EMA/657046/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Beprana

naproxcinod

Procedure No.: EMEA/H/C/002159/

Applicant: NicOX S.A

Note

Rapporteurs' day 180 joint assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ADP	adenosine diphosphate
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APTC	Anti-Platelet Trialists' Collaboration
ARB	angiotensin II receptor blockers
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AT1	angiotensin II type 1
AUC	area under the curve
BD	butanediol
BDMN	butanediol mononitrate
bid	*bis in die* (twice daily)
BLQ	below the limit of quantification
BP	blood pressure
CAD	coronary artery disease
CCB	calcium channel blockers
cGMP	cyclic guanosine 3,5-monophosphate
CHD	coronary heart disease
CHMP	The Committee for Medicinal Products for Human Use
CI	confidence interval
CINOD	cyclooxygenase-inhibiting nitric oxide donator
CL	clearance
CNS	central nervous system
COX(-2)	cyclooxygenase (2)
CrCl	creatinine clearance
CSR	clinical study report
CV	cardiovascular
CYP1A2	isoenzyme 1A2 of cytochrome P450
DBP	diastolic blood pressure
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EMEA	European Medicines Agency
F	fraction of drug absorbed
FDA	Food and Drug Administration
fu	unbound fraction
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal

Abbreviation	Definition
GHB	gammahydroxybutyric acid
GST	glutathione s-transferase
HR	hazard ratio
IMP	investigational medicinal product
INR	international normalisation ratio
ISE	Integrated Summary of Efficacy
ISMB	Independent Safety Monitoring Board
ITT	intent-to-treat
IV	intravenous
K_{ow}	octanol-water partition coefficient
LOCF	last observation carried forward
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mLOCF	modified last observation carried forward
MAA	Marketing Authorisation Application
MHRA	The Medicines and Healthcare products Regulatory Agency
MPA	Medical Products Agency
MPID	mean pain intensity difference
NNH	numbers needed to harm
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OBPM	office blood pressure monitoring
PABA	para-aminobenzoic acid
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PP	per-protocol
PPI	proton pump inhibitor
PT	preferred term
PUB	Peptic ulcer bleeding
qd	*quaque die* (once daily)
QT	time between the beginning of the QRS complex and end of the T-wave
RAB	renin angiotensin blockers
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SEDDS	self-emulsifying drug delivery system
SEM	standard error of the mean

Abbreviation	Definition
SmPC	summary of product characteristics
SMQ	standard MedDRA query
SOC	system organ class
tid	*ter in die* (three times daily)
TxB_2	thromboxane B_2
VAS	visual analogue scale
vs	versus
Vu	volume of distribution
WOCF	worst observation carried forward
WOMAC™	Western Ontario and McMaster Universities Osteoarthritis Index

EXECUTIVE SUMMARY

Problem statement

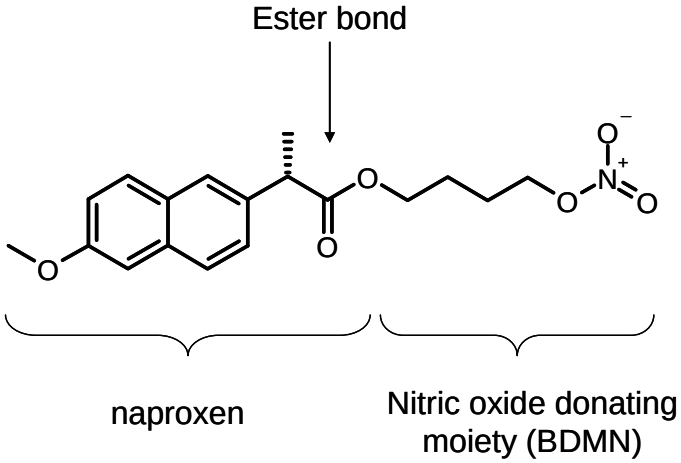
Osteoarthritis (OA) is a degenerative joint disease associated with pain, swelling, and loss of motion. The histopathologic hallmark is cartilage degeneration which may lead to exposed bone, deformation of the joint, growth of bone spurs, and fragments of cartilage floating in the synovial fluid, which in turn cause more pain and reduced mobility. In Europe the prevalence varies by country ranging from approximately 6% in Greece to 13% in Norway. Therefore, up to 35 million people in Europe would be affected by OA, with an incidence increasing with age. It is estimated that half of adults aged ≥ 65 years report symptoms of OA and the disease is more common in women than in men over the age of 50 years.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to manage inflammation and pain, and the majority of NSAID prescriptions are for the treatment of OA and other arthritic conditions. However a number of side-effects are associated with NSAID use. These include an increased risk of cardiovascular events, which are considered to be associated with the effects of NSAIDs on blood pressure (BP) and effects on the gastric mucosa, which can lead to peptic erosions and ulcers. There is a high prevalence of co-morbidities in the general OA population such as cardiovascular, gastrointestinal and metabolic diseases. Therefore, for both the patient and the physician, it is of utmost importance to balance the benefit of medication for pain relief and the risk associated with gastro-intestinal (GI) and cardiovascular safety.

About the product

Naproxcinod (also referred to as AR-P900758XX, AZD3582, or HCT 3012 in early studies) is a cyclooxygenase (COX)-inhibiting nitric oxide (NO) donator, which has been designed to provide at least the same anti-inflammatory and analgesic efficacy as marketed NSAIDs with an improved safety profile, particularly with respect to GI safety and BP. This profile was intended to be achieved by designing a molecule with two active moieties both of which are released following rapid, systemic metabolic cleavage. The first moiety comprises the long established NSAID naproxen to provide relief from the signs and symptoms of OA; the second is a novel NO-donating moiety the release of which is designed to counteract the detrimental effects of naproxen on BP and to some extent provide protection from the effects of naproxen on the GI tract and other organs. NO possesses marked vascular smooth-muscle relaxant properties through activation of soluble guanylyl cyclase and consequent formation of cyclic guanosine monophosphate (cGMP).

Figure 1: Structure of Naproxcinod



Since naproxen and the NO donating moiety are combined in this product via the ester bound in a 1:1 relation no dose titration of NO was possible and the applicant does not address this issue in the dossier. In this context it is not expected that both therapeutic principles, naproxen and NO, are dosed

in their appropriate therapeutic range. More justification is needed why both compounds were not combined as single entities thus allowing titration of pharmacological effects of naproxen on one hand and the NO donator on the other hand.

The development programme/Compliance with CHMP Guidance/Scientific Advice

CHMP scientific advice was sought by AstraZeneca and finalised in April 2003 (EMEA/CPMP/SAWP/2254/03). Subsequently, in September 2006, additional scientific advice was sought by NicOx, following return of the product from Astra Zeneca, and a revision of the clinical development program (EMEA/CHMP/SAWP/359675/2006). Scientific advice was also obtained from the MHRA in 2002 and 2006 (AZD3582: AstraZeneca-MCA Scientific Advice) and (046/HCT 3012: NicOx-MHRA Scientific Advice) and from the Medical Products Agency (MPA) in 2006 (HCT 3012: NicOx-MPA Scientific Advice).

The overall clinical development programme consisted of 34 clinical studies and involved a total of 6747 subjects (patients and healthy volunteers). A total of 4023 subjects received naproxcinod, although some of these were in cross over studies so they would also have received other medication (placebo or naproxen). A total of 1633 subjects received naproxen, 1412 received placebo, 342 received rofecoxib and 55 received ibuprofen. The studies conducted are summarised in the tabular overview of clinical studies.
The focus of the development plan was to demonstrate both efficacy in patients with OA of the large joints, in line with the guidelines CPMP/EWP/784/97 Rev. 1 and NO-derived beneficial effects on BP and GI safety. The clinical development programme was primarily designed to demonstrate efficacy of naproxcinod compared to placebo and as a secondary assessment of efficacy, the non-inferiority of naproxcinod to naproxen was also investigated.

General comments on compliance with GMP, GLP, GCP

GMP:

The CHMP has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the CHMP has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For the active substance manufacturer a certificate confirming GMP compliance in the manufacturing of the active substance is submitted.
Additionally the qualified persons of the finished product manufacturers have assured that the production of the active substance is in compliance with the guidelines on Good manufacturing practices for starting materials.

GCP:

Investigational site audits revealed three irregularities affecting study conduct were uncovered; two during routine audit by the sponsor and the other during a routine site audit by the FDA.

- An audit by the sponsor of Site 114 in Study HCT 3012-X-302 revealed that, in contravention to the requirements of the protocol, site personnel or people associated with the site personnel had been recruited into the study. Consequently, the main safety and efficacy analyses in this study that support registration were conducted excluding the relevant data for all 7 randomised patients at this site.
- In Study HCT 3012-X-302, 2 patients (1 patient enrolled at Site 105 and at Site 126) were also excluded from the main efficacy analyses because it was the same patient enrolled separately at two sites.

All analyses were replicated including data from Site 114 and the two patients and were regarded as sensitivity analyses after all planned analyses were completed and reported in the HCT 3012-X-302 CSR. No statistically different outcomes were evident in the sensitivity analysis. No adverse effects on the Type I error rate were observed between the analysis supporting registration and the sensitivity analysis due to the small number of patients excluded from the main analysis (9 patients).

- In May 2009 (after database lock and CSRs sign-off for Studies HCT 3012-X-301 and HCT 3012-X-302), the sponsor received a letter from the FDA reporting that a general site audit of Site 069 in Study HCT 3012-X-301 and Site 061 in Study HCT 3012-X-302 run by the same investigator had revealed a number of irregularities in the conduct of studies, including, but not limited to, those sponsored by NicOx. The FDA reported inadequate and inaccurate records and a protocol violation. Consequently, the primary and key secondary efficacy data collected in Studies HCT 3012-X-301 and HCT 3012-X-302 were reanalysed excluding the data for the 36 randomised patients (25 in Study 301, 11 in Study 302) recruited at these sites. The results of the analyses excluding the patients from site 069 and site 061 were not clinically significantly different from the results including these patients. The only notable change that occurred when data from site 061 were excluded from Study HCT 3012-X-301 analyses was that the naproxcinod 375 mg bid dose was no longer non-inferior to naproxen 500 mg bid at Week 13 for the WOMAC™ pain subscale score. The only notable change when data from site 069 were excluded from the analysis of Study HCT 3012-X-302 was that naproxcinod 750 mg bid was no longer statistically significantly different from placebo (overall) at Week 13 for the cumulative rate of discontinuations due to lack of efficacy/worsening of the disease (P = 0.0544 without site 069; P = 0.0287 with site 069).

A routine GCP inspection for studies HCT 3012-X-301 and HCT 3012-X-303 in two investigator sites and one sponsor site (INS/GCP/2010/04) revealed a critical deviation in the site 804 of study 303:
Several discrepancies between Data Listings and source documents (Case report form CRF) regarding the Womac scale values, , were detected.
According to the protocol and the Statistical Analysis Plan the primary efficacy analysis was supported by three coprimary variables: mean change from baseline to week 13 in Womac pain and function subscales and in patient's overall rating of disease status.

The review of the Womac scales for all subjects included in the trial at this investigator site (48 patients) showed a high number of discrepancies at Baseline and at Week 13 visit. The possible cause for these discrepancies seems to be a failure in the data management process and consequently might impact others investigator sites.
The impact of this finding on the quality of the data for the overall study were assessed and sensitivity analysis undertaken. The issue related to measurement errors has been adequately addressed and it was concluded that data are robust and valid.

Type of application and other comments on the submitted dossier

The Marketing Authorisation Application (MAA) for Beprana (EMEA/H/C/2159) was submitted via the centralised procedure in accordance with Art. 3(2)(a) (New active substance) of regulation No 726/2004/EC. The application is also submitted in accordance with the requirements according to Regulation (EC) No 1901/2006 ("Paediatric Regulation")

- *Significance of paediatric studies*

The European Medicines Agency has waived the obligation to submit the results of studies with Beprana in all subsets of the paediatric population in primary osteoarthritis.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

The new active substance naproxinod is a derivative of the well known active substance Naproxen unifying in addition to the active principle of naproxen also the active principle of a NO donator in one molecule.
Unusually, the active substance is an oily liquid at room temperature. It is only very slightly soluble in aqueous solutions and also has low permeability. Hence, it is a Class IV compound according to the Biopharmaceutics Classification System, having a slow rate of absorption after oral administration. In order to increase the rate of absorption, drug delivery as an emulsion was investigated using a self-emulsifying drug delivery system (SEDDS). In SEDDS formulations, the active substance is mixed with an emulsifier, so that once released in the gastro-intestinal tract, the aqueous environment of the gastro-intestinal tract and its motility result in emulsion formation.
The mixture of naproxcinod plus emulsifier is filled into hard gelatin capsules to provide a convenient and appropriate presentation for administration to the patient.

Drug substance

The synthesis starts with Naproxen which is esterified at the acetyl moiety with 1-ol-4-nitroxy-butane to insert the second active principle a nitroxy-group which acts as NO donator.

Because of the fact that Naproxen starting material is supplied with CEP and the subsequent synthesis consists of few reaction steps which are uncomplicated in view of preparative organic chemistry the synthesis of the new active substance is problem-free beside the fact that the nitrification reaction needs to be retarded to avoid a go-through of the reaction to an explosion.

Impurities, first of all related substances, are effectively separated by the purification methods of preparative organic chemistry which are based on solvent extraction.

The specification of the active substance, especially in view to the impurities, is appropriate.

In the first assessment (day 80) only few points for clarification / consideration in the synthesis of the active substance are raised before a marketing authorisation can be granted. After the day 120 response most raised questions can be considered as solved. However two points for clarification in view to the active substance remain unclear (see list of outstanding issues).

Drug Product

Naproxcinod capsules are conventional hard gelatin capsules which contain the drug substance formulated in a self-emulsifying drug delivery system (SEDDS). The capsules are packed in opaque PVDC coated PVC/aluminium blisters.

In general, the information presented is acceptable and sufficient to guarantee the quality of Naproxcinod capsules. No major objections have been identified. The data submitted on the quality of the drug product reflects a well researched and well defined product. The ingredients, the manufacturing process and the in-process controls of the drug product correspond to the current standard of pharmaceutical technology and are suitable to guarantee an appropriate product quality. Process validation data has been submitted on three production scale batches.

Nevertheless it should be aware that the chosen capsule size No. 0 is big and may be difficult for some patients to swallow but it is obvious that the chosen dosage together with the excipients needs this big capsule size.

The description of the analytical test methods is adequate. The validation results are plausible.

All relevant quality criteria are specified in accordance with internationally acknowledged pharmacopoeias. The specified limits are in line with the requirements of the CHMP Guidelines and are guarded by the finished product.

The proposed shelf life is supported by the updated results of the stability studies submitted.

Discussion on chemical, pharmaceutical and biological aspects

In general the applicant's answers in regard to the product's quality sufficiently covered the other concerns raised during the centralised procedure. Nevertheless there are still some points for clarification unresolved, see list of outstanding issues.

Conclusions on the chemical, pharmaceutical and biological aspects

Regarding to the quality aspects, this application could be approvable, if all remaining concerns are satisfactory addressed.

Non clinical aspects

Pharmacology

The non-clinical testing program for evaluation of primary pharmacodynamics was designed to assess the activity of naproxcinod as an anti-inflammatory, analgesic, and anti-pyretic agent in established animal models. Comparison with naproxen at equimolar doses served as reference control in most studies.

Studies for evaluation of secondary pharmacodynamics were primarily aimed at identifying the contribution of the NO-donating moiety of naproxcinod on systemic blood pressure and the gastrointestinal system, properties that distinguish effects of naproxcinod from those of naproxen.

Safety pharmacology studies were conducted to ascertain the potential for adverse effects after a single oral or intravenous dose of naproxcinod on CNS, respiratory, cardiovascular, gastrointestinal, and renal function.

Primary Pharmacodynamics

In vitro activity

The results from *in vitro* studies using isolated COX-1 and COX-2 enzymes demonstrated that naproxcinod and its non-naproxen metabolites (BDMN and BD) are essentially devoid of COX inhibitory activity under non-metabolic conditions, demonstrating that enzymatic (esterase) cleavage of the molecule is needed for the release of naproxen and substrate inhibition.

When studied in whole cell preparations, as e.g. the mouse monocyte-macrophage cell line RAW 264.7, COX inhibition by naproxcinod was fully realized. The results from the *in vitro* whole cell studies demonstrated that naproxcinod is similarly active against COX-1 and COX-2 enzymes when metabolized to release naproxen. The other main metabolite, BDMN, was inactive.

In human synoviocytes, naproxcinod (IC_{50} = 23 µM) and naproxen (IC_{50} = 5.9 µM) inhibited cytokine-stimulated PGE_2 release in a concentration-dependent manner, indicating a strong COX-2 inhibition.

The potential anti-inflammatory activity of the NO moiety of naproxcinod was also evaluated *in vitro*. Naproxcinod (288 µM) inhibited LPS-induced nitrite production (iNOS) in murine macrophages (J774 cells) suggesting that donation of NO from naproxcinod can affect (reduce) cellular expression of iNOS.

In vitro screening for activity against other enzymes showed that naproxcinod (3 µM) slightly inhibited phospholipase A2 (by 20%) but had no effect on 5-lipoxygenase or NO synthase activities.

In vivo activity

Antiinflammatory activity

In *in vivo* studies using a rat carrageenan-induced airpouch model of inflammation, a single oral dose of 15 and 30 µmol/kg of naproxcinod was significantly effective in reducing exudate volume and leukocyte infiltration. When naproxcinod (5-30 µmol/kg) was administered directly into the airpouch or given by oral administration, similar reductions in exudate volume, leukocyte infiltration, exsudate PGE_2 levels and whole blood TxB_2 levels were attained. These results show that naproxcinod significantly reduced the activities of both COX-1 and COX-2 in this model of inflammation.

Significant decreases in PGE_2, TxB_2 and 6-keto-$PGF_{1\alpha}$ were noted in a rat LPS model of inflammation pretreated with 43.2 µmol/kg of naproxcinod or 39.7 µmol/kg of naproxen.

In a rat adjuvant-induced arthritis model, the anti-inflammatory activity of oral administration of 43.2 µmol/kg/day of naproxcinod given once daily for 7 days was as effective as 39.7 µmol/kg/day of naproxen. In another study, oral administration of 11.5 or 23 µmol/kg/day of naproxcinod once daily for 28 days significantly reduced arthritis scores.

In a similar model, paw edema was reduced in rats that received a single daily oral (gavage) dose of 13 and 46 µmol/kg/day of naproxcinod or 12 and 39.7 µmol/kg/day of naproxen for up to 21 days.

In an adjuvant-induced arthritis model in the rat using radiographic endpoints, oral administration of 57.6 µmol/kg of naproxcinod bid for 21 days suppressed periostitis, erosions, and mineralization. An oral dose of 3 µmol/kg of naproxcinod was also effective against inflammation induced in a Streptococcal Cell Wall (SCW) arthritic rat model (a model characterized by edema and hyperalgesia). Plasma concentrations of naproxen at this dose were 10.7 µmol/mL 2 hours after dosing.

In a rat paw edema model, edema formation decreased in a dose-dependent manner with a single oral dose of naproxcinod [ED_{50} = 18 µmol/kg] to a similar extent as naproxen [ED_{50} = 20 µmol/kg] but produced less gastric damage [UD_{50} = 20 µmol/kg] than naproxen [UD_{50} = 5 µmol/kg]. In another study using this model, a single oral dose of 14.4 µmol/kg of naproxcinod significantly reduced edema formation.

Naproxcinod was also active as an anti-inflammatory agent in a model of LPS-induced lung inflammation in rats pretreated with a single intraperitoneal injection of 57.6 µmol/kg of naproxcinod, and in a rat wound healing model, enhancing collagen deposition with oral administration of 41.7 µmol/kg/day of naproxcinod.

Analgesic activity

The analgesic properties of naproxcinod were demonstrated by an increase in pain threshold in a rat adjuvant arthritis model with oral dosing of 13 and 46 µmol/kg/day of naproxcinod for 21 days that was comparable to that induced by 12 and 39.7 µmol/kg of naproxen.

A similar decrease in nociception was noted in a rat carrageenan-induced paw edema model after a single oral dose of naproxcinod [ED_{50} = 1.2 and 2.9 µmol/kg at 3 and 5 hours post dosing, respectively]. A similar response was noted with naproxen, but durability had substantially diminished by 5 hours after dosing.

Naproxcinod at 1 µmol/kg (0.35 mg/kg) significantly reduced nociception in a time- and dose-dependent manner in a rat carrageenan-induced paw edema model with an effect size greater than that of an equimolar dose of naproxen. R-naproxcinod (at 10 µmol/kg or more) also decreased nociception, whereas R-naproxen (100 µmol/kg) was ineffective.

In a phenylquinone-induced writhing study in mice, a single oral dose of 8.6 or 17.2 µmol/kg of naproxcinod resulted in a significant analgesia response.

A single oral dose of 0.9, 2.9, or 8.6 µmol/kg of naproxcinod was effective in reducing pain (writhing) associated with intraperitoneal injection of magnesium sulphate in mice.

SC injection of 4.6 - 483 µmol/kg of naproxcinod markedly reduced formalin-induced pain using adult male albino mice. However, oral administration of naproxcinod in this mouse pain model was ineffective at the highest dose tested of 50 µmol/kg.

In a rat formalin-induced pain model, nociception was markedly reduced with naproxcinod [ED_{50} = 0.138 µmol/kg].

Antipyretic activity

The antipyretic property of naproxcinod was established in a rat model of yeast-induced fever. A single oral administration of 3 µmol/kg (1 mg/kg) of naproxcinod significantly reduced the yeast-induced fever and was comparable to 1 µmol/kg (0.2 mg/kg) of naproxen.

Conclusions

The pharmacological profile obtained from *in vitro* and *in vivo* pharmacodynamic studies showed that naproxcinod was as effective as equimolar doses of naproxen for anti-inflammatory, analgesic and antipyretic activity. Naproxcinod was also shown to modulate the NO-signaling pathway (for example, increase of intracellular cGMP) consistent with anti-inflammatory/antioxidant activity of physiological submicromolar concentrations of NO described in literature.

Secondary Pharmacodynamics

The secondary pharmacodynamic studies have been specifically performed to assess the added value of systemically delivered nitric oxide with naproxcinod, with a particular attention devoted to the cardiovascular and the gastrointestinal systems.

Cardiovascular system

In vitro studies

-Precontracted arterial rings: Naproxcinod induced a concentration-dependent relaxation of norepinephrine pre-contracted arterial rings from rabbit and rat aorta and from human internal mammary arteries.
- Isolated heart model: In an isolated rabbit heart model, ischemia-reperfusion significantly impaired ventricular function, and naproxcinod restored cardiac functionality in a concentration-dependent manner. Perfusion with naproxen, on the other hand, further aggravated myocardial ischemic damage.

Ex-vivo studies

In aortic rings from spontaneously hypertensive rats (SHR), *in vivo* naproxcinod treatment significantly improved acetylcholine-elicited ex-vivo vasorelaxation, while naproxen had no effect.

In vivo studies

- Blood pressure studies: Three main blood pressure studies have been run in three different models of induced hypertension in rodents, a spontaneous model, a reno-vascular surgery model and a model of suppression of endogenous NO synthesis. In all these models, naproxcinod reduced blood pressure for an extended period (1 to 4 weeks) compared to equimolar doses of naproxen, which had no effect or significantly worsened the induced hypertension.
Interestingly, non hypertensive animals used as control, did not show a significant naproxcinod effect on blood pressure, suggesting that nitric oxide activity is more pronounced when vascular function is impaired.

Mechanistically, naproxcinod has been shown *in vitro* to modulate the vascular tone of isolated animal and human vessels through the nitric oxide specific signaling pathway. *In vivo*, intravenous infusion of naproxcinod induced a dose-dependent decrease in blood pressure which was accompanied by an increase in exhaled NO, a clear indication of systemic nitric oxide delivery.

- Unlike naproxen, naproxcinod protects rabbit hearts from ischemia/reperfusion injury *in vivo*.

Kidney function

Unlike naproxen, naproxcinod administered for one week did not alter renal medullar and cortical oxygenation.

Gastrointestinal tract

Particular attention has been paid to the GI tract safety after naproxcinod administration in several animal models, ranging from acute damage to repeated administration (up to 4 weeks) in both normal and diseased animals. In most models studied, naproxcinod presented an advantageous profile in terms of GI damage induction compared to naproxen. The association with acetylsalicylic acid has also been studied, confirming the reduced induction of damage by naproxcinod.

The gastrointestinal sparing activity, attributed to the NO donation by naproxcinod, was observed in both stomach and intestine, and in presence of a complete mucosal prostaglandins inhibition, as

observed with naproxen. It is suggested that NO may counteract at the GI level the deficiency in prostaglandins.

Conclusion on primary and secondary pharmacodynamics

In summary, naproxcinod was as effective as naproxen in controlling inflammation and inflammation-related effects due to COX-1/COX-2 activation in the animal models. In the secondary pharmacology models, naproxcinod showed an improved safety profile on the gastrointestinal tract and an effect on blood pressure (reduction or no increase in blood pressure), confirming its nitric oxide releasing properties.

Safety Pharmacology

Safety pharmacology studies were conducted to ascertain the potential for adverse effects after a single oral or intravenous dose of naproxcinod on CNS, respiratory, cardiovascular, gastrointestinal, and renal function.

CNS

- Single oral doses of up to 695 mg/kg of naproxcinod to mice did not affect behavior or neurological parameters (modified Irwin's test). However, in a more discrete study, a single oral dose of 104 mg/kg [312 mg/m^2] of naproxcinod to mice depressed spontaneous locomotor activity.

- Single oral administration of up to 104 mg/kg [624 mg/m^2] of naproxcinod to rats did not produce any selective or significant CNS effects (modified Irwin's test) other than a transient stillness noted within 5 minutes of dosing at ≥ 34.7 mg/kg [≥ 208.2 mg/m^2].

- A single oral dose of up to 104 mg/kg of naproxcinod to rats also did not affect spontaneous locomotor activity or alter PTZ-induced seizure threshold.

Cardiovascular function

In vitro

- Naproxcinod weakly inhibited peak tail current in the hERG assay with an IC_{50} of 10.2 µM and in the cardiac atrial myocyte assay with an IC_{50} of 4.6 µM. These concentrations correspond to 235 and 107 times, respectively, the mean C_{max} of 9.85 ng/mL for naproxcinod following daily oral administration of 750 mg *bid* of naproxcinod (the maximum recommended human dose) for 14 days (Study No. HCT3012-MPK-113).

In vivo

- A single oral dose of up to 104 mg/kg [624 mg/m^2]($C_{2\,h}$ = 70.5 µg/mL) of naproxcinod to male rats did not produce alterations in respiratory or cardiovascular function and did not affect core body temperature.

- Single IV administration of up to 3.4 mg/kg [40.8 mg/m^2] of naproxcinod to male NZW rabbits did not result in any relevant biological alterations in respiratory or cardiovascular function.

- Single IV administration of naproxcinod at 8.68 mg/kg [173.4 mg/m^2] (mean plasma naproxcinod concentration at the highest dose level = 5131 ng/mL) to male beagle dogs did not result in any significant change in the QT interval.

- In male and female minipigs, a single oral dose of up to 104 mg/kg [3640 mg/m^2] of naproxcinod did not affect core body temperature, blood gases (pCO_2 or pO_2), pH, or methemoglobin formation. There was evidence of a slight decrease in respiratory rate in all naproxcinod treated groups at 30 minutes after dosing (dose- but not time-related) and a slight decrease in blood pressure (systolic) that was transient in the 10.4 and 34.7 mg/kg groups (mean plasma naproxen concentrations = 33-225 and 138-267 µg/mL, respectively) but prolonged in the 104 mg/kg group (mean plasma naproxen concentration = 165-317 µg/mL). There were no effects of oral administration of naproxcinod on ECG intervals or waveforms.

- An additional study in minipigs with intravenous infusion of naproxcinod at doses up to 3.5 mg/kg [122.5 mg/m^2] did not result in treatment-related effects on cardiovascular or respiratory parameters other than a decrease in pCO_2 and a corresponding increase in pO_2.

In summary, *in vivo* studies in rodent and non-rodent species by the oral and intravenous routes of administration with naproxcinod did not result in any relevant alterations in ECG interval or waveforms

or in significantly altered chronotropic or inotropic function. Moreover, naproxcinod did not affect ventricular repolarization in clinical subjects following oral administration of 4500 mg of naproxcinod, corresponding to 3 times the maximum recommended human daily dose (HCT 3012-X-103), or 6 times the maximum dose given in a single administration (750 mg). The mean peak plasma concentration (C_{max}) in this study was 136 ng/mL. The extraordinary high concentrations of naproxcinod needed to significantly affect potassium channel currents *in vitro* and the absence of *in vivo* preclinical or clinical effects indicates a very low risk for QT prolongation with exposure to naproxcinod.

Gastrointestinaltract

- A single oral dose of 104 mg/kg [624 mg/m^2] of naproxcinod (mean naproxen plasma $C_{0.5\ h}$ = 119.7 µg/mL) to rats did not affect gastric emptying or intestinal propulsion.

Kidney function

- Oral administration of naproxcinod of 104 mg/kg [624 mg/m^2] (mean naproxen plasma $C_{5.25\ h}$ = 131 µg/mL) to rats did not affect urinary parameters other than a delay in the diuretic response during the first 2.5 hours. This may be related to peripheral vasodilation (as was observed in the minipig study) and not necessarily a direct effect on the kidney.

- Naproxcinod did not affect urinary parameters in female dogs on low sodium diets following cumulative intravenous doses of 0.076, 0.288, or 1.318 mg/kg/40 minute period (total dose), reflecting systemic exposure of 19, 104, 486 ng/mL, respectively.

Conclusion on safety pharmacology

Overall, naproxcinod has been found to be without serious side effects on the major organ systems such as the kidneys, the cardiovascular, respiratory, gastrointestinal and the central nervous system.

Pharmacodynamic drug interactions

One nonclinical pharmacodynamic interaction study in rat was conducted with sildenafil. No remarkable effects on arterial blood pressure and heart rate were observed in this study,

Pharmacokinetics

The pharmacokinetics (PK) and toxicokinetics (TK) of naproxcinod have been evaluated in various species. Only some of these studies were conducted in compliance with Good Laboratory Practice (GLP); all other PK studies were conducted in accordance with good scientific principles.

Methods

Validated methods for the determination of (i) naproxcinod in plasma (LC-MS/MS), (ii) the active NSAID metabolite, naproxen (and its metabolites), in plasma and urine (HPLC-fluorimetric determination, LC-MS/MS for rat plasma) and (iii) nitrate/nitrite (HPLC/UV or Griess reaction) were developed and utilized. Stability of naproxcinod and naproxen in biological samples has been established.

Labelled naproxcinod-derivatives were synthesized to evaluate (i) the metabolic fate of the naproxen moiety based on [^{3}H]naproxcinod, (ii) the metabolic fate of BDMN and its derivatives based on [^{14}C]naproxcinod; (iii) the amounts of nitrate formed based on [^{15}N]naproxcinod.

Absorption

In vitro data

In vitro permeability of naproxcinod and naproxen was compared using rat intestinal mucosal preparations in the Ussing chamber both as pure compound or in different formulations. The intestinal permeability of naproxcinod was found to be low when applied as pure substance but medium permeability was determined when used in formulation. There were no marked differences in the

apparent permeability of naproxcinod between different self-emulsifying drug delivery systems (SEDDS) using the Ussing chamber model.

Naproxcinod is, at least in part, hydrolysed to naproxen when passing through GI epithelia. The permeability of naproxen was greater than that of naproxcinod, and thus the extent of naproxcinod hydrolysis to naproxen may affect the extent of drug absorption. Naproxcinod was not a substrate for intestinal efflux systems.

