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

Aspirin and NSAIDs studied in PRECISION:
Aspirin-NSAID Interactions

Pfizer Inc
### Speakers

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<td><strong>Milton L. Pressler, MD</strong></td>
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<td></td>
<td>Vice President, Clinical Development</td>
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<td></td>
<td>Pfizer Inc, New York, NY</td>
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<tr>
<td>Introduction, Background on Celecoxib, Ibuprofen, Naproxen Interaction with Aspirin</td>
<td><strong>Jack Cook, PhD</strong></td>
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<td>Vice President, Clinical Pharmacology</td>
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<td>Global Product Development</td>
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<td>Pfizer Inc, Groton, CT</td>
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<tr>
<td>Concluding Remarks</td>
<td><strong>Milton L. Pressler, MD</strong></td>
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<td></td>
<td>Vice President, Clinical Development</td>
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<tr>
<td></td>
<td>Pfizer Inc, New York, NY</td>
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</tbody>
</table>
FDA requested the Advisory Committee be made aware of data involving all NSAIDs that were studied in PRECISION and their potential interaction with aspirin.
Presentation Objectives

- Provide an overview of the interaction of the concomitant use of low dose aspirin (ASA) with the three NSAIDs included in the PRECISION trial
  - Emphasis on data related to Pfizer marketed products (CXB, OTC IBU)
  - Specific naproxen (NPX) data deferred to the manufacturer in attendance

- Demonstrate that each of the NSAIDs needs to be considered individually when evaluating how they interact with ASA

CXB=Celecoxib; IBU=Ibuprofen; OTC=Over The Counter
Introduction, Background on Celecoxib and Ibuprofen Interaction with Aspirin

Jack Cook, PhD
Vice President, Clinical Pharmacology
Global Product Development
Pfizer Inc
Aspirin Antiplatelet Effect

- ASA irreversibly inhibits platelet COX-1 activity
  - Acetylation of a serine residue in the active site for COX-1
  - Steric hindrance that prevents arachidonic acid from being metabolized
  - Reduction of the production of thromboxane A2 (TxA2), a potent platelet agonist
  - Leading to reduced platelet aggregation

Platelet COX-1 Enzyme

Red spot depicts catalytic site. Green spot depicts serine residue at position 529.

Hoak 1983; Parks 1981; Patrono 2011; Fitzgerald & FitzGerald 2013
Figure adapted from Catella-Lawson et al. N Engl J Med 2001 Dec 20;345(25):1809-17.
COX=Cyclooxygenase
NSAID Interference with Aspirin Pharmacodynamic Considerations

- Concomitant administration of NSAIDs
  - NSAIDs and ASA occupy nearby sites on COX-1 enzyme
  - Potential to interfere with ASA's ability to gain access to its COX-1 binding site by steric interference
  - Concomitant administration of NSAIDs may reduce ASA’s ability to inhibit platelet aggregation

Platelet COX-1 Enzyme

Figure adapted from Catella-Lawson et al. N Engl J Med 2001 Dec 20;345(25):1809-17.
PK and PD Considerations NSAID Interactions with Aspirin

**Half-Life**
- **Aspirin**: 15-20 minutes
- **Ibuprofen**: 1.8-2 hours
- **Celecoxib**: 11 hours

**COX-1 Binding**
- **ASA irreversible binding**
  - Sustained antiplatelet effect for the lifespan of the platelet
- **IBU reversible binding**
  - Relatively transient effect compared to long-term suppression of platelet activity as ASA
- **CXB COX-2 selective**

PD=Pharmacodynamic; PK=Pharmacokinetic
Ex Vivo Platelet Function Tests

- COX-1
  - inhibits
  - ASA
  - ASA + NSAID
  - Thromboxane A2 (TxA2)
    - metabolism
    - Thromboxane B2 (TxB2)
  - Collagen
  - Arachidonic Acid
  - ADP
  - Platelet Aggregation

ADP=Adenosine Diphosphate
Celecoxib
Consistent Findings Across Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No Interference with Normal Mechanisms of Platelet Aggregation and Hemostasis</th>
<th>Absence of Impairment of ASA Anti-Platelet Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leese 2000¹</td>
<td>✓</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>Wilner 2002²</td>
<td>Not Assessed</td>
<td>✓</td>
</tr>
<tr>
<td>Renda 2006³</td>
<td>Not Assessed</td>
<td>✓</td>
</tr>
<tr>
<td>Gladding 2008⁴</td>
<td>Not Assessed</td>
<td>✓</td>
</tr>
<tr>
<td>Lee 2010⁵</td>
<td>Not Assessed</td>
<td>✓</td>
</tr>
<tr>
<td>Li 2014⁶</td>
<td>Not Assessed</td>
<td>✓</td>
</tr>
<tr>
<td>Ruzov 2016⁷</td>
<td>Not Assessed</td>
<td>✓</td>
</tr>
</tbody>
</table>

Leese 2000: Assessment of Effects of Supratherapeutic Doses of Celecoxib on Platelet Function

- Evaluation of the effects of CXB and NPX on platelet function without co-administration of ASA

**Drug intake**  
Placebo, Celecoxib or Naproxen

**Healthy Adults**  
N=24

**Randomization**

- Placebo
- Celecoxib 600 mg BID
- Naproxen 500 mg BID

**Blood samples for platelet aggregation, bleeding time and TxB2 levels**

- Day 1  
  - Single morning dose
- Day 3  
  - Two doses (12 hours apart)
- Day 10  
  - Single morning dose

**Day 1**
- 30 minutes before dosing
- 8 hours after dosing

**Day 10**
- 30 minutes before dosing
- 4, 6, 8 hours after dosing

BID=twice daily; mg=milligram
Leese 2000: Celecoxib Does Not Interfere with Platelet Aggregation and TxB2 Formation

- CXB did not interfere with normal mechanisms of platelet aggregation and TxB2 formation

### Platelet Aggregation

<table>
<thead>
<tr>
<th></th>
<th>Day 1: 30 minutes predose</th>
<th>Day 1: 8 hours postdose</th>
<th>Day 10: 8 hours postdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib 600 mg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen 500 mg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Change from Baseline in Serum TxB2 Concentrations

- **Placebo, n=8**
- **Celecoxib 600 mg BID, n=8**
- **Naproxen 500 mg BID, n=8**

* *p<0.05

Adapted from Leese 2000

SE=Standard Error

Author: Jack Cook
Li 2014: Assessment of Drug-Drug Interactions with Aspirin Following Exposure of Single Therapeutic Dose of NSAIDs

- NSAID-ASA interaction was assessed in an open-label two period trial
- Aspirin responsiveness was tested in the absence (period 1) and presence of IBU, NPX, or CXB (period 2)

**Period 1**
ASA response

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug Intake</th>
<th>Blood Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hr</td>
<td>No NSAIDs, to assess subjects ASA-responsiveness</td>
<td></td>
</tr>
<tr>
<td>2 hr</td>
<td>ASA 325 mg; N=21</td>
<td></td>
</tr>
<tr>
<td>26 hr</td>
<td>2 hr before ASA, 24 hr after ASA</td>
<td></td>
</tr>
</tbody>
</table>

**Period 2**
NSAID/ASA interaction

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug Intake</th>
<th>Blood Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hr</td>
<td>Washout (&gt;2 weeks)</td>
<td></td>
</tr>
<tr>
<td>2 hr</td>
<td>IBU 600 mg; N=7, NPX 500 mg; N=7, CXB 200 mg; N=7</td>
<td></td>
</tr>
<tr>
<td>26 hr</td>
<td>Before NSAIDs, 24 hr after ASA</td>
<td></td>
</tr>
</tbody>
</table>

hr=hour
Li 2014: Celecoxib Does Not Affect the Activity of Aspirin

Inhibition of Aggregation

- 24 hours after the ASA dose, platelets were fully inhibited in the presence of CXB and NPX

Inhibition of Serum TxB2

- 24 hours after the ASA dose
  - Presence of CXB did not affect the activity of ASA
  - IBU blunted inhibition of thromboxane formation by ASA markedly

Ratio = 1 is no inhibition of aggregation or TxB2
Celecoxib

Conclusion

- Overall, the body of evidence supports
  - The absence of relevant direct effect of CXB on platelet function
  - The absence of impairment of the pharmacodynamic response to ASA
## Ibuprofen

### Consistent Findings Across Published Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>IBU’s Ability to Impair ASA’s Antiplatelet Effect</th>
<th>Time-Dependent Interaction of ASA with IBU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catella-Lawson 2001¹</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cryer 2005²</td>
<td>Not Applicable</td>
<td>✓</td>
</tr>
<tr>
<td>Renda 2006³</td>
<td>✓</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>Gladding 2008⁴</td>
<td>✓</td>
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</tr>
<tr>
<td>Gengo 2008⁵</td>
<td>✓</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>Hong 2008⁶</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Schuijt 2009⁷</td>
<td>✓</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>Awa 2012⁸</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Yokoyama 2013⁹</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Saxena 2013¹⁰</td>
<td>✓</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>Meek 2013¹¹</td>
<td>✓</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>Li 2014¹²</td>
<td>✓</td>
<td>Not Assessed</td>
</tr>
</tbody>
</table>

Effect of Timing of Ibuprofen Administration and ASA

- Catella-Lawson (2001) showed that administration of a single dose of IBU 400 mg 2 hours after aspirin intake preserves the irreversible inhibition of platelet COX-1 induced by ASA in healthy individuals.

