CI-1

# Naproxcinod (NDA 22-478)

**United States Food and Drug Administration**

**Joint Meeting of the Arthritis Advisory Committee with the Drug Safety and Risk Management Advisory Committee**

**12 May 2010**

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# Introduction and Background

**Elizabeth Robinson, PhD**

**President**

**NicOx Research Institute Srl**

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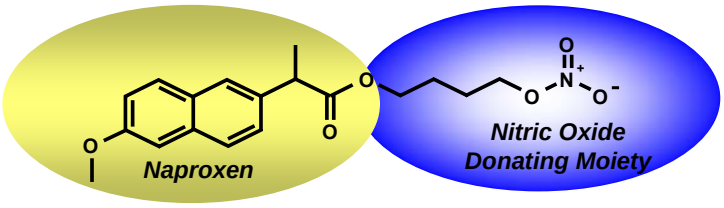
## NicOx Research Platform




**Naproxcinod**

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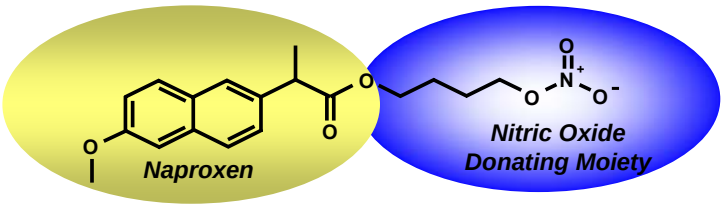
## Product Concept

- Established efficacy of NSAID (naproxen)
- Pharmacological effects of nitric oxide




**Naproxcinod**

- **Proposed indication: Relief of signs and symptoms of osteoarthritis (OA)**

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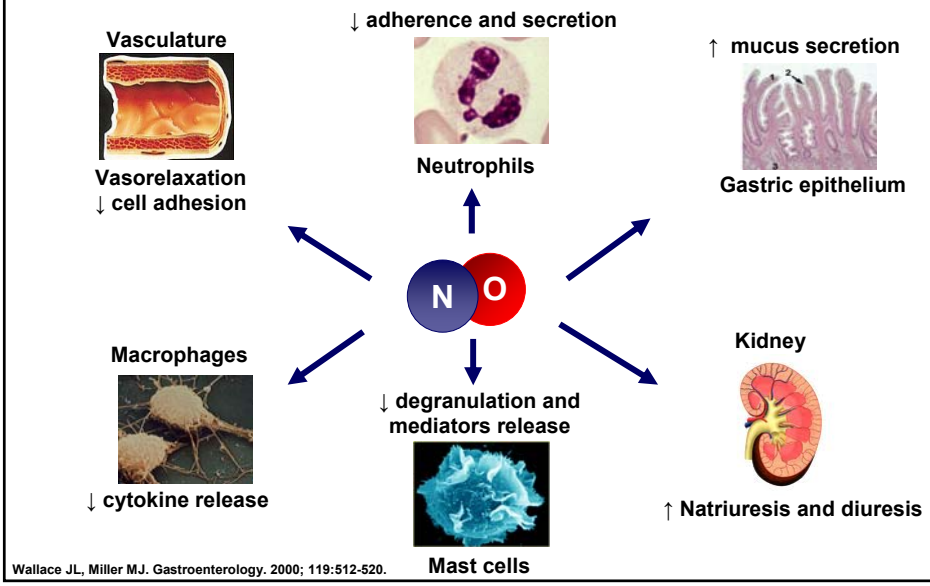
## Nitric Oxide: An Endogenous Signalling Molecule




Wallace JL, Miller MJ. Gastroenterology. 2000; 119:512-520.

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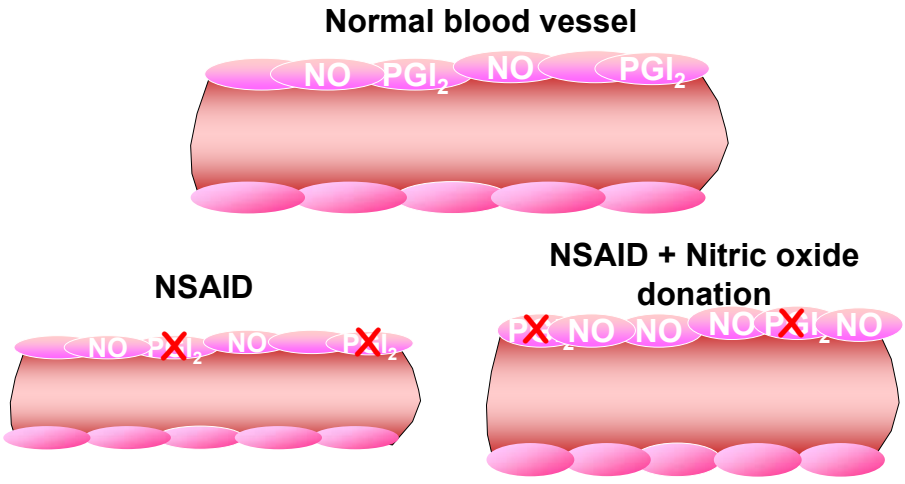
## How Can Nitric Oxide Mitigate the Increase in Blood Pressure Observed With NSAIDs?



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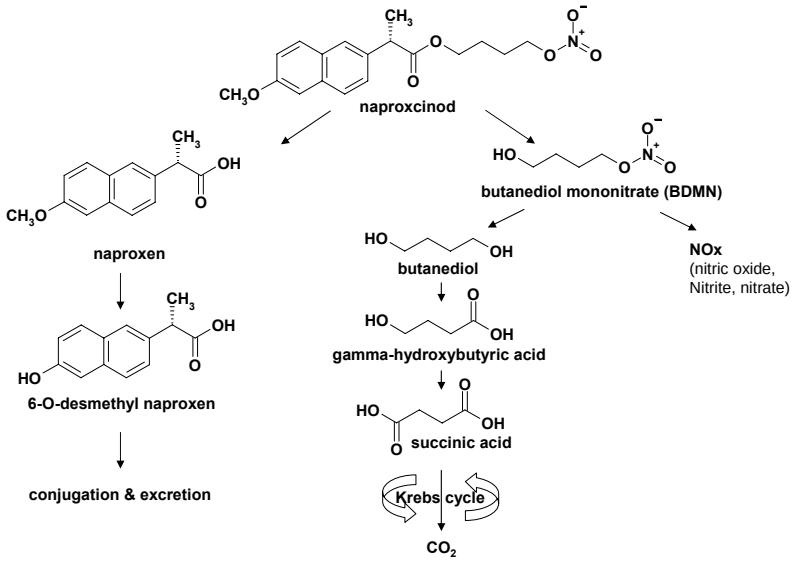
## Naproxcinod Metabolic Pathway

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## Naproxcinod: Comprehensive Development Program

- 35 registration clinical trials
- Large safety database
  - Over 6,700 patients in trials
  - Over 4,000 subjects/patients exposed to naproxcinod
- Special Investigation Studies
  - 24-hour Ambulatory Blood Pressure Monitoring (ABPM)
  - Exploratory GI endoscopy

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## Naproxcinod Is an Effective NSAID With a Favorable Safety Profile for OA Patients

- Effective for the relief of signs and symptoms of osteoarthritis (OA)
  - 375 mg twice daily
  - 750 mg twice daily
- Safe and well-tolerated in OA patients
- Lower impact on blood pressure

*Class warnings for GI, CV and hypertension same as NSAIDs class*

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## Presenters

| | |
|---|---|
| **Marc Hochberg, MD**<br>Professor of Medicine<br>Head, Division of Rheumatology and Clinical Immunology<br>University of Maryland School of Medicine<br>Baltimore, MD | **Management of OA: Rationale for Naproxcinod** |
| **Pascal Pfister, MD, MFPM**<br>NicOx, Chief Scientific Officer<br>Head of R&D | **Naproxcinod Efficacy and Overall Safety** |
| **William White, MD**<br>Professor and Chief, Division of Hypertension and Clinical Pharmacology<br>Calhoun Cardiology Center<br>University of Connecticut School of Medicine<br>Farmington, CT | **Blood Pressure Effects of Naproxcinod** |
| **Michael Weber, MD**<br>Professor of Medicine<br>SUNY Downstate Medical College of Medicine<br>Brooklyn, NY | **Importance of SBP Levels in Patients with OA** |
| **Marc Hochberg, MD** | **Management of OA: Benefit Risk of Naproxcinod** |

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# External Consultants

| | |
|---|---|
| **Byron L. Cryer, MD** | John C Vanatta Professor of Medicine<br>Head, Division of Gastroenterology<br>University of Texas Southwestern Medical School<br>North Texas Veterans Health Care System<br>Dallas, TX |
| **John Constant, PhD** | Vice President, Scientific Affairs, PRA International<br>Vancouver, BC, Canada |
| **Gretchen S. Dieck, PhD** | Vice President, Safety, Epidemiology & Risk Management, UBC<br>Blue Bell, PA |
| **Garret FitzGerald, MD** | Professor of Medicine and Professor and Chair of Pharmacology<br>University of Pennsylvania School of Medicine<br>Philadelphia, PA |
| **Jon Lundberg, MD, PhD** | Professor in Nitric Oxide Pharmacologics<br>Karolinska Institute<br>Department of Physiology and Pharmacology<br>Stockholm, Sweden |
| **Thomas Schnitzer, MD, PhD** | Professor, Division of Rheumatology<br>Northwestern University Feinberg School of Medicine<br>Physical Medicine & Rehabilitation<br>Chicago, IL |
| **Megan Shram, PhD** | Research Scientist Clinical Pharmacology<br>Kendle Early Stage<br>Toronto, ON, Canada |

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# Management of OA: Rationale for Naproxcinod

**Marc C. Hochberg, MD, MPH**

Professor of Medicine
Head, Division of Rheumatology and Clinical Immunology
University of Maryland School of Medicine
Baltimore, MD

CR-2

## Construct of OA: 2010

- Most common form of arthritis
- Incidence and prevalence are higher in women than in men
- Accounts for more functional limitation, work loss, and physical disability than any other chronic disease
- Most common indication for total joint replacement
- Associated with excess mortality
  - Concomitant GI and CV disease

Hochberg MC. *Semin Arthritis Rheum.* 2010;39:321-2.

CR-3

## Management of OA: OARSI Recommendation #1

- Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities

OARSI = Osteoarthritis Research Society International;
Zhang W, et al. *Osteoarthritis and Cartilage*. 2008;16:137-162.

CR-4

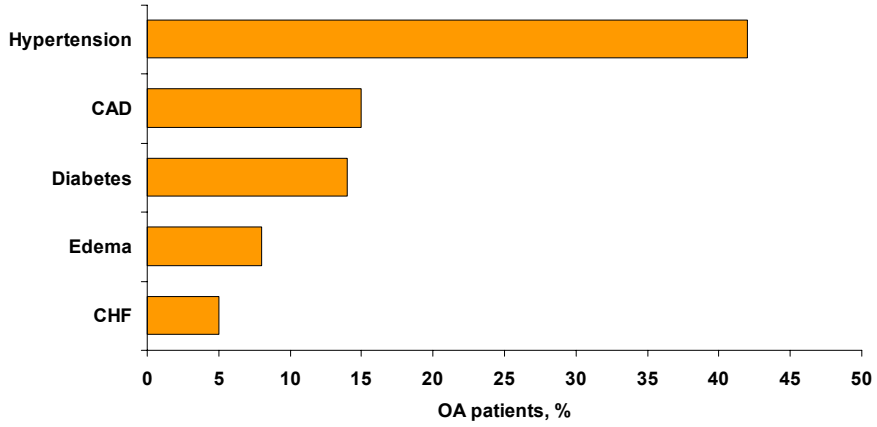
## Summary of Evidence
### Nonselective NSAIDs

| Benefits: Symptom Relief | Harms: GI, CV, and Other |
|---|---|
| ▪ Good evidence for superior efficacy versus both placebo and acetaminophen<br>▪ Good evidence for comparable efficacy with each other | ▪ Good evidence that all are associated with comparable, dose-dependent increases in risk of serious GI events versus nonuse; misoprostol or PPIs can attenuate this risk<br>▪ Fair evidence that high doses of ibuprofen and diclofenac carry risk of serious CV events compared with coxibs<br>▪ Fair evidence that naproxen is associated with lower risk of CV events than coxibs |

PPI = Proton pump inhibitor.
http://effectivehealthcare.ahrq.gov/ehc/products/2/67/Analgesicsexecsum.pdf

CR-5

## Patients with OA Often Have Comorbidities




CAD = Coronary artery disease. Ingenix Pharmaceutical Services. Phase III assessment of patient characteristics for users of NSAID/COX-2 medications using United Healthcare claims data. December 29, 2000.

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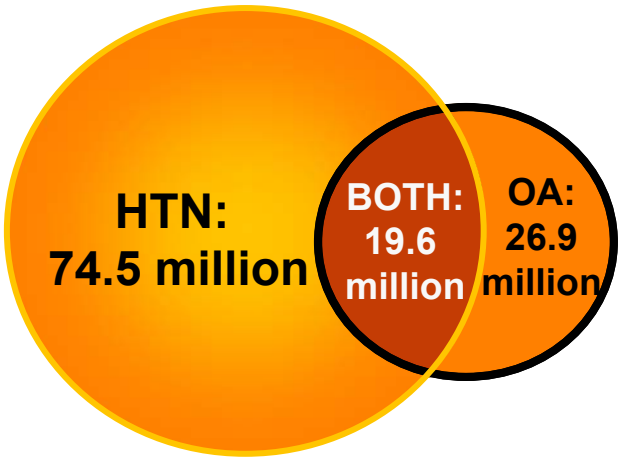
## Concomitant Occurrence of Hypertension and Osteoarthritis




Lloyd-Jones D, et al. *Circulation*. 2010;121:e1-e170; Lawrence RC, et al. *Arthritis Rheum.* 2008;58:26-35; Wang PS, et al. *Hypertension*. 2005;46:273-279

CR-7

## Effects of NSAIDs on Blood Pressure

- Meta-analyses included data from
  - 54 studies with 123 treatment arms including 1324 patients (1213 [94%] hypertensive)[a]
  - 50 studies with 771 patients[b]
- Nonselective NSAIDs raise MAP by ~3-5 mm Hg
- This effect on MAP was greater in:
  - Patients with hypertension
  - Hypertensive patients treated with ACE inhibitors, diuretics, or β-blockers

MAP = Mean arterial pressure.
[a]Pope JE, et al. *Arch Intern Med*. 1993;153:477-489; [b]Johnson AG, et al. *Ann Intern Med*. 1994;121:289-300.

