Naproxcinod
FDA: Efficacy and Safety Review

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Presentation Overview

I. Background – Naproxcinod
- Regulatory History
- Clinical Development Program

II. Clinical and Statistical Review of Efficacy
- Efficacy versus placebo
- Non-Inferiority analyses

III. Major Safety Findings
- Deaths, Serious Adverse Events, Discontinuations, Common Adverse Events, GI Adverse events

IV. Special Safety Studies
- GI endoscopy studies
- Effects on blood pressure

V. Conclusions

Naproxcinod: Overview

- New Molecular Entity
- Cox-inhibiting and nitric oxide-donating properties
- Intact Naproxcinod has no Cox-inhibiting activity; enzymatic cleavage in vivo results in 2 active metabolites:
  1. Naproxen: anti-inflammatory/analgesia
  2. Nitric oxide (NO): purported ↑ GI/BP safety profile

Naproxcinod - Overview

Proposed:

- **Indication**: Relief of signs and symptoms of osteoarthritis
- **Dosage form**: 375 mg hard gelatin capsule
- **Dosing regimen**: 375 mg or 750 mg twice daily

Key Regulatory History

Efficacy

- Claim of efficacy for proposed indication requires superiority to placebo or active comparator in 12 – week, replicated, adequate and well-controlled studies
- Primary endpoints
  - WOMAC pain
  - WOMAC function
  - Patient Overall rating of disease status
- Pivotal studies involving target joints (hip, knee) should be separate
- 1° statistical analysis should be change from baseline at 13 weeks

Safety

- Database must meet ICH guidelines (≥1500 total patient exposures, ≥ 300 patient exposures X 6 months, ≥100 patient exposures X 1 year at maximum proposed dose)

Key Regulatory History

Gastrointestinal safety claims

- Division recommended replicated 12-week endoscopy studies.
- Not acceptable to have combined analysis of studies of different design and duration and using different comparators for inclusion in label.

Key Regulatory History

Blood Pressure Safety Claims

- Ambulatory blood pressure monitoring (ABPM)
  - Need studies to assess naproxcinod effect on BP over time (adequate monitoring in 3 month trial could support BP effect in clinical section)
  - Obtain readings at baseline & end-of-study
  - Include full-dosing interval
  - BP monitoring program should discuss methods of BP measurement and whether standardized across studies
    - Timing of BP measurements to dosing time in PC studies
    - Proportion of elderly pts who underwent orthostatic tests
    - Description of BP data pooling and methods used

Clinical Development Program (35 Completed Studies)

- **Phase 1 studies (26)**: single and escalating doses, comparative BA & BE, mass balance, PK in healthy young and elderly subjects and Japanese subjects, DDI, HTN, OA with HTN, special population (hepatic and renal impaired), ABPM, GI endoscopy, QT study
- **Phase 2 studies (5)**: dose-range studies (2), single-dose studies for acute dental pain (2), and1 GI endoscopy study
- **Phase 3 studies (4)**: 3 adequate and well controlled studies (OA of knee/hip), 1 long-term safety extension study

EFFICACY

Phase 3 Efficacy Studies
Study 301/301(E)

- **Design:** Randomized, double-blind, placebo and naproxen-controlled, parallel group, efficacy and safety study
- **Population:** OA of the knee
- **Treatment groups:**
  - Naproxcinod 750 mg twice daily
  - Naproxcinod 375 mg twice daily
  - Placebo twice daily
  - Naproxen 500 mg twice daily
- **Conduct:** 13-week, R/DB/PC/AC efficacy treatment period
- **Primary Efficacy Endpoints:**
  - WOMAC pain subscale score
  - WOMAC function subscale score
  - Patient overall rating of disease status

Phase 3 Efficacy Studies

Study 302

- Similar to Study 301
- Differences
  - 26-week naproxen controlled portion
  - 26-week naproxen safety study

Study 303

- Similar to Study 301
- Differences
  - Target joint (hip)
  - Countries: US, Europe
  - No naproxcinod 375 mg dosage group

Efficacy Analyses

- Superiority comparison
  1. Naproxcinod 750 mg twice daily to Placebo (Study 301, Study 302, and Study 303)
  2. Naproxcinod 375 mg twice daily to Placebo (Study 301and Study 302)

Applicant's Results Study 301

	Naproxcinod 750 mg (N=224)	Naproxcinod 375 mg (N=234)	Naproxen 500 mg bid (N=220)
Change from Baseline at Week 13 in WOMAC™ Pain Subscale Score (mm)			
Differences in LS mean (SEM) versus placebo	-10.67 (2.55)	-9.49 (2.52)	-12.77 (2.56)
p-value for treatment effect	<0.0001	0.0002	<0.0001
Change from Baseline at Week 13 in WOMAC™ Physical Function Subscale Score (mm)			
Differences in LS mean (SEM) versus placebo	-10.62 (2.53)	-8.66 (2.50)	-13.73 (2.54)
P-value for treatment effect	<0.0001	0.0006	<0.0001
Change from Baseline at Week 13 in Patient Overall Rating of Disease Status			
Differences in LS mean (SEM) versus placebo	0.51 (0.10)	0.42 (0.10)	0.65 (0.01)
p-value for treatment effect	<0.0001	<0.0001	<0.0001

- Study 302 and Study 303 had similar results (naproxcinod beat placebo for all 3 endpoints)

Evaluation of Superiority

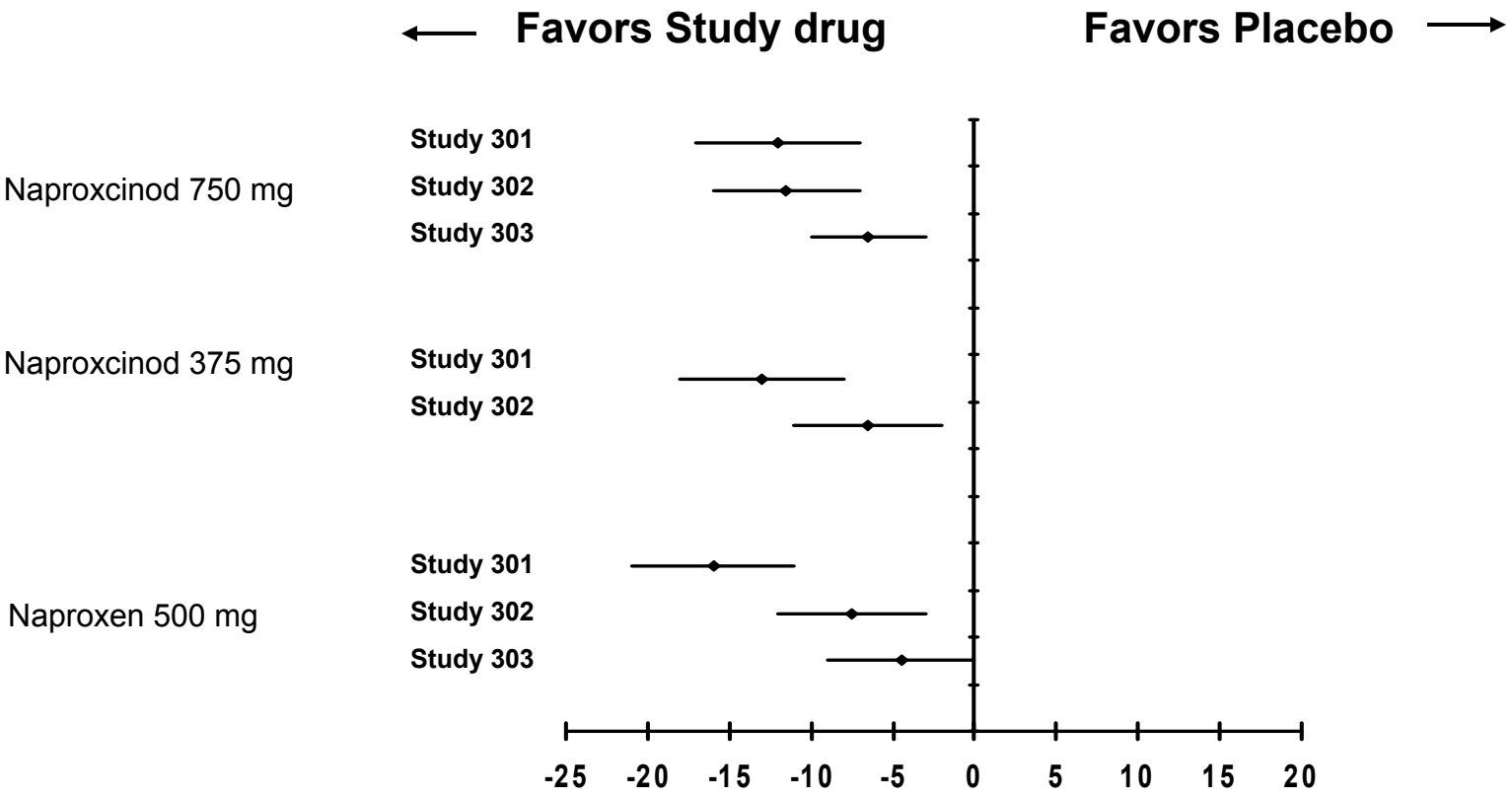
- Primary analysis
  - Analysis of Covariance

- Comparisons
  - First, compare Naproxcinod 750 mg to placebo (Studies 301, 302, and 303)
  - Second, compare Naproxcinod 375 mg to placebo (Studies 301 and 302)

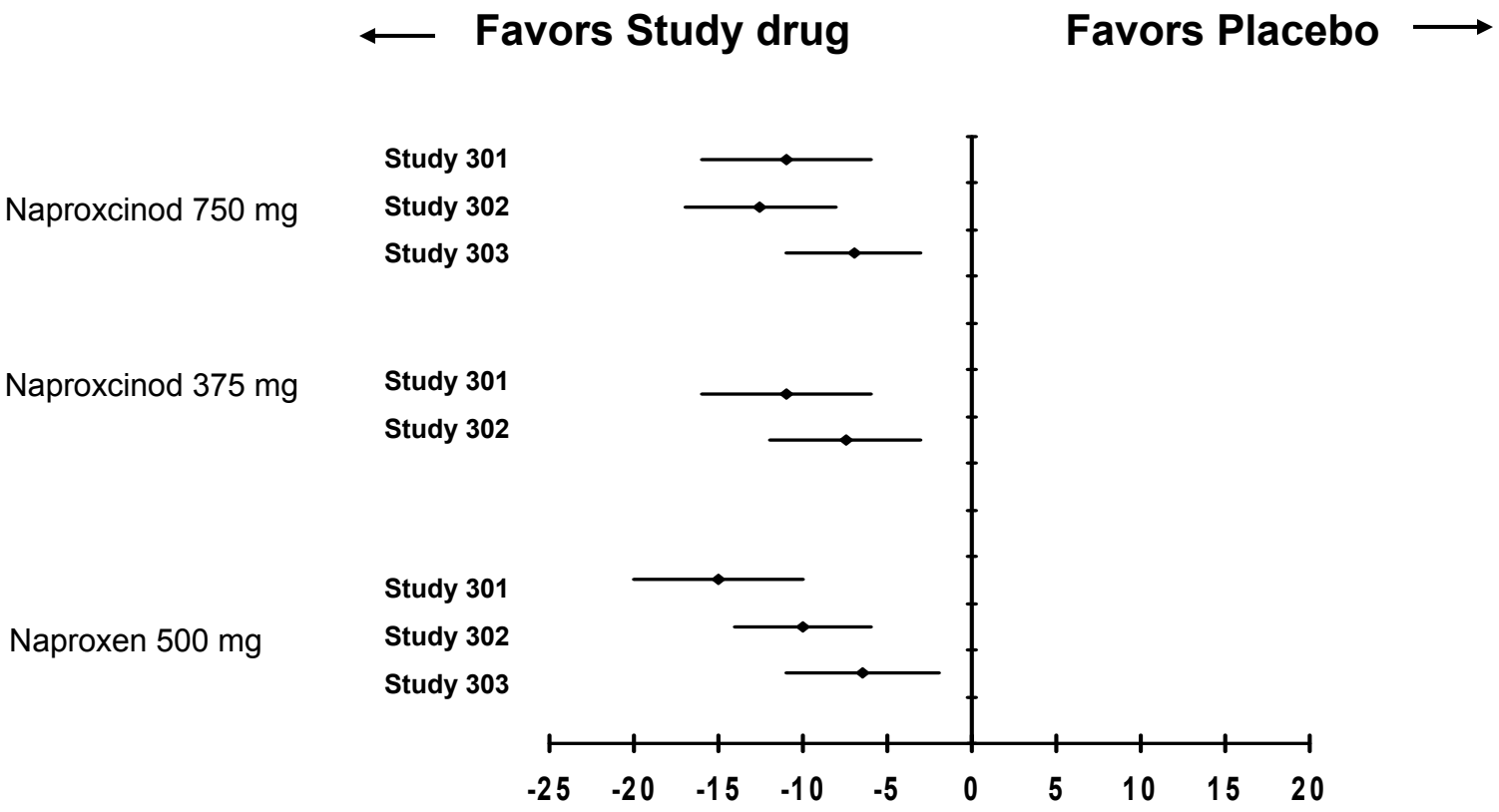
Evaluation of Superiority

- Applicant's imputation
  - Study 301
    - LOCF: last post-baseline observation carried forward
  - Studies 302 and 303
    - mLOCF: Dropouts due to treatment-related adverse events, the worst observation was carried forward, otherwise, LOCF
- Agency's imputation
  - BOCF: baseline observation carried forward

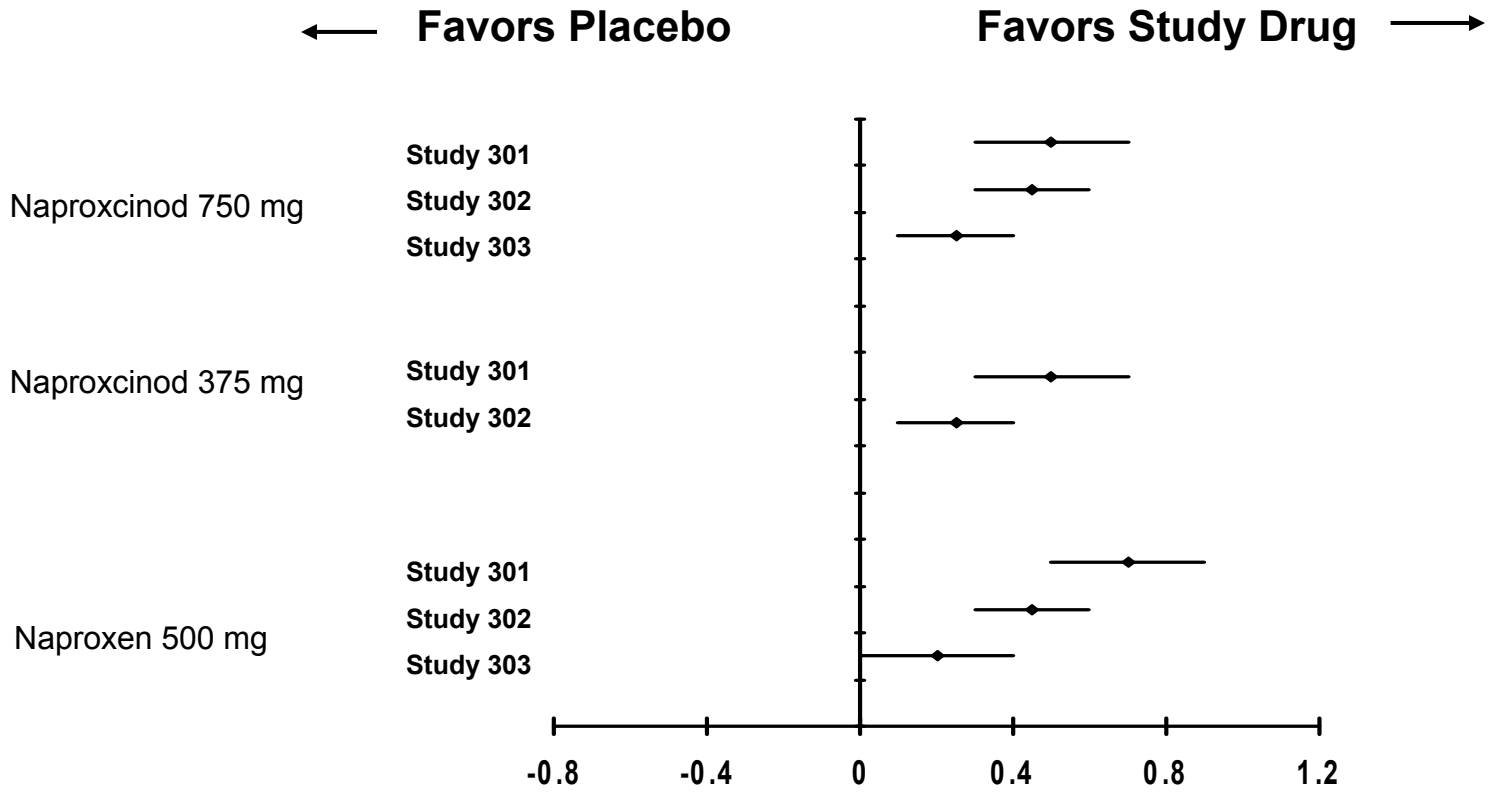
Evaluation of Superiority
WOMAC Pain



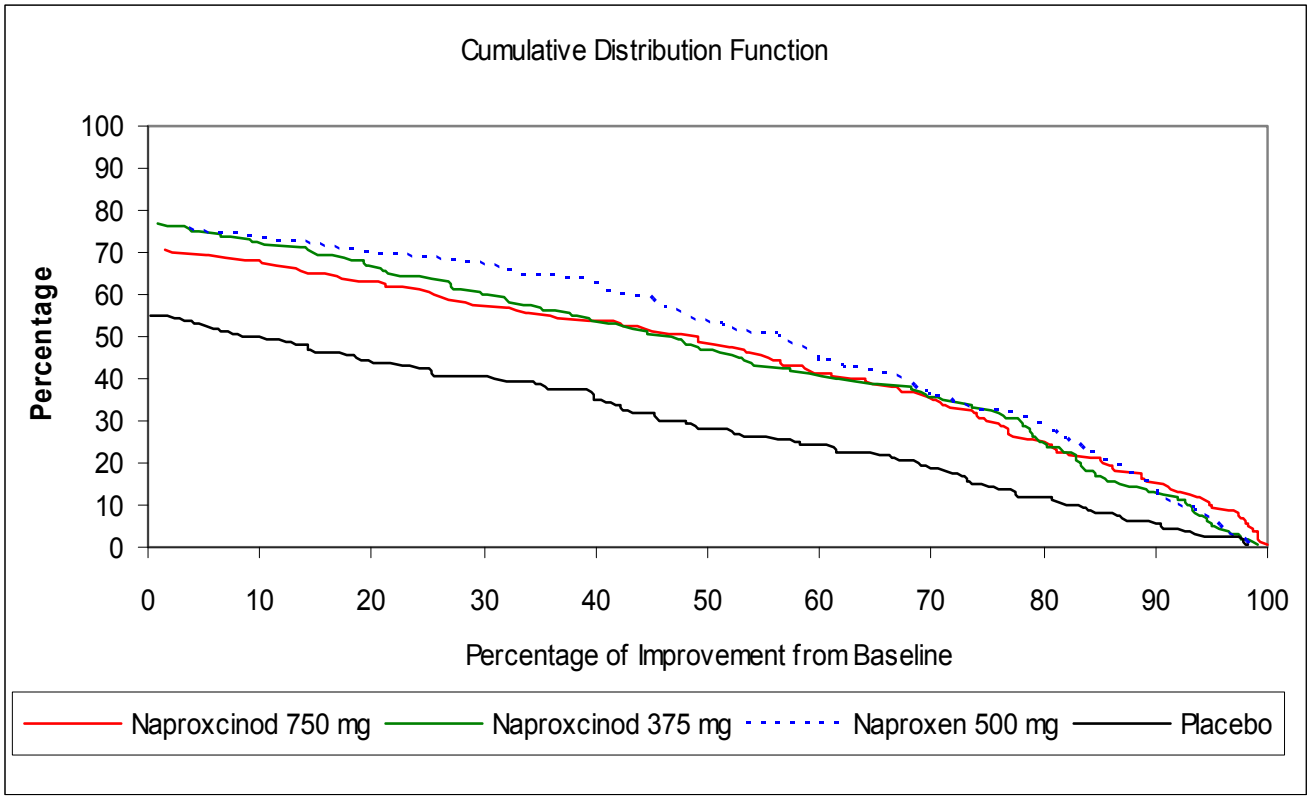
Evaluation of Superiority
WOMAC Function



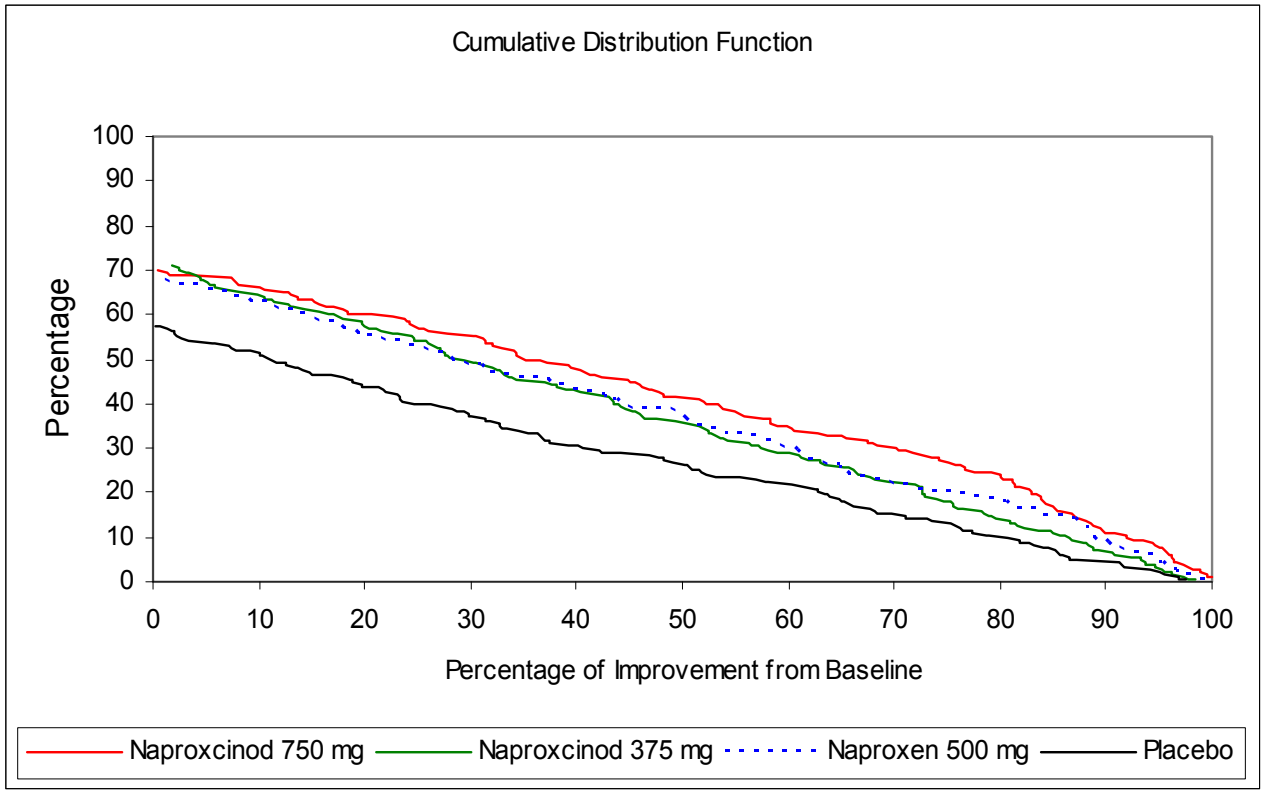
Evaluation of Superiority
Patient's Overall Rating of Disease Status



