European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT
FOR
QUTENZA

International Nonproprietary Name:
capsaicin

Procedure No. EMEA/H/C/000909

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant NeurogesX UK Ltd. submitted on 30 August 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Qutenza, through the centralised procedure under Article 3 (2) b of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 1 June 2006. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The applicant applied for the following indication treatment of peripheral neuropathic pain in adults. Qutenza can be used alone or in combination with other pain medications.

Scientific Advice
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Beatriz Silva-Lima** Co-Rapporteur: **János Borvendég**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 30 August 2007.
- The procedure started on 27 September 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2007 (The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2007.
- During the meeting on 24 January 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 January 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 September 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 31 October 2008.
- During the CHMP meeting on 20 November 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During the CHMP meeting on 16-19 February 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 16-19 March 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Qutenza on 19 March 2009. The applicant provided the letter of undertaking on 9 March 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The active substance of Qutenza cutaneous patch 179 mg is capsaicin. Capsaicin is a selective agonist of the transient receptor potential vanilloid 1 receptors (TRPV1). TRPV1 are expressed abundantly on small-diameter sensory neurons, e.g. nociceptors. Persistent stimulation of the TRPV1 receptors may result in the nociceptor desensitization with its consequent lack of sensitivity to relevant noxious stimuli. This may subsequently lead to analgesic effects and offer viable therapeutic option for various pain syndromes.

Neuropathic pain as defined by the International Association for the Study of Pain is the pain initiated or caused by a primary lesion or dysfunction in the nervous system. Clinical features of peripheral neuropathy may include disabling symptoms of burning, stinging, shooting pain or electrical sensations, paresthesias, allodynia and hyperalgesia. These clinical features are usually associated with an underlying disease state such as diabetes mellitus, a history of herpes zoster outbreak, malnutrition or human immunodeficiency virus (HIV) infection and therapy. Present knowledge suggests that the optimal treatment of neuropathic pain should be based on the underlying mechanism in each patient; however this is not always feasible.
Currently used medications in the treatment of neuropathic pain include tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, anticonvulsants, non-steroidal anti-inflammatory agents and opioids. Nevertheless, systemic treatments can exhibit limited efficacy and tolerability, and some undesirable adverse reactions. Non-pharmacological treatments such as transcutaneous nerve stimulation and psychological therapy have had some degree of success.

It has been suggested that high concentrations of capsaicin rapidly delivered to the skin might activate and quickly desensitize cutaneous nociceptors resulting in pain relief and less burning sensation than low concentrations of capsaicin. Consequently, Qutenza is presented as a high concentration capsaicin cutaneous patch (8%) containing 179 mg of capsaicin per patch (640 micrograms per cm^2 of the patch).

This application has been submitted under Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application. The initial indication at the submission was: treatment of peripheral neuropathic pain in adults. Qutenza can be used alone or in combination with other pain medications. Qutenza Cutaneous Patch was granted eligibility for submission to obtain the Community Marketing Authorisation under Article 3(2)b of the Regulation No. 726/2004 (Significant Technical Innovation).

2.2 Quality aspects

Introduction

Qutenza is a cutaneous patch used for the treatment of peripheral neuropathic pain. Qutenza patch is 280 cm^2 and contains 179 mg of capsaicin (8% w/w). It is supplied as a procedure kit which includes one or two single use patches of the same strength of the active ingredient, capsaicin (8%) and a tube of cleansing gel. Other ancillary items are also part of the kit such as stretchable stockings (to assist in maximising adhesion of the patch to the skin), nitrile gloves (to protect the healthcare professional applying and removing the patch), waste bag and gauze.

The patch has a rectangular shape and rounded corners and may be cut to appropriate size and shape to match the treatment area.

Each patch is composed of three layers:

a) backing layer consisting of polyethylene terephthalate (PET) film
b) self adhesive matrix layer containing capsaicin, amine-resistant silicone-type adhesives, diethylene glycol monoethyl ether (DGME), silicone oil and ethyl cellulose.
c) removable protective layer, which is a transparent fluoropolymer coated polyester film.

The primary packaging for each patch is a pre-printed, laminated, heat-sealed sachet composed of paper, aluminium and polyacrylnitril (PAN) layers bonded with a suitable adhesive.

Cleansing gel is supplied to remove residual capsaicin from the skin after application of the Qutenza Cutaneous Patch. Cleansing gel is a topical gel and consists primarily of macrogol 300, which solubilises capsaicin allowing it to be wiped from the skin after treatment. Cleansing Gel has no therapeutic value in treating neuropathic pain. Other than macrogol 300, Cleansing Gel contains Carbopol 1382, purified water, sodium hydroxide, disodium edetate and butylhydroxy anisole.

Active Substance

The active substance is capsaicin (*trans*-8-methyl-N-vanillyl-6-nonenamide) produced synthetically and is present as the *trans*-isomer. Although there are two geometric isomers of capsaicin, only trans-capsaicin occurs naturally. Its molecular formula is $C_{18}H_{27}NO_3$ and its molecular weight is 305.42. Capsaicin structural formula is as follows:

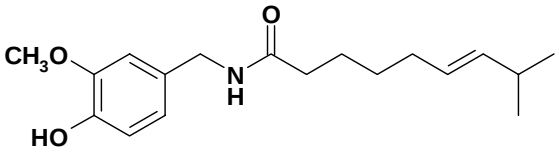

Figure 1: Chemical structure of capsaicin

Capsaicin is white to light yellow powder with a melting point between 66°C–70°C and LogP (octanol/water) of 3.20. Capsaicin is freely soluble in acetone, acetonitrile, dichloromethane, ethanol, ethyl acetate, methanol, 2-propanol, methyl ethyl ketone. It is soluble in toluene and slightly soluble in water.

Capsaicin is unlikely to form solvates or hydrates and is non-hygroscopic. Capsaicin has no chiral centre.

Manufacture
Capsaicin is synthesised in 5 steps. The in process controls have been identified in development studies as being critical to ensure the synthetic manufacturing process can consistently produce active substance meeting the release specifications.

Confirmation of the chemical structure of capsaicin was provided by elemental analysis, nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC), Fourier transform infrared spectroscopy (diffuse reflectance and transmission), mass spectrometry and X-ray powder diffraction.

Polymorphic forms of capsaicin were investigated. Thermal data and variable temperature X-ray powder diffraction (XRPD) data indicated that there is one stable crystalline form (A) at ambient temperature and one metastable crystalline form (B) of capsaicin at high-temperature which reverts to form A on cooling to room temperature.

These results confirmed that the active substance has the proposed structure (*trans*-capsaicin) when synthesized by the proposed manufacturing process.

Specification
The active substance specification includes tests for appearance (active substance and colour of solution), identification (IR), assay (HPLC), related compounds (HPLC), loss on drying (PhEur), water content (Karl Fisher), residual solvents (GC), heavy metals (PhEur), melting point (PhEur) and sulphated Ash (PhEur).

Batch analysis data provided for the 12 batches confirm satisfactory compliance and uniformity with the proposed specification.

Stability
Two batches manufactured by each of the two manufacturing sites for the active substance were stored at 25°C/60% RH for 24 months and 60 months (long term storage conditions) and at 40°C/75% for 6 months and 10 months (accelerated conditions), respectively. In addition, photostability test was performed in one batch of active substance following ICH photostability testing guidance. No significant changes were observed on storage.

The stability studies showed that the active substance is stable and confirm the proposed re-test period.

Medicinal Product

Pharmaceutical Development
Qutenza is a micro-reservoir patch, a sub-category of the reservoir type, which uses multiple mini drug reservoirs instead of a single reservoir unit. The amphiphilic solvent chosen was diethylene glycol monoethyl ether (DGME) because it ensures a good solubility of capsaicin and avoids crystallisation during storage.

Capsaicin cutaneous patch was developed to deliver sufficient active substance in the skin over a short application time to provide prolonged pain relief. The product was developed to deliver capsaicin at a much higher rate than existing treatments into the tissues at the dermal application site. Therefore, formulation development focused on achieving a very short lag-time for dermal delivery of capsaicin. The site of action of the active substance is the nociceptors in the skin; hence systemic absorption is not required for therapeutic activity. This is reflected in the creation of a new standard term for products like this - “cutaneous patch”. The clinical pharmacology studies confirmed the lack of systemic absorption of capsaicin.

The rapid delivery of the active substance and the short lag-time can be achieved by an initial flow of DGME into the skin and uptake of water in the patch. This results in an increase in the thermodynamic activity of the drug within the matrix. Comparison to a conventional matrix patch showed that the increase in thermodynamic activity led to 2-fold increase in permeation through the skin.

Adventitious Agents
None of the excipients used in the formulation of capsaicin cutaneous patch are of human or animal origin.

Manufacture of the Product
The manufacturing process uses standard equipment for the patch production steps that can be described as follows: mixing of active and non-active components, coating and laminating of films, punching the patches to size, and packaging within heat-sealed sachets.

There are several in-process controls such as microscopic examination following addition of capsaicin to the adhesive to assess matrix uniformity and to ensure absence of undissolved particles, control of coating weight, visual inspection of the dried matrix film to identify and mark any defective parts in the coated film, visual inspection of the imprinting and tightness of the sachets.

The manufacturing process validation has been performed using two production scale batches. The results showed that the manufacturing process is well controlled.

Product Specification
The product specification includes tests controlled by validated methods for appearance (backing film, matrix, protective liner, sachet), adhesive force, peel force, tightness of the pouches, identity (IR and UV), assay (HPLC), related substances (HPLC), *in vitro* dissolution (PhEur), residual solvents, DGME and DGME degradants (GC), content uniformity (PhEur) and microbial purity (PhEur).

Batch analysis data provided for batches manufactured at the proposed commercial manufacturing site comply with the specifications and indicate consistent and reproducible manufacture.

Stability of the Product
Stability data were provided on five batches of capsaicin cutaneous patch at long term (25°C/60%RH) and accelerated (40°C/75%RH) conditions, and two of those batches have also been stored at 5°C.

The parameters tested were aspect, microscopic examination, print on the pouches, capsaicin content, degradation products, adhesive force, peel force, *in vitro* dissolution, content of diethylene glycol monoethyl ether, content of diethylene glycol, content of ethylene glycol, content of 2-ethoxyethanol, tightness of pouches, water content and microbial limit test.

In summary, the stability results support the shelf-life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product are well characterised and documented. The manufacturing process used for capsaicin cutaneous patch is a standard process that has been developed for the manufacture of transdermal patches. These processes are performed on standard equipment commonly used for the manufacture of patches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

2.3 Non-clinical aspects

Introduction
Qutenza (NGX-4010) cutaneous patch is intended to be used for the management of peripheral neuropathic pain in adults. The active pharmaceutical ingredient of Qutenza is capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide). Capsaicin is the most abundant pungent molecule contained in chilli peppers. Although there are two geometric isomers of capsaicin, only trans-capsaicin occurs naturally. Capsaicin, which in the course of this dossier is used generically to refer to trans-capsaicin employed in Qutenza, is a synthetic product of high purity presented in the form of a cutaneous patch.

Pharmacology
The pharmacology of capsaicin has been extensively studied in animals and the bibliographic review of primary and secondary pharmacological studies has been provided. Moreover, data from a validated rodent model of post-surgical pain supports the analgesic efficacy of single administration of local high-concentration capsaicin for acute nociceptive pain.

Primary pharmacodynamics
The mechanism of capsaicin analgesic action is related to its highly selective agonist properties for the transient receptor potential vanilloid 1 receptors (TRPV1) expressed abundantly in nociceptors. Persistent stimulation of the TRPV1 receptors may result in their desensitisation with consequent lack of nociceptor sensitivity to relevant noxious stimuli. The long-term desensitisation of nociceptors induced by TRPV1 agonist exposure may not only reduce the ability of nociceptor tips to initiate electrical signals, but it has been long known that nociceptor nerve terminals exposed to capsaicin lose the capacity to uptake and retrogradely transport neurotrophic factors such as NGF to the cell body. Without a constant supply of NGF, many

nociceptors lose their ability to maintain a hyperexcitable phenotype. This effect is claimed to be reversible providing fibre terminals can recover from desensitized condition.

In vitro studies
The literature review provided the potency of capsaicin for TRPV1 receptors in different species obtained from different studies. The largest comparable data sets for capsaicin potency and efficacy referred to in the application arise from measurements of intracellular calcium responses in cells stably expressing TRPV1.
EC_{50} values at temperature of 20°C-25°C and pH ~7.4 were reported as:

- Human: 74.1 nM and 12.5 nM [Smart, 2000] and [Witte, 2002] respectively.
- Rat: 33.9 nM and 13.5 nM [Jerman, 2000] and [Witte, 2002]
- Mouse 3.7 nM [Correll, 2004].

TRPV1 activation is highly dependent on temperature and pH, being higher if measured at physiological temperatures or in acidic conditions (Cortright, 2004).

In vivo studies
A study by Pospisilova and Palesek has addressed the proposed anti-analgesic properties of capsaicin in a mouse model of post-incisional mechanical hyperalgesia and allodynia. 0.1ml of 49mM capsaicin solution injected in the hind paw was studied and shown to be efficacious. This corresponds to a much lower dose/animal than that used in toxicology studies and proposed for human use.

Secondary pharmacodynamics
A number of pharmacological activities, which are thought not to be mediated through activation of TRPV1, have been described for capsaicin. It appears however that the non-TRPV1-mediated actions typically occur at much higher concentrations (often in the micromolar range) than those required for TRPV1 activation (in the low nanomolar range).

Safety pharmacology programme
Central nervous system (rodent CNS behavioural test)
The capsaicin potential to produce changes in the central nervous system (CNS) was assessed using Irwin observation test in rats. The capsaicin dose of 32 mg was administered via a 50 cm^2 trimmed patch applied for up to 3 hours. The animals were observed for general behavioural, autonomic and motor effects. No behavioural or physiological changes were noted in rats exposed cutaneously to capsaicin in comparison with the control group.

Cardiovascular and respiratory effects in anaesthetised dogs
Capsaicin effects on cardiovascular and respiratory systems were assessed in beagle dogs given iv ascending doses of 0.03, 0.1 and 0.3 mg/kg, respectively. The administration of low (0.03 mg/kg) and intermediate (0.1mg/kg) dose of capsaicin had no measurable effects on cardiovascular function while the highest dose (0.3 mg/kg) of capsaicin caused an increase in heart rate and blood pressure. The cardiovascular effects observed after the highest dose of capsaicin were transient. Similarly, only the 0.3 mg/kg dose of capsaicin resulted in a transient increases in peak inspiratory flow (PIF), peak expiratory flow (PEF), tidal volume (TV), minute volume (MV) and rate of respiration.