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## NSAID Class Label: Blood Pressure Warning

**HYPERTENSION**

**NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to increased incidence of CV events.**

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## Importance of Systolic Blood Pressure Reduction at the Population Level

| Reduction in SBP mmHg | % Reduction in Mortality | | |
|---|---|---|---|
| | Stroke | CHD | Total |
| 2 | -6 | -4 | -3 |
| 3 | -8 | -5 | -4 |
| 5 | -14 | -9 | -7 |

National High Blood Pressure Education Coordination Program Committee.
Whelton P et al. *JAMA* 2002;288:1882-1888.

CR-10

## There Remains an Unmet Medical Need for the Management of OA

- The benefits and risks of NSAID use must be balanced
  - Benefits: Relief of symptoms and improvement in function
  - Major risks: Cardiovascular and Gastrointestinal safety
- More therapeutic options are needed that provide the benefits of NSAIDs while mitigating the safety concerns of NSAIDs
  - Increases in blood pressure

CE-1

# Naproxcinod
# Efficacy and Overall Safety

**Pascal Pfister, MD, MFPM**

NicOx, Chief Scientific Officer
Head of R&D

CE-2

## Overview

- Development objectives
- Efficacy
  - Clinical program
  - Phase III OA studies
- Safety
  - Overall database
  - OA Phase 2/3 studies

CE-3

## Naproxcinod—Development Objectives

- To demonstrate efficacy for the relief of the signs and symptoms of osteoarthritis vs placebo
- To demonstrate the overall safety and tolerability profile of naproxcinod
- Also to assess the pharmacological effect of the Nitric Oxide (NO) donating moiety on Blood Pressure

CE-4

## Clinical Overview
### 35 Studies—Over 6700 Subjects or Patients

- Efficacy and safety studies in OA
  - Two dose ranging studies
  - Three pivotal Phase 3 studies
  - One long term safety extension study
- Special investigation studies
  - Blood pressure: 3 ABPM studies

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## Naproxcinod Efficacy Profile

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## Naproxcinod Dose Selection

- Two phase 2 dose-ranging studies [from 125 mg *bid* to 1125 mg *bid*]
  - Naproxcinod 375 mg *bid* was the lowest effective dose
  - Naproxcinod 750 mg *bid* was the highest effective dose

CE-7

## Three Adequate Well-Controlled
### Phase 3 OA Studies

| | 301 | 302 | 303 |
|---|---|---|---|
| Indication | OA (Knee) | OA (Knee) | OA (Hip) |
| N of patients randomized | 918 | 1011 | 810 |
| Study design | Double-blind, randomized, multicenter, placebo and naproxen-controlled, parallel groups | | |
| Duration | 13 weeks *vs.* placebo (3 studies), 52 weeks *vs.* naproxen (302) | | |
| Co-primary endpoints | Mean change from BL at Week 13 for naproxcinod vs. placebo<br>– WOMAC™ pain subscale score<br>– WOMAC™ physical function subscale score<br>– Patients' overall rating of disease status | | |

ITT = Intent to treat.

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## Population Demographics
### Phase 3 OA Studies

| ITT Population (N = 2703) | Placebo (n = 803) | Naproxcinod 375 mg *bid* (n = 481) | Naproxcinod 750 mg *bid* (n = 789) | Naproxen 500 mg *bid* (n = 630) |
|---|---|---|---|---|
| Mean age, years (SD) | 61.6 (9.4) | 60.5 (9.6) | 61.7 (9.7) | 60.9 (9.7) |
| Age category, n (%) | | | | |
| < 65 years | 518 (65%) | 328 (68%) | 502 (64%) | 420 (67%) |
| ≥ 65 years | 285 (36%) | 153 (32%) | 287 (36%) | 209 (33%) |
| Females, n (%) | 551 (69%) | 352 (73%) | 530 (67%) | 435 (69%) |
| Caucasians, n (%) | 698 (87%) | 391 (81%) | 694 (88%) | 540 (86%) |
| African Americans, n (%) | 87 (11%) | 76 (16%) | 81 (10%) | 79 (12.5%) |
| BMI, kg/m$^2$ (SD) | 31.9 (7.1) | 33.9 (8.0) | 31.8 (7.2) | 32.5 (7.4) |

Studies included: HCT 3012-X-301, -302, -303.

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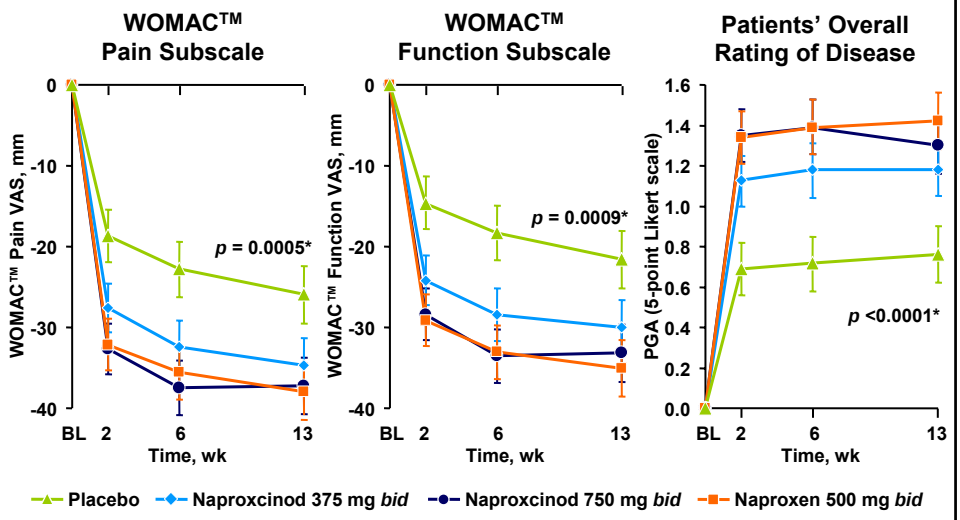
# Patient Disposition
## Phase 3 OA Studies

| | Placebo n = 803 | Naproxcinod 375 mg *bid* n = 481 | Naproxcinod 750 mg *bid* n = 789 | Naproxen 500 mg *bid* n = 630 |
|---|---|---|---|---|
| ITT population | | | | |
| Completed | 571 (71.1%) | 382 (79.4%) | 607 (76.9%) | 491 (77.9%) |
| Main reasons for discontinuation | | | | |
| Adverse event(s) | 50 (6.2%) | 25 (5.2%) | 63 (8.0%) | 48 (7.6%) |
| Lack of efficacy | 97 (12.1%) | 32 (6.7%) | 39 (4.9%) | 30 (4.8%) |
| Violation of entry criteria | 19 (2.4%) | 10 (2.1%) | 28 (3.5%) | 22 (3.5%) |
| Withdrawn consent | 44 (5.5%) | 20 (4.2%) | 39 (4.9%) | 22 (3.5%) |
| Lost to follow-up | 14 (1.7%) | 6 (1.2%) | 5 (0.6%) | 6 (1.0%) |
| Other | 8 (1.0%) | 6 (1.2%) | 8 (1.0%) | 11 (1.7%) |

Studies included 301, 302, and 303 up to 13 weeks treatment.

CE-10

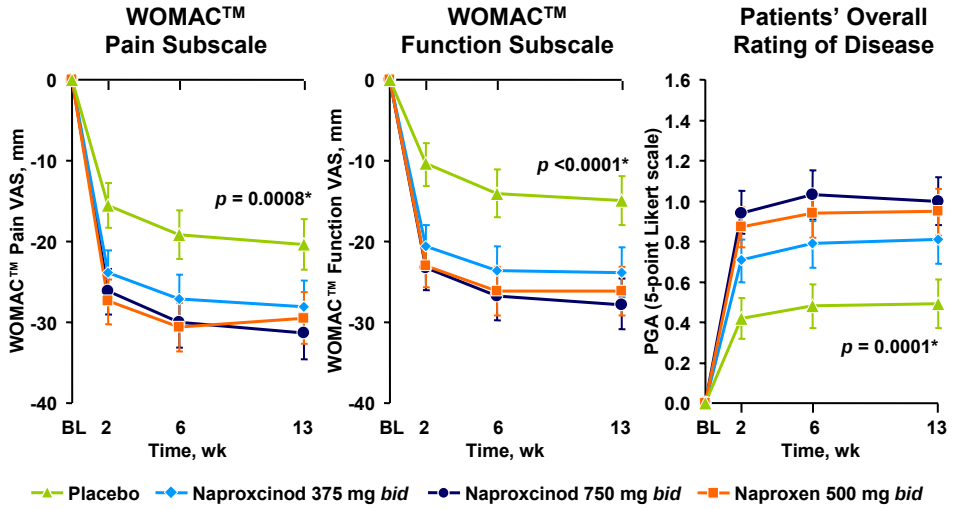
# Naproxcinod Met All Co-Primary Endpoints
## Study 301 - LS Mean Change (95%, CI) from Baseline at Week 2, 6 and 13 (ITT)




PGA = Patient Global Assessment; VAS = Visual analog scale; * At Wk 13.

CE-11

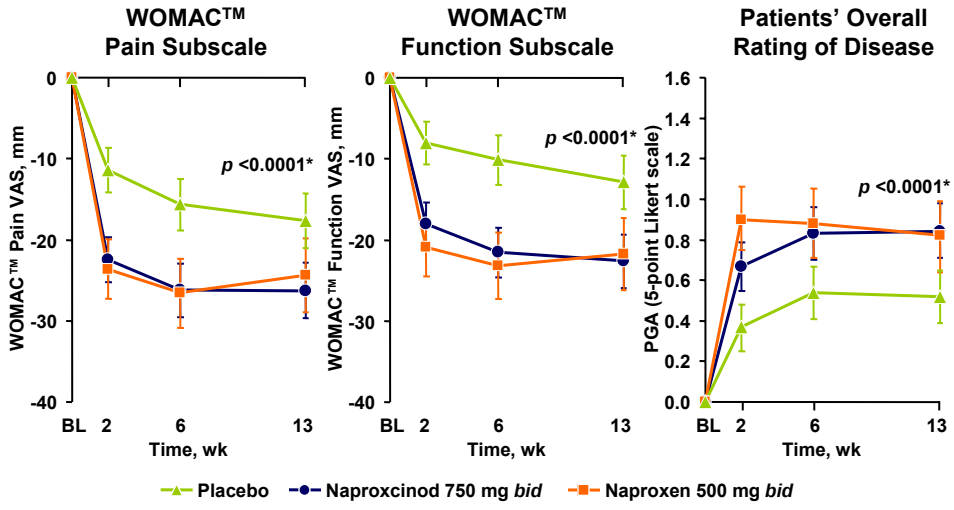
## Naproxcinod Met All Co-Primary Endpoints
### Study 302 - LS Mean Change (95%, CI) from Baseline at Week 2, 6 and 13 (ITT)




PGA = Patient Global Assessment; VAS = Visual analog scale; * At Wk 13.

CE-12

## Naproxcinod Met All Co-Primary Endpoints
### Study 303 - LS Mean Change (95%, CI) from Baseline at Week 2, 6 and 13 (ITT)




PGA = Patient Global Assessment; VAS = Visual analog scale; * At Wk 13.