The *in vitro* stability of naproxcinod in GI tract was investigated. Some hydrolysis of naproxcinod to naproxen occurred in most incubations with degradation half-lives between 0.6 and 6 hours in rat material and 3 and 10 hours in human jejunal and gastric fluids, respectively. In human gastrointestinal preparations, naproxcinod was partially hydrolyzed to naproxen but with a $t_{1/2}$ compatible with absorption of the intact molecule. Thus it is likely that absorption of parent drug, naproxcinod, occurs after drug administration and further hydrolysis is likely to happen in the enterocytes and/or portal blood stream.

Naproxcinod was shown to be unstable at room temperature in plasma from all species, including human. However, at 4ºC the drug was stable in plasma from the minipig and human but not from the mouse and rat. Accordingly, naproxcinod was not determined in mouse or rat PK or TK studies.

In vivo data

Rat

The absolute bioavailability (BA) of naproxen was determined in rats after administration of equimolar doses of oral and intravenous naproxen, and oral naproxcinod. The BA of oral naproxen was virtually complete (96%); the absolute BA of naproxen after administration of naproxcinod intravenously and orally is around 83%. The relative oral BA of naproxen after equimolar doses of naproxcinod is around 54%.

Minipig

The BA of naproxen after administration of equimolar (15 µmol/kg) oral doses of naproxcinod and naproxen was compared to that after IV naproxcinod (0.75 µmol/kg). The dose normalized absolute BA after oral naproxcinod averaged 106%, suggesting complete absorption. However, the absolute BA after oral naproxen was 32% greater than after naproxcinod, suggesting nonlinearity in pharmacokinetics upon dose normalization. Food decreased the rate [lower C_{max} and longer time to reach C_{max} (t_{max})] but not the extent (AUC) of naproxcinod absorption in minipigs.

In the minipig, very small amounts of naproxcinod reached the plasma. At the maximum concentration observed in plasma (C_{max}), the naproxcinod concentration was ≤0.2% of that of naproxen. After IV administration to the minipig, naproxcinod was very rapidly eliminated with a $t_{1/2}$ of 0.3 hours. In minipigs, the calculated total body clearance (CL) of naproxcinod after IV administration was 10.5 L/kg.hr, and the volume of distribution (V_{ss}) was 3.43 L/kg.

After oral administration of a mixture of [^{3}H]naproxcinod and [^{14}C]naproxcinod to minipigs, all of the plasma [^{3}H] was associated with naproxen. The [^{14}C] expressed as naproxcinod equivalents was markedly lower than [^{3}H] expressed as naproxen equivalents. This demonstrated the metabolic fate of the [^{14}C] in the nitrooxy-butyl portion of the molecule.

Rabbit

Naproxcinod was undetectable in plasma from the pregnant rabbit after a single oral dose of 208 mg/kg/day (HCT 3012-TOX-303).

Dog

Unlike the other species, relatively significant concentrations of naproxcinod were detectable in dog plasma, from which it was relatively slowly eliminated, with a $t_{1/2}$ of 4-7 hours. Thus, the pharmacokinetics of naproxcinod in the dog is different than in other species.

Distribution

Rat

The tissue distribution of radioactivity was measured in male pigmented rats by quantitative whole body autoradiography (QWBA) after administration of a single dose of [^{3}H]naproxcinod (oral and IV) and [^{14}C]naproxcinod (oral). The [^{14}C] radiolabel was rapidly and extensively distributed into bile, liver,

gastric mucosa, kidney, as well as proliferating cells, e.g. bone marrow and intestinal epithelium, consistent with the distribution of small carbon fragments. After the oral dose, tissue [^{3}H] peaked generally at 1 hour, and declined such that concentrations were below the limit of quantification (BLOQ) by 48 hours. Highest concentrations were found in blood, renal medulla and lungs, and the lowest were found in brain and spinal cord. Most of the tissue [^{3}H] concentrations were less than those in whole blood at all times tested. No $^{3}H_2O$ was present in 1-hour plasma, however $^{3}H_2O$ was observed at 5, 16 and 48 hours (4%, 34% and >90% of plasma [^{3}H], respectively), and thus the radioactivity measured at the later time intervals was somewhat nonspecific.

Radioactivity ([^{3}H] and [^{14}C]) distribution as determined by QWBA in pregnant rats was similar to that in males. Radioactivity was transferred to the fetus, with peak fetal concentrations attained at 5 hours after the oral dose, as compared to 1 hour in the dams. Elimination from the fetus was slower than from the dams. For most tissues measured, e.g. blood and liver, the concentrations in the dams were higher than in the fetus (fetus/dam ratio = 0.26 for both), except for a higher ratio for fetal brain which was probably due to incomplete formation of the blood-brain barrier.

In lactating rats, the [^{3}H] concentrations were higher in maternal plasma than in milk. At the t_{max} (0.5 hours) after the oral dose, the milk/plasma radioactivity ratio was 0.13. The elimination rate from milk was slower than that from plasma.

Rabbit

Naproxcinod administered by gavage to gravid rabbits daily from gestation day (GD) 6 to GD18 was BLOQ at the highest dose of 208 mg/kg/day.

Minipigs

After oral administration of a mixture of [^{3}H]naproxcinod and [^{14}C]naproxcinod to minipigs, the concentrations of both isotopes in whole blood were lower than those in plasma (measured at 0.25 and 24 hours; blood/plasma ratios = 0.52-0.77). Thus there was no accumulation of drug derived material in red blood cells.

Protein binding

The protein binding of naproxcinod was not assessed due to its low concentrations in plasma and poor stability, especially in animal species. However, based on *in silico* estimates, the degree of plasma protein binding of naproxcinod was estimated to be negligible at only 0.1%.

Naproxen binding to plasma proteins was high and saturable, with the extent of binding in the rank order minipig>rat>mouse, and was higher in females than in males of all species. At plasma naproxen concentrations of 10-230 µg/mL, the extent of concentration-dependent binding ranged from 99.9-90.5% in minipigs, 98.6-80.4% in rats, and 92.5-68.5% in mice, as compared to 99.7% reported for humans at therapeutic concentrations.

Metabolism

In vitro

The *in vitro* metabolism of naproxcinod was studied in liver microsomes from mouse, rat, minipig, rabbit and human, and in hepatocytes from rat and human. The overall metabolic profile was similar in all species. The hydrolysis to naproxen in microsomes was very rapid, and was virtually complete within 5 minutes. The principal liquid chromatography (LC) peak was O-desmethyl naproxen (M6), and thus the primary sequence of *in vitro* metabolism was rapid hydrolysis to naproxen followed by dealkylation. There were additional metabolites in hepatocytes, presumably conjugates. The glucuronide of naproxen (M8) was identified in human hepatocytes, and additional conjugates were observed in rat hepatocytes. The profile after naproxen incubation was similar to that after incubation with naproxcinod. The kinetics for naproxen demethylation was similar for all species, with the exception of the rabbit, where the intrinsic clearance (CL_{int}) was 1-2 orders of magnitude higher than in other species.

In vitro, flavin-containing monooxygenases did not contribute to the demethylation of naproxen in human liver microsomes, and thus the biotransformation of naproxen, as reported in the literature, is primarily mediated by cytochrome P450 (CYP) isozymes.

In *in vitro* studies with human and rat liver fractions, naproxcinod was hydrolyzed to naproxen and BDMN and BDMN was further metabolized to nitrate. In none of the *in vitro* studies (plasma, gastric juice, liver) the denitrated naproxcinod was detected, showing that the nitric oxide release occurs only after the hydrolysis of naproxcinod.

An enzyme inhibition study with human liver microsomes showed that the only potential inhibition by naproxcinod is with CYP1A2, with an IC_{50} of 7.61 µmol. This was a noncompetitive inhibition, the implication of which is dependent upon the amount of administered naproxcinod reaching the liver intact. Naproxen at 100 µmol did not inhibit any CYP enzyme, but there was some inhibition at 1000 µmol: 30% for CYP1A2, 64% for CYP2C9, and 50% for CYP2C19 (no IC_{50} could be calculated). Naproxcinod had a very slight inhibitory effect on the specific marker for CYP1A2, phenacetin O-deethylation, with an inhibition constant (Ki) value of approximately 31 µM. Since the C_{max} of naproxen after administration of multiple high doses of naproxcinod (1125 mg twice daily) to human subjects averages 324 µmol (Report SP-NON-0001, 2.7.2.2.1), the inhibition observed at 1000 µmol is not considered to be of clinical relevance.

Induction of CYP was evaluated in the 3 month toxicity study in rats (Report HCT 3012-TOX-108). There was no induction of CYP1A, CYP3A or CYP4A in response to oral dosing of naproxcinod.

Aside from the rapid conversion of naproxcinod to naproxen in the liver, an *in vitro* study with intestinal sections and mucosal extracts from rat and minipig, and human intestinal fluids showed that the intestine does indeed convert naproxcinod to naproxen. The activity was due at least in part to carboxylesterases present in these tissues.

In vivo

Following single oral administration of naproxcinod, the rate of absorption was generally rapid, with mean peak naproxen concentrations observed at 0.5-2 hours in mice and rats, 1-5 hours in minipigs, and 0.75 hours in dogs. The mean terminal elimination half-life ($t_{1/2}$) of naproxen in the various studies was 1.6-4 hours in mice, 4-8 hours in rats, 2-5 hours in rabbits, but longer in minipigs (9-18 hours) and substantially longer in dogs (40-63 hours). In mice, rats and minipigs, the naproxen $t_{1/2}$ was generally independent of dose level and duration of treatment.

The toxicokinetics of naproxen were evaluated in the naproxcinod toxicity studies in mice, rats, rabbits and minipigs, as well as in the carcinogenicity studies in mice (drug administered twice daily) and rats (once daily). In rats and minipigs, the exposure to naproxen was sex independent; however, in mice, plasma naproxen concentrations were 2-3 times higher in females than in males.

There was a good relationship between dose level and plasma AUC values of naproxen, except at the highest doses. Thus, in mice, total plasma naproxen was dose related but less than dose proportional, except at the two highest doses in the carcinogenicity study (109 and 208 mg/kg/dose twice daily), where the exposure was similar. The AUCs in rats were generally close to dose proportional up to 35 mg/kg/day, above which the increases were less than dose proportional. Plasma naproxen was dose proportional (up to 208 mg/kg/day) in pregnant rabbits. In minipigs, the AUCs of naproxen were less than dose proportional up to the highest naproxcinod doses tested (104 mg/kg/day in the 12 month study). Thus, in rodents, there was some saturation, probably associated with protein binding, as has been reported previously for naproxen. There was no evidence of naproxen accumulation in plasma upon multiple dosing in any species at any dose.

Plasma nitrate concentrations were measured in the course of the carcinogenicity studies, showing exposure of animals.

The *in vivo* metabolites of naproxcinod were evaluated based on radioactivity profiles in mouse, rat and minipig urine (the major excretory route), and in rat bile after oral administration of [^{3}H]naproxcinod.

No unchanged drug was excreted in urine or rat bile. Conjugation was more extensive in rodents than in the minipig. The sulfate conjugate of 6-O-desmethyl naproxen (M4) was the principal urinary metabolite excreted by the mouse (30% of urinary [^{3}H]) and rat (63% in females and 87% in males), while unconjugated 6-O-desmethyl naproxen (M6) was the principal urinary metabolite in the minipig (37% of the integrated LC peak in females and 55% in males). Naproxen represented only 1-2% of the urinary [^{3}H] in mice, 0% in rats and 4-7% in minipigs. Minor amounts of other conjugates of naproxen and 6-O-desmethyl naproxen were found in the urine of mice and minipigs, but not in the urine of rats.

However, rat bile contained low amounts of other conjugates of 6-O-desmethyl naproxen as well as M6 as the principal metabolite (37-55% of the biliary [^{3}H]).

Urinary nitrate comprised about 8% of the dose in mice, and 17% of the dose in minipigs. The results showed that naproxcinod is very extensively metabolized both to nitrates and via hydrolysis (cleavage of the ester bond) to naproxen, followed by dealkylation to 6-O-desmethyl naproxen (M6), and that both naproxen and M6 give rise to several conjugates to variable degrees between species. No qualitative species differences in metabolism occur.

Excretion

After oral administration of [^{14}C]naproxcinod, the expired air contained 84% of the label in mice, 49% in rats and 47% in minipigs. Thus, the radiolabel in the nitrooxy-butyl portion of the molecule was extensively metabolized. In contrast, $^{3}H_2O$ represented <1% of the dose in mice and 2-4% in rats.

Following a single oral dose, the urine contained 63-68% of the administered [^{3}H] in mice, 62-68% in rats, and 77-83% in minipigs. Thus, the data show that the drug was very well absorbed in the three species, and that urine is an appropriate matrix to study the excreted metabolites of the drug.

Bile from bile cannulated rats contained 29% of orally administered [^{3}H]naproxcinod. When bile collected from treated rats was intraduodenally infused into untreated rats, 30% (females) – 43% (males) of the infused dose was resecreted in their bile, thus demonstrating that a significant portion of drug derived material undergoes enterohepatic recirculation in the rat. Thus, a portion of the radioactivity recovered in feces of mice (15-24%), rats (14-16%), and minipigs (2%) may be due to naproxen metabolites which had undergone biliary excretion.

Pharmacokinetic drug interactions

No nonclinical pharmacokinetic drug interaction studies have been conducted. This is scientifically justified considering the results of the *in vitro* CYP studies conducted with naproxcinod and the metabolic profile pathway of the compound. The potential for human drug-drug interactions (pharmacokinetic and/or pharmacodynamic studies) have been evaluated for warfarin (HCT 3012-X-109), sildenafil (HCT 3012-X-107), nitroglycerin (SP-NON-0021), antihypertensive agents (SP-NON-0022), and antacids (HCT 3012-X-108).

Conclusion

The overall profile of the metabolic disposition of naproxcinod in the laboratory animal species used in the toxicological evaluation of the drug is similar to that in humans. The oral bioavailability of the parent drug naproxcinod is low, due to its presystemic hydrolysis to naproxen and BDMN during absorption. The subsequent biotransformation of naproxen occurs via hydroxylation and dealkylation to 6-*O*-desmethyl naproxen (M6), and the formation of several conjugates of naproxen and M6. BDMN is further metabolized to release nitric oxide/nitrite/nitrate and butanediol, the latter of which enters the metabolic carbon pool. The primary route of excretion of naproxen and its metabolites is via the urine.

Toxicology

The design of the toxicology testing program for naproxcinod was based on general requirements for preclinical safety testing for new drug candidates as outlined in the ICH M3 Guidance Document.

The preclinical safety assessment to support oral administration of naproxcinod involved the use of rodent and non-rodent models. The testing program included general toxicity studies with single and repeated oral dosing in rodents (mice and rats) and non-rodents (minipigs), *in vitro* and *in vivo* genotoxicity studies (bacterial reverse mutation assay, mammalian cell mutation assay, micronucleus test in mice, and an unscheduled DNA synthesis assay), carcinogenicity bioassays (mice and rats), and reproduction and developmental toxicity studies (rats and rabbits).

The species selected for the general toxicology program (mice, rats, and minipigs) are standard species used for preclinical safety evaluations. Comparative pharmacokinetics (toxicokinetics) and metabolism studies with naproxcinod established the relevance of these models to clinical exposure.

Single dose toxicity

Single dose toxicity studies were conducted in mice, rats and minipigs.

Mouse studies: A single IV application of naproxcinod to male and female mice at a maximum feasible dose of 116 mg/kg [348 mg/m^2] was well tolerated and did not result in systemic toxicity.
Naproxcinod administered as a single oral dose to male and female mice at 500 mg/kg [1500 mg/m^2] or more was associated with mortality, clinical signs of toxicity (males), and injury of the GI tract (ulcerations). The maximum non-lethal dose for males was 1000 mg/kg [3000 mg/m^2] and 500 mg/kg [1500 mg/m^2] for females.

Rat studies: A single IV application of naproxcinod to male and female rats at a maximum feasible dose of 116 mg/kg [696 mg/m^2] was well tolerated and did not produce systemic toxicity.
A single oral dose of 250 mg/kg [1500 mg/m^2] or more was associated with clinical signs, body weight loss, and marked GI injury. Mortality/morbidity ensued at ≥ 500 mg/kg [≥ 3000 mg/m^2]. The maximum tolerated dose was 250 mg/kg [1500 mg/m^2] for male and female rats.

Minipig studies: A single oral dose of 400 mg/kg [14000 mg/m^2] of naproxcinod was tolerated.

Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in mice, rats and minipigs.

Mouse studies: Oral (gavage) toxicity studies of 7 days, 14 days and 13 weeks duration were performed. In the 13 weeks study, daily doses up to 139 mg/kg bid were well tolerated. Higher liver weights were observed in the 139 mg/kg bid group males and did correlate with the higher ASAT and ALAT levels in the same group. The NOAEL was 38 mg/kg bid (114 mg/m^2 bid).

Rat studies: Oral (gavage) toxicity studies of 7 days, 14 days, 3 months and 6 months duration were performed. Chronic daily administration of naproxcinod to rats for 6 months at 50 mg/kg/day was associated with mortality and significant renal and GI pathology. Doses of up to 16 mg/kg/day in males and up to 35 mg/kg/day in females were tolerated. Renal pathology was noted microscopically in males at ≥ 8 mg/kg/day and in females at ≥ 16 mg/kg/day. GI lesions occurred in males at ≥ 4 mg/kg/day and in females at ≥ 8 mg/kg/day. The NOAEL was <4 mg/kg/day in males and <8 mg/kg/day in females, the lowest doses evaluated. At higher doses (35 mg/kg/day) additional histopathological findings were noted in the thyroid gland of males (follicular cell hyperplasia, hypertrophy, decreased colloid) in the 3 month study.

Minipig studies: Oral (gavage) toxicity studies of 5 days, 14 days, 3 months and 12 months duration were performed in Ellegaard Göttingen SPF minipigs. In the 12 months study, naproxcinod doses up to 104 mg/kg/day were well tolerated. Target organs were the stomach (glandular) and the kidneys. Atrophy noted in the thymus was considered to be stress-related. The increase in hematopoietic cell density in the bone marrow was likely a physiological adaptive response secondary to the inflammation associated with gastric mucosal ulceration/perforation and the subsequent peritonitis. The NOAEL for naproxcinod was 40 mg/kg/day.

Genotoxicity

Naproxcinod was tested for genotoxicity in a standard battery of *in vitro* and *in vivo* tests. To further proof the irrelevance of inconclusive finding in the mammalian cell *in vitro* test an additional an UDS test in rat liver was performed as an *in vivo* follow up assay. In conclusion there was no relevant evidence for an *in vivo* relevant genotoxic potential of naproxcinod in the preformed assays. However, it is currently not clear whether all naproxcinod metabolites were formed under the applied *in vitro* assay conditions.

Carcinogenicity

Two long-term studies were conducted in rodents (mice and rats).

CTD 2.6.6, Table 1: **Oral Carcinogenicity studies with Naproxcinod**

Species	Duration	Dose levels (mg/kg/day)	Report No. (Tabular Format)
Mouse	96 weeks (M)[a] 90 weeks (F)[a]	0(W), 0(E), 20, 76, 278[b], 416[c] (0, 0, 10, 38, 139[b], 208[c] *bid*)	HCT 3012-TOX-402 (2.6.7.10.A)
Rat	104 weeks (M)[a] 92 weeks (F)[a]	0(W), 0(E),, 4, 8, 16 (M) 0, 8, 16, 35 (F)	HCT 3012-TOX-401 (2.6.7.10.B)

a: Actual duration. The protocol duration was 108 weeks.
b: Dose decreased to 152 mg/kg/day (76 mg/kg/*bid*) from Week 49 (females) and Week 74 (males).
c: Dosing was discontinued from Week 75 to the end of the study.
W = purified water control group, E = vehicle control group

Mouse study: Mortality was higher in the naproxcinod-treated groups compared to the control groups and was related to GI and abdominal lesions. Because of an increase in mortality encountered in the 139 mg/kg bid groups during the study, this dose was reduced to 76 mg/kg bid from Week 49 onward for females and from Week 74 onward for males. In the 208 mg/kg bid groups, dosing was completely stopped on Week 75 and the mice continued untreated on study. Overall exposure to the metabolite naproxen (protein-bound plus free fraction) in the high dose male (366 µg/ml x hr) and female groups (511 µg/ml x hr) was lower than maximal clinical exposure (1586 µg/ml x hr). The GI tract, pancreas, kidney, thymus, spleen, bone marrow, liver, and abdominal cavity were identified as sites of non-neoplastic histopathological changes.

Higher incidences ($p<0.05$) of hemolymphoreticular granulocytic leukemia, hepatocellular tumors, Harderian gland adenomas (males), and histiocytic sarcomas (females) were noted in treated mice when compared to the purified water control group. Of these, the total of combined hepatocellular tumors (adenomas and carcinomas) for females that received 208 mg/kg bid reached a statistical significance level of $p \leq 0.01$. According to the Applicant, this statistical significance is most likely due to a lower than expected occurrence of hepatocellular tumors in the control group. As such, in the opinion of the Applicant, there were no tumors considered treatment-related.

Rat study: Mortality was similar between the treated and control groups but a higher incidence of rats with abdominal and renal lesions occurred in the 35 mg/kg/day female group. As a result of a higher mortality in the female placebo control and 35 mg/kg/day group, the females were sacrificed on Study Week 93. Overall exposure to the metabolite naproxen (protein-bound plus free fraction) in the high dose male (596 µg/ml x hr) and female groups (1203 µg/ml x hr) was lower than maximal clinical exposure (1586 µg/ml x hr). The GI tract and the kidneys were identified as main sites of non-neoplastic histopathological changes, males being more sensitive than females.

Statistically significant higher incidences of parathyroid adenoma(s) (trend) and thyroid C-cell adenomas ($p<0.05$) occurred in naproxcinod-treated males compared to the control group. According to the Applicant, these types of neoplasms are classified as common tumors in this species and the incidences of rats with tumors in both controls and treated groups were consistent with the background pattern of findings in rats of this strain. As such, in the opinion of the Applicant, there were no tumors considered treatment-related.

Reproductive and developmental toxicity

Reproductive toxicity studies did not show any effect on male and female fertility and no teratogenicity in rats.
In the embryofetal development study in rabbits, signs of maternal toxicity were evident at the highest dose tested. The number of does with macroscopic findings in the liver, kidneys, or stomach increased dose-dependently. In the high dose group, abortions, total early intrauterine losses and hence increased postimplantation loss were also noted. In the high dose group an increased number of fetuses with specific effects on sternebrae (incomplete ossification, misaligned) were seen, while non-specific skeletal findings (minor abnormalities, variations) were significantly increased in fetuses of the mid and high dose groups.
Based on the known effects of naproxen on delivery, drug treatment was suspended in the treatment groups for some days before delivery in the prenatal and postnatal development study in rats. The high dose group had more days without treatment before delivery than the low and mid dose groups.

Despite discontinuation of treatment an increased mortality/morbidity related to dystocia was observed in the low and mid dose groups. Consistent with dystocia, gestation length was increased in all treated groups. As a consequence of dystocia, which was more pronounced in the low and mid dose group due to the shorter discontinuation of treatment before delivery compared to the high dose group, the number of stillborn pups and pups destroyed or pups found dead during the first 24 hours of life was significantly increased in these groups and thus mean litter sizes were reduced accordingly. No effect on pup survival was noted after culling on postnatal day 4. The only effects noted on postnatal development of the pups after culling were slightly reduced pup weights in the high dose group from postnatal 7 to 14, a delay of vaginal opening by one day in the mid and high dose female pups, and a pre-coital interval of 15 or 16 days in 2 mid dose pairs and 1 high dose pair, but fertility of the F1-generation was not affected and pregnancy rates, preimplantation and postimplantation data were comparable among all groups.

In distribution studies in pregnant rats it was shown that naproxcinod is transferred to the fetus and secreted into the milk. Fetal exposure was also demonstrated in the prenatal and postnatal development studies in blood samples of pups culled on postnatal day 4.

Local tolerance

Naproxcinod is administered to man by the oral route and this was the general route used in the toxicity studies. No specific studies on local tolerance have been conducted and this is considered scientifically justified for an orally administered product.

Other toxicity studies

- Immunotoxicity

In accordance with ICH guidance S8, the oral repeated dose toxicity studies conducted with naproxcinod were reviewed for potential immunotoxic effects. The Applicant concluded that, based on these non-clinical studies, naproxcinod does not appear to present a concern for immunotoxicity.

- Dependence

Gamma-hydroxybutyric acid (GBH) is one of the metabolites of naproxcinod derived from the BDMN part of the molecule. Besides other pharmacodynamic effects, GBH has been shown to have a potential for induction of drug dependence in humans. No specific nonclinical studies on dependence were conducted. This is considered justified since no clinical signs of CNS mediated effect in safety pharmacology, repeated dose toxicology studies and clinical trials were observed.

- Metabolites

Naproxcinod is a prodrug, giving, after ester cleavage, rise to naproxen and a NO-donating moiety, BDMN. The toxicity of naproxen and its metabolites is well established from non-clinical studies and from long-term clinical usage. However, pharmacologiccal and toxicological data for BDMN and its metabolites have not been presented. According to the Applicant, it can be assumed that the safety of BDMN, as a major naproxcinod-metabolite, was qualified in the toxicology studies conducted with naproxcinod.

- Studies on impurities

Based on the proposed drug substance and drug product specifications, several impurities have a specification limit that exceeds the qualification threshold (according to relevant ICH guidance documents). These impurities however were adequately qualified with respect to general toxicity and genotoxicity. In particular, test results did not reveal any *in vivo* relevant genotoxic potential of these impurities.

- Other studies

Poloxamer

The drug formulation for the clinical program (and the intended market product) contains poloxamer as an ´inactive` ingredient at 224.4 mg/600 mg capsule. Poloxamers have been shown not to be absorbed or metabolized and published information indicates *de minimus* toxicity at relevant dose levels with oral administration. Poloxamers are not mutagenic, carcinogenic, and do not affect

reproduction or development. Other studies show that the poloxamer used in this formulation does not have pyrogenic properties, is not an ocular or skin irritant (rabbit or human), and is not readily absorbed across abraded skin into the systemic circulation. The Applicant concludes that poloxamer can be considered safe for use as an inactive pharmaceutical ingredient at the proposed levels in the naproxcinod capsules. This was, affirmed in the naproxcinod nonclinical toxicity program, in which, according to the Applicant, no relevant difference between the placebo control and the tap water control groups were observed. The isolated differences observed, mainly involving the body weight, the spontaneous activity, the body temperature or some hematological parameters, occurred only in rodents in dose tolerance or range finding toxicity studies, were generally of limited severity, present only in one gender and frequently inconsistent between studies and were therefore not considered of toxicological relevance.

p-Aminobenzoic acid (PABA)

Literature data show that PABA was relatively non-toxic in single and repeated dose toxicity studies. Potential target organs identified at relatively high dose levels were liver, kidney, GI tract, adrenal gland and thyroid. PABA was not mutagenic and did not affect reproduction/fertility or embryofetal endpoints. In humans, doses of 300-400 mg/day did not cause any adverse effect. PABA is classified in IARC Group 3 (compounds with inadequate evidence of carcinogenicity). Overall, at the maximum recommended therapeutic dose of naproxcinod, total exposure to PABA would be low. This provides a safety margin >45-fold relative to intake of dietary supplements containing PABA and >100-fold relative to the repeat-dose animal testing that has been conducted.

Phototoxicity

No phototoxicity studies were conducted with naproxcinod. Naproxcinod drug substance did not show significant light absorption in the range between 290 and 700 nm. The safety of the NSAID metabolite is well established through clinical use. The absence of specific studies on phototoxicity is therefore acceptable.

Ecotoxicity/environmental risk assessment

The Applicant provided an environmental risk assessment according to the guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/447/00, June 2006) Phase I and II. No PBT assessment is necessary based on a provided log K_{OW} of 3.2 to 3.7 for the active substance naproxcinod.

The Applicant provides data on physical chemical properties and fate (log K_{OW}, log K_{OC} and ready biodegradability) except data on a water-sediment study.

The provided effect data include acute toxicity data and data on chronic toxicity. Considering the provided toxicity data and refined PEC values, the Applicant calculates several risk quotients. All PEC/PNEC ratios are clearly below the threshold of 1.

The Applicant concluded that it appears highly unlikely that the active ingredient naproxcinod will pose a problem at environmental concentrations. Furthermore the Applicant provided a literature study about an ERA of the main metabolite, naproxen, in which it is also concluded that naproxen is unlikely to cause any significant risk to surface water.

Discussion on non-clinical aspects

Discussion on pharmacology

Rationale for development of naproxcinod as a dual-acting prodrug

Naproxcinod is a member of the new pharmacological class of NO-liberating NSAIDs. Naproxcinod has been developped as a dual-acting prodrug, releasing, after cleavage of an ester bond, a cyclooxygenase-inhibiting metabolite (naproxen) and an NO-liberating metabolite (BDMN) in a fixed

molar ratio (1:1). It is therefore not possible to separately optimise dosage and/or application frequency for both components.

The Applicant was therefore asked to comment on potential advantages of naproxcinod in comparison to a free combination of an NSAID with a NO-liberating drug, which would allow a separate dosage optimisation, based on the specific pharmacological and pharmacokinetic properties of the single components (see Day 120 Non-clinical Question 2).
The Applicant argues that the physiochemical characteristics and the pharmacological activity profile of naproxcinod cannot be replicated by the simple combination of its chemical components (naproxen, BDMN), since naproxcinod and BDMN differ in the kinetic of formation of NO-derived metabolites in circulation and accordingly in their pharmacodynamic properties, making reference to the observation that BDMN caused a more sudden increase in plasma nitrite than naproxcinod, e.g. reflected in a different behaviour in terms of blood pressure response of L-NAME treated hypertensive rats. However, a delayed release of BDMN-derived metabolites could in principle also be achieved by using a suitable retard formulation of BDMN.
In his response to Day 120 Clinical Question 4, the Applicant has provided some preliminary data about pharmacokinetics of BDMN in humans. Although these data do not allow a full characterisation, it is obvious that BDMN has a rather short plasma half-life in humans (estimated to be < 2h) when compared with naproxen (plasma half-life > 10h). Therefore, while a bid dosing of naproxcinod in humans appears to be justified by pharmacokinetic data for naproxen, a bid dosing does not appear to be optimal for the BDMN component, and the observed fluctuations in blood pressure response may well reflect these pharmacokinetic properties of BDMN. Apparently, during the development program for naproxcinod, the pharmacological activity was optimized for the naproxen component, whereas the NO-related effects were considered as additional, potential benefits, not further adjusted for optimal dose and posology.
Overall, the missing flexibility in dosing of the naproxen and BDMN component of naproxcinod is still considered to represent a major disadvantage, which adversely affects the overall benefit-risk evaluation of naproxcinod (see also clinical discussion on this issue).

Absence of data for effects of naproxcinod in a specific animal model of osteoarthritis

The indication sought for naproxcinod is ´relief of signs and symptoms of osteoarthritis in adults`. A variety of non-clinical models of osteoarthritis is available. However, data for antiinflammatory and analgetic effects and for long-term safety/tolerability of naproxcinod in a specific non-clinical osteoarthritis model have not been provided. The following concerns were based on available literature data:
- Since there are data indicating potential pro-inflammatory effects of NO in osteoarthritis, the efficacy of naproxicinod, as an NO-liberating naproxen derivative, to relief signs and symptoms of osteoarthritis may well be different from that established for naproxen.
- Some NSAIDs have been reported to adversely affect cartilage and joint structure during long-term treatment of osteoarthritis. Since there are reports about potential adverse effects of NO on cartilage and joint structure in osteoarthritis, the effects of naproxicinod, as a NO-liberating naproxen derivative, on cartilage and joint structure may be different from those established for naproxen.