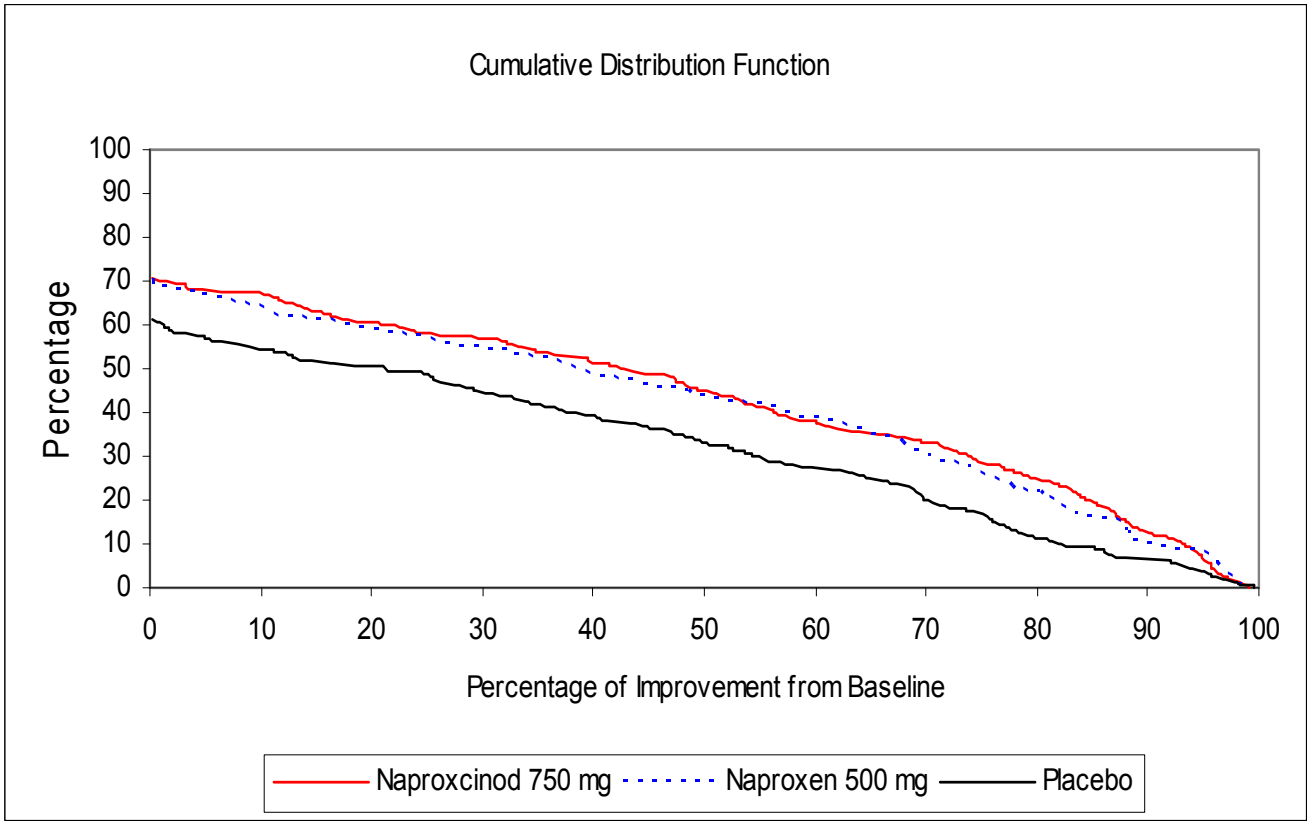
Continuous Responder Curve
Study 301



Continuous Responder Curve Study 302



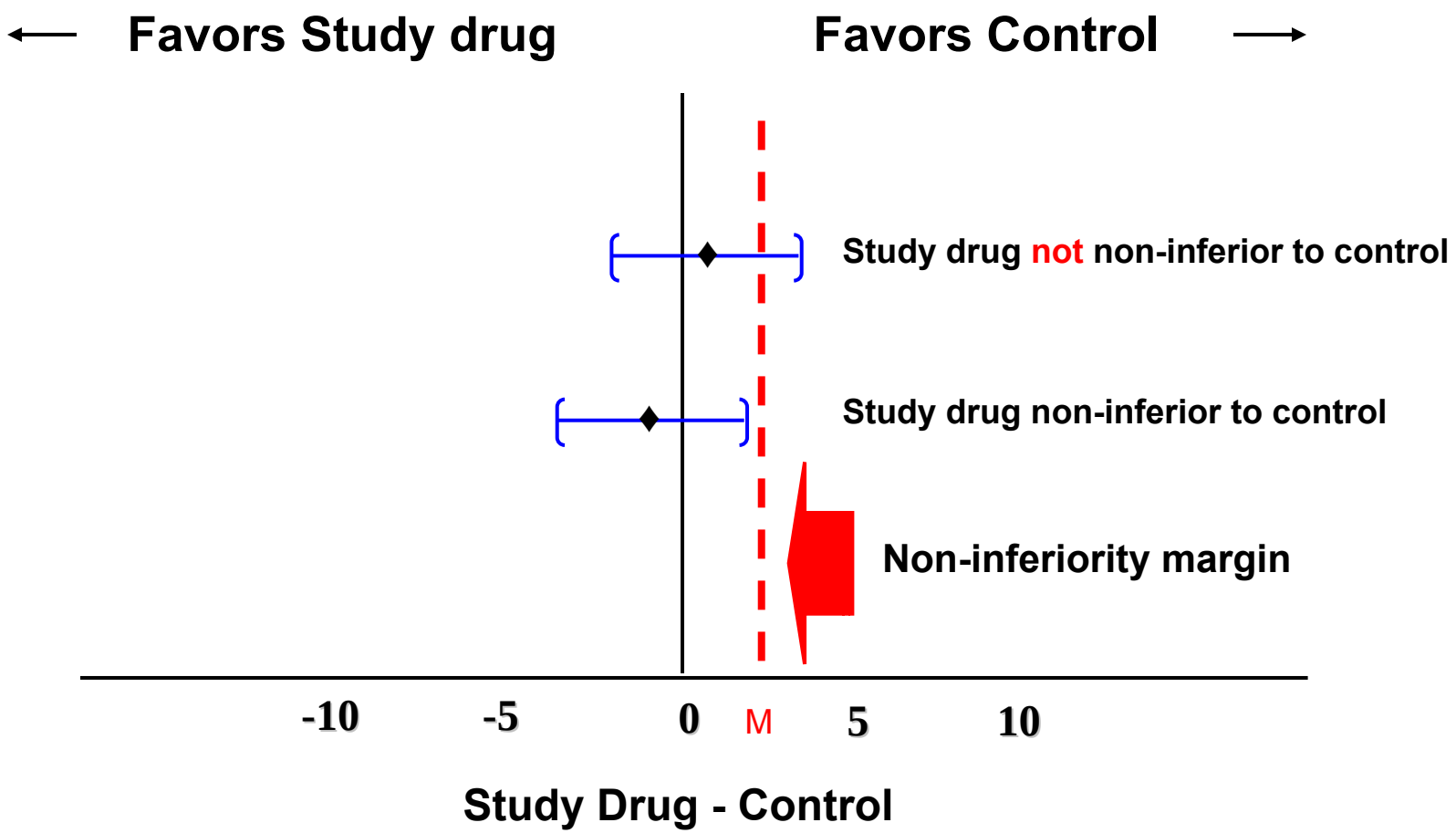
Continuous Responder Curve Study 303



Evaluation of Non-inferiority

- In general, NI design seeks to show that a difference in response between an active control and a test drug is less than some margin
- Reasons for use
  - To demonstrate efficacy when placebo is unethical
  - To demonstrate comparative effectiveness

Evaluation of Non-inferiority



Evaluation of Non-Inferiority

- Active control: Naproxen 500 mg bid
- Applicant's rationale:
  - Show similar efficacy between naproxcinod and naproxen
  - Attempt to make comparable safety claims regarding GI safety and BP effects

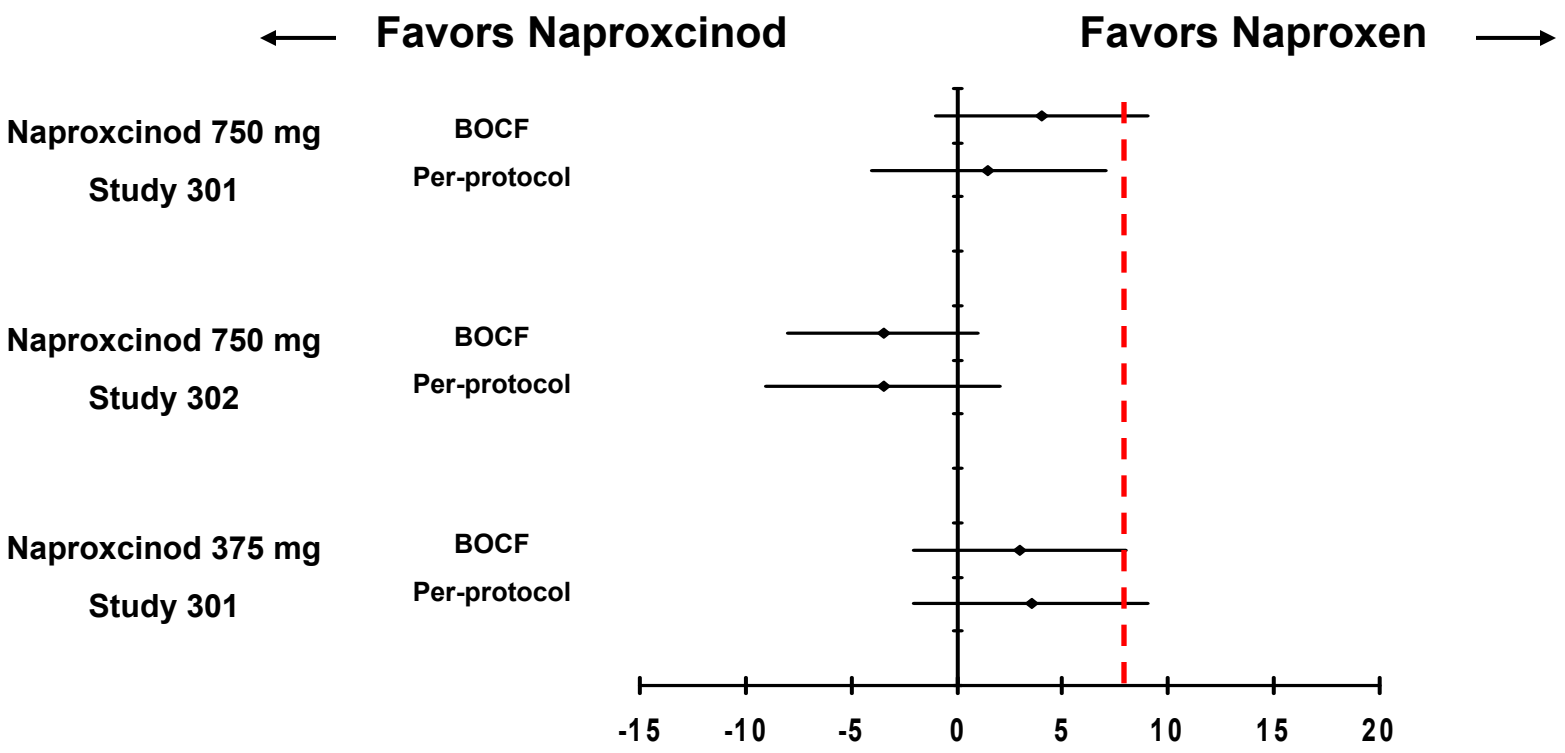
Evaluation of Non-inferiority

- Naproxcinod 750 mg vs Naproxen (Study 301, Study 302)
- Naproxcinod 375 mg vs Naproxen (Study 301)

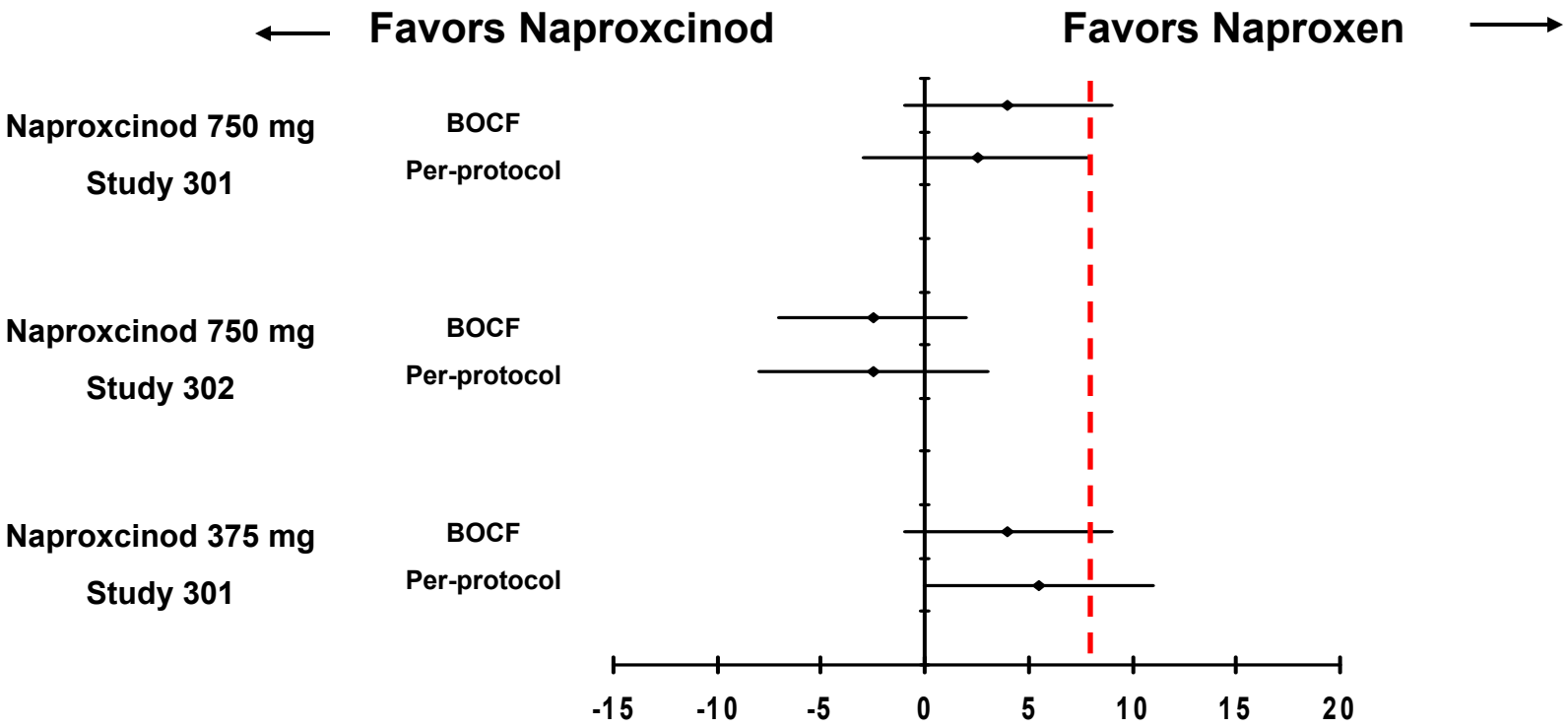
- WOMAC pain and function (Study 301, Study 302)
  - Upper limit of 95% CI < 8 mm

- Patient's overall rating of disease status (Study 301)
  - Lower limit of 95% CI > -0.4

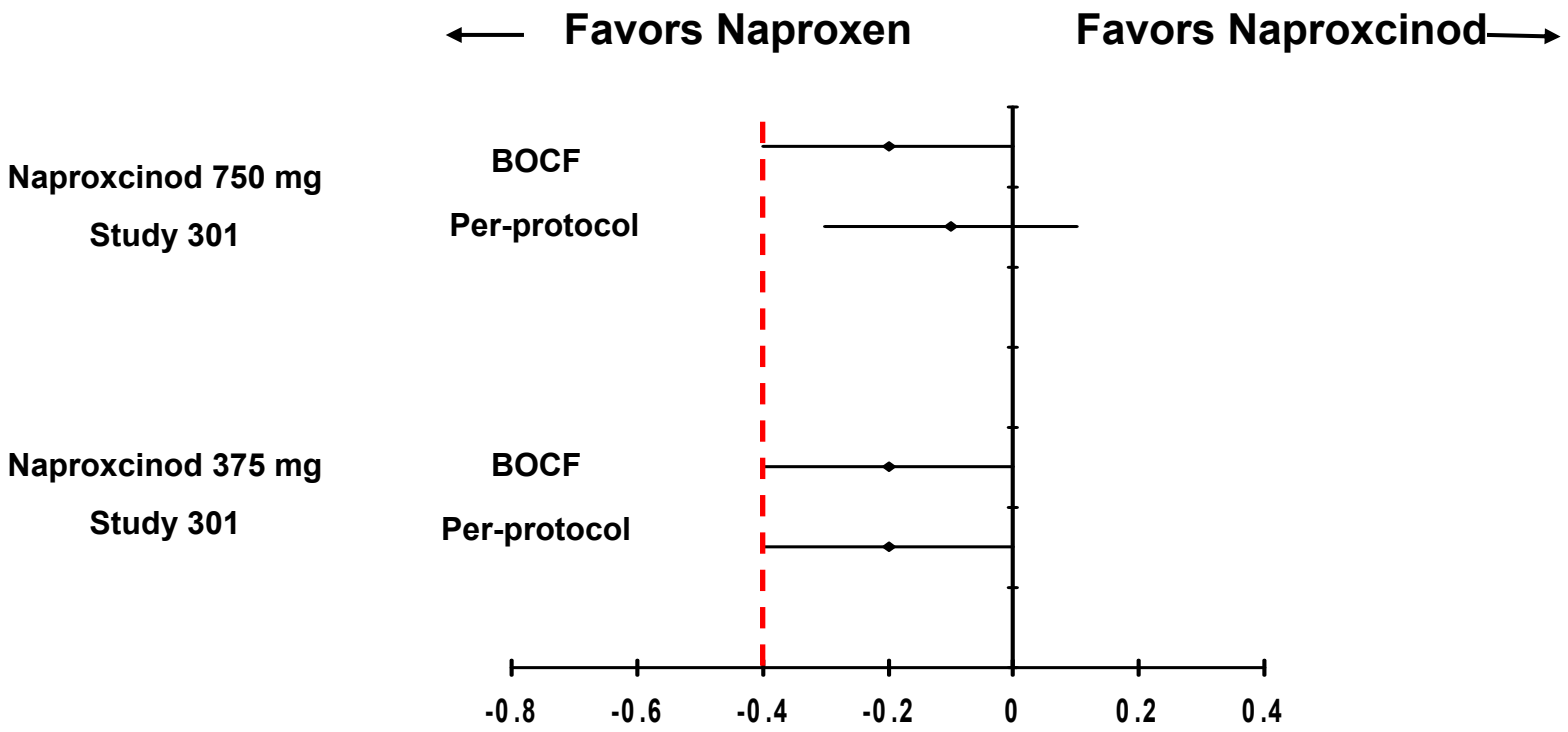
Evaluation of Non-inferiority
WOMAC Pain



Evaluation of Non-inferiority
WOMAC Function



Evaluation of Non-inferiority
Patient's Overall Rating of Disease Status



Efficacy Summary

Superiority to Placebo

- Naproxcinod was superior to placebo in 3 adequate and well-controlled studies involving osteoarthritis of the knee and hip

Non-inferiority to Naproxen

- The Applicant has not provided replicated evidence to support the non-inferiority of naproxcinod to naproxen even using a NI margin that was 70% of the treatment effect size (8 mm for WOMAC pain and function, 0.4 for patient overall rating of disease status)

SAFETY

Naproxcinod Exposure

- 4033 subjects/patients treated with at least one dose
- Duration
  - 893 patients for at least 26-weeks
  - 621 patients for at least 52-weeks
  - 264 patients at maximum dose (1500 mg/day) ≥ 52 weeks

Deaths

	Naproxcinod (N=4023)	**Placebo** (N=1412)	**Naproxen** (N=1633)	**Rofecoxib** (N=342)
Deaths	3 (0.07%)	0	1 (0.06%)	0

Deaths in Naproxcinod Treatment Group

- Patient 011-006 (79 y/o F): Motor Vehicle Accident
- Patient 112-005 (69 y/o M): Coronary Artery Disease
- Patient 147-004 (73 y/o F): Asphyxia secondary to homicide

Serious Adverse Events
(Placebo – Controlled OA Studies up to 13 - weeks)

	All Naproxcinod (N=2411)	Placebo (N=1114)	Naproxen (N=1175)
Any SAE	32 (1.3%)	20 (1.8%)	13 (1.1%)
System Organ Class **Preferred Term**			
Gastrointestinal	7 (0.3%)	4 (0.4%)	3 (0.3%)
GI hemorrhage	3 (0.1%)	0	1 (<0.1%)
Upper GI hemorrhage	1 (<0.1%)	0	0
Duodenal ulcer	1 (<0.1%)	0	0
Cardiac disorders	6 (0.2%)	5 (0.4%)	1 (<0.1%)
Atrial fibrillation	2 (<0.1%)	1 (<0.1%)	0
Myocardial infarction	1 (<0.1%)	0	1 (<0.1%)
Arteriosclerosis Coronary Artery	1 (<0.1%)	0	0

Adverse Events Leading to Discontinuation (Placebo - Controlled OA Studies up to 13 - weeks)

	All Naproxcinod (N=2411)	Placebo (N=1114)	Naproxen (N=1175)
Overall Incidence	154 (6.4%)	71 (6.4%)	72 (6.1%)
System Organ Class **Preferred Term**			
Gastrointestinal	61 (2.5%)	32 (2.9%)	45 (3.8%)
Dyspepsia	15 (0.6%)	4 (0.4%)	9 (0.8%)
Nausea	11 (0.5%)	6 (0.5%)	7 (0.6%)
Abdominal pain (Upper)	9 (0.4%)	5 (0.4%)	12 (1.0%)
Nervous system	30 (1.2%)	15 (1.3%)	7 (0.6%)
Headache	10 (0.4%)	7 (0.6%)	3 (0.3%)
Dizziness	9 (0.4%)	4 (0.4%)	1 (<0.1%)
Paraesthesia	2 (<0.1%)	0	1 (<0.1%)

Summary of GI TEAEs
(Placebo – Controlled OA studies up to 13 - weeks)

Term	All Naproxcinod (n=2411)	Placebo (N=1114)	Naproxen (N=1175)
GI AEs	615 (25.5%)	199 (17.9%)	315 (26.8%)
Most Common GI TEAES			
Dyspepsia	129 (5.4%)	37 (3.3%)	67 (5.7%)
Diarrhea	123 (5.1%)	44 (3.9%)	49 (4.2%)
Nausea	116 (4.8%)	38 (3.4%)	44 (3.7%)
Constipation	81 (3.4%)	17 (1.5%)	42 (3.6%)
Upper abdominal pain	66 (2.7%)	21 (1.9%)	54 (4.6%)
GI SAEs	7 (0.3%)	4 (0.4%)	3 (0.3%)

Common Adverse Events

(≥2% Placebo - Controlled OA studies up to 13 - weeks)

	Naproxcinod				
Preferred Term	**All doses (N=2411)**	**750 mg bid (N=1470)**	**375 mg bid (N=598)**	**Placebo (N=1114)**	**Naproxen (N=1175)**
Headache	399 (16.5%)	230 (15.6%)	52 (8.7%)	136 (12.2%)	187 (15.9%)
Dyspepsia	129 (5.4%)	90 (6.1%)	15 (2.5%)	37 (3.3%)	67 (5.7%)
Diarrhea	123 (5.1%)	72 (4.9%)	22 (3.7%)	44 (3.9%)	49 (4.2%)
Nausea	116 (4.8%)	64 (4.4%)	20 (3.3%)	38 (3.4%)	44 (3.7%)
Back Pain	113 (4.7%)	57 (3.9%)	20 (3.3%)	36 (3.2%)	43 (3.7%)

Special Safety Studies

- Nitric oxide (NO) donating group effects:
  - Gastrointestinal System
    - Endoscopy Studies in healthy subjects and OA patients
  - Cardiovascular System (BP)
    - Ambulatory blood pressure monitoring studies
    - Pooled orthostatic BP analysis from three Phase 2 studies
    - Pooled BP analysis of phase 3 OA trials

Conclusions

- Naproxcinod (375 mg and 750 mg twice a day) is more effective than placebo in the relief of signs and symptoms of OA
- Similarity to naproxen has not been demonstrated
- General safety profile of naproxcinod is consistent with that of the NSAID drug class

BP effect of naproxcinod

DCRP Review

Joint Meeting of the Arthritis Advisory Committee (AAC)

and Drug Safety and Risk Management Advisory Committee (DSaRM)

May 12, 2010

Suchitra Balakrishnan MD, PhD

Disclaimer

- All data presented is from sponsor's analyses, DCRP did not perform any independent statistical analyses

Issues related to BP effect

- Efficacy:
  - antihypertensive (vs. placebo equivalent)
  - relative effect compared to active comparator (naproxen)
- Safety issues related to hypotensive effect at peak
- *(No acute withdrawal data e.g. within 72 hrs of treatment cessation are available)*

Comparative claim for superiority related to BP effects

- Issues:
  - across class comparison for (CINOD compound vs. naproxen) superiority related to a safety issue
  - relevance of effect on BP has to be balanced against comparative efficacy and other safety (cardiac and non-cardiac) and approvability issues

How is a drug approved as a antihypertensive?

- Superior to placebo or is superior in ABPM studies compared to baseline measurements in two adequate and well controlled studies
  - active comparator in 2 studies for a superiority claim
  - the effect is persistent throughout the dosing interval
  - peak/trough ratio not more than factor of 2
- *References-ICH E-10, Antihypertensive guidance, 97th DCRP advisory committee meeting July 18, 2002 to discuss superiority claim for candesartan vs. losartan*

BP data from the naproxcinod program

- Ambulatory Blood Pressure Monitoring (ABPM) to evaluate the 24-hour BP effect (Studies HCT-3012-X-104, 111 and 112).
- Office Blood Pressure Measurements to evaluate the peak effect (pooled phase 1 & phase 2 and Phase 3 program).
- Orthostatic Blood Pressure Measurements to evaluate the effects on BP and HR after orthostatic challenge tests
  - first dose effect- SP-NON-0005, 0010 and 0017
  - chronic effects- phase 2 studies-3012-X-111, SP-NON-0005, 0010 and 0017; phase 3 study-3012-X-302

- Drug-drug interaction studies [SP-NON-22, 21 (NTG), 3012-X-107(siladenafil)].