CE-13

## Rationale for Comparability Naproxcinod 750 mg *bid* vs Naproxen 500 mg *bid*

- Efficacy of naproxcinod (primary objective)
  - Superiority vs placebo in three adequate and well controlled studies
- Comparison with naproxen (secondary objective)
  - Safety characterization through BP studies
  - Efficacy comparison to inform risk/benefit assessment

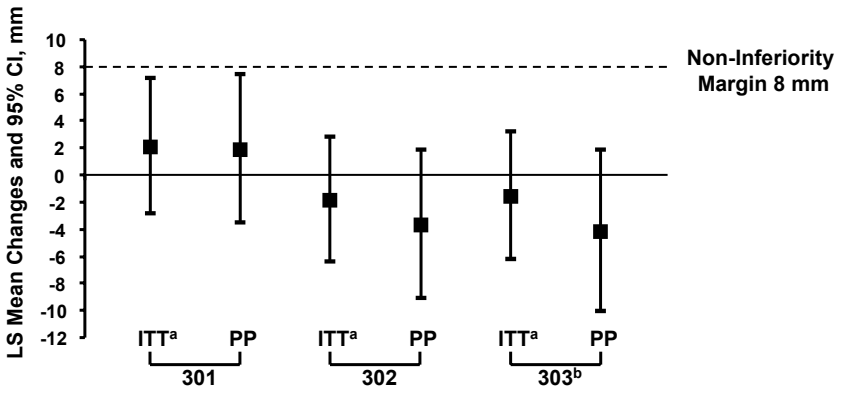
CE-14

## WOMAC™ Pain and Function: Rationale of Non-Inferiority Margin

- Treatment effect size of naproxen (vs. placebo) in phase 2 dose-ranging studies was ~12 mm for WOMAC™ Pain and Function
- NicOx chose 70% of the treatment effect as the NI margin for Phase 3 studies: 8 mm
- No previously reported NSAIDs trials used a NI margin of less than 10 mm
- Few published studies to quantify the treatment effect size of naproxen

CE-15

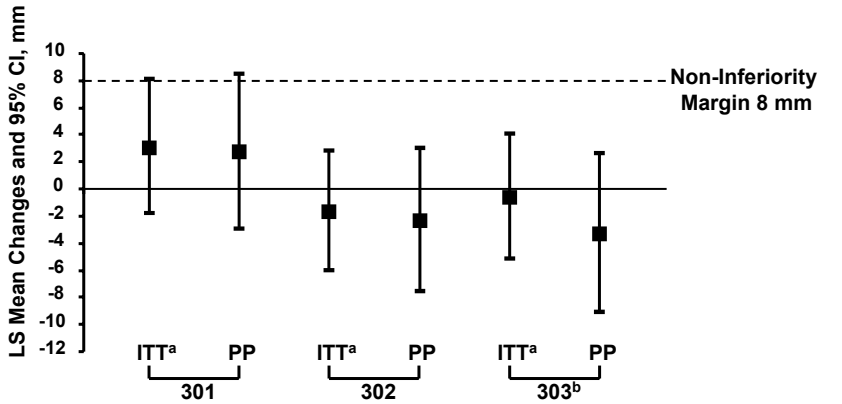
## Comparable Efficacy of Naproxcinod 750 vs Naproxen
### WOMAC™ Pain at Week 13




[a] Modified LOCF imputation method
[b] Not prospectively planned

CE-16

## Comparable Efficacy of Naproxcinod 750 vs Naproxen
### WOMAC™ Function at Week 13

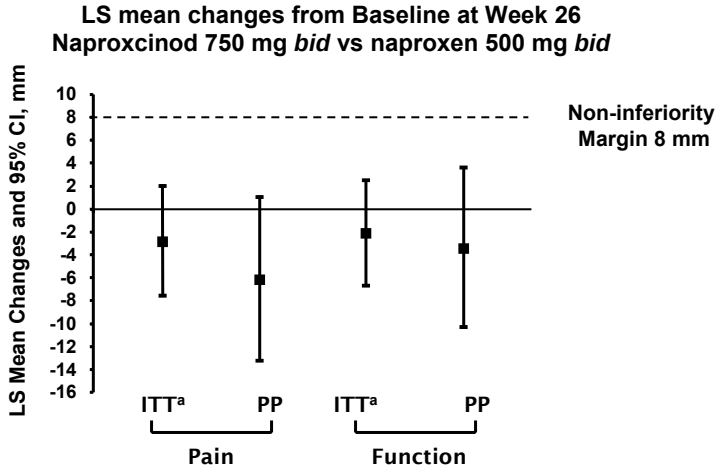



[a] Modified LOCF imputation method
[b] Not prospectively planned

CE-17

## Comparable Efficacy of Naproxcinod vs Naproxen Sustained up to 26 weeks

### WOMAC™ Pain and Function Study 302, 26 Weeks

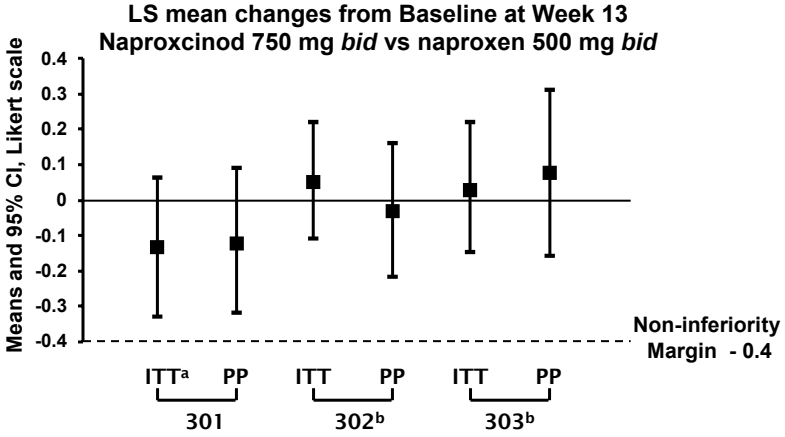



[a] Modified LOCF imputation method

CE-18

## Similar Efficacy of Naproxcinod vs Naproxen

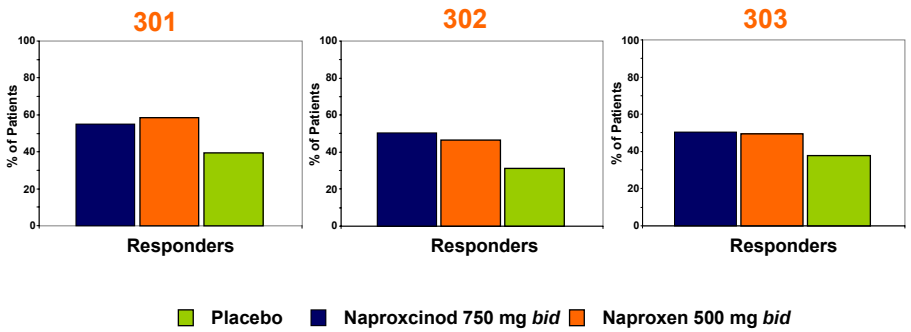
### Patients' Overall Rating of Disease Status (5 pt. Likert scale)




[a] Modified LOCF imputation method
[b] Not prospectively planned

CE-19

## Similar Efficacy of Naproxcinod vs Naproxen
### Modified OARSI Responder Rates (ITT)




A modified OARSI responder was defined as:
≥50% improvement in WOMAC™ pain or physical subscale score that was ≥20% of the scale at Baseline OR
≥20% improvement in the WOMAC™ pain and physical function subscale scores that were ≥10% and <20% of the scale at Baseline

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## Similar Numbers Needed to Treat
### Modified OARSI Responder Rates

| | NNT |
|---|---|
| ▪ 301 | |
| – Naproxcinod 750 mg *bid* | 6 |
| – Naproxen 500 mg *bid* | 5 |
| ▪ 302 | |
| – Naproxcinod 750 mg *bid* | 5 |
| – Naproxen 500 mg *bid* | 7 |
| ▪ 303 | |
| – Naproxcinod 750 mg *bid* | 8 |
| – Naproxen 500 mg *bid* | 8 |

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## Naproxcinod 750 mg *bid* Comparable to Naproxen 500 mg *bid*
### Preponderance of Evidence

- WOMAC Pain and Function:
  - Upper bound of 95% Confidence Interval ~ 4 mm for 302 and 303[b]
- Similar findings:
  - Modified OARSI responder rates
  - Numbers Needed to Treat[b]
  - Discontinuation due to lack of efficacy or worsening of disease
  - Patient reported Outcomes:
    - Patient overall rating of disease status
    - QOL (SF36)

[b] Not prospectively planned

CE-22

## Efficacy Summary

- Substantial evidence of effectiveness
  - Three, adequate and well-controlled trials in patients with OA of the hip or knee
- The efficacy of naproxcinod 750 mg *bid* is comparable to that of naproxen 500 mg *bid*

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# Naproxcinod Safety Profile

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# The Naproxcinod Safety Database Far Exceeds ICH Requirements

## All Studies

| | Duration of treatment (weeks) | | | | |
|---|---|---|---|---|---|
| Total daily dose, n (%)[a] | Any | ≥ 6 | ≥ 13 | ≥ 26 | ≥ 52 |
| All naproxcinod | 4023 | 2533 (63.0%) | 1387 (34.5%) | 893 (22.2%) | 521 (13.0%) |
| Low dose (< 750 mg) | 338 | 84 (24.9%) | 0 | 0 | 0 |
| 750 mg | 1341 | 864 (64.4%) | 611 (45.6%) | 463 (34.5%) | 257 (19.2%) |
| 375 mg *bid* | 1007 | 788 (78.3%) | 611 (60.7%) | 463 (46.0%) | 257 (25.5%) |
| 1500 mg | 2222 | 1440 (64.8%) | 776 (34.9%) | 430 (19.4%) | 264 (11.9%) |
| 750 mg *bid* | 2156 | 1440 (66.8%) | 776 (36.0%) | 430 (19.9%) | 264 (12.2%) |
| High dose (> 1500 mg) | 306 | 92 (30.1%) | 0 | 0 | 0 |

[a] Percentages are based on the number of patients in each treatment group as applicable.

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## Serious Adverse Events and Deaths
### All Studies

| n (%), [Event per 100 patient yrs] | Placebo (n = 1412) | Naproxcinod All (n = 4023) | Naproxcinod 375 mg *bid* (n = 1007) | Naproxcinod 750mg *bid* (n = 2156) | Naproxen 500 mg *bid* (n = 1633) |
|---|---|---|---|---|---|
| Any SAE | 20 (1.4) [ 11 ] | 75 (1.9 ) [ 8 ] | 28 (2.8) [ 7 ] | 43 (2.0) [ 8 ] | 28 (1.7) [ 9 ] |
| Any Death | 0 | 3 (<0.1) [ <1 ] | 3 (0.3) [ <1 ] | 0 | 1 (<0.1) [ <1 ] |

For the calculation of the number of events per 100 patient years, all episodes of an adverse event are counted (ie, all events during treatment and follow-up, including unique episode repeats). It is calculated within each treatment group as: [(number of events) / ((sum of durations of study drug exposure for all patients)/365.25)]*100.

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## Adverse Events by Selected SOC
### All Studies

| n (%), [Event per 100 patient yrs] | Placebo (n = 1412) | Naproxcinod 375 mg *bid* (n = 1007) | Naproxcinod 750 mg *bid* (n = 2156) | Naproxen 500 mg *bid* (n = 1633) |
|---|---|---|---|---|
| Any AE | 667 (47.2) [ 878 ] | 602 (59.8) [ 359 ] | 1230 (57.1) [ 656 ] | 888 (54.4) [ 817] |
| GI Disorders | 234 (16.6) [ 183 ] | 203 (20.2) [ 64 ] | 520 (24.1) [ 149 ] | 394 (24.1) [ 206 ] |
| Nervous System Disorders | 236 (16.7) [ 242 ] | 121 (12.0) [ 46 ] | 374 (17.3) [ 161 ] | 256 ( 15.7) [ 207 ] |
| Skin and Sub. Tissue Disorders | 37 (2.6) [ 21 ] | 50 (5.0) [ 12 ] | 81 (3.8) [ 17 ] | 65 (4.0) [ 24 ] |
| Renal and Urinary Dis. | 10 (0.7) [ 5 ] | 22 (2.2) [ 5 ] | 31 (1.4) [ 6 ] | 22 (1.3) [ 7 ] |
| Cardiac Disorders | 19 (1.3) [ 11 ] | 21 (2.1) [ 4 ] | 48 (2.2) [ 10 ] | 24 (1.5) [ 7 ] |
| Vascular Disorders | 29 ( 2.1) [ 16 ] | 48 (4.8) [ 10 ] | 71 (3.3) [ 12 ] | 37 (2.3) [ 11 ] |

SOC = System organ class

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NicOx

## Safety Profile
## In All OA Phase 2 &3 Studies

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## Baseline Comorbidities in OA Patients
### All Placebo Controlled OA Studies up to 13 Weeks

| n (%) | Placebo (n = 1116) | Naproxcinod 375 mg *bid* (n = 601) | Naproxcinod 750 mg *bid* (n = 1472) | Naproxen 500 mg *bid* (n = 1175) |
|---|---|---|---|---|
| Hypertension | 528 (47.3%) | 277 (46.1%) | 615 (41.8%) | 503 (42.8%) |
| Dyslipidemia | 379 (34.0%) | 259 (43.1%) | 362 (24.6%) | 307 (26.1%) |
| Diabetes | 127 (11.4%) | 78 (13.0%) | 157 (10.7%) | 119 (10.1%) |
| ≥1 risk factor for high cardiovascular risk* | 706 (63.3%) | 398 (66.2%) | 795 (54.0%) | 662 (56.3%) |
| High cardiovascular risk | 315 (28.2%) | 205 (34.1%) | 335 (22.8%) | 274 (23.3%) |
| Low-dose aspirin use (≤ 325 mg) | 186 (16.7%) | 128 (21.3%) | 208 (14.1%) | 156 (13.3%) |

CV risk factors were diabetes, hypertension, dyslipidemia.
*High CV risk subjects were identified as having ≥ 2 of the following risk factors (diabetes, hypertension, dyslipidemia) OR a medical history of CV event.