There was no evidence of QTCF and QTCB interval prolongation. In vitro tests assessing QT interval prolongation were not conducted. However a comprehensive analysis of the interaction of capsaicin with different ion channels was performed. Taking into consideration that low plasma levels are expected after Qutenza patch application the interaction with cardiac channels is not probable.

Pharmacodynamic drug interactions
Pharmacodynamic drug interaction studies are discussed in section 3.5 of AR.

Pharmacokinetics

Two *in-vivo* single-dose studies in rats and one single-dose cutaneous study in mini-swine were conducted using the proprietary patch formulation. In addition, a number of *in-vitro* studies using human, dog and rat liver microsomes and fresh human skin have been performed.

Absorption
The table below shows the particulars of the three single-dose studies together with bioavailability values.

Species	N	Dose (mg/kg)	Route	F (bioavailability) (%)
Rat	15	32	dermal	21.4%
Rat	18	32	dermal	Males: 5.78% Females 3.59%
Mini-swine	3	64	dermal	4.2%

The extent of absorption was markedly higher in the first rat study as compared to the second one.

In rats the plasma and blood concentration profiles had double-peak character with an early T_{max} at 3 hours and second smaller peak at 72 hours, respectively. In mini-swine plasma radioactivity could be detected only in the first four hours and the peak concentration was measured at 2 h. T_{max} corresponded to the patch removal time.

Distribution
Capsaicin-related radioactivity measured at 72 hours post-application in rats was widely distributed. The skin radioactivity was very high and reached 900000 ng eq/g. The tissue concentrations in other organs in the decreasing order were: in liver (2860 ng eq/g), lymph nodes (1670 ng eq/g), adrenal glands (1690 ng eq/g), kidneys (1490 ng eq/g), heart (1440 ng eq/g) and lungs (1070 ng eq/g). Lower radioactivity was also detected in spleen (642 ng eq/g), brain (428 ng eq/g) and plasma (482 ng eq/g).
The second study in rats yielded different results. At 72 hours after the patch application capsaicin-related radioactivity was present in a limited number of organs. It was relatively low in lymph nodes (63.3ng eq/g), ovaries (40.9 ng eq/g), slightly higher in kidney (255-433 ng eq/g) and liver (543-599 ng eq/g), and could not be detected in other organs or plasma. In the skin significant radioactivity (3770-6420 ng eq/g) could be measured even after 2 weeks of the path removal.

In mini-swine no radioactivity was detected in sampled tissues (adrenal glands, brain, heart, kidneys, liver, lungs, lymph nodes and spleen) with the exception of the skin at the application site which contained 1.23% of the administered dose.

Protein binding
Plasma protein binding of capsaicin was assessed in rat, rabbit, dog and human plasma samples. Capsaicin was highly bound to plasma proteins in all four species over the concentration range of 50 to 500 ng/mL. The mean percentage of plasma-bound capsaicin ranged from 92.8% to 94.3% in human, 92.0% to 93.2% in dog, 91.1% to 92.4% in rabbit and 90.8% to 91.2% in rat. The binding was independent of the concentration and time in all species

Metabolism
In vitro studies
The metabolism of $^{[14C]}$capsaicin was assessed *in vitro* following incubation with rat, dog, and human hepatic microsomes and S-9 fraction.
Biotransformation was determined at 1 and 10 µM $^{[14C]}$capsaicin with 1 mg microsomal protein/mL for 0, 5, 10, 20, and 30 minutes. $^{[14C]}$capsaicin metabolism was rapid in rat microsomes and S-9 fraction as compared to dogs and humans. In humans, the rate of formation of the metabolites was faster than in dog. Generally, the rate of metabolism in microsomes was faster than the S-9 fraction.
For all species, the metabolism of $^{[14C]}$capsaicin was less extensive at the 10-µM concentration as compared to the 1-µM concentration, suggesting saturability of metabolism.

In vitro metabolism studies with [14C]capsaicin resulted in the formation of several products. Three major metabolites were detected and tentatively identified as 16-hydroxy-capsaicin, 17-hydroxy-capsaicin, and 16,17-dehydro-capsaicin. CYP2C9 was identified as the primary enzyme responsible for converting [14C]capsaicin to 16-hydroxy-capsaicin and 16,17-dehydro-capsaicin. CYP2C19 may also contribute to the formation of 16-hydroxy-capsaicin. CYP enzyme(s) responsible for 17-hydroxy-capsaicin formation remain unidentified. Capsaicin inhibits major CYP isoenzymes, i.e. CYP1A2, CYP2C9 and CYP2C19, with IC_{50} values of 2.1, 2.0 and 3.2 mcM, respectively. Capsaicin appeared also to inhibit CYP2B6, CYP2D6 and CYP3A4/5 directly with extrapolated IC_50 values of 24, 18, 38 and 12 mcM, respectively. The skin metabolism of capsaicin was also evaluated in-vitro. It resulted that 25% of capsaicin was metabolized after 20 hours regardless of the initial concentration.

In vivo studies
The profile of plasma capsaicin metabolites was determined in samples collected from male and female rats at 3 hours post-dose. The analysis showed up to five metabolites in addition to the unchanged parent drug. Unchanged drug plasma concentrations in male and female rats corresponded to 9.86% and 10.5% of the radioactivity in the samples. At 3 hours post-dose, most of the circulating radioactivity was associated with vanillin (males 64.1% and females 47.3%, respectively).

Capsaicin metabolism in rat skin (administration site)
The profile of capsaicin metabolites in skin (test site) was determined in samples collected from male and female rats at 3 hours post-dose. The HPLC analysis showed that most of the radioactivity was associated with the unchanged drug. Concentrations of the parent drug in male and female skin (test site) were 224,000 and 119,000 ng eq/g of [14C]capsaicin respectively, corresponding to 98.9% and 84.8% of the radioactivity in the sample. Vanillylamine was detected in female skin only, and accounted for 15.2% of the radioactivity in the sample at 3 hours post-dose.

Excretion
The total excreted amount of capsaicin was low (about 3%-5%), while duration of excretion was very long, reaching more than 14 days in mini-swine. In male and female rats the unchanged parent drug concentration in urine within 96 hours post-dose accounted for 0.04% and 0.03% of the administered dose. Vanillic acid-sulfate (M2A) was the major metabolite in the urine of male rats and accounted for 1.26% of the dose, while in female rats it accounted for 0.67% of the administered dose. Vanillylamine was the major metabolite in the urine of female rats and accounted for 1.09% of the dose, while in male rats it accounted for 1.07% of the administered dose. Unchanged parent drug in male and female faeces within 96 hours post-dose accounted for 0.09% and 0.05% of the administered dose, respectively. O-demethyl-capsaicin (M6A) was the major metabolite in faeces of male and female rats and accounted for 0.88% and 0.45% of the administered dose, respectively.

Relevance to human pharmacokinetics
ADME studies reflect a significant species difference in the transfer of capsaicin from the patch into the skin and the systemic circulation. Since the pig is believed to be the most predictive species for human percutaneous absorption (Schmook, 2001) limited systemic absorption of capsaicin from the patch is expected in humans.

Toxicology
Nonclinical studies with either Qutenza (NGX-4010) or other formulations of capsaicin included GLP-compliant single-dose studies in rat and dog, 4 week studies (weekly 3 hour administration) in rat and mini-swine, fertility and general reproductive toxicity in the rat (daily 3 hour exposure for 7 weeks in males and 3 weeks in females), developmental toxicity in rat and rabbit (daily 3 hour exposure during organogenesis) and a peri- and post-natal study in the rat with daily 3 hour exposure from Day 7 of gestation to Day 20 of lactation. Genotoxicity study and carcinogenicity study using a short-term model were also conducted. In addition, cutaneous sensitization in

guinea pigs and phototoxicity by cutaneous application in rats, as well as an *in silico* analysis of capsaicin, capsaicin metabolites and its potential impurities ware carried out.

The toxicology studies conducted are listed in the table below.

Study Type and Duration	Route of Administration	Species	Compound Administered
Single-dose toxicology	Cutaneous; one ~ 3 hr application	Rat and dog	NGX-4010
Repeated-dose toxicology	Cutaneous; once/week 3 hr application for 4 weeks	Rat and mini-pig	NGX-4010
Repeated-dose toxicology	Intravenous infusion over 15 minutes every day for 14 days	Dog	Capsaicin powder dissolved in diethylene glycol monoethyl ether and then diluted with phosphate buffered saline (2:1)
Ames assay	*In vitro* with and without metabolic activation (rat liver S-9)	*S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2uvrA	Capsaicin powder in dimethyl sulfoxid
Mouse lymphoma cell mutation assay	*In vitro* with and without metabolic activation (rat liver S-9)	Mouse lymphoma L5178Y cell line; clone 3.7.2.C	Capsaicin powder in dimethyl sulfoxid
Chromosomal aberration assay	*In vitro* with and without metabolic activation (rat liver S-9)	Cultured aguman lymphocytes	Capsaicin powder in dimethyl sulfoxid
Micronucleus Test in Bone Marrow of CD-1 Mice 0 hour + 24 hour Oral Dosing and 48 hour Sampling	Oral gavage	Mouse	Capsaicin powder suspended in 0.5% carboxymethyl cellulose
26 week cutaneous carcinogenicity study in Tg.CA mice	Cutaneous one ~ 3 hr exposure weekly for 26 weeks	Mouse	Capsaicin powder dissolved in diethylene glycol monoethyl ether
Male and female fertility and general reproductive toxicology	Cutaneous; one 3 hour exposure daily for 7 weeks (male) or 3 weeks (female)	Rat	NGX-4010
Developmental toxicology	Cutaneous; one 3 hr application daily from Gestation Day 7 through 17 (rats) or 19 (rabbits)	Rat and rabbit	NGX-4010 (rat) Capsaicin in diethylene glycol monoethyl ether (rabbit)
Developmental and peri/post-natal reproductive toxicology	Cutaneous; one 3 hr application daily from Gestation Day 7 through Lactation Day 20	Rat	NGX-4010
Cutaneous sensitisation by closed patch technique	Cutaneous	Guinea pig	NGX-4010
Phototoxicity screening	Cutaneous; one application of up to 3 hr	Rat	NGX-4010

Single dose toxicity with toxicokinetics

NGX-4010 was applied cutaneously to male and female rats at either 16 mg/rat (25 cm^2 patch) or 32 mg/rat (50 cm^2 patch) for approximately 3 hours. Adverse effects attributed to the treatment included scabs or sores in the cervical, dorsal and sacral regions at the edges of the patch placement site at the 32 mg/rat dose level. They were however attributed to mechanical effect of the adhesive.

The NOAEL in rats corresponded approximately to 64 mg/kg, which is about 6 times higher than the proposed maximum human cutaneous exposure. The plasma concentration corresponding to the NOAEL was 38.8 and 61.8 ng/mL in the male and female rats, respectively, which is about two to four times higher than the maximum detected human plasma level (17.8 ng/mL).

In dogs the maximum dose of 256 mg/dog or 28 mg/kg is about 3 times higher than the proposed maximum human cutaneous exposure level. This dose did not produce capsaicin-related toxic alterations or detectable capsaicin plasma levels with the exception of two cases when plasma levels were near the lower detection limit, i.e. 10 ng/ml.

Repeat dose toxicity with toxicokinetics
In repeat-dose toxicity studies NGX-4010 was tested in rat and mini-pigs, while dogs were administered capsaicin intravenously.
Male and female rats were treated with NGX-4010 at 16 mg/rat (25 cm^2 patch) or 32 mg/rat (50 cm^2 patch) for 3 hours once a week for 4 weeks. There were no test article-related deaths or significant effects on clinical pathology results, organ weight differences, microscopic or macroscopic observations in the study. The NOAEL appeared to be 32 mg/rat or 128 mg/kg (assuming 250 g as average weight of a rat), i.e. about 12-times higher than the maximum human cutaneous exposure. Exposure in the rats was confirmed at all dose levels in all animals in the toxicokinetic satellite groups.

Male and female mini-pigs were treated with NGX-4010 at either 128 mg/pig (200 cm^2 patch) or 384 mg/pig (600 cm^2 patch) for 3 hours once a week for 4 weeks followed by a 2 week recovery period. The highest dose used in the study, i.e. 384 mg/pig or 25.6 mg/kg (assuming 15 kg as average weight of a pig), was approximately 2.4 times higher than the maximum proposed cutaneous exposure in humans. Test article-related behavioural observations included scratching and rubbing of the administration site noted in high-dose group of female pigs on Day 15 and one low-dose group of male pigs and one high-dose group male on Day 30. There were no other test article-related effects of toxicological importance. Scratching and rubbing of the administration site observed during the study was probably due to local pain induced by the patch.

In dogs capsaicin was administered intravenously at doses of 0.03, 0.1 or 0.3 mg/kg daily for 14 days. The test article-related behavioural observation in the study included vocalization in dogs receiving 0.3 mg/kg/day of capsaicin and elevated ALT in male and female dogs administered 0.3 mg/kg/day of capsaicin. The difference in ALT levels was statistically significant ($p < 0.05$) for females only. The NOAEL for capsaicin appeared to be 0.1 mg/kg/day.

Genotoxicity
Genotoxicity was assessed using the Ames test (Salmonella typhimurium strains TA 1535, TA 1537, TA 98 and TA 100 and Escherichia coli strain WP2uvrA), the mouse lymphoma assay, in vitro chromosomal aberration assay with human peripheral blood lymphocytes and in vivo mouse micronucleus assay.
Capsaicin did not show genotoxic potential in the Ames test, the chromosomal aberration assay and the mouse micronucleus assay. A weak positive response in the in vitro mouse lymphoma assay was observed.

Carcinogenicity
Carcinogenic potential of capsaicin was evaluated in a 26 week cutaneous toxicity study using a transgenic mouse model (Tg.AC mice). No increased incidence of preneoplastic or neoplastic skin lesions were observed as a result of capsaicin treatment.

Reproduction Toxicity with toxicokinetics
The effects of capsaicin on male and female fertility and general reproductive toxicology were assessed in rats. Male rats were exposed to NGX-4010 patches for 3 hours once a day for 7 weeks, while female rats – for 3 weeks. An adverse effect on sperm production and sperm motility was noted at all dose levels (25, 37.5 and 50 cm^2, respectively). In females, the Fertility Index (number of pregnancies per number of rats that mated) and the number of pregnancies per number of rats in cohabitation were reduced for all doses (25, 37.5 and 50 cm^2). No other Caesarean-sectioning or litter parameters were affected by application of NGX-4010 patches even at the highest dose of 50 cm^2.
Based on the results, NOAEL for maternal and paternal toxicity of NGX-4010 as well as for reproductive toxicity was less than a patch size of 25 cm^2 e.g. 16 mg/cm^2.