Therefore, the Applicant was asked to provide a detailed discussion concerning the potential role of NO in the pathophysiology of osteoarthritis, including effects of NO on cartilage and joint structure, with a specific focus on potential interactions of the NO and the prostaglandin/cyclooxygenase system (see Day 120 Non-clinical Question 1).
As documented by the literature overview provided by the Applicant, it is currently unclear whether NO has beneficial or detrimental effects on cartilage and joint structure in osteoarthritis and it may well be that the final outcome is dependent on local intraarticular concentration of NO, its oxidative state, interactions with the prostaglandin/cyclooxygenase system or on duration of exposure. From a non-clinical point of view, the question whether naproxcinod, besides its acute inflammatory activity, has beneficial or detrimental long-term effects on cartilage and joint structure in OA is therefore still unresolved.
However, the Applicant has meanwhile provided a radiological assessment of long-term effects of naproxcinod on progression of OA in patients (see Day 120 Clinical question 2), which did not show a signal for detrimental long-term effects on cartilage and joint structure. It is acknowledged that this data supersede a request for additional non-clinical evaluation of this issue.

Discussion on pharmacokinetics

Pharmacokinetics of butanediolmononitrat (BDMN) and its metabolites

Little information has been provided by the Applicant in the initially submitted documentation concerning pharmacokinetics of BDMN in animal and in clinical studies. However, a more detailed characterisation of the ADME of BDMN and its metabolites is considered important for an adequate interpretation of the results of the non-clinical studies performed with naproxcinod and for an estimation of safety factors concerning NO-related effects for human application of naproxcinod. Therefore, the Applicant was asked to detail the following points (see Day 120 Non-clinical Question 5):

- location where BDMN is released from naproxcinod
- pharmacokinetics of BDMN (absorption including AUC and Cmax-values, distribution, metabolisation, excretion),
- spectrum of metabolites derived from BDMN (including information about potential formation of reactive intermediates during release of NO/nitrite/nitrate from BDMN),
- location where metabolisation of BDMN takes place.
- similarly, ADME of the BDMN metabolites NO, nitrite and nitrate should be characterized in more detail for the animal species used for non-clinical evaluation of naproxcinod and for humans.

As requested, the Applicant has provided evidence about the location where BDMN is released from naproxcinod (intensively in the liver, partially in the gastrointestinal wall and in blood) and has provided some preliminary data about the pharmacokinetic profile of BDMN in animals and in humans (see day 120 Clinical Question 4).

However, no information has been provided about mechanism, location and extent of NO-formation from naproxcinod and about intermediate products expected to be formed in this process. However, NO is not only the pharmacologically active principle responsible for the BDMN-related effects of naproxcinod, but may also be involved in putative toxicological processes. More information about the aforementioned parameters is therefore considered important for an interpretation not only of the pharmacological but also the toxicological studies (e.g. on carcinogenicity, genotoxicity) performed with naproxcinod (see day 120 Non-Clinical Questions 9 and 14).

Chemical interaction of NO, nitrite and nitrate with other drugs

NO, nitrite and nitrate have been shown to have the potential to chemically interact with other drug substances, resulting possibly in the formation of reactive reaction products with toxicological significance (e.g. N-nitroso compounds). Therefore, the Applicant was asked to comment on the potential of naproxcinod or its metabolites to elicit such reactions (see Day 120 Non-clinical Question 6).

The Applicant has provided evidence that neither naproxcinod nor the BDMN component directly release relevant amounts of nitrite in vivo. Since nitrate released from BDMN may be partly transformed in saliva to nitrite and then to other NO-related species in the stomach, the formation of nitrosoproline was investigated after multiple administration of naproxcinod and L-proline as an established marker for endogenous nitrosation in humans. Preliminary results showed that the nitrosamine levels remained below the limit of detection of the bioanalytical method after naproxcinod application. Therefore, this issue is currently only partly resolved. The final results of the nitrosoproline test should be provided.

Discussion on toxicology

Discussion on single and repeat-dose toxicity

GI lesions (erosions, ulcerations, bleeding, peritonitis) and nephropathy (e.g. papillary necrosis) are common and expected findings with NSAID compounds. However, the liver (mouse) and the thyroid gland (rat) appeared to be additional target organs for naproxcinod-related toxicity.

Naproxcinod has been developped as a NO-liberating naproxen-derivative with the intention to achieve a better GI tolerability profile than naproxen, based on the assumption that NO might protect the GI tract from the adverse (ulcerogenic) effects of NSAIDs. As shown by the single and repeat-dose toxicity studies, GI toxicity is still the dose-limiting factor for naproxcinod. Since naproxen was not used as comparator in these studies, it remains unclear whether NO-released from naproxcinod did at least offer some protection.

CTD 2.6.6, Table 2: Summary of Naproxcinod Critical Doses and Dose Limiting Toxicity

Species*	Duration	Naproxcinod				Dose Limiting Toxicity
		NOAEL		MTD		
		mg/kg/day (µmol/kg/day)	Naproxen AUC_{0-24} (µg/mL•hr)	mg/kg/day (µmol/kg/day)	Naproxen AUC_{0-24} (µg/mL•hr)	
Mice	3 months	76 (220)	184 (M) 437 (F)	278 (800)	345 (M) 506 (F)	Maximal Feasible Dose
Rats	6 months	< 4 (12) (M) < 8 (23) (F)	143 (M) 315 (F)	16 (46)(M) 35 (101)(F)	541 (M) 1051 (F)	GI and Renal Lesions
Minipigs	12 months	40 (115)	1336 (M) 1861 (F)	104 (300)	2210 (M) 2093 (F)	GI and Renal Lesions

* Humans-AUC_{0-24} = 1586 µg/mL.hr following oral administration of 10 mg/kg *bid* (data from the pooled pharmacokinetic analysis from Phase I Clinical Trials)

Discussion on genetic toxicity

The Applicant was asked to demonstrate that the Aroclor 1254-induced rat liver S9 fraction is suitable to explore the *in vitro* genotoxicity of all metabolites of naproxcinod in the Ames test (see Day 120 Non-clinical Question 14).
In his response document, the Applicant did not provide information about the formation of BDMN metabolites other than nitrate following naproxcinod hydrolysis by S9. In particular, it is still unclear to which extent the active BDMN metabolite, NO, which has been show to have a genotoxic potential in different *in vivo* and *in vitro* assay systems, including the Ames test, was formed under the applied assay conditions (e.g. A. Kitasato et al.: Inflammatory cytokines promote inducible nitric oxide synthase-mediated DNA damage in hamster gallbladder epithelial cells, World J Gastroenterol 2007, 13:6379-84; M. Jaiswal. et al.: Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res 2000, 60:184-190.; E. Felley-Bosco: Role of nitric oxide in genotoxicity: implication for carcinogenesis. Cancer and Metastasis Reviews 1998, 17:25-37; Wind DA et al.: DNA deaminating ability and genotoxicity of nitric oxide and its progenitors. Science 1991, 254:1001-1003; Lee D-H et al.: Mutagenesis induced by the nitric oxide donor sodium nitroprusside in mouse cells. Mutagenesis 2007,22:63-67).
Therefore, this issue is still unresolved. The Applicant should provide qualitative and quantitative data about the BDMN metabolites formed under the applied assay conditions, with a particular focus on the formation of NO. This information is considered important for a correct interpretation of the toxicological (e.g. carcinogenicity) studies performed with naproxcinod (see Day 120 Non-Clinical Questions 5 and 9).

Discussion on carcinogenicity/tumorigenicity

Mouse carcinogenicity study

According to the statistical evaluation performed by the Applicant, for female mice receiving naproxcinod 208 mg/kg bid, the incidence of hepatocellular tumors (adenomas plus carcinomas) was significantly ($p< 0.01$) higher than for the water control group. A significance level of $p<0.01$ had been predefined by the Applicant to represent a relevant signal for an increase in tumor incidence of common tumors. Nevertheless, the Applicant came to the conclusion that this statistically significant increase is most likely due to a lower than expected occurrence of hepatocellular tumors in the control group and that, as such, no tumors were considered treatment-related by the Applicant.

As shown in the Table below, the overall incidence of hepatocellular tumors in (male plus female) mice was 3.9% in control animals and 9.8% in naproxcinod-treated animals (OR 2.80, 99% CI 1.21-7.35), clearly indicating (in extension to the results presented by the Applicant for the pair-wise comparison of the naproxcinod-dosed groups with the control group) an overall increase in hepatocellular tumor incidence in naproxcinod-treated animals at a significance level of $p<0.01$ (assessor´s calculation, based on profile likelihood confidence intervals of the logistic model for nominal responses using the factors treatment and gender).

The available control groups were of sufficient size (all together 306 animals), so that reference to historical control values is not necessary for assay interpretation. A pooling of data obtained for the purified water control group and the vehicle control group is based (i) on statistical reasons, since no significant difference in hepatocellular tumor incidence was observed between the two control groups; (ii) the study design, describing that naproxcinod, with the exception of the high dose (208 mg/kg/bid) group (which was applied in a pure vehicle solution), was applied in vehicle solution appropriately diluted with water to otain the desired drug concentration.

Taking into account that mortality was increased in the high dose (139 mg/kg bid and 208 mg/kg bid) naproxcinod-treated mice compared with the control groups and that the mice receiving 208 mg/kg bid were only exposed for 75 weeks while the other groups were exposed for 90 (male) respectively 96 weeks (females), the actual incidence rates of hepatocellular tumors in the high-dose naproxcinod-treated mice can be expected to be higher than the values reported right now. Therefore, the Applicant was asked to provide an estimation of the true hepatocellular tumor incidences, taking into account the mentioned co-variables mortality and time of exposure. However, such data were not submitted by the Applicant.

The increased incidence of hepatocellular tumors was observed at an naproxen exposure (unbound plus free naproxen) lower (high dose male mice: 366 µg/hr x ml, high dose female mice: 511 µg/hr x ml) than the maximal exposure in human clinical studies (1586 µg/hr x ml) at a 750 mg bid dosing. Exposure data for BDMN are not available. The Applicant has provided a calculation showing that Cmax-values of unbound naproxen were higher in the rodent carcinogenicity studies than in the clinical studies with a 750 mg bid naproxcinod dosing. However, for a calculation of the exposure (AUC) to free naproxen, it would have to be taken into account that the terminal elimination half-life of naproxen is considerably shorter in rodents (e.g. 1.6 – 4 h in mice) than in humans (mean $t_{1/2}$ value for naproxen formed after naproxcinod application 18.5 h).

Assessor´s Table: Incidences of hepatocellular tumors in the oral mouse carcinogenicity study (HCT 3012-TOX-402)

Gender	**Tumor Type**	**Control**			**Naproxcinod (mg/kg *bid*)**				
		0 (W)	0 (E)	**Σ Con**	10	38	139	208	**Σ Nap**
Male	Adenoma	9/102	2/51	11/153 7.2%	3/51	8/51	9/51	8/51	28/204 13.7%
	Carcinoma	1/102	0/51	1/153 0.7%	3/51	3/51	1/51	1/51	8/204 3.9%
	All	10/102	2/51	12/153 7.8%	6/51	11/51	10/51	9/51	36/204 17.6%
Female	Adenoma	0/102	0/51	0/153 0.0%	0/51	1/51	1/51	0/51	2/204 1.0%
	Carcinoma	0/102	0/51	0/153 0.0%	0/51	0/51	0/51	2/51	2/204 1.0%
	All	0/102	0/51	0/153 0.0%	0/51	1/51	1/51	2/51	4/204 2.0%
All	Adenoma	9/204	2/102	11/306 3.6%	3/102	9/102	10/102	8/102	30/408 7.4%
	Carcinoma	1/204	0/102	1/306 0.3%	3/102	3/102	1/102	3/102	10/408 2.5%
	All	10/204	2/102	12/306 3.9%	6/102	12/102	11/102	11/102	40/408 9.8%

W = purified water control group, E = vehicle emulsion control group

Since naproxen was reported to be not tumorogenic in long-term rodent carcinogenicty studies, there is concern that the observed increase in hepatocelular tumor incidence could be related to BDMN, released from naproxcinod, and/or to BDMN metabolites (e.g. NO, nitrite, nitrate). Therefore, more data on pharmacokinetics of BDMN and/or its metabolites in animal and in human clinical studies are considered as important for an aequate study interpretation and as basis for calculation of exposure-based safety factors for NO-related effects of naproxcinod (see day 120 Non-clinical Question 5).

Results from shorter-term repeat-dose toxicity studies in mice also indicate the liver as a target organ for naproxcinod toxicity (e.g. in the 3-month study, increases in liver weight and aminotransferase plasma levels have been observed in naproxcinod-treated male mice).

Rat carcinogenicity study

According to the statistical evaluation of the Applicant, significantly higher incidences of parathyroid adenomas (trend) and of thyroid C-cell adenomas ($p<0.05$) occurred in naproxcinod treated male rats when compared to the control group (CTD 2.6.6). According to the Applicant, these types of neoplasms are classified as common tumors in this species and the incidences of rats with tumors in both controls and treated groups were consistent with the background pattern of findings in rats of this strain. As such, in the opinion of the Applicant, there were no tumors considered treatment-related.

This conclusion is not agreed. As depicted in the table below, the overall incidence of thyroid C-cell adenomas in (male plus female) mice was 4.3% in control animals and 10.3% in naproxcinod-treated animals (OR 2.60, 99% CI 1.15-6.43, calculation as described for the mouse carcinogenicity study), indicating an overall increase in thyroid C-cell adenoma in naproxcinod-treated animals at a

significance level ($p<0.01$,) predefined by the Applicant to represent a relevant signal for common tumors.

The available control groups were of sufficient size (all together 329 animals), so that reference to historical control values is not necessary for assay interpretation. A pooling of the data obtained for the water control group and the vehicle control group is based on the study design, describing that naproxcinod, with the exception of the high dose group (which was applied in a pure vehicle solution), was applied in vehicle solution appropriately diluted with water to otain the desired drug concentration.

Assessor´s table: Incidences of thyroid C-cell adenomas in the rat carcinogenicity study (HCT 3012-TOX-401)

Gender	**Tumor Type**	**Control**			**Naproxcinod (mg/kg *bid*)**				
		0 (W)	0 (E)	**Σ Con**	4	8	16	35	**Σ Nap**
Male	C-Cell Adenoma	8/110	0/55	8/165 4.8%	7/54	4/53	10/54		21/161 13.0%
Female	C-Cell Adenoma	6/109	0/55	6/164 3.7%	-	4/52	3/54	5/52	12/158 7.6%
All	C-Cell Adenoma	14/219	0/110	14/329 4.3%	7/54	8/105	13/108	5/52	33/319 10.3%

W = water control group, E = vehicle control group

The increased incidence of thyroid C-cell adenomas was observed at an exposure (based on total naproxen exposure) lower (high dose male rats: 596 µg/hr x ml, high dose female rats: 1203 µg/hr x ml) lower than the maximal exposure in human clinical studies (1586 µg/hr x ml). The Applicant has provided a calculation showing that Cmax-values of unbound naproxen were higher in the rodent carcinogenicity studies than in the clinical studies with a 750 mg bid naproxcinod dosing. However, for a calculation of the exposure (AUC) to free naproxen it would have to be taken into account that the plasma half-life of naproxen is considerably shorter in rodents than in humans (see mouse carcinogenicity study).

Since naproxen was reported to be not tumorogenic in long-term rodent carcinogenicty studies, there is concern that the observed increase in thyroid C-cell adenoma could be related to BDMN, released from naproxcinod, and/or BDMN metabolites (e.g. NO, nitrite, nitrate). In this respect, more data on exposure to BDMN and/or its main metabolites in animal studies and in human clinical studies are considered important, as explained above.

In addition, results from shorter-term repeat-dose toxicity studies in rats also indicate the thyroid as a target organ for adverse naproxcinod effects. For example, in the 3-month study, histopathological finding concerning the thyroid (follicular cell hyperplasia, hypertrophy, decreased colloid) were observed in naproxcinod-treated rats.

Specific issues

On basis of the observed increased incidences of hepatocellular tumors and thyroid C-cell adenomas in naproxcinod-treated mice and rats, respectively, the Applicant was asked to provide a mechanistic explanation for the observed increases in tumor incidences and to provide clear evidence that this are species-specific effects and not of relevance for naproxcinod application to humans, taking into account (i) literature data about tumorigenic effects of nitroglycerine (another NO-donating drug), (ii) literature data about tumorigenic effects of the naproxcinod metabolites nitrite/nitrate (iii) historical control values for tumor incidences in mice and rats, (iv) the fact that adverse effects on liver and thyroid were also observed in shorter-term toxicity studies in mice and rats, respectively and (v) the fact that the real tumor risk for the high dose naproxcinod groups may have been greater than currently reported based on an increased mortality/lower time of exposure.

Furthermore, the Applicant was asked to discuss the utility of short- or medium-term carcinogenicity studies to elucidate potential underlying mechanisms.

In his response the Applicant focused on the following issues:
Results of genetic toxicity studies: The Applicant argues that neither naproxcinod nor its metabolite BDMN are genotoxicants and therefore it is unlikely that naproxcinod may act as direct carcinogen. It is agreed that the currently presented genotoxicity studies did not show a signal for genotoxic effects of naproxcinod. However, it is still unclear whether all relevant metabolites of naproxcinod were formed under the applied assay conditions. In particular, it is still unclear to which extent the active naproxcinod metabolite, NO, which has been show to have a genotoxic potential in different *in vivo* and *in vitro* assay systems, including the Ames test, was formed (see Day 120 Non-clinical Question 14).

Statistical significance of the results: The Applicant argues that the statistical analysis performed for hepatocellular tumors and thyroid C-cell adenomas in rodents did not achieve a sufficient level of significance to suggest a possible carcinogenic effect of naproxcinod. However, a statistical analysis, taking into account the factors treatment and gender, shows a statistical significance of $p<0.01$ for both the increase in liver tumors and the increase in thyroid C-cell tumors, values which should not be neglected in the interest of patient safety.

Historical control data: The Applicant provided a review of published literature and of the historical database of Covance, showing that the incidence of mouse liver tumors and rat C-cell adenomas does vary considerably between different studies and that the tumor incidences observed in the naproxcinod studies were within the historical range. However, recourse to historical data is not essential for an interpretation of the naproxcinod carcinogenicity studies, since the different dose groups were adequately powered to allow for a valid statistical evaluation versus the water and the placebo control, resulting in p-values <0.01 for the observed increases in tumor incidence (see above). Furthermore, following the argumentation of the Applicant, an anti-carcinogenic effect would have to be assigned to poloxamer (see Non-clinical Question 13), because the incidence of liver tumors and of C-cell adenoma in the ´placebo control group` of the mouse and rat study, respectively, was clearly below the historical range provided by the Applicant.

Species-specific effects on liver: The Applicant argues that toxicological changes observed in the liver of male mice after chronic administration of naproxcinod were species-specific effects, not seen in rats or minipigs. While it is agreed that such effects were not observed in rats and minipigs, it is pointed out that concerns about potential liver toxicity of naproxcinod have also arisen from clinical trials in humans.

Effects of other NO-donors/exposure to NO: The Applicant argues that (i) other NO-donor drugs such as nitroglycerin and isosorbide mononitrate do not show univocal carcinogenic properties to suggest tumorigenicity related to the NO moiety and (ii) that results from epidemiological studies did not show a consistently increased risk for cancer with increasing consumption of nitrate. While this description is agreed, it is pointed out that differences in toxicological profile observed for different NO-donors may be related to differences in pharmacokinetic/toxicokinetic properties of these compounds with respect to NO-formation. For naproxcinod, pharmacokinetic data about the location, the mechanism and the time-course of NO-formation as well as the amount of NO-delivered are essentially missing.
For example, with regard to a potential induction of liver tumors, currently any relevant information about levels of NO formed in liver tissue of humans and animals following application of naproxcinod is absent. However, NO-derived products (e.g. peroxynitrite) have been show to be directly genotoxic in a number of *in vitro* and *in vivo* test systems (see Day 120 Non-clinical Question 14).

Carcinogenicity of other NSAIDs: The Applicant pointed out that a signal for a tumorgenic effect was also observed for some other NSAIDs, as for example indometacin. However, the review provided by the Applicant clearly shows that the vast majority of NSAIDs, including naproxen, was negative in rodent carcinogenicity studies. A carcinogenic risk associated with the use of naproxicnod would therefore heavily impact on the benefit risk balance of this compound.

Conclusion: In the rodent carcinogenicity studies, a highly significant increase in incidence of liver tumors and of thyroid C-cell tumors was identified. The clinical relevance of these tumorigenic effects is currently unknown and safety factors for clinical use of naproxcinod in humans cannot be calculated, since data about the exposure of animals in the carcinogenicity studies to BDMN/NO are missing. These uncertainties should be adequately reflected in the overall benefit risk evaluation of naproxcinod.

For an adequate interpretation of the naproxcinod carcinogenicity studies, more data about the pharmacokinetics of NO-formation following naproxcinod application (e.g. in liver tissue) would be important (see day 120 Non-clinical Question 5), In addition, for the performed genotoxicity studies, an adequate formation of NO from naproxcinod should be confirmed under the assay conditions applied (see Day 120 Non-clinical Question 14). Furthermore, the Applicant is still asked (see Day 120 Non-clinical Question 9), to discuss the utility of short- or medium-term carcinogenicity studies to elucidate potential underlying mechanisms.

Discussion on reproductive and developmental toxicity

According to the discussion provided by the Applicant, the significantly increased number of fetuses with renal pelvic cavitation and dilated ureter observed in a rat combined fertility and embryotoxicity study may indicate a slight advanced development of the fetuses, as these observations were considered to be transient observations just prior to birth indicating that the kidneys are functioning but the ability to urinate is not present yet. However, as no other indications of advanced development were noted in these fetuses, the reasoning appeared to be questionable and the Applicant was requested to comment (see day 120 Non-clinical Question 10).
The Applicant agreed that in the mentioned combined fertility and embryo toxicity study in the rat, renal findings do not appear to be associated with other signs indicative of advanced development as had been stated in the study report. The findings "renal cavitation" and "dilated ureter" are both classified as variations and these are not considered to be of lasting consequences. This is further supported by the fact that these variations had not been detected in the offspring in the course of the prenatal and postnatal development study where the same dosages had been used. However, keeping in mind that the exposure of the parent animals was much lower compared to the human exposure at the MRHD, historical control data are important for the final assessment. Currently the Applicant has submitted historical control data of Sprague Dawley rats from the years 1989 – 1992. These data are not useful for any comparison of findings obtained in a study performed in 2000. Therefore the Applicant is requested to submit historical control data which had been collected closer to the year of the study conduction (i.e. 1998 – 2002) for the used strain of Sprague Dawley rats (Crl:CD® (SD) IGS BR) in the testing facility.

Discussion on toxicity of metabolites

In the absence of concrete exposure data for BDMN and its metabolites in nonclinical studies, the interpretation of animal studies with naproxcinod is impaired, since it remains unclear whether BDMN exposure reached in animal experiments was sufficiently high to predict NO-related effects relevant for the clinical application of naproxcinod.
As requested, the Applicant has provided evidence about the location where BDMN is released from naproxcinod (intensively in the liver, partially in the gastrointestinal wall and in blood) and has provided some preliminary data about the pharmacokinetic profile of BDMN in animals and in humans (see day 120 Clinical Question 4).
However, no information has been provided about mechanism, location and extent of NO-formation from naproxcinod and about intermediate products expected to be formed in this process. However, NO is not only the pharmacologically active principle responsible for the BDMN-related effects of naproxcinod, but may also be involved in putative toxicological processes. More information about the aforementioned parameters is therefore considered important for an interpretation not only of the pharmacological but also the toxicological studies (e.g. on carcinogenicity, genotoxicity) performed with naproxcinod (see day 120 Non-Clinical Questions 9 and 14).

Discussion on ERA

No final conclusion on the ERA could be derived because of missing data or reliable studies. The Applicant was asked to (see Day 120 Non-clinical Question 16 -18).

- underpin the data on log D_{OW} for the main metabolite naproxen with literature references or study reports in sufficient detail so that the quality of the results can be established. If this is not possible the Applicant is asked to provide a study on bioconcentration of the active substance naproxcinod (OECD 305).

- provide a water-sediment-study according OECD 308 with the active metabolite naproxen. If there can be a significant shifting of the substance in the sediment demonstrated (> 10% of the substance

at any point in time after or at 14 d in sediment) the Applicant is asked for a toxicity test on sediment dwelling organisms (OECD 219 or OECD 225). Literature data presented in sufficient detail, so that the quality of the results can be established, can also be used.

- provide a study on long term toxicity in fish (Early Life Stage Toxicity Test, OECD 210) for the active metabolite naproxen with full study reports that the quality of the results can be established. Literature data presented in sufficient detail so that the quality of the results can be established can also be used.

In his response document, the applicant provided several literature references for the determination of the log Dow. The cited literature of Zhu et al. (2002) contains information on an experimentally determined (micro shake-flask method) log Dow resulting in a log Dow value of 0.23 (pH of 7.4). As this study can be accepted by CHMP and the log Dow-value of 0.23 falls clearly below the action limit of 3, no bioconcentration study is required.

It is appreciated that the applicant accepted to provide a water-sediment study according to OECD 308. Hence the applicant is asked to submit the full study reports in due time after completion.

It is pointed out that, if the results of the water-sediment study demonstrate significant shifting of naproxen into the sediment, effects on sediment organisms should be investigated in Tier B. In that case CHMP recommends performing a study according to OECD 219. A study according to OECD 219 reflects a more realistic scenario since the continuous entry of pharmaceuticals into water via the STP will be covered.

It is appreciated that the applicant accepted to provide an ELS study on fish according to OECD 210 and a reproduction study on daphnids according to OECD 211. Hence the applicant is asked to submit the full study reports in due time after completion.

Conclusion on non-clinical aspects

Based on the review of the non-clinical data for pharmacology, pharmacokinetics and toxicology several still outstanding issues have been identified. In particular, no information has been provided about mechanism, location and extent of NO-formation from naproxcinod/BDMN and about intermediate products expected to be formed in this process. However, NO is not only the pharmacologically active principle responsible for the BDMN-related pharmacological effects of naproxcinod, but may also be involved in putative toxicological processes. In particular, NO, has been show to have a genotoxic potential in different *in vivo* and *in vitro* assay systems, including the Ames test. For an adequate interpretation of the naproxcinod carcinogenicity studies, more data about the pharmacokinetics of NO-formation following naproxcinod application (e.g. in liver tissue) would be important. In addition, for the performed genotoxicity studies, an adequate formation of NO from naproxcinod should be confirmed under the assay conditions applied.

In the rodent carcinogenicity studies, a highly significant increase in incidence of liver tumors and of thyroid C-cell tumors was identified. The clinical relevance of these tumorigenic effects is currently unknown and safety factors for clinical use of naproxcinod in humans cannot be calculated, since data about the exposure of animals in the carcinogenicity studies to BDMN/NO are missing. These uncertainties should be adequately reflected in the overall benefit risk evaluation of naproxcinod.

Overall, the missing flexibility in dosing of the naproxen and BDMN component of naproxcinod is still considered to represent a major disadvantage, which adversely affects the overall benefit-risk evaluation of naproxcinod (see also clinical discussion on this issue).

Clinical aspects

Given the dual moiety nature of naproxcinod (naproxen and NO-donating moiety BDMN), the Clinical Development Programme has focused on investigating both the naproxen-derived efficacious effects of the drug on the signs and symptoms of OA and on its assumed NO-derived beneficial effects on BP and GI safety.

- **Tabular overview of clinical studies**

Naproxcinod Clinical Development Programme	Study numbers
First in man safety and tolerability	SP-NON-0001
Formulation screening, multiple doses safety and tolerability, food effect	SP-NON-0012, SP-NON-0028, SP-NON-0004, SP-NON-0016
Mass balance	SP-NON-0009
Maximum tolerated dose and Thorough QT study	HCT 3012-X-102, HCT 3012-X-103
Renal pharmacodynamic assessment	SP-NON-0013
Drug-drug interaction studies	HCT 3012-X-107, HCT 3012-X-108, HCT 3012-X-109, SP-NON-0021, SP-NON-0022
Special population studies	HCT 3012-X-105, HCT 3012-X-106, SP-NON-0015, SP-NON-0019, SP-NON-0007
Pain: Dental pain studies	SP-NON-0003, SP-NON-0018
Pain: Dose-ranging OA studies	SP-NON-0010, SP-NON-0017
Pain: Phase 3 OA studies	HCT 3012-X-301 (13 weeks) HCT 3012-X-301E (52 weeks) HCT 3012-X-302 (26-week part) HCT 3012-X-303 (13 weeks)
Gastrointestinal safety (endoscopic studies)	SP-NON-0002, SP-NON-0014, SP-NON-0027, SP-NON-0005
Blood Pressure: Ambulatory blood pressure monitoring: 24-hour BP effect in hypertensive OA patients and hypertensive subjects	HCT 3012-X-104, HCT 3012-X-111, HCT 3012-X-112

Pharmacokinetics

A total of 24 clinical pharmacology studies were conducted in healthy subjects and in patients with OA, hypertension and dental pain. Intrinsic variables evaluated in discrete studies with healthy subjects comprised evaluation of PK and PD in the elderly, in Japanese subjects, and in patients with renal or hepatic impairment. Extrinsic studies consisted of the evaluation of BP responses in the presence of nitroglycerin, and the determination of potential clinical PK (and where relevant PD) interactions with sildenafil, warfarin, antacid and various antihypertensive drugs. Both naproxcinod and total naproxen concentrations typically comprised the PK assessments and, in several studies, unbound plasma naproxen was also determined. In selected studies, the formation of nitrate, as final end-product from NO release, BDMN and γ-hydroxybutyric acid (GHB) were also assessed. The concentrations of plasma nitrates were considered to be a good marker for the bioavailability of the NO releasing portion of the molecule. GHB was measured in two studies, as a possible metabolite from BDMN and butanediol (BD).

In addition, the metabolic disposition was studied following a single oral dose of [3H],[15N]naproxcinod to healthy subjects.

Absorption

Following oral administration, naproxcinod is absorbed and is rapidly metabolised by hydrolysis, to the active moieties naproxen and BDMN before most of the naproxcinod reaches the systemic circulation. Study HCT 3012-MPK-013 investigated the stability of naproxcinod in ex vivo human gastric and jejunal juices. The study demonstrated that naproxcinod was stable in the stomach (degradation half-life = 10.8 +/- 2.7 h) and less stable in the jejunum (degradation half-life = 3.3 +/- 1.9h). The stability of naproxcinod in the GI tract, allows for the substantial absorption of intact naproxcinod, assuming adequate intestinal permeability.

In general, after naproxcinod administration to healthy subjects or to patients, naproxcinod was rapidly converted to naproxen, resulting in plasma naproxcinod concentrations which were very low or close to the LLOQ. In the initial Phase 1 dose-ranging studies, doses of 50 and 125 mg naproxcinod did not elicit detectable plasma concentrations of parent drug, but did generate quantifiable naproxen concentrations. A Phase 1 study (HCT 3012-X-114) was provided by the applicant post submission. Results show that naproxinod is almost exclusively converted in S-naproxen. Very low plasma levels of R-naproxen are observed even after repeated dose administration of naproxinod. However, in order to allow the assessment of this study, the applicant should provide all details of this study (see LoOI).

The observation that 94% of the radioactivity was excreted in the urine showed that orally administered naproxcinod was completely available, i.e. either absorbed as the parent or its main claimed metabolites. In vitro data indicating that naproxcinod undergoes first-pass metabolism most probably in the intestinal wall and in the liver were provided. However, no further in-situ and/or in vivo experiments have been performed to clarify the exact immediate biotransformation of naproxcinod to naproxen and BDMN following oral administration. Therefore, the hydrolysis mechanism in vivo is still not fully clarified. Although the exact mechanism of biotransformation in vivo remains hypothetical, the point is considered resolved.