- In contrast, inhibition of serum thromboxane formation and ASA-induced platelet aggregation was inhibited when a single daily dose of IBU was given 2 hours before ASA.

- Administration of 400 mg IBU every morning for 6 days TID 2, 7, and 12 hours after a daily dose of enteric-coated ASA was also found to inhibit the effect of ASA on platelets.

- These and other findings prompted further investigations.

TID=three times daily
Ibuprofen: Pfizer (Wyeth) Studies
Separation of Dosing to Minimize Aspirin Interactions

Studies examining the effects of IBU 400 mg on platelet aggregation

Study AA-02-21
• How soon could one take IBU after ASA?

Study AA-02-22
• How much time is needed to separate IBU and ASA when IBU is taken before ASA?

Study AA-04-24
(Cryer 2005)
• Can one take ASA QD and IBU TID with a regimen that would minimize the interaction?

- Provide data regarding the separation of dosing to minimize IBU interactions with ASA
- Data were taken into account by FDA in the drug information for HCPs. The OTC label instructs consumers to talk to their doctor or pharmacist if they are taking ASA for heart attack or stroke

HCP=Health Care Professional; QD=once daily
Ibuprofen
Pfizer (Wyeth) Study AA-02-21: Ibuprofen Dosed After ASA

- IBU can be administered as soon as 30 minutes after taking an immediate-release ASA 81 mg tablet

% Inhibition of TxB2 (♦) or Platelet Aggregation (□) vs. IBU Dose Time Relative to ASA Dosing

% inhibition=100 *[level at baseline-post baseline level)/level at baseline]
Ibuprofen Pfizer (Wyeth) Study AA-02-22: Ibuprofen Dosed Before ASA

- IBU can be administered 8 hours before taking an immediate release ASA 81 mg

% Inhibition of Outcome Parameters 24 Hours After Day 6 ASA Dosing

% inhibition = 100 * [(level at baseline - post baseline level) / level at baseline]

Author: Jack Cook
Source: Clinical/Statistical Report AA-02-22, Table S.1.
Ibuprofen
Pfizer (Wyeth) Study AA-04-24 (Cryer 2005)

- Prospective, multiple-dose, single-center, double-blind, randomized, parallel, placebo-controlled 18-day study

Healthy Adults
N=35

ASA 81 mg QD
8 days

ASA 81 mg QD
1 hour
+Placebo
7 hours
+Placebo
13 hours
+Placebo
10-Day Treatment

ASA 81 mg QD
1 hour
+IBU 400 mg
7 hours
+IBU 400 mg
13 hours
+IBU 400 mg
10-Day Treatment

Blood samples for TxB2 levels
Taken 24 hours following after previous days ASA dose

Day 1
Day 9
Day 10
Day 12
Day 16
Day 19
**Ibuprofen Pfizer (Wyeth) Study AA-04-24 (Cryer 2005)**

- IBU did not interfere with an immediate release ASA 81 mg tablet

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>TxB2 Inhibition(^a) at Days 0, 1, 3, 7, and 10 of Study Period(^b) % Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>IBU 400 mg TID: Inhibition</td>
<td>98.85 (0.64)</td>
</tr>
<tr>
<td>Placebo TID: Inhibition</td>
<td>98.72 (1.06)</td>
</tr>
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</table>

\(^a\) TxB2 measured at 24 hrs after previous dose of ASA
\(^b\) All subjects first completed an 8-day aspirin run-in period (81 mg QD) and continued taking aspirin throughout the study period
† p=0.003 vs. placebo
‡ p=0.023 vs. placebo
SD=Standard Deviation
Ibuprofen

Conclusion

- Presence of IBU within the COX-1 enzyme competitively blocks the access of ASA, reducing the antiplatelet activity of ASA.

- Inhibition of ASA antiplatelet effect by IBU can be avoided by the timing and sequence of administration of the drugs:
  - Can be minimized by taking IBU at least 8 hours before or 30 minutes after immediate release ASA.
Concluding Remarks

Milton L. Pressler, MD
Vice President, Clinical Development
Pfizer Inc
Summary and Conclusions

- Multiple studies confirm no effects of celecoxib on platelet function. There is no evidence of interaction of celecoxib with aspirin in humans.

- Existing data demonstrate a pharmacodynamic interaction *ex vivo* between 400 mg ibuprofen and low dose aspirin on platelet function. Timing and sequence of ibuprofen dosing can mitigate interaction with aspirin effects. However, there are limitations with applying this dosing paradigm to chronic use of prescription ibuprofen, and enteric coated forms of aspirin.

- The clinical relevance of these interactions with platelet biomarkers has not been established. Our presentation on PRECISION later today will provide specific information regarding the relevance of these laboratory observations.
Joint Meeting of the FDA
Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

The PRECISION Study and Implications for Cardiovascular Safety of Celecoxib, Ibuprofen, and Naproxen

April 24-25, 2018
FDA White Oak Campus
Silver Spring, MD
# Speakers

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<td><strong>Introduction and Perspective on PRECISION</strong></td>
<td>Milton L. Pressler, MD</td>
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<td>Vice President, Clinical Development</td>
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<td></td>
<td>Pfizer Inc, New York, NY</td>
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<tr>
<td><strong>The PRECISION Trial</strong></td>
<td>Steven E. Nissen, MD</td>
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<tr>
<td>Prospective Randomized Evaluation of Celecoxib</td>
<td>Professor and Chair, Cardiovascular Medicine</td>
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<td>Integrated Safety versus Ibuprofen Or Naproxen</td>
<td>Cleveland Clinic, Cleveland, OH</td>
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<td><strong>Rheumatologist’s Perspective</strong></td>
<td>Stanley B. Cohen, MD</td>
</tr>
<tr>
<td>Implications for OA/RA Patient Management</td>
<td>Clinical Professor of Rheumatology</td>
</tr>
<tr>
<td></td>
<td>UT Southwestern Medical School, Dallas, TX</td>
</tr>
<tr>
<td><strong>Concluding Remarks</strong></td>
<td>Milton L. Pressler, MD</td>
</tr>
<tr>
<td>Contribution of PRECISION to Guide the Safe and Appropriate Use of Celecoxib</td>
<td>Vice President, Clinical Development</td>
</tr>
<tr>
<td>and its Comparators</td>
<td>Pfizer Inc, New York, NY</td>
</tr>
</tbody>
</table>

OA=Osteoarthritis; RA=Rheumatoid Arthritis
# Additional Academic/Pfizer Participants

<table>
<thead>
<tr>
<th>Area</th>
<th>Participant</th>
</tr>
</thead>
</table>
| Statistics    | Katherine E. Wolski, MPH  
Statistics  
Cleveland Clinic Research, Cleveland, OH |
| Safety        | Richard Xia, MD  
Senior Director, Safety Risk Lead  
Pfizer Inc, New York, NY |
| Statistics    | Wayne Wisemandle  
Head, Clinical Statistics  
Pfizer Inc, Lake Forest, IL |
| Regulatory    | Amanda Jones  
Global Regulatory Portfolio Lead: CNS/Pain  
Pfizer Inc, Walton Oaks, UK |
| Epidemiology  | Veronica Frajzyngier, PhD  
Director, Epidemiology  
Pfizer Inc, New York, NY |
| OTC           | David Kellstein, PhD  
Global Medical Affairs Lead, Pain  
Pfizer Inc, Madison, NJ |

CNS=Central Nervous System
Introduction and Perspective on PRECISION

Milton L. Pressler, MD
Vice President, Clinical Development
Pfizer Inc, New York, NY
Scope of Our Presentation

- Rationale for undertaking a CV outcomes study for symptomatic treatments of chronic osteoarthritis (OA) and rheumatoid arthritis (RA)
- Contextualize the circumstances leading up to PRECISION so the key design elements are understood
- PRECISION study results followed by a rheumatologist’s perspective
- Review the results from PRECISION, what has been learned, the impact on the understanding of CV safety of the drugs tested
  - Discuss clinical/regulatory implications of PRECISION for prescribers
Arthritis Treatment Landscape

- In a recent survey, 52.5 million adults in the US (22.7% of all adults) had doctor-diagnosed arthritis\(^1\)
  - Arthritic conditions → most common causes of disability among US adults\(^2\)

- Arthritic pain
  - Pain relief represents an important focus of treatment for arthritic patients
  - NSAIDs are an attractive alternative to opiates or acetaminophen in these patients. Millions of adults are regular users of NSAIDs\(^3\), even though they may cause GI bleeding and renal impairment

- No single NSAID is universally effective among patients\(^4\)

---

   GI=Gastrointestinal
A Brief History on Cardiovascular Risk with COX-2 Inhibitors

- Celecoxib approved December 1998; rofecoxib approved May 1999
  - Widespread adoption due to GI concerns with nonselective NSAIDs
- VIGOR\(^1\) trial (2000)
  - Increased CV risk with rofecoxib 50 mg vs. naproxen 1000 mg in RA patients
  - Increased CV risk confirmed with lower dose of rofecoxib 25 mg in the APPROVe\(^2\) trial – all rofecoxib doses withdrawn 2004
- Celecoxib evaluated in colonic polyposis and Alzheimer’s disease
  - APC\(^3\), PreSAP\(^4\) and ADAPT


ADAPT=Alzheimer’s Disease Anti-inflammatory Prevention Trial; APC=Adenoma Prevention with Celecoxib; APPROVe=Adenomatous Polyp Prevention on Vioxx; PreSAP=Prevention of Colorectal Sporadic Adenomatous Polyps; VIGOR=Vioxx Gastrointestinal Outcomes Research
Adjudicated Serious CV Thromboembolic Events
VIGOR (Vioxx Gastrointestinal Outcomes Research) Study (2000)