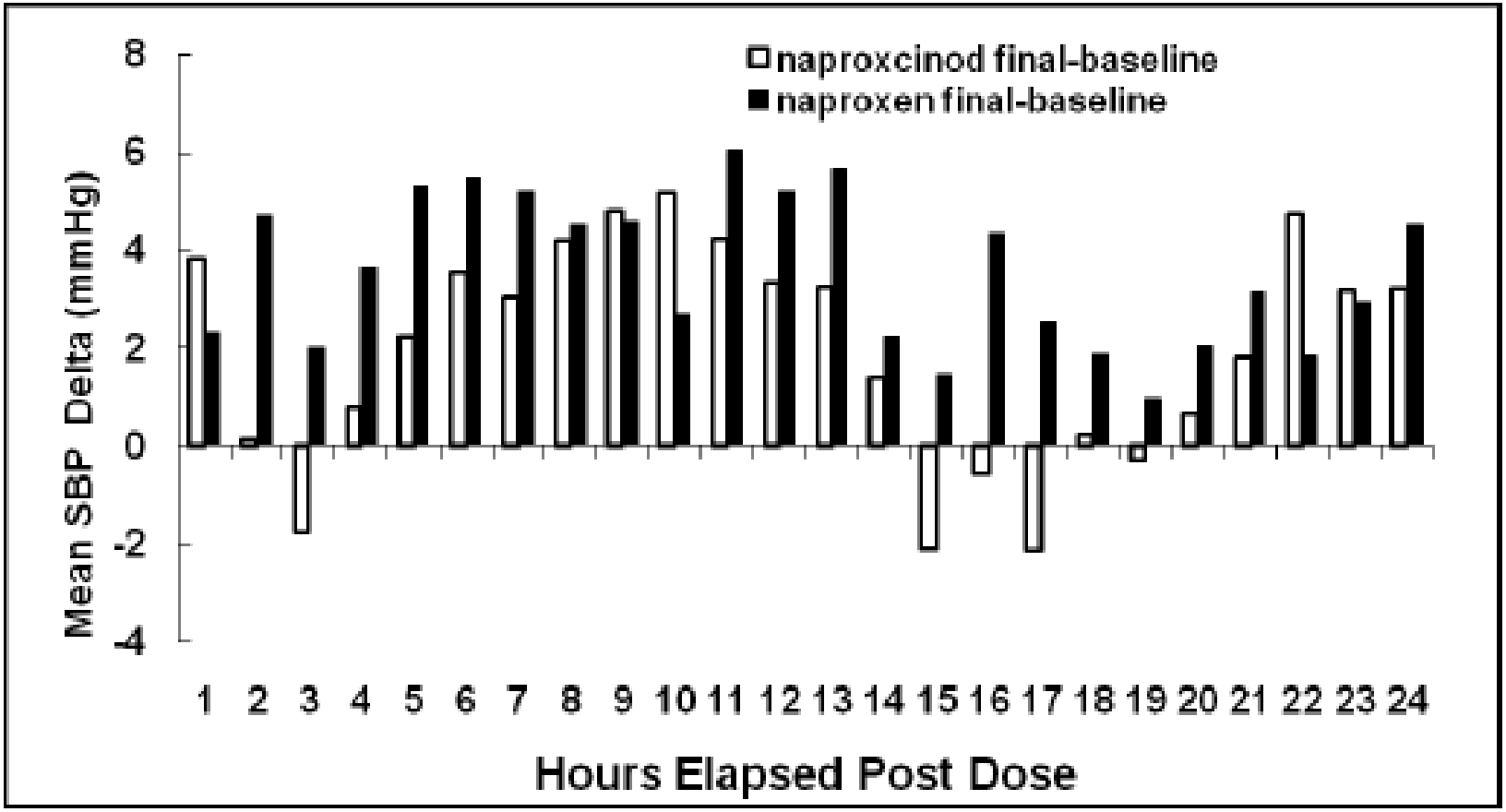
Efficacy-ABPM studies only

- Only ABPM studies have trough effect reported.
- Cuff BP used to qualify subject in trial, concurrent placebo arm is not needed with ABPM since change from baseline reflects drug effect

ABPM studies

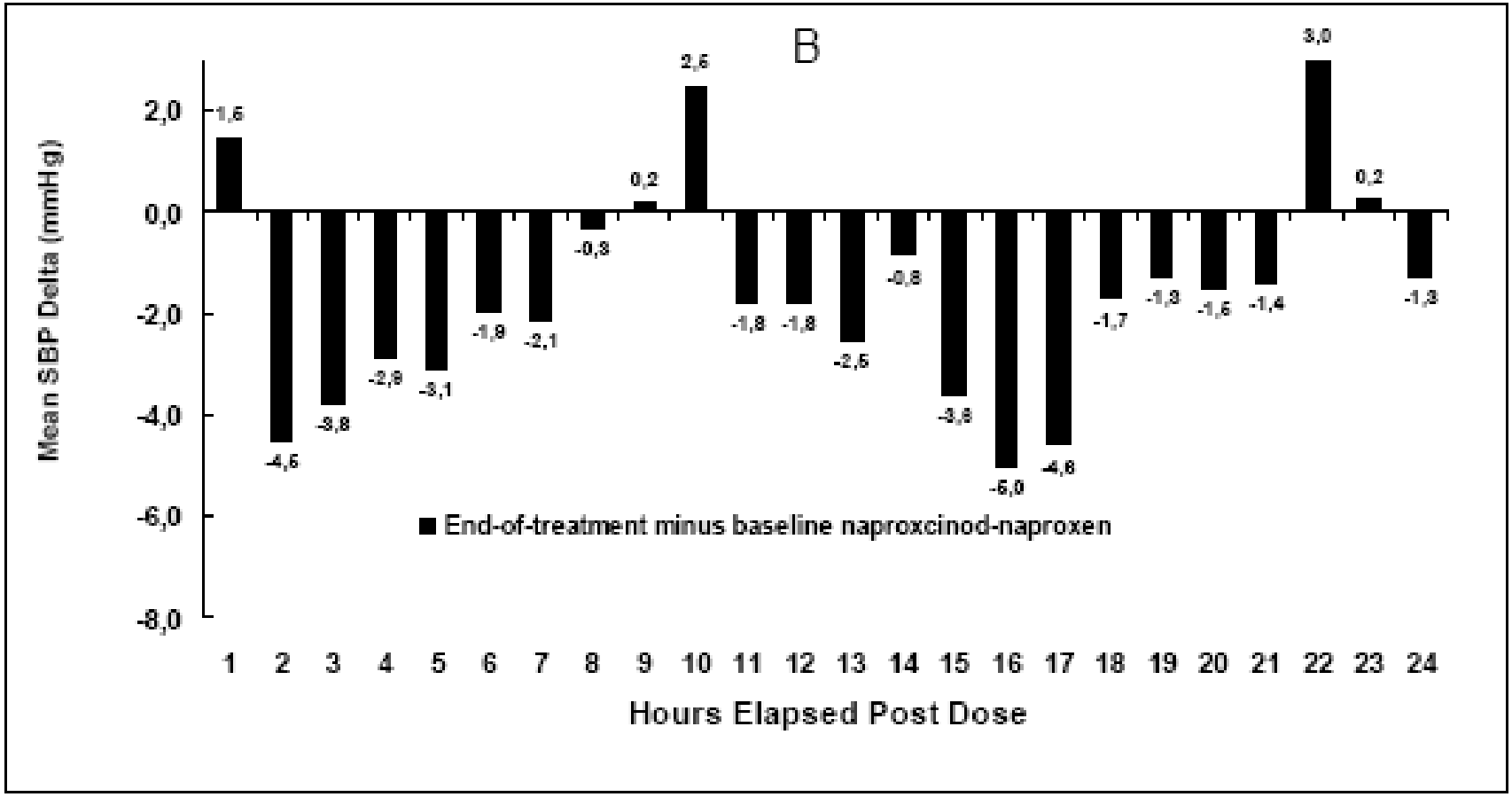
	104	112	111
Design	Multicenter, DB, Randomized, Cross-Over, Naproxen Controlled Study	Multicenter, DB, Randomized, Naproxen and Ibuprofen-controlled, Parallel-Group Pharmacological Study	Multicenter, DB, Randomized, Forced Titration to maximum dose, Naproxen-Controlled, Parallel-Group Pharmacodynamic Study
Subjects	Stable essential HTN (no OA), 50-75 yrs of age	Patients with osteoarthritis (OA) and controlled essential hypertension.	Patients with osteoarthritis (OA) and controlled essential hypertension.
Active treatment	Naproxen 500mg bid and Naproxcinod (750 mg bid) for 2 periods of 14 days	Naproxcinod (375 mg and 750 mg, bid) compared to naproxen and to Ibuprofen for 90 days each	Naproxcinod (in doses ranging from 375 mg to 1125 mg, bid) and naproxen for 3 weeks each.
Randomized (safety)	131 (65/66)	299 (59/65/60/60/55)	118 (59/59)
Randomized (mITT)	121 (61/60)	213 (44/49/46/40/34)	103 (51/52)
cABPM		155 (36/36/32/28/23)	66 (36/30)

ABPM data-change from baseline SBP- Study 3012-X-104, naproxcinod 750 mg vs. naproxen 500 mg



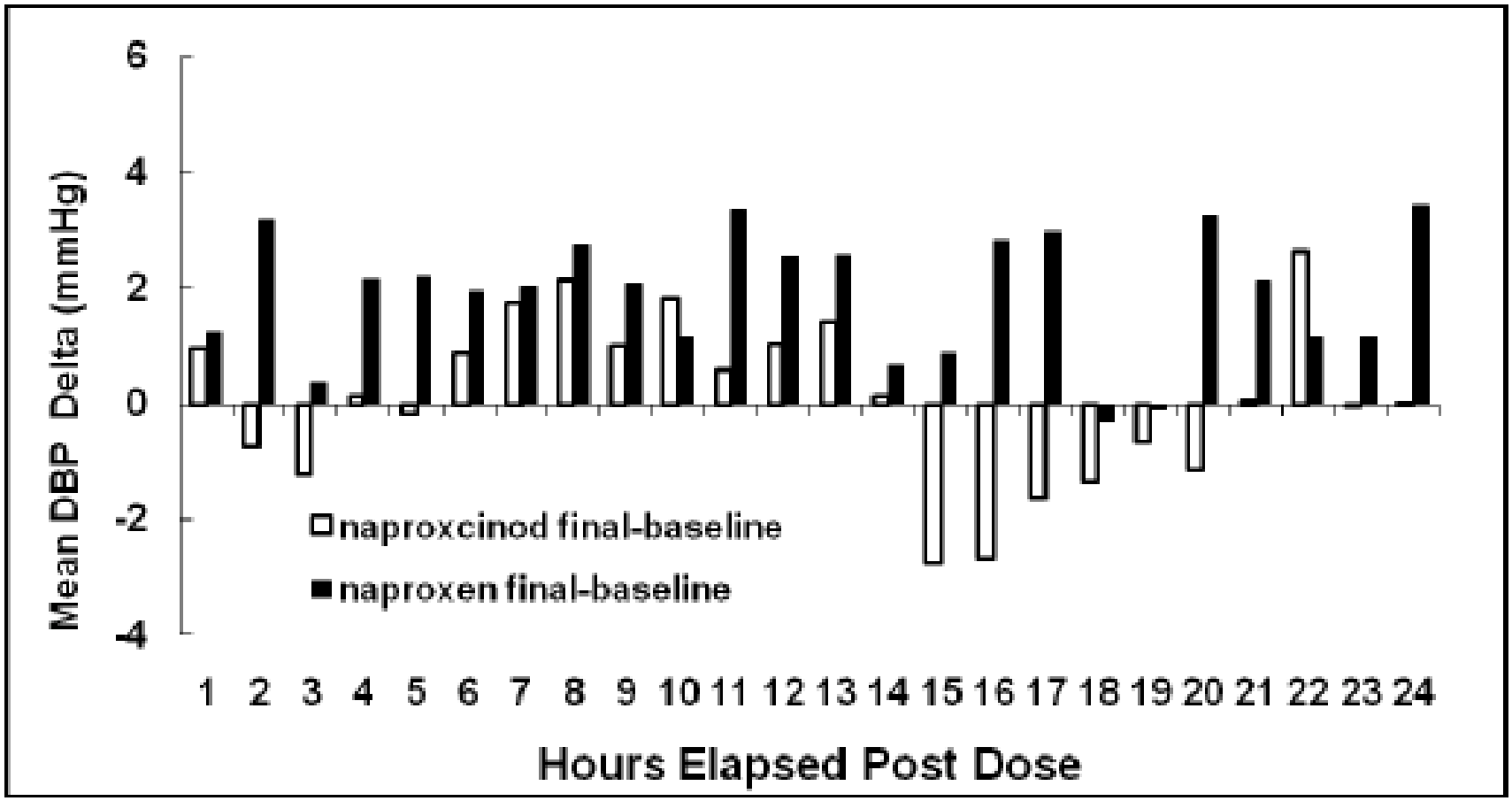
Source: Table 14.5.1

ABPM data, difference in SBP, Study 3012-X-104, naproxcinod 750 mg *minus* naproxen 500 mg



Source: Table 14.5.1

ABPM data-change from baseline DBP- Study 3012-X-104, naproxcinod 750 mg vs. naproxen 500 mg



Source: Table 14.5.2

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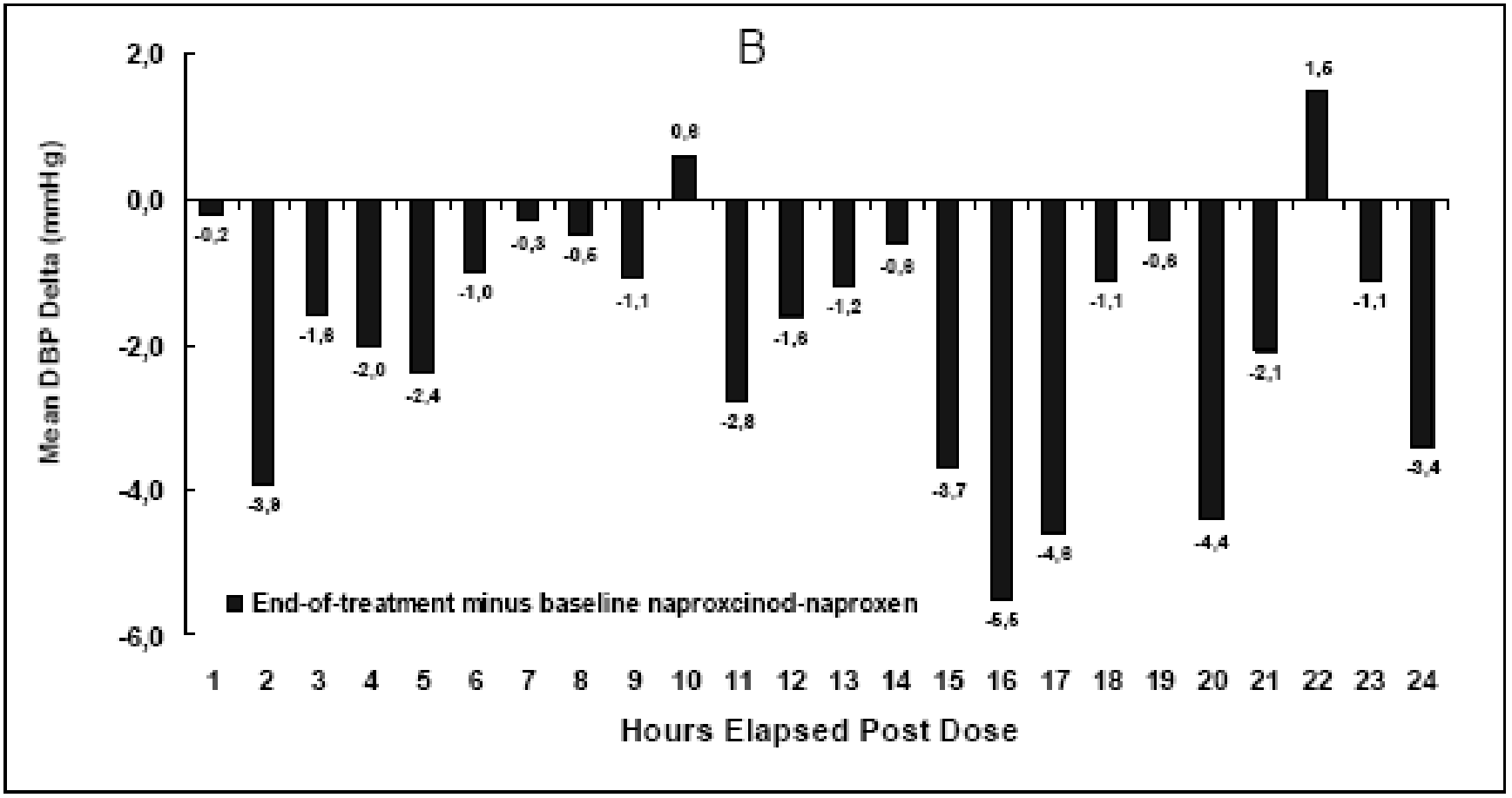
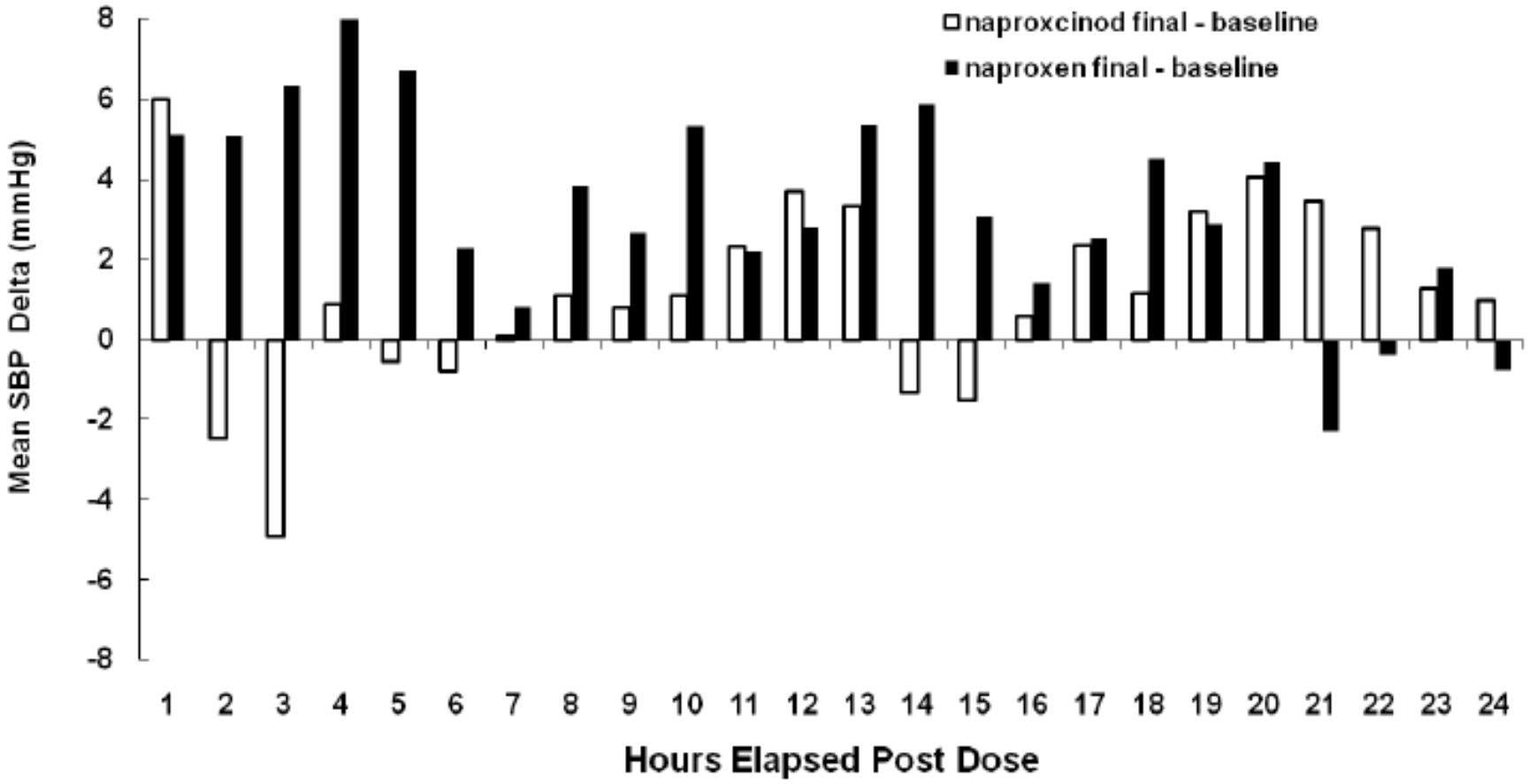


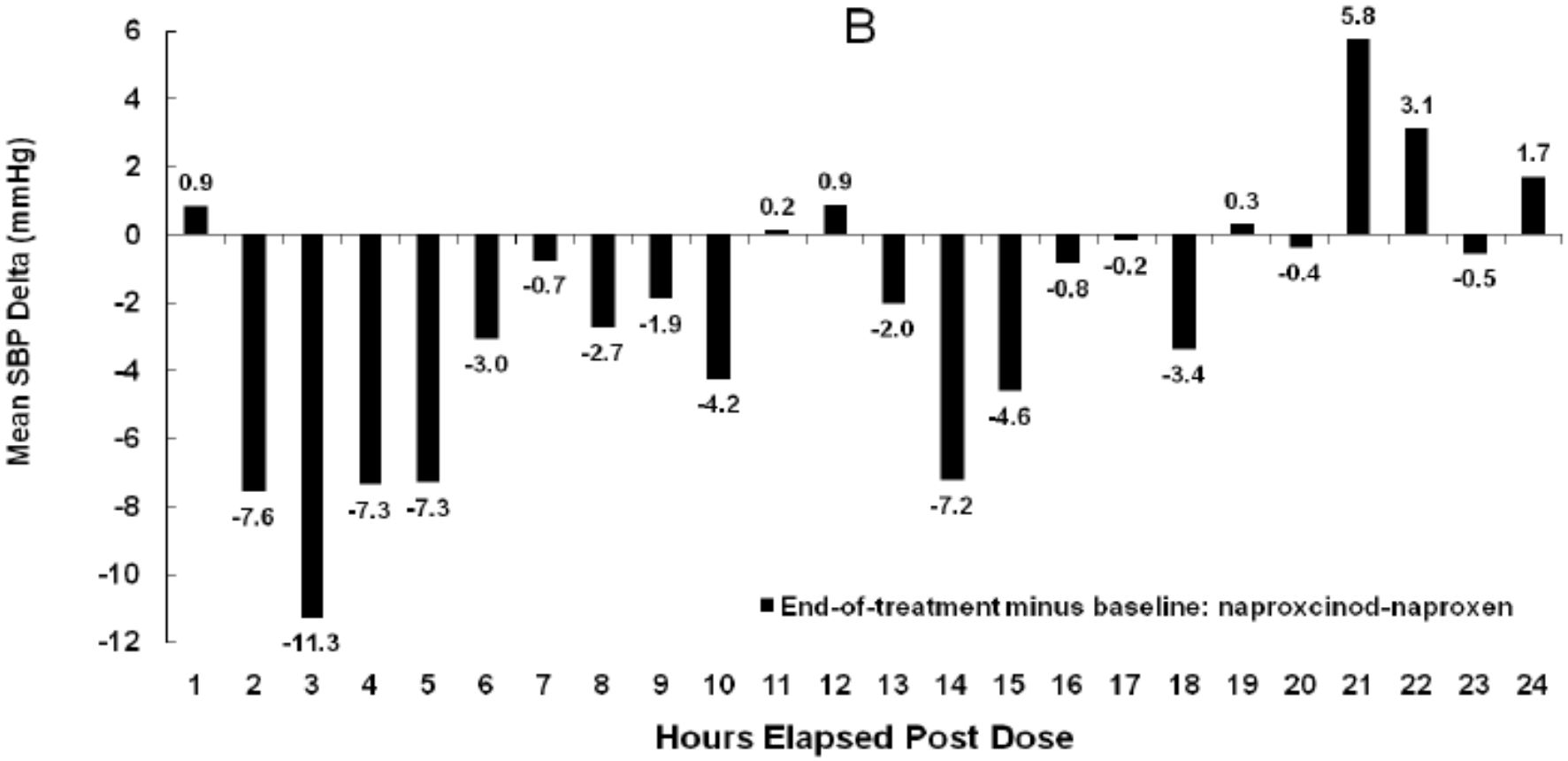
Source: Table 14.5.2

ABPM data-change from baseline SBP- Study 3012-X-112, naproxcinod 750 mg vs. naproxen 500 mg



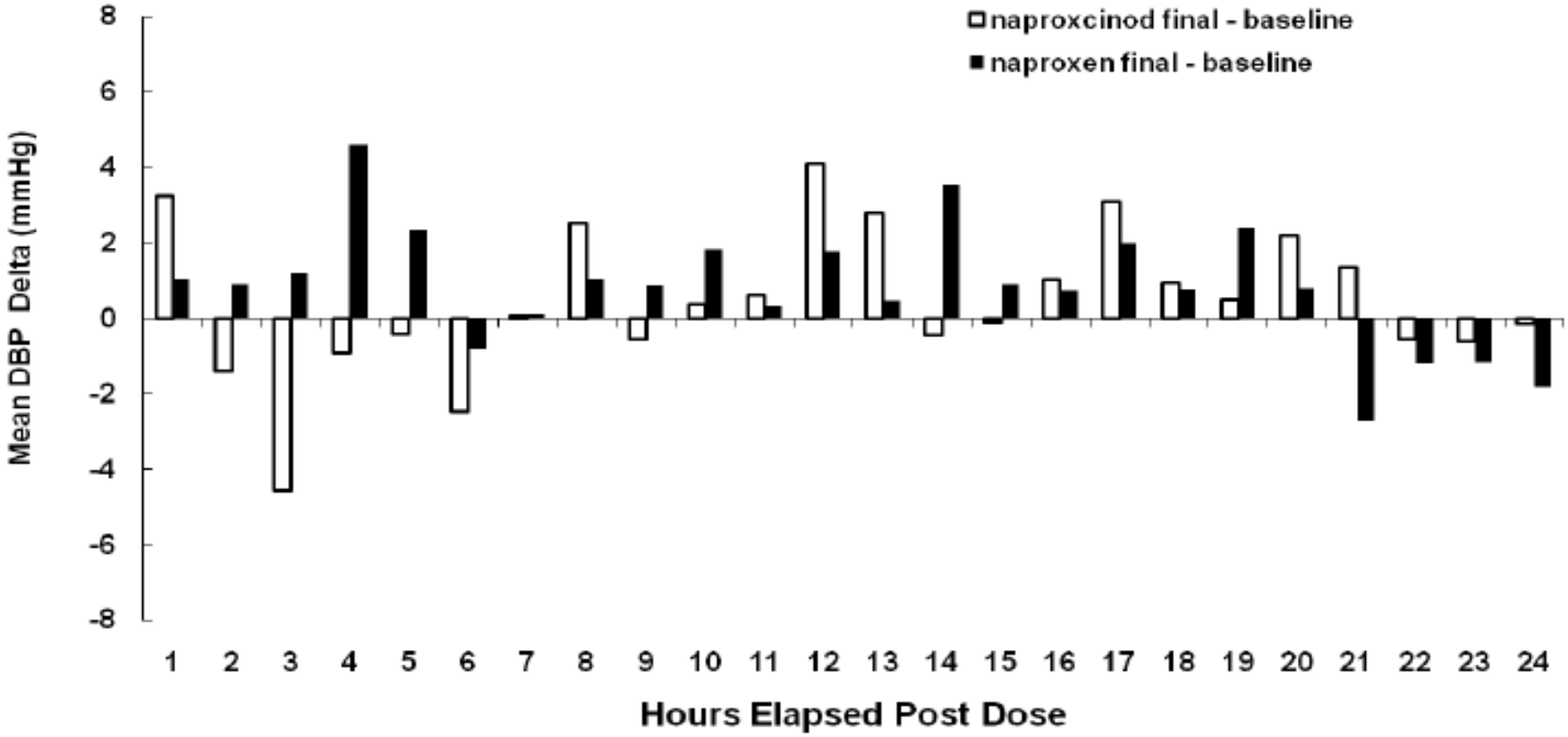
Source: Figure 112_ABPM_016

ABPM data, difference in SBP, Study 3012-X-112, naproxcinod 750 mg *minus* naproxen 500 mg