Distribution

Naproxcinod has very low solubility and for this reason the distribution characteristics after an intravenous dose were not evaluated, in human subjects. Thus, the fraction of drug absorbed (F), clearance (CL) and volume of distribution (Vu) in humans are not available. According to the results obtained from extensive in vitro and in vivo biotransformation studies, naproxcinod undergoes extensive first-pass metabolism and rapid metabolic clearance and this represents the reason for the very low plasma levels more than a high Vu.

The apparent Vu for unbound naproxen as determined by population PK analyses conducted in dental pain patients (SP-NON-0003) was 3920 L for an average patient weighing 69.5 kg (56.4 L/kg), and was found to be linearly related to body weight. In a separate population PK analysis conducted in patients with OA (SP-NON-0010), the Vu was estimated to be 7660 L for an average patient weighing 91 kg (84.2 L/kg). The Vu increased with body weight at a rate of 1.5-1.6%/kg in both studies. The large Vu for unbound naproxen is markedly greater than the values of 0.1 – 0.2 L/kg reported in the literature for total naproxen after oral administration.

The Population PK integrated approach carried out using data from studies SP-NON-0010, HCT 3012-X-302, SP-NON-0017 and HCT 3012-X-111 (HCT 3012-MPK-104), using a model of one-compartment with sequential zero/first-order absorption estimated a volume of distribution (V/F), for a 70 kg patient, of 3630 L for naproxcinod and 9401 L for naproxen.

The large apparent Vu for naproxen in contrast to the known literature data for naproxen was justified by variability in the phase 2 studies. Population PK analysis of unbound naproxen were presented in subjects with osteoarthritis of the knee and in patients with dental pain. Subjects enrolled in the OA study SP-NON-0010 were obese (BMI of over 30 kg/m2) and the larger body weight may have led to the different Vu in comparison to studies using subjects having a normal weight. Typical volume of distribution of total naproxen in healthy male and female subjects (0.18 and 0.13 L/kg, respectively) reported with the current population PK model were consistent to those previously reported in the literature after dosing with naproxen (i.e., 0.1-0.2 L/kg).

Excretion

Naproxcinod is hydrolysed to its principal metabolites naproxen and BDMN. The naproxen is conjugated in the liver and excreted in the urine. No unchanged drug or naproxen has been detected in urine. After administration of a single oral dose of [3H][15N]naproxcinod, the recovery of [3H] in the excreta was virtually complete, with most of the dose (94%) excreted in urine, and 2% recovered in faeces. Most of the administered radioactivity (94%) was excreted within the first 24 hr after administration. The majority of the urinary [3H] was due to conjugates of naproxen and 6-O-desmethyl naproxen. Approximately 62% of the administered [15N]naproxcinod appeared in urine as [15N]nitrate.

The observation that 94% of the radioactivity was excreted in the urine showed that orally administered naproxcinod was completely available, i.e. either absorbed as the parent or its claimed metabolites.

Metabolism

The conversion of naproxcinod to naproxen, in hepatic microsomes is very rapid, occurring in less than 5 minutes in pooled human liver microsomes (HCT 3012-MPK-014 and HCT 3012-MPK-015). The rapid hydrolysis of naproxcinod to naproxen is followed by dealkylation to 6-O-desmethylnaproxen. It has been previously shown that CYP2C9 and CYP1A2 together account for the majority of the human liver demethylation of naproxen.

The metabolism of BDMN is claimed to occur in the liver mediated by glutathione s-transferase (GST).

Due to the extensive in vivo pre-systemic and systemic conversion of naproxcinod to naproxen and BDMN, maximum naproxcinod concentrations following a single dose of 750 mg of naproxcinod have been assessed to be approximately 13.6 ng/mL in the fed state and 8.00 ng/mL in the fasted state. The time to maximum concentration is around 2-3 hours. The BDMN metabolite is also short lived and therefore the PK data rely on plasma concentrations of naproxen as the active NSAID moiety.

The profile of metabolism of naproxen generated from naproxcinod is consistent with the known metabolic profile of administered naproxen.

However, Naproxcinod administration results in a more sustained naproxen plasma concentration than does an equimolar dose of naproxen administration, and lower naproxen bioavailability:

When 500 mg naproxen was administered, either as single dose (SP-NON-003; SP-NON-0013) or as bid doses for 12 days (SP-NON-0002) or 21 days (HCT 302-X-11), the naproxen mean Cmax was 6-53% higher and the mean AUC was 5-40 % higher than after an equimolar dose of naproxcinod (750 mg). Similar differences in Cmax (39% higher) and AUC (20% higher) were found after a supratherapeutic dose of naproxen (3000mg) than after an equimolar dose of naproxcinod (4500 mg) (HCT 3012-X-103). The t ½ of naproxen is similar after naproxcinod (range 10.5-22.3 h, mean ± SD 18.5 ±2.65 h, Table 60 Module 2.72.) or naproxen (range 11.9-16.8 h, mean ± SD 14.5 ± 1.43 h in study SP-NON-0013, Table 38) administration. Concurrent with the lower naproxen Cmax, the rate of naproxen absorption appears to be slower after therapeutic doses of naproxcinond (mean tmx = 2.43 to 4.50 h) than of naproxen (mean tmax = 1.83 to 2.45 h).

This lower naproxen bioavailability out of naproxcinod does not seem to have a negative influence of efficacy (SEE PIVOTAL STUDIES) but overall it does not present an advantage and onset of efficacy was not really discussed.

In addition, although BDMN is claimed to be an active moiety the pharmacokinetic profile and its contribution to pharmacokinetics of naproxcinod/naproxen is still not clarified.

Pharmacokinetic and Bioavailability/Bioequivalence studies during biopharmceutical development and food effect

Biopharmaceutical development

Naproxcinod administered as a pure substance (namely encapsulated naproxcinod) showed unacceptable PK characteristics in vivo (ie, median tmax around 24 hours and undetectable levels of naproxcinod in circulation).

The goal of the formulation development programme was to maximise the rate of absorption of naproxcinod, so as to enable fast onset of analgesic activity through the rapid availability of naproxen.

A selection of 11 formulations and 4 pre-formulations of naproxcinod have been investigated both in vitro and in vivo.
The majority of the initial formulations failed to provide a suitable pharmacokinetic (PK) profile due to slow absorption, resulting in a long tmax. During the formulation development it became apparent from the initial studies that it would be necessary to incorporate an emulsifying agent into the formulation, in order to facilitate the emulsification of naproxcinod upon contact with gastrointestinal (GI) fluids. Thus, an emulsifying agent was added to the formulation to make a self-emulsifying drug delivery system (SEDDS) formulation. Administration of naproxcinod without an emulsifying agent (encapsulated naproxcinod) resulted in undetectable naproxcinod levels in plasma, compared to the SEDDS were naproxcinod was detectable. In addition, lower Cmax of the active moiety naproxen (12 µg/mL) and a longer median tmax (around 24 hours) compared to the SEDDS, which resulted in a Cmax of approximately 26.2 µg/mL and a median tmax of 3 hours. The AUCinf of the active metabolite naproxen did not differ between the pure substance and the SEDDS formulation. Further development was performed to optimise the delivery of naproxcinod and naproxen by varying the ratio of the components. Different emulsifying agent and excipients and emulsifying agent/excipient ratios were screened. Based on the targeted pharmacokinetic characteristics of rapid absorption and maximum bioavailability of both naproxcinod and naproxen, the formulation selected for the clinical development was the naproxcinod SEDDS capsule 375 mg, incorporating Poloxamer.
Stability studies during the clinical development programme indicated slower dissolution profiles for aged capsules (32-24 months), as a result of the cross-linking of the gelatine of the capsule shells. Even though, in vivo bioequivalence (based on plasma naproxen concentrations) was demonstrated between "aged" capsules (32 to 34 months of age) and new capsules (4 to 6 months of age) (SP-NON-0028) it was decided to incorporate PABA into the formulation. The PABA minimises the capsule shell-cross linking, increasing the consistency of the in vitro dissolution profile tests over time. Between-study comparisons of the clinical pharmacokinetics of naproxcinod and naproxen before and after PABA addition did not show any apparent differences in bioavailability. The revised formulation was used in all Phase 3 studies. In addition, later stage Phase 1 clinical pharmacokinetic and drug-drug interaction studies were also performed with the PABA-containing formulation. The addition of PABA to avoid aging of the capsules is deemed a minor modification, considering overall the particular characteristics of the drug substance and the formulation.

Effect of formulation and food effect studies

Three studies (SP-NON-0001, SP-NON-0004 and SP-NON-0012) investigated the effect of formulation and the effect of food on the bioavailability of naproxcinod and naproxen in healthy volunteers, following administration of naproxcinod as a single 375 mg dose. A total of five different formulations were tested across these three studies.
Results from the first study (SP-NON-0001) indicated that the emulsion was more rapidly absorbed than the capsule, while in the second study (SP-NON-0004), the capsule absorption rate was in the order proposed commercial formulation > proposed commercial formulation with half the content of poloxamer > formulation containing a different poloxamer> pure substance; indeed, no naproxcinod was detectable when administered as the pure substance and naproxen tmax was delayed to 24 h, thereby confirming the requirement of a SEDDS to enable rapid absorption. The absorption time was prolonged by approximately 2-3 h by reducing the poloxamer content . Concomitantly, the Cmax decreased with the increase in tmax.
The results of Study SP-NON-0004 showed that food increased the plasma concentrations of naproxcinod. The Cmax increased about 4-fold when naproxcinod was administered after a high fat meal, but still remained relatively low, i.e. in the nM (ng/mL) range.
However, the increase in plasma naproxcinod following a high fat meal did not result in a difference in the total systemic exposure (AUC) to naproxen. Food slightly reduced the absorption rate of naproxen. In the fed state, an average delay of approximately 0.5-0.75 h was observed in the naproxen plasma concentration vs time profile from time of dose administration until tmax. Some plasma concentration vs time profiles showed a pronounced delay in absorption, whereas others were similar to those observed in the fasted state. It is well-known that food intake reduces the gastric emptying rate, and that this may cause a delay in the absorption of drugs. Food increased the mean naproxen Cmax by around 10%. The lower boundary of the 90% CI for Cmax (0.78-1.08) was only slightly beyond the

criteria for bioequivalence. Accordingly, this small increase in Cmax with food is not considered clinically meaningful.
It was concluded that naproxcinod can be administered with or without food. The pivotal Phase 3 studies were conducted with drug administered with food, or without a specified fasting interval.
However, since the pharmacokinetic profile of naproxcinod versus naproxen is not fully clarified, naproxcinod should only be administered with food (see SPC). It has to be taken into account that the average delay of approximately 0.5-0.75 h that was observed in the naproxen plasma concentration vs time profile from time of dose administration until tmax could result in a later onset of efficacy.

Study SP-NON-0012 was designed to evaluate 3 newer formulations against the reference/commercial formulation, with the objective of obtaining a formulation which matched the bioavailability of the proposed commercial formulation, but which would fit into a smaller capsule size. A comparison of the fed vs fasted state for the 5 formulations evaluated in SP-NON-0012 was undertaken. The systemic exposure to naproxcinod and systemic uptake rate of naproxen were affected by the choice of formulation and intake of food, whereas the AUC of naproxen was not. The systemic exposure to naproxcinod was favoured by a rapidly absorbed formulation and co-administration of food.
None of the tested formulations was considered to improve the bioavailability characteristics of the proposed commercial formulation.

The rationale for choosing the proposed commercial formulation for subsequent studies is basically accepted. However, a rank order correlation has been claimed by the applicant between in vitro dissolution and in vivo pharmacokinetics during the development process of optimising the SEDDS formulation which is of utmost importance for bioavailability. Considering the pronounced formulation related differences it is recommended to specify the relation between in vitro dissolution of the prodrug and naproxen pharmacokinetics. This is all the more considered relevant since it is requested to waive bioequivalence studies based on comparative in vitro dissolution data. Some inconsistencies were noted in the response document with respect of the final formulation indicating that even substantial formulation differences may be hardly correctly reflected in vivo (see LoOI).The in vitro dissolution method and respective data are considered non-predictive for in vivo product performance and do not ensure unchanged biopharmaceutic similarity and/or consistency in case of formulation modifications. It is acknowledged that in vitro dissolution used as for usual solid oral formulations may not be the optimal way to investigate the particular characteristics of a SEDDS, i.e. additional tests should be considered to achieve meaningful test results.

Bioequivalence

The primary objective of study SP-NON-0028 was to compare the rate and extent of absorption of naproxen from aged and new 375 mg naproxcinod capsules in healthy volunteers. In vitro dissolution studies showed the occurrence of gelatine cross-linking in naproxcinod capsules upon storage, with a resultant effect on the in vitro dissolution rate (see below). The secondary objectives were to assess the safety and tolerability of a single 375 mg capsule dose of naproxcinod in fasting healthy subjects.
As in previous studies, the plasma concentrations of naproxcinod after the 375 mg dose were low or BLOQ. Although the Cmax and AUCt values for naproxcinod were similar after administration of the aged or new capsules, the low/negligible plasma concentrations precluded a determination of bioequivalence based on parent drug.
The overall rate and extent of exposure to naproxen after administration of the aged and new naproxcinod capsules were similar so aged capsules do not seem to influence bioavailability according to the presented in vivo data.
However, as far as the in vitro dissolution results are concerned no further conclusions can be drawn.

Safety

There was an increased probability of dizziness associated with naproxcinod exposure of 0.042, 0.055, 0.086, and 0.13 at naproxcinod doses of 125, 375, 750, and 1125 mg bid respectively. This was not found with naproxen; this was not unexpected given the effects of NO/GHB on dizziness and increasing NO/GHB exposure at higher naproxcinod exposures. Dyspepsia was also associated with naproxcinod exposure. Probabilities of dyspepsia were 0.064, 0.092, 0.17, and 0.28 at naproxcinod doses of 125, 375, 750, and 1125 mg bid. No safety evaluation was provided for each of the 24 pharmacology

studies in the respective summary of the dossier. For the discussion of the AE dizziness and dyspepsia see also clinical safety section.

Pharmacodynamics

Overall the presentation of pharmacodynamic data was not very easy to follow in the Summary of Clinical Pharmacology Studies.
The applicant conducted 12 PD studies, evaluating the gastrointestinal effect of naproxcinod compared to naproxen and rofecoxib (3), the effect on ambulatory blood pressure compared to naproxen and ibuprofen(3), the effect in post surgical dental pain compared to naproxen and rofecoxib (2), the effect on QT/QTc (2), the renal effect (1) and one safety study. This later study is presented in the safety section.

In general, NSAIDs do not have a clear PK/PD relationship over a wide range of doses. NSAIDs are associated with a flat dose response curve and a plateau across a wide range of doses. Once the plateau of the curve is reached no additional analgesic efficacy is detectable with higher doses. This effect has been seen with naproxcinod in that doses of greater than 1500 mg per day were not associated with any greater efficacy (SP-NON-0017).

In vivo, naproxcinod is metabolised to the NSAID naproxen, and to a NO-releasing moiety. NO possesses marked vascular smooth-muscle relaxant properties through activation of soluble guanylyl cyclase and consequent formation of cyclic guanosine monophosphate (cGMP). The applicant claims that the release of NO from naproxcinod result in effects on the cardiovascular (CV) system as well as protection of the gastrointestinal (GI) tract and other organs. Increases in cGMP should be a reflection of NO release. Plasma concentrations of cGMP were measured in several studies and exhibited diurnal variability and generally increased with dose in some studies (SP-NON-0001). In other studies, (SP-NON-0019, SP-NON-0021), cGMP levels did not appear to be related to dose level and there was no major difference between active drug and placebo. In other studies (SP-NON-0015), naproxcinod did not influence cGMP levels. Thus, the cGMP data were variable across studies and the findings inconclusive.
NO is thought to stimulate many GI protective factors that are negatively affected by NSAIDs, such as mucus production, secretion of bicarbonate and increased blood-flow in the gastric mucosa. The results of three Phase1 studies suggest an improved short-term gastrointestinal endoscopic profile of naproxcinod compared with naproxen but not compared to rofecoxib.

The study evaluating the effect of naproxcinod on QT/QTc shows that Naproxcinod mildly blocks hERG and other potassium channel currents. This does not translate in a QTc prolongation in animal models or healthy volunteers at therapeutic doses. However, it does at least with the supra-therapeutic dose and may be associated with QTc prolongation in patients whose repolarisation reserve is low such as patients with congenital LQTS, or asymptomatic "channelopathies", hence if associated with relevant electrolyte disturbances, or bradycardia among others. The study cannot be considered as negative. Such a risk is mild, and could be mentioned in the SmPC.

Due to NO release, naproxcinod may counteract the rise in BP commonly seen with NSAIDs in both normotensive and hypertensive patients. NO has been shown to down-regulate the synthesis of angiotensin converting enzyme (ACE) in the endothelium, as well as Angiotensin II type 1 receptors (AT1) in vascular smooth muscle cells, thus having the potential to decrease Angiotensin II production and action. Study results are not consistent with an improved overall blood pressure profile of naproxcinod in comparison to naproxen (see safety section).
The pharmacodynamic activity of the NO donating moiety seems not to be sufficiently evaluated. It remains unclear how the claim of beneficial effect on blood pressure and gastrointestinal safety can be attributed to the NO release with plasma concentrations of BDMN in the nanomolar range.
The concept of the fixed conjugate, which does not allow individual titration of the NO component, is still not sufficiently clear with regard to its mechanism and characteristics of the NO moiety and the total combination. There might be specific thresholds for single effects at different doses and for the NO moiety a potential tachyphylaxia with regard to the hypotensive effect is identified. Insofar, the BP effect of naproxcinod compared to naproxen is not considered sustained over long-term treatment. A

dose related hypotensive effect was documented within the regular measurements within both BP studies, however, sudden AEs and SAEs caused by partly unknown mechanism and co-factors frequently occurred. The increased risk related to naproxcinod 750 mg *bid* reached statistical significance. Dizziness and hypotension as the most frequently observed potential hypotension-related AEs are considered a disorder for the elderly with consecutive impact on potentially severe health outcome. The claimed indication however implies mostly the elderly, therefore these AEs are considered clinically relevant.

Possible interactions with anticoagulants, antihypertensive medicinal products, sildenafil and nitrogylcerins have been identified and respective information is included in the SPC. Possible interactions of naproxen (e.g. methotrexate, lithium) were taken into account and included also in the Naproxcinod SmPC.
Data on pharmacodynamic interaction between naproxen and the nitric oxide moiety were provided in the answer to the Day 120 LoQ and don´t indicate an interaction as far as the COX inhibitory activity is concerned.

Discussion on clinical pharmacology

Naproxcinod was designed to release the two active moieties naproxen (NSAID related activities) and the NO donating moiety 1,4 butanediol mononitrate (BDMN; nitric oxide related effects) which are purported to be responsible for the dual pharmacological action of naproxcinod.
Since naproxen and the NO donating moiety are combined in this product via the ester bound in a 1:1 relation no dose titration of NO was possible. In this context it is not expected that both therapeutic principles, naproxen and NO, are dosed in their appropriate therapeutic ranges. More justification is needed why both compounds were not combined as single entities thus allowing titration of pharmacological effects of naproxen on one hand and the NO donator on the other hand.
The targeted bioavailability profile of naproxcinod was rapid bioavailability of naproxcinod after oral administration of an immediate release formulation so as to enable the quick release of naproxen and BDMN and its NO conversion products into the circulation.
Administration of naproxcinod as pure substance revealed poor naproxcinod and naproxen bioavailability characteristics compared to the formulated drug products. A selection of 11 formulations and 4 pre-formulations of naproxcinod have been investigated both in vitro and in vivo. Of the capsule formulations tested, the formulation with the relatively higher naproxen Cmax and earlier tmax, (2-4 h) appeared to have the most favourable absorption characteristics. Therefore, the proposed formulation with the emulsifying agent Poloxamer was chosen for the subsequent Phase 1, 2 and 3 studies as well as for the "to be marketed" drug product. None of the other formulations improved the bioavailability characteristics of the reference formulation. The rationale for choosing the proposed formulation formulation for subsequent studies is basically accepted. However, a rank order correlation has been claimed by the applicant between in vitro dissolution and in vivo pharmacokinetics during the development process of optimising the SEDDS formulation which is of utmost importance for bioavailability. Considering the pronounced formulation related differences it is recommended to specify the relation between in vitro dissolution of the prodrug and naproxen pharmacokinetics. The in vitro dissolution method used and respective data are considered non-predictive for in vivo product performance and do not ensure unchanged biopharmaceutic similarity and/or consistency in case of formulation modifications. It is acknowledged that in vitro dissolution used as for usual solid oral formulations may not be the optimal way to investigate the particular characteristics of a SEDDS, i.e. additional tests should be considered to achieve meaningful test results.

The inclusion of PABA in the formulation, to address the gelatine cross-linking observed with earlier batches of the commercial formulation), did not impact significantly the in vitro dissolution profile; the exception to this was in the aged batches (32-34 months), in which PABA was not included, where the gelatine cross-linking had led to slower dissolution rate. The mean t½ of naproxen ranged from 16 to 22 h, independent of formulation.
In vivo data did not show any influence of aged and new capsules on bioavailability. In contrast, in vitro data were not consistent in this case. Considering also other comparative in vitro data as presented no further conclusions can be drawn. This is because no relationship has been found between in vivo and in vitro results and in several cases the experimental methods were not in line

with the final method for batch release. A summarized presentation of in vitro dissolution profiles generated by means of different experimental methods (e.g. different pancreatin concentrations) is not acceptable to demonstrate similarity.
It is highly questionable whether the PopPK approach has sufficient sensitivity to ensure that the to-be-marketed formulation has the claimed biopharmaceutic characteristics. It is not obvious which kind of relationship can be claimed between pharmacokinetic characteristics of naproxen and in vitro dissolution of the prodrug. Considering the particular impact of the bioavailability-modifying formulation and the limited possibilities to quantify the pro-drug it has to be justified that comparative in vitro dissolution may be used to indicate biopharmaceutic product similarity and/or consistency in this case.

A total of 24 clinical pharmacology studies were conducted in healthy subjects and in patients with OA, hypertension and dental pain several of which included pharmacokinetic sampling.
In general, after naproxcinod administration to healthy subjects or to patients resulting plasma naproxcinod concentrations were very low or close to the LLOQ, indicating rapid conversion of naproxcinod to naproxen. A Phase 1 study (HCT 3012-X-114) was provided by the applicant post submission. Results show that naproxinod is almost exclusively converted in S-naproxen. Very low plasma levels of R-naproxen are observed even after repeated dose administration of naproxinod. However, in order to allow the assessment of this study, the applicant should provide all details of this study (see LoOI).
In the initial Phase 1 dose-ranging studies, doses of 50 and 125 mg naproxcinod did not elicit detectable plasma concentrations of parent drug, but did generate quantifiable naproxen concentrations. The observation that 94% of the radioactivity was excreted in the urine showed that orally administered naproxcinod was completely available, i.e. either absorbed as the parent or its claimed metabolites. However, it is deemed necessary to investigate how naproxcinod is transported into the system i.e. whether biotransformation may start already prior or during transport through the intestinal membrane. Particular characteristics of naproxcinod as claimed to act as an inactive prodrug should be elucidated.
The profile of metabolism of naproxen generated from naproxcinod is consistent with the known metabolic profile of administered naproxen. However, it remains unclear why availability of naproxen from naproxcinod is markedly reduced in comparison to naproxen from naproxen (up to 53% for Cmax and up to 40% for AUC). In addition, although BDMN is claimed to be an active moiety the pharmacokinetic profile and its contribution to pharmacokinetics of naproxcinod/naproxen is still not clarified.
Inherent with the very low plasma naproxcinod concentrations was the observation of high intersubject variability in its PK, thus rendering statistical evaluations of similarities, differences and/or relationships between treatment groups and PK variables for naproxcinod extremely difficult. As expected, the intersubject variability in naproxen concentrations was substantially less than that of naproxcinod, and accordingly this active NSAID was the primary naproxcinod metabolite upon which PK (dose/concentration) and PD responses (concentration/response) were judged.
The applicant states that inconsistent pharmacokinetic data are available for BDMN both in healthy and hepatically impaired subjects. It remains unclear how the claim of beneficial effect on blood pressure and gastrointestinal safety can be attributed to the NO release with plasma concentrations of BDMN in the nanomolar range. Sound justification for this concept is needed from the clinical point of view.

At higher doses, Cmax and AUC values of naproxcinod seem to be dose related (or close to dose proportional) but typically more than 1000-fold lower for Cmax and AUC than those of naproxen. When sufficient plasma samples were obtained with detectable analyte concentrations, the plasma t1/2 of naproxcinod was calculated to be 1.1 h, reflecting rapid metabolic clearance, although the actual volume of distribution of the drug was not determined. With the therapeutic dose regimen of 750 mg bid, predose naproxcinod concentrations were usually BLOQ, and thus no steady-state of naproxcinod was attained.

Upon administration of single or twice daily equimolar doses of naproxcinod (750 mg) and naproxen (500 mg), the Cmax and AUC of naproxen are clearly lower after naproxcinod than after naproxen. Both drugs are very well absorbed, thus extent of absorption was not the apparent cause for this difference. However, concurrent with the lower Cmax, the naproxen mean tmax was later after naproxcinod (2.4-4.5 h) than after naproxen (1.8-2.5 h), thereby resulting in more sustained plasma

naproxen after naproxcinod administration. This lower naproxen bioavailability out of naproxcinod does not seem to have a negative influence on efficacy (SEE PIVOTAL STUDIES) but overall it does not present an advantage and onset of efficacy was not really discussed.

There was no untoward accumulation of naproxen after multiple doses of naproxcinod beyond that which would be expected based on the t1/2 of naproxen. Typically, steady-state naproxen concentrations were attained within 3-5 days of administration of naproxcinod 750 mg bid.

Food intake seems to have a considerable impact on plasma naproxcinod concentration as reflected by a higher Cmax. However, the increase in plasma naproxcinod following a high fat meal did not result in a relevant difference in the total systemic exposure (AUC) to naproxen.
The mean naproxen Cmax increased by around 10%. The lower boundary of the 90% CI for Cmax (0.78-1.08) was only slightly beyond the criteria for bioequivalence. Accordingly, this small increase in Cmax with food is not considered clinically meaningful.
Since the pharmacokinetic profile of naproxcinod versus naproxen is not fully clarified and since pivotal studies were conducted with food, naproxcinod should only be administered with food (see SPC). However, an average delay of approximately 0.5-0.75 h was observed in the naproxen plasma concentration vs. time profile from time of dose administration until tmax which could result in a later onset of efficacy.
Despite the lack of major PK differences between healthy young subjects and elderly, it is recommended, as for all other NSAIDs, for elderly patients to initiate the treatment at the lowest effective dose (375 mg bid). However, it is important to note that in the ≥ 75 years subgroup no difference in the primary endpoints versus placebo was found for the naproxcinod 375 mg *bid* dose regimen which questions this recommendation with regard to efficacy. With respect to the clinical relevance of the efficacy data of the 375 mg *bid* dose see clinical section.

Conclusions on clinical pharmacology

Upon administration of single or twice daily equimolar doses of naproxcinod (750 mg) and naproxen (500 mg), the Cmax and AUC of naproxen are clearly lower after naproxcinod than after naproxen. Both drugs are very well absorbed, thus extent of absorption was not the apparent cause for this difference. However, concurrent with the lower Cmax, the naproxen mean tmax was later after naproxcinod (2.4-4.5 h) than after naproxen (1.8-2.5 h), thereby resulting in more sustained plasma naproxen after naproxcinod administration. This lower naproxen bioavailability out of naproxcinod does not seem to have a negative influence on efficacy (SEE PIVOTAL STUDIES) but overall it does not present an advantage and onset of efficacy was not really discussed.

Some inconsistencies were noted in the response document with respect of the final formulation indicating that even substantial formulation differences may be hardly correctly reflected in vivo (see LoOI).The in vitro dissolution method and respective data are considered non-predictive for in vivo product performance and do not ensure unchanged biopharmaceutic similarity and/or consistency in case of formulation modifications. It is acknowledged that in vitro dissolution used as for usual solid oral formulations may not be the optimal way to investigate the particular characteristics of a SEDDS, i.e. additional tests should be considered to achieve meaningful test results. Although BDMN is claimed to be an active moiety the pharmacokinetic profile and its contribution to pharmacokinetics of naproxcinod/naproxen is still not clarified. No specific relationship can be established between pharmacokinetic data, i.e. dose related exposure to BDMN, and clinical effects of BDMN in humans.

The pharmacodynamic activity of the NO donating moiety seems not to be sufficiently evaluated. It remains unclear how the claim of beneficial effect on blood pressure and gastrointestinal safety can be attributed to the NO release with plasma concentrations of BDMN in the nanomolar range.

The concept of the fixed conjugate, which does not allow individual titration of the NO component, is still not sufficiently clear with regard to its mechanism and characteristics of the NO moiety and the total combination.

Clinical efficacy

Dose-response studies and main clinical studies

Dose response studies
Two Phase 2 dose ranging studies (SP-NON-0010 and SP-NON-0017) explored the analgesic efficacy, safety and tolerability of naproxcinod doses, from 125 mg bid to 1125 mg bid, in patients with OA of the knee and the hip, compared with placebo, naproxen and rofecoxib during 6 weeks of treatment.

Study SP-NON-0010
This study used a 10 mm difference in the WOMAC™ pain sub-score as being the non-inferiority margin based on a publication (Ehrich et al, 2000) where a margin of 9.7 mm in the pain sub-score was the minimal clinically detectable difference. Here the applicant quotes wrongly 9.3 which was the MPCI in WOMAC™ function subscale. Naproxcinod 375 mg *bid* and 750 mg *bid* were superior to placebo and non-inferior to rofecoxib 25 mg *qd* in the WOMAC™ pain subscale score whilst naproxcinod 125 mg *bid* was not statistically significantly different from placebo. Since 9.7 was the MPCI for WOMAC pain a lower non-inferior margin should have been used, see also rationale for the non-inferior margin of the phase 3 studies where non-inferior margin of 8 is considered as not clinically relevant when using the WOMAC pain and function subscale scores.
No dose response model was fitted using regression techniques. Since only three doses of naproxcinod were tested, and the two upper dose groups showed similar effects, a reasonable fit would also not have been possible with the design used. If the 10mm difference as minimal clinically important difference had been used to define a minimum effective dose (MED), the MED estimate would have been around 300 mg, depending on the underlying model, however accompanied by a rather wide confidence interval. The study design and results do not allow for a reliable MED estimate.

Study SP-NON-0017
The study had no formal sample size calculation, but it was estimated to have at least 90% power to detect a difference of 11 mm or more between the rofecoxib and placebo treatment groups in the WOMAC™ pain subscale score. The study showed that the naproxcinod 1125 mg bid dose was not superior to the naproxcinod 750 mg dose bid (p=0.87; 95% CI -6 to 5). Hence, there appears to be no advantage to increase the dose above 750 mg twice a day. Data from study SP-NON-0017 were provided separately for the subgroups of hip OA and knee OA and confirmed that naproxcinod had a numerically lower efficacy improvement in hip OA than in knee OA. These data are conistent with data from study SP-NON-0005 and are comparable to naproxen. Similar findings are reported from literature.

Based on the data of these studies the selection of 375 mg bid and 750 mg bid dose regimens of naproxcinod administered twice a day for the pivotal phase 3 studies seems to be reasonable. However the 375 mg dose was not investigated in hip OA.

Main clinical studies

Study HCT-3012-X-301:
This was a Parallel, Randomised, Double-Blind, 13-Week, Placebo- and Naproxen-Controlled, Multicenter Study of Naproxcinod (375 mg bid and 750 mg bid) in Patients with Osteoarthritis of the Knee.

