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Sponsor:

Pfizer

Study Purpose:

Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen; A Randomized, Double Blind, Parallel-Group Study Of Cardiovascular Safety In Osteoarthritis or Rheumatoid Arthritis Patients With or at High Risk for Cardiovascular Disease Comparing Celecoxib With Naproxen and Ibuprofen.

Objective:

To assess the effect of celecoxib when compared to traditional (non-selective) nonsteroidal anti-inflammatory drugs (NSAIDs) on cardiovascular events, gastrointestinal events, renal events and symptomatic benefit in subjects with osteoarthritis (OA) or rheumatoid arthritis (RA) with cardiovascular disease (CVD) or at high risk for developing CVD.

Inclusion:

1. Men and women, 18 years of age or older at the time of consent;
2. If the subject is female and of childbearing potential, or less than 2 years postmenopause, she must have been using adequate contraception since her last menses and will use adequate contraception during the study. She should not be lactating and must have a negative pregnancy test within 24 hours prior to receiving the first dose of study medication. Women less than 2 years postmenopause are considered of childbearing potential for the purpose of this study and adequate contraception being considered medically acceptable is contraception such as hormonal contraception, intrauterine device, or barrier method plus spermicide;
3. Clinical diagnosis of OA or RA with a duration of at least 6 months (refer to Appendix 6 for American College of Rheumatology (ACR) criteria for general guidance only);
4. All subjects must have required a chronic analgesic regimen for at least 6 months. RA subjects who are receiving disease modifying anti-rheumatic drug (DMARD) or oral corticosteroid therapy (less than or equal to 20 mg prednisone

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or equivalent) in addition to their chronic analgesic regimen should have been on the same DMARD or corticosteroid for 3 months and on a stable dosing regimen for 1 month (defined as doses and frequency of administration are unchanged);

5. In the investigator's opinion, the subject requires and is eligible for chronic, daily therapy with an NSAID to control arthritis signs and symptoms;

6. Subject with established or at high risk for CVD defined as one of the following (a-d):

a. Coronary disease

- History of stable angina; *or*
- History of MI, unstable angina, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery **at least 3 months prior to randomization; *or***
- An angiographic stenosis greater than 50% by visual estimation at catheterization.

b. Occlusive disease of non-coronary arteries

- History of TIA or ischemic stroke at least 3 months prior to randomization, *or*
- Angiographic or ultrasound diagnosis of carotid artery stenosis $\geq 50\%$, *or*
- History of carotid endarterectomy at least 3 months prior to randomization, *or*
- Symptomatic peripheral arterial disease (eg, intermittent claudication), *or*
- Other arterial surgery or angioplasty for atherosclerotic vascular disease at least 3 months prior to randomization

c. Diabetes mellitus: clinical diagnosis of Type I or Type II diabetes

d. High risk of atherosclerotic vascular disease, which requires at least 3 of the following

- Age >55 years
- History of hypertension
- History of dyslipidemia (defined as LDL >160 mg/dL [4.144 mmol/L] or high-density lipoprotein (HDL) <40 mg/dL [1.036 mmol/L] in females and <35 mg/dL [0.906 mmol/L] in males). Subjects currently undergoing lipid lowering therapy with a statin drug, Omacor® (prescription omega-3-acid ethyl esters) or prescription niacin (≥ 1000 mg/day) will automatically meet this criterion.
- Family history of premature CVD (defined as history of myocardial infarction, angina pectoris, heart failure, cardiac death or coronary revascularization [including PCI and CABG]; does NOT include history of hypertension), stroke, carotid endarterectomy, or other arterial surgery or angioplasty for atherosclerotic vascular disease in a parent, grandparent or sibling with first symptom onset or diagnosis before age 55 years for males and 65 years for females
- Current smoking (defined as any cigarette smoking within the past 30 days)
- History of microalbuminuria, urine protein/creatinine ratio >2

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- Left ventricular hypertrophy (LVH) as evidenced by electrocardiogram (ECG) or echocardiography
 - Documented Ankle Brachial Index (ABI) <0.9 (See Appendix 10)
7. In the opinion of the investigator, the subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures for the duration of the study; Evidence of a personally signed and dated informed consent document indicating that the subject (or legally acceptable representative) has been informed of all pertinent aspects of the trial.