Hazard Ratio
(Rofecoxib vs. Naproxen)
Overall = 2.4

Rofecoxib 50 mg QD
N=4047

Naproxen 500 mg BID
N=4029

p<0.05

Adapted from www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_6_cardio.doc
APPROVe: Increased Risk of APTC Events with Long-Term Rofecoxib Use (25 mg/day)

Long-term, double-blind, placebo-controlled trial of 2586 patients

<table>
<thead>
<tr>
<th>Month</th>
<th>Patients at Risk</th>
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<tbody>
<tr>
<td>0</td>
<td>Rofecoxib 1287</td>
</tr>
<tr>
<td>6</td>
<td>1129</td>
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<tr>
<td>12</td>
<td>1057</td>
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<td>18</td>
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<td>36</td>
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<td>0</td>
<td>Placebo 1299</td>
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<td>6</td>
<td>1195</td>
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<td>12</td>
<td>1156</td>
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<td>30</td>
<td>1001</td>
</tr>
<tr>
<td>36</td>
<td>835</td>
</tr>
</tbody>
</table>

p=0.008

APPROVe: Increased Risk of APTC Events with Long-Term Rofecoxib Use (25 mg/day)


a. Thrombotic events include fatal/nonfatal MI, unstable angina, cardiac death, fatal/nonfatal ischemic stroke, transient ischemic attack, peripheral arterial or venous thrombosis, pulmonary embolism

Bars represent 95% CI

APTC=Anti-Platelet Trialists Collaboration
A Brief History on Cardiovascular Risk with COX-2 Inhibitors

■ Celecoxib approved December 1998; rofecoxib approved May 1999
  – Widespread adoption due to GI concerns with nonselective NSAIDs

■ VIGOR\(^1\) trial (2000)
  – Increased CV risk with rofecoxib 50 mg vs. naproxen 1000 mg in RA patients
  – Increased CV risk confirmed with lower dose of rofecoxib 25 mg in the APPROVe\(^2\) trial – all rofecoxib doses withdrawn 2004

■ Celecoxib evaluated in colonic polyposis and Alzheimer’s disease
  – APC\(^3\), PreSAP\(^4\) and ADAPT

Serious CV Events (MACE) in Placebo-Controlled Trials of Celecoxib (APC, PreSAP and ADAPT Trials)

<table>
<thead>
<tr>
<th>Trial Comparison</th>
<th>Hazard Ratio (95% CI)</th>
<th>Comparator n</th>
<th>Placebo n</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC, N=2035</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib 200 mg BID vs. Placebo</td>
<td>2.8 (1.1, 7.2)</td>
<td>685</td>
<td>679</td>
</tr>
<tr>
<td>Celecoxib 400 mg BID vs. Placebo</td>
<td>3.4 (1.4, 8.5)</td>
<td>671</td>
<td>679</td>
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<tr>
<td>PreSAP Trial, N=1561</td>
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<tr>
<td>Celecoxib 400 mg QD vs. Placebo</td>
<td>1.2 (0.6, 2.4)</td>
<td>933</td>
<td>628</td>
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<tr>
<td>ADAPT Trial, N=2528</td>
<td></td>
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</tr>
<tr>
<td>Celecoxib 200 mg BID vs. Placebo</td>
<td>1.14 (0.61, 2.15)</td>
<td>726</td>
<td>1083</td>
</tr>
<tr>
<td>Naproxen 220 mg BID vs. Placebo</td>
<td>1.57 (0.87, 2.81)</td>
<td>719</td>
<td>1083</td>
</tr>
</tbody>
</table>

CV events are: composite of CV death, nonfatal myocardial infarction, or nonfatal stroke
MACE=Major Adverse Cardiovascular Event
Risk of APTC Events with Celecoxib is Dose-Dependent

**CNT: Meta-Analysis of Randomized Controlled Trials**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Rate Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib 800 mg daily vs. Placebo</td>
<td>2.96 (1.21, 7.25)</td>
</tr>
<tr>
<td>Celecoxib 400 mg daily vs. Placebo</td>
<td>1.29 (0.81, 2.04)</td>
</tr>
<tr>
<td>Celecoxib 200 mg daily vs. Placebo</td>
<td>0.95 (0.30, 3.00)</td>
</tr>
</tbody>
</table>

Boxed in green indicates approved doses in US
CNT=Coxib and traditional NSAID Trialists

p-value for trend = 0.05
Celecoxib Comparison

- Celecoxib\textsuperscript{a} vs. Ibuprofen\textsuperscript{b} \quad 1.01 (0.48, 2.13)
- Celecoxib\textsuperscript{a} vs. Naproxen\textsuperscript{b} \quad 0.93 (0.46, 1.88)

Individual NSAID Comparisons

- Celecoxib\textsuperscript{a} vs. Placebo \quad 1.36 (1.00, 1.84)
- Ibuprofen vs. Placebo \quad 1.44 (0.89, 2.33)
- Naproxen vs. Placebo \quad 0.93 (0.69, 1.27)

Risk estimates of naproxen/ibuprofen vs. placebo based on imputed data and indirect comparisons, leading to internally inconsistent results, as discussed at FDA meeting in 2014.

\textsuperscript{a} Any dose
\textsuperscript{b} Any dose included, but almost all doses were maximum prescription: ibuprofen 2400 mg daily; and naproxen 1000 mg daily (*rarely 440 mg*)

Key Takeaways from 2014 and 2015 Deliberations

- Initial impression that naproxen carried lower CV risk was related to fact its estimated effect was driven by indirect comparisons that were largely dominated by its comparison with high doses of the COX-2 inhibitor with the most consistent CV toxicity, i.e., rofecoxib 50 mg daily.

- In general, observational studies were consistent with greater CV events with rofecoxib than with celecoxib, but reported similar CV risks for celecoxib vs. nonselective NSAIDs.

- The Committee understood that PRECISION would provide a randomized controlled comparison and test these hypotheses in a head-to-head comparison of naproxen vs. other NSAIDs and celecoxib.
The PRECISION Trial

Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen

Steven E. Nissen MD MACC

Disclosure

Study Sponsor: Pfizer
Consulting: Many pharmaceutical companies
Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.
This presentation reflects the views and analyses of the academic leadership of the PRECISION Trial. My travel expenses are funded by the academic coordinating center – Cleveland Clinic Coordinating Center for Clinical Research (C5R).
Background

- The withdrawal of the selective COX-2 inhibitor, rofecoxib, raised questions about CV safety of these drugs, including the sole remaining COX-2 inhibitor in USA, celecoxib.

- A 2005 FDA Advisory Panel recommended conducting a cardiovascular outcome trial to clarify the relative safety of celecoxib compared with non-selective NSAIDs.

- The PRECISION trial was designed with the advice and consent of FDA to address cardiovascular, GI and renal safety of representative drugs within this class.
“…observational studies are best at finding relative risks that are more than 2. I think that I would pay some attention to relative risks of 1.5. I get very nervous about adjusted relative risks of 1.2.”

  Professor and Chair
  Department of Population Medicine
  Executive Director of the Harvard Pilgrim Health Care Institute
  Harvard Medical School
Objectives of the PRECISION Trial

• The primary objective was *noninferiority* assessment of the cardiovascular risk of celecoxib vs. two widely used non-selective NSAIDs, naproxen and ibuprofen, in osteoarthritis and rheumatoid arthritis patients.

• Other objectives included comparative safety of celecoxib vs. these two NSAIDs for all-cause mortality, gastrointestinal and renal adverse events.
All members of the Executive Committee agreed not to accept payments for related work on NSAIDs from any maker of these drugs.
Osteoarthritis or rheumatoid arthritis patients with established CV disease or increased risk who required NSAIDs for ≥ 6 months for symptom relief

- Celecoxib 100 mg b.i.d
- Ibuprofen 600 mg t.i.d
- Naproxen 375 mg b.i.d.
- Esomeprazole 20-40 mg

Option to increase dosage for unrelieved symptoms to naproxen 500 mg b.i.d., ibuprofen 800 mg t.i.d. or celecoxib 200 mg b.i.d (RA only)

580 primary events with a minimum follow up of 18 months
Adjudicated Endpoints

- For *noninferiority*, the primary analyses used the APTC endpoint: cardiovascular death, including hemorrhagic death; nonfatal myocardial infarction or nonfatal stroke.

- Other pre-specified safety endpoints:
  - *Expanded* major adverse cardiovascular events – APTC endpoint plus revasc., hosp. for unstable angina or TIA.
  - Composite of gastrointestinal events including iron deficiency anemia of GI origin (HCT drop ≥10%, Hgb ≥ 2 gms).
  - Major renal events (including hospitalization for renal failure).
  - Hospitalization for hypertension or CHF.
Study Milestones and Drug Exposure

• 31,857 patients screened and 24,081 randomized at 923 global centers beginning October 23, 2006

• Drug exposure (all now generic in USA):
  – Celecoxib mean daily dose, 104 mg b.i.d.
  – Ibuprofen mean daily dose, 681 mg t.i.d.
  – Naproxen mean daily dose, 426 mg b.i.d.

• Mean duration of drug treatment 20.3 months and mean follow up 34.1 months with 607 primary APTC events.
To establish noninferiority, the trial design required pairwise comparison of celecoxib with other drugs to meet four criteria:

- An upper 97.5% confidence interval (CI) ≤ 1.33 for intention-to-treat (ITT) analysis, truncated at 30 months.