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# Summary of Adverse Events
## All Placebo Controlled OA Studies up to 13 Weeks

| n, (%) [Events per 100 patient yrs] | Placebo (n = 1116) | Naproxcinod 375 mg *bid* (n = 601) | Naproxcinod 750 mg *bid* (n = 1472) | Naproxen 500 mg *bid* (n = 1175) |
|---|---|---|---|---|
| Patients with ≥ 1 AE | 554 (49.6%) [787] | 301 (50.1%) [688] | 830 (56.4%) [1175] | 682 (58.0%) [1159] |
| Patients with ≥ 1 GI AE | 200 (17.9%) [158] | 109 (18.1%) [156] | 377 (25.6%) [288] | 315 (26.8%) [302] |
| Patients with ≥ 1 CV[a] AE | 60 (5.4%) [35] | 38 (6.3%) [33] | 102 (6.9%) [50] | 84 (7.1%) [47] |
| Patients with ≥ 1 SAE | 20 (1.8%) [11] | 7 (1.2%) [8] | 22 (1.5%) [10] | 13 (1.1%) [8] |
| Patients with ≥ 1 GI SAE | 4 (0.4%) [2] | 1 (0.2%) [2] | 6 (0.4%) [3] | 3 (0.3%) [2] |
| Patients with ≥ 1 CV SAE | 7 (0.6%) [4] | 3 (0.5%) [2] | 5 (0.3%) [2] | 4 (0.3%) [2] |
| Patients who discontinued due to an AE | 72 (6.5%) [53] | 36 (6.0%) [41] | 97 (6.6%) [63] | 72 (6.1%) [58] |
| Deaths | 0 | 0 | 0 | 1 (0.1%) |

[a] Percentages are based on the number of patients in each treatment group.
Patients with >1 event within a particular parameter are counted only once for that parameter

CE-30

# AEs ≥ 3% in Any Treatment Group
## All Placebo Controlled OA Studies up to 13 Weeks

| n (%) | Placebo (n = 1116) | Naproxcinod 375 mg *bid* (n = 601) | Naproxcinod 750 mg *bid* (n = 1472) | Naproxen 500 mg *bid* (n = 1175) |
|---|---|---|---|---|
| Headache | 136 (12.2) | 52 (8.7) | 230 (15.6) | 187 (15.9) |
| Dyspepsia | 37 (3.3) | 15 (2.5) | 90 (6.1) | 67 (5.7) |
| Diarrhea | 45 (4.0) | 22 (3.7) | 72 (4.9) | 49 (4.2) |
| Nausea | 39 (3.5) | 20 (3.3) | 64 (4.3) | 44 (3.7) |
| Nasopharyngitis | 34 (3.0) | 12 (2.0) | 59 (4.0) | 39 (3.3) |
| Back Pain | 36 (3.2) | 21 (3.5) | 58 (3.9) | 43 (3.7) |
| Abdominal Pain Upper | 21 (1.9) | 7 (1.2) | 49 (3.3) | 54 (4.6) |
| Dizziness | 24 (2.2) | 15 (2.5) | 47 (3.2) | 24 (2.0) |
| Arthralgia | 29 (2.6) | 16 (2.7) | 46 (3.1) | 45 (3.8) |
| Constipation | 17 (1.5) | 17 (2.8) | 44 (3.0) | 42 (3.6) |
| Abdominal Pain | 17 (1.5) | 3 (0.5) | 28 (1.9) | 38 (3.2) |
| U Resp Tract Infection | 24 (2.2) | 21 (3.5) | 18 (1.2) | 27 (2.3) |

CE-31

## Most Common Adverse Events Leading to Discontinuation (≥ 0.4% in Any Treatment Group)

### All Placebo Controlled OA Studies up to 13 Weeks

| n (%) | Placebo (n = 1116) | Naproxcinod 375 mg *bid* (n = 601) | Naproxcinod 750 mg *bid* (n = 1472) | Naproxen 500 mg *bid* (n = 1175) |
|---|---|---|---|---|
| Any AE | 72 (6.5) | 36 (6.0) | 97 (6.6) | 72 (6.1) |
| Dyspepsia | 4 (0.4) | 3 (0.5) | 11 (0.7) | 9 (0.8) |
| Arthralgia | 1 (< 0.1) | 4 (0.7) | 3 (0.2) | 1 (< 0.1) |
| Headache | 7 (0.6) | 1 (0.2) | 8 (0.5) | 3 (0.3) |
| Nausea | 7 (0.6) | 2 (0.3) | 7 (0.5) | 7 (0.6) |
| Diarrhea | 7 (0.6) | 0 | 6 (0.4) | 5 (0.4) |
| Dizziness | 4 (0.4) | 1 (0.2) | 6 (0.4) | 1 (< 0.1) |
| Abdominal Pain Upper | 5 (0.4) | 2 (0.3) | 5 (0.3) | 12 (1.0) |
| Abdominal Pain | 4 (0.4) | 0 | 4 (0.3) | 7 (0.6) |

CE-32

## Safety Profile by Target Organ

CE-33

## Cardiovascular Safety
### All Studies

| n (%) [Events per 100 patient yrs ] | Placebo (n = 1412) | Naproxcinod 375 mg *bid* (n = 1007) | Naproxcinod 750 mg *bid* (n = 2156) | Naproxen 500 mg *bid* (n = 1633) |
|---|---|---|---|---|
| CV SAE | 7 (0.5) [3] | 10 (1.0) [2] | 9 (0.4) [2] | 6 (0.4) [2] |
| Patients with ≥ 1 Cardiac AE | 19 (1.3) [11] | 21(2.1) [7] | 48 (2.2) [10] | 24 (1.5) [7] |
| Vascular AE | 29 (2.1) [16] | 48 (4.8) [10] | 71 (3.3) [10] | 37 (2.3) [11] |

CE-34

## All Probable and Confirmed Cardiovascular or Renal-Related Adverse Events
### All Phase 2 and 3 OA Studies up to 65 Weeks

| n (%) [Events per 100 patient yrs] | Placebo (n = 1116) | Naproxcinod 375 mg *bid* (n = 824) | Naproxcinod 750 mg *bid* (n = 1672) | Naproxen 500 mg *bid* (n = 1175) |
|---|---|---|---|---|
| Any coronary artery disease / myocardial infarction-related AEs | 11 (1.0) [7] | 10 (1.2) [3] | 25 (1.5) [4] | 17 (1.4) [7] |
| Any cardiac failure–related event | 16 (1.4) [9] | 35 (4.2) [8] | 44 (2.6) [9] | 49 (4.2) [16] |
| Any cerebrovascular–related event | 1 (<0.1) [< 1] | 1 (0.1) [< 1] | 2 (0.1) [< 1] | 0 |
| Any renal-related event | 1 (<0.1) [1] | 5 (0.6) [2] | 9 (0.5) [2] | 6 (0.5) [2] |
| Any cardiovascular- or renal-related event | 29 (2.6) [17] | 49 (5.9) [13] | 74 (4.4) [16] | 71 (6.0) [25] |

CE-35

## AntiPlatelet Trialist Collaboration (APTC) Events
### All Phase 2 and 3 OA Studies up to 65 Weeks

| n (%) [Events per 100 patient yrs] | Placebo n = 1116 | Naproxcinod 375 mg *bid* n = 824 | Naproxcinod 750 mg *bid* n = 1672 | Naproxen 500 mg *bid* n = 1175 |
|---|---|---|---|---|
| APTC Events | 1 (<0.1) [ 0.5] | 2 (0.2) [ 0.4 ] | 3 (0.2) [ 0.5] | 2 (0.2) [ 0.6] |

**MedDRA Preferred Terms: Myocardial infarction (MI), Acute myocardial infarction (AMI), Cerebrovascular accident, all Cardiovascular deaths (as defined by the AntiPlatelet Trialists' Collaboration, 1994)**

For the calculation of the number of events per 100 patient years, all episodes of an adverse event are counted (ie, all events during treatment and follow-up, including unique episode repeats). It is calculated within each treatment group as: [(number of events) / ((sum of durations of study drug exposure for all patients)/365.25)]*100.

CE-36

## Summary of GI Adverse Events
### Placebo-Controlled OA Studies up to 13 Weeks

| Patients with ≥ 1, n (%) [Events per 100 patient yrs] | Placebo (n = 1116) | Naproxcinod 375 mg *bid* (n = 601) | Naproxcinod 750 mg *bid* (n = 1472) | Naproxen 500 mg *bid* (n = 1175) |
|---|---|---|---|---|
| GI AE | 200 (17.9) [158] | 109 (18.1) [156] | 377 (25.6) [288] | 315 (26.8) [302] |
| Discontinuations due to GI AE | 33 (3.0) [22] | 14 (2.3) [14] | 40 (2.7) [26] | 45 (3.8) [33] |
| GI SAE | 4 ( 0.4) [2] | 1 ( 0.2) [2] | 6 ( 0.4) [3] | 3 ( 0.3) [2] |

CE-37

## Perforations, Ulcers, Bleedings and Obstructions (PUBs)

### Placebo-Controlled OA Studies up to 13 Weeks

| n (%) [Events per 100 patient yrs] | Placebo n = 1116 | Naproxcinod 375 mg *bid* n = 601 | Naproxcinod 750 mg *bid* n = 1472 | Naproxen 500 mg *bid* n = 1175 |
|---|---|---|---|---|
| Any PUBs | 1 (< 0.1) [<1] | 7 (1.2) [7] | 11 (0.7) [5] | 10 (0.9) [6] |

### All Studies

| n (%) [Events per 100 patient yrs] | Placebo n = 1412 | 375 mg *bid* n = 1007 | 750 mg *bid* n = 2156 | Naproxen 500 mg *bid* n = 1633 |
|---|---|---|---|---|
| Any PUBs | 1 (< 0.1) [<1] | 10 (1.0) [2] | 20 (0.9) [3] | 14 (0.9) [5] |

CE-38

## Bleeding-Related AEs
### All Studies

| n (%) [Events per 100 patient yrs] | Placebo (n = 1412) | Naproxcinod 375 mg *bid* (n = 1007) | Naproxcinod 750 mg *bid* (n = 2156) | Naproxen 500 mg *bid* (n = 1633) |
|---|---|---|---|---|
| All Bleeding-Related AEs | 12 (0.8) [7] | 35 (3.5) [8] | 51 (2.4) [9] | 38 (2.3) [12] |

All clinical terms explicitly referring to hemorrhage, hematoma, bleeding, ecchymosis, purpura, petechiae, treatment for hematoma/bleeding/hemorrhage, and rupture of blood vessels were included.
All laboratory “bleeding” terms; i.e., blood urine (stating explicitly that blood was present in urine), bleeding time prolonged, were included.

CE-39

## Hepatic Safety
### All Studies

- Hy's Law (for potential drug-induced liver injury)
  - 1 placebo-treated patient
- No SAE due to hepatic enzyme elevation
- ALT/AST elevations
  - Occurred in < 1% of patients
  - Were transient

Hy's law for potential drug-induced liver injury: ALT/AST >3X ULN, ALP < 2X ULN, total bilirubin ≥ 2X ULN

CE-40

## Overall Safety Summary

- No unexpected safety issues with naproxcinod
- The incidence of AEs leading to discontinuation were similar across all treatment groups
- The incidence of SAEs was low and similar between treatment groups

CE-41

## Conclusions: Naproxcinod Efficacy and Safety

- Naproxcinod is effective at the proposed doses (375 mg and 750 mg *bid)*
- Naproxcinod has a favorable safety and tolerability profile
- Naproxcinod 750 mg bid has comparable efficacy to the equimolar dose of naproxen (500 mg *bid*)

# Blood Pressure Effects of Naproxcinod

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**Professor and Chief,**
**Hypertension and Clinical Pharmacology**
**Calhoun Cardiology Center**
**University of Connecticut School of Medicine**
**Farmington, CT**



## Presentation Overview

- Effect of NSAIDs on blood pressure
- Non-clinical effects of naproxcinod on blood pressure
- Ambulatory BP studies
- Blood pressure safety evaluation
  - Integrated BP analyses from Phase 3 pivotal studies
  - Drug interactions with sildenafil and nitrates
  - Potential hypotension-related adverse events
  - Evaluation for orthostatic hypotension

CB-3

## Comorbidities in Arthritis Patients

| Comorbidity | OA | RA |
|---|---|---|
| Hypertension | 42% | 35% |
| GI complications | 23% | 23% |
| Coronary artery disease | 15% | 14% |
| Diabetes | 14% | 13% |
| Edema | 8% | 9% |
| CHF | 5% | 6% |
| AMI | 3% | 3% |

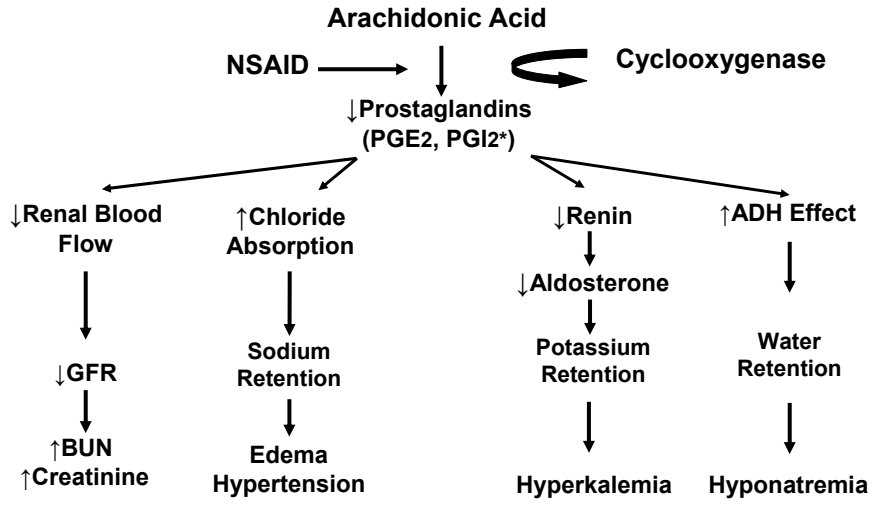
**NSAID Users**

In a large national plan*, more than 50% of patients on NSAID therapy also had a comorbid hypertensive diagnosis

*Ingenix Pharmaceutical Services. Phase III assessment of patient characteristics for users of NSAID/COX-2 medications using United Healthcare claims data. December 29, 2000.

CB-4

## Renal and BP Effects Associated with NSAID-Induced Cyclooxygenase Inhibition




*Prostacyclin

CB-5

## Pharmacology of Naproxcinod: Cardiorenal Models

- BP reduction versus naproxen in animal models
  - Spontaneously hypertensive rats (SHR)
  - Renovascular hypertension (rat)
  - L-NAME hypertension (rat)
- Protects isolated heart from ischemia-reperfusion (rabbit)
- Different behavior on kidney oxygenation vs naproxen

L-NAME = L-$N_g$ arginine methyl ester.