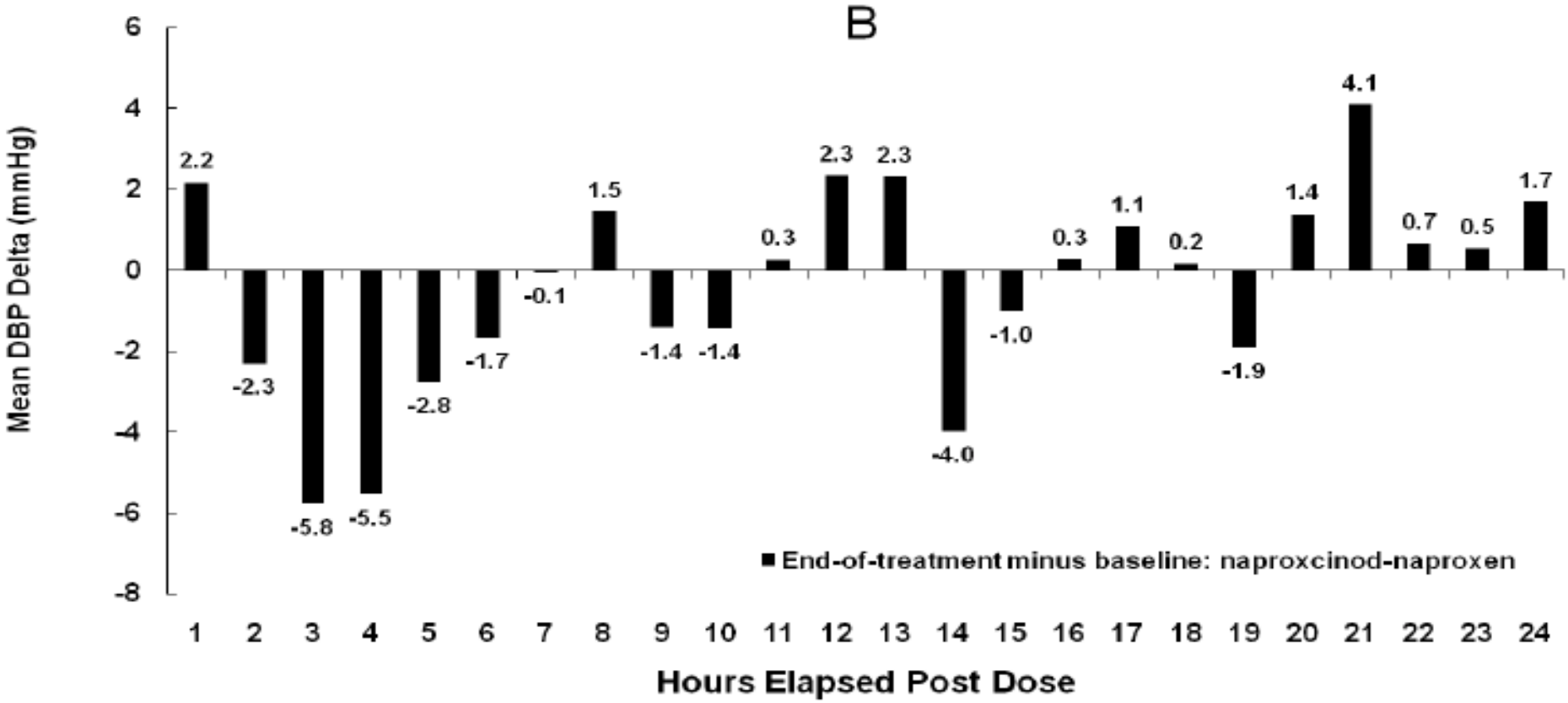
Source: Figure 112_ABPM_017 (B)

ABPM data-change from baseline DBP- Study 3012-X-112, naproxcinod 750 mg vs. naproxen 500 mg



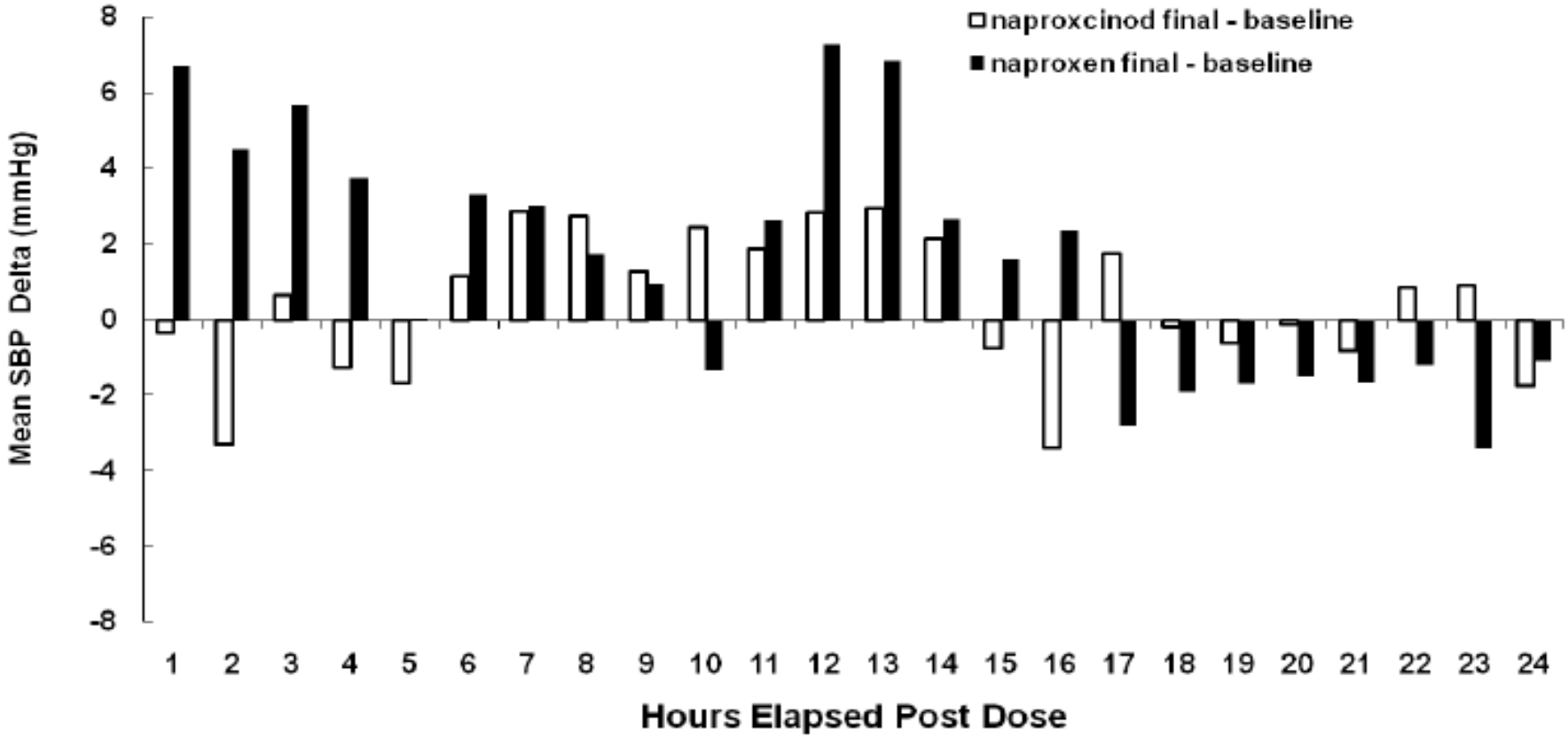
Source: Figure 112_ABPM_018

ABPM data, difference in DBP, Study 3012-X-112, naproxcinod 750 mg *minus* naproxen 500 mg



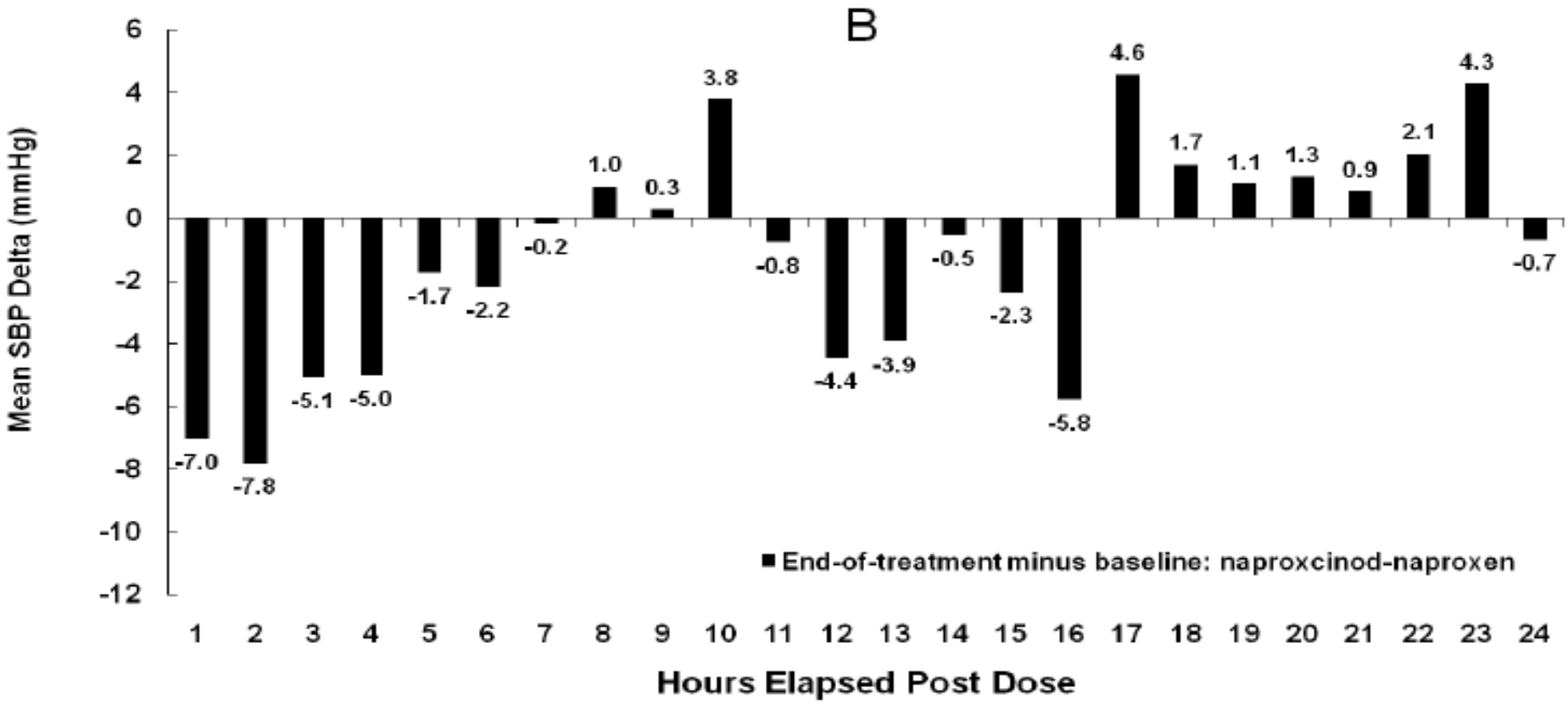
Source: Figure 112_ABPM_019 (B):

ABPM data-change from baseline SBP- Study 3012-X-112, naproxcinod 375 mg vs. naproxen 250 mg



Source: Figure 112_ABPM_020:

ABPM data, difference in SBP, Study 3012-X-112, naproxcinod 375 mg *minus* naproxen 250 mg



Source-Figure 112_ABPM_021 (B):

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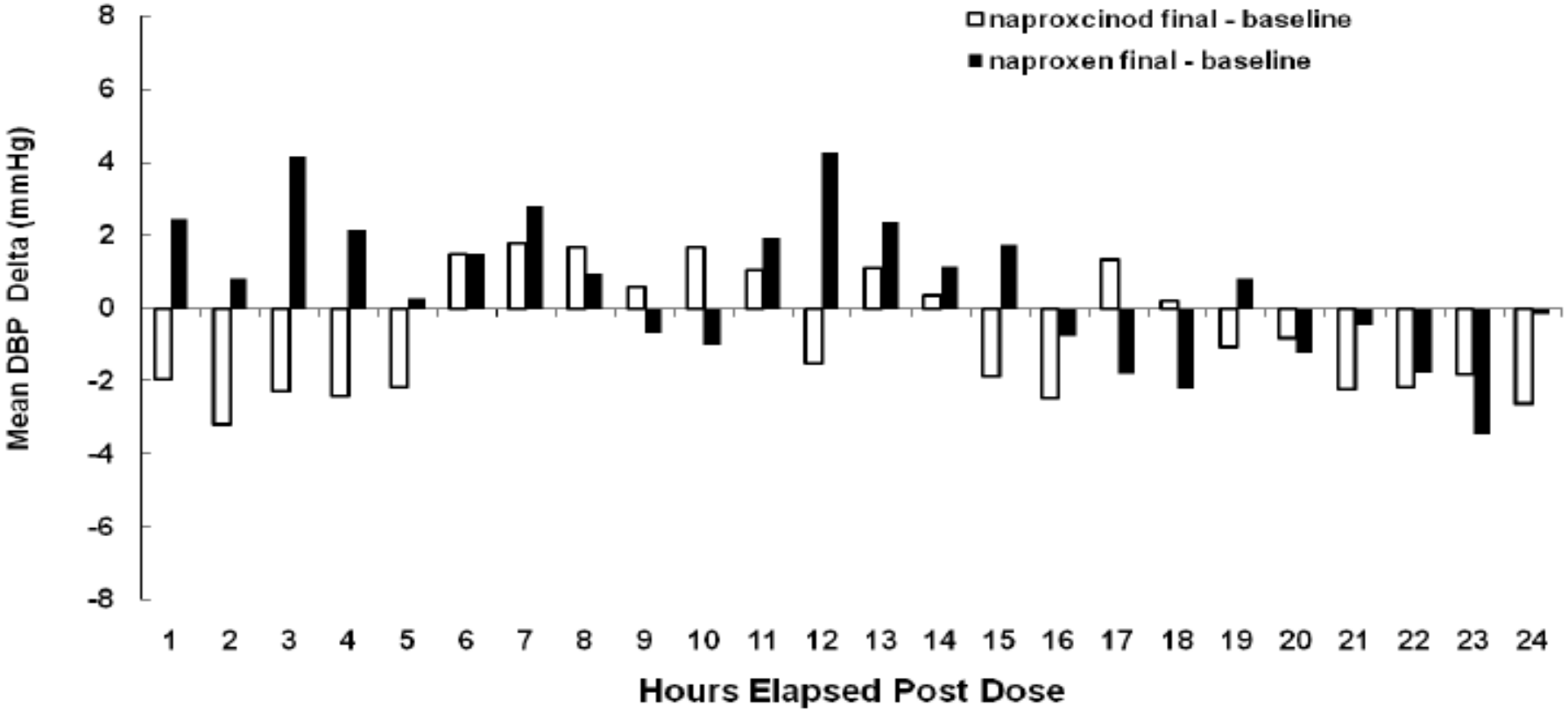
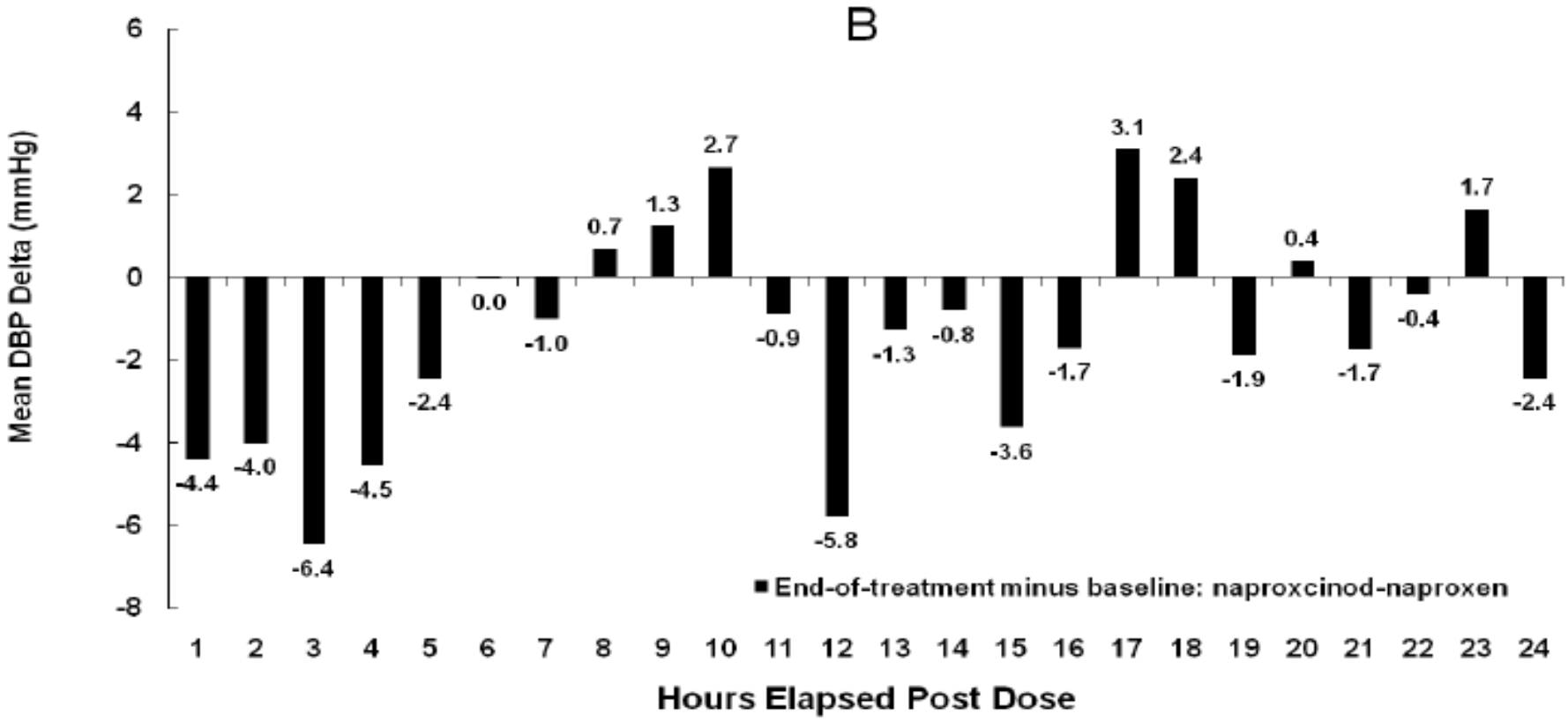


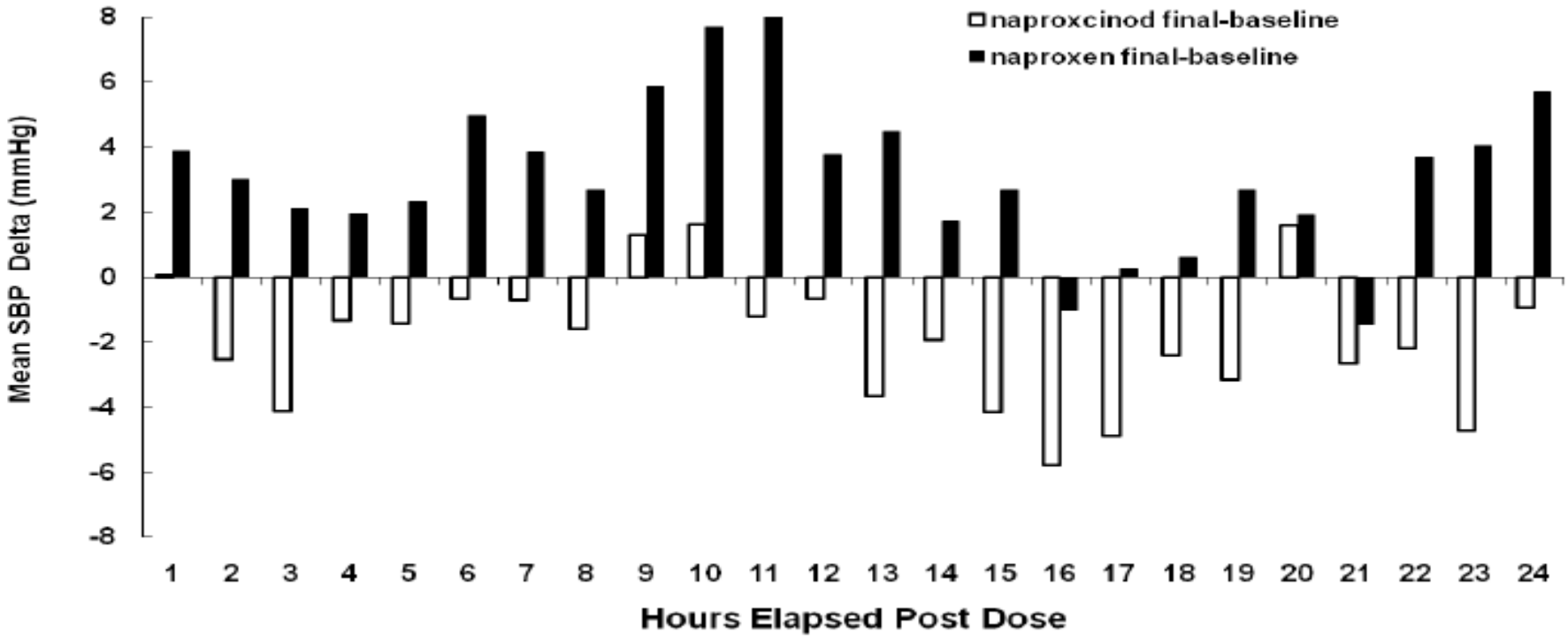
Source: Figure 112_ABPM_022

ABPM data, difference in DBP, Study 3012-X-112, naproxcinod 375 mg *minus* naproxen 250 mg



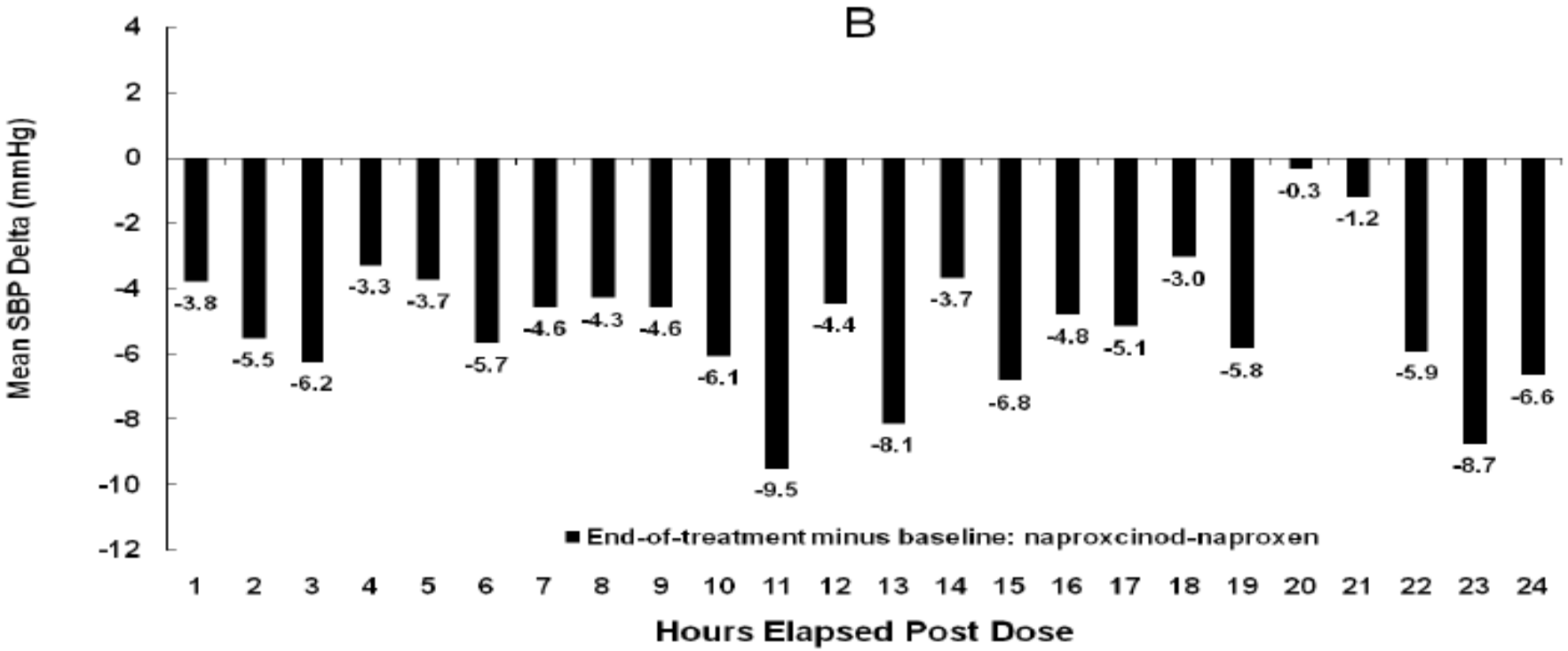
Source- Figure 112_ABPM_023 (B):