- An upper 97.5% CI ≤ 1.40 for on-treatment analysis truncated at 42 months (defined as events occurring while the patient was taking study drug and 30 days thereafter)

- A HR ≤ 1.12 for both ITT and on-treatment populations
Rationale for ITT and On-Treatment Analyses

• Intention-to-treat (ITT) analysis is preferred in efficacy studies because it preserves the integrity of randomization and represents a conservative assessment of benefits.

• However, ITT analysis can dilute safety signals by including events occurring after patients stop the therapy.

• On-treatment analysis offers complementary insights in safety studies because it includes events occurring only while patients are actually taking study drugs.

• To ensure a rigorous safety assessment, we pre-specified achieving noninferiority using both approaches.
## Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib N=8072</th>
<th>Ibuprofen N=8040</th>
<th>Naproxen N=7969</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.0</td>
<td>63.2</td>
<td>63.3</td>
</tr>
<tr>
<td>Female Gender</td>
<td>64.1%</td>
<td>64.4%</td>
<td>63.9%</td>
</tr>
<tr>
<td>White</td>
<td>75.0%</td>
<td>74.5%</td>
<td>74.4%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>89.9%</td>
<td>89.7%</td>
<td>90.1%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>10.1%</td>
<td>10.4%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>23.1%</td>
<td>22.8%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Prior Aspirin Use (stratified)</td>
<td>45.8%</td>
<td>46.2%</td>
<td>45.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35.2%</td>
<td>35.9%</td>
<td>34.7%</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>20.9%</td>
<td>20.9%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125.3</td>
<td>125.4</td>
<td>125.0</td>
</tr>
</tbody>
</table>
Noninferiority Analysis for Primary APTC Endpoint

Intention-to-Treat

- Cele vs. Ibu, HR 0.85 (0.70-1.04), *P*<0.001*
- Cele vs. Nap, HR 0.93 (0.76-1.12), *P*<0.001*
- Ibu vs. Nap, HR 1.08 (0.90-1.31), *P*<0.02*

On-Treatment

- Cele vs. Ibu, HR 0.81 (0.65-1.02), *P*<0.001*
- Cele vs. Nap, HR 0.90 (0.71-1.15), *P*<0.001*
- Ibu vs. Nap, HR 1.12 (0.89-1.4), *P*<0.025*

*Noninferiority* *p* values
Analyses of Secondary Safety Endpoints

Secondary and tertiary safety analyses were pre-specified to provide a more complete assessment of the relative safety of comparators. Analyses are not adjusted for multiplicity.

We will present both ITT and on-treatment analyses with hazard ratios and 95% CIs.
Expanded Major Adverse Cardiovascular Events

### Intention-to-Treat

- Cele vs. Ibu, HR 0.87 (0.75-1.01), $P=0.06$
- Cele vs. Nap, HR 0.97 (0.83-1.12), $P=0.64$
- Ibu vs. Nap, HR 1.11 (0.96-1.29), $P=0.15$

*Ibuprofen 15% higher (borderline significant)*

### On-Treatment

- Cele vs. Ibu, HR 0.82 (0.69-0.97)
- Cele vs. Nap, HR 0.95 (0.80-1.13)
- Ibu vs. Nap, HR 1.17 (0.99-1.38)
Time-to-Death from Cardiovascular Causes

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.84 (0.61-1.16), *P*=0.30
- Cele vs. Nap, HR 0.78 (0.57-1.07), *P*=0.13
- Ibu vs. Nap, HR 0.93 (0.69-1.26), *P*=0.64

**On-Treatment**

- Cele vs. Ibu, HR 0.64 (0.42-0.99)
- Cele vs. Nap, HR 0.69 (0.45-1.07)
- Ibu vs. Nap, HR 1.08 (0.73-1.60)
Time to All-Cause Mortality

Intention-to-Treat

<table>
<thead>
<tr>
<th>Event (%)</th>
<th>Months Since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cele vs. Ibu, HR 0.92 (0.73-1.17), (P=0.49)</td>
<td></td>
</tr>
<tr>
<td>Cele vs. Nap, HR 0.80 (0.63-1.00), (P=0.052)</td>
<td></td>
</tr>
<tr>
<td>Ibu vs. Nap, HR 0.87 (0.70-1.09), (P=0.22)</td>
<td></td>
</tr>
</tbody>
</table>

Naproxen 25% higher (borderline significant)

On-Treatment

<table>
<thead>
<tr>
<th>Event (%)</th>
<th>Months Since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cele vs. Ibu, HR 0.68 (0.48-0.97)</td>
<td></td>
</tr>
<tr>
<td>Cele vs. Nap, HR 0.65 (0.46-0.92)</td>
<td></td>
</tr>
<tr>
<td>Ibu vs. Nap, HR 0.96 (0.70-1.31)</td>
<td></td>
</tr>
</tbody>
</table>
**Time-to-Composite Gastrointestinal Event**

### Intention-to-Treat

- Cele vs. Ibu, HR 0.65 (0.50-0.85), $P=0.002$
- Cele vs. Nap, HR 0.71 (0.54-0.93), $P=0.01$
- Ibu vs. Nap, HR 0.108 (0.85-1.39), $P=0.53$

### On-Treatment

- Cele vs. Ibu, HR 0.44 (0.32-0.61)
- Cele vs. Nap, HR 0.45 (0.33-0.63)
- Ibu vs. Nap, HR 1.03 (0.80-1.34)

**Graphs**

- **Patients with an Event (%)**: Intention-to-Treat (left) and On-Treatment (right).
  - Celecoxib vs. Ibuprofen: Ibuprofen 54% higher.
  - Ibuprofen vs. Naproxen: Naproxen 41% higher.
- **Months Since Randomization**: 0 to 30.
- **Legend**:
  - Ibuprofen
  - Naproxen
  - Celecoxib

**Results**

- **Celecoxib vs. Ibuprofen**: HR 0.65 (0.50-0.85), $P=0.002$
- **Celecoxib vs. Naproxen**: HR 0.71 (0.54-0.93), $P=0.01$
- **Ibuprofen vs. Naproxen**: HR 0.108 (0.85-1.39), $P=0.53$

**Comparison**

- Celecoxib shows a significant reduction in gastrointestinal events compared to both Ibuprofen and Naproxen.
- Ibuprofen is 54% higher than Celecoxib, while Naproxen is 41% higher than both Ibuprofen and Celecoxib.
Time-to-Composite Serious Renal Event

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.61 (0.44-0.85), \(P=0.004\)
- Cele vs. Nap, HR 0.79 (0.56-1.12), \(P=0.19\)
- Ibu vs. Nap, HR 1.29 (0.95-1.76), \(P=0.10\)

**On-Treatment**

- Cele vs. Ibu, HR 0.54 (0.37-0.80)
- Cele vs. Nap, HR 0.66 (0.44-0.97)
- Ibu vs. Nap, HR 1.21 (0.86-1.70)

Ibuprofen 64% higher
Post Hoc: Any Adjudicated CV, GI or Renal Event

**Intention-to-Treat**

Cele vs. Ibu, HR 0.78 (0.69-0.87), *P*<0.001
Cele vs. Nap, HR 0.87 (0.77-0.99), *P*=0.03
Ibu vs. Nap, HR 1.13 (1.01-1.26), *P*=0.04

Ibuprofen 28% higher (NNH - 59)
Naproxen 15% higher (NNH - 117)

**On-Treatment**

Cele vs. Ibu, HR 0.69 (0.61-0.79)
Cele vs. Nap, HR 0.78 (0.68-0.90)
Ibu vs. Nap, HR 1.13 (0.997-1.28)
## Selected Investigator-Reported Adverse Effects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib N=8030</th>
<th>Ibuprofen N=7992</th>
<th>Naproxen N=7933</th>
<th>Celecoxib vs. Ibuprofen P value</th>
<th>Celecoxib vs. Naproxen P value</th>
<th>Ibuprofen vs. Naproxen P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2.8%</td>
<td>5.5%</td>
<td>4.2%</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased BP</td>
<td>2.3%</td>
<td>3.1%</td>
<td>2.5%</td>
<td>0.001</td>
<td>0.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.7%</td>
<td>13.0%</td>
<td>11.0%</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.8%</td>
<td>3.4%</td>
<td>1.9%</td>
<td>&lt;0.001</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.4%</td>
<td>4.3%</td>
<td>5.2%</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.0%</td>
<td>6.8%</td>
<td>7.2%</td>
<td>0.004</td>
<td>0.05</td>
<td>0.38</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>3.6%</td>
<td>3.4%</td>
<td>2.8%</td>
<td>0.45</td>
<td>0.006</td>
<td>0.04</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.4%</td>
<td>3.2%</td>
<td>3.0%</td>
<td>0.003</td>
<td>0.01</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Effects on Blood Pressure
Hypertension

Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial

Frank Ruschitzka¹*†, Jeffrey S. Borer²†, Henry Krum‡, Andreas J. Flammer¹, Neville D. Yeomans³, Peter Libby⁴, Thomas F. Lüscher¹, Daniel H. Solomon⁴, M. Elaine Husni⁵, David Y. Graham⁶, Deborah A. Davey⁷, Lisa M. Wisniewski⁷, Venu Menon⁷, Rana Fayyad⁸, Bruce Beckerman⁸, Dinu Iorga⁸, A. Michael Lincoff⁶, and Steven E. Nissen⁶; on behalf of the PRECISION-ABPM Investigators

¹Cardiology, University Heart Center, University Hospital Zurich, Switzerland; ²Cardiovascular Medicine, Schiavone Cardiovascular Translational Research Institute, State University of New York, Downstate College of Medicine, New York, NY, USA; ³Cardiovascular Medicine, Western Sydney University, Campbelltown, NSW, Australia; ⁴Cardiovascular Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; ⁵Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH, USA; ⁶Cardiovascular Medicine, Baylor College of Medicine, Veterans Affairs Medical Center, Houston, TX, USA; ⁷Department for Cleveland Clinic, Cleveland Clinic, Cleveland, OH, USA; and ⁸Cardiovascular Medicine, Pfizer, New York, NY, USA
ABPM Study Design

• A pre-specified substudy of the PRECISION trial performed in 444 patients at 60 US centers.