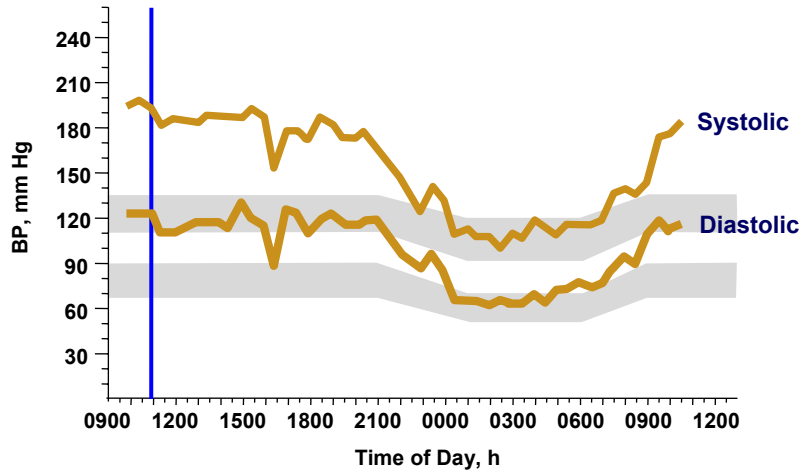
CB-6

## Clinic and Ambulatory Blood Pressure Differences

| | Pros | Cons |
|---|---|---|
| Clinic | • Ease of measurement<br>• Associated with clinical trial outcome data | • Lack of reproducibility<br>• White-coat effect<br>• Masked hypertension<br>• Observer bias |
| ABPM | • Larger number of measurements obtained<br>• Sleep measurements obtained<br>• Provides superior ability to evaluate drug treatment effect<br>• Minimal to no placebo effect (removal of observer bias) | • More expensive blood pressure method<br>• Inconvenient for patient to do repeatedly |

CB-7

## Blood Pressure Profile Over 24-hour Period




CB-8

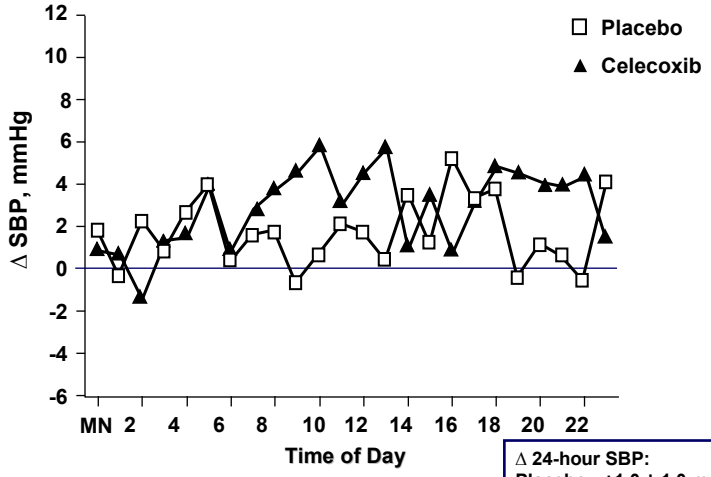
## Long-term Reproducibility of Clinic and Ambulatory Blood Pressure Components in Older People

| BP parameter | SD of differences | Sample size required for a 5 mmHg effect |
|---|---|---|
| Clinic SBP | 17.8 | 199 |
| 24-hour SBP | 11.7 | 86 |
| Awake SBP | 12.7 | 101 |
| Sleep SBP | 13.7 | 118 |
| Trough SBP | 19.4 | 236 |

White WB et al. *J Hum Hypertens*. 2010 Mar 4. [Epub ahead of print]

CB-9

## Effect of Celecoxib 200 mg *bid* vs Placebo on Ambulatory SBP in ACE inhibitor Treated Hypertensive Patients

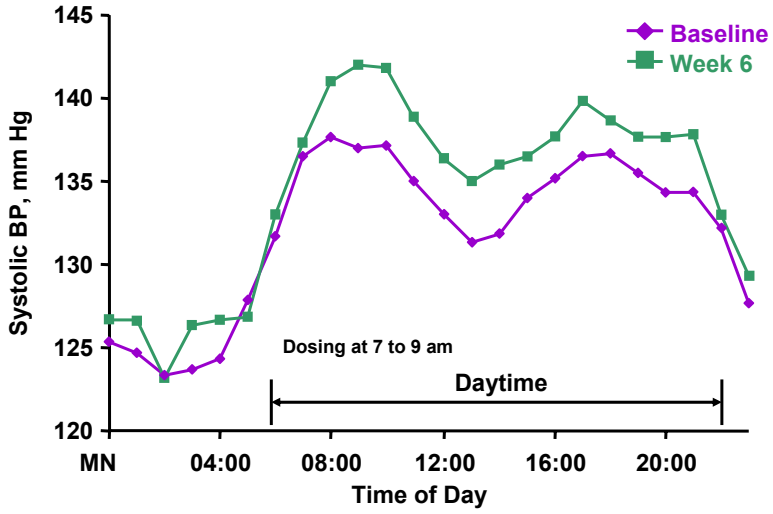



Δ 24-hour SBP:
Placebo: +1.0 ± 1.0 mmHg
Celecoxib: + 2.6 ± 0.9 mmHg

White WB et al. *Hypertension.* 2002;39:929-934.

CB-10

## CRESCENT: Effects of Rofecoxib (25 mg ) on Ambulatory Systolic BP




Sowers J and White WB et al *Arch Intern Med* 2005; 165: 161-168.

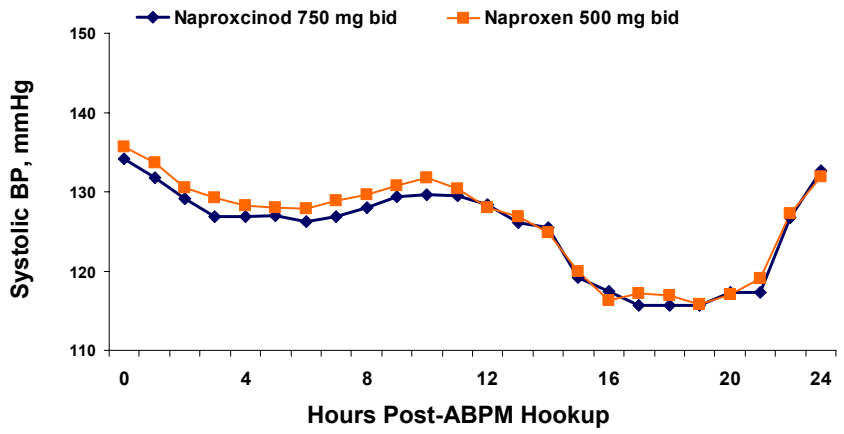
CB-11

## Ambulatory BP Monitoring (ABPM) Studies

- Study 104: 14 day cross-over study of treated hypertensives without OA – naproxcinod and naproxen
- Study 111: Forced titration, treated hypertensive patients with OA - naproxcinod and naproxen
- Study 112: Parallel arm, treated hypertensive patients with OA – naproxcinod, naproxen, and ibuprofen

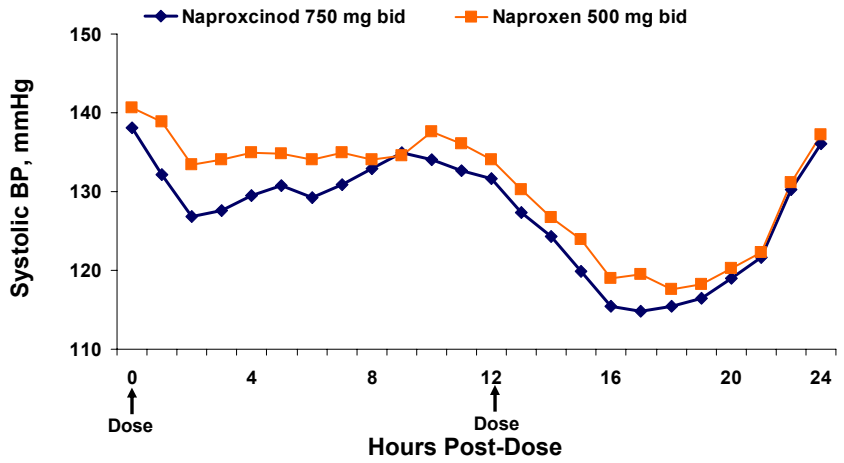
CB-12

## Study 104
## Hypertensives Without OA Pilot Cross-over Study
### Baseline 24-hour Systolic BP Profiles



CB-13

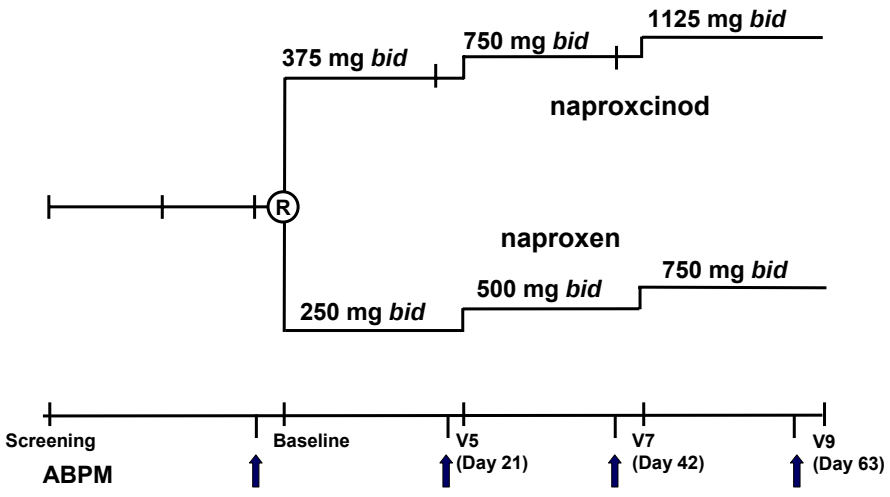
## Study 104
## Hypertensives Without OA Pilot Cross-over Study
### 24-hour Systolic BP Profiles after 14 Days of Treatment




Mean changes from baseline in 24-hour SBP between naproxcinod and naproxen -1.6 ± 1.1 mmHg, p = 0.122

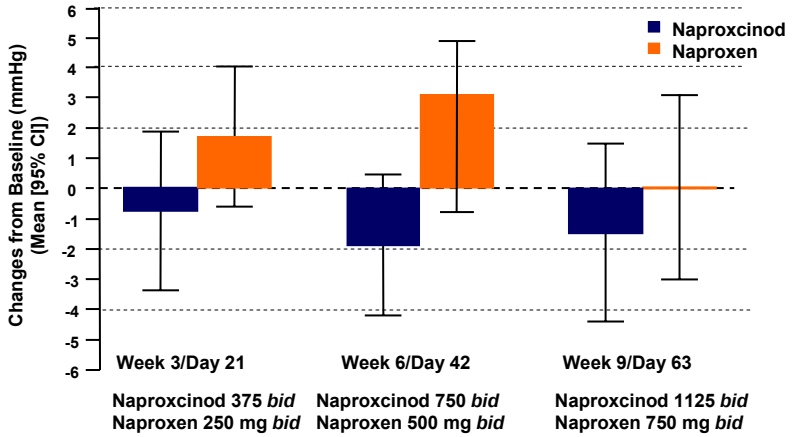
CB-14

## Study Design—111 ABPM Study
### Population: Treated Hypertensives with OA
### Primary Endpoint: Changes from Baseline in 24-hour SBP



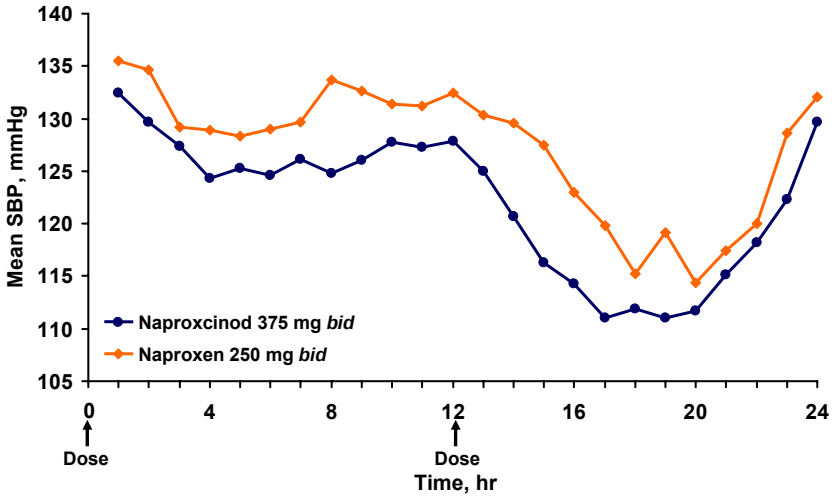
CB-15

## Changes in 24-hour Ambulatory Systolic Blood Pressure
### Study 111




CB-16

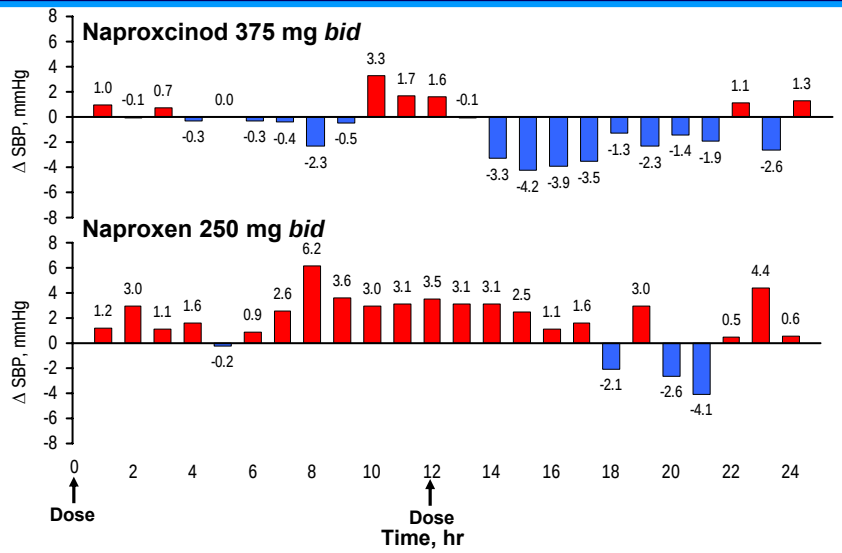
## Systolic Blood Pressure After 3 Weeks of Active Treatment (Low Dose)
### Study 111— OA Patients with Treated HTN