ABPM data, change from baseline SBP, Study 3012-X- 111, naproxcinod 750 mg *minus* naproxen 500 mg



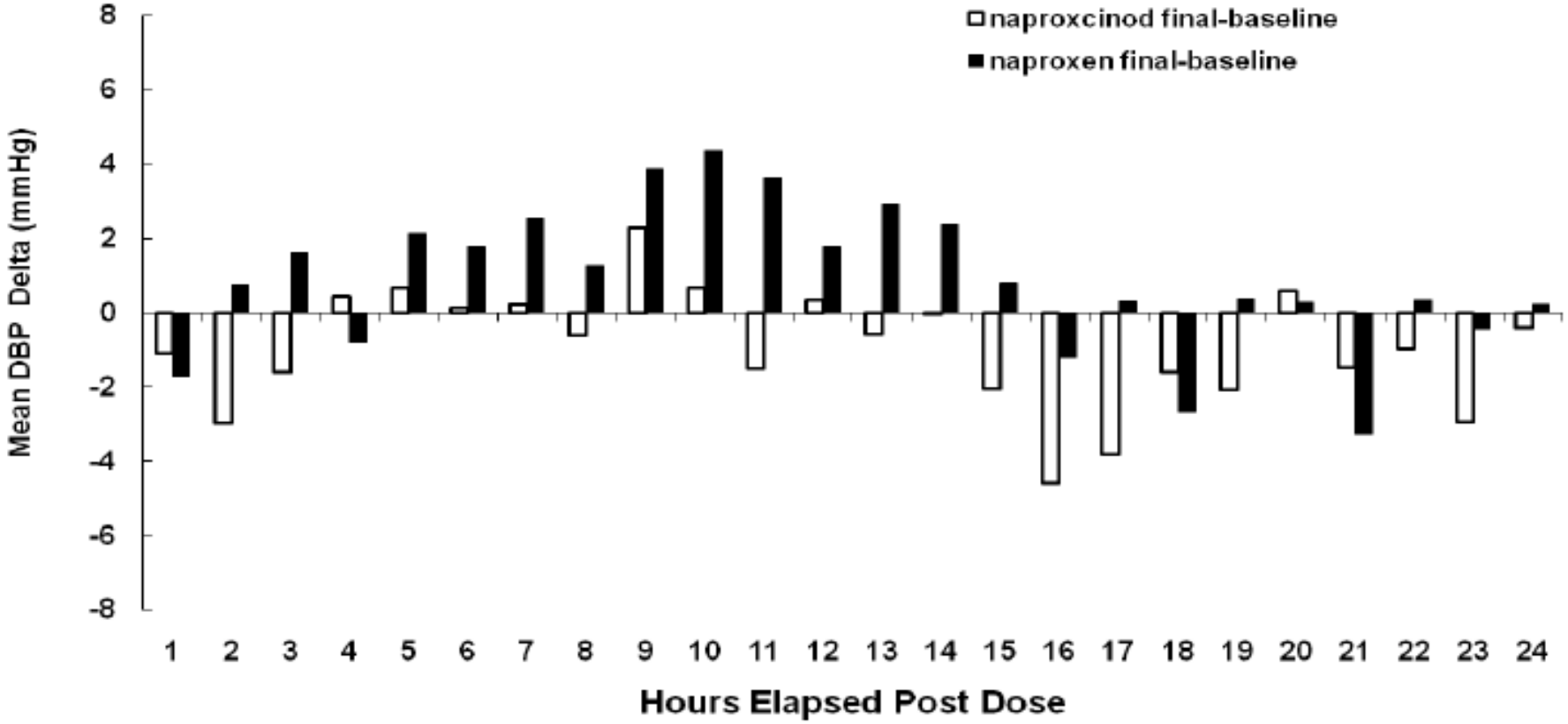
Source: Figure 111_ABPM_021:

ABPM data, difference in SBP, Study 3012-X-111, naproxcinod 750 mg *minus* naproxen 500 mg



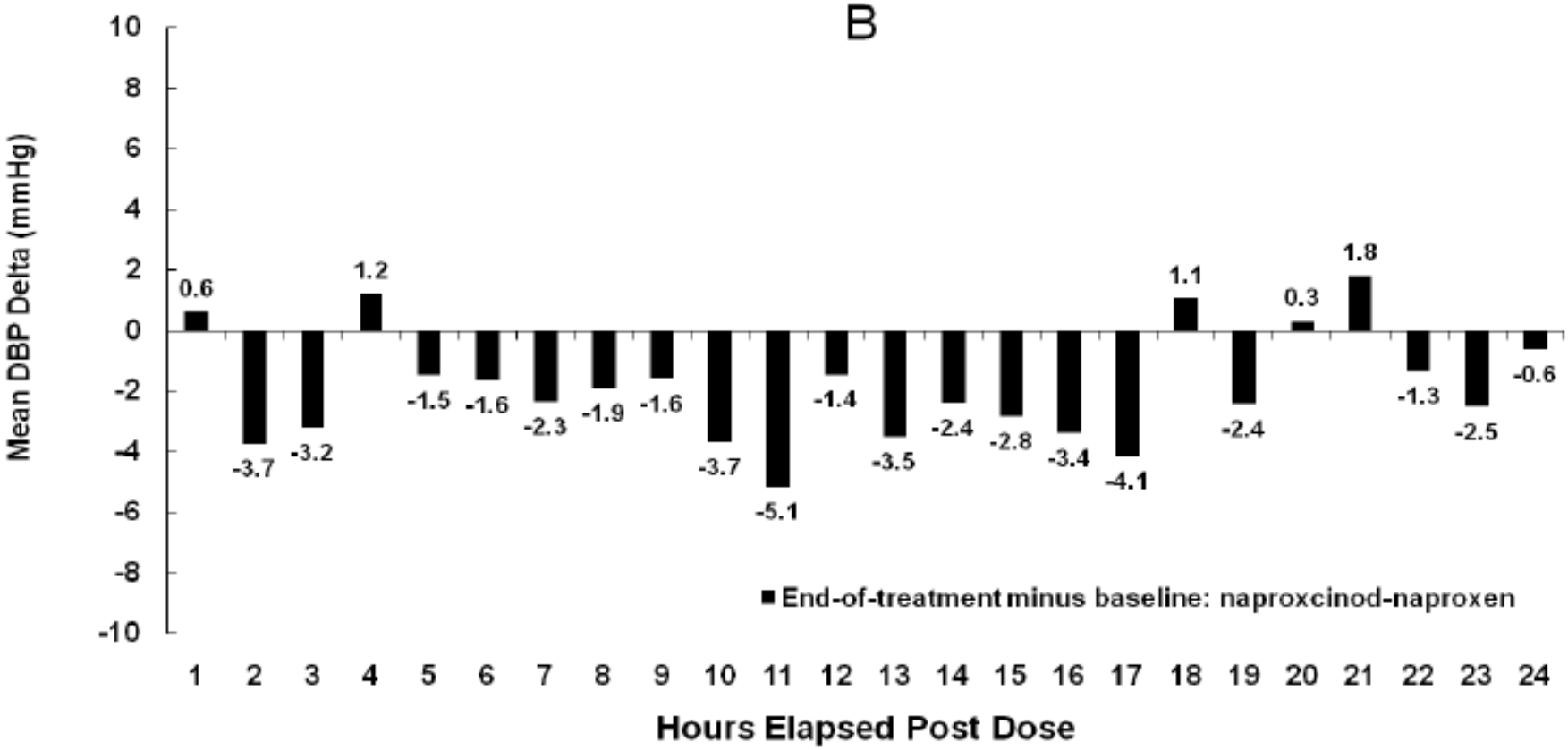
Source: Figure 111_ABPM_022 (B)

ABPM data-change from baseline DBP- Study 3012-X-111, naproxcinod 750 mg vs. naproxen 500 mg



Source: Figure 111_ABPM_027:

ABPM data, difference in DBP, Study 3012-X-111, naproxcinod 750 mg *minus* naproxen 500 mg



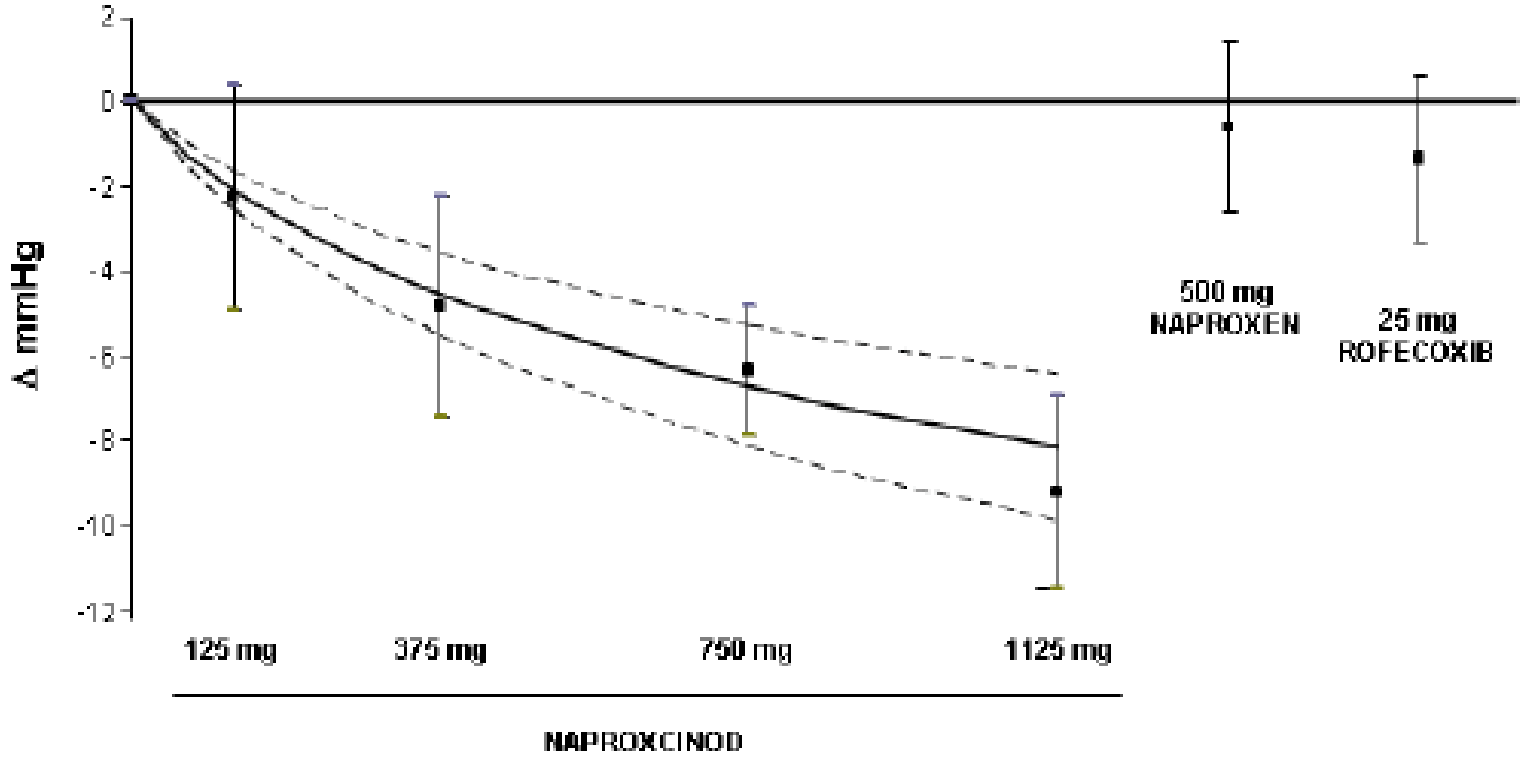
Source: Figure 111_ABPM_028 (B)

Conclusion for efficacy

- The BP effect due to naproxcinod was not consistently less than baseline through the dosing interval. Naproxcinod is therefore not approvable as an antihypertensive agent.
- Relative to equimolar doses of naproxen, with naproxcinod there appears to be a replicable lowering effect on SBP and DBP at peak (i.e. 1-4 hours post-dosing) across studies but not at trough.
- More than two-fold changes in peak-trough effects were noted in some ABPM recordings suggesting that the proposed dosing regimen does not have a consistent effect throughout the dosing interval .

Safety issues- first dose effects at peak-phase 2 (exploratory analyses)

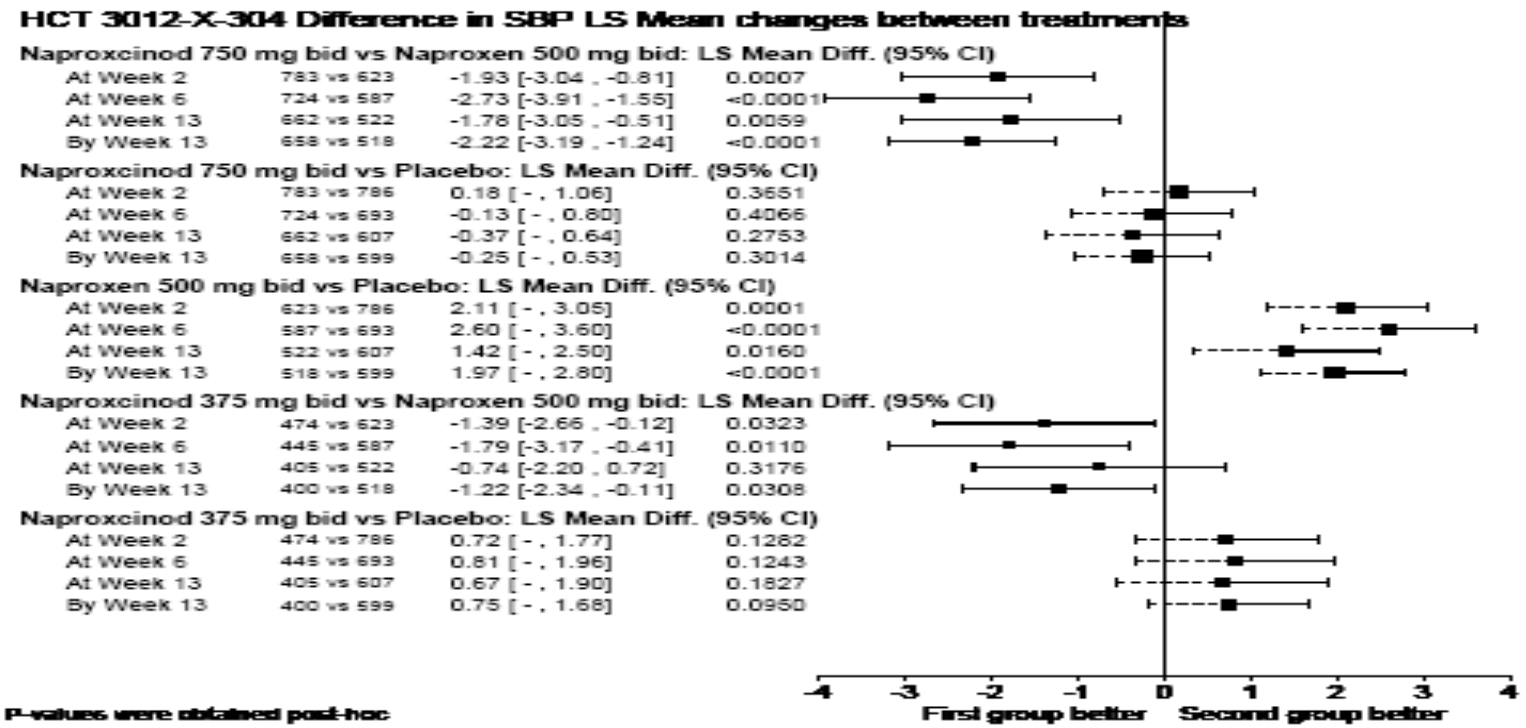
Figure 18: Effect of Treatments on Mean Change in SBP during 3 Hours Postdose Relative to Placebo (OA Subjects)



Source: Figure 18, Integrated BP report, Module 5.3.5.3

Peak effect with chronic therapy (phase 3 studies- pre-specified analyses)

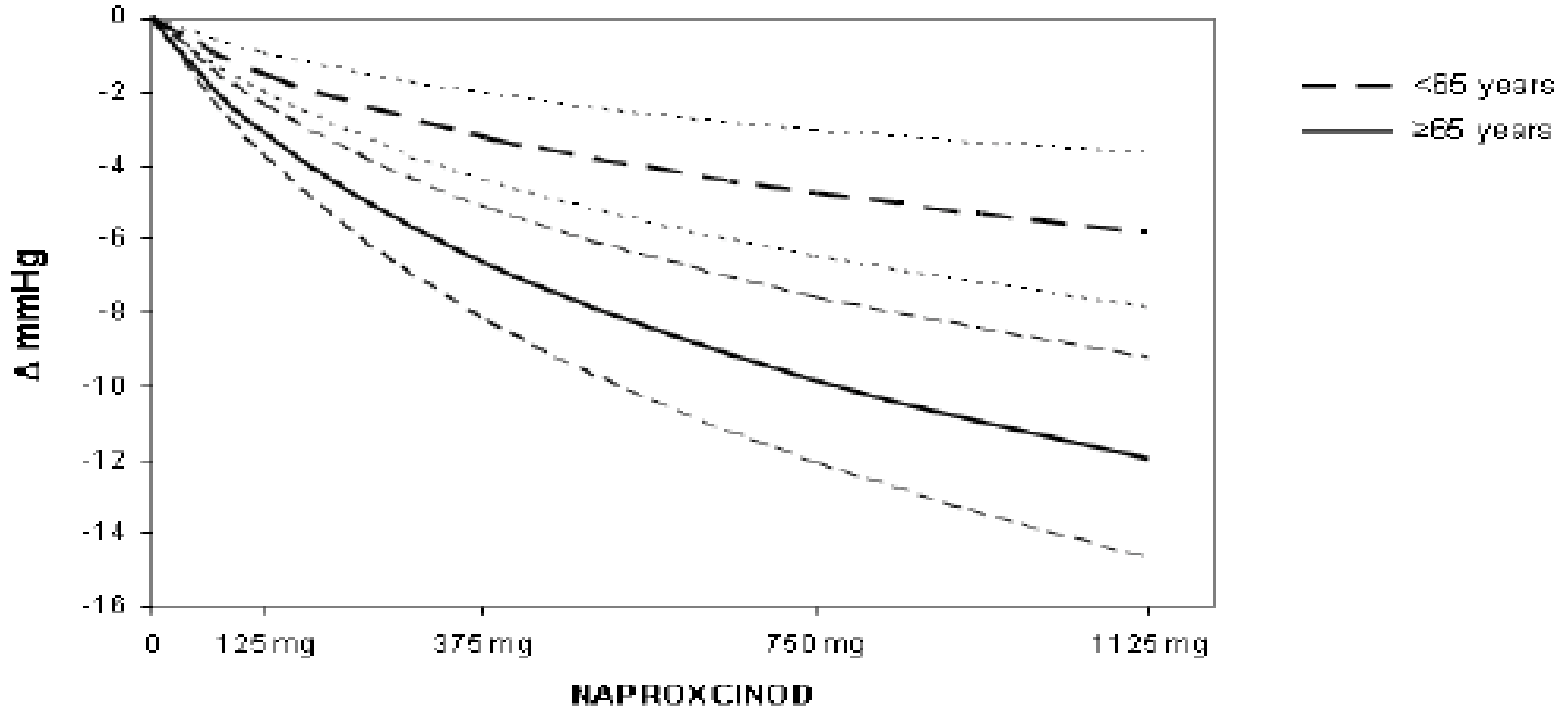
Figure 31: Difference in SBP LS mean changes between treatments



Source; Figure 31, Integrated BP report, Module 5.3.5.3

Phase 2- subgroup analyses- < 65 and ≥ 65, first dose effect

Figure 20: Effect of Naproxcinod on Mean Change in SBP during 3 Hours Post dose Relative to Placebo in Age Groups <65 and ≥65 Years



The bold lines represent the two different age groups with 95% CI (dashed lines).

Source: Figure 20, Integrated BP report, Module 5.3.5.3

Hypotension-related adverse events

- In all placebo controlled OA studies up to 13 weeks, potential hypotension-related AEs were- 4.7 % (1500 mg/day or 750 mg bid/ n=1470),3.7% (750 mg/day or 375 mg bid/n=598), 2.9% in placebo and 2.6% for naproxen -*Source- table 21, ISS.*
- The most common potential hypotension-related AE was dizziness [3.2% at 750 mg *bid* and 2.5% at 375 mg *bid*], 2.2% of placebo patients, 2.0% of naproxen-treated patients
- In the pooled analyses of the phase 2 studies SP-NON 0005, 00101and 0017, hypotension related AEs were only seen with naproxcinod but incidence was equal in all doses (table 8.1-orthostatic BP report).
- In summary there was a slight increase in hypotension related AEs with naproxcinod with a trend for a dose-dependent effect.

HR effects

- First dose effects recorded in Phase 2 studies (SP-NON 0010 and SP-NON-0017) –mean change less than 3-4 bpm and not consistent
  - similar result with HR over time reported in other studies
  - acute withdrawal data (e.g., within first 72 hours) for HR and BP not available

Subgroup-elderly (contd)

- Analyses of peak effect in subjects over 75 yrs of age from all placebo controlled studies was limited by small sample size of 85 subjects spread over four treatments.
- Decline in SBP persistent at week 6, small effects on DBP, no consistent effects on HR.

Drug interactions

Table 19: Maximum Fall in Blood Pressure in Hypertensive Patients Treated with Various Classes of Antihypertensive Agents after Administration of a Single Dose of 750 mg Naproxcinod or Placebo

Anti-hypertensive agent	Group	Maximal fall in BP (mm Hg ± SD)			
		Within 4 hr after first dose		In 2 min within 4 hr	
		Supine SBP	Supine DBP	Orthostatic change in SBP	Orthostatic change in DBP
ß-blockers (n = 18)	Naproxcinod	24.9 ±9.7	17.8 ±5.6	16.1 ±9.8	8.6 ± 8.2
	Placebo	16.2 ± 10.3	10.9 ±5.7	7.8 ± 8.5	5.9 ±5.1
Ca-antag (n=17)	Naproxcinod	24.8 ± 9.7	17.1 ±5.6	7.4 ± 8.4	7.8 ±5.1
	Placebo	13.1 ±9.3	10.9 ± 5.4	7.7 ±8.7	9.4 ±10.1
ACE inhib (n = 11)	Naproxcinod	28.4 ±7.5	21.5 ±3.8	7.7 ±9.4	7.4 ±7.6
	Placebo	15.8 ±6.6	13.0 +/- 5.7	7.7 ± 7.3	4.7 ±8.7

Source: SP-NON-0022, Tables 17, 19, 21 and 23.

Safety-Outcome data

- Information available to date is insufficient with respect to cardiac outcomes due to limited safety database and limited time period (1 yr)
- Sponsor submitted a post-hoc analyses of data from completed Phase 2/3 studies for Treatment Emergent Coronary Artery Disease/Myocardial Infarction, Cardiac Failure, Cerebrovascular and Renal -related Adverse Events by Preferred Term and Overall Study Group to DCRP- number of events low and results no better than naproxen

Comparative claim for BP and safety issues

- DCRP view
  - based on information available to date a consistent effect on both systolic and diastolic BP is mainly present at peak.
  - the effect through the dosing interval is variable
  - typically drugs with meaningful effects on cardiac outcomes have an effect on systolic and diastolic BP that persists through the dosing interval. In this case the potential impact on cardiac outcomes is unclear.
  - potential safety issues due to hypotensive effect at peak in vulnerable subjects would have to be considered. Caution should be advised regarding concomitant use with PDE-5 inhibitors like sildenafil, nitroglycerin and antihypertensive treatments especially at first dose.