• Ambulatory blood pressure measured every 20 minutes during daytime and every 30 minutes at night.

• The primary end point was the change from baseline in 24-hour mean systolic blood pressure at Month 4.

• A post hoc analysis compared the percentage of normotensive patients (24-hour SBP <130mmHg and DBP <80mmHg) who became hypertensive at Month 4.
4 Month Change in 24 Hour ABPM for Naproxen

N = 147

LS Mean Change (SE)
+1.58 mm Hg (1.0)

Systolic Blood Pressure (mmHg)

Time of Day

Naproxen Baseline
Naproxen Month 4
4 Month Change in 24 Hour ABPM for Ibuprofen

N = 151

LS Mean Change (SE) +3.65 mm Hg (1.0)

Ibuprofen Baseline
Ibuprofen Month 4

Systolic Blood Pressure (mmHg)

Time of Day

MN-26
4 Month Change in 24 Hour ABPM for Celecoxib

Systolic Blood Pressure (mmHg)

N = 146

LS Mean Change (SE)
-0.26 mm Hg (1.0)

Celecoxib Baseline
Celecoxib Month 4

Time of Day
Change in 24 Hour Systolic BP after 4 Months

Celecoxib

Naproxen

Ibuprofen

Change in Systolic BP (mm Hg)

-0.26

(-2.25-1.74)

1.58

(-0.40-3.57)

3.65

(1.72-5.58)

P < 0.001

P = 0.08

P = 0.12

European Heart Journal (2017) 38, 3282–3292
**Normotensive* Patients Developing Hypertension**

![Graph showing percentage of patients developing hypertension with different medications.](image)

- **Celecoxib**: 10.3%
- **Naproxen**: 19.0%
- **Ibuprofen**: 23.2%

\[ P = 0.04 \]
\[ P = 0.004 \]

*24 hour ambulatory BP <130/80 mm Hg*
Adjudicated Hospitalization for Hypertension

Intention-to-Treat

On-Treatment

Cele vs. Ibu, HR 0.59 (0.36-0.98), *P*=0.04
Cele vs. Nap, HR 0.70 (0.41-1.18), *P*=0.18
Ibu vs. Nap, HR 1.18 (0.75-1.86), *P*=0.49

Cele vs. Ibu, HR 0.58 (0.33-1.01)
Cele vs. Nap, HR 0.67 (0.38-1.19)
Ibu vs. Nap, HR 1.17 (0.71-1.93)
Questions About PRECISION

- Could retention and treatment discontinuation rates have meaningfully influenced the primary outcome analyses of the trial?

- Did potential interference of ibuprofen or naproxen with the beneficial effects of aspirin explain the primary findings of the study?

- Did the trial evaluate comparable doses of celecoxib, ibuprofen and naproxen?

- Are the results of PRECISION consistent or inconsistent with the CNT meta-analysis?
Adherence and Retention

• The trial academic leadership was aware that previous pain trials, even short term studies had lower than optimal adherence and retention.

• Patients with unrelieved pain rapidly become frustrated and withdraw at high rates from pain trials.

• By design, we included pathways to manage disease flares including TENS, tramadol, low dose opioids, intra-articular steroids or hyaluronic acid, etc.

• When we observed higher than desired rates of non-retention, multiple initiatives addressed both investigators and patients.
Rates of Follow up Across Treatment Groups

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>91%</td>
<td>89%</td>
<td>81%</td>
</tr>
<tr>
<td>18 months</td>
<td>89%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rates of Drug Discontinuation During Follow up

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>Percentage of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>37%</td>
</tr>
<tr>
<td>18 months</td>
<td>46%</td>
</tr>
<tr>
<td>24 months</td>
<td>59%</td>
</tr>
<tr>
<td>30 months</td>
<td>69%</td>
</tr>
</tbody>
</table>

ITT analysis: 59%
On treatment analysis: 69%

- Ibuprofen
- Naproxen
- Celecoxib

MN-34
## Comparative Rates of Non-Adherence and Non-Retention in Chronic NSAID/Coxib Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Follow-up</th>
<th>Non-Adherence</th>
<th>Non-Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARGET</td>
<td>lumiracoxib, ibuprofen, naproxen</td>
<td>12 months</td>
<td>39%</td>
<td>39%</td>
</tr>
<tr>
<td>MEDAL</td>
<td>etoricoxib, diclofenac</td>
<td>18 months</td>
<td>24%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36 months</td>
<td>81%</td>
<td>53%</td>
</tr>
<tr>
<td>PRECISION</td>
<td>celecoxib, ibuprofen, naproxen</td>
<td>18 months</td>
<td>46%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 months</td>
<td>59%</td>
<td>19%</td>
</tr>
</tbody>
</table>
### Characteristics of Non-Adherent Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63.2</td>
<td>63.6</td>
<td>63.5</td>
</tr>
<tr>
<td>Female Gender</td>
<td>64.0%</td>
<td>64.2%</td>
<td>64.0%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>9.7%</td>
<td>10.4%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Aspirin Use</td>
<td>46.1%</td>
<td>46.1%</td>
<td>46.2%</td>
</tr>
<tr>
<td>Smoking</td>
<td>21.5%</td>
<td>21.1%</td>
<td>21.4%</td>
</tr>
<tr>
<td>VAS Score (mm)</td>
<td>55.1</td>
<td>54.7</td>
<td>54.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36.6%</td>
<td>37.2%</td>
<td>36.3%</td>
</tr>
<tr>
<td>History of CAD</td>
<td>24.9%</td>
<td>23.8%</td>
<td>23.7%</td>
</tr>
<tr>
<td>History of HTN</td>
<td>78.4%</td>
<td>79.4%</td>
<td>77.9%</td>
</tr>
<tr>
<td>Statin Use</td>
<td>54.4%</td>
<td>53.2%</td>
<td>54.1%</td>
</tr>
</tbody>
</table>
# Characteristics of Non-Retained Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>61.7</td>
<td>62.3</td>
<td>62.2</td>
</tr>
<tr>
<td>Female Gender</td>
<td>63.7%</td>
<td>65.5%</td>
<td>65.2%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>10.6%</td>
<td>11.6%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Aspirin Use</td>
<td>42.9%</td>
<td>42.3%</td>
<td>42.3%</td>
</tr>
<tr>
<td>Smoking</td>
<td>24.4%</td>
<td>22.6%</td>
<td>23.9%</td>
</tr>
<tr>
<td>VAS Score (mm)</td>
<td>56.9</td>
<td>56.0</td>
<td>56.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37.5%</td>
<td>36.9%</td>
<td>36.5%</td>
</tr>
<tr>
<td>History of CAD</td>
<td>22.2%</td>
<td>23.0%</td>
<td>21.8%</td>
</tr>
<tr>
<td>History of HTN</td>
<td>77.1%</td>
<td>76.9%</td>
<td>74.2%</td>
</tr>
<tr>
<td>Statin Use</td>
<td>51.9%</td>
<td>49.9%</td>
<td>50.1%</td>
</tr>
</tbody>
</table>
### Sensitivity Analysis Imputing Potential Missing Events

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (n=8072)</th>
<th>Ibuprofen (n=8040)</th>
<th>Naproxen (N=7969)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary events</td>
<td>188</td>
<td>218</td>
<td>201</td>
</tr>
<tr>
<td>Pairwise comparison</td>
<td>0.86 (0.70-1.04)</td>
<td>0.94 (0.77-1.15)</td>
<td></td>
</tr>
<tr>
<td>Subjects who withdrew</td>
<td>1337</td>
<td>1368</td>
<td>1316</td>
</tr>
<tr>
<td>Additional events needed to</td>
<td>59</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>exceed noninferiority boundary</td>
<td>80</td>
<td>22</td>
<td>-</td>
</tr>
</tbody>
</table>

**Comment from FDA statistician**

“In order for the upper bound of the 95% CI for the odds ratio of APTC events associated with celecoxib to exceed the pre-set margin of 1.33, the imputed number of events in the celecoxib arm would have to be three times as large as in the naproxen arm and four times as large as in the ibuprofen arm.”
Summary: Adherence and Retention Analyses

- Similar rates of non-adherence and non-retention observed for all three treatment groups.

- Baseline characteristics were similar across treatment groups for non-adherent and non-retained patients.

- On-treatment analyses also show highly significant $P$ values for non-inferiority, reinforcing ITT results.

- Sensitivity analyses evaluating potential effects of missed events show that even an extreme imbalance disfavoring celecoxib cannot change the non-inferiority conclusion.
Did potential interference of ibuprofen or naproxen with beneficial effects of aspirin explain the primary findings of the study?
Clinical Effects of Aspirin-NSAID Interactions

• The *potential* interaction between aspirin and ibuprofen or naproxen have been described in the platelet function laboratory.