Mean changes from baseline in 24-hour SBP between naproxcinod and naproxen
-2.5 ± 1.8 mmHg, p = 0.166

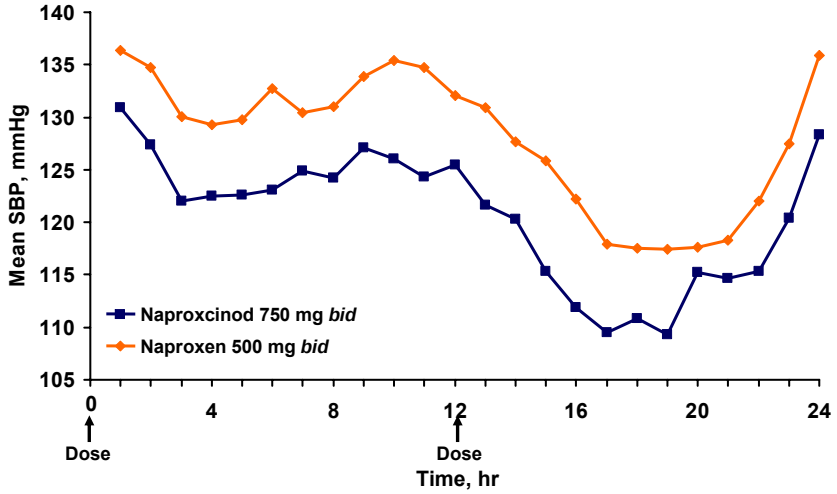
CB-17

## Changes from Baseline in Hourly Systolic BP
## Study 111— 3 weeks




CB-18

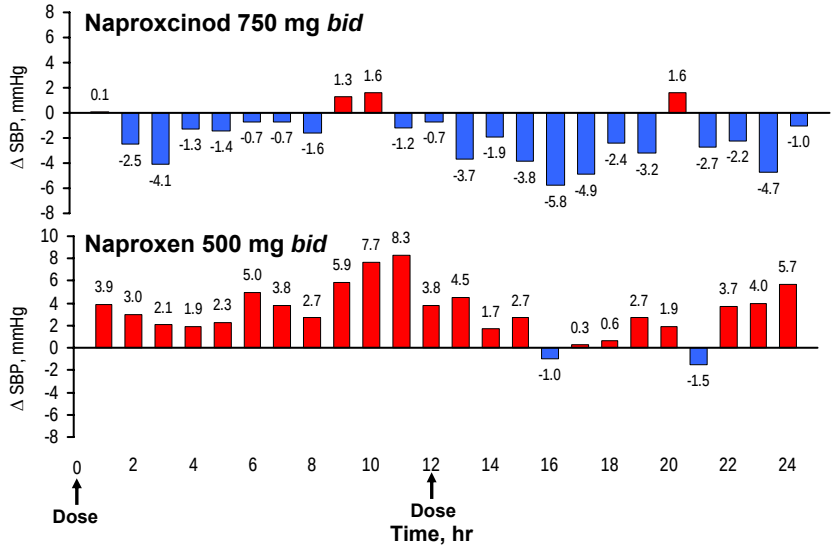
## Systolic Blood Pressure After 6 Weeks of Active Treatment (High Dose)
## Study 111 — OA Patients with Treated HTN




Mean changes from baseline in 24-hour SBP
between naproxcinod and naproxen -5.0 ± 1.8 mmHg, p = 0.008

CB-19

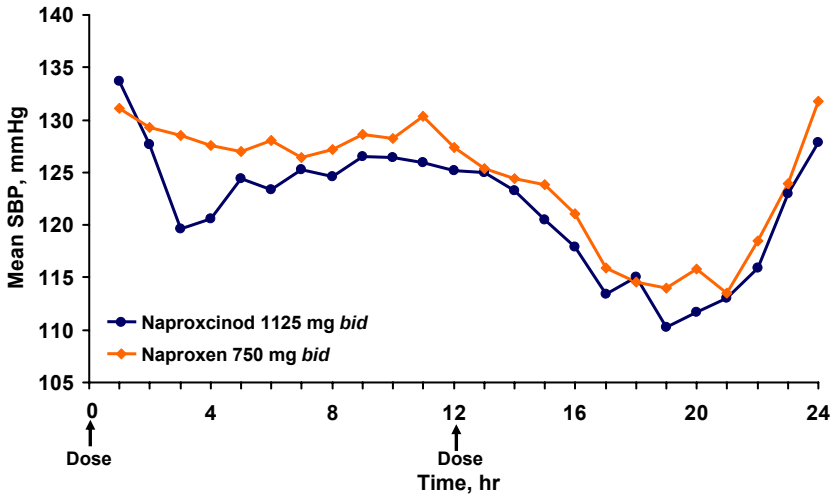
## Changes from Baseline in Hourly Systolic BP Study 111 – 6 weeks




CB-20

## Systolic Blood Pressure After 9 Weeks of Active Treatment (Supratherapeutic Dose)

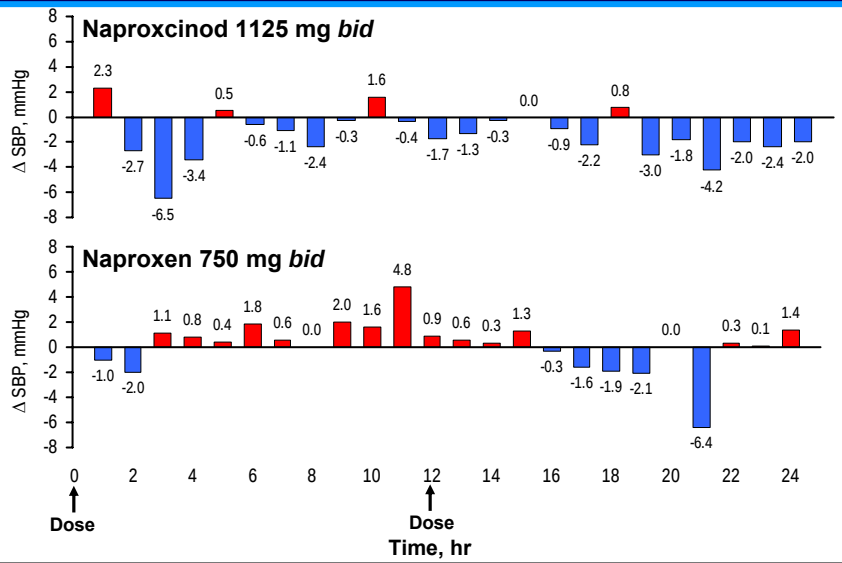
### Study 111 — OA Patients with Treated HTN




Mean changes from baseline in 24-hour SBP between naproxcinod and naproxen -1.5 ± 2.1 mmHg, p = 0.475

CB-21

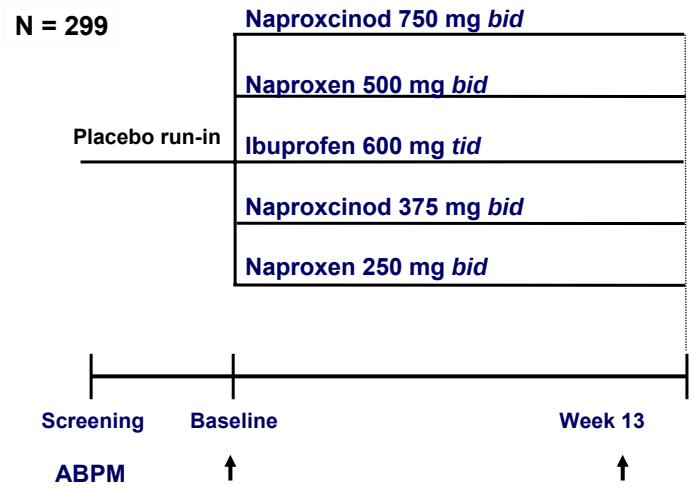
## Changes from Baseline in Hourly Systolic BP Study 111—9 weeks




CB-22

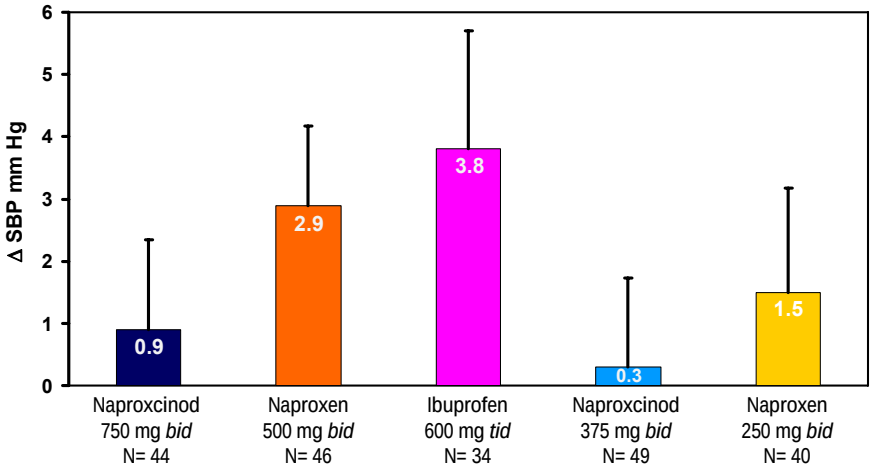
## Study Design—112 ABPM Study

**Population: Treated Hypertensives with OA**
**Primary Endpoint: Change in 24-hour SBP on naproxcinod 750 mg vs naproxen 500 mg**



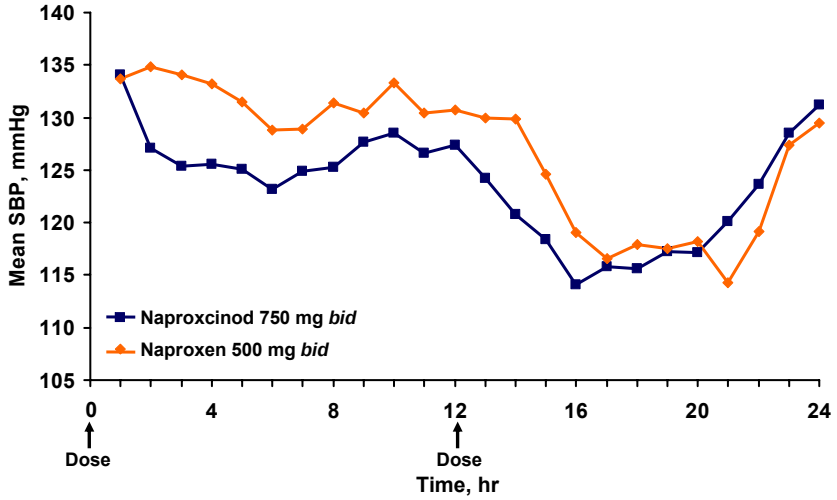
CB-23

## Mean Changes from Baseline in 24-hour Ambulatory Systolic Blood Pressure
### Study 112 — OA Patients with Treated HTN




CB-24

## Systolic BP for Naproxcinod 750 mg and Naproxen 500 mg at 13 Weeks
### Study 112 — OA Patients with Treated HTN

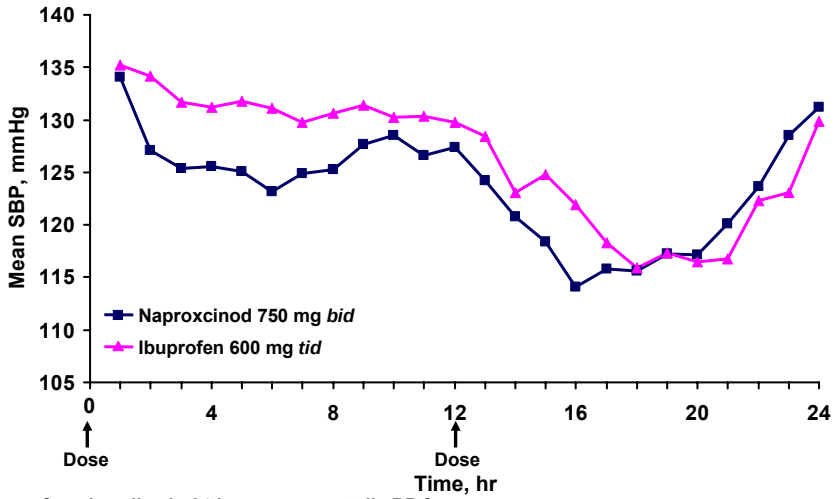



Changes from Baseline in 24-hour mean systolic BP for naproxcinod – naproxen -2.0 ± 2.2 mmHg , p = 0.375