In the developmental toxicity study in rat with the administration of patches, delays in skeletal ossification, evident as significant reductions in the average number of ossified hind-limb and fore-limb phalanges and metatarsals and a significant increase incidence of incompletely ossified 1st sternebra in the litter, occurred at the highest dose tested (50 cm^2 patch/rat=110 mg/kg if calculated with an average body weight of 290.8 g/rat at day 13 of gestation) which was tenfold of the maximum human dose (10.7 mg/kg). The significance of these findings for humans is unknown. The developmental NOAEL was determined as a patch size of 37.5 cm^2 (24 mg/rat).

In the rabbit developmental study animals were treated with capsaicin dissolved in DGME. Moderate erythema, flaking, wrinkling and lesions at the application site occurred at statistically significant incidences in the 3, 6.5 and 13 microLitres/cm2 dosage groups (17.4, 37.8 and 75.6 mg/kg if calculated with the average body weight of 3.44 kg/rabbit at day 13 of gestation). There was no dose relationship in the incidence of these findings and the observed irritation appeared to be related, at least in part, to the vehicle (DGME). There were no other toxicologically important clinical findings and body weights, food consumption, maternal necropsy findings, Caesarean section and litter parameters were unremarkable. Accordingly, the maternal NOAEL of capsaicin was less than 3 microLitres/cm^2 (60 mg/rabbit=17.4 mg/kg, about 1.6 times higher than the maximum human exposure) based on the local irritation observed, and the developmental NOAEL was greater than 13 microLitres/cm^2 (260 mg/rabbit=75 mg/kg, about 25x higher than in humans).

In the study assessing prenatal and postnatal development, including maternal function NGX-4010 patches at doses of 16 mg/rat (25 cm^2), 24 mg/rat (37.5 cm^2) or 32 mg/rat (50 cm^2) were applied once daily to pregnant female rats from Day 7 of gestation to Day 20 of lactation inclusive. Delivery and litter observations were unaffected by the treatment. The reproductive NOAEL and the NOAEL for viability and growth in the offspring was greater than 32 mg/animal/day (114 mg/kg/day if calculated with the mid-treatment period body weight).

Toxicokinetic evaluation was performed in the range finding study prior to developmental toxicity study (same doses as the main study) in rats and rabbits. In the rat study plasma levels were generally undetectable within 24 hours after patch application on GD 7 in the three treated groups (25, 37.5 and 50 cm^2), with the exception of one sample in the 25 cm^2 dose group at 6 hours post-application. After application on GD 17, plasma levels of capsaicin were detected in the 37.5 and 50 cm^2 dose groups at 2 hours post-application; the average values were dose-dependent. Capsaicin was detectable in the plasma sample of just one rat at 3 hours post-dosage in the 37.5 cm^2 dose group.
In rabbits measurable plasma concentrations of capsaicin occurred 6 hours, 15 minutes and 5 minutes after the first dose on GD 7 in the 3, 10 and 30 mcL/cm^2 dose groups, respectively. On GD 7, the highest concentrations of capsaicin occurred in the 3 mcL/cm^2 dose group at 6 hours post-dosage and at 3 hours post-dosage in the 10 and 30 mcL/cm^2 dose groups. Capsaicin was present in plasma samples before dosage on GD 19. After dosage on GD 19, plasma levels increased in all dose groups, although the changes were variable. On average, the highest concentration of capsaicin occurred at 5 minutes, 30 minutes and 6 hours post-dosage in the 3, 10 and 30 mcL/cm^2 dose groups, respectively. Plasma concentrations increased in a dosage-dependent manner at all time-points in the three treated groups.

Local tolerance
The local tolerance was assessed within the single and repeat dose studies. The delayed contact hypersensitivity potential of NGX-4010 patches was evaluated in albino guinea pigs. The NGX-4010 patch was found to be a mild cutaneous sensitizer. This information is reflected in the SmPC.

The phototoxicity of capsaicin was examined in rats. Capsaicin was found to be devoid of phototoxic potential.

Other toxicity studies
A computerised evaluation of structure/activity relationship between capsaicin, its metabolites and impurities potentially present in the capsaicin supplied for the NGX-4010 cutaneous patch was conducted. The analysis did not identify any previously unknown toxicity.

Ecotoxicity/environmental risk assessment
An environmental risk assessment has been completed based on CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/ CHMP/ SWP/4447/00).
An octanol/water partition coefficient study was conducted at the request of the CHMP. The study was conducted using the OECD 107 guideline in a GLP-compliant facility. The results of this study indicate that the Log Kow value for capsaicin is approximately 3.5. Therefore capsaicin is not a Persistent, Bioaccumulative and Toxic (PBT) substance.
Based on the highest recommended dose (1000 cm^2 corresponding to 640 mg), a worst-case PEC in surface water of 0.035 µg/L has been calculated based on the maximum cutaneous absorbed single dose of 7 mg (1.1% of 640 mg, the total capsaicin single dose applied to patch) and using default values. On the basis of this assessment, the $PEC_{SURFACEWATER}$ value for capsaicin exceeds the PEC action limit of 0.01µg/L. However, as the posology recommends a dosing frequency of a single exposure of one hours' duration every three months the CHMP considered that the product does not present a significant risk to the environment.

Discussion on the non-clinical aspects
The toxicological profile of capsaicin path was assessed in a sufficient set of studies which appropriately covered the main requirements in relation to the proposed conditions of use. The main findings are local adverse effects since very low plasma levels are expected after application of Qutenza cutaneous patch in humans. No specific concerns apart from cutaneous reactions including rash, expected based on the mechanism of action, were identified. Genotoxicity studies performed with capsaicin showed a weak mutagenic response in mouse lymphoma assay. This information is reflected in the SmPC. Other genotoxicity assays yielded negative results. The carcinogenic potential of capsaicin was negative. Reproductive effects included reduced male and female fertility which may be taken into account when deciding on the use of the patch in men and women of reproductive age. Whether these effects are reversible has not been established; however there is no apparent reason to believe they will be irreversible. This information is reflected in the SmPC. Delayed ossification was observed in the rat teratology study at doses above therapeutic level in humans. This information is reflected in the SmPC. No phototoxic concerns were raised.

2.4 Clinical aspects

Introduction
Qutenza (NGX-4010) is a cutaneous patch intended for the treatment of peripheral neuropathic pain. The active pharmaceutical ingredient of Qutenza is capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide; 6- nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl] -8-methyl-, (6E)). The pharmacological activity of capsaicin includes activation of Transient Receptor Potential Vanilloid 1 receptors (TRPV1) located in the skin, e.g. cutaneous nociceptors. Following exposure to capsaicin, cutaneous nociceptors become less sensitive to a variety of stimuli, including further capsaicin exposure or thermal stimuli. A high concentration capsaicin cutaneous patch (8%) was developed which can deliver high dose of capsaicin in a short time in order to rapidly de-functionalise pathophysiologically hyperactive cutaneous nociceptors.

A scientific advice for this product has been sought from Sweden, United Kingdom, the Netherlands and Germany. One of the issues discussed concerned the possibility of using a low-concentration capsaicin patch as a control in pivotal clinical trials. It was concluded that the use of a traditional placebo arm will not permit studies to remain blinded; hence the use of low-concentration capsaicin control would be the best approach.

The clinical development program consisted of 14 clinical studies, including the 2 Phase 1 studies in healthy volunteers (Studies C101 and C115) and 12 Phase 2/3 studies in subjects with peripheral neuropathic pain (Studies C102, C106, C107, C108, C109, C110, C111, C112, C116, C117, 118 and C119).

The table below summarises clinical development program for Qutenza at the time of submission.

Study No.	Study Phase	Indication	Status	Title of Study	Country
C101	1	Healthy Volunteer	Completed	A Phase I, Open-Label Study of Capsaicin–Induced Changes in Cutaneous Nerve Fiber Density and Function in the Skin of Healthy Volunteers	USA
C115	1	Healthy Volunteer	Completed	A Randomized, Controlled, Open-Label Study to Investigate the Effect of NGX-4010 on Epidermal Nerve Fiber Density and Sensory Function in Healthy Volunteers	USA
C102	2	PHN	Completed	A Double-Blind Controlled Pilot Study of High-Concentration Capsaicin Patches in the Treatment of Pain Associated with Postherpetic Neuralgia	USA
C106	2	PHN	Completed	An Open-Label, Extension Study of High-Concentration Capsaicin Patches for the Treatment of Postherpetic Neuralgia	USA]
C108	2/3	PHN	Completed	A Randomized, Double-Blind, Controlled Dose Finding Study of NGX-4010 for the Treatment of Postherpetic Neuralgia	USA
C110	2/3	PHN	Completed	A Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia	USA
C116	3	PHN	Completed	A Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia	USA
C109	2	HIV	Completed	An Open-Label Pilot Study of High-Concentration Capsaicin Patches in the Treatment of Painful HIV-Associated Neuropathy	USA
C107	2/3	HIV	Completed	A Randomized, Double-Blind, Controlled Dose Finding Study of NGX-4010 for the Treatment of Painful HIV-Associated Distal Symmetrical Polyneuropathy	USA
C112	3	HIV	Terminated by Sponsor	A Multicenter, Randomized, Double-Blind, 12 Week Controlled Study of NGX-4010 for the Treatment of Painful HIV-Associated Neuropathy	USA]
C111	2	PHN PDN HIV	Completed	A Randomized, Open-Label Study of the Tolerability of Three Local Anesthetic Formulations in Conjunction with NGX-4010 for the Treatment of Neuropathic Pain	USA
C118	2	PHN, HIV	Completed	A Multicenter, Open-Label, Phase 2 Study of NGX-4010 for the Treatment of Neuropathic Pain in Patients with Painful HIV-Associated Neuropathy (HIV-AN) or Postherpetic Neuralgia (PHN).	USA
C117	3	PHN	Completed	A Multi-center Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia	Canada USA
C119	3	HIV	Ongoing	A Multicenter Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Painful HIV-Associated Neuropathy	AustraliaCanada UK USA

The claimed indication is:

- treatment of peripheral neuropathic pain in adults. Qutenza can be used alone or in combination with other pain medications.

The approved indication is:

- treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

Qutenza development program was conducted in accordance with the Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain (CHMP/EWP/252/03 Rev. 1).

There is no paediatric development programme. According to the European legislation valid at the time of submission there was no need to submit a paediatric investigation plan before July 2008.

GCP

The Clinical trials were performed in accordance with GCP.

A statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC was provided.

Pharmacokinetics

Methods

Analytical methods
Two HPLC methods, i.e. HPLC –Fl and HPLC/MS/MS were employed in the determination of capsaicin and its metabolites in human plasma. The latter method was introduced to increase sensitivity and detection limits. All analyses including sample handling, sample preparation, instrumental analysis and data reporting have been conducted according to the principles of GLP as applied to bioanalytical chemistry. Validation results, namely accuracy and precision, were within acceptable ranges.

Absorption
No specific human PK studies have been performed, however during three Phase 2 [C102, C108, C111] and two Phase 3 studies [C107 and C116] blood samples were collected to determine capsaicin plasma levels after 60 minute patch application. 31% patients from post-herpetic neuralgia (PHN) group, 5% from HIV-AN group, and 3% of diabetic patients displayed quantifiable levels of capsaicin at any time point. Capsaicin plasma levels ranged from 0.52 to 4.64 ng/mL.
Capsaicin permeation through the skin was also assessed in *in vitro* studies using heat-separated epidermis with Franz diffusion cells and full-thickness skin. Approximately 0.9% of the total content of capsaicin was recovered from the skin following 240 minute sampling after 60 minute patch application. In the second study: 0.7%, 0.9% and 1.1% of the patch content was found in the skin after 30, 60 and 90 minutes, respectively.

Bioavailability
Based on the results of the *in-vitro* skin permeation studies it appears that about 1% of capsaicin is diffused from the patch to the skin.

Bioequivalence
In vitro and *in vivo* studies demonstrate that systemic absorption of capsaicin after cutaneous application of Qutenza is almost negligible and that plasma levels obtained are not sufficient to determine usual pharmacokinetic parameters.

Food interaction
No oral absorption takes place with this medicinal product.

Distribution
Plasma Protein Binding
Plasma protein binding study was performed in many species including humans. Over the concentration range of 50 to 500 ng/mL the mean percentage of capsaicin bound to human plasma proteins was 92.8%-94.3%. The binding was independent of the capsaicin plasma levels.

Metabolism and Elimination
The metabolism and elimination of capsaicin was investigated *in-vitro* in human materials.

In a study using human liver microsomes three major metabolites were detected and tentatively identified as 16-hydroxy-capsaicin, 17-hydroxy-capsaicin, and 16, 17-dehydro-capsaicin.

In vitro biotransformation of capsaicin was also assessed using intact human fresh skin samples. The biotransformation assessed 20 hours post-incubation was slow and the majority of the sample radioactivity was associated with unchanged capsaicin. The levels of capsaicin-related radioactivity ranged from 74.0% to 95.6% for all studied concentrations (1, 3 and 10 mcM). The main metabolites were vanillylamine and vanillic acid. At all studied concentrations (1, 3 and 10 mcM) the radioactivity levels for vanillylamine were 4.37- 19.8% and for vanillic acid - 0.11-7.97%, respectively.

Pharmacokinetics of metabolites
Attempt was made to measure main metabolites in the plasma; however their concentrations were below Limit of Quantification (LOQ).

Consequences of possible genetic polymorphism
An *In Vitro* reaction phenotyping study was designed to identify human cytochrome P450 (CYP) enzymes involved in capsaicin metabolism. Results suggested that CYP2C9 was the primary enzyme responsible for converting $^{[14]}$C-capsaicin to 16-hydroxy-capsaicin and 16,17-dehydro-capsaicin. CYP2C19 may also contribute to the formation of 16-hydroxy-capsaicin. The CYP enzyme(s) responsible for 17-hydroxy-capsaicin formation remained unidentified.

Dose proportionality and time dependencies
The relationship between capsaicin concentration in the patch and absorbed amount was investigated *in-vitro*. The permeation studies showed that the rate decreases with the decreasing capsaicin patch concentration.