• However, the actual clinical effects of this theoretical interaction have never been adequately verified in a randomized clinical trial.

• For ethical reasons, we could not randomize to aspirin, but did stratify for aspirin use at baseline.

• This approach provided the opportunity to examine whether the *theoretical* NSAID platelet function interaction actually affected major cardiovascular outcomes.
Baseline and End-of-Study Usage of Aspirin

Percentage of Patients Taking Aspirin (%)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Remained at Study End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>45.8%</td>
</tr>
<tr>
<td>Naproxen</td>
<td>45.8%</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>46.2%</td>
</tr>
</tbody>
</table>

MN-42
Aspirin Interaction Testing: Theoretical vs. Observed

**Subgroup**
- Not taking low-dose Aspirin
- Taking low-dose Aspirin

**HR (95% CI)**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Celecoxib N=8030</th>
<th>Ibuprofen N=7990</th>
<th>Naproxen N=7933</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taking low-dose Aspirin</td>
<td>0.78 (0.58, 1.04)</td>
<td>81</td>
<td>97</td>
<td>0.40</td>
</tr>
<tr>
<td>Taking low-dose Aspirin</td>
<td>0.93 (0.71, 1.20)</td>
<td>107</td>
<td>116</td>
<td></td>
</tr>
</tbody>
</table>

**Theoretical effect if ibuprofen interferes with aspirin efficacy**

*Based on CNT

MN-43
Effect of Aspirin Coadministration on the Safety of Celecoxib, Naproxen, or Ibuprofen

Grant W. Reed, MD, MSc, Mouin S. Abdallah, MD, MSc, Mingyuan Shao, MS, Kathy Wolski, MPH, Lisa Wisniewski, RN, Neville Yeomans, MD, Thomas F. Lüscher, MD, Jeffrey S. Borer, MD, David Y. Graham, MD, M. Elaine Husni, MD, MPH, Daniel H. Solomon, MD, MPH, Peter Libby, MD, Venu Menon, MD, A. Michael Lincoff, MD, Steven E. Nissen, MD

ABSTRACT

BACKGROUND The safety of nonsteroidal anti-inflammatory drug (NSAID) and aspirin coadministration is uncertain.

OBJECTIVES The aim of this study was to compare the safety of combining NSAIDs with low-dose aspirin.

METHODS This analysis of the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen) trial included 23,953 patients with osteoarthritis or rheumatoid arthritis at increased cardiovascular risk randomized to celecoxib, ibuprofen, or naproxen. The on-treatment population was used for this study. Outcomes included composite major adverse cardiovascular events, noncardiovascular death, gastrointestinal or renal events, and components of the composite. Cox proportional hazards models compared outcomes among NSAIDs stratified by aspirin use following propensity score adjustment. Kaplan-Meier analysis was used to compare the cumulative
Effects of Aspirin on Safety: Expanded MACE

Aspirin

Cele vs. Ibu, HR 0.84, P=0.12
Cele vs. Nap, HR 0.96, P=0.69
Ibu vs. Nap, HR 1.13, P=0.26

No Aspirin

Cele vs. Ibu, HR 0.74, P=0.04
Cele vs. Nap, HR 0.90, P=0.47
Ibu vs. Nap, HR 1.21, P=0.18
Effects of Aspirin on Relative Safety: GI Outcomes

**Aspirin**

- Cele vs. Ibu, HR 0.58, \( P = 0.02 \)
- Cele vs. Nap, HR 0.52, \( P = 0.003 \)
- Ibu vs. Nap, HR 0.90, \( P = 0.57 \)

**No Aspirin**

- Cele vs. Ibu, HR 0.31, \( P < 0.001 \)
- Cele vs. Nap, HR 0.38, \( P < 0.001 \)
- Ibu vs. Nap, HR 1.23, \( P = 0.26 \)
Effects of Aspirin on Safety: Renal Outcomes

Patients with an Event (%)

<table>
<thead>
<tr>
<th></th>
<th>No Aspirin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cele vs. Ibu, HR 0.50, P=0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cele vs. Nap, HR 0.77, P=0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibu vs. Nap, HR 1.55, P=0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cele vs. Ibu, HR 0.52, P=0.05
Cele vs. Nap, HR 0.48, P=0.02
Ibu vs. Nap, HR 0.92, P=0.75

Ibuprofen          Naproxen           Celecoxib
Composite of Cardiovascular, Renal, GI Safety

**Aspirin**

- Cele vs. Ibu, HR 0.79, *P* = 0.01
- Cele vs. Nap, HR 0.85, *P* = 0.08
- Ibu vs. Nap, HR 1.08, *P* = 0.42

**No Aspirin**

- Cele vs. Ibu, HR 0.55, *P* < 0.001
- Cele vs. Nap, HR 0.66, *P* < 0.001
- Ibu vs. Nap, HR 1.19, *P* = 0.08
Did the trial evaluate comparable doses of celecoxib, ibuprofen and naproxen?
Withdrawals for Insufficient Clinical Response

Percentage Withdrawn for Insufficient Clinical Response

- Celecoxib: 9.5%
- Naproxen: 8.3%
- Ibuprofen: 8.4%

Statistical significance:
- P = 0.01
- P = 0.02
- P = 0.80
Comparative Effects: Anti-Arthritic Efficacy over Time

Visual Analog Pain Scale (VAS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change from Baseline</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>-9.67 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>-9.73 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>-10.32 ± 0.27*</td>
<td></td>
</tr>
</tbody>
</table>

* P=0.02 vs. celecoxib  
  P=0.03 vs. ibuprofen

Disability Index (HAQ-DI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change from Baseline</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>-0.12 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>-0.11 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>-0.11 ± 0.01</td>
<td></td>
</tr>
</tbody>
</table>

P=NS for all comparisons

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Additional Measures of Anti-Arthritic Efficacy

Global Assessment of Arthritis

Overall Change in LS Means of Scores:
- Celecoxib: -0.270 ± 0.01
- Ibuprofen: -0.276 ± 0.01
- Naproxen: -0.289 ± 0.01*

* p=0.02 vs. celecoxib

Use of Rescue Medications

P=NS for all comparisons

- Ibuprofen: 24.8%
- Naproxen: 26.1%
- Celecoxib: 25.8%

* p=0.02 vs. celecoxib
Summary: Dosing of Study Drugs

- For osteoarthritis patients (90% of study population), maximal approved doses are celecoxib (200 mg daily), ibuprofen (3200 mg daily) and naproxen (1500 mg daily).

- The average achieved doses as a proportion of maximal allowed doses were 100% for celecoxib, 64% for ibuprofen and 57% for naproxen.

- If maximal therapeutic doses of ibuprofen and naproxen had been used, their adverse effects on BP, renal function and GI toxicity would likely have been even more apparent.

- The doses achieved were clinically relevant and generally comparable based on several different efficacy analyses.
Comparison: PRECISION vs. CNT Meta-Analysis

CNT: Direct Comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib vs. Ibuprofen</td>
<td>1.01 (0.48-2.13)</td>
</tr>
<tr>
<td>Celecoxib vs. Naproxen</td>
<td>0.93 (0.46-1.88)</td>
</tr>
</tbody>
</table>

PRECISION Comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib vs. Ibuprofen</td>
<td>0.86 (0.70-1.04)</td>
</tr>
<tr>
<td>Celecoxib vs. Naproxen</td>
<td>0.94 (0.76-1.12)</td>
</tr>
</tbody>
</table>

Favors Celecoxib
Favors Comparator
Conclusions: Celecoxib vs. Ibuprofen

- Numerically fewer APTC events occurred with celecoxib than ibuprofen, meeting all 4 noninferiority criteria ($P<0.001$).

- In ITT analyses, chronic treatment with prescription doses of ibuprofen, compared with celecoxib, was associated with:
  - Higher rates of gastrointestinal and renal adverse events and higher rates of hospitalization for HTN.

- In the on-treatment sensitivity analysis, ibuprofen showed:
  - Higher rates of MACE, cardiovascular death, all-cause mortality and major gastrointestinal and renal events.
Conclusions: Celecoxib vs. Naproxen

• Numerically fewer APTC events occurred with celecoxib than naproxen, meeting all 4 noninferiority criteria ($P<0.001$).

• In ITT analyses, chronic treatment with prescription doses of naproxen, compared with celecoxib, was associated with:
  – Higher rates of gastrointestinal adverse events and a borderline significant increase in all-cause mortality.

• In the on-treatment sensitivity analysis, naproxen showed:
  – Higher rates of all-cause mortality and major gastrointestinal and renal events.
PRECISION: Additional Conclusions

- These findings challenge the widely-held view that naproxen provides superior cardiovascular safety.

- Adherence and retention were lower than typical CV outcome trials, but similar to other NSAID pain studies with no strong evidence for an effect on the primary noninferiority findings.

- Dosages used in the trial provided similar anti-arthritis efficacy.

- Results were consistent regardless of aspirin administration, although with narrower advantages for celecoxib.

- Clinically meaningful differences in effects on blood pressure represent a potential factor in differences in CV outcome.
Additional Conclusions

• The results reflect the relative safety of these 3 drugs and not the more than 20 other currently marketed NSAIDs.

• No direct inferences are possible regarding the effects of NSAIDs compared with placebo.