CB-25

## Systolic BP for Naproxcinod 750 mg and Ibuprofen 600 mg at 13 Weeks

### Study 112 — OA Patients with Treated HTN




Changes from baseline in 24-hour mean systolic BP for naproxcinod – ibuprofen -2.8 ± 2.3 mmHg, p = 0.230

## Blood Pressure Safety Assessment

CB-27

## Integrated Clinic Blood Pressure Analyses
### Study 304

- Three large pivotal OA trials*
  - 301: 918 patients with knee OA
  - 302: 1011 patients with knee OA
  - 303: 810 patients with hip OA
- Blood pressure Data
  - Standardized Office BP Measurements
    - According to AHA guidelines 3 hours post-dosing
  - Pre-specified integrated safety analysis of 3 trials large enough to analyze sub-groups on antihypertensive drug therapies

All phase 3 trials were:
- Double-blind
- Placebo & naproxen-controlled
- 3 standard co-primary efficacy endpoints at 13 weeks

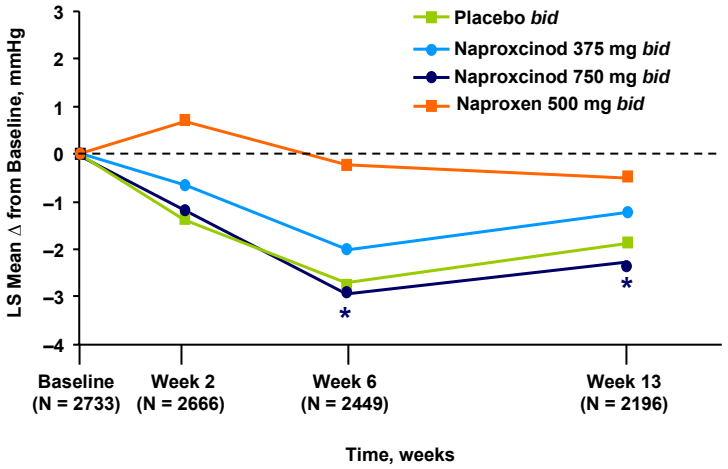
CB-28

## Baseline Characteristics
### Integrated BP Analysis 304—Phase 3 OA Studies

| N, (%) Total N = 2734 | Placebo (N = 811) | Naproxcinod 375 mg *bid* (N = 487) | Naproxcinod 750 mg *bid* (N = 799) | Naproxen 500 mg *bid* (N = 637) |
|---|---|---|---|---|
| Age, years (SD) | 62 (9.4) | 61 (9.5) | 62 (9.7) | 61 (9.7) |
| Hypertension | 417 (51.4) | 230 (47.2) | 389 (48.7) | 313 (49.1) |
| Diabetes | 105 (12.9) | 67 (13.8) | 114 (14.3) | 82 (12.9) |
| ≥ 1 risk factor for high cardiovascular risk | 562 (69.3) | 331 (68.0) | 507 (63.5) | 417 (65.5) |
| Antihypertensive therapy | 349 (43.7) | 207 (42.5) | 279 (43.8) | 365 (45.0) |
| Low-dose aspirin use (≤ 325 mg) | 162 (20.0) | 109 (22.4) | 181 (22.7) | 133 (20.9) |

CB-29

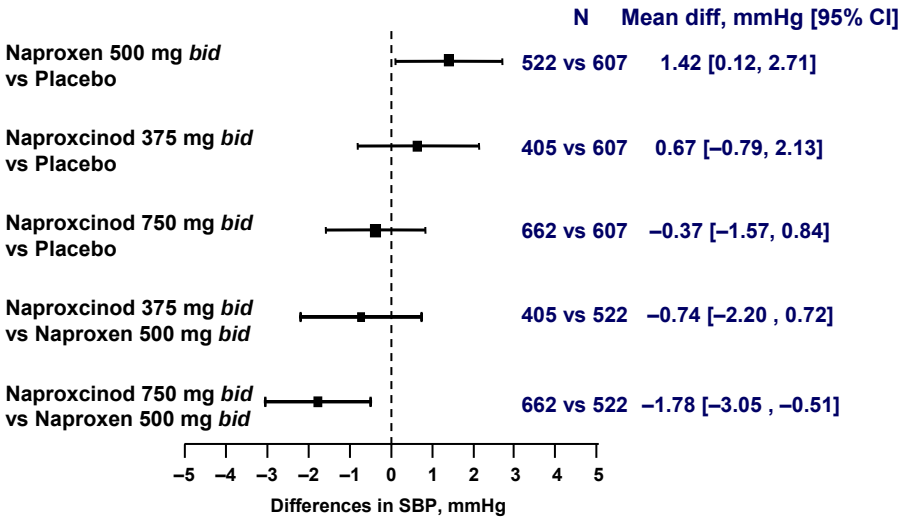
## Systolic BP Mean Changes Over 13 Weeks
### Integrated Safety Population




**P* < 0.01 versus Naproxen

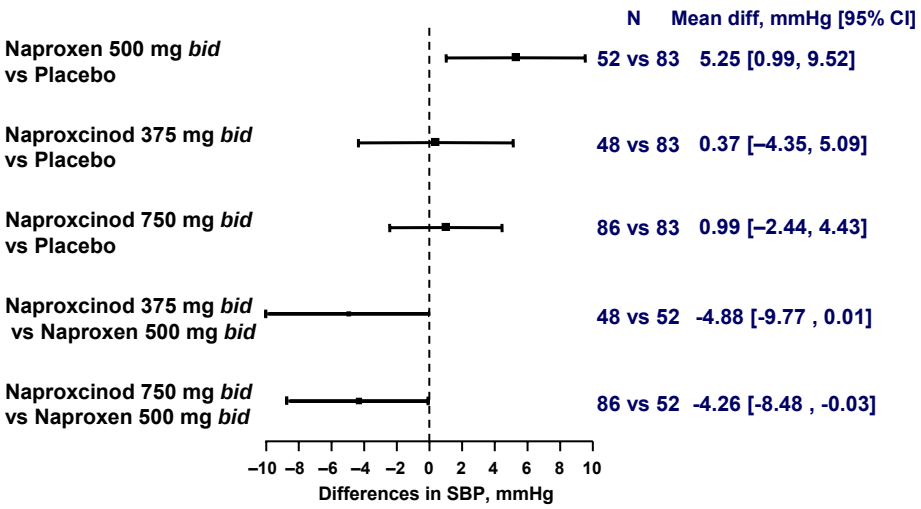
CB-30

## Change in SBP at 13 Weeks
### Integrated Safety Population (N = 2196)



CB-31

## Change in SBP at 13 Weeks
### RAS Inhibitor Monotherapy Subgroup (N = 332)




RAS = Renin-angiotensin system.

CB-32

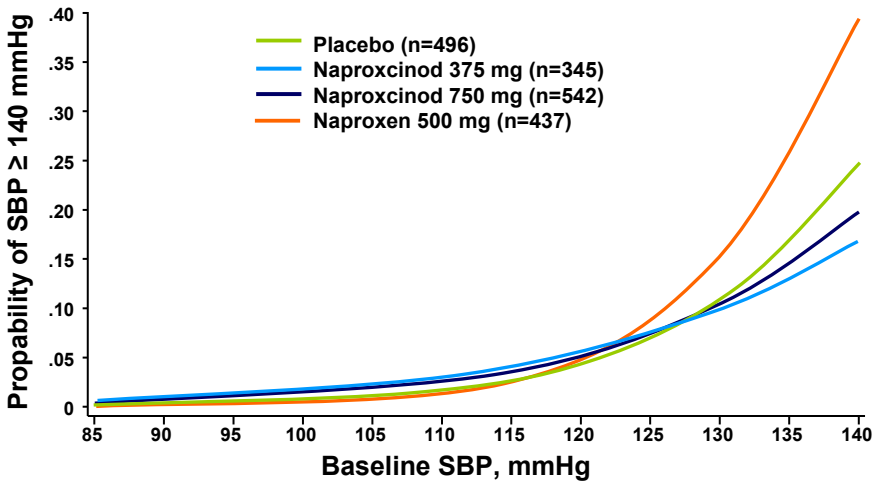
## Percentage of Patients with Increases from Baseline in Systolic Blood Pressure at Week 13

| Characteristic | Placebo | Naproxcinod 750 mg *bid* | Naproxcinod 375 mg *bid* | Naproxen 500 mg *bid* |
|---|---|---|---|---|
| Pooled Safety Population, N at wk 13 | 607 | 662 | 405 | 522 |
| ≥ 5 mmHg | 26.7 | 28.4* | 26.9* | 34.3** |
| ≥ 10 mmHg | 15.8 | 15.3* | 18.0 | 20.7† |
| ≥ 20 mmHg | 3.6 | 2.4 | 4.2 | 5.9 |

*$p < 0.02$ compared to naproxen 500 mg.
**$p < 0.05$ compared to placebo.
†$p = 0.055$ compared to placebo.

CB-33

## Probability of Systolic BP ≥ 140 mmHg in Patients with Baseline SBP < 140 mmHg at Week 13

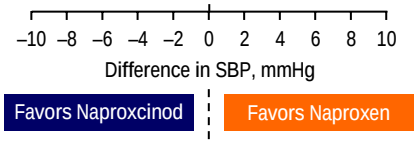



Results from logistic regression by treatment group, with baseline SBP as continuous fixed effect

CB-34

## Summary of Mean Changes from Baseline in Systolic Blood Pressure Across Trials
### Naproxcinod 750 mg *bid* vs Naproxen 500 mg *bid*

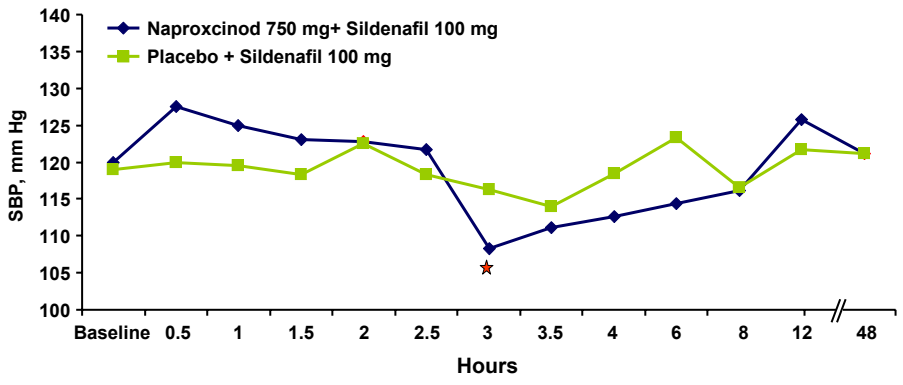
| Study | BP Measurement | n | Mean Changes in SBP (95% CI) |
|---|---|---|---|
| Integrated BP (304) | Office SBP (13 weeks) | 662 vs 522 | – 1.8 (–3.1, –0.5) |
| Study 104 | Mean 24-hr (2 weeks) | 103 vs 100 | – 1.6 (–3.8, 0.5) |
| Study 111 | Mean 24-hr (6 weeks) | 46 vs 45 | – 5.0 (–8.6, –1.4) |
| Study 112 | Mean 24-hr (13 weeks) | 44 vs 46 | – 2.0 (–6.4, 2.4) |



# Evaluation for Potential Hypotension

CB-36

## Drug Interaction Study—Sildenafil
### SBP from Baseline to Postdose Day 7



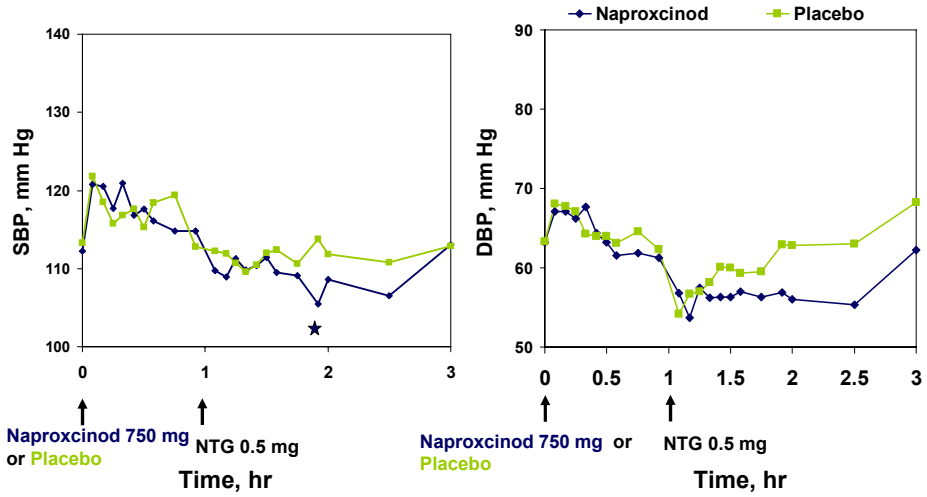

Four subjects experienced seven episodes of orthostatic hypotension during the study: 2 subjects in the naproxcinod 750 mg *bid* group and 2 subjects in the placebo *bid* group

★ *P* = 0.0046
LS Mean (SE) –8.6 (3.0)
90% CI: –13.8, –3.5

CB-37

# Drug Interaction Study—Nitroglycerin
## Systolic and Diastolic Profile

★ The LS means difference at 1h 55 min was: –8.33; *P*-value= 0.0004




CB-38

# Potential Hypotension—Related Adverse Events
## All Placebo-controlled Studies up to 13 Weeks

| | Patients, n (%) | | | |
|---|---|---|---|---|
| | | Naproxcinod | | Naproxen |
| | Placebo n = 1116 | 375 mg *bid* n = 601 | 750 mg *bid* n = 1472 | 500 mg *bid* n = 1175 |
| Dizziness | 24 (2.2) | 15 (2.5) | 47 (3.2) | 24 (2.0) |
| Hypotension | 1 (<0.1%) | 0 | 9 (0.6) | 2 (0.2) |
| Syncope | 2 (0.2) | 1 (0.2) | 4 (0.3) | 2 (0.2) |
| Orthostatic hypotension | 0 | 4 (0.7) | 4 (0.3) | 2 (0.2) |
| Blood pressure decreased | 0 | 0 | 4 (0.3) | 0 |
| Presyncope | 0 | 0 | 1 (<0.1) | 0 |
| Dizziness postural | 0 | 1 (0.2) | 0 | 0 |
| Vertigo | 6 (0.5) | 1 (0.2) | 8 (0.5) | 3 (0.3) |

CB-39

# Formal Orthostatic Hypotension Evaluation
## Study 302—3 Hour Post Dosing

**Definition: 1 minute Standing SBP < 90 mmHg when Supine SBP ≥ 90 mmHg OR Decrease From Supine to Standing Position ≥ 20 mmHg**

| Visit | Placebo *bid* N = 259 | Naproxcinod 375 mg *bid* N = 247 | Naproxcinod 750 mg *bid* N = 248 | Naproxen 500 mg *bid* N = 256 |
|---|---|---|---|---|
| Baseline Pre-Dose | 8 (3.1%) | 5 (2.0%) | 7 (2.8%) | 5 (2.0%) |
| Baseline 3 Hr Post-Dose | 6 (2.3%) | 2 (0.8%) | 6 (2.4%) | 1 (0.4%) |
| Week 2 Post-Dose | 7 (2.7%) | 5 (2.0%) | 5 (2.0%) | 2 (0.8%) |
| Week 13 Post-Dose | 2 (0.8%) | 3 (1.2%) | 5 (2.0%) | 2 (0.8%) |

One patient (0.4%) in the placebo group had a standing SBP < 90 mmHg AND Decrease from Supine ≥ 20 mmHg at the 1 min. time point.