Exclusion:

1. The subject has had acute joint trauma with active symptoms which may interfere with the assessment of arthritis;
2. The subject has a planned surgical or other invasive procedure to be performed during the course of the study;
3. The subject has:
 - known allergy or hypersensitivity to celecoxib, ibuprofen or naproxen, *or*
 - has experienced asthma, urticaria or allergic-type reactions after taking sulfonamides, proton pump inhibitors (PPIs), lactose or NSAIDs.Subjects with hypersensitivity to or who cannot tolerate esomeprazole or PPIs may be treated with other gastroprotective agents permitted per protocol (i.e. histamine-2 blockers) at the discretion of the investigator; however, subjects should be treated with esomeprazole provided by the study unless they are not able to tolerate, *and/or*
 - known true allergy to aspirin (acetyl salicylic acid [ASA]; ie, has experienced urticaria, rash, severe difficulty breathing, asthma, nasal polyps, sinusitis/rhinitis);
4. The subject has received treatment with rheumatologic disease modifying agents or oral corticosteroids which has not been stable (defined as on the same medications for 3 months and on the same dosing regimen for 1 month prior to randomization; see Section 5.5.3);
5. The subject is receiving treatment with oral corticosteroids at a daily dose >20 mg prednisone or equivalent;
6. The subject requires and is receiving treatment with >325 mg aspirin/day;
7. The subject is currently taking or has a significant likelihood of requiring treatment during the study period with medication not permitted by the study protocol (See Sections 5.5.1 and 5.5.2), including warfarin or other coumadin anticoagulant or lithium;
8. The subject has a documented MI or stroke within 3 months prior to randomization;
9. The subject has undergone CABG surgery, or any major surgery (cardiac or noncardiac) within 3 months prior to randomization;
10. The subject has planned coronary (PCI or CABG), cerebrovascular (ie, carotid endarterectomy / PTA with or without stent) or peripheral (ie, peripheral arterial bypass, PTA or aortic aneurysm repair) revascularization at the time of study

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screening; in case of planned revascularization, the subject can be re-screened no sooner than 3 months after revascularization;

11. The subject has an unstable condition defined as any of the following:

a. Unstable angina (AHA/ACC definition) within 3 months prior to randomization

b. Uncontrolled hypertension (defined as systolic BP greater than 140 mmHg and/or diastolic BP greater than 90 mmHg at the Baseline visit; (See 7.3.2 Physical Exam and Vital Signs)

12. The subject has evidence of cardiac electrophysiologic instability including uncontrolled complex ventricular arrhythmia, uncontrolled atrial fibrillation or flutter, or uncontrolled supraventricular tachycardias within 3 months prior to randomization. The presence of an implantable defibrillator is not a contraindication to enrollment;

13. The subject has NYHA Class III or IV CHF or known left ventricular dysfunction with ejection fraction $\leq 35\%$;

14. The subject has been diagnosed with or has been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within 60 days prior to randomization;

15. The subject has a history of GI perforation, obstruction, or bleed within 6 months prior to randomization;

16. The subject has inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis, diverticulitis, diverticulosis with any known history of bleeding) or other known, active, significant GI, hepatic, renal or coagulation disorders.

17. The subject has an aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), or blood urea nitrogen (BUN) exceeding 2.0 times the upper limit of normal; creatinine exceeding 1.7 mg/dL (150 μ mol/L) in men or 1.5 mg/dl (133 μ mol/L) in women;

18. The subject has an active malignancy of any type. Subjects who have a history of basal cell or squamous cell carcinoma of the skin that has been successfully treated are eligible. Subjects with a history of other malignancies that have been successfully treated and who have no evidence of recurrence for at least 5 years before randomization are also eligible;

19. The subject has any medical (including known history of major hematological, renal, vascular, or hepatic abnormalities) or psychological / psychiatric condition (including documented unstable or uncontrolled alcoholism or drug abuse) or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and in the judgment of the investigator, would make the subject inappropriate for entry into this trial;

20. The subject has previously participated in this study or participated in any other clinical trial involving investigational or marketed products within 30 days prior to Screening;

21. The subject has ongoing litigation or compensation related to his/her overall arthritic condition including past or current long-term treatment with NSAID or

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COX-2 selective inhibitors.

Status:

Active enrollment

If you have any questions, please feel free to contact the coordinators, and they will be happy to answer any questions you have regarding this study.