Study HCT-3012-X-302:
This was a 53 Week Study on Analgesic Efficacy and Safety of Naproxcinod (HCT 3012): 26-Week, Randomised, Parallel-Group, Double-Blind, Placebo (13 Weeks)- and Naproxen (26 Weeks)-Controlled, Multicenter Study of Naproxcinod (375 mg *bid* and 750 mg *bid*) with a 26-Week Naproxen-Controlled Safety Follow-up in Patients with Osteoarthritis of the Knee, and a 1-week Post-treatment Safety Follow-up.

Study HCT-3012-X-303

This was a 13-Week, Multicenter, Randomised, Parallel-Group, Double-Blind, Placebo bid and Naproxen 500 mg bid, Controlled Study on the Efficacy on Signs and Symptoms, and Safety of Naproxcinod (HCT 3012) 750 mg bid, in Patients with Osteoarthritis of the Hip.

Studies HCT 3012-X-301 and HCT 3012-X-302 included 963 naproxcinod patients out of 1929 randomised patients with OA of the knee. Study HCT 3012-X-303 included 323 patients treated with naproxcinod out of 810 randomised patients with OA of the hip. Since only naproxcinod 750 mg bid was evaluated for OA of the hip, only this dose can be recommended in the SPC for this subgroup. In Studies HCT 3012-X-301 and HCT 3012-X-303, patients were treated for 13 weeks; in Study HCT 3012-X-302, patients were treated for 52 weeks, but only data from the placebo-controlled 13-week period and the naproxen-controlled 26-week period have been included in this efficacy summary. The reason for the inclusion of data only up to 26 weeks from study HCT 3012-X-302 is that data from the Week-26 visit to Week-53 visits were not yet available when data integration was performed. However, serious adverse events occurring between the Week-26 visit to Week-53 visits have been included in the submission.

Naproxcinod is a new pharmaceutical moiety and little is know on pro-inflammatory effects due to the NO containing moiety. According to the OA guideline (CPMP/EWP/784/97 Rev. 1) structural changes should be monitored for at least one year after the first start of treatment to establish that a symptom modifying drug does not have deleterious effects on the joint. This was one of the secondary objectves in Study HCT-3012-X-302 and data were provided in the answer to the day 120 LoQ.

- **Patient disposition and baseline data**

Discontinuation rates were in general low and similar across studies and groups with a slightly higher rate in the overall placebo group for discontinuation due to lack of efficacy. However, in all three studies discontinuations due to lack of efficacy was higher in the naproxcinod 375 mg bid dose compared to the other active treatment groups and in study HCT 3012-X-303 discontinuation due to lack of efficacy in the naproxcinod 750 mg *bid* group was twice as high in comparison to naproxen (6,2% vs 3,2%) which might be indicative of a lower efficacy of the 375 mg bid dose for knee OA and the naproxcinod 750 mg bid dose in patients with hip OA.

In all three studies, most patients (around 90%) had a WOMAC™ pain category of high at baseline (ie ≥ 60 mm) with around 50 % entering the study with a medical history of hypertension. Overall, the demographic and baseline characteristics were representative of the general population suffering from OA.
There was no statistically significant difference among the treatment groups for any demographic of screening/baseline variable in the overall ITT population except in study HCT 3012-X-303 for ethnicity (p=0.0492). While the ethnicity profile was similar for all three groups of this study (with more than 90% of the North American patients in each group being "Not Hispanic or Latino"), the statistically significant difference was caused by a particularly high percentage of "Not Hispanic or Latino" patients in the naproxcinod 750 mg bid group (124/125, 99,2%).

- **Treatments**

Studies HCT 3012-X-301, -302:
Eligible patients were administered the following treatments:

- naproxcinod 375 mg bid
- naproxcinod 750 mg bid
- naproxen 500 mg bid
- placebo bid

In **Study HCT 3012-X-303** the 375 mg Naproxcinod dose was not examined.
Since only naproxcinod 750 mg bid was evaluated for OA of the hip, only this dose can be recommended in the SPC for this subgroup.

- **Objectives**

The three pivotal phase III studies had essentially the same objectives except for non-inferiority versus naproxen which was not formally studied in study HCT-3012-X-303.

Study HCT-3012-X-301 and Study HCT-3012-X-302:
The primary objective of these studies was to show, at Week 13, that naproxcinod (375 mg bid and 750 mg bid) was superior to placebo in relieving OA signs and symptoms in patients with OA of the knee.

The secondary objectives of these studies were:
- To show, at Week 13, that naproxcinod 750 mg bid was non-inferior to naproxen 500 mg bid in relieving OA signs and symptoms in patients with OA of the knee.
- To evaluate the effect of naproxcinod (both doses), placebo, and naproxen on blood pressure.
- To evaluate the general safety and tolerability of naproxcinod.

In **Study HCT-3012-X-302**
The following secondary objectives will be presented in a separate report (through Week 53):
- To assess if there were any radiological changes at Week 52 in naproxcinod compared with naproxen subjects (target joint radiographs were taken at Screening and after 52 weeks of treatment, or if early termination occurred after Week 26)
- To compare the general safety and tolerability of both doses of naproxcinod versus naproxen 500 mg bid up to 52 weeks and with one week posttreatment follow-up (Week 53)

Study HCT-3012-X-303
The primary objective of the study was to demonstrate that naproxcinod 750 mg bid was superior to placebo bid in relieving OA signs and symptoms in patients with OA of the hip.

The secondary objectives of this study were as follows:
- To evaluate the effect on BP of naproxcinod 750 mg *bid*, vs. placebo *bid*, and naproxen 500 mg *bid*, as measured by office blood pressure monitoring (OBPM) in patients with hip OA
- To evaluate the general safety and tolerability of naproxcinod 750 mg *bid*, vs. placebo *bid*, and naproxen 500 mg *bid*

- **Outcomes/endpoints**

Primary endpoints
The three co-primary efficacy assessments were the WOMAC™ subscale scores for pain and physical function and the patients' overall rating of disease status using the ITT and PP populations. The pain and physical function subscale scores utilised VAS evaluations, whereas the patients' overall rating of disease status used a Likert Scale. These assessments were available in each patient's local language.

Key Secondary endpoints
- Non-inferiority of naproxcinod 750 mg bid and naproxcinod 375 mg bid compared with naproxen 500 mg bid for the same parameters as primary endpoints for study **HCT-3012-X-301** and Non-inferiority of naproxcinod 750 mg bid compared with naproxen 500 mg bid for the mean change from Baseline in WOMAC™ pain subscale score at Week 13 and Week 26 and the mean change from Baseline in WOMAC™ physical function subscale score at Week 13 and Week 26 for study **HCT-3012-X-302**

- Modified OARSI responder rate

- Cumulative rate of discontinuation due to lack of efficacy/worsening of disease using the ITT population.

In addition to those listed above, secondary endpoints included the WOMAC™ composite pain, stiffness, and function subscale scores, VAS pain intensity at rest and during walking, investigators' overall rating of disease status, patients' and investigators' overall rating of the treatment, patients' and investigators' overall rating of response to therapy, the eight domains and two summary scores (mental and physical component scores) of the SF-36 and amount of rescue medication used.

The WOMAC™ questionnaire has been validated as an appropriate assessment of efficacy for drugs designed to improve the symptoms of OA (Bellamy, 1988). The choice of secondary endpoints is in line with the EMA guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97 Rev. 1).

- **Statistical methods**

Planned analyses were pre-specified in the Sponsor's statistical analysis plans (SAP) for each of the studies. The primary analysis in each study was not modified and the study designs and statistical plans did not change from that planned in the original study protocols. However, additional analyses were conducted as described below; these additional analyses were necessary due to the removal of the data on patients recruited at Site 061/069 and Site 114 from the efficacy analyses.

In the Phase 3 studies, the analysis of each primary efficacy endpoint was based on an analysis of covariance (ANCOVA) model with treatment group and centre as factors and baseline value (WOMAC™ pain subscale score, WOMAC™ physical function subscale score, and patients' overall rating of disease status, respectively) as a covariate. The model included all treatment groups with pair-wise treatment comparison p-values calculated by linear contrasts in the model. For each analysis, a two-sided test with a p-value less than or equal to 0.05 was considered statistically significant. If more than 50% of the patients had come from "small" centres (centres with fewer than three patients in at least one treatment group) then the centre was to be removed from the ANCOVA model.
In Study HCT 3012-X-301, for the primary ITT analyses, missing values in the efficacy variables were imputed using the method of last observation carried forward (LOCF) from the previous visit (scheduled or unscheduled visit). Baseline values were not carried forward if they were the last data observed as described. In the other two Phase 3 studies (HCT 3012-X-302 and HCT 3012-X-303), missing post-baseline values used in the primary efficacy analyses were based on a more conservative modified LOCF (mLOCF) imputation. The mLOCF utilised the imputation of missing values as follows:

- Missing data due to treatment-related AE drop out or an AE that resulted in permanent discontinuation of study medication were replaced by the worst observation carried forward (WOCF): for each patient dropping out due to a treatment-related AE, the worst observation from scheduled or unscheduled visits was used to replace the missing values. Baseline values were used if they were the worst data observed
- Missing data due to any reason other than a treatment-related AE drop out or an AE which resulted in permanent discontinuation of study medication were imputed using LOCF from previous visit (scheduled or unscheduled visits). Baseline values were carried forward if they were the last data observed

This same mLOCF method was used as an additional sensitivity analysis in Study HCT 3012-X-301, after database lock, following recommendations from the FDA, and was used for the pooled analyses presented in this clinical overview. This sensitivity analysis using the mLOCF method was not considered to have had any effect on the validity of Study HCT 3012-X-301 and confirmed the robustness of the data.
Study HCT 3012-X-301 was powered to reach statistical significance for the comparisons of naproxcinod versus placebo (superiority comparison) and for the comparisons of naproxcinod versus naproxen (non-inferiority comparison) at 13 weeks, in the two WOMAC™ variables and in patients' overall rating of disease status. The sample size calculation was driven by the non-inferiority comparisons, which required a greater number of subjects than the superiority versus placebo analysis. However, Studies HCT 3012-X-302 and HCT 3012-X-303 were powered to reach statistical significance for the superiority comparison for each of the active treatment versus placebo (overall) at 13 weeks in the three co-primary endpoints.

The a priori choice of the non-inferiority margin used in these studies is detailed below.

Due to the exclusion of data from patients at Site 061/069 (see Section 2.5.4.1.1), (failure to comply with GCP) the efficacy analyses of Studies HCT 3012-X-301 and HCT 3012-X-302 were repeated after sign-off of the reports. The re-analysis of the primary and key secondary efficacy data excluded the data on 36 patients from the ITT and PP populations. The analyses excluding Site 061/069 did not change the overall interpretation of the efficacy results of the studies. The only notable change that

occurred when data from Site 061/069 were excluded from Study HCT 3012-X-301 was that the naproxcinod 375 mg bid dose was no longer non-inferior to naproxen 500 mg bid at Week 13 for the WOMACTM pain subscale score. The only notable change when data from Site 061/069 were excluded from the analysis of Study HCT 3012-X-302 was that naproxcinod 750 mg bid was no longer statistically significantly different from placebo (overall) at Week 13 for the cumulative rate of discontinuations due to lack of efficacy/worsening of the disease (p=0.0544 without Site 061/069 included; p=0.0287 with Site 061/069 included).

In addition, in Study HCT 3012-X-302, the main safety and efficacy analyses that support registration were conducted excluding Site 114, at which the entry criteria for several patients had been violated (HCT 3012-X-302, Section 9.6.4: the patients that were enrolled were site staff or people associated with the site staff). One patient from Site 105 and one patient from Site 126 were also excluded from the main efficacy analyses, because it was the same patient enrolled separately at the two sites. All analyses were replicated (including data from Site 114 and the two patients) and were regarded as sensitivity analyses after all planned analyses were completed and reported in the CSR. No statistically different outcomes were evident in the sensitivity analysis. No adverse effects on the Type I error rate were observed between the analysis supporting registration and the sensitivity analysis due to the small number of patients excluded from the main analysis.
In Study HCT 3012-X-303, additional analyses, not planned prior to unblinding, were performed to investigate statistically significant treatment by centre interactions. These investigations confirmed the validity of the results for the treatment comparisons observed in the original analyses (HCT 3012-X-303, Appendix 16.1.9).

Studies 301 and 302 were conducted in the US only. In these two studies, over 50% of the patients came from small centers; therefore, the factor center was removed from the model.
In Study 303, less than 50% of the patients came from small centers, therefore the factor center was kept in the model. This is acceptable.

The imputation of missing data is crucial in the comparison to an active control when assessing noninferiority. The sponsor should provide additional sensitivity analyses where missing data are imputed using multiple imputation techniques. In cases where a LOCF analysis is conservative for superiority testing to placebo by diminishing the treatment effect, it is anti-conservative in noninferiority testing since an effect in favor of the control may be hidden. The proposed modified LOCF (mLOCF) appears even more conservative with respect to the placebo comparison, and, consequently, more anti-conservative for non-inferiority testing. Therefore, the noninferiority test must always consider both, the ITT as well as the PP population.
The following sensitivity analyses were performed on the three primary efficacy endpoints for the intent-to-treat (ITT) population in each of Studies HCT 3012-X-301, -302, and -303 and presented in the answer to the Day 120 LoQ:
1) Imputation of missing data using Baseline Observation Carried Forward (BOCF):
2) Imputation of missing data using Multiple Imputation (MI) techniques:
3) Analysis of changes from baseline across visits using Mixed-Effect Model Repeated Measures (MMRM):
The results of the BOCF analysis differ from those obtained in the FDA assessment. According to the FDA assessment the upper CI limits of the treatment difference between Naproxcinod 750 mg and Naproxen on WOMAC pain and function were 9 mm for the ITT population (instead of 8 mm in the presented analysis), with mean values of 4 mm (instead of 3 mm in the presented analysis).
The other sensitivity analyses are based on the missing at random assumption and do not accounts for a potential missingness process not at random. Therefore at least the MMRM model appears overoptimistic.
Due to the difference in the BOCF analysis to the FDA assessment the presented results appear questionable. Further sensitivity analyses not based on missing at random assumption are required (see LoOI).

In addition, a sensitivity analysis with imputation techniques that borrow information from other subjects including the corresponding variability as multiple imputation techniques do should be conducted.

Considerations related to Non-inferiority as a Secondary Objective

The non-inferiority of naproxcinod versus naproxen was evaluated in:

- Study HCT 3012-X-301 for the three co-primary endpoints for both naproxcinod 750 mg bid and 375 mg bid and for both intent-to-treat (ITT) and per-protocol (PP) populations
- Study HCT 3012-X-302 for WOMAC™ pain and physical function subscale scores for naproxcinod 750 mg bid, representing the dose regimen equimolar to naproxen 500 mg bid, only, for both the ITT and PP populations and for the mean change from baseline to Week 13 and to Week 26

The upper limit of the 95% CI of the difference between naproxcinod and naproxen in the mean change from Baseline was compared with a specific margin that was defined a priori. Non-inferiority of naproxcinod compared with naproxen was considered to be demonstrated if the upper limit of the 95% CI fell below 8 mm for the WOMAC™ pain and physical function scores and if the lower limit of the 95% CI fell above -0.4 for patients' overall rating of disease status.

According to the applicant, the non-inferiority margin of 8 mm on the WOMAC™ VAS pain and physical function subscale scores is thought to be supported by the literature (Ehrich, 2000) which demonstrated that the minimal clinically relevant difference that the WOMAC™ score could detect was 9.3 mm for the pain sub-scale and 9.7 mm for the physical function subscale. Hence, an 8 mm difference was not considered to be clinically relevant when using the WOMAC™ pain and physical function subscale scores. In addition the superiority of naproxen 500 mg bid over placebo was shown to be of the order of 9 to12 mm in the Phase 2 studies SP-NON-0005 and SP-NON-0010. Therefore, in the applicant´s opinion a non-inferiority margin of 8 mm for both WOMAC™ pain and physical function subscale scores would appear to be appropriate in assessing the non-inferiority of naproxcinod to naproxen.

A non-inferiority margin of -0.4 grades was chosen for the patients' overall rating of disease status as has been reported to be the minimum perceptible clinical improvement detectable for the 5-point Likert scale when used for the investigator's global assessment of disease status (Ehrich, 2000). This difference was therefore interpreted to be the maximum difference in response that still allows it to be concluded that naproxcinod is not worse than naproxen.

As indicated above, studies HCT 3012-X-302 and HCT 3012-X-303 were powered to reach statistical significance for the superiority comparison for each of the active treatment versus placebo (overall) at 13 weeks in the three co-primary endpoints. Therefore non-inferiority analysis in study HCT 3012-X-302 is only explorative.

The non-inferiority margin of 8 mm is not considered adequate. Compared with a difference of the comparator to placebo of 12 mm, this would mean that only 33 % of the difference to placebo is maintained.

Even with a non-inferiority margin of 8 mm, the non-inferiority assessment failed in study 301, for both the PP analysis as well as the BOCF analysis. Furthermore the results of the BOCF analysis differ from those obtained in the FDA assessment. According to the FDA assessment the upper CI limits of the treatment difference between naproxcinod 750 mg *bid* and naproxen 500 mg *bid* on WOMAC pain and function were 9 mm for the ITT population.

Applying a more reasonable margin of 4 mm, all analyses both in the PP as well as the ITT population failed to show non-inferiority in both endpoints in Study 301.

The large differences between study 301 and 302 in the non-inferiority assessment suggest an important between study variability with respect to the Naproxinod-Naproxen comparison. No repeated evidence is given for the non-inferiority to Naproxen. Furthermore, due to the large between-study differences the transferability of the study results is disputable.

- **Results**

Study HCT-3012-X-301

Primary endpoints:

WOMAC™ Pain, WOMAC™ Physical Function and Patients' Overall Rating of Disease Status

Both naproxcinod 750 mg *bid* and 375 mg *bid* were statistically significantly superior to placebo for the three co-primary efficacy endpoints in the ITT population (LOCF analysis).

Although statistically significant, results should also be clinically relevant. The MPCI is usually considered to be 9.7 for pain. This was not reached for the 375 mg bid dose. These results are endorsed by the ITT (mLOCF) analysis where the results for the comparison versus placebo were -10.67, -9.49, -12.77 for naproxcinod 750 mg bid, naproxcinod 375 mg bid and naproxen 500 mg bid respectively as well as by the PP analysis (excluding Marker site) where the results for the comparison versus placebo were -12,95, -9.62 and -14.98 for naproxcinod 750 mg bid, naproxcinod 375 mg bid and naproxen 500 mg bid, respectively.

Comparison of the Active Treatments versus Placebo for the Three Co-Primary Endpoint Study HCT 3012-X-301—ITT Population, LOCF Analysis

	Naproxcinod 750 mg *bid* (N = 224)	**Naproxcinod 375 mg *bid* (N = 234)**	**Naproxen 500 mg *bid* (N = 220)**
Change from Baseline at Week 13 in WOMAC™ Pain Subscale Score (mm)			
n	214	229	218
Difference in LS mean (SEM)[a]	-11.26 (2.545)	-8.75 (2.504)	-12.03 (2.533)
95% CI for difference in LS mean	(-16.26, -6.27)	(-13.66, -3.84)	(-17.00, -7.06)
p-value for treatment effect [b]	<0.0001	0.0005	<0.0001
Change from Baseline at Week 13 in WOMAC™ Physical Function Subscale Score (mm)			
n	213	228	218
Difference in LS mean (SEM)[a]	-11.56 (2.546)	-8.38 (2.506)	-13.41 (2.531)
95% CI for difference in LS mean	(-16.56, -6.57)	(-13.30, -3.46)	(-18.38, -8.44)
p-value for treatment effect [b]	<0.0001	0.0009	<0.0001
Change from Baseline at Week 13 in Patients' Overall Rating of Disease Status			
n	214	229	217
Difference in LS mean (SEM)[a]	0.54 (0.101)	0.42 (0.100)	0.66 (0.101)
95% CI for difference in LS mean	(0.34, 0.74)	(0.23, 0.62)	(0.46, 0.86)
p-value for treatment effect [b]	<0.0001	<0.0001	<0.0001

Of note, the maximum effect on pain, function and patients´overall rating of disease status was seen at week 6 for all dose regimens.

Since it is well known that clinical effects from pharmacological interventions in knee OA are small and have the most pronounced effect short-term (Bjordal et al, 2006) this is not surprising. At week 6 for the ITT (mLOCF) and PP population the difference versus placebo was also for Naproxcinod 375 mg bid not only statistically but also clinically relevant for the primary endpoints WOMAC™ Pain and Function and Patient´s overall rating of disease status. Therefore, in principal the efficacy versus placebo for both dose regimens of naproxcinod seems to be proven, however, the naproxcinod 375 mg bid dose performed worse in comparison to the 750 mg bid dose and no comparison to the equivalent dose of naproxen is available.
Since pharmacokinetic data may be indicative of higher plasma exposure in patients with low body weight (see Sections II.1.5 and II.1.8), the applicant should present a subgroup-analysis according to

weight and gender to estimate their influence on clinical efficacy. This might be helpful to understand the impacts on dosing recommendations.

Results of Key Secondary Endpoints

In the ITT population using the LOCF imputation method, naproxcinod 750 mg bid was statistically non-inferior to naproxen 500 mg bid for each of the three endpoints assessed. However, in the PP population, naproxcinod 750 mg bid was statistically non-inferior to naproxen 500 mg bid for the mean change from baseline at Week 13 in the WOMAC™ pain subscale score and the patient's overall rating of disease status but not in the WOMAC™ physical function subscale score.

For the mean change from Baseline at Week 13, the difference in LS mean +/- SEM for the comparison of naproxcinod 750 mg bid versus naproxen 500 mg bid was as follows for each of the co-primary endpoints.

For WOMAC™ pain subscale score:

- 0.77 +/- 2.520 mm (95% CI [-4.18, 5.71]) in the ITT population
- 1.94 +/- 2.802 mm (95% CI [-3.56, 7.45]) in the PP

For WOMAC™ physical function subscale score:

- 1.85 +/- 2.518 mm (95% CI [-3.10, 6.79]) in the ITT population
- 2.75 +/- 2.903 mm (95% CI [-2.95, 8.45]) in the PP population

For patients' overall rating of disease status:

- -0.12 +/- 0.100 (95% CI [-0.31, 0.08]) in the ITT population
- -0.11 +/- 0.107 (95% CI [-0.32, 0.10]) in the PP population

In the ITT population using the LOCF analysis, naproxcinod 375 mg bid was not statistically non-inferior to naproxen 500 mg bid for any of the endpoints. In the PP population, naproxcinod 375 mg bid was statistically non-inferior to naproxen 500 mg bid for the mean change from baseline at Week 13 in the patient's overall rating of disease status but not the other two endpoints.

For the mean change from Baseline at Week 13, the difference in LS mean +/- SEM for the comparison of naproxcinod 375 mg bid versus naproxen 500 mg bid was as follows for each of the co-primary endpoints.

For WOMAC™ pain subscale score:

- 3.28 +/- 2.478 mm (95% CI [-1.59, 8.14]) for the ITT population
- 3.38 +/- 2.736 mm (95% CI [-1.99, 8.75]) for the PP population

For WOMAC™ physical function subscale score:

- 5.03 +/- 2.477 mm (95% CI [0.16, 9.89]) for the ITT population
- 5.80 +/- 2.833 mm (95% CI [0.23, 11.36]) for the PP population

For patients' overall rating of disease status:

- -0.23 +/- 0.099 (95% CI [-0.43, -0.04]) for the ITT population
- -0.18 +/- 0.104 (95% CI [-0.38, 0.03]) for the PP population

With respect to the chosen non-inferiority of 8 mm the non-inferiority of naproxcinod 750 mg *bid* to naproxen 500 mg *bid* was demonstrated for the mean change from Baseline in WOMAC™ pain subscale and WOMAC™function subscale score at Week 13 for both the ITT and PP population but not for function in the PP population (ie, upper limit of 95% CI was above non-inferiority margin of 8 mm).

Since the ITT analysis, in general as well as in this study, tends to shrink the effect size, a non inferiority test can never be based on the ITT population only. Therefore the analysis on the PP population must be considered. Furthermore, the rationale for the non-inferiority margin is not acceptable and was already questioned in the previous scientific advice meetings. A lower margin of ideally 4 mm should have been chosen. Using this margin none of the analysis demonstrated non-inferiority to Naproxen.

Secondary Efficacy Endpoints

For the key secondary endpoints of the **modified OARSI responder rates** at the end of treatment (Week 13) and **the rate of discontinuation due to lack of efficacy/worsening of the disease** through Week 13, both naproxcinod dose groups were significantly better than the placebo group. For

these two endpoints, there were no statistically significant differences between the naproxen group and either naproxcinod group.
However, overall, the naproxcinod 375 mg bid performed worse in comparison to placebo than the 750 mg bid dose and was inferior to the active comparator.

Study HCT-3012-X-302:
Primary endpoints:
WOMAC™ Pain, WOMAC™ Physical Function and Patients' Overall Rating of Disease Status
Both naproxcinod 750 mg bid and 375 mg bid were statistically significantly superior to placebo for the three co-primary efficacy endpoints.

Comparison of the Active Treatments versus Placebo for the Three Co-Primary Endpoints in 13-Week Double-Blind Portion of Study HCT 3012-X-302—ITT Population, mLOCF Analysis

	Naproxcinod 750 mg *bid* (N = 242)	**Naproxcinod 375 mg *bid* (N = 247)**	**Naproxen 500 mg *bid* (N = 254)**
Change from Baseline at Week 13 in WOMAC™ Pain Subscale Score (mm)			
n	241	247	254
Difference in LS mean (SEM)[a]	-10.9 (2.32)	-7.7 (2.31)	-9.2 (2.29)
95% CI for difference in LS mean	(-15.5, -6.4)	(-12.2, -3.2)	(-13.7, -4.7)
p-value for treatment effect[b]	<0.0001	0.0008	<0.0001
Change from Baseline at Week 13 in WOMAC™ Physical Function Subscale Score (mm)			
n	242	247	252
Difference in LS mean (SEM)[a]	-12.8 (2.23)	-8.8 (2.22)	-11.2 (2.21)
95% CI for difference in LS mean	(-17.2, -8.5)	(-13.2, -4.5)	(-15.6, -6.9)
p-value for treatment effect [b]	<0.0001	<0.0001	<0.0001
Change from Baseline at Week 13 in Patients' Overall Rating of Disease Status			
n	241	245	254
Difference in LS mean (SEM)[a]	0.51 (0.085)	0.32 (0.084)	0.46 (0.084)
95% CI for difference in LS mean	(0.34, 0.68)	(0.16, 0.49)	(0.29, 0.62)
p-value for treatment effect [b]	<0.0001	0.0001	<0.0001

The difference versus placebo for naproxcinod 375 mg bid was not clinically relevant in the overall ITT population and similarly in the PP-population (WOMAC™ Pain: -7.2 (-12.6, -1.7), WOMAC™ Physical Function: -8.5 (-13.8,-3.1), subject´s overall rating of disease status 0.32 (0.15, 0.47)). The applicant should present a subgroup-analysis according to weight and gender to estimate their influence on clinical efficacy (see above). Of note, the effect of the 375 mg bid dose was also not clinically relevant at week 6 for the parameters pain and patients´overall rating of disease status.

No per protocol assessments are provided for weeks 2 and 6.

Results of Key Secondary Endpoints at 13 Weeks

Analysis of the key secondary endpoints showed that naproxcinod 750 mg bid was statistically non-inferior to naproxen 500 mg bid for the two endpoints assessed (ie, mean change from baseline at Week 13 in WOMAC™ pain subscale score and WOMAC™ physical function subscale score) for both the ITT and PP populations.
For the mean change from Baseline at Week 13, the difference in LS mean +/- SEM for the comparison of naproxcinod 750 mg bid versus naproxen 500 mg bid was as follows for each of the co-primary endpoints.
For WOMAC™ pain subscale score:

- -1.8 +/- 2.33 mm (95% CI [-6.4, 2.8]) in the ITT population
- -3.6 +/- 2.78 mm (95% CI [-9.1, 1.8]) in the PP population

For WOMAC™ physical function subscale score:

- -1.6 +/- 2.24 mm (95% CI [-6.0, 2.8]) in the ITT population
- -2.3 +/- 2.71 mm (95% CI [-7.6, 3.0]) in the PP population

With respect to the chosen non-inferiority of 8 mm the non-inferiority of naproxcinod 750 mg *bid* to naproxen 500 mg *bid* was demonstrated for the mean change from Baseline in WOMAC™ pain subscale and WOMAC™function subscale score at Week 13 for the ITT and PP population (ie, upper limit of 95% CI was below non-inferiority margin of 8 mm).
In this study, a lower non-inferiority margin of 4 mm would have been met, in both the ITT as well as the PP population.

Secondary Efficacy Endpoints
For the key secondary endpoint of the modified OARSI responder rate at the end of treatment (Week 13), the active treatment groups were significantly higher than the placebo group. For the rate of discontinuation due to lack of efficacy/worsening of the disease through Week 13, the active treatment groups demonstrated a lower rate of discontinuation due to lack of efficacy/worsening of the disease than the placebo group, but the differences were not statistically significant (p = 0.0544 for naproxcinod 750 mg bid, p = 0.4506 for naproxcinod 375 mg bid, and p = 0.2748 for naproxen 500 mg bid) for the ITT population.
The results of the key secondary endpoint discontinuation due to lack of efficacy/worsening of the disease are not consistent with the result of the primary endpoint.

Results of Key Secondary Endpoints at 26 Weeks
The decrease (improvement) seen in the mean WOMAC™ pain subscale score from Baseline to Week 13 was maintained through Week 26 in all three active treatment groups in the ITT population. Both naproxcinod doses demonstrated a maximum response at Week 26, and the greatest improvement for the naproxen group was at Week 15. The LS mean +/- SEM change from Baseline (mLOCF) in WOMAC™ pain subscale score at Week 26 was -33.6 +/- 1.75 mm in the naproxcinod 750 mg bid group, -31.2 +/- 1.73 mm in the naproxcinod 375 mg bid group, and -30.8 +/- 1.71 mm in the naproxen 500 mg bid group.

The decrease (improvement) seen in the mean WOMAC™ physical function subscale score from Baseline to Week 13 was maintained through Week 26 in all three active treatment groups in the ITT population. The LS mean +/- SEM change from Baseline (mLOCF) in WOMAC™ physical function subscale score at Week 26 was -29.7 +/- 1.69 mm in the naproxcinod 750 mg bid group, -27.6 +/- 1.69 mm in the naproxcinod 375 mg bid group, and -27.4 +/- 1.65 mm in the naproxen 500 mg bid group.

The increase (improvement) seen in the mean patients' overall rating of disease status from Baseline to Week 13 was maintained through Week 26 in all three active treatment groups in the ITT population. The LS mean +/- SEM change from Baseline (mLOCF) in the patients' overall rating of disease status at Week 26 was 1.02 +/- 0.062 in the naproxcinod 750 mg bid group, 0.89 +/- 0.061in the naproxcinod 375 mg bid group, and 0.88 +/- 0.060 in the naproxen 500 mg bid group.

The modified OARSI responder rates seen at Week 13 were maintained though Week 26 in the three treatment groups, and the cumulative rates of discontinuation due to lack of efficacy/worsening of

disease through Week 26 were similar in the three treatment groups (6.2% in the naproxcinod 750 mg bid group, 10.5% in the naproxcinod 375 mg bid group, and 7.9% in the naproxen 500 mg bid group). The latter finding is consistent with a lower efficacy for the 375 mg bid dose.

Study HCT-3012-X-303
Primary endpoints: WOMAC™ Pain, WOMAC™ Physical Function and Patients' Overall Rating of Disease Status

Naproxcinod 750 mg *bid* was statistically significantly superior to placebo for the three co-primary efficacy endpoints.