• These data do not provide conclusive evidence regarding the safety of intermittent treatment or use of low-dose over-the-counter preparations.
A Clinical Strategy Based on PRECISION

For arthritis patients who require NSAIDs to achieve an acceptable quality of life, particularly those at high cardiovascular, GI or renal risk, the PRECISION Trial suggests that a clinical strategy of starting patients on celecoxib 200 mg daily may be the safest approach, reserving full therapeutic doses of ibuprofen and naproxen for patients who do not respond to celecoxib.
Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., M. Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., Frank Ruschitzka, M.D., Michael Gaffney, Ph.D., Bruce Beckerman, M.D., Manuela F. Berger, M.D., Weihang Bao, Ph.D., and A. Michael Lincoff, M.D., for the PRECISION Trial Investigators*

ABSTRACT

BACKGROUND
The cardiovascular safety of celecoxib, as compared with nonselective nonsteroidal antiinflammatory drugs (NSAIDs), remains uncertain.
Some Final Thoughts

After the withdrawal of rofecoxib, many observers assumed that all COX-2 inhibitors increased major adverse cardiovascular events. Existing randomized trials were small and relatively short in duration. Observational studies and meta-analyses showed inconsistent results with relative risks typically in the range of 0.8 to 1.2. The PRECISION trial demonstrates the importance of determining the risks and benefits of therapies based upon randomized trials rather than theoretical considerations. The findings highlight differences in outcomes that appear related to multiple pharmacological effects of these drugs, not necessarily their COX-1 vs. COX-2 selectivity.
Rheumatologist’s Perspective:
Implications for OA/RA Patient Management

Stanley Cohen MD
Clinical Professor of Internal Medicine, UT Southwestern Medical School
Medical Director, Metroplex Clinical Research Center
Director, Rheumatology Division, Presbyterian Hospital
Dallas, Texas
Rheumatoid Arthritis

- Chronic, inflammatory, systemic autoimmune disease
- Prevalence 1% of population\(^1\) (1.3 million in the United States\(^2\))
- Age of onset: 40-70 years of age\(^1\) (~65% women\(^1\))
- Causes significant disability\(^1,3\)
- Accompanied by increased risk of cardiovascular events, serious infections, lung cancer and lymphoma
- Cornerstone of management: disease-modifying drugs (DMARDs)
- NSAIDs represent adjunctive therapy

3. Arthritis & Rheumatism (Arthritis Care & Research); April 15, 2008; vol59, no4; pp474-480. American College of Rheumatology.
Osteoarthritis

- Osteoarthritis (OA) is far more common than rheumatoid arthritis (RA) (30 million US adults according to CDC)
- Although affecting all ages, osteoarthritis is most common in people >65 years
- Common risk factors: age, obesity, previous joint injury, overuse of the joint, weak thigh muscles, and genes
- The lifetime risk of developing symptomatic knee OA is ≈ 40% in men and ≈ 50% in women. Risk rises to 60% in those with body mass index ≥30 kg/m²
- One in 12 people ≥60 years have hand OA
- Chronic pain with limitation of physical activity

CDC 2018
CDC=Center for Disease Control
Most Patients in PRECISION Had Osteoarthritis

- Treatment is focused entirely on the management of symptoms
- Long-term management of the disease relies on
  - Anti-inflammatory and analgesic agents
  - Physical rehabilitation and exercise
  - Avoidance of obesity
Pharmacological Treatment of Osteoarthritis

- **Primary**
  - Nonsteroidal anti-inflammatory drugs (NSAIDs): Ease inflammation and related pain. Mainstay of treatment for OA, whereas adjunctive for RA

- **Secondary (all suboptimal)**
  - **Analgesics**: Acetaminophen, tramadol, opioids (narcotics)
  - **Corticosteroids**: Short-term benefit from intra-articular corticosteroids, but no role for oral corticosteroids
  - **Intra-articular hyaluronans**: Benefit controversial

- Avoidance of NSAIDs leads to increased reliance on opioids
Efficacy of Celecoxib vs. Nonselective NSAIDs in NDA Trials of Osteoarthritis (1)

At week 12, mean improvement in the WOMAC composite with celecoxib 100 mg BID and 200 mg BID was superior to placebo (p<0.05) and similar to naproxen 500 mg BID. The mean OA severity index with celecoxib 100 mg BID was superior to naproxen 500 mg BID (p<0.05)

* * *

* p<0.05
WOMAC=Western Ontario and McMaster Universities
Efficacy of Celecoxib vs. Nonselective NSAIDs in NDA Trials of Osteoarthritis (2)

- Celecoxib was associated with significant improvements in all 3 WOMAC subscales (pain, stiffness, and physical function) and total composite WOMAC score (p<0.001)
- Celecoxib 100 mg BID was significantly better than naproxen in decreasing pain scores (p<0.001)
- Celecoxib was better than placebo and comparable with naproxen in improving aspects of functional status in patients with OA

**p=0.001
PRECISION: Change from Baseline in Pain VAS

### Osteoarthritis

**Overall Change in Means of VAS Scores**
- Celecoxib: $-11.0 \pm 0.25$
- Ibuprofen: $-11.1 \pm 0.26$
- Naproxen: $-11.7 \pm 0.25$

### Rheumatoid Arthritis

**Overall Change in Means of VAS Scores**
- Celecoxib: $-6.19 \pm 0.68$
- Ibuprofen: $-7.86 \pm 0.66$
- Naproxen: $-6.68 \pm 0.68$

**Month:**
0 - 1 - 2 - 4 - 8 - 12 - 18 - 24 - 30

Celecoxib vs. Naproxen, $p=0.002$

Celecoxib vs. Ibuprofen, $p=0.02$

Means from least square regression

VAS=Visual Analogue Scale
Main Findings of the PRECISION Trial

- PRECISION largely studied osteoarthritis (90% of study population) because these patients constitute the most prevalent cause of chronic arthritic pain.

- For patients with osteoarthritis, maximal approved daily doses are celecoxib (200 mg), ibuprofen (3200 mg) and naproxen (1500 mg).

- Therefore, compared to maximal allowed doses, patients enrolled in the PRECISION trial achieved doses of 100% (200 mg) for celecoxib, 64% (2046 mg) for ibuprofen and 57% (852 mg) for naproxen.

- At the doses used in the PRECISION trial, OA patients treated with celecoxib experienced similar relief of pain and did not have higher cardiovascular risk than patients treated with ibuprofen and naproxen. However, at these doses, patients treated with celecoxib were likely to experience less toxicity related to blood pressure, renal function and gastrointestinal bleeding.
When selecting a treatment that is intended to alleviate the symptoms of a chronic disease, providers and patients desire a treatment that is best tolerated as long as it can be reasonably expected to achieve therapeutic goals in a large proportion of patients.

Based on the results of the PRECISION trial, in patients with osteoarthritis, treatment with celecoxib 200 mg daily can be expected to achieve clinically meaningful pain relief, without an increase in cardiovascular risk and with the likelihood of less GI and renal toxicity, when compared to the doses of ibuprofen and naproxen that were studied.
Concluding Remarks

Contribution of PRECISION to Guide the Safe and Appropriate Use of Celecoxib and its Comparators

Milton L. Pressler, MD
Vice President, Clinical Development
Pfizer Inc, New York, NY
Summary
For Arthritis Patients, PRECISION Provides Important Information

- A large, clinically relevant trial of currently used drugs in practice
  - Highly representative and generalizable to patients with chronic arthritis pain, who are largely those with osteoarthritis
  - Studied approved and clinically relevant doses of celecoxib vs. doses of two nonselective NSAID comparators, naproxen and ibuprofen
  - Carefully designed; prespecified non-inferiority. Findings are unaltered by considerations of missing data; no evidence for aspirin interaction
  - Applicable to long-term prescription use, not short-term OTC use of NSAIDs

- Robust and consistent results across prespecified and post hoc analyses
Summary
PRECISION Greatly Expands the Clinical Trials Safety Database

- One of the largest randomized arthritis study of clinical outcomes to date
  - >24,000 patients
  - Blinded adjudication of predefined APTC, GI, renal, HTN, CHF outcomes
  - Embedded substudy to precisely measure BP changes by ABPM

- Total follow-up in PRECISION was **68,430** patient-years
  - **45,717** patient-years for celecoxib vs. naproxen comparison
  - **45,651** patient-years for celecoxib vs. ibuprofen comparison

- In CNT meta-analysis of prior RCTs, follow-up was
  - **31,631** patient-years for all 5 coxibs\(^a\) vs. naproxen comparison
  - **11,668** patient-years for all 5 coxibs\(^a\) vs. ibuprofen comparison

---

\(^a\) celecoxib, rofecoxib, lumiracoxib, etoricoxib, valdecoxib

ABPM=Ambulatory Blood Pressure Measurement; BP=Blood Pressure; CHF=Congestive Heart Failure; HTN=Hypertension; RCT=Randomized Clinical Trial
Summary
Situation in 2018 as Compared to 2014

■ PRECISION is consistent with prior knowledge on safety
  – Findings fully consistent with results of direct comparisons in CNT for the doses used of celecoxib, naproxen and ibuprofen in patients with osteoarthritis
  – Provides substantial CV safety data on 200 mg celecoxib, the clinically relevant dose for patients with osteoarthritis
  – Effects in the trial not influenced by concomitant treatment with aspirin
  – Provides important insights into changes in BP and renal function
  – Supports a more favorable GI safety profile of celecoxib as compared to two non-selective NSAIDs – even with concomitant PPI treatment

■ Physicians should be made aware of these results

PPI=Proton Pump Inhibitor
Overall Conclusions

- Celecoxib continues to demonstrate a favorable benefit/risk profile for treatment of patients with arthritic pain, especially for those with osteoarthritis.