Prototype Patch Formulation ID	Capsaicin Concentration (% w/w)	Permeation Rate[a] (mcg/hr.cm^2)
CAP 21	8	0.58[b]
CAP 23	6	0.50[b]
CAP 24	6	0.49[b]
CAP 25	4	0.37[c]
CAP 47	0.08	0.16[d]

[a] Determined from 0 to 8 hours and calculated by linear fitting
[b] Heat separated epidermis from 47 years old female breast; mean of n = 3
[c] Heat separated epidermis from 47 years old female breast; mean of n = 2
[d] Heat separated epidermis from 37 years old female breast; mean of n = 2

Special populations
Based on PK data Qutenza cutaneous patch can be considered as locally applied and acting pharmaceutical form. PK studies in special populations are considered not relevant.

Pharmacokinetic interaction studies
CYP inhibition
The ability of capsaicin to inhibit major CYP enzymes was investigated only *in vitro*. Capsaicin inhibited CYP1A2, CYP2C9 and CYP2C19 with IC_{50} values of 2.1, 2.0 and 3.2 mcM, respectively. It also appeared to inhibit CYP2B6, CYP2D6 and CYP3A4/5 with extrapolated IC_{50} values of 24, 18, 38 and 12 mcM, respectively. Capsaicin caused also marked metabolism-dependent inhibition of CYP2B6, i.e. the enzyme activity of samples containing 10 mcM capsaicin decreased approximately 52% when pre-incubated for 30 minutes. Capsaicin had the potential to cause moderate metabolism-dependent inhibition of CYP2D6. The enzyme activity of samples containing 10 mcM capsaicin decreased approximately 27% when pre-incubated for 30 minutes.
CYP2C9 has been shown to be the primary enzyme responsible for converting capsaicin in-vitro.
Results of the interaction study show that capsaicin is capable of inhibiting its own metabolism and the self-inhibition of capsaicin metabolism might be a contributing factor to its very long elimination period.
CYP induction
Capsaicin enzyme inducer properties were investigated in cultured human hepatocytes. Capsaicin did not cause an increase in activity of any of the studied enzymes, suggesting that it is not an inducer of CYP isoenzymes.

Pharmacokinetics using human biomaterials
The absorption, distribution, metabolism, elimination, bioavailability, genetic polymorphism, dose proportionality and dose dependencies, and pharmacokinetic interaction studies were conducted with the use of human-derived material (please see above).

Pharmacodynamics

Mechanism of action
Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1) formerly known as the vanilloid receptor 1 (VR1). TRPV1 is a ligand-gated, non-selective cation channel preferentially expressed on small diameter sensory neurons, e.g.

nociceptors which specialize in the detection of painful or noxious stimuli. Thus, TRPV1 is expressed selectively on C-fibers and to a lesser extent Aδ-fibers.

Primary and Secondary pharmacology
Following exposure to capsaicin, cutaneous nociceptors become less sensitive to a variety of stimuli, including further capsaicin exposure or thermal stimuli. Prolonged capsaicin exposure results also in reduced spontaneous and stimulus-evoked pain intensity. These effects of capsaicin are frequently referred to as "desensitisation" or "defunctionalisation" and represent the rationale for a development of various capsaicin formulations for the management of chronic pain syndromes. In vitro studies have demonstrated that following capsaicin exposure of sensory neurons, defunctionalisation occurs within minutes and can be achieved with relatively low capsaicin concentrations.

The two Phase 1 human volunteer studies (C101, C115) conducted during the Qutenza (NGX-4010) clinical development program provided relevant information on pharmacodynamics. Study C101 was a phase 1, open-label study in healthy volunteers to evaluate the safety and tolerability of Qutenza following 30, 60 or 120 minute application. It also examined pharmacodynamic effects on epidermal nerve fibre density (ENFD) and function at 7 days after treatment. The treatment with Qutenza for 60 or 120 minutes resulted in a significantly lower mean nerve fibre density at day 7 (4.8 and 4.4 neurites/mm, respectively) as compared to placebo (11.8 neurites/mm; $p < 0.001$ for both comparisons) or the low-concentration capsaicin patch for 120 minutes (10.9 neurites/mm; $p < 0.01$ for both comparisons). A 30 minute treatment with Qutenza resulted in a reduction in mean nerve fibre density (7.6 neurites/mm) as compared with placebo; however, this reduction was not statistically significant. Treatment with Qutenza for 60 or 120 minutes resulted in a small but statistically significant reduction in sensitivity to warmth (i.e., higher warmth detection threshold) on day 7 (+1.9°C and +1.1°C, respectively). There were no statistically significant within-treatment or between-treatment effects for sensitivity to cold.

Study C115, a phase I controlled, open-label study in healthy volunteers, investigated the effect of Qutenza on ENFD and sensory function at 1, 12 and 24 weeks following 60 minute application. The treatment with Qutenza resulted in 80% reduction in ENFD compared to untreated sites at week 1. After 12 weeks a 20% reduction was noted and by week 24 full recovery of ENFD was observed. The reduction in ENFD was associated with small, transient alterations in the nerve fibre function. At week 1 following patch removal a 15% reduction in the number of detected sharp stimuli was noted. The effects on sharp pain perception returned to normal by week 12. Heat perception and mean cooling thermal threshold were relatively unaffected.

The effects of Qutenza on sensory nerve function are addressed by pharmacovigilance and risk minimisation measures.

Clinical efficacy
Twelve studies were conducted during the Qutenza clinical development program to assess the efficacy (together with safety and tolerability) of Qutenza in subjects with peripheral neuropathic pain, i.e. post-herpetic neuralgia (PHN), HIV-associated neuropathy (HIV-AN), and painful diabetic neuropathy (PDN). In all studies the 8% Qutenza patch was utilised (640 mcg/cm^2). Control patch(es) used throughout the studies contained low-concentration of capsaicin (3.2 mcg/cm^2).
Of the studies, 8 were double-blind controlled trials or included a double-blind controlled part (C102, C107, C108, C110, C112, C116, C117 and C119), while 3 were open-label studies (C109, C111 and C118). Additionally, study C106 was an open-label extension of study C102. Studies C107 and C108 included an open-label extension following the double-blind controlled part.
Five controlled studies were conducted in subjects with PHN, including phase 3 main studies C116 and C117, and the phase 2/3 supportive studies C102, C108 and C110. The remaining three controlled studies were conducted in subjects with HIV-AN (phase 3 main studies C107 and C119, and phase 3 Study C112).
With regard to the open-label studies, study C109 enrolled subjects with HIV-AN, study C118 – subjects with HIV-AN, and PHN; while study C111 enrolled subjects with PHN, HIV-AN, and

PDN. Open-label extension studies (or studies that included an open-label extension part) enrolled subjects with PHN (Studies C106 and C108) or HIV-AN (Study C107).

Dose response study(ies)
No dedicated dose-response studies have been performed. The efficacy of multiple durations of patch application, i.e. 30, 60 or 90 minutes was assessed in three studies from the NGX-4010 clinical development program:
1) Study C107, the Phase 3 main trial in subjects with HIV-AN, assessed duration of 30, 60 and 90 minutes;
2) Study C108, a Phase 2/3 supportive trial in subjects with PHN, assessed duration of 30, 60 and 90 minutes;
3) Study C111, an open label mixed population study (i.e., PHN, HIV-AN and PDN subjects) conducted to assess the tolerability of Qutenza in conjunction with topical application of one of three lidocaine-based local anaesthetic products, assessed duration of 60 and 90 minutes.

Main study(ies)
The therapeutic efficacy of Qutenza (NGX-4010) was evaluated in four main phase 3 studies, two studies in postherpetic neuralgia, and two studies in HIV-AN.

- **Studies in subjects with Postherpetic Neuralgia**
    - C116 - A Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia
    - C117 - A Multicenter Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia

- **Studies in subjects with HIV-AN**
    - C107 - A Randomized, Double-Blind, Controlled Dose Finding Study of NGX-4010 for the Treatment of Painful HIV-Associated Distal Symmetrical Polyneuropathy
    - C119 - A Multicenter, Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Painful HIV-Associated Neuropathy

Study C119 was still ongoing during the centralised procedure, hence the evaluation of the efficacy and safety data was based on preliminary results.

Unless specified otherwise information presented in the following sections applies to all main studies.

METHODS

Qutenza main studies were similar in design - 12-week, randomised, double-blind, controlled, multicentre phase 3 studies. The only exception was study C107 in which double blind phase was followed by a 40 week open label extension. Studies C107 and C116 were conducted entirely in the US, study C117 was conducted in the US and Canada, and study C119 in Australia, US, Canada and UK.

In all four main studies prior to placement of patch(es) containing the study drug subjects received a single 60 minute application of a topical local anaesthetic on painful area(s) (maximum total surface area of 1000 cm^2). In addition all subjects were permitted to use rescue pain medication for treatment-related discomfort.

Efficacy of Qutenza was evaluated using several pain inventories and other assessment tools including Numeric Pain Rating Scale (NPRS), modified Brief Pain Inventory (BPI) Short Form, Gracely Pain Scale, Short-Form McGill Pain Questionnaire (SF-MPQ), Short Form-36 version 2® Health Survey (SF-36v2), Patient Global Impression of Change (PGIC), Self-Assessment of Treatment (SAT).

Safety and tolerability were assessed by continuous monitoring of adverse events (AEs) and periodic assessments of clinical laboratory parameters, vital signs, physical examinations, electrocardiograms (ECGs), dermal assessments, targeted neurological/sensory assessments, and rescue medication and concomitant medication usage. In addition, at selected sites, plasma samples were obtained before and after treatment for analysis of capsaicin and capsaicin metabolites.

Study Participants

Eligible subjects were at least 18 years of age and had moderate to severe neuropathic pain (NPRS score of 3 to 9 inclusive) secondary to PHN or HIV-AN. Subjects were allowed to receive stable chronic pain medication regimens, but were not permitted to use any topical pain medications or opioid medication, unless opioid analgesics were orally or transdermally administered and did not exceed a total daily dose of 60 mg/day morphine equivalents.

Treatments

Subjects with PHN received a single treatment with either Qutenza or control patch(es) applied to the painful areas for 60 minutes. Subjects with HIV-AN received a single treatment with either Qutenza or control patch(es) applied to the painful areas for 30, 60 or 90 minutes in study C107 or 30 and 60 minutes in study C119. Following the treatment, patch(es) were removed and the treatment area(s) were cleaned with a study supplied cleansing gel. Subjects were monitored for 1-2 hours before being discharged and were asked to return for follow-up visits at 4, 8, and 12 (Termination Visit) weeks after treatment (studies C116, 117, 119), or, in study C107, at week 1, 4 and 12.

In study C107 the 12-week double-blind phase was followed by a 40-week open-label extension in which subjects could be eligible for up to 3 open-label re-treatments with Qutenza for 60 minutes, a minimum of 12 weeks apart. Subjects entering the open-label extension were scheduled for follow-up at weeks 24, 36, and 52 (Termination Visit).

Objectives
The primary objective of the studies in PHN subjects (C116, C117) was the assessment of Qutenza efficacy over 12 weeks after single patch administration for 60 minutes. The primary objective of the studies in HIV-AN subjects (C107, C119) was the assessment of Qutenza efficacy over 12 weeks after single patch application for 30, 60, or 90 minutes (C107) and 30 or 60 minutes (C119). The secondary objective of all main studies was the evaluation of the safety and tolerability of Qutenza. Study C107 assessed also optimal dose selection (i.e., application duration) for the treatment of painful HIV-AN and the efficacy, safety, and tolerability of repeated treatment(s) over 1 year.

Outcomes/endpoints
The primary efficacy variable was the mean percent change in "average pain for the past 24 hours" NPRS scores from baseline to weeks 2–8 in PHN studies C116, C117, or weeks 2-12 in HIV-AN studies C107, C119. Week 1 NPRS scores were not analysed in the primary endpoint to avoid the potential for bias from allowed rescue medication use.

A number of secondary and ancillary efficacy variables were also evaluated as presented below.

Secondary and ancillary endpoints			
Studies in PHN		**Studies in HIV-AV**	
Study C116	**Study C117**	**Study C107**	**Study C119**
Percent change in "average pain for the past 24 hours" NPRS scores from baseline to weeks 2–12	Percent change in "average pain for the past 24 hours" NPRS scores from baseline to weeks 2–12	Proportion of subjects achieving a ≥ 30%, ≥ 50%, or ≥ 2 units decrease in "average pain for the past 24 hours" NPRS scores from baseline during weeks 2 to 12	Proportion of subjects achieving a ≥ 30%, ≥ 50%, or ≥ 2 units decrease in "average pain for the past 24 hours" NPRS scores from baseline during weeks 2 to 12
Proportion of subjects achieving a 30% and 50% decrease in their "average pain for the past 24 hours" NPRS scores from baseline to weeks 2–12	Proportion of subjects achieving a 30% and 50% decrease in their "average pain for the past 24 hours" NPRS scores from baseline to weeks 2-12	Change in Gracely Pain Scale scores from baseline to week12	Change in SF-MPQ and SF-36v2™ from baseline to week 12
PGIC/CGIC at weeks 8 and 12 (termination)	PGIC/CGIC at weeks 8 and 12 (termination)	Change in Short-Form McGill Pain Questionnaire (SF-MPQ) from screening to week 12	PGIC and CGIC at several time points (weeks 4, 8, and 12/Termination)
SAT at week 12/ Termination	SAT at week 12/Termination	PGIC and CGIC at several time points (weeks 1, 4, 12, 52)	SAT at week 12/Termination
		SAT at week 12	

Additional efficacy variables for re-treatments during open-phase of study C107 included: (1) percent change in the "average pain for the past 24 hours" NPRS score from Baseline to Weeks 2–12 of each re-treatment during the open-label phase; and (2) proportion of responders (at the ≥ 30% and ≥ 50% level) on average during Weeks 2–12 following each re-treatment during the open-label phase.

Sample size
The sample size was determined based on a Student's t-test to detect a difference of 10% (studies C116 and C117) or 15% (study C107) between Qutenza and control groups' change from baseline in NPRS scores, and a standard deviation of 31%, at the 0.05 significance level and 90% power.

At the time of evaluation of data from study C119 detailed information on sample size evaluation was unavailable.

Randomisation
Studies C116, C117: Subjects were randomised at screening to receive either Qutenza or control patches for 60 minutes according to a 1:1 allocation scheme.
Study C107: Subjects were stratified at study entry by neurotoxic antiretroviral exposure and randomisation occurred separately within these strata. For the double-blind phase subjects were randomized in a 3:3:3:1:1:1 allocation scheme to receive either Qutenza or control patches for 30, 60 and 90 minutes. In the open-label phase subjects were randomly assigned according to a 1:1 allocation scheme to receive 60 minute Qutenza treatment(s) in the currently painful areas only or the currently painful areas and the initial treatment areas. Randomized treatment assignment was determined for each subject upon entry to the open-label phase and applied to all re-treatments received.
Study C119: Subjects were randomised to receive Qutenza or control patches for 30 or 60 minutes according to a 2:2:1:1 allocation scheme.
In all studies numbers were assigned only once, and no subject was randomised into the study more than once.