BP effect of naproxcinod

DCRP Review

Joint Meeting of the Arthritis Advisory Committee (AAC)

and Drug Safety & Risk Management Advisory Committee (DSaRM) ,

May 12, 2010

Suchitra Balakrishnan MD, PhD

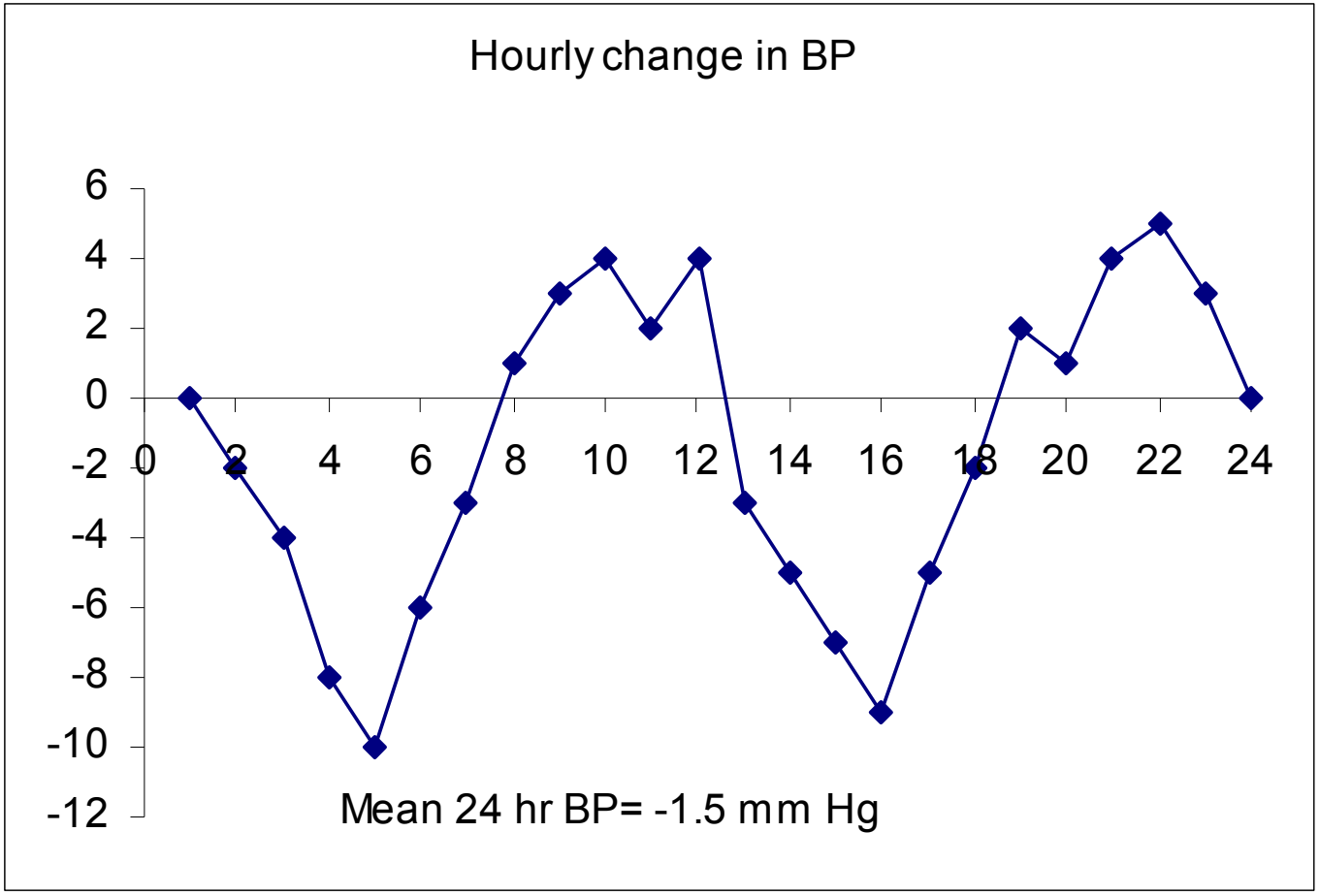
BACK-UP slides

Studies 104, 111, 112

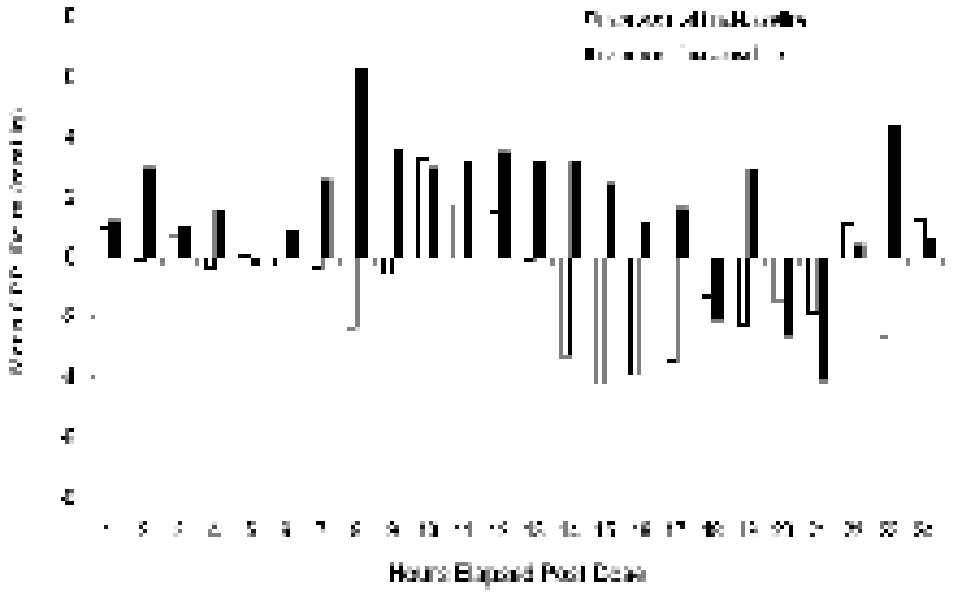
	104	112	111
Design	Multicenter, DB, Randomized, Cross-Over, Naproxen Controlled Study	Multicenter, DB, Randomized, Naproxen and Ibuprofen-controlled, Parallel-Group Pharmacological Study	Multicenter, DB, Randomized, Forced Titration to maximum dose, Naproxen-Controlled, Parallel-Group Pharmacodynamic Study
Subjects	Stable essential HTN (no OA), 50-75 yrs of age	Patients with osteoarthritis (OA) and controlled essential hypertension.	Patients with osteoarthritis (OA) and controlled essential hypertension.
Active treatment	Naproxen 500mg bid and Naproxcinod (750 mg bid) for 2 periods of 14 days	Naproxcinod (375 mg and 750 mg, bid) compared to equimolar doses of naproxen (250 mg and 500 mg, bid) and to Ibuprofen (600 mg, tid) for 90 days each	Naproxcinod (in doses ranging from 375 mg to 1125 mg, bid) and naproxen (in doses ranging from 250 mg to 750 mg, bid) for 3 weeks each. ABPM was recorded for each dose escalation at the end of the treatment period
Randomized (safety)	131 (65/66)	299 (59/65/60/60/55)	118 (59/59)
Completed (safety)	117	225 (18 discontinued due to AEs)	103 (10 discontinued due to AEs)
Randomized (mITT)	121 (61/60)	213 (44/49/46/40/34)	103 (51/52)
Completed (mITT)	116		
cABPM		155 (36/36/32/28/23)	66 (36/30)
Comment		Was double-blind maintained? - all groups were given placebo tid at the end (for 2 weeks)	No randomized withdrawal to placebo (for 2 weeks) at end of study

Modified intent to treat (mITT) population defined as all randomized subjects who had at least one acceptable follow-up ABPM.
Compliant ABPM population (cABPM) included all randomized patients who received IMP, had successful ABPM at baseline and at all follow-up visits, who completed the study, and who had no major protocol deviations during the study.
Sources: Compiled from CSR's for HCT3012-X-104, 111 and 112

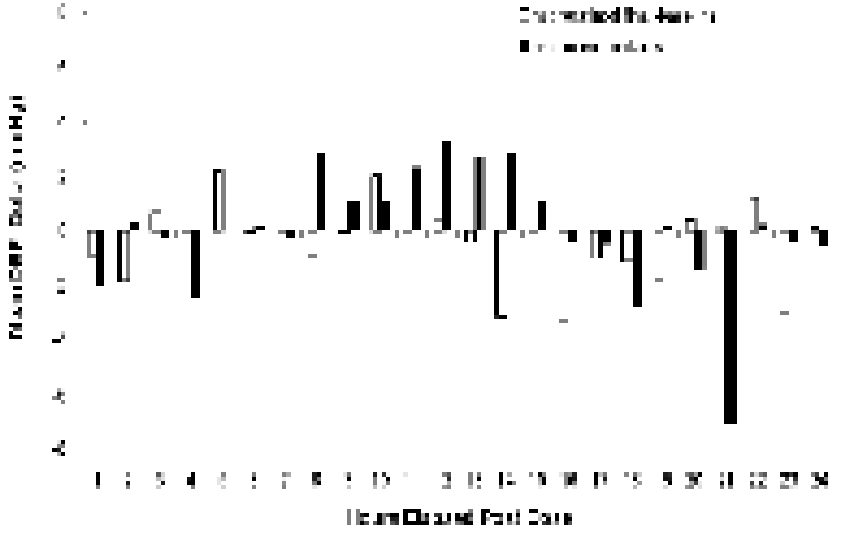
Hourly 24 hour profile vs. 24 hour Mean BP



ABPM data-change from baseline SBP & DBP- study 3012-X-111

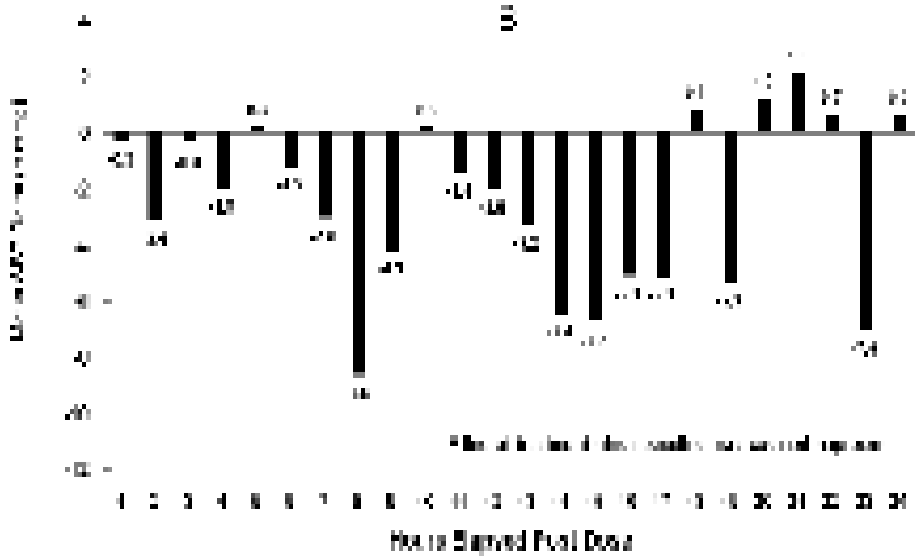


Mean Hourly Systolic Blood Pressure (SBP) Effects of Naproxcinod 375 mg *bid (low dose)* and Naproxen 250 mg *bid* at Week 3/Day 21 when Compared to Their Respective Baseline Hourly SBPs (mITT Population), Source: Figure 111_ABPM_019
Average SEM Ranged from 1.8 to 2.8 mm Hg (Table 111_ABPM_007)

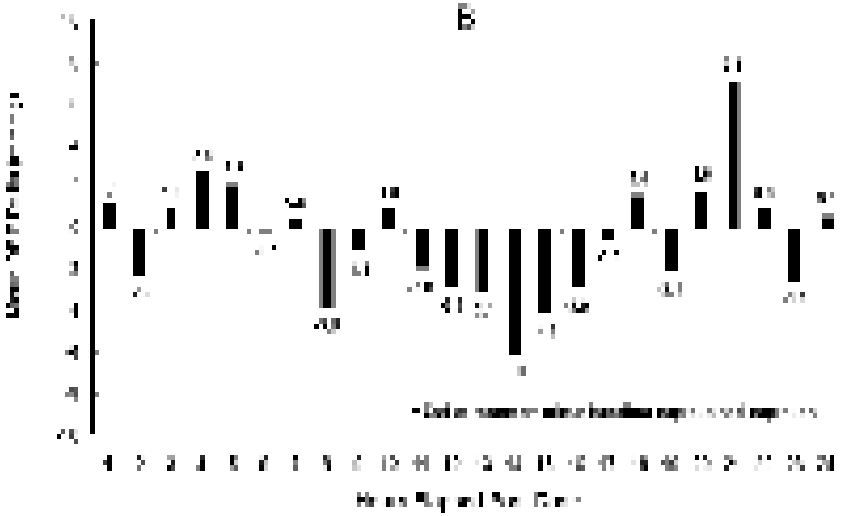


Mean Hourly Diastolic Blood Pressure (DBP) Effects of Naproxcinod 375 mg *bid (low dose)* and Naproxen 250 mg *bid* at Week 3/Day 21 when Compared to Their Respective Baseline Hourly DBPs (mITT Population), Source: Figure 111_ABPM_025
(Average SEM Ranged from 1.1 to 2.1 mm Hg-Table 111_ABPM_009)

ABPM-study 111 (contd)- Naproxcinod-naproxen



Mean Hourly Systolic Blood Pressure (SBP) Differences between the two End-of-Treatment (Week 3/Day 21) Profiles for Naproxcinod 375 mg *bid* and Naproxen 250 mg *bid* after an Adjustment for Baseline (mITT Population), Source: Figure 111_ABPM_020 (B)



Mean Hourly Diastolic Blood Pressure (DBP) Differences between the Two End-of-Treatment (Week 3/Day 21) Profiles for Naproxcinod 375 mg *bid* and Naproxen 250 mg *bid* after an Adjustment for Baseline (mITT Population), Source; Figure 111_ABPM_026 (B)

Study 111, NPX 1125 mg-NP 750

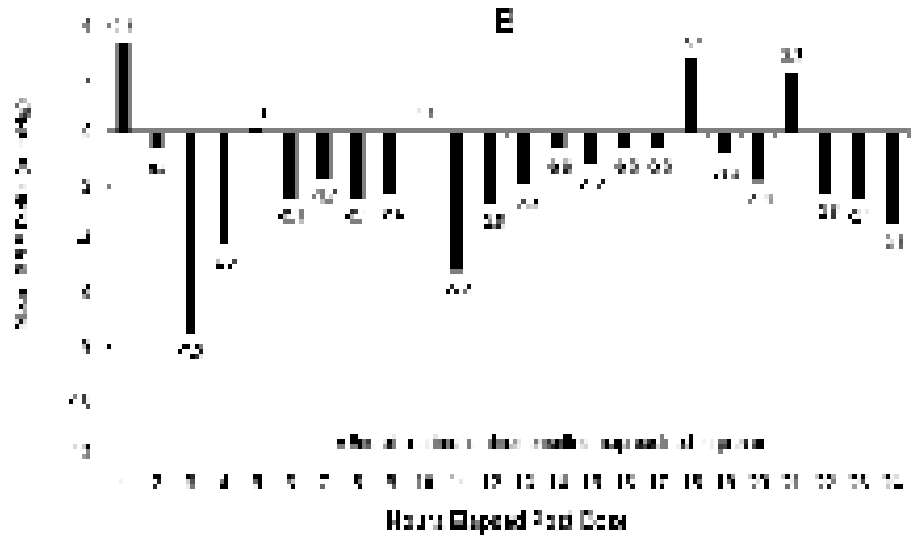


Figure 111_ABPM_024 (B): Mean Hourly Systolic Blood Pressure (SBP) Differences between the Two End-of-Treatment (Week 9/Day 63) Profiles for Naproxcinod 1125 mg *bid* and Naproxen 750 mg *bid* after an Adjustment for Baseline (mITT Population)

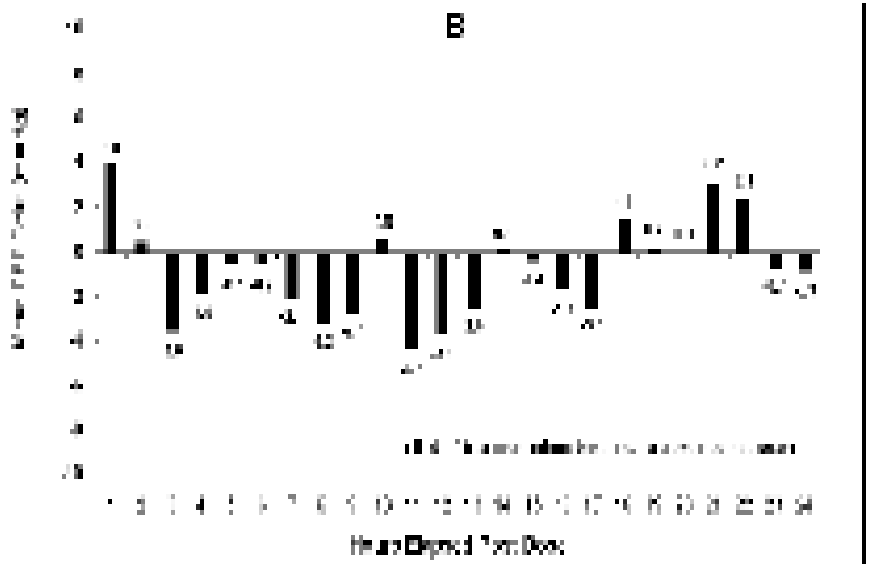


Figure 111_ABPM_030 (B): Mean Hourly Diastolic Blood Pressure (DBP) Differences between the Two End-of-Treatment (Week 9/Day 63) Profiles for Naproxcinod 1125 mg *bid* and Naproxen 750 mg *bid* after an Adjustment for Baseline (mITT Population)

Study -104- CI

Hours elapsed	Mean Change from baseline (NC 750 mg)	Mean Change from baseline NX 500 mg	Difference	SEM (NC)	SEM (NX)	Sum of squares	Square root of sum of squares	(X) 1.96
SBP								
2	0.2	4.7	-4.5	1.56	1.5	4.6836	2.164163	4.241759
10	5.2	2.7	2.5	1.44	1.46	4.2052	2.050658	4.019291
11	4.3	6.1	-1.8	1.36	1.51	4.1297	2.032166	3.983046
16	-0.6	4.4	-5	1.88	2	7.5344	2.744886	5.379977
23	3.2	3	0.2	1.55	1.5	4.6525	2.156965	4.227652
24	3.2	4.5	-1.3	1.31	1.5	3.9661	1.991507	3.903354
DBP								
2	-0.7	3.2	-3.9	1.07	0.9	1.9549	1.398177	2.740428
10	1.8	1.2	0.6	1.11	0.99	2.2122	1.487347	2.915199
11	0.6	3.4	-2.8	1.07	0.98	2.1053	1.450965	2.843892
16	-2.7	2.8	-5.5	1.34	1.54	4.1672	2.041372	4.001089
23	0	1.1	-1.1	1.07	1.04	2.2265	1.492146	2.924606
24	0	3.4	-3.4	0.96	1.03	1.9825	1.408013	2.759705

Study-112, CI high dose

Hours elapsed	Mean Change from baseline (NC 750 mg)	Mean Change from baseline NX 500 mg	Difference	SEM (NC)	SEM (NX)	Sum of squares	Square root of sum of squares	X 1.96
SBP								
3	-4.9	6.3	-11.2	2.61	2.47	12.913	3.593466	7.043194
10	1.1	5.3	-4.2	3.53	2.97	21.2818	4.61322	9.041911
11	2.3	2.2	0.1	2.71	2.72	14.7425	3.839596	7.525609
14	-1.3	5.9	-7.2	2.34	3.42	17.172	4.143911	8.122066
23	1.3	1.8	-0.5	2.42	2.31	11.1925	3.345519	6.557218
24	1	-0.8	1.8	2.47	2.32	11.4833	3.388702	6.641856
DBP								
3	-4.6	1.2	-5.8	1.89	1.5	5.8221	2.412903	4.72929
10	0.4	1.9	-1.5	2.41	1.98	9.7285	3.119054	6.113347
11	0.6	0.3	0.3	2.03	1.74	7.1485	2.673868	5.240389
14	-0.4	3.6	-4	1.89	2.01	7.6122	2.759022	5.407682
23	-0.6	-1.1	0.5	1.58	1.96	6.338	2.517538	4.934375
24	-0.1	-1.8	1.7	1.73	1.98	6.9133	2.629316	5.153458

Study 112 CI, low dose

Hours elapsed	Mean Change from baseline (NC 375 mg)	Mean Change from baseline (NX 250 mg)	Difference	SEM (NC)	SEM (NX)	Sum of squares	Square root of sum of squares	X 1.96
SBP								
2	-3.3	4.5	-7.8	2.69	2.51	13.5362	3.679158	7.211149
10	2.4	-1.3	3.7	2.18	1.9	8.3624	2.891781	5.667892
11	1.9	2.6	-0.7	2.5	2.14	10.8296	3.290836	6.450038
16	-3.4	2.4	-5.8	2.66	2.53	13.4765	3.671035	7.195229
23	0.9	-3.4	4.3	2.75	2.41	13.3706	3.656583	7.166903
24	-1.8	-1.1	-0.7	2.81	2.27	13.049	3.61234	7.080186
DBP								
3	-2.3	4.2	-6.5	1.92	1.89	7.2585	2.69416	5.280554
10	1.7	-1	2.7	1.52	1.97	6.1913	2.488232	4.876935
11	1	1.9	-0.9	1.79	1.78	6.3725	2.524381	4.947787
15	-1.9	1.7	-3.6	2.17	1.72	7.6673	2.768989	5.427218
23	-1.8	-3.5	1.7	2.08	1.93	8.0513	2.837481	5.561463
24	-2.6	-0.2	-2.4	2.44	1.57	8.4185	2.901465	5.686872

Study 111, CI high dose

Hours elapsed	Mean Change from baseline (NC 750 mg)	Mean Change from baseline NX 500 mg	Difference	SEM (NC)	SEM (NX)	Sum of squares	Square root of sum of squares	X 1.96
SBP								
3	-4.1	2.1	-6.2	1.89	1.91	7.2202	2.687043	5.266604
10	1.6	7.7	-6.1	2.04	2.8	12.0016	3.464333	6.790092
3	-1.2	8.3	-9.5	2.21	2.37	10.501	3.240525	6.351428
15	-4.1	2.7	-6.8	2	2.14	8.5796	2.929095	5.741027
23	-4.7	4	-8.7	2.35	2.19	10.3186	3.212258	6.296025
24	-1	5.7	-6.7	2.16	2.42	10.522	3.243763	6.357776
DBP								
2	-3	0.8	-3.8	1.39	1.1	3.1421	1.772597	3.47429
10	0.7	4.3	-3.6	1.42	1.77	5.1493	2.269207	4.447646
11	-1.5	3.6	-5.1	1.56	1.58	4.93	2.22036	4.351906
16	-4.6	-1.2	-3.4	1.6	2.44	8.5136	2.917807	5.718902
23	-2.9	-0.4	-2.5	1.58	1.93	6.2213	2.494253	4.888737
24	-0.4	0.2	-0.6	1.23	1.4	3.4729	1.863572	3.652601

Study 111 low dose

Hours elapsed	Mean Change from baseline (NC 375 mg)	Mean Change from baseline (NX 250 mg)	Difference	SEM (NC)	SEM (NX)	Sum of squares	Square root of sum of squares	X 1.96
SBP								
2	-0.1	3	-3.1	2.35	2.06	9.7661	3.125076	6.125149
10	3.3	3	0.3	1.91	2.26	8.7557	2.959003	5.799646
11	1.7	3.1	-1.4	2.23	2.3	10.2629	3.203576	6.279009
15	-4.2	2.5	-6.7	2.13	2.11	8.989	2.998166	5.876406
23	-2.6	4.4	-7	2.57	2.85	14.7274	3.837629	7.521754
24	1.3	0.6	0.7	2.27	2.17	9.8618	3.14035	6.155087
8	-2.3	6.3	-8.6	1.91	2.41	9.4562	3.075093	6.027183
DBP								
2	-1.8	0.4	-2.2	1.31	1.31	3.4322	1.85262	3.631135
10	2	1	1	1.41	1.33	3.757	1.938298	3.799065
11	0.4	2.3	-1.9	1.71	1.47	5.085	2.254994	4.419789
14	-3.1	2.9	-6	1.53	1.9	5.9509	2.439447	4.781315
23	-2.9	-0.4	-2.5	1.78	1.54	5.54	2.35372	4.613292
24	0.1	-0.5	0.6	1.48	1.38	4.0948	2.023561	3.96618

Study 111 supratherapeutic dose

Hours elapsed	Mean Change from baseline (NC 1125 mg)	Mean Change from baseline NX 750 mg	Difference	SEM (NC)	SEM (NX)	Sum of squares	Square root of sum of squares	X 1.96
SBP								
3	-6.5	1.1	-7.6	1.81	2.44	9.2297	3.038042	5.954563
10	1.6	1.6	0	2.71	2.8	15.1841	3.896678	7.637489
11	-0.4	4.8	-5.2	2.47	2.5	12.3509	3.514385	6.888194
15	0	1.3	-1.3	2.3	2.33	10.7189	3.273973	6.416987
23	-2.4	0.1	-2.5	2.5	2.32	11.6324	3.41063	6.684836
24	-2	1.4	-3.4	2.3	2.23	10.2629	3.203576	6.279009
DBP								
3	-4.2	-0.6	-3.6	1.48	1.65	4.9129	2.216506	4.344352
10	-0.4	-1	0.6	1.95	1.8	7.0425	2.653771	5.201391
11	-1.3	3.2	-4.5	1.96	1.82	7.154	2.674696	5.242405
16	-2.2	-0.4	-1.8	1.74	2.37	8.6445	2.940153	5.7627
23	-2.3	-1.6	-0.7	1.98	1.5	6.1704	2.484029	4.868697
24	-2.1	-1.2	-0.9	1.51	1.57	4.745	2.178302	4.269472

Back up slide-> 75yrs peak change in SBP

Time	Naproxcinod	placebo	Naproxen
First dose-1hr	-6.7± 14.3	4.6± 16.4	-0.9± 6.2
First dose-3hr	-8.0 ± 16.7	0.6± 19.6	-2.7± 7.7
1 week-1hr	-6 1± 11.6	-2.2± 14.6	9.2± 7.69
1week -3hr	-3.1± 16.2	-9.1± 22.9	1.0± 14.0
Week 2	-3.1± 16.7	-3.4± 13.7	3.0± 6.9
Week 4	-6.4± 15.7	0.3± 13.3	3.8± 9.9
Week 6	-7.1± 18.3	-6.4± 14.6	2.0± 10.1
Endpoint	-4.8± 19	-5.9± 13.6	1.8± 9.4

(from Sponsor's data, change in SBP at peak in subjects over 75)