- The results of PRECISION should be included in the USPI
  - PRECISION provides robust and important information on CV safety to guide prescription use of clinically relevant doses of celecoxib, naproxen and ibuprofen.
Approach to Changes in Celecoxib USPI From PRECISION

- Description of study design and population
- Description of drugs and doses tested
- Principal findings
  - Over a mean follow-up of 34 months, celecoxib met four prespecified non-inferiority criteria, thus demonstrating no greater risk for cardiovascular events than naproxen or ibuprofen at the doses used in the study.
Backup Slides Called
Cross-In: Taking Non-Randomized Study NSAIDS for ≥7 Consecutive Days
## Rate of Dose Escalation Among ITT Patients with Dispensing Records in IVRS

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib BID N=8072</th>
<th>Ibuprofen TID N=8040</th>
<th>Naproxen BID N=7969</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients Escalated Dose, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5.9; 57.5 intended(^a)</td>
<td>55.4</td>
<td>55.2</td>
</tr>
<tr>
<td>RA</td>
<td>56.0</td>
<td>56.6</td>
<td>54.9</td>
</tr>
<tr>
<td>OA</td>
<td>0.3; 57.7 intended(^a)</td>
<td>55.3</td>
<td>55.3</td>
</tr>
<tr>
<td><strong>Average Dispensed Dose, Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>104 (18)</td>
<td>682 (82)</td>
<td>426 (51)</td>
</tr>
<tr>
<td>RA</td>
<td>142 (41)</td>
<td>682 (82)</td>
<td>425 (51)</td>
</tr>
<tr>
<td>OA</td>
<td>100 (3)</td>
<td>682 (82)</td>
<td>426 (51)</td>
</tr>
</tbody>
</table>

\(^a\) Including OA patients who intend to dose escalate, but not allowed per prescription of the medication

IVRS=Interactive Voice Response System
Taking Non-Randomized Celecoxib, Ibuprofen, Naproxen or Other NSAIDS for ≥1 Day Before Treatment Discontinuation Through 42 Months

![Graph showing patients' usage of different NSAIDS.]

- **Non-Randomized Celecoxib:** 1.92, 3.28, 1.31, 8.66
- **Non-Randomized Ibuprofen:** 1.83, 3.19, 1.29, 8.28
- **Non-Randomized Naproxen:** 1.85, 3.23, 1.55
- **All Other NSAIDS:** 8.66, 8.28, 8.57

*SA-185*
Clinically Significant Iron-Deficiency Anemia of GI Origin

Definition

- The first occurrence of clinically significant iron-deficiency anemia of GI origin is a tertiary endpoint
- Clinically significant iron-deficiency anemia are defined as
  - Clinically significant iron-deficiency anemia of defined GI origin (excluding esophageal causes other than erosive esophagitis)
    - No clinical evidence of acute GI hemorrhage but with fall in Hct ≥10% points and/or Hgb ≥2 gm/dL from baseline with likely causative lesion on colonoscopy or EGD (or small bowel investigation) with
      » Iron-deficiency anemia. The diagnosis of iron deficiency is indicated by Hgb <12 gm/dl for women or <13 gm/dl for men and the presence of any or all of the following parameters: low serum ferritin (<15 μg/dl), low mean corpuscular volume (MCV, <83 fl), low serum iron, or high total iron binding capacity (TIBC)
      » No non-GI source of anemia identified
  - Clinically significant iron-deficiency anemia of presumed occult GI origin including possible small bowel blood loss
    - No overt clinical evidence of acute GI hemorrhage but with fall in Hct ≥10% points and/or Hgb ≥2 gm/dl from baseline and with no evidence of likely causative lesion on EGD or colonoscopy (or small bowel investigation) with
      » Iron-deficiency anemia. The diagnosis of iron deficiency is indicated by Hgb <12 gm/dl for women or <13 gm/dl for men and the presence of any or all of the following parameters: low serum ferritin (<15 μg/dl), low mean corpuscular volume (MCV, <83 fl), low serum iron, or high total iron binding capacity (TIBC)
      » With or without heme-occult positive stools

EGD=Esophagogastroduodenoscopy; Hct=Hematocrit; Hgb=Hemoglobin
Adjudication of Hospitalization for Hypertension

1. Hospitalization, defined as any admission to a hospital ward, observation unit, clinical decision unit, even if the duration of stay is less than 24 hours (does not include doctor office visits) for hypertension defined as either

2. Hypertensive urgency: SBP >180 mmHg or DBP >110 mmHg with minimal or no end organ damage, or

3. Hypertensive Emergency: elevated BP (>180/110) with acute end-organ damage

   a. Acute end organ damage to be defined as
      • Neurologic symptoms as defined by encephalopathy, hemorrhagic or ischemic stroke, papilledema
      • Cardiac damage: unstable angina or acute MI, heart failure with pulmonary edema
      • Renal damage as exhibited by proteinuria, hematuria, or acute renal failure
      • Aortic dissection
Efficacy in Arthritis in Visual Analog Scale by Treatment Group

**Mean, mm (SE)**

- **Celecoxib 100-200 mg BID**
- **Ibuprofen 600-800 mg TID**
- **Naproxen 375-500 mg BID**

*p < 0.05 for treatment comparison of change from baseline*

a. p < 0.05, celecoxib was worse than ibuprofen which was worse than naproxen
b. p < 0.05, ibuprofen was worse than naproxen
# Indications of Similar Pain Management Among Three Treatment Groups: Proportion of Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Celecoxib 100-200 mg BID N=8072 %</th>
<th>Ibuprofen 600-800 mg TID N=8040 %</th>
<th>Naproxen 375-500 mg BID N=7969 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-in: Adding non-randomized study medication</td>
<td>9.0</td>
<td>9.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Taking rescue medication (mostly opioids, &gt;99%) anytime during the study</td>
<td>25.8</td>
<td>24.8</td>
<td>26.1</td>
</tr>
<tr>
<td>Intended dose escalation</td>
<td>57.5</td>
<td>55.4</td>
<td>55.2</td>
</tr>
<tr>
<td>Discontinue treatment due to insufficient clinical response</td>
<td>9.5</td>
<td>8.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders while on study treatment</td>
<td>28.3</td>
<td>26.5</td>
<td>27.6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9.9</td>
<td>8.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.9</td>
<td>6.6</td>
<td>7.0</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>13.7</td>
<td>12.7</td>
<td>12.7</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>5.7</td>
<td>5.3</td>
<td>5.3</td>
</tr>
</tbody>
</table>
# Study Medication Dispensing (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 100-200 mg BID</th>
<th>Ibuprofen 600-800 mg TID</th>
<th>Naproxen 375-500 mg BID</th>
<th>Total N=24,081</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Dispensing Data, n (%)</td>
<td>8069 (99.9)</td>
<td>8036 (99.9)</td>
<td>7966 (99.9)</td>
<td>24,071 (99.9)</td>
</tr>
<tr>
<td>Average dose, mean (SD)</td>
<td>104.31 (18.371)</td>
<td>681.69 (81.884)</td>
<td>426.11 (51.427)</td>
<td>–</td>
</tr>
<tr>
<td>RA Patients with Dispensing Data, n (%)</td>
<td>813 (10.0)</td>
<td>832 (10.3)</td>
<td>790 (9.9)</td>
<td>2435 (10.1)</td>
</tr>
<tr>
<td>Average dose, mean (SD)</td>
<td>141.56 (41.43)</td>
<td>681.88 (82.19)</td>
<td>424.69 (51.029)</td>
<td>–</td>
</tr>
<tr>
<td>OA Patients with Dispensing Data, n (%)</td>
<td>7256 (89.8)</td>
<td>7204 (89.6)</td>
<td>7176 (90.0)</td>
<td>21,636 (89.8)</td>
</tr>
<tr>
<td>Average dose, mean (SD)</td>
<td>100.14 (3.208)</td>
<td>681.67 (81.854)</td>
<td>426.27 (51.472)</td>
<td>–</td>
</tr>
</tbody>
</table>

Dosing records were retrieved from a tele-randomization system (Impala). These records may not completely reflect what investigators had dispensed to study patients. Calculations in this table have excluded medication kits that were known to be incorrectly dispensed, such as those reported by the investigator sites.
## Analysis of Time to First Occurrence of an Antiplatelet Trialists’ Collaboration (APTC) Endpoint – Statin Use Analysis (ITT Population Through 30 Months)

<table>
<thead>
<tr>
<th>Comparison Statin Use</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Celecoxib vs. Naproxen</strong></td>
<td></td>
</tr>
<tr>
<td>With Statin Use at Baseline</td>
<td>0.96 (0.74, 1.25)</td>
</tr>
<tr>
<td>Without Statin Use at Baseline</td>
<td>0.88 (0.65, 1.19)</td>
</tr>
<tr>
<td><strong>Celecoxib vs. Ibuprofen</strong></td>
<td></td>
</tr>
<tr>
<td>With Statin Use at Baseline</td>
<td>0.80 (0.62, 1.03)</td>
</tr>
<tr>
<td>Without Statin Use at Baseline</td>
<td>0.93 (0.69, 1.27)</td>
</tr>
</tbody>
</table>

The hazard ratios favor celecoxib in all scenarios with and without statin use at baseline.