Statistical methods
For all main studies the Intent-to-Treat (ITT) or modified ITT analyses included all subjects enrolled, randomised, who received study drug, and had at least 3 days of non-missing "average pain for the past 24 hours" NPRS scores for the calculation of baseline NPRS score. The Per Protocol (PP) analysis included all subjects from the ITT analysis without any major protocol violations. The Safety analysis included all subjects who were randomised and who received study drug. Demographic and baseline characteristics were compared using t-test and Mantel-Haenszel method. Baseline observation carried forward (BOCF) and Last observation carried forward (LOCF) approaches were used to impute missing value(s). For safety summaries, subjects who terminated early from the studies were included in those summaries for which data were available. All statistical tests were 2-sided and were performed at a significance level of 0.05. For treatment comparisons gender stratified analysis of covariance (ANCOVA) model was used.

RESULTS

Patients flow
The number of patients who were randomised, completed or withdrew from main studies (including blinded phase of C107) is presented below.

Study	No pts randomised	No pts completed	No pts discontinued
C116	All = 402 Qutenza = 206 Control = 196	All = 365 Qutenza = 187 Control = 178	All = 37 Qutenza = 19 Control = 18
C117	All = 416 Qutenza = 212 Control = 204	All = 378 Qutenza = 192 Control = 186	All = 38 Qutenza = 20 Control = 18
C107 blinded	All = 307 Qutenza = 225 Control = 82	All = 272 Qutenza = 201 Control = 71	All = 35 Qutenza = 24 Control = 11
C119	All = 494 Qutenza = 332 Control = 162	All = 461 Qutenza = 309 Control = 152	All = 33 Qutenza = 23 Control = 10

There were no large imbalances in numbers of patients discontinuing for various reasons except for more patients lost to follow up in Qutenza group in study C107.

Conduct of the study
Minor amendments were made to studies protocols. They were reviewed and approved by the IEC/IRB prior to implementation. These did not affect outcome or statistical analyses.

Baseline data
Study C116, C117: The average age of subjects enrolled in the studies was 70-71 years. Most subjects were White (92-94%) and non-Hispanic (95-98%). Gender distribution was fairly equal, with slightly more female subjects enrolled (52-56%). No significant differences between Qutenza and control groups were noted for any demographic characteristics. With regard to subjects' pain characteristics, there were no statistically significant differences between the Qutenza and Control groups except for concomitant pain medication use in study C116. More subjects in the Qutenza group were using concomitant opioid, non-SSRI antidepressant, and/or anticonvulsant pain medications at baseline compared to the control group (50% vs. 38%); this difference was statistically significant (p = 0.0209). The variation between groups was largely due to more subjects in the Qutenza group using anticonvulsant medications (Qutenza = 38%; Control = 25%). The mean treatment area was 329.8 cm^2 for the Qutenza group and 349.2 cm^2 for the Control group (p = 0.375).
Study C107, C119: The mean age of subjects in the studies was approximately 48-50 years. Majority of the subjects were male (85-93%). Most subjects were Caucasian (61-69%) or Black/African American (22-25%) and not of Hispanic or Latino ethnicity (83-92%).
No statistically significant differences were observed between each Qutenza group and the pooled control group with respect to all demographic and baseline characteristics evaluated. No statistically significant differences were observed between each Qutenza group and the pooled control group with respect to duration of pain, pain level at screening, and baseline pain level. No statistically significant differences were observed between the Qutenza groups compared to the pooled control group in use of concomitant pain medication.

Numbers analysed
The ITT analysis included all subjects enrolled in the study who were randomised, received the study drug and had at least 3 days of non-missing "average pain for the past 24 hours" NPRS scores for the calculation of baseline NPRS score. Unavailability of any follow-up NPRS scores was not a criterion for exclusion from the ITT analysis and in such cases the baseline NPRS score was carried forward. The PP analysis included all subjects from the ITT analysis without any major protocol violations.

	Analysis populations, n (%)	Qutenza	Control
Study C116	Safety analysis	205 (100%)	197 (100%)
	Intent-to-treat analysis	206 (100%)	196 (100%)
	Per-Protocol Analysis	177 (86%)	161 (82%)

	Analysis populations, n (%)	Qutenza	Control
Study C117	Safety analysis	212 (99%)	204 (100%)
	Intent-to-treat analysis	212 (99%)	204 (100%)

	Analysis populations, n (%)	Qutenza	Control
Study C107	Safety analysis	225 (100%)	82(100%)
	Intent-to-treat analysis	225 (100%)	82(100%)
	Per Protocol Analysis	173(77%)	66(80%)

At the time of evaluation of data from study C119 detailed information on numbers analysed was unavailable.

Outcomes and estimation
Primary efficacy analysis
Studies in PHN
Study C116 and C117: Following a single 60-minute Qutenza patch application a 29.6% reduction in pain in study C116 and 32.0% reduction in pain in study C117 was observed during weeks 2 to 8. The results were statistically superior to the control group, i.e. 19.9%; p = 0.001 and 24.4%; p = 0.0108, in C116 and C117 respectively.
Studies in HIV-AN
Study C107: Based on pooled results for all Qutenza groups a 22.8% decrease from baseline in NPRS scores during the primary analysis period (Weeks 2 to 12) was observed, a reduction that was statistically greater than the reduction seen in control subjects (10.7%; p = 0.0026). Reductions in NPRS scores from baseline in the 30 and 90 minute individual dose groups (27.7%; p = 0.0007 and 24.7%; p = 0.0046) were also statistically significantly higher than the reduction seen in the control group. The difference between the 60 minute dose group and the control group did not reach statistical significance.
Study C119: The results did not reach statistical significance in the primary efficacy endpoint. An approximately 30% reduction in pain during Weeks 2 to 12 was observed following treatment with Qutenza; however, this was not significantly greater than the reduction observed in the control group.

Secondary and Ancillary efficacy analyses
Studies in PHN
The results of several other assessments of treatment response evaluated in the studies (i.e., secondary endpoints) provide supportive evidence of the efficacy of Qutenza.

	Outcomes	
Secondary/Ancillary endpoints	***Study C116***	***Study C117***
The mean percent change in NPRS scores from baseline during weeks 2–12	Qutenza (−29.9%) Control group (−20.4%); p = 0.0016	Qutenza (−32.3%) Control (−25.0%); p = 0.0172
Proportion of responders (≥30% reduction in pain from baseline) during weeks 2–12	Qutenza subjects (44%) Control subjects (35%); p = 0.0487	Qutenza subjects (47%) Control group (35%); p = 0.0212
Proportion of subjects with mean percent decrease from baseline ≥ 50% during weeks 2-12	Qutenza subjects (26%) control subjects (21%); p > 0.05	Qutenza group (30%); Control group (21%); p=0.0349
PGIC – feeling improved at week 8 and 12	Qutenza subjects vs. Control subjects: week 8 (57% vs. 46%; p = 0.0293) and week 12/Termination (57% vs. 46%; p = 0.0409)	Qutenza subjects vs. Control subjects: week 8 (62% vs. 51%; p = 0.0301) and week 12/Termination (61% vs. 47%; p = 0.0047)
SAT – improvement in pain relief, activity level, and quality of life at week 12	Qutenza subjects vs. Control subjects (p = 0.008)	Qutenza subjects vs. Control subjects (p = 0.0026 for each category)
CGIC – judged by the investigator to have felt improved at weeks 8 and 12		Qutenza subjects vs. control subjects at week 8 (63% vs. 52%; p = 0.0298) and week 12 (63% vs. 48%; p = 0.0033).

Studies in HIV-AN
The results of several other assessments of treatment response evaluated in the study C107 (i.e., secondary endpoints) provide supportive evidence of the efficacy of Qutenza.

	Outcomes
Secondary/Ancillary endpoints	***Study C107***
Proportion of responders (≥30% reduction in pain from baseline) during weeks 2–12	Qutenza (34%) Control group (18%); p = 0.0093
Proportion of subjects with mean percent decrease from baseline ≥ 50% during weeks 2-12	Qutenza subjects (21%) control subjects (12%); p > 0.05
Gracely Pain Scale scores at Week 12	Qutenza subjects (−0.21) Control subjects (−0.04); p = 0.0058
SFMPQ scores at Week 12	Qutenza subjects (−8.3) Control subjects (−3.2); p = 0.0004
SAT – improvement in pain relief, activity level, and quality of life at week 12	Qutenza subjects vs. Control subjects p ≤ 0.0014 (for each category)
Global impression of change at week 12 rated by the subject (PGIC) and the clinician (CGIC)	Qutenza subjects vs. Control subjects PGIC, p = 0.0003 CGIC, p = 0.0059

In study C119 the results of the secondary efficacy endpoint analyses generally reflected those of the primary endpoint and no statistically significant differences between Qutenza and the control group were observed. The results of several secondary measures of response (PGIC/CGIC, SF-36v2™ and SAT) tended to favour treatment with Qutenza compared with control; however, statistically significant differences between treatments were not consistently demonstrated.

Analysis performed across trials (pooled analyses and meta-analysis)

Integrated analysis

New integrated analyses of efficacy focusing on the following posology, i.e. 60-minutes for treatment of PHN and 30-minutes for treatment of HIV-AN were performed by indication, evaluating change in NPRS scores from baseline to weeks 2 to 12 for all 12- week controlled efficacy trials including main and supportive studies (Studies C107, C108, C110, C116, C117 and C119). These analyses evaluated the 60-minute data from the PHN studies and the 30-minute data from the HIV-AN studies and evaluated changes from baseline to weeks 2 to 12 regardless of indication. The results of those analyses were presented during oral explanation.

HIV-AN

The results of the integrated analysis of two phase 3 HIV-AN studies (C107 and C119) showed the following:

1) 30- and 60-minute doses provide comparable pain reductions during weeks 2-12 (-27.0% and -27.5%, respectively);

2) 30-minute dose is statistically superior to control (p=0.0026);

3) single 30-minute treatment provides a rapid decrease in NPRS scores that is significantly greater than control during Week 2 and maintained for 12 weeks;

4) 39% of Qutenza subjects treated for 30 minutes experience a 30% or greater reduction in pain during weeks 2-12 that is significantly greater than control. 37% of Qutenza subjects treated for 30-minutes experience a 2-unit or greater reduction in pain during weeks 2-12 that is significantly greater than control. Results were comparable between the LOCF and BOCF approaches confirming the robustness of the data;

5) sixty-five percent of Qutenza subjects treated for 30-minutes report being improved (very much, much, or slightly) on the PGIC questionnaire at week 12 compared to 42% of Control subjects;

6) treatment with Qutenza on the feet for 30 minutes in patients with HIV-AN is well tolerated with transient, self-limited application site pain and application site erythema as the most common adverse effects.

PHN
The results of the integrated analysis of four 12-week controlled PHN studies (C108, C110, C116 and C117) show the following:
1) single 60-minute treatment is efficacious in reducing peripheral neuropathic pain during weeks 2-12 and statistically superior to control (p=0.0002);
2) single 60-minute treatment provides a rapid decrease in NPRS scores during Week 1 and this decrease is maintained for 12 weeks;
3) 45% of Qutenza subjects treated for 60 minutes experience a 30% or greater reduction in pain during weeks 2-12 that is significantly greater than control; 40% of Qutenza subjects treated for 60-minutes experience a 2-unit or greater reduction in pain during weeks 2-12 that is significantly greater than control;
4) results are comparable between the LOCF and BOCF approaches confirming the robustness of the data;
5) sixty-one percent of Qutenza subjects treated for 60-minutes report being improved (very much, much, or slightly) on the PGIC questionnaire compared to 48% of Control subjects;
6) treatment with Qutenza for 60 minutes in patients with PHN is well tolerated with transient, self-limited application site pain and application site erythema as the most common side effects.

PHN and HIV-AN
Results showed statistically significant improvements in NPRS score in the Qutenza treatment group compared to control for each indication supporting the conclusion that a 30-minute application Qutenza is effective in treating pain due to HIVAN and a 60-minute application is effective in treating PHN pain.

Subgroup analysis
In order to determine the potential impact of gender, age, baseline pain score, concomitant neuropathic pain medication use, rescue medication use, and type of neuropathic pain on the efficacy profile of Qutenza subgroup analyses were conducted.

Across 3 of the studies conducted in PHN subjects (pivotal Study C116 and supportive Phase 2/3 Studies C108 and C110) and in pivotal Study C107 conducted in HIV-AN subjects, the mean percent reduction in NPRS scores was consistently larger in the Qutenza group compared to control regardless of gender, age, or baseline pain score. Although most comparisons were statistically significant, statistical significance was not achieved in all subgroups; a finding likely due to the small sample sizes of these subgroups.

Gender, Age and Baseline Pain
Although the net treatment effects (i.e., Qutenza versus control) were similar between females and males and between younger subjects and older subjects, females and younger subjects reported larger percent reductions in pain scores regardless of treatment group compared with males and older subjects, respectively. Qutenza-treated subjects with baseline scores less than the median showed larger percent reductions in pain scores compared to Qutenza-treated subjects with higher baseline pain scores. However, although the percent reduction was greater in Qutenza-treated subjects with lower baseline pain scores, the absolute change in NPRS scores was similar regardless of baseline pain level.

Concomitant neuropathic pain medication use
With regard to concomitant neuropathic pain medication use, in PHN Studies C116, C108 and C110 and HIV-AN Study C107, the mean percent reduction in NPRS scores was consistently larger in the Qutenza group compared to control regardless of whether Qutenza was used alone or in combination with other concomitant neuropathic pain medications. In general, the mean percent change in NPRS scores continued to be statistically significantly greater in the Qutenza

group compared to control both in subjects who did or did not use concomitant pain medications, with the exception of users in Study C110 and nonusers in Study C108.

To assess the potential impact of concomitant neuropathic pain medication use on the outcome of the two pivotal studies, Studies C116 and C107 were analysed using a gender-stratified ANCOVA model with baseline pain and concomitant pain medication use as covariates. In both studies, the percent reduction in pain from baseline was similar to the reduction seen in the original primary analysis and remained highly statistically significant.

Rescue medication use
The potential impact of rescue medication use was assessed in pivotal Studies C116 and C107. Across the two studies, the mean percent change in NPRS scores was consistently higher in the Qutenza group compared to control regardless of rescue medication use. In general, improvements in pain were similar for Qutenza subjects who received rescue medications for treatment-related pain compared to subjects who did not receive rescue medications. In addition to demonstrating that the use of opioid rescue medications did not influence the analgesic effect of Qutenza, the data demonstrating similar responses in subjects receiving and subjects not receiving rescue medications provide further evidence of the adequacy of the blinding of the clinical studies.