Comparison of the Active Treatments versus Placebo for the Three Co-Primary Endpoints in Study HCT 3012-X-303—ITT Population, mLOCF Analysis

	Naproxcinod 750 mg *bid* (N=323)	**Naproxen 500 mg *bid* (N=156)**
Change from Baseline at Week 13 in WOMAC™ Pain Subscale Score (mm)		
n	323	156
Difference in LS mean (SEM)[a]	-7.84 (1.923)	-6.34 (2.392)
95% CI for difference in LS mean	(-11.61, -4.06)	(-11.04, -1.65)
p-value for treatment effect [b]	< 0.0001	-
Change from Baseline at Week 13 in WOMAC™ Physical Function Subscale Score (mm)		
n	322	155
Difference in LS mean (SEM)[a]	-8.79 (1.871)	-8.22 (2.323)
95% CI for difference in LS mean	(-12.46, -5.11)	(-12.78, -3.66)
p-value for treatment effect [b]	< 0.0001	-
Change from Baseline at Week 13 in Patients' Overall Rating of Disease Status		
n	320	153
Difference in LS mean (SEM)[a]	0.35 (0.075)	0.32 (0.094)
95% CI for difference in LS mean	(0.20, 0.50)	(0.13, 0.50)
p-value for treatment effect [b]	< 0.0001	-

The analysis of the PP population confirmed the results observed in the ITT population, showing that naproxcinod 750 mg bid was statistically significantly superior to placebo for these co-primary endpoints (p = 0.0069, pain subscale score; p = 0.0039, function subscale score; p = 0.0004, patient's overall rating of disease status).

The difference versus placebo was not clinically relevant neither for naproxcinod nor for naproxen at week 13. In the PP analysis the difference was even smaller -6.61 for naproxcinod 750 mg bid and -2.46 for naproxen for WOMAC pain subscale.
However, the 6 week data for the mLOCF population are both statistically significant and nearly clinically relevant for Womac Pain (-9.81 for Naproxcinod 750 mg bid and -10.8 for Naproxen 500 mg bid) and Womac Function (-10.44 (-13.82,-7.07) for Naproxcinod 750 mg bid and -12.67 (-16.86,-8.49) for Naproxen 500 mg bid) which is reassuring taking into account that NSAIDs may have their

highest effect on efficacy early in the course of treatment (Bjordal et al 2006). No per protocol data are provided for earlier measurement time points. Although the OA guideline states that compounds having demonstrated efficacy either at the hip or at the knee level will be registered for "treatment of osteoarthritis of the knee and the hip" (CHMP/EWP/784/97 Rev.1) and although the difference in response being less in patients with OA of the hip has been noted before in other studies described in the literature (Svensson et al, 2006) and was consistently found for naproxen and naproxcinod in this study the clinical relevance of the results in hip OA has not been convincingly demonstrated.

To discuss the clinical relevance of the effect of naproxcinod 750 mg *bid* on hip OA, the Applicant chose to demonstrate the non inferiority of naproxcinod 750 mg *bid* with equivalent dose of naproxen performing *post hoc* analysis. For the Applicant, the demonstration of non inferiority to naproxen implies *de facto* that the efficacy of naproxcinod 750 mg *bid* in hip OA was clinically relevant. This point of view is not shared. The assay sensitivity was indeed questioned for the study 303 when comparing both naproxcinod and naproxen to placebo. The non inferiority margin for co-primary endpoints was greater than the magnitude of effect of naproxen in this study. In this particular study, magnitude of naproxen effect could be not clinically relevant, in light of the above mentioned deficiency.

The Applicant should discuss the magnitude of effect of naproxcinod 750 mg *bid* on hip OA for the three co-primary efficacy variables, in the light of pain perception and waited analgesic effect on hip OA (for example, the Applicant could discuss the results of study 303, expressed as a level of pain on VAS at week 13 compared with PASS scores as described in Tubach et al), (see LoOI).

Since the 750 mg bid dose has only low efficacy, dose recommendation for hip OA including the 375 mg bid dose as currently stated in the SPC can thus not be endorsed on the basis of these data.

Secondary Efficacy Endpoints
For the key secondary endpoints of the modified OARSI responder rates at the end of treatment (Week 13) and the rate of discontinuation due to lack of efficacy/worsening of the disease through Week 13, naproxcinod 750 mg bid was significantly better than placebo. Nearly twice as many patients discontinued due to lack of efficacy in the naproxcinod group compared to the naproxen group (6.2 vs 3.2 %).

Other secondary endpoints in Studies HCT 3012-X-301, -302 and -303
VAS pain intensity at rest and during walking, investigators' overall rating of disease status, patients' and investigators' overall rating of the treatment, patients' and investigators' overall rating of response to therapy, the eight domains and two summary scores (mental and physical component scores) of the SF-36®, amount of rescue medication used were additional secondary endpoints.

Here a comprehensive data analysis was not provided in the clinical summary or overview. The applicant should provide a comprehensive analysis to show whether the results of these endpoints were consistent with the findings of the primary endpoint. E.g for pain at rest naproxcinod at week 13 was no longer statistically significant versus placebo for the 375 mg bid dose (-6.21) and not clinically relevant for the 750 mg bid dose (-8.14). Similarly for pain at walking where the improvement in comparison to placebo was -7.30 for the 375 mg bid dose.

Persistence of Efficacy
The persistence of efficacy of naproxcinod is demonstrated in one Phase 3 study, HCT 3012-X-302. In this study, 751 patients were randomised in the naproxcinod 750 mg bid, naproxcinod 375 mg bid, and naproxen 500 mg bid groups. Of these 751 patients, 483 patients (64.3%) completed the 26-week period of the study. In this study, the improvement seen from Baseline to Week 13 in the mean WOMAC™ pain and physical function subscale scores, and patients' overall rating of disease status was maintained through Week 26 for both naproxcinod doses and the naproxen group.

In addition, in Study HCT 3012-X-301E, an open-label extension to Study HCT 3012-X-301, improvements in patient assessments of disease status were maintained for up to 52 weeks.

Clinical studies in special populations

No specific efficacy studies were performed in any special patient populations. PK data in special populations are discussed in the pharmacokinetic section.

The results of the three co-primary endpoints were assessed for subpopulations of patients based on patient gender, race, age, and baseline WOMAC™ pain subscale score (based on the first question of the pain subscale of the WOMAC™ questionnaire) in the integrated Phase 3 OA studies.
The subgroup analysis for gender clearly shows that the difference versus placebo for WOMAC™ pain in female patients was 8.33 for naproxcinod 750 mg bid, 8.6 for for naproxcinod 375 mg bid and 8.54 for naproxen 500 mg bid in contrast to male patients where the difference was 13.16, 11.12 and 13.41 for naproxcinod 750 mg bid, naproxcinod 375 mg bid and naproxen 500 mg bid respectively. The lower difference *vs*. placebo in mean change from baseline in WOMAC™ pain at Week 13 in female patients compared to male patients occurred both in the naproxcinod and naproxen treatment groups. This lower "active *minus* placebo" difference can be explained by a higher placebo effect at Week 13 in females than in males (-22.83 mm and -18.71 mm respectively). The additional analyses presented by the applicant show that the effects vs. placebo in female patients in the naproxcinod groups appear to be similar to those observed in the naproxen treatment group; thus confirming the clinical relevance of naproxcinod effect in this subgroup of patients. Lower mean decreases in WOMAC™ pain were observed in female patients than in male patients in each active treatment group including naproxen.
The effect of baseline weight was similar in all treatment groups.
The analysis by age subgroups showed greater improvements in the WOMAC™ scores in the active treatment groups as compared to the placebo group for all three age categories (ie,, patients younger than 65 years, patients 65 years and over, and patients 75 years and over; this group is a sub-set of the ≥65 years of age group). Results for the naproxcinod 750 mg bid and naproxen 500 mg bid treatment groups were similar. In the naproxcinod 375 mg bid and placebo treatment groups treatment effects were smaller in patients aged ≥75 years compared with the other age groups. It is recommended, as for all other NSAIDs, for elderly patients to initiate the treatment at the lowest effective dose (375 mg bid). Since in the ≥ 75 years subgroup no difference versus placebo in the primary endpoints was found for the naproxcinod 375 mg bid dose regimen and justification for this recommendation with regard to efficacy cannot be accepted.
The race of the patient does not appear to have an effect on the efficacy of naproxcinod for the WOMAC™ assessments.
A greater treatment effect was seen for patients in the high pain category compared with those in the low pain category for each of the three co-primary endpoints across the treatment groups.

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

The efficacy data from the three Phase 3 studies were considered suitable for pooling because the studies had similar study designs, including similar efficacy measurements, and the patient populations were generally homogeneous with respect to demographic characteristics and baseline severity of OA.
Comparison versus placebo
Consistent positive results were seen for the three co-primary endpoints in the Phase 3 studies in patients with OA of the knee or hip. The choice of these endpoints reflects the recommendations in the EMEA guideline (CPMP/EWP/784/97). For the three co-primary endpoints in each of the studies, both naproxcinod doses were statistically significantly better than placebo and naproxcinod 750 mg bid provided similar results to naproxen 500 mg bid. The magnitude of changes in the three co-primary efficacy endpoints was greater in the studies of OA of the knee than in the study of OA of the hip (approximately 5 mm more on the WOMAC™ pain subscale). As depicted above for each study separately the efficacy of the 375mg bid dose was not uniformly proven and cannot be recommended for treatment of hip OA.

Non-inferiority analysis
For the pooled ITT population for patients with OA of the knee (pooled data from Studies HCT 3012-X-301 and HCT 3012-X-302), naproxcinod 750 mg bid was statistically non-inferior to naproxen 500 mg bid for the two endpoints: change from Baseline at Week 13 in the WOMAC™ pain and physical function subscale scores. For both these endpoints, the estimated upper limits of the 95%

CIs for difference in least squares (LS) means in the comparison of naproxcinod 750 mg bid and naproxen 500 mg bid were all < 4 mm, which is much lower than the pre-specified non-inferiority limit of 8 mm. These results were supported by those for the PP population at Week 13.
Results of the non-inferiority analysis of naproxcinod 750 mg bid versus naproxen 500 mg bid as a key secondary endpoint were consistent between the two studies that assessed this endpoint (HCT 3012-X-301 and HCT 3012-X-302) and the pooled analysis.
The conclusion with respect to non-inferiority to Naproxen based on the pooled analysis of studies 301 and 302 is not acceptable. Although an additive study effect is included in the analysis, a different treatment effect in both studies, i.e. an interaction between study and treatment cannot be excluded. Actually, the treatment effects appear to be different in both studies, especially in the PP population. Such an important difference in the effect size may question the generalization of the study results to the overall population. Furthermore, it is unclear whether the pooled analysis was pre-planned or whether it was a post-hoc analysis based on known results.
Additional justification was given in the answer to the Day 120 LoQ. The absence of a significant treatment-by-study interaction does not rule out the possibility of different treatment effects between study 301 and 302 since the studies were not powered for this hypothesis. In general, the absence of a significant difference cannot be used to conclude the absence on an effect. Although study differences might be due to chance, the descriptive analyses showed a difference of about 5 mm (depending on the type of analysis) between studies in the Naproxcinod-Naproxen difference. It is acknowledged that an interaction cannot formally be proven, however, in the light of an acceptable non-inferiority margin of 4 mm, this difference underlines the necessity of repeated evidence at outlined in the EMA Points to Consider on meta-analyses and one pivotal study which cannot be replaced by a pooled evaluation. Furthermore, as the applicant acknowledged, a post-hoc analysis is always problematic, since by knowing the data a number of different analyses can be considered and performed with only those that are successful being reported.
As a conclusion non-inferiority of Naproxcinod 750 mg bid cannot unequivocally be established.

Supportive study(ies)

Efficacy data were collected in two additional studies: **SP-NON-0005** and **HCT 3012-X-112**.
In the GI endoscopy safety Study SP-NON-0005, a flare design was used and efficacy data results similar to the one observed in the Phase 2 dose ranging studies were obtained. In the ABPM Phase 1 Study HCT 3012-X-112, efficacy data were collected but no flare design was applied making difficult any comparison of the data with the other efficacy studies. However, the same efficacy trends were observed.

Dental pain
Two studies (SP-NON-0003 and SP-NON-0018) examined the efficacy of naproxcinod in acute pain using the established dental pain model of pain following extraction of impacted mandibular wisdom teeth (lower eighth molars). These studies investigated the analgesic efficacy and safety of single oral doses of naproxcinod ranging from 375 mg to 2250 mg, compared to naproxen 500 mg, rofecoxib 50 mg and placebo in patients following the extraction of impacted mandibular third molars.
The results of the Phase 2 Study SP-NON-0003 showed that the 750 mg, 1500 mg and 2250 mg doses of naproxcinod were statistically significantly superior to placebo for each primary efficacy endpoint and that the time to onset of pain relief for naproxcinod 750 mg is comparable to naproxen 500 mg.
Again the 375 mg bid dose performed worse.

Discussion on clinical efficacy

Given the dual moiety nature of naproxcinod (naproxen and NO-donating moiety BDMN), the Clinical Development Programme has focused on investigating both the naproxen-derived efficacious effects of the drug on the signs and symptoms of OA and on its purported NO-derived beneficial effects on BP and GI safety.
As already depicted in the pharmacology section, it remains to be demonstrated that both therapeutic principles, naproxen and NO, are dosed in their appropriate therapeutic ranges. More justification is

needed why both compounds were not combined as single entities thus allowing titration of pharmacological effects of naproxen on one hand and the NO donator on the other hand.

According to the Guideline on clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis (CPMP/EWP/784/97) extrapolation of results obtained in the lower limb to the hand is not possible due to the pathophysiological and functional differences in OA of the knee or hip and OA of the hand. Therefore, since Naproxcinod is claimed to be a new active substance, the general claim for the relief of signs and symptoms of osteoarthritis was not accepted which is agreed by the applicant. The wording of the indication was changed to "for the relief of the signs and symptoms of osteoarthritis of the knee and the hip".

Two Phase 2 dose ranging studies (SP-NON-0010 and SP-NON-0017) explored the analgesic efficacy, safety and tolerability of naproxcinod doses, from 125 mg bid to 1125 mg bid, in patients with OA of the knee and the hip, compared with placebo, naproxen and rofecoxib during 6 weeks of treatment.
Based on the data of these studies the selection of 375 mg *bid* and 750 mg *bid* dose regimens of naproxcinod administered twice a day for the pivotal phase 3 studies seems to be reasonable. However the 375 mg dose was not investigated in hip OA.
Data were provided separately for the subgroups of hip OA and knee OA and confirmed that naproxcinod had a numerically lower efficacy improvement in hip OA than in knee OA. These data are comparable to naproxen. Similar findings are reported from literature.

Three double-blind placebo and active controlled pivotal Phase 3 studies investigated the efficacy of naproxcinod for the symptomatic relief of OA. Studies HCT 3012-X-301 and HCT 3012-X-302 included 963 naproxcinod patients out of 1929 randomised patients with OA of the knee. Study HCT 3012-X-303 included 323 patients treated with naproxcinod out of 810 randomised patients with OA of the hip.
In Studies HCT 3012-X-301 and HCT 3012-X-303, patients were treated for 13 weeks; in Study HCT 3012-X-302, patients were treated for 52 weeks, but only data from the placebo-controlled 13-week period and the naproxen-controlled 26-week period have been included in this efficacy summary.

The relevant efficacy of any agent should be viewed primarily as the placebo-corrected efficacy that matches, in the same study, a standard active control with proven clinical relevance (for naproxcinod, naproxen was chosen as the standard active control).
The improvements in the WOMAC™ scores seen in the three co-primary endpoints represent clinically meaningful changes for patients with knee OA and the magnitudes of the effects were comparable between naproxcinod 750 mg bid and naproxen 500mg bid. Placebo-adjusted reductions in the range of 9 to 12 mm on the WOMAC™ visual analogue scales for pain and function and an increase of 0.4 on the patients' global assessment of the disease status Likert scale are considered to represent clinically perceptible and relevant changes to patients with OA of the hip or knee (Ehrich, 2000).
In the Phase 3 studies in patients with OA of the knee, naproxcinod 750 mg bid demonstrated results in these ranges for the difference from placebo of the mean change from Baseline to Week 13 for all three co-primary endpoints in the ITT population. For the WOMAC™ pain subscale score, the difference from placebo in LS mean change from Baseline at Week 13 was -11.3 mm (95% CI: -16.26,-6.27) and 10.9 mm (95% CI: -15.5,-6.4) in Studies HCT 3012-X-301 and HCT 301-X-302, respectively, ($p < 0.0001$). For the WOMAC™ function subscale score, the difference from placebo in LS mean change from Baseline at Week 13 was -11.56 (95 % CI: -16.56,-6.57) and -12.8 (95% CI: -17.2,-8.5) in Studies HCT 3012-X-301 and HCT 301-X-302, respectively ($p < 0.0001$). For the change from baseline at week 13 in Patient´s Overall Rating of Disease Status the difference from placebo in LS mean change was 0.54 (95 % CI: 0.34, 0.74) and 0.51 (95 % CI: 0.34, 0.68) in Studies HCT 3012-X-301 and HCT 301-X-302, respectively ($p < 0.0001$).
However, the clinical relevance of the efficacy of naproxcinod has not been convincingly endorsed by the non-inferiority analysis. The chosen non-inferiority margin of 8 mm appears much too high in the light of the treatment effect of Naproxen as compared to placebo being 12 mm, and was already questioned in preceeding scientific advice meetings. A non-inferiority margin of 8 mm would mean that 2/3 of the treatment effect of Naproxen is lost. Even with a non-inferiority margin of 8 mm, the non-inferiority assessment failed in study 301, for both the PP analysis as well as the BOCF analysis. Furthermore the results of the BOCF analysis differ from those obtained in the FDA assessment.

According to the FDA assessment the upper CI limits of the treatment difference between naproxcinod 750 mg and naproxen on WOMAC pain and function were 9 mm for the ITT population.
Applying a more reasonable margin of 4 mm, all analyses both in the PP as well as the ITT population failed to show non-inferiority in both endpoints.
The large differences between study 301 and 302 in the non-inferiority assessment suggest an important between study variability with respect to the Naproxinod-Naproxen comparison. No repeated evidence is given for the non-inferiority to Naproxen. Furthermore, due to the large between-study differences the transferability of the study results is disputable.

In addition, the 375 mg bid dose cannot be endorsed. For the naproxcinod 375 mg bid dose, with the exception of the endpoint Patient´s Overall Rating of Disease Status in Study HCT 3012-X-301, although statistically significant ($p < 0.0001$) no clinically relevant results were found for the primary endpoints (WOMAC™ pain: -8.75/-7.7 (95 % CI: -13.66,-3.84)/ (95 % CI: -12.2, -3.2), WOMAC™ function -8.38/- 8.8 (95 % CI: -13.30,-3.46)/ (95 % CI: -13.2, -4.5), Patient´s Overall Rating of Disease Status 0.42/0.32(95 % CI: 0.23, 0.62)/ (95 % CI: 0.16, 0.49)). Overall, the data on efficacy are too sparse to provide information on lower dose of naproxcinod in comparison to the equivalent dose of naproxen.
As the studies were not powered to non inferiority, the conclusion of the applicant that similar efficacy was similar after 3 weeks of treatment as well as 13 weeks is somewhat excessive.
Provided results can only be considered as a suggestion of comparable efficacy and need to be confirmed in appropriate clinical trials, which compare in a head to head design naproxcinod 375 mg bid and equivalent dose of naproxen (250 mg bid). Non-inferiority of the lower dose of naproxcinod to equivalent dose of naproxen for all three co-primary endpoints was not demonstrated.

For patients with hip OA the lower dosage 375mg bid was not evaluated. Furthermore, efficacy data versus placebo for the 750 mg bid dose in this subindication in Study HCT 3012-X-303 (WOMAC™ pain: -7.84 (95% CI: -11.61, -4.06), WOMAC™ function -8.79 (95 % CI: -12.46, -5.11), Patient´s Overall Rating of Disease Status 0.35 (95 % CI:0.20, 0.50)) were not convincing. Although the difference in response being less in patients with OA of the hip has been noted before in other studies described in the literature (Svensson et al, 2006) and was consistently found for naproxen and naproxcinod in this study the clinical relevance of the results in hip OA has not been convincingly demonstrated. The Applicant should discuss the magnitude of effect of naproxcinod 750 mg *bid* on hip OA for the three co-primary efficacy variables, in the light of pain perception and waited analgesic effect on hip OA.
Since the 750 mg bid dose has only low efficacy, dose recommendation for hip OA including the 375 mg bid dose as currently stated in the SPC can thus not be endorsed on the basis of these data.

Conclusions on clinical efficacy

There is some evidence for efficacy for the relief of signs of symptoms of osteoarthritis of the knee or hip, however efficacy data are not very impressive in comparison to naproxen to counterbalance the safety concerns since

- non-inferiority versus naproxen has not unequivocally been shown
- the clinical relevance of the magnitude of effect of naproxcinod 750 mg bid in hip OA has not convincingly been demonstrated
- the 375 mg bid dose was not investigated for hip OA
- the justification for the 375 mg bid dose as the lowest effective dose is not based on head to head comparisons in randomised clinical trials to equivalent doses of naproxen. Non- inferiority of the lower dose naproxcinod to naproxen for all three co-primary endpoints was not demonstrated.

Clinical safety

Patient exposure

Among the 4018 subjects and patients treated with at least one dose of naproxcinod, a total of 1339 were treated with naproxcinod for at least 13 weeks, 674 were treated for at least 26 weeks, and 288 were treated for at least 52 weeks. Of the 1339 subjects and patients treated with naproxcinod for at least 13 weeks, a total of 583 were treated with 750 mg per day (all 375 mg bid) and 756 were treated with 1500 mg per day (all naproxcinod 750 mg bid).

Extent of Exposure for Naproxcinod (by Total Daily Dose) and Comparators– All Completed Clinical Studies (Groups 1- 4)

Total Daily Naproxcinod Dose, and Comparators n (%)[a]	Duration of Treatment (Weeks)[b]							
	Any Duration	≥1 Week	≥6 Weeks	≥13 Weeks	≥26 Weeks	≥39 Weeks	≥52 Weeks	≥65 Weeks
All Naproxcinod (N=4018)[c]	4018 (100.0)	3316 (82.5)	2528 (62.9)	1339 (33.3)	674 (16.8)	353 (8.8)	288 (7.2)	128 (3.2)
750mg per day (N=1338)	1338 (100.0)	1088 (81.3)	861 (64.3)	583 (43.6)	345 (25.8)	177 (13.2)	144 (10.8)	70 (5.2)
1500mg per day (N=2220)	2220 (100.0)	2056 (92.6)	1438 (64.8)	756 (34.1)	329 (14.8)	176 (7.9)	144 (6.5)	58 (2.6)
High dose (> 1500mg per day) (N= 306)	306 (100.0)	196 (64.1)	92 (30.1)	0	0	0	0	0
Placebo (N=1410)	1410 (100.0)	1167 (82.8)	872 (61.8)	482 (34.2)	0	0	0	0
Naproxen (N=1633)	1633 (100.0)	1523 (93.3)	1141 (69.9)	514 (31.5)	139 (8.5)	0	0	0

Note: All 34 studies are included (Study Groups 1 to 4); data for Study HCT 3012-X-302 are up to 26 weeks only. The current submission included data for Study HCT 3012-X-302 up to 26 weeks only. Available data from Weeks >26-52 will be integrated into Group 1.0 in the 120-day Safety Update.

[a] Percentages are based on the number of patients in each treatment group as applicable. Due to the inclusion of crossover studies subjects may appear more than once across treatment groups.

[b] Duration of therapy (days) = (Date of Last Dose of Study Drug in the study period of interest) - (Date of First Dose of Study Drug) + 1. For single-dose studies, each single dose is counted as one day. Duration of therapy (weeks) = duration in days divided by 7. For those studies with a placebo run-in and/or washout period (HCT 3012-X-104, HCT 3012-X-111 and HCT 3012-X-112), these periods are not included in the placebo group N or calculation of duration of therapy.

[c] For several 'Duration of Treatment' columns, the total in the 'All Naproxcinod' row is less than the sum of the corresponding four daily naproxcinod dose groups as the study design of some studies allowed for patients to be treated with more than one naproxcinod daily dose regimen.

Overall patient exposure is in accordance with the safety recommendations of the OA Guideline and is therefore considered adequate.

Adverse events

In total no apparent difference is seen in the comparison of the overall AEs between naproxcinod and naproxen in the OA population. The study group 1.1 is considered the most important group of data because therapeutical dose and the target patient group are assessed. However, analyses in detail indicate an increased risk of getting GI ulcer, hepatic related AEs and hypo-hypertension related AEs. There are possible changes in the risk profile over time identified with respect to specific AEs (hepatic, hypertension).

In detail:

GI safety

PUBs

The applicant presented the GI safety data as requested separately for GI AEs (GI discomfort) and PUBs. The most important question was whether naproxcinod has an advantage with regard to PUBs as these are the most clinically relevant events associated with GI toxicity. The currently presented data analysis shows for the treatment duration of 3 month which is considered a clinically most relevant time frame for OA the following results:

PUBs All Placebo-Controlled OA Studies Up to 13 Weeks:

	Placebo **n = 780**	**Naproxcinod 375 mg bid** **n = 470**	**Naproxcinod 750 mg bid** **n = 1137**	**Naproxen 500 mg bid** **n = 907**
Any PUB, n (%) **[Events per 100 patient years]** Per Protocol Population	0	2 (0.425%) [2]	4 (0.352%) [2]	4 (0.441%) [2]
	Placebo **n = 1116**	**Naproxcinod 375 mg bid** **n = 601**	**Naproxcinod 750 mg bid** **n = 1472**	**Naproxen 500 mg bid** **n = 1175**
Any PUBs, n (%) **[Events per 100 patient years]** Total safety population	1 (< 0.089%) [<1]	7 (1.165%) [7]	11 (0.747%) [5]	10 (0,851%) [6]

With regard to PUBs it is indicated that naproxcinod 375 mg *bid* and 750 mg *bid* re both factor 10 worse than placebo. In comparison to naproxen 500 mg bid no apparent difference in the incidence of PUB frequency is seen. This is also indicated in the per protocol analysis where all patients received study treatment continuously for 3 month (not only at least one dose as determined for the safety population) under controlled conditions. An evaluation of the development of GI ulcer is considered at least meaningful after 3 month treatment duration. Since OA is a flaring disease the usual treatment duration is expected between 1 and 3 month. Insofar the data from the controlled OA Studies up to 13 weeks are considered mostly relevant.
A dose dependent increase of PUBs for naproxcinod is not shown.
The presented endoscopic studies do not show a significant difference to naproxen. In addition mostly healthy subjects were assessed and mainly the duration of studies does not allow meaningful evaluation (<6 weeks).

On the base of the presented data no clinically relevant advantage of naproxcinod 375 mg and naproxcinod 750 mg bid is shown with regard to PUBs in comparison to Naproxen 500 mg bid. Accordingly the argumentation of the applicant that gastroduodenal ulcer were less frequent with naproxcinod compared to naproxen because of the protective effect on the GI tract of Nitric oxide (NO) cannot be followed.

GI discomfort

The presented data analysis shows for the treatment duration of 3 month which is considered a clinically most relevant time frame for OA the following results:

Any GI AE (All Placebo-Controlled OA Studies Up to 13 Weeks):

	Placebo n = 780	Naproxcinod 375 mg bid n = 470	Naproxcinod 750 mg bid n = 1137	Naproxen 500 mg bid n = 907
Any GI AE, n (%) [Events per 100 patient years] Per Protocol Population	115 (14.7%) [109]0	81 (17.2%) [116]	277 (24.4%) [241]	220 (24.3%) [241]
	Placebo n = 1116	**Naproxcinod 375 mg bid n = 601**	**Naproxcinod 750 mg bid n = 1472**	**Naproxen 500 mg bid n = 1175**
Any GI AE, n (%) **[Events per 100 patient years]** Total safety population	200 (<17.9%) [158]	109 (18.1%) [156]	377 (25.6%) [288]	315 (26.8%) [302]

The overall incidence of GI AE (GI discomfort) is comparable between naproxcinod 750 mg bid and Naproxen 500 mg bid. Naproxcinod 375 mg bid seems to be comparable with the frequency documented in the placebo group. However, when looking in detail at the GI AEs documented for naproxcinod diarrhea and nausea were numerically slightly increased compared to naproxen. At least diarrhea may be clinically relevant as the elderly are more prone for dehydration and water electrolyte imbalance.

On this base a distinct clinically relevant advantage of naproxcinod in comparison to naproxen with regard to GI AEs (GI discomfort) is considered not apparent.

Noticeable was that when analyzing the presented tables with the data of the 13 Non-Serious Syncope and Related Events patients a frequent co-medication with H2 inhibitors was indicated. Depending on the proportion of patients in the analysed study populations it may have an impact on GI safety outcome if not in the between group comparison than at least in the overall incidence of GI events.

Hypotension related AEs

A dose–related increase in the Exposure Adjusted Relative-Risk (ARR) of occurrence of any "Potential Hypotension-Related" AEs is observed for naproxcinod especially within the first 3 months.

All active treatment groups present a higher incidence than placebo; however, in looking at the adjusted relative risks (RRs are based on event rates per 100 patient years adjusted versus placebo), the naproxcinod 750 mg bid group reached an ARR that is statistically significant with 2.2 (95% CI: 1.23-4.00) in the Safety Per Protocol Population, 2.15 (95% CI: 1.30- 3.55) in the safety population and 3.25 (0.85-12.43) for the Per Protocol Population - Drug-Related Adverse Events. For naproxcinod 375 mg bid numerically slightly elevated RRs and frequencies of hypotensive events versus naproxen 500mg were documented.

In detail to this the according values are shown in the tables below:

All Placebo controlled OA studies up to 13 weeks – "Potential Hypotension-Related" Adverse Events (enlarged definition) in the Safety Per Protocol Population

n, (%), [Events per 100 patient years]	Placebo *bid* N=780	Naproxcinod 375mg *bid* N=470	Naproxcinod 750mg *bid* N=1137	Naproxen 500 mg *bid* N=907
Any "Potential Hypotension-Related" Adverse Event	***22 (2.8%) [16]***	***18 (3.8%) [20]***	***49 (4.3%) [36]***	***28 (3.1%) [26]***

Adjusted Relative-Risk Active vs. Placebo	***-***	***1.23 (0.64- 2.37)***	***2.22 (1.23- 4.00)***	***1.62 (0.87- 3.02)***

All Placebo Controlled OA Studies up to 13 Weeks – "Potential Hypotension-Related" Adverse Events (enlarged definition) in Safety Population

N, (%), [Events per 100 patient years]	**Placebo *bid* N=1116**	**Naproxcinod 375mg *bid* N=601**	**Naproxcinod 750mg *bid* N=1472**	**Naproxen 500 mg *bid* N=1175**
Any "Potential Hypotension-Related" Adverse Event	***34 (3.0%) [22]***	***25 (4.2%) [26]***	***76 (5.2%) [48]***	***37 (3.1%) [28]***
Adjusted Relative-Risk Active vs. Placebo	***-***	***1.15 (0.65-2.02)***	***2.15 (1.30-3.55)***	***1.26 (0.72-2.19)***

Phase 3 Placebo Controlled OA Studies up to 13 Weeks – Any "Potential Hypotension-Related" Adverse Events (enlarged definition) – Per Protocol Population - Only Drug-Related Adverse Events

N, (%), Events per 100 patient years	**Placebo *bid* N=569**	**Naproxcinod 375mg *bid* N=382**	**Naproxcinod 750mg *bid* N=614**	**Naproxen 500 mg *bid* N=496**
Any "Potential Hypotension-Related" event	***4 (0.7%) [3]***	***4 (1.0%) [4]***	***13 (2.1%) [9]***	***3 (0.6%) [3]***
Adjusted Relative Risk Active vs. Placebo (95% CI)	***-***	***1.49 (0.33-6.79)***	***3.25 (0.85-12.43)***	***1.15 (0.23-5.72)***

AEs in detail

The naproxcinod 375mg/750 mg *bid* total ARR increase is mainly driven by dizziness and hypotension. However, as the applicant admitted also few cases of syncope could be correlated with a blood pressure decrease. When looking at two numbers behind the decimal point it can be recognised that for the 750mg strength the incidences are more than doubled for some of the single AEs in comparison to naproxen.