Orthostatic hypotension, hypotension related AEs

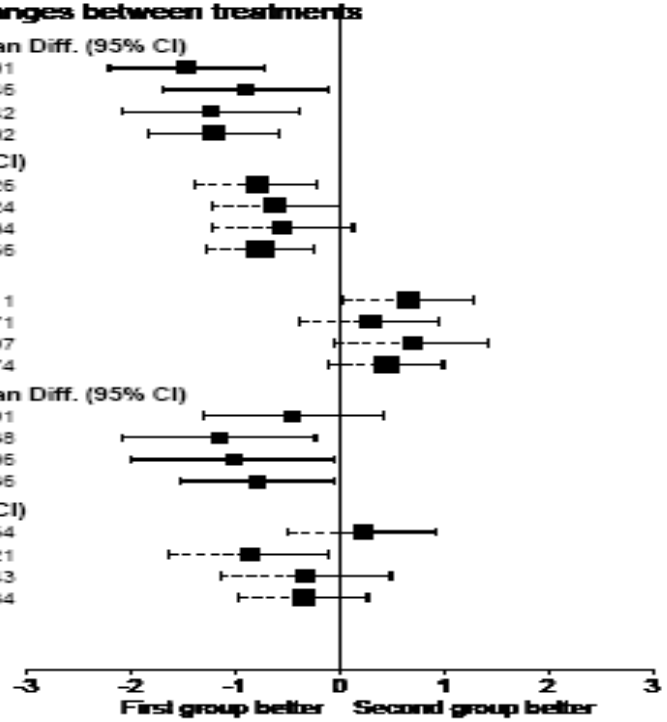
- Orthostatic hypotension at peak effect, especially at first dose may be a safety issue in the elderly
- In the phase 2 studies sporadic orthostatic BP reductions were seen with similar incidences in the HCT 3012, placebo and active comparator arms (naproxen and rofecoxib) at any time over the observation periods except for the first dose of 750 mg and above of HCT 3012
- Orthostatic hypotension was defined in the study protocol as a decrease in SBP ≥ 25 mmHg or in DBP ≥ 15 mmHg at least once during the study.
  - in all double blind, placebo-controlled OA studies upto 13 weeks, subjects who experienced a potentially hypotension-related treatment-emergent AE (TEAE) was 5.6% for naproxcinod treated patients [4.7% at 750 mg bid and 3.7% at 375 mg bid], 2.9% for placebo-treated patients and 2.6% for naproxen-treated patients (500 mg bid). (source ISS table 21)

Back up-dDBP_phase 3

Figure 33: Difference in DBP LS Mean changes between treatments

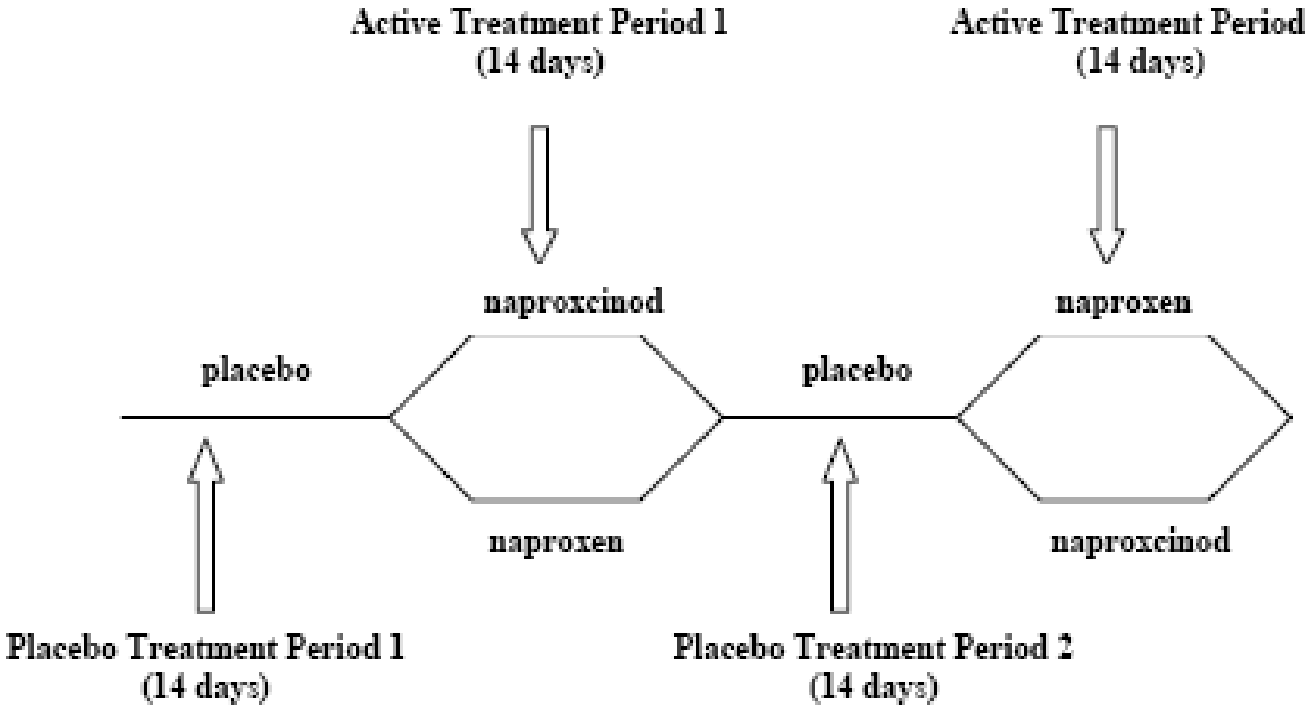
HCT 3012-X-304 Difference in DBP LS Mean changes between treatments

Naproxcinod 750 mg bid vs Naproxen 500 mg bid: LS Mean Diff. (95% CI)			
At Week 2	783 vs 623	-1.46 [-2.21 , -0.71]	0.0001
At Week 6	724 vs 587	-0.90 [-1.69 , -0.12]	0.0246
At Week 13	662 vs 522	-1.24 [-2.09 , -0.39]	0.0042
By Week 13	658 vs 518	-1.21 [-1.84 , -0.58]	0.0002
Naproxcinod 750 mg bid vs Placebo: LS Mean Diff. (95% CI)			
At Week 2	783 vs 786	-0.80 [- , -0.21]	0.0126
At Week 6	724 vs 693	-0.61 [- , 0.01]	0.0524
At Week 13	662 vs 607	-0.55 [- , 0.13]	0.0904
By Week 13	658 vs 599	-0.76 [- , -0.26]	0.0066
Naproxen 500 mg bid vs Placebo: LS Mean Diff. (95% CI)			
At Week 2	623 vs 786	0.66 [- , 1.29]	0.0411
At Week 6	587 vs 693	0.29 [- , 0.96]	0.2371
At Week 13	522 vs 607	0.69 [- , 1.42]	0.0597
By Week 13	518 vs 599	0.45 [- , 0.99]	0.0874
Naproxcinod 375 mg bid vs Naproxen 500 mg bid: LS Mean Diff. (95% CI)			
At Week 2	474 vs 623	-0.45 [-1.31 , 0.41]	0.3091
At Week 6	445 vs 587	-1.16 [-2.08 , -0.24]	0.0138
At Week 13	405 vs 522	-1.02 [-1.99 , -0.04]	0.0406
By Week 13	400 vs 518	-0.79 [-1.52 , -0.06]	0.0336
Naproxcinod 375 mg bid vs Placebo: LS Mean Diff. (95% CI)			
At Week 2	474 vs 786	0.22 [- , 0.93]	0.3064
At Week 6	445 vs 693	-0.87 [- , -0.10]	0.0321
At Week 13	405 vs 607	-0.33 [- , 0.49]	0.2543
By Week 13	400 vs 599	-0.34 [- , 0.27]	0.1784

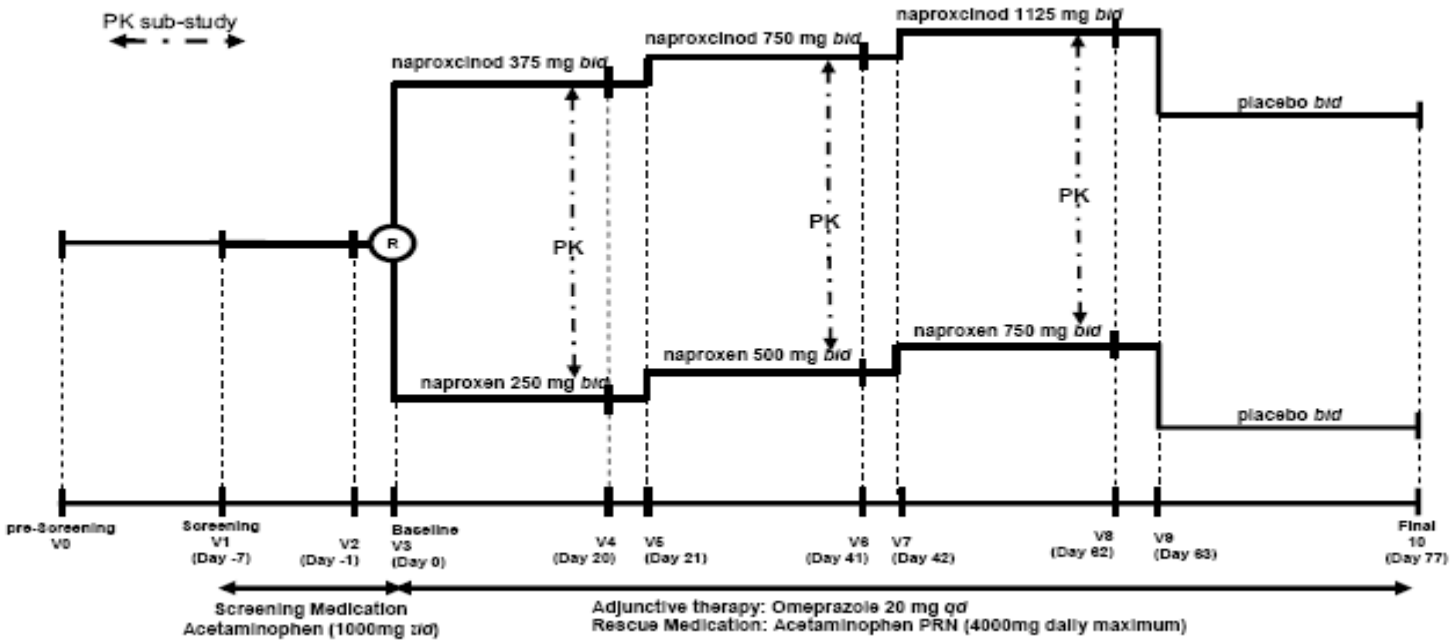


P-values were obtained post-hoc

Study- 104-cross-over multicenter study (120 subjects) with HTNH

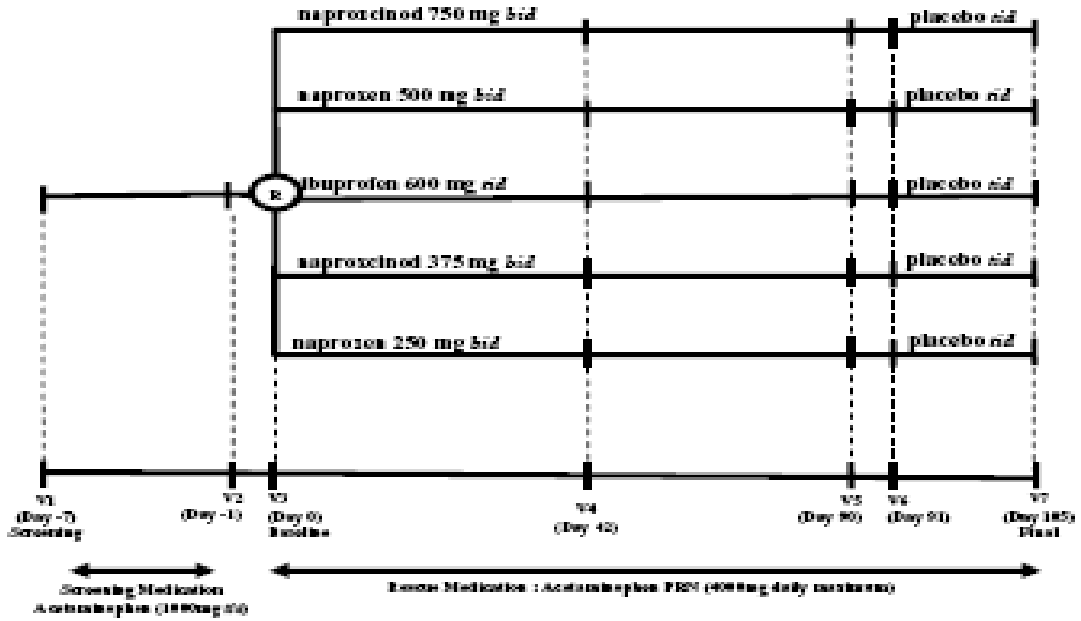


Design -111


PK sub-study
naproxcinod 375 mg bid
naproxcinod 750 mg bid
naproxcinod 1125 mg bid
placebo bid
R
PK
PK
PK
naproxen 250 mg bid
naproxen 500 mg bid
naproxen 750 mg bid
placebo bid
pre-Screening V0
Screening V1 (Day -7)
V2 (Day -1)
Baseline V3 (Day 0)
V4 (Day 20)
V5 (Day 21)
V6 (Day 41)
V7 (Day 42)
V8 (Day 62)
V9 (Day 63)
Final 10 (Day 77)
Screening Medication
Acetaminophen (1000mg tid)
Adjunctive therapy: Omeprazole 20 mg qd
Rescue Medication: Acetaminophen PRN (4000mg daily maximum)

Design 112

Figure 1 **Study Design (Protocol Version 2.0)**



Back up-drug interaction slide

Table 20: Statistical Analyses of the Comparisons Between a Single or Daily *bid* doses for 5 Days of 750 mg Dose of Naproxcinod vs. Placebo on the Maximal Fall in Blood Pressure in Hypertensive Subjects Treated with Antihypertensive Agents

Maximal fall in blood pressure: variable	Antihypertensive agent	Contrast estimates between naproxcinod and placebo	
		Estimate (SE)*	95% CI
Supine SBP within 4 hr after first dose	ß-blockers	8.8 (2.5)	3.5; 14.1
	Ca antagonists	10.9 (2.3)	5.9; 15.9
	ACE inhibitors	12.6 (12.1)	7.8; 17.3
Supine DBP within 4 hr after first dose	ß-blockers	6.8 (1.3)	4.1; 9.4
	Ca antagonists	6.7 (1.5)	3.6; 9.8
	ACE inhibitors	8.2 (1.9)	3.7; 12.6
Orthostatic change in SBP within 2 min within 4 hr after first dose	ß-blockers	8.3 (2.6)	2.7; 13.9
	Ca antagonists	-1.4 (1.9)	-5.5; 2.7
	ACE inhibitors	-0.1 (3.0)	-7.2; 6.9
Orthostatic change in DBP within 2 min within 4 hr after first dose	ß-blockers	3.7 (1.9)	-0.3; 7.7
	Ca antagonists	-2.8 (2.5)	-8.2; 2.6
	ACE inhibitors	4.3 (2.1)	-0.5; 9.1
Supine SBP within 4 hr after last dose on day 5	ß-blockers	5.1 (2.4)	-0.0; 10.1
	Ca antagonists	5.1 (1.6)	1.8; 8.5
	ACE inhibitors	5.7 (3.4)	-2.3; 13.6
Supine DBP within 4 hr after last dose on day 5	ß-blockers	3.1 (1.6)	-0.4; 6.6
	Ca antagonists	2.2 (1.4)	-0.8; 5.2
	ACE inhibitors	3.9 (1.3)	0.8; 7.0

*SE = standard error.
Source: SP NON-0022, Tables 18, 20, 22, 24, 28 and 30.

Naproxcinod (NDA 22-478)

Endoscopy Studies

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Medical Reviewer
Division of Gastroenterology Products
ODE3/CDER/FDA

Outline

- Overview
- Background
- Endoscopy Studies
  - Studies 0002 and 0027
  - Study 0005
- Overall Summary
- Conclusions

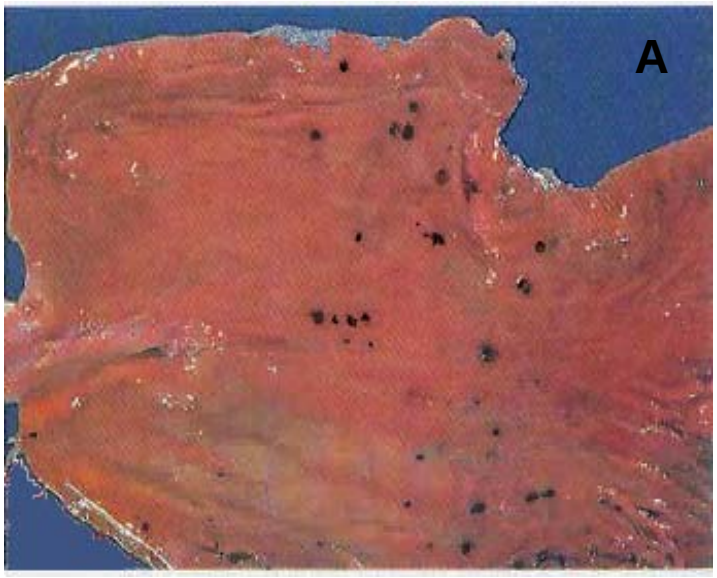
Background

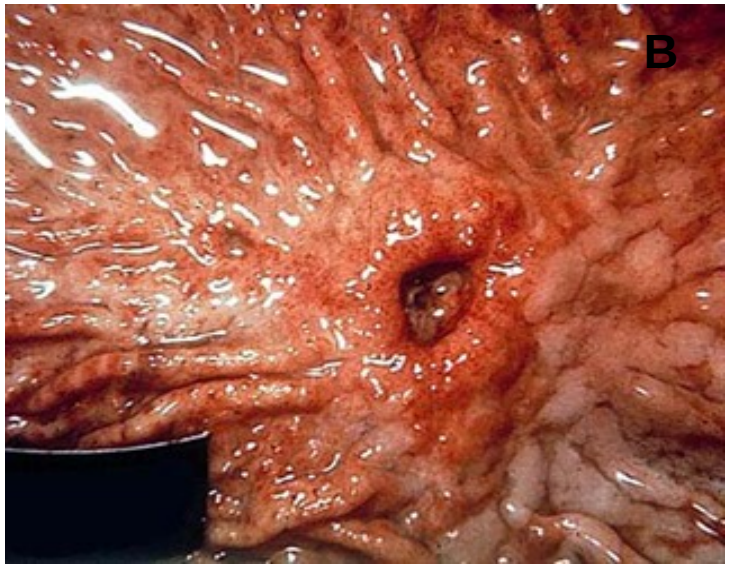
NSAID-Induced GI Tract Lesions*

- **Erosion:** superficial mucosal lesion <3 mm, not penetrating muscularis mucosa
- **Peptic ulcer:** Mucosal lesion extends through muscularis mucosa into submucosa or deeper.

*From Crawford. Robbins Pathologic Basis of Disease. Philadelphia, W.B. Saunders, 1999, p 793.

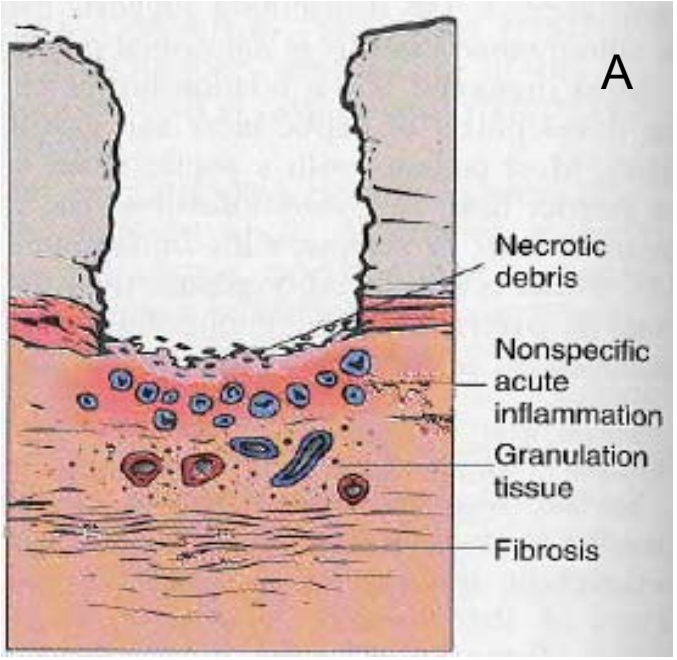
Diagnostic GI Pathology: Gastric Erosion vs. Peptic Ulcer

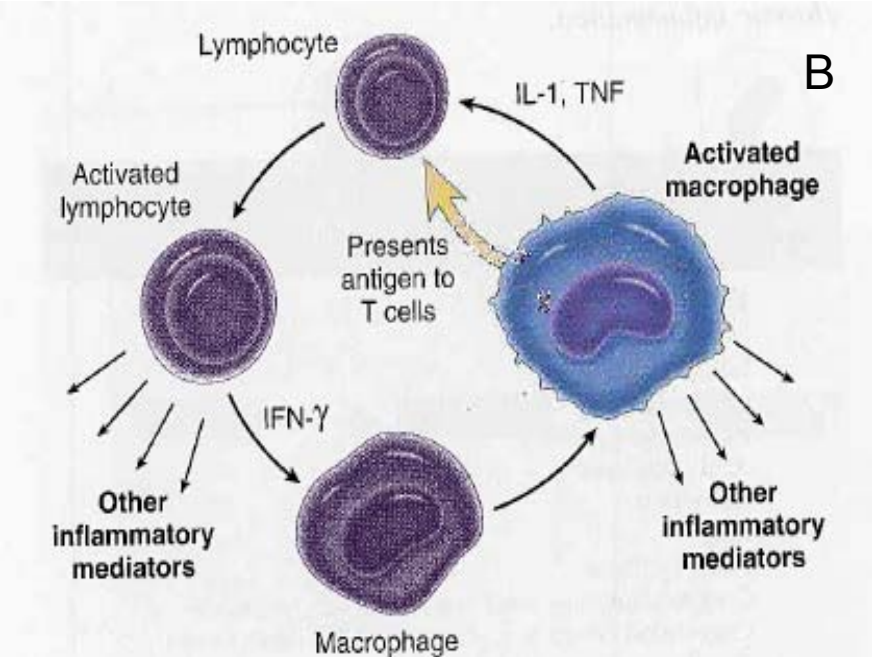




Crawford. Peptic Ulcer Disease. In Cotran (ed.) Robbins Pathologic Basis of Disease. P796, 1999.

Chronic inflammation & peptic ulcer





Crawford. Peptic Ulcer Disease. In Cotran (ed.) Robbins Pathologic Basis of Disease. P796, 1999; Picker. Acute & Chronic Inflammation. P82, Ibid.

Summary of Clinical Findings*

	Erosion	Peptic Ulcer
Disease category	Acute erosive gastritis	Chronic peptic ulcer disease
Spontaneous healing	Yes	No
Complications	None	Intractable bleeding, Perforation, Obstruction

*From Crawford. Robbins Pathologic Basis of Disease. Philadelphia, 1999, p 793; Owen. Diagnostic Surgical Pathology. Philadelphia, 1999, p 1316.

Pathogenic Association*

- Erosion is not a precursor of chronic peptic ulcer, having a totally different pathobiology.
- NSAID toxicity & H. pylori infection are strongly associated with peptic ulcer development.

*From Crawford. Robbins Pathologic Basis of Disease. Philadelphia, 1999, p 793; Owen. Diagnostic Surgical Pathology. Philadelphia, 1999, p 1316; Malfertheiner. Peptic ulcer disease. Lancet. 374:1449-1461, 2009.

Risk Factors for NSAID-related GI Complications*

- Risk Factors for NSAID-related GI Complications include:*
  - age > 65 years
  - high dose NSAID therapy
  - previous history of peptic ulcer disease
  - H. pylori infection
  - concurrent use of aspirin (including low dose aspirin), corticosteroids, or anticoagulant
- H. Pylori is an independent and additive risk factor and needs to be addressed separately*

*Lanza FL, Chan FK, et.al (2009). "Guidelines for Prevention of NSAID-Related Ulcer Complications:" *The American Journal of Gastroenterology.* 104(728-738).