Type of neuropathic pain
Based on an analysis of data across Studies C116, C107, and C111 (a mixed population study of subjects with PHN, HIV-AN and PDN), it is concluded that Qutenza is effective in subjects with multiple different peripheral neuropathic pain conditions. Across all studies and neuropathic pain conditions tested, Qutenza-treated subjects experienced greater improvements in NPRS scores compared to control. These changes were statistically significant in Studies C116 (PHN) and C107 (HIV-AN), in which statistical comparisons were made.

With regard to HIV-AN, Study 107 provides evidence that Qutenza is effective both in subjects without prior exposure to neurotoxic antiretroviral agents as well as in subjects with painful neuropathy who were receiving neurotoxic antiretroviral agents. Although statistical significance was not reached in the latter group, this was likely due to the small sample size according to the Applicant.

Clinical studies in special populations
No studies in subjects with either renal or hepatic impairment were conducted.
The efficacy of Qutenza in children and adolescents younger than 18 years of age has not been studied.

Supportive study(ies)

PHN		**HIV-AN**		**PHN, HIV-AN, PDN**	
Phase 2/3 supportive studies	Study C102 Study C108 Study C110	Phase 3 supportive study	Study C112		
Open-label study	Study C106 (extension of C102)	Open-label study	Study C109	Open-label study	Study C111 Study C118 (HIV-AN, PHN only)

Studies in PHN subjects

Study Title	**Study design and**	**Study duration**	**Primary endpoints**

	treatment		
Study C102 - A Double-Blind Controlled Pilot Study of High Concentration Capsaicin Patches in the Treatment of Pain Associated with Postherpetic Neuralgia	Phase 2, multicentre, randomised, controlled, double blind, 2-phase (pilot + blinded); 60 min single application	4 weeks	Change in mean NPRS scores (average of morning and evening scores from day 8 through to day 28) as compared to average of morning and evening pre-treatment scores (Days −10 to −1)
Study C108 – A Randomised, Double-Blind, Controlled Dose Finding Study of NGX-4010 for the Treatment of Postherpetic Neuralgia	Phase 2/3 randomised, double blind, dose-finding, 2-phase (blinded + open label); 30, 60 or 90 min single application	12 week double-blind period followed by a 40 week open-label extension; open-label phase of the study was terminated prematurely due to negative results in blinded phase	Percent change from baseline in the "average pain for the past 24 hours" NPRS score for weeks 2 to 8 (i.e. average of scores during weeks 2 to 8 as compared to baseline)
Study C110 - A Randomised, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia	Phase 3 randomised, double-blind, controlled study; 60 min single application	12 weeks	Percent change in "average pain for the past 24 hours" NPRS scores from Baseline to Weeks 2 to 8
Study C106 - An Open-Label, Extension Study of High-Concentration Capsaicin Patches for the Treatment of Postherpetic Neuralgia	Phase 2, multicentre, uncontrolled open-label extension of study C102; up to three additional 60 minute, single applications	40 weeks	Change in mean NPRS scores (morning and evening average) compared to study C102 baseline measured: (1) at week 12 after initial study C102 treatment (Study C106); (2) at termination of study C106; (3) for each treatment in Study C106

Efficacy results in patients with PHN in additional studies

Similar reductions in mean percent change from baseline in NPRS scores following treatment with Qutenza were observed across the supportive controlled studies conducted in PHN subjects (studies C102, C108 and C110). Reductions in the total Qutenza groups were statistically superior to those observed in the control group for studies C102 (p=0.003) and C108 (p=0.0286). In the study C108 statistically significant difference was also present between Qutenza 90 minute treatment group and control group (p=0.0438), while there was no statistically significant difference between controls and both Qutenza 30 and 60 minute treatment groups. In study C110 the reduction in pain in the Qutenza group was not statistically greater than the reduction seen in the control group (p=0.296).

Treatment of PHN subjects with Qutenza during the 48 week open-label study C106 resulted in 30.0% to 34.1% reductions in NPRS scores from baseline.

The proportion of responders was also consistently numerically superior following Qutenza treatment compared with control in study C108 with trends favouring the Qutenza-treated group during both weeks 2 to 8 and weeks 2 to 12. Study C110 did not demonstrate any differences in responder rates between Qutenza and control.

Subjects with HIV-Associated Neuropathy

Study Title	Study design and treatment	Study duration	Primary endpoints	Results
Study C112 - A Multicentre, Randomised, Double-Blind, 12 Week Controlled Study of NGX-4010 for the Treatment of Painful HIV-Associated Neuropathy	Phase 3, multicentre, randomised, double-blind, controlled study; 60 min single application	12 weeks; study terminated after enrollment of five patients due to sponsor business conditions and the unblinding of the results of Study C107	Percent change in mean NPRS scores for "average pain for the past 24 hours" from Baseline to Weeks 2-12	No efficacy data were analysed

Study C109 – An Open-Label Pilot Study of High-Concentration Capsaicin Patches in the Treatment of Painful HIV-Associated Neuropathy	Phase 2, open-label exploratory study; 60 min single application	12 weeks	Percent change in mean NPRS scores for "average pain for the past 24 hours" from baseline to weeks 2 to 12	39.7% decrease in mean NPRS scores for "average pain for the past 24 hours" for weeks 2 to 12 compared to baseline

Mixed Population (PHN, HIV-AN, PDN)

Study Title	Study design and treatment	Study duration	Primary endpoints	Results
Study C111 - A Randomized, Open-Label Study of the Tolerability of Three Local Anaesthetic Formulations in Conjunction with NGX-4010 for the Treatment of Neuropathic Pain	Phase 2 randomised, open-label, multicentre study; 60 or 90 min single application	12 weeks	Percent change in mean NPRS scores for "average pain for the past 24 hours" from baseline to weeks 2 to 12	18.2%-50.4% reductions in NPRS scores from baseline
Study C118 – A Multicenter, Open-label, Phase 2 Study of NGX-4010 for the Treatment of Neuropathic Pain in Patients with Painful HIV-Associated Neuropathy (HIV-AN) or Postherpetic Neuralgia (PHN)	Phase 2, multicentre, open-label study; 60 min single application	50 weeks	Percent change in mean NPRS scores for "average pain for the past 24 hours" from baseline to weeks 2 to 12	39.7% decrease in mean NPRS scores for "average pain for the past 24 hours" for weeks 2 to 12 compared to baseline

Discussion on clinical efficacy

Qutenza cutaneous patch was assessed in four main trials: two studies in PHN patients (study C116, C117) and two studies in HIV-AN patients (study C107, C119). In both studies conducted in PHN subjects, the efficacy of 60 minute single application of Qutenza was assessed. In HIV-AN subjects efficacy of single applications for 30, 60 and 90 minutes were assessed in study C107, while 30 and 60 minute single applications were evaluated in study C119. In the main studies a total of 975 subjects received Qutenza, 418 patients with PHN and 557 patients with HIV-AN. The average age of subjects enrolled in the PHN studies was 70 years. Patients in HIV-AN studies were younger, the average age in this group was 50 years. All patients presented mild to moderate pain (NPRS score of 3 to 9 inclusive) at the study entry. In all main studies the 8% Qutenza cutaneous patch was used;

a low-concentration capsaicin patch (0.04%) served as a comparator in order to maintain the integrity of the double-blind design due to the expected capsaicin-related application site effects (burning sensation). Moreover, initial efficacy of Qutenza was assessed in 91 patients with PDN enrolled in a 12-week phase 2 randomised, open-label, multicentre study (study C111).

The primary efficacy endpoint used throughout the Qutenza clinical development program was the mean percent change from baseline in Numeric Pain Rating Scale (NPRS) scores (with 0 indicating no pain and 10 indicating worst possible pain) measured at week 8 in PHN studies and week 12 in HIV-AN studies. Several secondary endpoints were used across the Qutenza clinical development programme. Changes from baseline in NPRS scores at multiple time points served as secondary endpoints, and the percentage of subjects who met the "responder" definition (which was generally established as a 30% or greater reduction from baseline in NPRS scores) were also used. Additional pain assessment instruments (e.g., Short-Form McGill pain questionnaire, Gracely Pain Scale, Brief Pain Inventory), subject- and investigator-rated global ratings (PGIC, CGIC) were also utilised during the program. Overall quality of life assessments were obtained using a Sponsor-designed self-assessment of treatment (SAT) and the SF-36.

The initial analysis of efficacy data from main studies produced inconclusive results. In study C107 conducted in HIV-AN subjects inconsistency with regards to efficacy in different time windows (30, 60 and 90 minutes) was observed, i.e. differences on the NPRS score between the 60 minute group and the control group did not reach statistical significance. In the second HIV-AN study (C119) there were no statistically significant differences in the primary endpoint between both treatment groups (30 and 60 minutes) and the control group leading to the uncertainty regarding effective treatment duration. Studies C116 and C117 conducted in PHN subjects showed Qutenza efficacy in reducing NPRS scores; nevertheless, the robustness of these findings was found not to be satisfactory as the supportive studies in PHN subjects (C108, C110) did not confirm the results. The clinical relevance of the small effect size in main studies C107 and C116 was questioned given that the 2 point reduction in pain was not achieved. Consequently, the CHMP requested additional analysis of efficacy data. In response a new integrated analysis was submitted focusing on 60-minute treatment duration in PHN and 30-minute duration in treatment of HIV-AN. The analysis was performed separately for each indication and evaluated change in NPRS scores from baseline to weeks 2 to 12 for all 12-week controlled efficacy studies (studies C108, C110, C116, C117 for PHN; studies C107 and C119 for HIV-AN). Results of the analysis showed a significant reduction in pain scores after 30 minute Qutenza application in the treatment of HIV-AN (27%; p=0.0026) and 60 minute Qutenza application in PHN (29.6%, p=0.0001). Analysis of several secondary endpoints, e.g. proportion of responders, proportion of patients achieving 2-unit reduction in pain, PGIC score provided supportive evidence of the efficacy of Qutenza in both HIV-AN and PHN. Results of the integrated analysis were also presented during oral explanation. The CHMP found the results of integrated analysis acceptable and acknowledged that effect size can be small due to the use of low concentration capsaicin patch as a control.
Clinical data presented in support of the indication for treatment in PDN were considered not to be sufficient; hence the initial indication was modified to exclude diabetic patients. This information is reflected in the SmPC.

Clinical safety
The overall safety profile of Qutenza has been evaluated during 12 studies conducted in subjects with peripheral neuropathic pain, i.e. in 8 double-blind controlled studies or studies including a double-blind controlled part (Studies C102, C107, C108, C110, C112, C116, C117 and C119), and 3 open-label studies (Studies C109, C111 and C118). Additionally, study C106 was an open-label extension of study C102. Nine trials were completed at the time of the MAA submission and three trials (C117, C118 and C119) were still ongoing.
In addition to the 12 studies conducted in subjects with peripheral neuropathic pain, 2 studies were conducted in healthy volunteers (Studies C101 and C115).
Adverse events (AEs), including AEs of potential interest to Qutenza (e.g., application site reactions and cardiac events), clinical laboratory tests, vital signs and physical examination findings were evaluated across all studies conducted during the Qutenza clinical development program. In some studies, additional assessments relevant to the safety profile of Qutenza were performed including: ECG; pain and dermal assessments before, during and after treatment; targeted neurological and sensory assessments; sharp pain and tactile threshold assessments; quantitative sensory testing (QST); nerve conduction evaluations; and measurement of capsaicin and capsaicin metabolites in plasma.

Patient exposure
Including the three clinical trials completed after the submission of the MAA (C117, C118 and C119), a total of 2357 subjects were enrolled in these studies and 1696 received Qutenza. Of these 1696 subjects, 128 were originally randomized to control, and subsequently received open-label Qutenza treatments. A total of 661 subjects received a single low-concentration capsaicin control patch treatment as their only treatment. Though subjects in Study C118 (PHN and HIV-AN) were enrolled in previous Qutenza studies they were evaluated as separate subjects due to the variable duration between study enrollments, i.e., they are represented twice, unless indicated otherwise.

In the 8 controlled studies, a total of 1327 subjects received a single application of Qutenza. For those subjects who received Qutenza, 148 subjects received a 90 minute treatment, 868 subjects received a 60 minute treatment, and 311 subjects received a 30 minute treatment. In the control group (789 subjects), 54 subjects received a 90 minute treatment, 613 subjects received a 60 minute treatment, and 122 subjects received a 30 minute treatment.

Qutenza Exposure by Duration and Indication (Integrated controlled studies)

	Qutenza				Control			
Subjects, n (%)	90 min (n = 148)	60 min (n = 868)	30 min (n = 311)	Total (n = 1327)	90 min (n = 54)	60 min (n = 613)	30 min (n = 122)	Total (n = 789)
Indication								
PHN	73 (49)	622 (72)	72 (23)	767 (58)	25 (46)	495 (81)	23 (19)	543 (69)
HIV-AN	75 (51)	246 (28)	239 (77)	560 (42)	29 (54)	118 (19)	99 (81)	246 (31)

In the three open-label studies a total of 235 subjects received Qutenza, including 59 subjects who received a 90 minute treatment and 176 subjects who received a 60 minute treatment.

Qutenza Exposure by Duration and Indication (Integrated Open-Label Studies)

Subjects, n (%)	Qutenza 90 min n = 59	Qutenza 60 min n = 176	Qutenza Total n = 235
PHN	12 (20)	67 (38)	79 (34)
HIV-AN	0	65 (37)	65 (28)
PDN	47 (80)	44 (25)	91 (39)

The size of the treatment area tended to vary by indication. The majority of subjects with PHN received treatment over an area of ≤ 500 cm2 in size, whereas the majority of subjects with HIV-AN and PDN received treatment over an area of ≥ 750 cm2 in size.

Qutenza Exposure by Size of Treatment Area and Indication

Subjects, n (%)	TOTAL	PHN[b]	HIV-AN[a]	PDN[c]
Area ≤ 250 cm^2	389 (23)	382 (42)	7 (1)	0
Area > 250 cm^2 and ≤ 500 cm^2	362 (21)	319 (35)	42 (6)	1 (1)
Area > 500 cm^2 and ≤ 750 cm^2	264 (16)	151 (16)	102 (15)	11 (12)
Area > 750 cm^2 and ≤ 1000 cm^2	206 (12)	65 (7)	123 (18)	18 (20)
Area > 1000 cm^2	474 (28)	2 (0.2)	411 (60)	61 (67)
Total Number of Subjects	**1695**	**919**	**685**	**91**

Adverse events
Qutenza treatment was associated with transient, expected, capsaicin-related application site adverse events including erythema, pain, pruritus, oedema, dryness and papules. Application site reactions were mostly mild or moderate, non serious and resolved spontaneously within 7 days with no known sequelae. The overall incidence of adverse events was similar in younger (< 65 years of age) and older (≥ 65 years of age) subjects and the incidence of application site erythema was less in subjects with HIV-AN compared to subjects with PHN.