The occurrence of these AEs was indicated predominantly within 30-60 days (also at day 1 of the treatment, see also applicant's response to Q42 figure 1) after starting the treatment.

In detail to this the according values are shown in the tables below with merged associated terms and calculated with two numbers behind the decimal point:

All Placebo Controlled OA Studies up to 13 Weeks – "Potential Hypotension-Related" Adverse Events (enlarged definition) in Safety Population

N, (%), [Events per 100 patient years]	Placebo *bid* N=1116	Naproxcinod 375mg *bid* N=601	Naproxcinod 750mg *bid* N=1472	Naproxen 500 mg *bid* N=1175
Any "Potential Hypotension-Related" Adverse Event	***34 (3.0%) [22]***	***25 (4.2%) [26]***	***76 (5.2%) [48]***	***37 (3.1%) [28]***
Adjusted Relative-Risk Active vs. Placebo	***-***	***1.15 (0.65-2.02)***	***2.15 (1.30-3.55)***	***1.26 (0.72-2.19)***
Dizziness	**24 (2.15%) [17]**	**16 (2.66%) [19]**	**47 (3.19%) [30]**	**24 (2.04%) [18]**
Vertigo	**6 (0.54%) [3]**	**1 (0.17%) [0.8]**	**8 (0.54%) [3]**	**3 (0.26%) [2]**
Hypotension	**1 (0.09%) [0.5]**	**4 (0.67%)0 [3]**	**17 (1.16%) [9]**	**4 (0.34%) [2]**
Syncope/ Presyncope	**2 (0.18%) [1]**	**1 (0.17%) [0.8]**	**5 (0.34%) [2.4]**	**2 (0.17%) [1]**
Road traffic accident	**0**	**0**	**2 (0.14%) [2]**	**1 (0.085%) [1]**

Safety related to the 375 mg bid dose
In contrary to the applicant it can not be supported that naproxcinod 375 mg bid demonstrates generally a more favorable safety profile compared to naproxcinod 750 mg bid especially with regard to gastrointestinal adverse events. It has not been sufficiently shown that clinically relevant AEs as GI ulcers are dose dependant. For details it is referred to the according risk and efficacy comments.
With regard to the greater magnitude of BP effect of the higher dose this might be a dose threshold related to the NO moiety.
In general it might be that because of the more or less combined drug with different effect thresholds of the single moieties every bid dose has a different qualitative pharmacodynamic profile. That may imply that not only the efficacy quantitatively increases with the higher dose but safety characteristics qualitatively change.

SAEs
In all studies, six patients reported seven"*Potential Hypotension-Related*" SAEs, 5 of these patients got naproxcinod. 3 of them got a syncope, two with 750mg *bid* and one with 375mg. One experienced vertigo (375mg bid) and one outcome was fatal (375mg bid) because of a road traffic accident.
In the naproxen group one SAE was documented because of an accidental overdose of hypertensive treatment.
Approx. 1% of OA patients discontinued the treatment with naproxcinod because of hypotension related AEs in comparison to 0.26% in the naproxen groups.

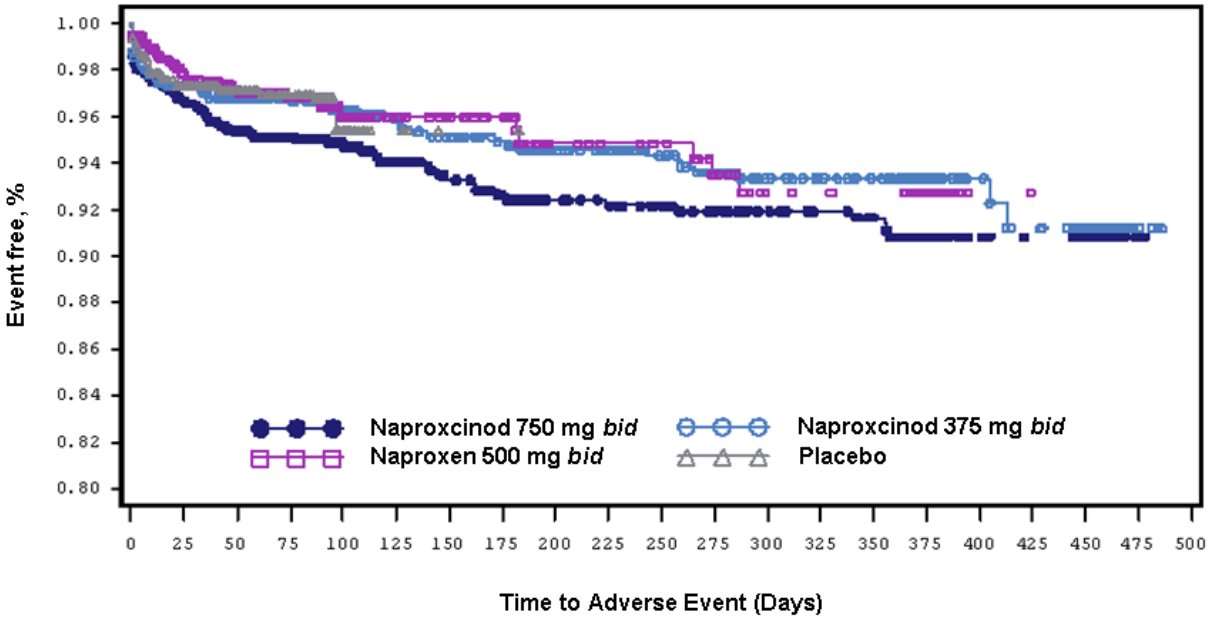
Although only few patients experienced SAEs it is indicated that syncope occurred more frequent in the naproxcinod group and here led to SAEs. A direct relation to hypotension could not be discovered for the SAEs as controls of BP were in normal range. Because of the known interaction with sildenafil there might be possible trigger conditions which boost or support according acute reactions as may be: e.g. postprandial blood volume shift into the GI tract, other vasodilatating agents (preferably venous system), warm ambient temperature. However, at present the concrete mechanism of action is not clear on the base of the presented data.

Although a rare event, road traffic accidents were reported more frequent for naproxcinod 750 mg bid, especially with long-term treatment, one SAE with fatal outcome was documented. No further health related data were available to explain the cause of the accident

AEs and Long-term treatment

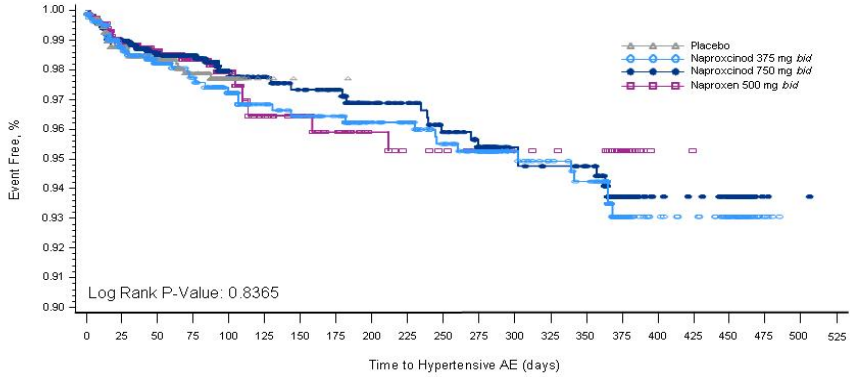
The long-term safety results indicate that the total risk of getting a hypotensive related AE with the 375mg bid dose diminishes with increasing treatment duration. Also the 750mg bid dose shows a diminished risk when compared versus naproxen after 3 months of treatment (events per 100 patient years and the adjusted Relative-Risk Active vs. Placebo).

Any "Potential hypotension-Related" Adverse Events over time for Group 1.0



It is known that long-term therapy with organic nitrates results in a development of nitrate tolerance blunting their haemodynamic efficacy.
In this regard the table below is of specific interest because it may indicate NO tachyphylaxis in a proportion of patients because it shows especially for the 375 mg bid dose an increasing occurrence of hypertensive related AEs after approx. one year of treatment. This effect is more pronounced than for the naproxcinod 750 mg bid dose and much more pronounced than for naproxen. Up to 3 months of treatment no difference between the groups could be detected and up to 250 days the 750 mg bid dose shows less hypertensive AEs than naproxen followed by the 375 mg bid dose.
In this context the overall hypotensive effect of the NO moiety of naproxcinod may give way over time to an increasing hypertensive effect dominantly caused by the naproxen moiety. However, a concrete mechanism and time relation of this balance between the two drugs is unclear at present. Looking at the clinically relevant AEs and SAEs the impact on vessels may be as well abrupt and/or lingering.

"*Hypertension-Related*" Adverse Events over Time: Kaplan-Meier Estimates for Group 1.0 (OA studies up to 65 Weeks)



	Placebo	Naproxcinod 375 mg *bid*	Naproxcinod 750 mg *bid*	Naproxen 500 mg *bid*
Patients, n	1116	824	1672	1175
Hypertensive AE, n (%)	21 (1.9%)	35 (4.2%)	44 (2.6%)	24 (2.0%)
Censored , n (%)	1095 (98.1%)	789 (95.8%)	1628 (97.4%)	1151 (98.0%)

Estimated proportion of patients who had not experienced a hypertensive AE. p-value is based on the log rank test for equality of the distribution function of the time to hypertensive AE among the treatment groups. A significant p-value means that at least two of the treatment groups differ.

However, the incidences of single AEs such as dizziness, hypotension and syncope do not vary over time with regard to their difference to naproxen as listed in the table below:

Placebo Controlled OA Studies up to 65 Weeks – "Potential Hypotension-Related" Adverse Events (enlarged definition) in Safety Population

N, (%), [Events per 100 patient years]	Placebo *bid* N=1116	Naproxcinod 375mg *bid* N=824	Naproxcinod 750mg *bid* N=1672	Naproxen 500 mg *bid* N=1175
Any "Potential Hypotension-Related" AE	***34 (3.0%) [22]***	***45 (5.5%) [11]***	***97 (5.8%) [24]***	***42 (3.6%) [20]***
Adjusted Relative-Risk Active vs. Placebo	**-**	***0.49 (0.24-1.01)***	***1.07 (0.60-1.90)***	***0.88 (0.48-1.61)***
Dizziness	**24 (2.15%) [17]**	**24 (2.91%) [6.4]**	**55 (3.28%) [14]**	**24 (2.04%) [11]**
Vertigo	**6 (0.54%) [3]**	**6 (0.73%) [1.2]**	**10 (0.60%) [2]**	**3 (0.26%) [1]**
Hypotension	**1 (<0.09%) [0.5]**	**6 (0.73%) [1.2]**	**18 (1.08%) [3.7]**	**4 (0.34%) [1.2]**
Syncope/ Presyncope	**2 (0.18%) [1]**	**3 (0.37%) [0.6]**	**8 (0.48%) [1.5]**	**3 (0.26%) [1]**
Road traffic accident	**0**	**3 (0.37%) [0.6]**	**4 (0.24%) [1]**	**2 (0.17%) [0.6]**

BP Course over the day

In general, the hourly SBP/DBP measures give information about the usual post-dose change in BP over the day. The merged results (mean and maximum values) from both BP studies are as followed:

Mean Changes from Baseline and Differences in the Mean 24-Hour Systolic Blood Pressure (mm Hg) for Naproxcinod 375 mg bid and 750 mg bid, and the Corresponding Doses of Naproxen 250 mg *bid* and 500 mg *bid* at End-Treatment – Study HCT 3012-X-112 (mITT Population)

	Naproxcinod 375 mg *bid*	**Naproxcinod 750 mg *bid***	**Naproxen 250 mg *bid***	**Naproxen 500 mg *bid***
n	49	44	40	46
Mean (SD)	0.3 (10.01)	0.9 (9.55)	1.5 (8.06)	2.9 (11.39)

With the known daily variabilities after dose the usual mean BP change from baseline is approx. +6 to -6, for SBP and +4 to -5 for DBP for 750mg naproxcinod, +3 to -4 for SBP and +2 to -4 for DBP for 375mg naproxcinod and +8 to -4 for SBP and +5 to -7 for DBP for 250/500mg naproxen accordingly (estimated from the figures 4,5,6,7,12,13,14,15 in applicant's response to Q42). The standard deviation was found to be approx. 7 to 16%, with lower values for DBP; there were no distinct differences between the groups.

The maximum SBP and DBP decreases in the naproxcinod groups were -82 mmHg and -59 mmHg, respectively. The maximum SBP and DBP decreases in the naproxen treatment group were -79 mmHg and -50 mmHg, respectively.

The maximum SBP and DBP increases in the naproxcinod treatment groups were+68 mmHg and +48 mmHg, respectively.
The maximum SBP and DBP increases in the naproxen treatment group were +70 mmHg and +55 mmHg, respectively.

Results of OBPM (2 to 4 hr post morning dose) and ABPM (mean 24 hr) showed that at both doses of naproxcinod, BP levels were predominantly lower compared to those of equimolar doses of naproxen up to 13 weeks. The DBP lowering effect of naproxcinod is dose dependent, similarly to the SBP lowering effect, but of smaller magnitude.

Only few patients with at least one post- naproxcinod baseline decrease of SBP ≥ 20 mmHg and concomitant hypotension related AEs were documented (1.4%) for the 750mg naproxcinod and 2.1% for the 375mg strength. For naproxen 0.4% was listed.

In summary,

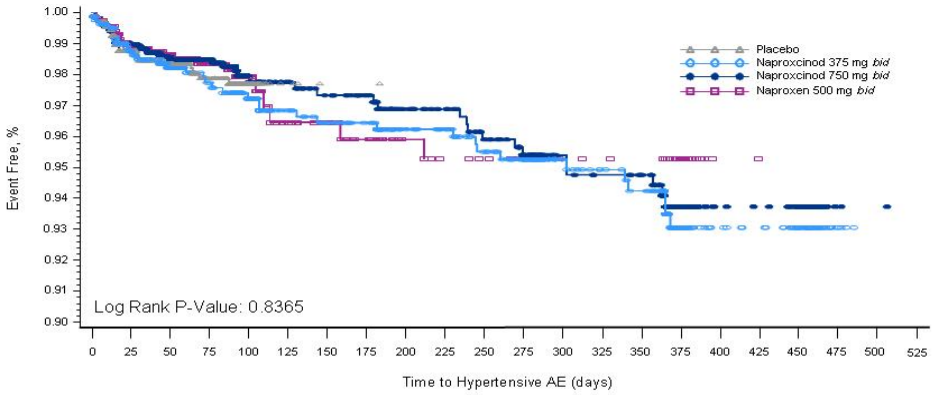
- BP change may vary individually, over the course of the day and especially over time of treatment in clinically relevant magnitude.
- It is indicated that after 3 months of treatment with naproxcinod the tendency for a hypertensive effect may increase, possibly on the base of a tachyphylaxis of the NO moiety.
- A specific mechanism related to the AEs is not clear; however, clinically relevant SAEs like syncope occurred suddenly. Only few patients with hypotension experienced also hypotensive related AEs. Some vasodilatory agents are identified to distinctly interact with naproxcinod by potentiating the hypotensive effect. Overall, hypotensive related AEs are considered not predictable for a treatment with naproxcinod at present.
- There are more frequent hypotension related AEs in the naproxcinod groups compared to naproxen (5.2% versus 3.1%, safety population); this applies especially for the SAEs (5 patients with AEs versus one in the naproxen group). The naproxcinod 750 mg bid group had an ARR for hypotension related AEs that is statistically significantly greater than in the placebo group with 2.22 (95% CI: 1.23-4.00, pp-population) and 2.15 (95% CI: (1.30- 3.55), safety-population).

- Although a dose related mean less pronounced hypertensive effect in comparison to naproxen is apparent within the first three month of treatment, the frequency of hypotensive related AEs is numerically increased, which reaches statistical significance for the 750 mg bid dose.

Hypertension related AEs

The applicant stated that the presented baseline data show an overall very high proportion of patients with high CV risk (22.8%, naproxcinod 750 mg bid group) with similar percentage in the naproxen group. However, the proportion of high CV risk patients at baseline in the naproxcinod 375 mg bid group and the placebo group is higher (34.1% and 28.2%) and thus is explained by the applicant to be responsible for the identified increase in reported cases with hypertension in the whole naproxcinod group in comparison with naproxen.
The proportion of patients with hypertension at baseline was similar between the groups.
A reanalysis was performed including a cluster of hypertension related AEs.
In the Group 1.1 data up to 13 weeks no difference was apparent between the groups with regard to hypertension related AEs. However in the analysis including data up to 65 weeks, the incidence of AEs was higher in the naproxcinod groups than in the naproxen group and in the placebo group, with number of cases more than doubled in the naproxcinod 375 mg bid group. This is also detectable in the Kaplan-Meier estimate (below) which shows a dose related increased occurrence of hypertension related AEs for the naproxcinod groups not before 275 days of treatment (details see also comment to Q 42a):

"*Hypertension-Related*" Adverse Events over Time: Kaplan-Meier Estimates for Group 1.0 (OA studies up to 65 Weeks)



	Placebo	Naproxcinod 375 mg *bid*	Naproxcinod 750 mg *bid*	Naproxen 500 mg *bid*
Patients, n	1116	824	1672	1175
Hypertensive AE, n (%)	21 (1.9%)	35 (4.2%)	44 (2.6%)	24 (2.0%)
Censored , n (%)	1095 (98.1%)	789 (95.8%)	1628 (97.4%)	1151 (98.0%)

Estimated proportion of patients who had not experienced a hypertensive AE. p-value is based on the log rank test for equality of the distribution function of the time to hypertensive AE among the treatment groups. A significant p-value means that at least two of the treatment groups differ.

These findings are considered to be in accordance with the development of a NO tolerance during long term treatment. Insofar data from patients treated only up to 13 weeks could not sufficiently show this long term effect and would dilute the results of an according analysis.

A distinct difference with regard to hypertension related AEs between the groups with more patients with a history of hypertension and those with fewer patients with a history of hypertension is not indicated. The applicant is requested to present an analysis including only data from patients who were treated exclusively 65 weeks (pp-population). It should be pointed out that in the presentation of hypertension related AEs and also with regard to BP destabilization the naproxcinod group was not shown to be numerically better than the naproxen group. Solely the 750 mg naproxcinod group showed a statistically significant difference versus naproxen for the Proportion of Patients with ≥10 mmHg increase in SBP at Week 13 in the Integrated Blood Pressure Analysis (HCT 3012-X-304). However, a diminishing impact by NO on the BP increasing effect of the naproxen moiety of 750 mg napoxcinod in first weeks of treatment is shown (see comments to Q42a).

With regard to the analysis of Study HCT-3012-X 111 (ABPM daytime SBP ≤135 mmHg (controlled hypertensive patients) who reached a daytime SBP >135 mmHg, pp-population) the applicant is requested to present also the data for week 6 and 9 for the 375 mg naproxcinod group in comparison with the equimolar dose of naproxen and the data for week 3 and 9 for the 750 mg accordingly in order to possibly find an early dose related development of hypertension related effect over time. In addition, the pp-population analyses of the time courses from the two BP studies should be presented.

In summary do the frequencies of the hypertensive related AEs not differ relevantly within the first three months and do not show an advantage in comparison to naproxen. In contrary to the opinion of the applicant a hypertensive effect during long-term treatment is indicated. The presented data do not sufficiently consider this treatment-duration related effect in their data analyses at present.

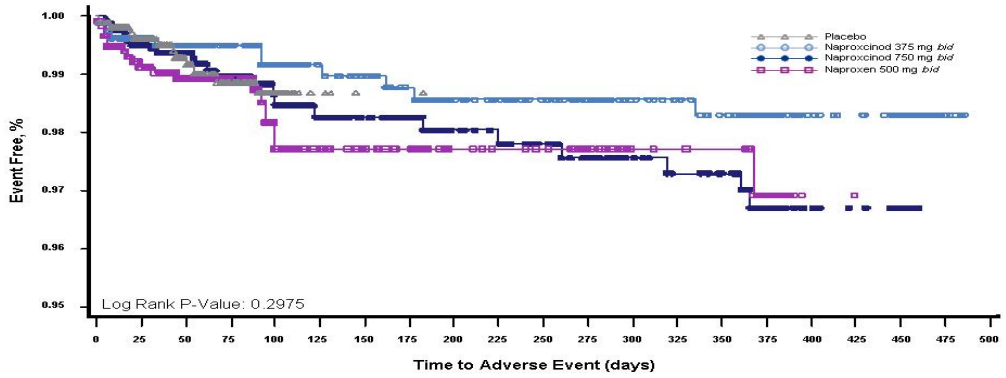
CV events

Due to the small number of patients and the rare CV events it is generally difficult to draw meaningful conclusions. Especially subgroup analyses with regard to high CV risk patients at baseline. in addition, for a comparison between the verum products the APTC endpoint is considered not that appropriate because it does not allow the differentiation between bleeding and thrombotic CV AEs. That implies the

consequence that the comparator may cause more bleeding and the test possibly more thromboses and no difference between the groups is apparent.
Overall, no comprehensible difference for CV AEs between naproxcinod 750 mg bid and naproxen 500 mg bid is indicated.
In detail, for naproxcinod 375 mg bid there are less Coronary Artery Disease or Myocardial Infarction Events documented, however, other calculations (e.g. CV AEs as SOCs) show more incidences in the lower dose group of naproxcinod copared to naproxcinod 750 mg or naproxen 500 mg (12.7% vs 9.2% vs 9.1%). This elevated incidence however, diminished when the AEs were related to the time of treatment (Any CV AE per 100 patient years, (24 vs 34 vs 40). The per protocol analysis shows no advantage of the 375 mg bid dose (0.9% [6] vs 0.8 [4] vs 0.7% [4] respectively). Therefore a consistent advantage or disadvantage with regard to MI and according CV AEs can not be stated.

The numbers of cerebrovascular AEs were too small for any evaluation.

Time to onset of first Coronary Artery Disease or Myocardial Infarction Events in OA Phase 2 and Phase 3 up to 65 weeks (Group 1.0) Safety Population



	Naproxcinod 750 mg *bid*	Naproxcinod 375 mg *bid*	Naproxen 500 mg *bid*	Placebo
No of Patients	1672	824	1175	1116
Adverse Event	25 (1.50%)	10 (1.21%)	17 (1.45%)	11 (0.99%)
Censored	1647 (98.50%)	814 (98.79%)	1158 (98.55%)	1105 (99.01%)

Estimated proportion of patients who had not experienced a CAD/MI-related AE at each time point.
P-value is based on log rank for equality of the distribution function of the time to AE among the treatment groups.
A significant p-value means that at least two of the treatment groups differ.

Hepatic-Related risk

The frequencies documented in all studies (safety population) shows the following distribution:

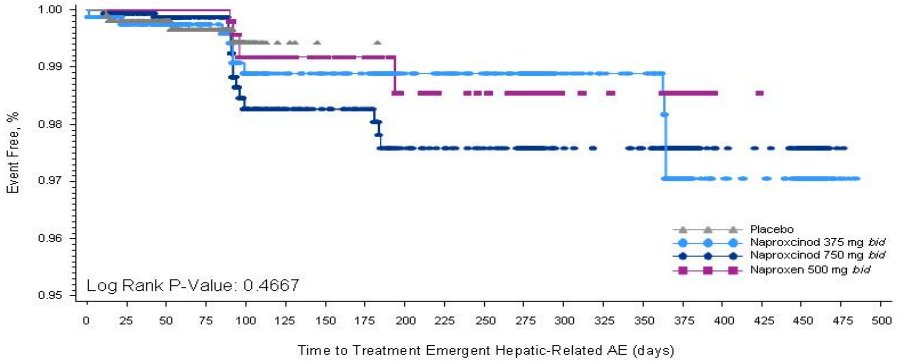
Incidence of Hepatic Adverse Events Reported in All Studies. Safety Population

	Placebo **N=1412**	**Naproxcinod 375 mg *bid* N=1007**	**Naproxcinod 750 mg *bid* N=2156**	**Naproxen** **N=1633**
PT	**n (%) [events per 100 patient yrs]**	**n (%) [events per 100 patient yrs]**	**n (%) [events per 100 patient yrs]**	**n (%) [events per 100 patient yrs]**
Patients with at least 1 hepatic AE	4 (0.3) [2]	15 (1.5) [4]	17 (0.8) [5]	6 (0.4) [3]
Hepatic Steatosis	0	1 (<0.1) [0.2]	0	0
Hepatomegaly	0	0	0	1 (<0.1)

	Placebo **N=1412**	**Naproxcinod 375 mg *bid* N=1007**	**Naproxcinod 750 mg *bid* N=2156**	**Naproxen** **N=1633**
PT	**n (%) [events per 100 patient yrs]**	**n (%) [events per 100 patient yrs]**	**n (%) [events per 100 patient yrs]**	**n (%) [events per 100 patient yrs]**
				[0.3]
ALT Increased	1 (<0.1) [0.5]	8 (0.8) [2]	11 (0.5) [2]	3 (0.2) [1]
AST Increased	0	5 (0.5) [1]	10 (0.5) [2]	5 (0.3) [2]
GGT Increased	1 (<0.1) [0.5]	4 (0.4) [0.8]	4 (0.2) [0.6]	1 (<0.1) [0.3]
Alkaline Phosphatase Increased	1 (<0.1) [0.5]	1 (<0.1) [0.4]	2 (<0.1) [0.3]	0
Hepatic Enzyme Increased	2 (0.1) [1]	0	2 (<0.1) [0.3]	0
Liver Function Test Abnormal	0	1 (<0.1) [0.2]	2 (<0.1) [0.3]	0
Transaminases Increased	0	0	1 (<0.1) [0.6]	0

Hepatic related events occurred uncommon to common in the naproxcinod groups. Overall, a tendency is indicated that the frequency is doubled in the 750 mg bid dose and triplicated for 375 mg bid dose versus naproxen.

Time to Onset of First Hepatic-Related Adverse Event All Phase 2 and Phase 3 Clinical OA Studies up to 65 Weeks



	Placebo	Naproxcinod 375 mg *bid*	Naproxcinod 750 mg *bid*	Naproxen 500 mg *bid*
Patients, n	1116	824	1672	1175
Treatment Emergent Hepatic-Related AE, n (%)	4 (0.4%)	12 (1.5%)	16 (1.0%)	4 (0.3%)
Censored, n (%)	1112 (99.6%)	812 (98.5%)	1656 (99.0%)	1171 (99.7%)

Estimated proportion of patients who had not experienced a Treatment Emergent Hepatic-Related AE. p-value is based on the log rank test for equality of the distribution function of the time to Treatment Emergent Hepatic-Related AE among the treatment groups. A significant p-value means that at least two of the treatment groups differ. Time-to-event axis is truncated at 500 days; there may be event times and censored times post-500 days. Although these times are not refelected on the graph, they were included in the calculations of survival times and logrank test statistic and p-value.

The curve over the time shows an increasing occurrence of hepatic related AEs after 3 month treatment duration for the 750mg bid dose. The lower dose maintains on a level which is comparable to naproxen up to 1 year. After treatment duration of 365 days the AEs increase then to a magnitude that is worse than documented for the 750 mg group. The progression of both strengths is considered comprehensive: the higher dose shows an increasing occurrence of AEs starting at approx. 3 month versus naproxen (or placebo) and the lower dose may show a delayed onset however then with a comparable magnitude as the 750 mg bid dose. Overall both strengths show an increased occurrence of hepatic related AEs compared to naproxen with a different onset related to treatment duration.

The overall incidence of ALT increases >3xULN in this treatment group was 0.8%. There were 3 patients treated with naproxcinod 750 mg *bid* which were found with ALT levels >10 x ULN at day 43 or day 50. Follow up values until resolution were requested but are not available. No patient was documented within the naproxen group,

The overall incidence of AST increases >3 x ULN in the naproxcinod 750 mg *bid* treatment group was 0.5%. There were 4 patients treated with naproxcinod 750 mg *bid* which were found with ALT levels >5 x ULN. One naproxen treated patient was documented in the group with AST elevations > 5 x ULN.

Although the applicant stated that in those patients treated with naproxcinod at therapeutic doses (375 mg *bid* and 750 mg *bid*), only 6 out of 32 patients reporting a hepatic AE had liver enzyme elevations ≥ 3xULN that could potentially be considered as an early signal of drug-induced liver injury a worse safety profile with regard to hepatic related AEs as compared to naproxen is indicated and liver injuries can not be excluded when the product is applied to numerous patients after marketing authorisation. At present, quantitatively definite safety statements can not be made on the base of the relatively small population assessed. However, according co-morbidities can be found in the naproxcinod groups as well as in the naproxen group insofar is a relative comparison of the groups considered quite trend-setting.

In summary seems the risk of elevation of ALT > 3x ULN in patients with OA treated up to 65 weeks numerically be increased in patients treated with naproxcinod 750 mg *bid* in comparison to naproxen 500 mg *bid*, placebo or naproxcinod 375 mg *bid* (0.8% *vs*. 0.3% *vs*. 0.3% *vs*. 0%). Three patients in the 750 mg *bid* group showed levels >10 x ULN and none in the naproxen group. The incidence of hepatic related AEs was found to be increased in the 750 mg *bid* and 375 mg *bid* groups in comparison to naproxen 500 mg *bid or* placebo (0.8% *vs*. 1.5% *vs*. 0.4% *vs*. 0.3%) with a delayed onset of

occurrence after one year of treatment in the lower dose (375 mg bid). However, definite safety statements can not be made on the base of the relatively small population assessed.

Eosinophils

These results support the hypothesis of a transient eosinophil elevation which is observed within the first 3 months of treatment. Mean values after 52 weeks of treatment does not show elevations. Patients with PCS changes in percentages from Baseline or any post-Baseline visit up to endpoint after 52 weeks were exclusively documented in the naproxcinod groups (0.9%). However, an analysis of PCS changes based on absolute values shows comparable results for naproxcinod 750 mg bid and naproxen 500 mg bid (2.9% vs 2.4%). 375 mg naproxcinod was slightly better (0.9%). Insofar a consistent trend is not identified. Moreover, it should be considered that the long-term treatment subgroups with the different treatment durations because of switching after 13 weeks are too small for a meaningful evaluation.

A relation between eosinophil elevation and asthma was intensively assessed but attained no correlation.

A specific warning with regard to anaphylactic reaction and asthma is proposed to be included by the applicant. Eosinophilia should also be adequately reflected within section 4.4 of the SPC/PIL and further on monitored.

NPL

In naproxcinod (0.23%) treated patients neoplasmas occurred more frequently compared to naproxen treated patients (0.07%) and slightly higher compared to placebo treated patients (0.17%). A thyroid neoplasma occurred in 1 out of 3017 naproxcinod treated patients. Though no firm conclusions can be drawn from this single case, this might be important, as a safety signal with respect to thyroid neoplasms derived from the non-clinical studies. Hepatic neoplasms which have also occurred during the non-clinial studies were not reported in the OA studies.

Structural changes

The long-term safety evaluation of joint damage was evaluated by radiography measuring the Joint Space Width (JSW) in the medial and lateral knee compartment after 52 weeks of either naproxcinod 375 mg bid, 750 mg bid or naproxen 500 mg bid treatment.