Current DGP Regulatory Approach
(Risk Reduction of NSAID-associated Ulcers Indication)

- Acceptable Primary Endpoint: The proportion of patients who develop ulcers (where ulcers are defined as ≥ 3 mm diameter and with depth)
- Unacceptable Primary Endpoints: Erosions (transient superficial lesion; not linked with peptic ulcer)
- An acceptable study duration is ≥ 6 months
  - Efficacy
  - Safety
- Erosion data not included in labeling

Endoscopy Studies
(0002, 0027, 0005)

Overview of Study Design Features

Study No. (n)	Population	Design	Treatment Duration	1° Endpoint
Study 0002 (n=31)	Healthy subjects	3-way crossover – Naproxcinod – Naproxen – Placebo	12 days (per period)	Number of erosions & ulcers*,#
Study 0027 (n=75)	Healthy subjects	5-treatment 2-period crossover – 3 Naproxcinod arms† – 2 Naproxen arms†	12 days (per period)	Number of erosions & ulcers*,#
Study 0005 (n=970)	Osteo-arthritis patients	3-arm parallel – Naproxcinod – Naproxen – Placebo	6 weeks	Incidence of ulcers*

*Ulcer defined as ≥ 3 mm diameter and with depth
#10 erosions defined as one ulcer in Studies 0002 and 0027
†3 different regimens of Naproxcinod and 2 different regimens of naproxen in 0027

Studies 0002 & 0027

Study Design (0002 & 0027)

	Study 0002 (n=31)	Study 0027 (n=75)
Population	▪ Healthy volunteers	▪ Healthy Volunteers
Study Arms	▪ Naproxcinod 750 BID ▪ Naproxen 500 BID ▪ Placebo BID	▪ Naproxcinod 750 BID ▪ Naproxcinod 375 BID ▪ Naproxcinod 750 QD ▪ Naproxen 500 BID ▪ Naproxen 250 BID
Design	▪ 3-way crossover ▪ 12 day washout period	▪ 2-period crossover ▪ ≥13 day washout period
Treatment Duration	▪ 12 days per period	▪ 12 days per period
Primary Endpoint	▪ Number of erosions and ulcers ▪ Ulcer defined as ≥ 3 mm diameter and with depth ▪ 10 erosions defined as 1 ulcer	▪ Number of erosions and ulcers ▪ Ulcer defined as ≥ 3 mm diameter and with depth ▪ 10 erosions defined as 1 ulcer

Demographics and Disposition (0002 & 0027)

	Study 0002 (n=31)	Study 0027 (n=75)
Demo-graphics	▪ 28 males; 3 females ▪ 30 Caucasian; 1 unspecified ▪ Median age: 32 years (Range: 22 to 57 years)	▪ 49 males; 26 females ▪ 75 Caucasian ▪ Median age: 27 years (Range: 20 to 60 years)
Dispo-sition	▪ 31 randomized and treated ▪ 29 analyzed for endoscopy	▪ 75 randomized and treated ▪ 73 analyzed for endoscopy

Endoscopy Results – Total Number of Ulcers (0002 & 0027)

	Study 0002 (n=29*)	Study 0027 (n=73#)
Baseline	▪ Naproxcinod: 0 ulcers ▪ Naproxen: 0 ulcers ▪ Placebo: 0 ulcers	▪ Naproxcinod arms†: 0 ulcers ▪ Naproxen arms‡: 0 ulcers
Day 12	▪ Naproxcinod: 0 ulcers ▪ Naproxen: 1 ulcer ▪ Placebo: 0 ulcers	▪ Naproxcinod arms†: 0 ulcers ▪ Naproxen arms‡: 0 ulcers

* n=29 in each treatment arm of Study 0002 (3-way crossover design)
# n=73 total in Study 0027 (2-period crossover design)
† n=48 in Naproxcinod arms (n=24: Naproxcinod 750 QD / 375 BID; n=24: Naproxcinod 750 BID / 375 BID)
‡ n=25 in Naproxen arms (Naproxen 500 BID / 250 BID)

Proposed Labeling Language (Special Studies*)

Study	Proposed Labeling Language (Special Studies*)
0002	In a double-blind, randomized, cross-over **short term study**, 31 healthy subjects received either {TRADENAME®} 750 mg bid or an equimolar dose of naproxen 500 mg for 12 days. Mucosal injury was evaluated by endoscopy. The **number of gastro-duodenal erosions and ulcers was 50% lower** with {TRADENAME®} than with naproxen ($p<0.05$).
0027	In another double-blind, cross-over endoscopy study in 75 healthy subjects, {TRADENAME®} 375 mg bid or 750 mg bid were compared with equimolar doses of naproxen 250 mg or 500 mg bid. There were **fewer gastro-duodenal erosions** with {TRADENAME®} (2.71 and 3.08 for {TRADENAME®} 375 mg bid and 750 mg bid, respectively) than with equimolar naproxen doses (6.16 and 6.68) ($p<0.05$).

*Special Studies: Section 14.3 of Proposed Label

Study 0005

Study Design (0005)

Population	▪ Osteoarthritis patients ▪ Current users of an NSAID or acetaminophen
Study Arms	Randomized 7:7:2 ▪ Naproxcinod 750 mg BID ▪ Naproxen 500 mg BID ▪ Placebo BID
Design	▪ 3-arm parallel design
Treatment Duration	▪ 6 weeks
Primary Endpoint	▪ Incidence of Ulcers (Ulcer defined as ≥ 3 mm diameter and with depth)

Demographics and Disposition (Study 0005)

Demo-graphics	▪ 27% males; 73% females ▪ 80% Caucasian; 3% Black; 17% Other ▪ Median age = 59 yrs (range: 38 to 76 yrs)
Dispo-sition	▪ 970 randomized and treated ▪ 898 analyzed for endoscopy

Selected Baseline Characteristics (Study 0005)

History of gastroduodenal ulcers	▪ Naproxcinod: 4% ▪ Naproxen: 3% ▪ Placebo: 2%
H. pylori (+)	▪ Naproxcinod: 49% ▪ Naproxen: 48% ▪ Placebo: 48%

Proportion of Patients With at Least One Ulcer (Study 0005)

Proportion Of Patients With At Least One Ulcer:

	Naproxcinod 750 mg	Naproxen 500 mg	Placebo
Baseline	**0.2%** (1/404)	**0.5%** (2/394)	**0%** (0/100)
Week 6	**9.7%** (39/404)	**13.7%** (54/394)	**0%** (0/100)

Incidence of Ulcers (Naproxcinod vs. Naproxen):

	Point Estimate (95% CI)	P-value
Naproxcinod 750 mg / Naproxen 500 mg	**0.70** (0.48, 1.03)	0.07

Subgroup Analysis by H. pylori Status (Study 0005)

	H pylori (+)			H pylori (-)		
	Naproxcinod 750 mg	Naproxen 500 mg	Placebo	Naproxcinod 750 mg	Naproxen 500 mg	Placebo
Baseline	0% (0/214)	1% (2/199)	0% (0/56)	0.5% (1/218)	0% (0/215)	0% (0/59)
Week 6	12.2% (24/197)	16.0% (31/189)	0% (0/50)	6.9% (14/202)	11.0% (22/204)	0% (0/49)

*From Clinical Study Report, SP-NON-0005, Table 23 (Page 99)
*H. Pylori status at Baseline and at Week 6

Proposed Labeling Language (Special Studies*)

Study	Proposed Labeling Language (Special Studies*)
0005	In a large **6 week** endoscopic study in 970 OA patients, the incidence of patients with at least one ulcer was **30% lower** for {TRADENAME®} 750 mg bid than for naproxen, although the difference was not statistically significant (p=0.07).

*Special Studies: Section 14.3 of Proposed Label

Overall Summary

Summary of Clinical Findings

- Studies 0002 and 0027
  - Small studies of short duration
  - DGP does not accept erosions as the primary endpoint
  - Only 1 ulcer identified in the naproxen group of Study 0002 (no other ulcers in either study)
- Study 0005
  - Proportion of patients with ≥ 1 ulcer at Wk 6:
    - 9.7% (Naproxcinod) vs. 13.7% (Naproxen)
  - Difference not statistically significant (p=0.07)
  - H. pylori (+) patients not excluded at baseline

Conclusion

Conclusion

- Erosion is not an acceptable regulatory primary endpoint.
- A 2-week or 6-week study of peptic ulcer is inadequate.
- Proposed labeling language in the Special Studies section should be removed.

Naproxcinod (NDA 22-478)

Endoscopy Studies

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Division of Gastroenterology Products
ODE3/CDER/FDA

BACK-UP SLIDES

Lanza Scale

	Lanza 1	Lanza 2
4	Ulcer	Ulcer and/or more than 10 erosions
3	Ulcer and/or more than 10 erosions	No ulcers and more than 5 and less than 11 erosions
2	No ulcers and more than one and less than 11 erosions	No ulcers and one or more erosions and less than 6 erosions
1	No ulcers and one erosion	No ulcers and erosions but any petechiae
0	No ulcers or erosions	No ulcers, erosions, and petechiae

Proposed Labeling Language (Special Studies*)

Study	Proposed Labeling Language (Special Studies*)
0002	In a double-blind, randomized, cross-over **short term study**, 31 healthy subjects received either {TRADENAME®} 750 mg bid or an equimolar dose of naproxen 500 mg for 12 days. Mucosal injury was evaluated by endoscopy. The **number of gastro-duodenal erosions and ulcers was 50% lower** with {TRADENAME®} than with naproxen ($p<0.05$).
0027	In another double-blind, cross-over endoscopy study in 75 healthy subjects, {TRADENAME®} 375 mg bid or 750 mg bid were compared with equimolar doses of naproxen 250 mg or 500 mg bid. There were **fewer gastro-duodenal erosions** with {TRADENAME®} (2.71 and 3.08 for {TRADENAME®} 375 mg bid and 750 mg bid, respectively) than with equimolar naproxen doses (6.16 and 6.68) ($p<0.05$).
0005	In a large **6 week** endoscopic study in 970 OA patients, the incidence of patients with at least one ulcer was **30% lower** for {TRADENAME®} 750 mg bid than for naproxen, although the difference was not statistically significant ($p=0.07$).
All 3	The clinical significance of these findings is unknown.

*Special Studies: Section 14.3 of Proposed Label

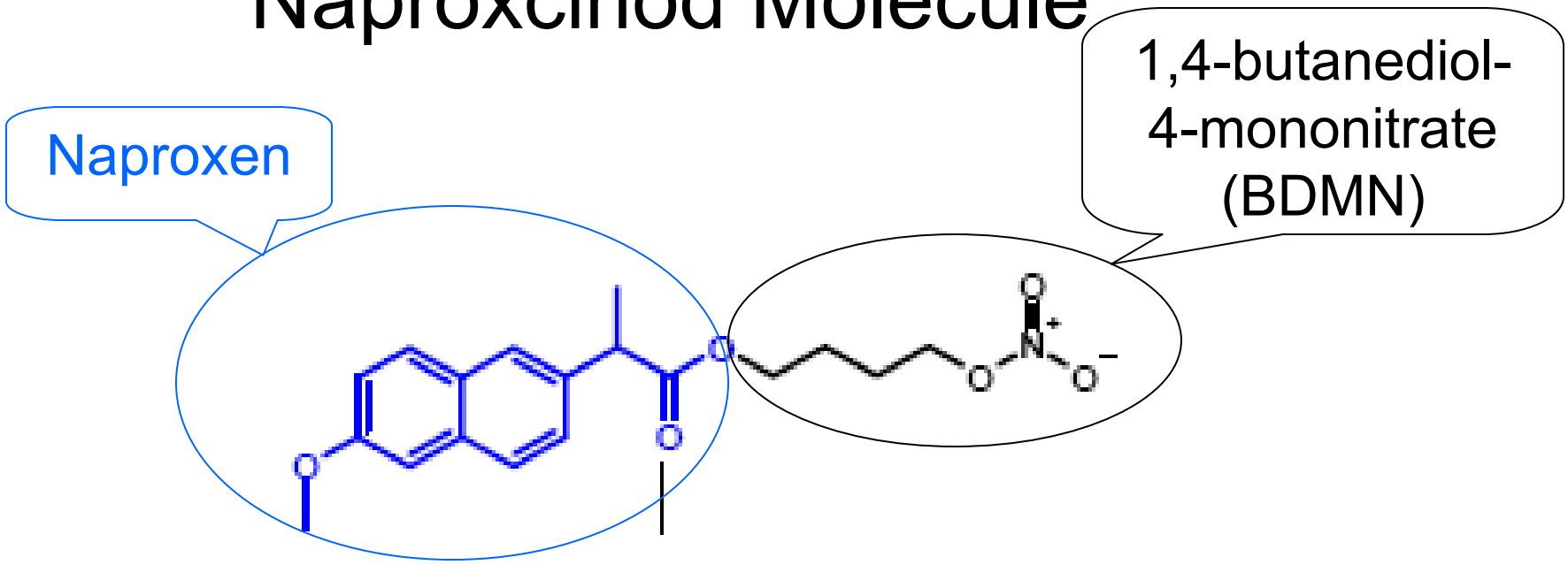
Pharmacokinetics of Naproxcinod and Naproxen

Joint Meeting of the Arthritis Advisory Committee (AAC) and Drug Safety and Risk Management Advisory Committee (DSaRM)

May 12, 2010

Wei Qiu, Ph.D
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology
CDER, FDA

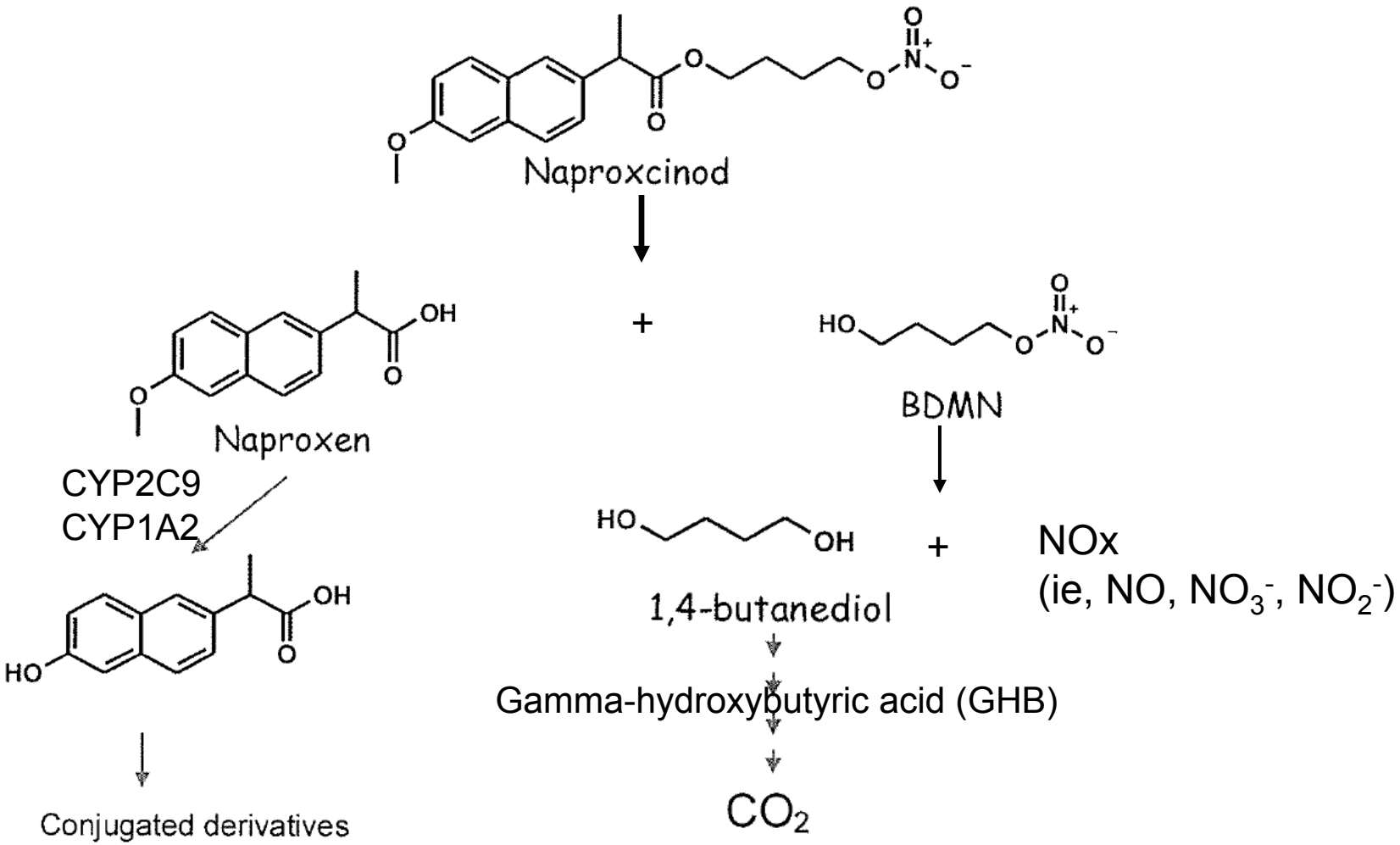
Naproxcinod Molecule



Naproxcinod

- Naproxcinod by itself is devoid of Cox-1 and Cox-2 pharmacological activity
- Naproxcinod molecular weight is 347
- Naproxen molecular weight is 230
- Naproxcinod 750 mg is equimolar to naproxen 500 mg

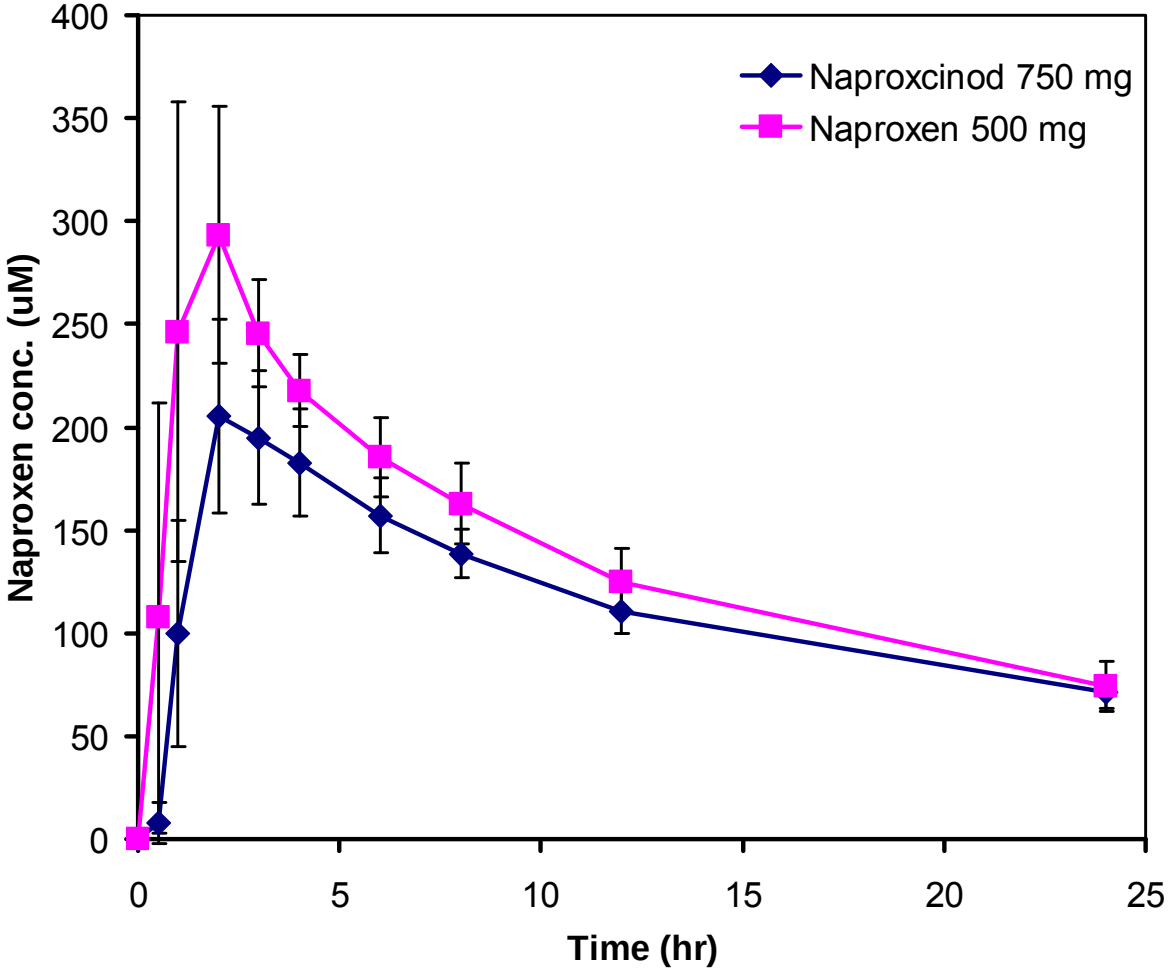
Metabolic Pathways of Naproxcinod



Metabolism of Naproxcinod

- Naproxcinod is extensively metabolized via carboxyl ester hydrolysis to form Naproxen and BDMN
- The metabolic profile of naproxen generated from naproxcinod is consistent with the known metabolic profile of administered naproxen
- BDMN is devoid of pharmacological activity and further metabolized to release NO
- Nitric oxide is quickly converted to nitrates excreted in urine
- A downstream metabolite of BDMN, GHB concentration is within the range of baseline levels

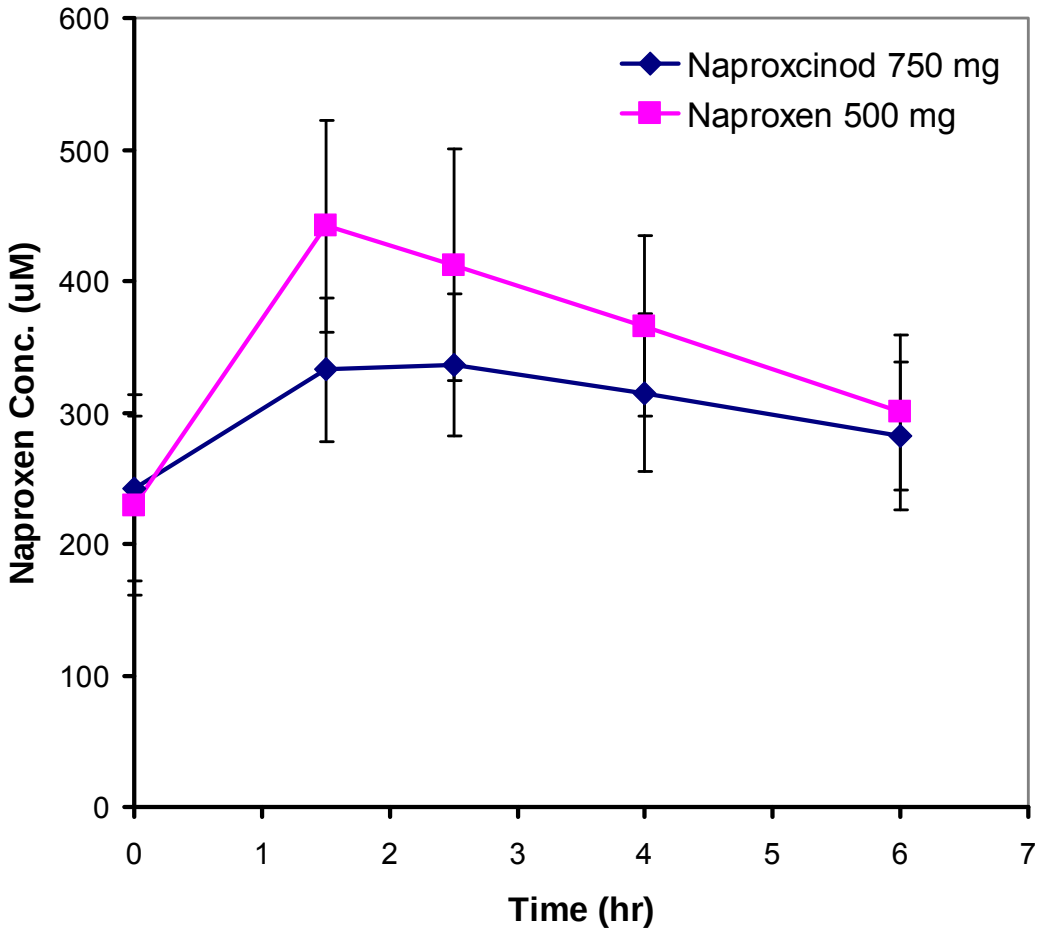
Naproxen Plasma Concentration-Time Profiles Following Single Dose Administration of Naproxcinod 750 mg and Naproxen 500 mg



Naproxen PK with Equimolar Single Doses of Naproxcinod (750 mg) and Naproxen (500 mg)

Study	Parameter	750 mg naproxcinod	500 mg naproxen	Change
0013	Cmax (μM)	210 (40.8)	317 (49.6)	34%↓
	AUC0-24h (μM.hr)	2772 (238)	3337 (376)	17%↓
	Tmax (hr)	2.0 (2.0 – 4.0)	2.0 (1.0 – 4.0)	--

Naproxen Plasma Concentration-Time Profiles Following Multiple Dose Administration of Naproxcinod 750 mg bid and Naproxen 500 mg bid



Naproxen PK with Equimolar Multiple Doses of Naproxcinod (750 mg bid) and Naproxen (500 mg bid)

	Parameter	750 mg naproxcinod	500 mg naproxen	Change
SP-NON-0002	Cmax (μM)	360 (42.5)	466 (75.5)	23% ↓
	AUCss (μM.hr)	3347 (462)	3624 (679)	8% ↓

Summary

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

- Overall, naproxen generated from naproxcinod has lower exposure as compared to equimolar naproxen administration. More so, in terms of Cmax compared to AUC values.

Joint Meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee

May 12, 2010

Discussion Question 1

1. Based on the results of the studies assessing the efficacy of naproxcinod and naproxen:

a. Is there evidence that naproxcinod is as effective as naproxen?

b. Is the applicant's choice of a noninferiority margin of 70% of the treatment effect size appropriate to determine that efficacy of the two products is similar?

i. If not, what would be an acceptable noninferiority margin for this situation?

c. Do you think that the reduced relative bioavailability may have been a factor in failure to demonstrate noninferiority?

Joint Meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee

May 12, 2010

Discussion Question 2

2. The data presented demonstrate that there is an average difference in blood pressure measurements, but no sustained effect throughout the dosing interval. Discuss whether the blood pressure effects of naproxcinod are likely to improve cardiovascular outcomes in patients requiring long-term treatment with naproxen.

a. Will the lack of sustained effect throughout the dosing interval result in a failure to reduce the risk for adverse cardiovascular outcomes?

b. Does the peak effect on blood pressure pose a potential safety concern for patients?

Joint Meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee

May 12, 2010

Discussion Question 3

3. **The data presented describe an effect on the occurrence of erosions, but were not of adequate design to assess an effect on the occurrence of ulcers.**

   Discuss whether the effects of naproxcinod to reduce the number of erosions in the absence of demonstrating an effect on gastric ulcers has clinical value in patients requiring long-term treatment with naproxen.

   a. **Are the studies submitted adequate to assess whether there is a meaningful effect on GI outcomes?**

   b. **If not, what changes should be made for future studies?**

   c. **Can the effect on GI outcomes be explained by the lower relative exposure to naproxen that result from dosing with naproxcinod?**

Joint Meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee

May 12, 2010

Vote Question 4

4. **Please vote on whether naproxcinod should be approved for the indication of the treatment of the signs and symptoms of osteoarthritis, taking into account the efficacy, pharmacokinetic and safety findings.**

(YES/NO/ABSTAIN)