Controlled studies
In the controlled studies (C102, C107, C108, C110, C112, C116, C117, C119) the overall incidence of AEs reported in the total Qutenza group was higher (84%) compared with the total control group (77%). The difference was primarily due to a higher incidence of application site AEs among subjects in the Qutenza groups compared with the control groups. Of the 12 individual AEs defined as being "most common" (≥ 3% of subjects in either total treatment group), 6 AEs were application site AEs (application site pain, application site erythema, application site papules, application site pruritus, application site dryness, and application site swelling). With the exception of application site erythema and application site swelling, these application site AEs occurred at a ≥ 3% higher incidence in the total Qutenza group compared with the total Control group. Nearly all of the application site reactions were of short duration and mild or moderate intensity. Two specific AEs (application site pruritus and application site swelling), irrespective of relationship to study drug, occurred at higher incidences among subjects treated with Qutenza for 90 minutes (13% and 10%, respectively) compared with subjects treated with Qutenza for 30 minutes (8% and 2%, respectively). No effect based on duration of exposure was noted for any SAEs, severe SAEs or severe AEs.

Open-label studies
Among the open-label studies, the pattern of the most common treatment-related AEs was similar to that seen for the controlled studies grouping. The majority of the most common treatment-related AEs in the open-label studies were application site AEs. The most common non-application site AEs identified in the open-label studies were nausea, blood pressure increased, and hyperaesthesia.

Treatment area
Based on pooled data from all patients, the overall incidence of AEs did not increase with increasing treatment area. Two individual AEs occurred at a higher incidence with increasing Qutenza surface area: application site dryness (2% [≤ 250 cm2], 3% [> 250 and ≤ 500 cm2], 8% [> 500 and ≤ 750 cm2] and 13% [> 750 cm2]) and application site swelling (1% [≤ 250 cm2], 3% [> 250 and ≤ 500 cm2], 5% [> 500 and ≤ 750 cm2] and 15% [> 750 cm2]).

Number of treatments
No increase in AEs of any type was noted with increasing number of treatments, supporting the conclusion that Qutenza is not associated with cumulative toxicity following multiple treatment cycles.

Demographics
With regards to demographic characteristics there was no consistent pattern of relationship between age, gender, race and the AE profile of Qutenza. The AEs in PDN subjects were similar to those experienced by subjects treated for PHN and HIV-AN. The incidence of AEs coded to the "Cardiac Disorders" SOC was comparable across all subgroup categories. The only exception was a higher incidence of cardiac disorders in older subjects (≥ 65 years of age) as compared to younger subjects (< 65 years of age) in both the Qutenza and control groups.

Serious adverse event/deaths/other significant events
Seven subjects with HIV-AN (Study C107, C119) and two subjects with PHN (Study C108, 117) died. None of the deaths were considered to be related to study drug treatment. In study C107, 4 subjects died as a result of complications associated with their HIV infection, 1 subject committed

suicide, and one subject died as a result of a suspected drug overdose. In study C119 one subject died from pre-existing cardiovascular condition (arteriosclerotic cardiovascular disease). The PHN subject who died during Study C108 was a 91-year-old male with suspected ileus, cholecystitis, pneumonia and anaemia. In study C117 81-year-old female died of diverticulitis.

In controlled studies the overall incidence of SAEs was similar in the total Qutenza group (6%) as compared with the total control group (4%). In the Qutenza group 16 events were reported in more than one subject. One event, myocardial infarction, was reported in more than 2 subjects: 5 subjects [0.4%] in the Qutenza group and 2 subjects [0.3%] in the control group. The remaining 15 events occurred in 2 subjects each (0.2%) in the Qutenza group: pneumonia, cholecystitis, appendicitis, lower respiratory tract infection, urinary tract infection, urosepsis, atrial fibrillation, bradycardia, cerebrovascular accident, subarachnoid haemorrhage, cholelithiasis, pneumothorax, chest pain, arthritis, and prostate cancer. There was a higher incidence of cardiac disorders reported as SAEs in the Qutenza group (16 cases, 1.2%) as compared with the control group (4 cases, 0.5%). The imbalance of cardiac events is most probably not attributable to the study medication. Only 1 SAE was considered to be possibly related to the study drug (elevated blood pressure during and after patch application).

In the open-label studies the overall incidence of SAEs (6%) was identical to the incidence seen in the Qutenza group in the controlled studies. A total of 8 events were reported; none of them was present in more than one subject. Only 1 subject experienced SAE (severe pain NOS) that was considered to be possibly related to the study drug. In the open-label extension studies the overall incidence of SAEs was 2-4%. Events categorized as Infections and Infestations were the most prevalent (1%). A total of 2 events were reported in more than one subject: myocardial infarction and cardiac failure congestive. Clostridium difficile colitis was reported twice by the same subject. Only 1 subject experienced an SAE that was considered to be possibly related to the study drug (moderate application site pain).

Cardiovascular AEs
Integrated results from all controlled studies indicate that treatment with Qutenza and control was associated with similar overall cardiac adverse event rate (3% of subjects treated with Qutenza experienced a cardiac AE vs. 3% of subjects treated with control).
Fifteen (15) severe AEs in the Cardiac Disorders SOC (1.1%) were observed in the Qutenza group and two (2) were reported in the control group (0.3%). They included events related to coronary artery insufficiency (myocardial infarction, acute myocardial infarction, acute coronary syndrome, angina pectoris, and coronary artery disease), heart rhythm abnormalities (arrhythmia, atrial fibrillation, complete AV block, bradycardia, supraventricular tachycardia, tachycardia, palpitations, and supraventricular extrasystoles), and miscellaneous cardiac disorders (congestive cardiac failure, cardiac tamponade, mitral valve incompetence and cardiac valve disease). None of the AEs had an incidence of more than 1% while myocardial infarction was the only AE observed in more than 1 subject. There was a higher incidence of cardiac disorders reported as SAEs in the Qutenza group (16 subjects, 1.2%) compared with the Control group (4 subjects, 0.5%). The variable timing of the events, the lack of a common pathology, the lack of a dose response, and the lack of association with detectable systemic capsaicin exposure suggest that this imbalance of cardiac events is not attributable to study medication.

In controlled studies the most common adverse events were hypertension in 3% of Qutenza treated subjects and 1% of control subjects. For Qutenza-treated subjects 4 (< 1%) cases of hypertension, 5 (< 1%) cases of increased blood pressure and 1 (< 1%) case of increased systolic blood pressure were judged at least possibly related to study medication. Vital signs collected on the day of treatment in the controlled studies showed transient small decreases in mean systolic and diastolic blood pressure during the application of topical anaesthetic increases to above the pre-treatment values after Qutenza or control patch application, and decreases to baseline following patch removal. Mean heart rates showed small decreases during application of the topical anesthetic with gradual return to pre-treatment values during the rest of the treatment. No trends in mean respiratory rates over time were apparent. No ECG changes related to treatment with Qutenza were noted.

Neurological AEs
For subjects with PHN, there was no evidence of impairment of neurological function over 12 weeks following a single application Qutenza (based on pooled results for allodynia assessments and tests of light brush sensation, pinprick, vibration, and warmth in studies C108, C110, C111, and C116). Following multiple Qutenza applications for up to 52 weeks, no evidence of impairment of neurological function was observed (based on tests of light brush sensation, pinprick, vibration, and warmth in Study C108).
For subjects with HIV-AN or PDN-related distal symmetric polyneuropathy (DSP) there was also no evidence of impairment of neurological function following treatment with Qutenza (deep tendon reflexes, vibration sense, warmth perception or sharp sensation) based on integrated results from Studies C107, C109, C111 and C112. Following multiple applications of Qutenza in Study C107, the majority of subjects either had no change or improved their neurological function.
In healthy volunteer Study C115 one week after patch application, there was a 15% reduction from baseline in the detection of sharp pain, which normalized by week 12. This information is reflected in the RMP. For subjects with painful DSP due to HIV-AN from Study C107 there was no evidence of impairment of sensory function as measured by quantitative sensory testing (QST) following treatment with Qutenza. A statistically significant difference in heat pain threshold (0.5) observed at Week 12 was primarily due to a decrease in the threshold observed in the control group. No statistically significant differences were observed at termination following multiple Qutenza applications for any of the QST parameters tested including heat, pain, cooling, and vibration thresholds. In the healthy volunteer study C101, small increases in warmth sensation threshold (1.1°C to 1.9°C) were observed at day 7 following a 60 and 120 minute Qutenza application

Laboratory findings
The comparison of laboratory-related AEs in subjects treated with Qutenza versus the low-concentration control patch do not suggest any effect of exposure to Qutenza on hematology or clinical chemistry laboratory values.

Safety in special populations
No studies in subjects with either renal or hepatic impairment were conducted. The Safety of Qutenza in children and adolescents younger than 18 years of age has not been studied. No clinical data on exposed pregnancies are available from the Qutenza clinical development program. This information is reflected in the SmPC.
The overall incidence of AEs was similar in younger (< 65 years of age) and older (≥ 65 years of age) subjects with PHN in the Qutenza group, whereas in the control group the incidence of AEs was higher in the younger PHN subjects. The overall incidence of AEs was similar in younger (< 65 years of age) and older (≥ 65 years of age) subjects with HIV-AN in the Qutenza group, however, due to the small numbers of HIV-AN subjects in the older age group, no meaningful comparisons of AE incidences could be made in this population.
The incidence of AEs coded to the "Cardiac Disorders" SOC was comparable across all subgroup categories with the exception of a higher incidence in older subjects (≥ 65 years of age) compared to younger subjects (< 65 years of age) in both the Qutenza and control groups.

Safety related to drug-drug interactions and other interactions
Only transient low levels of systemic absorption of capsaicin have been shown to occur in a minority of subjects following treatment with Qutenza. Interactions with other systemic medicinal products are highly unlikely. Capsaicin has been shown not to inhibit or induce liver cytochrome P450 enzymes at concentrations far in excess of those measured in blood samples from subjects treated with Qutenza.

Discontinuation due to adverse events
Of the 2357 subjects enrolled in the Qutenza studies 35 (1.5%) terminated treatment prematurely due to non-fatal AEs. In controlled studies the early treatment terminations due to AEs occurred in the Qutenza group in 11 cases, and in the control group in 5 cases. 19 subjects withdrew from

the open label studies. Majority of the events that led to discontinuation were considered not to be related to the study drug.

Overdose
No case of overdose has been reported during the Qutenza clinical development program. Due to the limited systemic absorption of capsaicin and requirements related to patch administration, overdosing is unlikely to occur.

Dependence
The potential for dependence during the use of Qutenza is unlikely. Qutenza produces minimal systemic exposure to capsaicin. Moreover, capsaicin has no recognized abuse potential and there is no history of capsaicin abuse despite it being widely available in natural products and topical preparations for centuries. Neither topical formulations of capsaicin nor foods containing capsaicin have been associated with development of dependence.

Post marketing experience
There is currently no postmarketing experience with this medicinal product.

Discussion on clinical safety
A total of 2357 subjects were enrolled in Qutenza development programme studies and 1696 received active treatment. Of these 1696 subjects, 128 were originally randomised to control, and subsequently received open-label Qutenza treatments. A total of 661 subjects received a single low-concentration capsaicin control patch. Adverse events (AEs), including AEs of potential interest to Qutenza (e.g., application site reactions and cardiac events), clinical laboratory tests, vital signs and physical examination findings were evaluated across all studies. In select studies, additional evaluations to assess the overall safety of Qutenza were also conducted, including: ECGs; pain and dermal assessments before, during and after treatment; targeted neurological and sensory assessments; sharp pain and tactile threshold assessments; quantitative sensory testing (QST); nerve conduction evaluations; and measurement of plasma levels of capsaicin and capsaicin metabolites.

Qutenza treatment was associated with transient, expected, capsaicin-related application site AEs including erythema, pain, pruritis, oedema, dryness and papules. Application site reactions were mostly mild and moderate, not serious by ICH criteria, and resolved spontaneously within 7 days with no known sequelae. The higher incidence of application site AEs is not unexpected given the predictable effects of topical administration of high concentrations of capsaicin. A temporary increase in blood pressure in subjects receiving Qutenza was seen. It was considered to be caused by pain experienced during the treatment procedure as the blood pressure returned to the values found in the control arms after patch removal. The only individual AE that appeared to be consistently related to duration of exposure was application site pain.

There was a higher incidence of cardiac disorders reported as SAEs in the Qutenza group (16 subjects, 1.2%) compared with the control group (4 subjects, 0.5%). It is concluded that the SAEs were unlikely to be causally related to treatment with Qutenza for the following reasons: 1) the SAEs occurred in subjects with prior history of coronary artery disease or known risk factors or both;
2) the SAEs occurred at variable times after exposure to Qutenza; and 3) the SAEs were not dose-related (i.e., they were not associated with longer patch application times or larger treatment areas).

Long term neurological assessment (12 months) of 365 patients (185 patients with PHN and 180 patients with HIV-AN) treated with more than a single exposure to Qutenza as well as data from 90 patients (52 patients with PHN and 38 patients with HIV-AN) treated with multiple exposures to Qutenza (maximum 8 treatments over 43 months) have not demonstrated any evidence of accelerated nerve damage. Similarly, long-term QST assessments in 37 HIV-AN subjects were consistent with the clinical neurological evaluations demonstrating no evidence of accelerated nerve damage following repeated Qutenza exposures. Nonetheless, concerns about the risk of

accelerated nerve damage remained unsolved. Therefore CHMP requested a commitment to conduct a long-term safety study in order to detect neurological impairment. This requirement is reflected in the RMP.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Application site reactions	Routine pharmacovigilance	Routine: Section 4.2 of the SPC, Posology and Method of Administration and Section 6.6 of the SPC, Special Precautions for Disposal and other Handling, explain how the patches should be used and disposed of. Adverse events are described in Section 4.8, Undesirable Effects, of the SPC.
Transient small increase in blood pressure during patch application	Routine pharmacovigilance	Routine: Section 4.4 of the SPC, Special Warnings and Special Precautions for Use, states that blood pressure should be monitored during Qutenza application and that subjects with increased pain should be treated with supportive treatment such as local cooling and oral analgesics (i.e., short acting opioids). For patients with unstable or poorly controlled hypertension or recent cardiovascular events, the risk of adverse cardiovascular effects due to the potential stress of the procedure should be considered prior to initiating Qutenza treatment. Additional: Establish an educational programme, including a supply of appropriate training materials addressing the need to monitor blood pressure during the treatment procedure and directions for supportive treatment for patients who experience increased pain during Qutenza administration. This programme will also address the need to evaluate the risk of adverse cardiovascular reactions due to the potential stress of the procedure in patients with unstable or poorly controlled hypertension or recent cardiovascular events prior to initiating Qutenza treatment.
Lack of response to opioid medication	Routine pharmacovigilance	Routine: Section 4.4 of the SPC, Special Warnings and Special Precautions for Use, states that subjects using high doses of opioid medications may be tolerant of the analgesic effect and may not respond to oral analgesics. It recommends taking a thorough medication history and to have an alternative pain reduction strategy in place prior to Qutenza treatment in these subjects. Additional: Establish an educational programme, including supply of appropriate training materials that address the need to put in place an alternative pain reduction strategy prior to initiating Qutenza treatment in patients using high doses of opioids and with suspected high opioid tolerance.