For a centralized independent review of the the radiographic processes see Safety Radiology Report (Appendix 16.1.14). Overall. 75,5 % (391/518) of the subjects who completed the study had evaluable X—Rays: 86 (17 %) and 107 (21%) subjects in the naproxcinod 750 mg bid and 375 mg bid group, 95 (18%) subjects in the naproxen bid group and 103 (20%) subjects in the placebo bid group, who after the Week 13 Visit received either dose of naproxcinod for the 9 remaining months: 42 (8%) subjects in the placebo naproxcinod 750 mg bid group and 61 (12%) subjects in the placebo-naproxcinod 375 mg bid group. Therefore, X-ray data are displayed for 5 groups of subjects: 3 groups who received 12 months of active treatment and 2 groups who received 9 months of active treatment.

The results of this analysis are presented for the 12 months groups in the table below:

Mean Change from Baseline in Target Joint Space Width (mm) by Compartment at Week 52 (53-Week Safety Population)

	Naproxcinod 750 mg bid N = 250	Naproxcinod 375 mg bid N = 250	Naproxen 500 mg bid N = 256

	Naproxcinod 750 mg bid N = 250	Naproxcinod 375 mg bid N = 250	Naproxen 500 mg bid N = 256
n	86	107	95
Medial compartment	0.130 (0.9236)	-0.064 (0.8117)	-0.118 (1.1836)
Lateral compartment	-0.109 (1.2182)	-0.145 (0.9818)	-0.153 (1.2157)

Source: HCT 3012-X-302 (53 weeks), Table 14.3.5.13, see also

In the present study, the mean changes from Baseline to Week 52 of the subject target JSW, both in the medial and lateral compartments, did not differ substantially between the naproxcinod and naproxen arms after one year of treatment. The mean changes from Baseline to Week 52 of the subject target JSW did not show any progression beyond the mean estimated joint space narrowing annual rate of 0.13 +/- 0.15 mm/year observed in the general OA population as reported in the literature (Emrani, 2008).

Serious adverse events and deaths

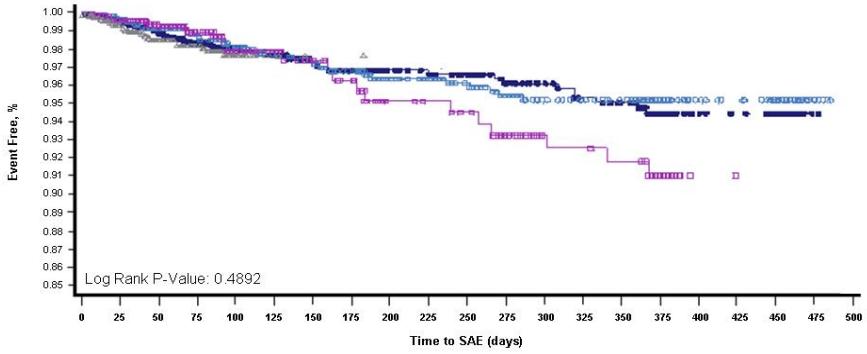
SAEs
The overall incidence of SAEs in the naproxcinod 375 mg group is numerically higher than in the other verum groups. The GI ralted SAEs are considered comparable between the verum groups and an increased incidence and RR is identified in the naproxcinod 375 mg group:

Overall Summary of specific Serious Adverse Events Group 1.0 (all Phase 2 and 3 OA studies up to 65 weeks)

N, (%), [Events per 100 Patients Yrs]	**Placebo *bid* (n = 1116)**	**Naproxcinod**			**Naproxen 500 mg *bid* (n = 1175)**
		All (n = 2839)	**375 mg *bid* (n = 824)**	**750 mg *bid* (n = 1672)**	
Serious AEs	20 (1.8%) **[11]**	70 (2.5%) **[8]**	27 (3.3%) **[7]**	40 (2.4%) **[8]**	25 (2.1%) **[9]**
Serious AEs Relative-Risk vs. Placebo	-	1.38 (0.84-2.25)	1.83 (1.03-3.24)	1.33 (0.78-2.27)	1.19 (0.66-2.13)
Gastrointestinal SAEs	4 (0.4%) **[2]**	13 (0.5%) **[1]**	3 (0.4%) **[<1]**	10 (0.6%) **[2]**	7 (0.6%) **[3]**
Gastrointestinal SAEs Relative-Risk vs. Placebo	-	1.28 (0.42-3.91)	1.02 (0.23-4.53)	1.67 (0.52-5.31)	1.66 (0.49-5.66)
Cardiovascular SAEs	7 (0.6%) **[4]**	17 (0.6%) **[2]**	9 (1.1%) **[2]**	7 (0.4%) **[1]**	6 (0.5%) **[2]**
Cardiovascular SAEs Relative-Risk vs. Placebo	-	0.95 (0.40-2.30)	1.74 (0.65-4.66)	0.67 (0.23-1.90)	0.81 (0.27-2.41)

The Kaplan-Meier curves of occurrence of these SAEs over time up to 65 weeks of treatment with either naproxcinod 375 mg *bid*, 750 mg *bid* or naproxen 500 mg *bid* do not show differences between the treatment groups up to 175 days with a trend favoring naproxcinod on long term treatment thereafter. However, it is indicated that there are numerically more SAEs in the naproxcinod group than in the other verum groups.

Time to onset of first Serious Adverse Event in Phase 2 and Phase 3 Placebo-controlled Studies Up to 65 Weeks (Group 1.0)



	Naproxcinod 750 mg *bid*	Naproxcinod 375 mg *bid*	Naproxen 500 mg *bid*	Placebo
No of Patients	1672	824	1175	1116
SAE, n (%)	40 (2.39%)	27 (3.28%)	25 (2.13%)	20 (1.79%)
Censored , n (%)	1632 (97.61%)	797 (96.72%)	1150 (97.87%)	1096 (98.21%)

Estimated proportion of patients who had not experienced a SAE at each time point.
p-value is based on the log rank test for equality of the distribution function of the time to SAE among the treatment groups.
A significant p-value means that at least two of the treatment groups differ.

Overall SAEs seems to be comparable between the verum groups with a trend for a better outcome within the naproxcinod groups in comparison to naproxen after 175 days of treatment towards long-term treatment. However, the 375mg bid dose of naproxcinod shows an increased risk (of overall and CV related SAEs (1.74 (0.65-4.66)).
Therefore the applicant is requested to describe these 9 cases more in detail.

Death
In context with the increased CV risk for naproxcinod 375 mg bid dose the deaths of two patients seem to be of interest and may be related to study drug because one death is a traffic accident and the other a SAE of coronary artery disease. Sudden hyper- or hypotension may cause syncopes and also exacerbations of coronary artery disease. Therefore both cases might be related.

Laboratory findings

Safety in special populations

Elderly

It is well known that the elderly are more prone to get AEs and SAEs. It is indicated that especially in the naproxcinod 375 mg bid dose the frequencies of the overall AEs and the SAEs are distinctly increased in comparison to the other verum groups. The applicant should discuss.

The proposed sentence to be included into section 4.4 of the SPC and the PIL accordingly could be accepted with the following changes if the above mentioned issue is solved:

"Caution should be exercised when treating elderly patients with naproxcinod, in particular those of 75 years of age or older as they are prone to experience adverse events more often and of more severity. Moreover, there is only limited data in these patients."

Women

Female patients seem to have more AEs with higher doses than men in particular concerning gastrointestinal and nervous system disorders. With regard to other SOCs the incidences are not consistent. Nevertheless, the female pharmacokinetic and pharmacodynamic specifics should be discussed by the applicant with regard to the dose weight relation not only in general but on the base of the data from the clinical and PK studies with naproxcinod.

Non-caucasian
The sample size is considered too small to identify differences between races.
However, the applicant should provide AE data of the different races assessed in the non-Caucasian patient group. For example Japanese patients may react different.

Pre-existing diabetes
The vascular disorders seem to increase with the dose in diabetic patients. The vascular disorders should be presented in detail.

Pre-existing hypertension
The sample size is considered too small to identify differences between the groups concerning Patients with hypertension.

Pre-existing hepatic impairment

Patients with mild to moderate hepatic impairment are assessed only for 7 days. The total experience with this patient group is scarce. However, there are data of liver toxicity from preclinical studies. Data should be presented for long term use from the clinical OA studies (3 months, 6 months, 1 year). At present the data for patients with mild moderate hepatic impairment are scarce.

Pre-existing renal impairment

Study HCT 3012-X-106 investigated the effects of repeated doses of naproxcinod 750 mg *bid*, administered for 7 days. The overall conclusion of this study was that plasma exposure to naproxcinod was slightly increased in mild and moderate renal impaired patients compared with matched healthy subjects. Despite the increased exposure in renal impaired patients, this did not impact the safety parameters nor the specific AEs, and in particular, there was no sign of aggravation of renal function. At present the long term data for patients with renal impairment are scarce. It is not recommended to prescribe naproxcinod in severe renal impaired patients.

Safety related to drug-drug interactions and other interactions

It is considered that there are several conditions and drugs which may have an impact on BP in combination with naproxcinod. In general the inclusion of the proposed paragraphs into the SPC is endorsed. However, there are several other drugs for which the magnitude of BP lowering effect in combination is not known. For example there are other products for the treatment of erectile dysfunction which have a much longer effect (tadalafil up to 36 h). Or the impact of postprandial blood shifts into the GI tract may influence BP in combination with naproxcinod. All these possibilities are not sufficiently assessed. Insofar it is considered adequate to at least list vasodilatating agents under 4.3. Other conditions should be further assessed.

Antihypertensive products
PK interactions were not studied for diuretics and angiotensin II receptor blockers (ARBs).

Lithium
When naproxcinod and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity. This should be adequately reflected in the SPC/PIL.

Methotrexate
Caution is advised because of possible enhancement of methotrexate toxicity since naproxen, among other NSAIDs, has been reported to reduce the tubular secretion of methotrexate. This should be adequately reflected in the SPC/PIL.

Discontinuation due to AES

Dizziness is indicated to be increased in comparison to the naproxen treated patient group (0.4% vs. <0.1%). The same is recognised for nervous system disorders (1.4% vs. 0.6%) and vascular disorders (0.5% vs. 0.3%). This is in accordance with the other safety data.

Discussion on clinical safety

Important risks and adverse events identified with naproxcinod largely correspond to those seen with naproxen or other NSAIDs. An advantage with regard to GI disorders or PUBs in comparison to naproxen is not shown. However, there are additional serious risks identified which are increased in comparison to naproxen. These are the following:

- A distinct risk signal of NO-induced dizziness, hypotension and hypotension related AEs for naproxcinod is identified. A time dependent dose relationship for this type of event is indicated. There are more frequent hypotension related AEs in the naproxcinod groups compared to naproxen (5.2% versus 3.1%, safety population); this applies especially for the SAEs (5 patients with AEs versus one in the naproxen group). The naproxcinod 750 mg bid group had an ARR for hypotension related AEs that is statistically significantly greater than in the placebo group with 2.22 (95% CI: 1.23-4.00, pp-population) and 2.15 (95% CI: (1.30- 3.55), safety-population). Some vasodilatory agents are identified to distinctly interact with naproxcinod by potentiating the hypotensive effect. Overall, hypotensive related AEs are considered not predictable for a treatment with naproxcinod at present.
- The frequencies of the hypertensive related AEs do not differ relevantly within the first three months and do not show an advantage in comparison to naproxen. In contrary to the opinion of the applicant a hypertensive effect during long-term treatment is indicated. The presented data do not sufficiently consider this treatment-duration related effect in their data analyses at present. This issue should be discussed by the applicant. Is there an inverse effect with increasing dose? Is there a change in the influence on blood pressure from a hypotensive effect at the beginning to a hypertensive effect with increasing time of treatment? The applicant is requested to present an analysis including only data from patients who were treated exclusively 65 weeks (pp-population).
- The risk of ALT > 3x ULN elevation in patients with OA treated up to 65 weeks is numerically increased in patients treated with naproxcinod 750 mg *bid* in comparison to naproxen 500 mg *bid*, placebo or naproxcinod 375 mg *bid* (0.8% *vs*. 0.3% *vs*. 0.3% *vs*. 0%). Three patients in the 750 mg *bid* showed levels >10 x ULN and none in the naproxen group. The incidence of hepatic related AEs was found to be increased in the 750 mg *bid* and 375 mg *bid* groups in comparison to naproxen 500 mg *bid or* placebo (0.8% *vs*. 1.5% *vs*. 0.4% *vs*. 0.3%) with a delayed onset of occurrence after one year of treatment in the lower dose (375 mg bid). The p-values for these values should be presented by the applicant.

Conclusions on clinical safety

It was intended to develop with naproxcinod a product with a more favorable risk profile compared to naproxen. However, important risks and adverse events are identified with naproxcinod which largely

correspond to those seen with naproxen but beyond that additionally further AEs and risks related to NO or the combination. An advantage with regard to GI PUBs or disorders in comparison to naproxen is not shown. Moreover, there are additional serious risks identified which are indicated to be increased for naproxcinod in comparison to naproxen: an increased frequency of hypotension, dizziness and hypotension related AEs, elevation of ALT and /or AST > 3x ULN up to > 10x ULN, hypertension related AEs related to long-term treatment. This is a major concern.

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the NicOx S.A. system of pharmacovigilance (Version 3.0 dated 20 October 2010). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management plan

Safety Specification

Limitations of the human safety database mainly include patients with renal and hepatic impairment exposed in specific studies.
Populations not studied in the pre-authorisation-phase due to exclusion criteria comprise children, pregnant or lactating women, NYHA grade III and IV patients and patients with severe renal or hepatic impairment. These aspects are reflected in the relevant sections of the SPC.
Additionally patients with osteoarthritis ACR functional class 4 (severe) have been excluded from pre-authorisation studies.
As the product had not been authorized no post-authorization exposure data were available at the data lock point of the RMP version 2.0.
For list of important identified or potential risks and missing information proposed by the applicant please see the table below.
Identified and potential interactions with other medicinal products, food and other substances include both interactions known to occur with Naproxen or other NSAID (i.e. interactions with other NSAIDs, anticoagulants, antihypertensive drugs, anti-platelet agents, SSRIs, corticosteroids) and interactions with substances that could cause cumulative vasodilatation (nitroglycerin, sildenafil). These aspects are accounted for in the interactions section of the SPC.
Accordingly pharmacological class effects may be divided into NSAID-related effects on the one hand and on NO-induced vasodilatation-related effects on the other hand.
The applicant expects that the potential for overdose is low and sees no potential for misuse for illegal purposes. The applicant acknowledges a potential for off label-use as the product could be used to treat other inflammatory or painful diseases or fever. Additionally off-label paediatric use cannot be excluded.

Pharmacovigilance Plan

Apart from routine pharmacovigilance practices additional pharmacovigilance activities have been specified by the applicant. Routine pharmacovigilance will comprise monitoring of case reports

including risk factors, co-medications and outcomes. There will be ongoing signal detection and safety evaluation. Milestones for reporting will be the PSURs.
Additional pharmacovigilance activities will comprise enhanced pharmacovigilance by means of special forms sent to the reporter in case of reports related to the important identified risks.
Additionally a post autorisation safety study on acute liver injury among users of naproxcinod and other NSAIDs is planned.

Risk Minimisation plan

Routine risk minimization activities (information in PIL and SPC) are considered sufficient for all ongoing safety concerns with the exception of blood pressure lowering adverse events. For this identified risk educational material for both health care professionals and patients is proposed.
Routine risk minimization activities consist of adequate labeling in the corresponding sections of the SPC.

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Important identified risks		
Blood pressure lowering adverse events	Routine pharmacovigilance Enhanced pharmacovigilance	Labelling Healthcare professional communication Patient brochure
Hepatic disorders (including increase in ALT or AST)	Routine pharmacovigilance Enhanced pharmacovigilance Post authorisation safety study	Labelling
Important potential risks and pharmacological class effects		
GI bleeding, ulceration and perforation	Routine pharmacovigilance	Labelling
GI non specific symptoms	Routine pharmacovigilance	Labelling
Upper GI AE's	Routine pharmacovigilance	Labelling
Haemodynamic oedema, effusion, and fluid overload	Routine pharmacovigilance	Labelling
Thrombotic cardiovascular events	Routine pharmacovigilance	Labelling
Hypertension events	Routine pharmacovigilance	Labelling
Anaphylactic reactions	Routine pharmacovigilance	Labelling
Renal effects	Routine pharmacovigilance	Labelling
Haematological effects	Routine pharmacovigilance	Labelling
Skin reactions	Routine pharmacovigilance	Labelling
Off-label use	Routine pharmacovigilance	Labelling
Off-label paediatric use	Routine pharmacovigilance	Labelling

Important missing information		
Severe hepatic impairment	Routine pharmacovigilance	Labelling
Severe renal impairment	Routine pharmacovigilance	Labelling
Fertility, pregnancy and lactation	Routine pharmacovigilance	Labelling
Congestive heart failure NYHA grade III and IV	Routine pharmacovigilance	Labelling
Osteoarthritis ACR functional class 4 (severe)	Routine pharmacovigilance	Labelling

ORPHAN MEDICINAL PRODUCTS

N/A

BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

Three double-blind placebo and active controlled pivotal Phase 3 studies investigated the efficacy of naproxcinod for the symptomatic relief of OA. Studies HCT 3012-X-301 and HCT 3012-X-302 included 963 naproxcinod patients out of 1929 randomised patients with OA of the knee. Study HCT 3012-X-303 included 323 patients treated with naproxcinod out of 810 randomised patients with OA of the hip.

In Studies HCT 3012-X-301 and HCT 3012-X-303, patients were treated for 13 weeks; in Study HCT 3012-X-302, patients were treated for 52 weeks, but only data from the placebo-controlled 13-week period and the naproxen-controlled 26-week period have been included in this efficacy summary.

The relevant efficacy of any agent should be viewed primarily as the placebo-corrected efficacy that matches, in the same study, a standard active control with proven clinical relevance (for naproxcinod, naproxen was chosen as the standard active control). Placebo-adjusted reductions in the range of 9 to 12 mm on the WOMAC™ visual analogue scales for pain and function and an increase of 0.4 on the patients' global assessment of the disease status Likert scale are considered to represent clinically perceptible and relevant changes to patients with OA of the hip or knee (Ehrich, 2000). In the Phase 3 studies in patients with OA of the knee, naproxcinod 750 mg bid demonstrated results in these ranges for the difference from placebo of the mean change from Baseline to Week 13 for all three co-primary endpoints in the ITT population.

For the WOMAC™ pain subscale score, the difference from placebo in LS mean change from Baseline at Week 13 was -11.3 mm (95% CI: -16.26,-6.27) and 10.9 mm (95% CI: -15.5,-6.4) in Studies HCT 3012-X-301 and HCT 301-X-302, respectively, ($p < 0.0001$). For the WOMAC™ function subscale

score, the difference from placebo in LS mean change from Baseline at Week 13 was -11.56 (95 % CI: -16.56,-6.57) and -12.8 (95% CI: -17.2,-8.5) in Studies HCT 3012-X-301 and HCT 301-X-302, respectively ($p < 0.0001$). For the change from baseline at week 13 in Patient´s Overall Rating of Disease Status the difference from placebo in LS mean change was 0.54 (95 % CI: 0.34, 0.74) and 0.51 (95 % CI: 0.34, 0.68) in Studies HCT 3012-X-301 and HCT 301-X-302, respectively ($p < 0.0001$).

The improvements in the WOMAC™ scores seen in the three co-primary endpoints represent clinically meaningful changes for patients with knee OA for the 750 mg bid dosage and the magnitudes of the effects were comparable between naproxcinod 750 mg bid and naproxen 500 mg bid.

Uncertainty in the knowledge about the beneficial effects

However, the clinical relevance of the efficacy of naproxcinod has not been convincingly endorsed by the non-inferiority analysis. The chosen non-inferiority margin of 8 mm appears much too high in the light of the treatment effect of Naproxen as compared to placebo being 12 mm, and was already questioned in preceeding scientific advice meetings. A non-inferiority margin of 8 mm would mean that 2/3 of the treatment effect of Naproxen is lost. Even with a non-inferiority margin of 8 mm, the non-inferiority assessment failed in study 301, for both the PP analysis as well as the BOCF analysis. Furthermore the results of the BOCF analysis differ from those obtained in the FDA assessment. According to the FDA assessment the upper CI limits of the treatment difference between naproxcinod 750 mg and naproxen on WOMAC pain and function were 9 mm for the ITT population.

Applying a more reasonable margin of 4 mm, all analyses both in the PP as well as the ITT population failed to show non-inferiority in both endpoints.

The large differences between study 301 and 302 in the non-inferiority assessment suggest an important between study variability with respect to the Naproxinod-Naproxen comparison. No repeated evidence is given for the non-inferiority to Naproxen. Furthermore, due to the large between-study differences the transferability of the study results is disputable.

For the naproxcinod 375 mg bid dose, with the exception of the endpoint Patient´s Overall Rating of Disease Status in Study HCT 3012-X-301, although statistically significant ($p < 0.0001$) no clinically relevant results were found for the primary endpoints compared to placebo (WOMAC™ pain: -8.75/-7.7 (95 % CI: -13.66,-3.84)/ (95 % CI: -12.2, -3.2), WOMAC™ function -8.38/- 8.8 (95 % CI: -13.30,-3.46)/ (95 % CI: -13.2, -4.5), Patient´s Overall Rating of Disease Status 0.42/0.32(95 % CI: 0.23, 0.62)/ (95 % CI: 0.16, 0.49)). The studies 301 and 302 were not powered to assess non inferiority of lower naproxcinod dose. Overall, the provided data on efficacy (in particular from phase 1 studies HCT 3012-X-111 and HCT 3012-X-112) are too sparse to give information on lower dose of naproxcinod in comparison to the equivalent dose of naproxen.

The conclusion of the applicant that efficacy was similar for naproxcinod 375 mg bid and equivalent dose of naproxen after 3 weeks of treatment as well as 13 weeks is somewhat excessive.

Provided results can only be considered as a suggestion of comparable efficacy and need to be confirmed in appropriate clinical trials, which compare in a head to head design naproxcinod 375 mg bid and equivalent dose of naproxen (250 mg bid). Non-inferiority of the lower dose of naproxcinod to naproxen for all three co-primary endpoints was not demonstrated.

For patients with hip OA the lower dosage 375 mg bid) was not evaluated. Furthermore, efficacy data versus placebo for the 750 mg bid dose in this subindication in Study HCT 3012-X-303 (WOMAC™ pain: -7.84 (95% CI: -11.61, -4.06), WOMAC™ function -8.79 (95 % CI: -12.46, -5.11), Patient´s Overall Rating of Disease Status 0.35 (95 % CI:0.20, 0.50)) were not convincing. Although the difference in response being less in patients with OA of the hip has been noted before in other studies described in the literature (Svensson et al, 2006) and was consistently found for naproxen and naproxcinod in this study the clinical relevance of the results in hip OA has not been convincingly demonstrated. The Applicant should discuss the magnitude of effect of naproxcinod 750 mg *bid* on hip OA for the three co-primary efficacy variables, on the basis of pain perception and waited analgesic effect on hip OA.

Since the 750 mg bid dose has only low efficacy, dose recommendation for hip OA including the 375 mg bid dose as currently stated in the SPC can thus not be endorsed on the basis of these data.

Naproxcinod was designed to release the two active moieties naproxen (NSAID related activities) and the NO donating moiety 1,4 butanediol mononitrate (BDMN; nitric oxide related effects) which are purported to be responsible for the dual pharmacological action of naproxcinod.

However, no specific relationship can be established between pharmacokinetic data, i.e. dose related exposure to BDMN, and clinical effects of BDMN in humans.

Since naproxen and the NO donating moiety are combined in this product via the ester bound in a 1:1 relation no dose titration of NO was possible. In this context it is not expected that both therapeutic principles, naproxen and NO, are dosed in their appropriate therapeutic ranges. More justification is needed why both compounds were not combined as single entities thus allowing titration of pharmacological effects of naproxen on one hand and the NO donator on the other hand.

The targeted bioavailability profile of naproxcinod was rapid bioavailability of naproxcinod after oral administration of an immediate release formulation so as to enable the quick release of naproxen and BDMN and its NO conversion products into the circulation. However, dissolution still takes 60 to 90 min to be almost completed thus identifying the product to be not typically immediate release based on pharmacopoeial definitions.

The naproxen mean Cmax was 6-53% higher and the mean AUC was 5-40 % higher than after an equimolar dose of naproxcinod (750 mg). Concurrent with the lower naproxen Cmax, the rate of naproxen absorption appears to be slower after therapeutic doses of naproxcinod (mean tmx = 2.43 to 4.50 h) than of naproxen (mean tmax = 1.83 to 2.45 h).

Overall, Naproxcinod administration results in a more sustained naproxen plasma concentration than does an equimolar dose of naproxen administration, and lower naproxen bioavailability.

Risks

Unfavourable effects

Important risks and adverse events are identified with naproxcinod which largely correspond to those seen with naproxen but beyond that include additional AEs and risks related to NO or the combination.

There are numerically more frequent hypotension related AEs in the naproxcinod groups compared to naproxen (5.2% versus 3.1%, safety population); this applies especially for the SAEs (5 patients with AEs versus one in the naproxen group). The naproxcinod 750 mg bid group had an ARR for hypotension related AEs that is statistically significantly greater than in the placebo group with 2.22 (95% CI: 1.23-4.00, pp-population) and 2.15 (95% CI: (1.30- 3.55), safety-population).

Although a dose related mean less pronounced hypertensive effect in comparison to naproxen is apparent within the first three month of treatment, the frequency of hypotensive related AEs is numerically increased, which reaches statistical significance for the 750 bid mg dose.

The risk of elevation of ALT > 3x ULN in patients with OA treated up to 65 weeks seems increased in patients treated with naproxcinod 750 mg *bid* in comparison to naproxen 500 mg *bid*, placebo or naproxcinod 375 mg *bid* (0.8% *vs*. 0.3% *vs*. 0.3% *vs*. 0%). Three patients in the 750 mg *bid* showed levels >10 x ULN and none in the naproxen group.

The incidence of hepatic related AEs was found to be increased in the 750 mg *bid* and 375 mg *bid* groups in comparison to naproxen 500 mg *bid or* placebo (0.8% *vs*. 1.5% *vs*. 0.4% *vs*. 0.3%) with a delayed onset of occurrence after one year of treatment in the lower dose (375 mg bid).

An advantage with regard to GI PUBs or disorders in comparison to naproxen has not been shown.

Uncertainty in the knowledge about the unfavourable effects

The pharmacodynamic activity of the NO donating moiety seems not to be sufficiently evaluated. It remains unclear how the claim of beneficial effect on blood pressure and gastrointestinal safety can be attributed to the NO release with plasma concentrations of BDMN in the nanomolar range.

The concept of the fixed conjugate, which does not allow individual titration of the NO component, is still not sufficiently clear with regard to its mechanism and characteristics of the NO moiety and the total combination. There might be specific thresholds for single effects at different doses and for the NO moiety a potential tachyphylaxia with regard to the hypotensive effect is identified. Insofar, the BP effect of naproxcinod compared to naproxen is not considered sustained over long-term treatment. A dose related hypotensive effect was documented within the regular measurements within both BP studies, however, sudden AEs and SAEs caused by partly unknown mechanism and co-factors frequently occurred. The increased risk related to naproxcinod 750 mg bid reached statistical significance. Dizziness and hypotention as the most frequently observed potential hypotension-related AEs are considered a disorder for the elderly with consequtive impact on potentially severe health outcome. The claimed indication however implies mostly the elderly, therefore these AEs are considered clinically relevant.

In detail:

It is not demonstrated that the potential advantages of naproxcinod in terms of BP changes are sufficient to justify the use of naproxcinod which may be associated to an increase in hypotension-related effects and liver toxicity.

It is not demonstrated that naproxcinod 375mg bid has a more favorable safety profile compared to naproxcinod 750 mg bid, especially with regard to PUBs AEs and hypertension-related AEs.

The absence of comparative safety data between naproxcinod 375 mg bid and naproxen 250 mg bid in controlled OA studies remains a major limitation for an accurate analysis of the risks associated with the lowest naproxcinod dose.

The available data collected during the naproxcinod clinical development program do not allow to accurately quantify a potential gastrointestinal benefit of the nitric oxide donating properties of naproxcinod over naproxen. Results from endoscopic studies, limited by their duration and the number of patients, are not sufficient to prove a gastrointestinal benefit of naproxcinod. Analysis of PUBs in all placebo-controlle OA studies did not indicate a significant advantage for naproxcinod 375 mg bid and naproxcinod 750 mg bid compared with naproxen (0.425% versus 0.352% versus 0.441%).

Concern is raised for patients ≥ 65 year, representing the main target population for OA treatment, with regard to gastrointestinal and hepatic safety profile, as well as hypotension-related AES.

Hypotension adverse events, are not predictable, which may represent a concern particularly in the elderly population, who are at higher risk for severe consequences due to blood pressure decrease. In addition, a specific mechanism for these hypotension-related AEs cannot be clearly established based on the provided data.

Data suggest a NO tolerance leading to potential hypertensive effect during long-term treatment.

A specific negative signal for naproxcinod with regards to cardiovascular events was not observed in studies. However, data are considered insufficient, particularly in long-term and in patients with co-morbidities, to accurately quantify this risk, known to be a class effect for NSAIDs**.**

An increased occurrence of hepatic-related AEs with both naproxcinod doses is demonstrated compared to naproxen, with a different onset related to treatment duration.

Adverse hepatic effects were also observed in nonclinical repeated dose toxicity studies with naproxcinod (male mice).

In addition, in the rodent carcinogenicity studies, a highly significant increase in incidence of liver tumors and of thyroid C-cell tumors was identified. The clinical relevance of these tumorigenic effects is currently unknown and safety factors for clinical use of naproxcinod in humans cannot be calculated, since data about the exposure of animals in the carcinogenicity studies to BDMN/NO are missing.

In this context it may however give cause for concern that for NO, the active principle formed from the BDMN part of naproxcinod, genotoxic and/or carcinogenic effects have been described in a number of *in vitro* and *in vivo* test systems.

Balance

Importance of favourable and unfavourable effects

With respect to efficacy there is some evidence for efficacy for the relief of signs of symptoms of osteoarthritis of the knee or hip, in particular for the highest naproxcinod dose (750 mg bid). However efficacy data are not very impressive in comparison to naproxen. The lower naproxen bioavailability out of naproxcinod does not seem to have a negative influence on efficacy but overall it does not present an advantage.
No improved GI safety or relevant beneficial effects on blood pressure have been demonstrated, which might have been expected from the concept of the product designed to release NO.
There are major safety concerns with regard to hypotensive events and potential liver toxicity. Based on the available non-clinical data, a potential tumorigenic effect cannot be ruled out. An advantage with regard to GI PUBs or disorders in comparison to naproxen is not shown.

Benefit-risk balance

There is no firm demonstration of a better benefit/risk balance with naproxinod compared with equivalent doses of naproxen.

Discussion on the benefit-risk assessment

Efficacy data are not very impressive in comparison to naproxen to counterbalance the safety concerns since

- non-inferiority versus naproxen has not unequivocally been shown
- the clinical relevance of the magnitude of effect of naproxcinod 750 mg bid dose in hip OA has not convincingly been demonstrated
- the 375 mg bid dose was not investigated for hip OA
- the justification for the 375 mg bid dose as the lowest effective dose is not based on head to head comparisons in randomised clinical trials to equivalent doses of naproxen. Non- inferiority of the lower dose naproxcinod to naproxen 500 mg bid for all three co-primary endpoints was not demonstrated

The advantage of the dose related limited BP diminishing effect of the NO moiety does not outweigh the increased risk of potentially severe AEs documented for naproxcinod.

An increased risk is identified with regard to hypotensive related AEs and liver toxicity. Based on the available non-clinical data, a potential tumorigenic effect cannot be ruled out. An advantage with regard to GI PUBs or disorders in comparison to naproxen has not been shown. The benefit-risk balance is considered not favourable.

Conclusions

The overall benefit-risk balance of Beprana is negative.