CB-40

# Conclusions

- Naproxcinod has lower 24-hour mean systolic BPs than naproxen (-2.0 to -5.0 mmHg) in hypertensive patients
- Clinic BP measurements for naproxcinod are similar to placebo; this is not the case for naproxen
  - In patients on RAS inhibitors, naproxcinod maintains BP effects similar to placebo while the increase in BP by naproxen is greater
- Naproxcinod does not induce clinically important reductions in BP nor does it cause postural hypotension
- Reductions in SBP have been observed when naproxcinod is co-administered with sildenafil or nitroglycerin

# Importance of Systolic Blood Pressure Levels in Patients with Osteoarthritis

**Michael A. Weber, MD**

**Professor of Medicine (Cardiology)**
**State University of New York**
**Downstate College of Medicine**



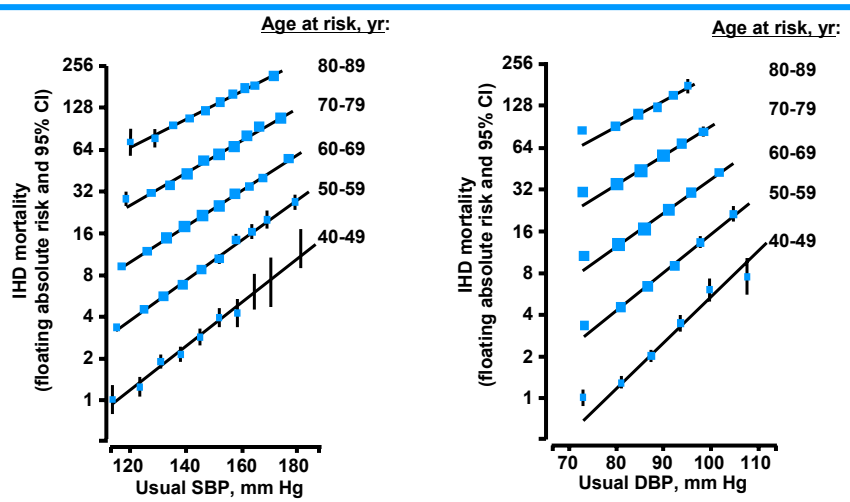
## Public Health Implications of Blood Pressure Differences

*Two principal sources of information:*

- Epidemiologic (natural history) data linking BP differences to cardiovascular outcomes
- Clinical trials data linking differences in achieved BP levels to cardiovascular outcomes

CM-3

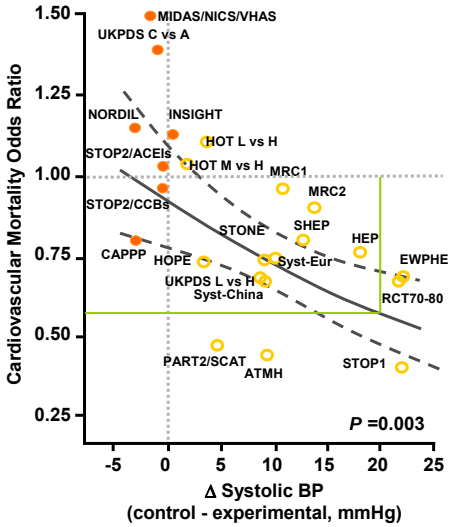
## Natural History: 61 Studies (1 Million Patients) 20 mmHg Increase in SBP Doubles Fatal CHD Risk (2 mmHg Causes 5-10% Increase in Risk)




Lewington A, for the Prospective Studies Collaboration. *Lancet,* 2002;360:1903–1913.

CM-4

## Systolic BP Reduction and CVD Mortality




Staessen JA et al. *Lancet.* 2001;358:1305 -1315.

CM-5

## Clinical Trials Meta-analysis
## Effects of Differences in Achieved SBP on Fatal Cardiovascular Events

**2 mmHg: 10% (- 4 to 24%)**

**5 mmHg: 17% ( 5 to 27%)**

Staessen JA et al, *Lancet* 2001; 358:1305-1315

CM-6

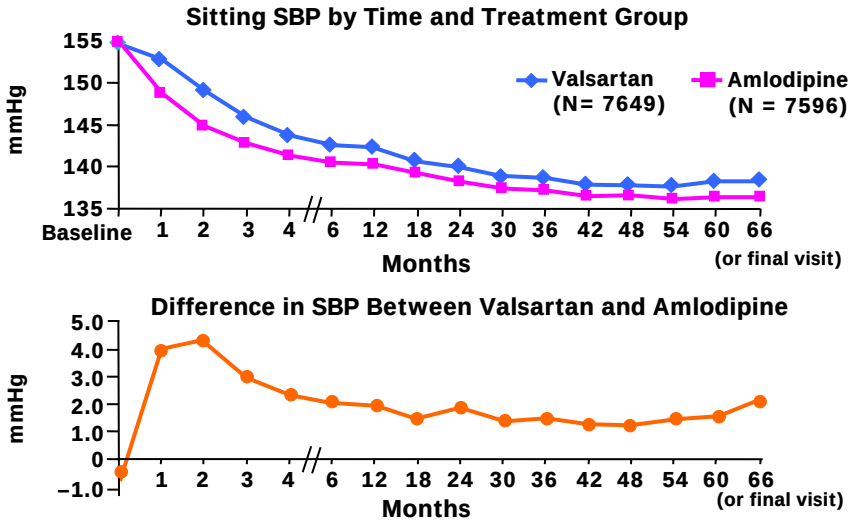
## Impact of Small Differences in SBP from ALLHAT

- **ALLHAT chlorthalidone vs doxazosin**
  **Δ SBP -3 mmHg**
  - **21% reduction in stroke (p = 0.001)**
  - **17% reduction in combined CV disease (p < 0.001)**
- **ALLHAT chlorthalidone vs lisinopril**
  **Δ SBP -2 mmHg**
  - **13% reduction in stroke (p = 0.02)**
  - **9% reduction in combined CV disease (p <0.001)**

ALLHAT Collaborative Research Group. *JAMA*. 2000;283:1967-1975.
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

CM-7

## VALUE: Systolic Blood Pressure in Study

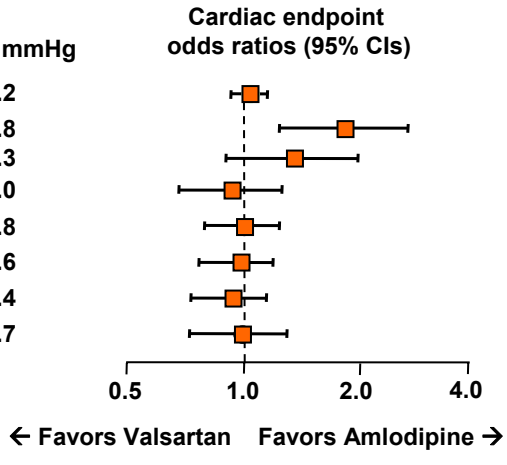



Julius S et al. *Lancet*. June 2004;363.

CM-8

## VALUE: Short Term SBP Reduction Can Affect Cardiac Outcomes

| Time Interval, mo | DSBP, mmHg |
|---|---|
| Overall study | 2.2 |
| 0 - 3 | 3.8 |
| 3 - 6 | 2.3 |
| 6 - 12 | 2.0 |
| 12 - 24 | 1.8 |
| 24 - 36 | 1.6 |
| 36 - 48 | 1.4 |
| Study end | 1.7 |




Julius S, et al. *Lancet*. 2004;363:2022-2031.

CM-9

## Naproxcinod Systolic BP Effects vs Naproxen

- All patients (Pooled data) 2.0 mmHg
- On RAS Monotherapy (Pooled data) 4.3 mmHg
- 24 Hour ABPM: 2 to 5 mmHg

***Impact***: Most hypertensive patients now receive an ACE inhibitor or ARB, often plus a thiazide, so benefit of naproxcinod (compared with naproxen) is > 4 mmHg in a large fraction of OA patients with hypertension

CM-10

## Blood Pressure Effects: Clinical Comparison of Naproxcinod with Naproxen

- Lower probability of meaningful BP elevations
- Lower probability of incident hypertension

*So, it is a reasonable assumption that use of naproxcinod (vs. naproxen) would reduce the need for extra medical visits to consider starting new BP therapy or to increase anti-hypertensive drug doses*

CM-11

# Final Comment

- Naproxcinod is not an anti-hypertensive agent. Its clinical BP effects are not different from placebo
- To the extent that increased BP might contribute to the unwanted cardiovascular effects of NSAIDs, potentially minimizing BP elevations during treatment of osteoarthritis might be of value

CC-1

# Management of OA: Benefit Risk of Naproxcinod

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**Head, Division of Rheumatology and Clinical Immunology**
**University of Maryland School of Medicine**
**Baltimore, MD**

CC-2

## Summary: Naproxcinod

- NO has the potential to address one of the important NSAID side effects
  - Vasodilatation resulting in a lack of increase in MAP
- Naproxcinod was developed to provide
  - Well documented analgesic/anti-inflammatory effects of naproxen
  - Favorable effects of NO on blood pressure
- Naproxcinod offers a significant benefit over naproxen and, by extrapolation, other NSAIDs, with respect to an effect on blood pressure

CC-3

## Naproxcinod for Treatment of OA

- **Significant efficacy on 3 co-primary endpoints in 2 similarly designed placebo-controlled RCTs for both doses in persons with knee OA**
- **Naproxcinod 750 mg *bid* had significant efficacy in a placebo-controlled RCT for patients with hip OA**

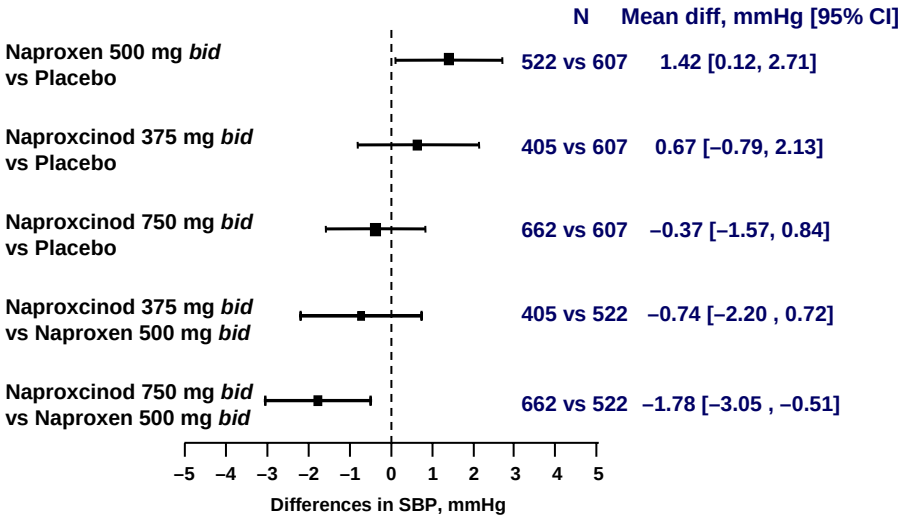
CC-4

## Naproxcinod for Treatment of OA

- **The totality of the evidence supports the conclusion that Naproxcinod 750 mg *bid* has comparable efficacy to naproxen 500 mg *bid***
  - Comparable efficacy for the co-primary endpoints of pain, function and patient global in Studies 301, 302 and 303
  - Similar proportion of patients achieved the secondary endpoint of OMERACT-OARSI Response
  - Similar NNT to achieve OMERACT-OARSI Response

CC-5

## Change in SBP at 13 Weeks
### Integrated Safety Population (N = 2196)




CC-6

## Naproxcinod for Treatment of OA

- Naproxcinod is effective for the relief of the signs and symptoms of OA
  - Proven efficacy c/w placebo at both doses
  - Similar effects on blood pressure c/w placebo
  - Better safety profile than naproxen
    - NO mitigates the effect on blood pressure