Temporary, minor decrease (1ºC to 2ºC) in the ability to detect heat stimuli and sharp sensations at the application site.	Routine pharmacovigilance	Routine: Stated in Section 4.8 of the SPC, Undesirable Effects. Section 4.4 of the SPC, Special Warnings and Special Precautions for Use, states that "Though no treatmentrelated reductions in neurological function have been observed in patients with peripheral neuropathic pain during clinical studies with Qutenza minor, temporary changes in sensory function (e.g. heat detection) have been reported following administration of capsaicin. Patients with increased risk for adverse reactions due to minor changes in sensory function should be cautious when using Qutenza. Additional: Establish an educational programme, including supply of appropriate training materials that address the need to warn patients about the increased risk for adverse reactions due to temporary changes in sensory function (e.g. heat detection) following administration of Qutenza.
Loss of neurosensory function after repeated treatments	To provide additional information regarding the long-term neurological safety of Qutenza as well as to collect long-term safety data after repeated treatments in subjects with peripheral neuropathic pain, the applicant commits to conduct an open-label repeated dose study that will include PHN and HIV-AN subjects.	Routine: Section 4.1 of the SPC, Therapeutic Indications, states that Qutenza is indicated in "non-diabetic adults". Section 4.4 of the SPC, Special Warnings and Special Precautions for Use, states that "Though no treatment related reductions in neurological function have been observed in patients with peripheral neuropathic pain during clinical studies with Qutenza, minor, temporary changes in sensory function (e.g. heat detection) have been reported following administration of capsaicin. Patients with increased risk for adverse reactions due to minor changes in sensory function should be cautious when using Qutenza". The same section also states that "There is only limited experience with Qutenza in patients with Painful Diabetic Neuropathy (PDN). Repeated treatments with Qutenza in patients with PDN have not been studied." This information is also communicated in the Package Leaflet.
Medication errors including unintentional contact with patch or other materials that have come in contact with treated area resulting in transient erythema and burning sensation or coughing or sneezing in case of inhalation of airborne capsaicin.	Routine pharmacovigilance	Routine: Section 4.2 of the SPC, Posology and Method of Administration explains how Qutenza should be safely applied and removed and specifically states that Qutenza should be removed slowly and gently by rolling the patch inward and that nitrile gloves should be worn at all times. Section 4.4 of the SPC, Special Warnings and Special Precautions for Use, states that care must be taken to avoid unintentional contact with the patches or other materials that have come in contact with the treated areas and that exposure of the skin to capsaicin results in transient erythema and burning sensation, with mucous membranes being particularly susceptible. It also states that inhalation of airborne capsaicin can result in coughing or sneezing, that health care professionals should wear nitrile gloves when handling patches and cleansing treatment areas,

		and that used patches should be disposed of immediately after use in an appropriate medical waste container. This same section explains what should be done in case Qutenza comes in contact with areas not intended to be treated and burning occurs, and warns that the cleansing gel for Qutenza contains butylhydroxyanisole, which may cause local skin reactions (e.g. contact dermatitis) or irritation of the eyes and mucous membranes. Section 4.9 of the SPC, Overdose, states what should be done in case of suspected overdose. Section 6.6 of the SPC, Special Precautions for Disposal and other Handling explains in detail how patches should be handled and disposed of. <u>Additional:</u> Clear instructions for use will be printed on a tear-off card on the inside flap of the product carton. Appropriate training materials that address the identified safety issues and demonstrate how to properly apply, remove and dispose of the capsaicin patch will be supplied to healthcare professionals.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

1. The Qutenza cutaneous patch is administered to adults by a physician or by a health care professional under the supervision of a physician.

2. Educational programme for healthcare professionals should be provided to address the identified safety issues and demonstrate how to properly apply, remove and dispose of the capsaicin patch. This educational programme should include the following:

a. Recommendations regarding the general handling and disposal measures for Qutenza
b. Instructions regarding the administration of Qutenza
c. Warnings and precautions, including the need:

- to monitor blood pressure during the treatment procedure
- to provide supportive treatment if patients experience increased pain during Qutenza administration
- in patients with unstable or poorly controlled hypertension or recent cardiovascular events: to evaluate, prior to initiating Qutenza treatment, the risk of adverse cardiovascular reactions due to the potential stress of the procedure
- in patients using high doses of opioids and with suspected high opioid tolerance: to put in place an alternative pain reduction strategy prior to initiating Qutenza treatment, as these patients may not respond to oral opioid analgesics when used for acute pain during and following the treatment procedure
- to warn patients about the increased risk for adverse reactions due to temporary changes in sensory function (e.g. heat detection) following administration of Qutenza
- to warn patients about the risk of local reactions (e.g. contact dermatitis) and of irritation of the eyes and mucous membranes associated with the cleansing gel of Qutenza.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product are well characterised and documented. The manufacturing process used for capsaicin cutaneous patch is a standard process that has been developed for the manufacture of transdermal patches. These processes are performed on standard equipment commonly used for the manufacture of patches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

Non-clinical pharmacology and toxicology

The toxicological profile of capsaicin path was assessed in a sufficient set of studies which appropriately covered the main requirements in relation to the proposed conditions of use. The main findings are local adverse effects since very low plasma levels are expected after application of Qutenza cutaneous patch in humans. No specific concerns apart from cutaneous reactions including rash, expected based on the mechanism of action, were identified. Genotoxicity studies performed with capsaicin showed a weak mutagenic response in mouse lymphoma assay. This information is reflected in the SmPC. Other genotoxicity assays yielded negative results. The carcinogenic potential of capsaicin was negative. Reproductive effects included reduced male and female fertility which may be taken into account when deciding on the use of the patch in men and women of reproductive age. Whether these effects are reversible has not been established; however there is no apparent reason to believe they will be irreversible. This information is reflected in the SmPC. Delayed ossification was observed in the rat teratology study at doses above therapeutic level in humans. This information is reflected in the SmPC. No phototoxic concerns were raised.

Efficacy

Qutenza cutaneous patch was assessed in four main trials: two studies in patients with post-herpetic neuralgia, PHN (study C116, C117) and two studies in patients with HIV associated neuropathy, HIV-AN (study C107, C119). In both studies conducted in PHN subjects, the efficacy of 60 minute single application of Qutenza was assessed. In HIV-AN subjects efficacy of single applications for 30, 60 and 90 minutes were assessed in study C107, while 30 and 60 minute single applications were evaluated in study C119. In the main studies a total of 975 subjects received Qutenza, 418 patients with PHN and 557 patients with HIV-AN. The average age of subjects enrolled in the PHN studies was 70 years. Patients in HIV-AN studies were younger, the average age in this group was 50 years. All patients presented mild to moderate pain (NPRS score of 3 to 9 inclusive) at the study entry. In all main studies the 8% Qutenza cutaneous patch was used;
a low-concentration capsaicin patch (0.04%) served as a comparator in order to maintain the integrity of the double-blind design due to the expected capsaicin-related application site effects (burning sensation). Moreover, initial efficacy of Qutenza was assessed in 91 patients with painful diabetic neuropathy (PDN) enrolled in a 12-week phase 2 randomised, open-label, multicentre study (study C111).

The primary efficacy endpoint used throughout the Qutenza clinical development program was the mean percent change from baseline in Numeric Pain Rating Scale (NPRS) scores (with 0 indicating no pain and 10 indicating worst possible pain) measured at week 8 in PHN studies and week 12 in HIV-AN studies. Several secondary endpoints were used across the Qutenza clinical development programme, e.g. changes from baseline in NPRS scores at multiple time points, and the percentage of subjects who met the "responder" definition (which was generally established as a 30% or greater reduction from baseline in NPRS scores). Additional pain assessment instruments (e.g., Short-Form McGill pain questionnaire, Gracely Pain Scale, Brief Pain Inventory), subject- and investigator-rated global ratings (PGIC, CGIC) were also utilised as a secondary endpoint during the program. Overall quality of life assessments were obtained using a Sponsor-designed self-assessment of treatment (SAT) and the SF-36.

The initial analysis of efficacy data from main studies produced inconclusive results. In study C107 conducted in HIV-AN subjects inconsistency with regards to the efficacy in different time windows

(30, 60 and 90 minutes) was observed, i.e. differences on the NPRS score between the 60 minute group and the control group did not reach statistical significance. In second HIV-AN study (C119) there were no statistically significant differences in the primary endpoint between both treatment groups (30 and 60 minutes) and the control group leading to the uncertainty regarding effective treatment duration in HIV-AN. Studies C116 and C117 conducted in PNH subjects showed Qutenza efficacy in reducing NPRS scores; nevertheless, the robustness of these findings was found not to be satisfactory as the supportive studies in PHN subjects (C108, C110) did not confirm the results. The clinical relevance of the small effect size in main studies C107 and C116 was questioned given that the 2 point reduction in pain was not achieved. Consequently, the CHMP requested additional analysis of efficacy data. In response a new integrated analysis was submitted focusing on 60-minute treatment duration in PHN and 30-minute treatment duration in HIV-AN. The analysis was performed separately for each indication and evaluated change in NPRS scores from baseline to weeks 2 to 12 for all 12-week controlled efficacy studies (studies C108, C110, C116, C117 for PHN; studies C107 and C119 for HIV-AN). Results of the analysis showed a significant reduction in pain scores after 30 minute Qutenza application in the treatment of HIV-AN (27% vs. 15.7% reduction) and 60 minute Qutenza application in PHN (29.6% vs. 22.3% reduction). Analysis of several secondary endpoints, e.g. proportion of responders, proportion of patients achieving 2-unit reduction in pain, PGIC score provided supportive evidence of the efficacy of Qutenza in both HIV-AN and PHN. Results of the integrated analysis were also presented during oral explanation. The CHMP found the results of integrated analysis acceptable and acknowledged that effect size can be small due to the use of low concentration capsaicin patch as a control. Clinical data presented in support of the indication for treatment in PDN were considered not to be sufficient; hence the indication proposed initially was modified to exclude diabetic patients.

Safety

The safety evaluation is based mainly on data from randomised clinical trials. Most frequently Qutenza treatment was associated with transient, expected, capsaicin-related application site AEs including erythema, pain, pruritis, oedema, dryness and papules. Application site reactions were mostly mild and moderate, not serious and resolved spontaneously within 7 days. The higher incidence of application site AEs is not unexpected given the predictable effects of topical administration of high concentrations of capsaicin. A temporary increase in blood pressure in subjects receiving Qutenza was seen. It was considered to be caused by pain experienced during the treatment procedure as the blood pressure returned to the values found in the control arms after patch removal. The only individual AE that appeared to be consistently related to duration of exposure was application site pain.

There was a higher incidence of cardiac disorders reported as SAEs in the Qutenza group (16 subjects, 1.2%) compared with the control group (4 subject, < 0.5%). It is concluded that the SAEs were unlikely to be causally related to treatment with Qutenza.

Long term neurological assessment (12 months) of 365 patients treated with more than a single exposure to Qutenza as well as data from 90 patients treated with multiple exposures to Qutenza (maximum 8 treatments over 43 months) have not demonstrated any evidence of accelerated nerve damage. Similarly, long-term nerve function testing in 37 subjects demonstrated no evidence of accelerated nerve damage following repeated Qutenza exposures. Nonetheless, concerns about the risk of accelerated nerve damage remained unsolved. Therefore CHMP requested a commitment to conduct a long-term safety study in order to detect neurological impairment. This requirement is reflected in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

User consultation

The Applicant has submitted results form the user testing of package leaflet which was performed in English. The main objectives of the readability testing test, i.e. well-finding, well-understanding and adequate use of information by the participants have been met. The key messages for safe use of

Qutenza have been identified and the questions reflected the key messages. The answers given by the test persons of all rounds and an overview of the answers were considered to be correct. According to the minimum 80% of positive results in both finding and understanding the information, the results of the tests are acceptable

Risk-benefit assessment

Results of the integrated analysis performed separately for each indication (PHN, HIV-AN) and duration of application (60 and 30 minutes, respectively) showed a significant reduction in pain from baseline to weeks 2 to 12 after 30 minute Qutenza application in HIV-AN (-27%) and 60 minute Qutenza application in PHN (-29.6%) compared to the control (-15.7% and -22.3%, respectively) for all 12-week controlled efficacy studies. Analysis of several secondary endpoints, e.g. proportion of responders, proportion of patients achieving 2-unit reduction in pain, PGIC score also provided supportive evidence of the efficacy of Qutenza in both HIV-AN and PHN. However, clinical data presented in support of the indication for treatment of PDN were considered not to be sufficient. It was concluded that Qutenza efficacy data support the use of the product in the treatment of neuropathic pain in non-diabetic adult patients.

Qutenza cutaneous patch is a topical treatment. Results from PK studies showed that systemic exposure to the active substance is negligible. The most common treatment-related adverse events are application site reactions. It was, therefore, concluded that Qutenza cutaneous patch represents a therapeutic alternative to systemic treatments used in neuropathic pain, i.e. opioids, NSAIDS, tricyclic and newer antidepressants, antiepileptic agents with an improved adverse effect profile.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: educational programme for healthcare professionals to address the identified safety issues (transient blood pressure increase, lack of response to opioids, temporary changes in sensory function, local reactions, e.g. contact dermatitis due to use of cleansing gel) and demonstrate how to properly apply, remove and dispose of the capsaicin patch.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Qutenza in the treatment of peripheral neuropathic pain in non-diabetic adults alone or in combination with other pain medications was favourable and therefore recommended the granting of the marketing authorisation.