists as potential agents for use in pain management. Curr Opin Invest Drug 1999;1: 65–71.

Sindrup SH, Jensen TS. Pharmacological treatment of pain in polyneuropathy. Neurology 2000;55:915–20.

Urban LA, Fox AL. NK_1-receptor antagonists – are they really without effect in the pain clinic? TiPS 2000;21:462–4.

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353: 1959–64.

15322149, 2006, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1016/j.ejpain.2005.08.001 by Claudia Cohen , Wiley Online Library on [28/08/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License