82nd Meeting - Cardiovascular and Renal Drugs Advisory Committee

The 82nd meeting of the Cardiovascular and Renal Drugs Advisory Committee was called to order by the chairman, Dr. Milton Packer, at 8:40 a.m., October 23, 1997. The committee was convened to discuss "Basic Statistical Considerations for the Evaluation of Active Controlled Clinical Trials." Since this discussion was not regarding specific products or issues there was no conflict of interest for participants present.

Dr. Robert Fenichel, Deputy Director of the Division of Cardio-Renal Drug Products, presented some views about the conduct of active controlled trials. Positive controlled trials are conducted when it is not possible to conduct a placebo-controlled trial. Thoughts have been evolving about these trials and are currently centered on the conduct of "putative-placebo" trials. These trials differ from so called equivalence trials because they succeed when finding a difference from a corporator drug not when failing to show a difference from a corporator drug.

The conduct of these trials involves assumptions about the efficacy and the confidence intervals around the efficacy of the corporator agent. Dr. Rory Collins addressed some of the factors influencing the outcome of such trials and effecting the evaluation of efficacy. This would include endpoint selection (with composite endpoints sometimes obscuring equivalence), the magnitude of the effect, power needed to detect this effect, patient population studied, event rate, compliance and the comparator agent.

Generally, active-controlled trials need to be larger than placebo-controlled trials and are more difficult to conduct and interpret due to an added number of indirect steps. Dr. Collins recommended that add-on studies might be a better design to demonstrate the effectiveness of treatments.

Dr. DeMets concurred with the conclusion that superiority trials are difficult and that equivalence trials are even more challenging. It is of utmost importance to diminish noise in the so-called equivalence trial, particularly with respect to issues of non-compliance. Non-compliance dilutes whatever difference could be detected and could result in showing equivalence when if fact two therapies are not equivalent.

In general discussion, following the presentations, Dr. Temple addressed the question of the active control, saying that it would be necessary for an active control to have a demonstrated definable difference from placebo. The chairman summarized the conclusions regarding active controlled trials. When beating a corporator agent, analysis of these trials is similar to a standard placebo-controlled trial. However, the difficulty of achieving a claim of equivalence is substantially greater than previously perceived.

The committee adjourned open session at 12:00 p.m.. They met in closed session on the afternoon of October 23, 1997.

The committee reconvened in open session at 9:05 a.m., on October 24, 1997. The committee was to discuss NDA 20-839, Plavix, clopidogrel, Sanofi Pharmaceuticals, to be indicated for the prevention of vascular ischemic events in patients with a history of symptomatic atherosclerosis.

Full waivers have been granted to Drs. Milton Packer, Dan Roden, Lemuel Moye and Ralph D'Agostino. A copy of these waivers is available from the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. It is also disclosed for the record that Dr. Robert Califf and his employer, the Duke University Medical Center, have interests which do not constitute a financial interest within the meaning of 18 USC, but which could create the appearance of a conflict of interest. The Agency has determined, notwithstanding these involvements, that the interest of the government in Dr. Califf's participation outweighs that the integrity of the Agency's programs and operations may be questioned.

The meeting was opened for public comment. Rochelle Trujillo, the communications director for the National Stroke Association, spoke about the severity and prevalence of stroke, the third leading cause of death and leading cause of adult disability. They encourage development of agents that can reduce the frequency of second stroke and await the committee's considered recommendation for clopidogrel.

Dr. Donald Easton presented data from the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE), a large, single, pivotal, safety-efficacy study that comprises the majority of the clinical data in the NDA. This was a 199,185-patient, 304-center, international, randomized, triple-blind, parallel-group study comparing clopidogrel (75 mg daily) to aspirin (325 mg daily).

The patients randomized had recent histories of myocardial infarction (within 35 days): recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs: or objectively established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (range 1-3 years).

The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not) or other vascular event. In general, deaths not easily attributable to nonvascular causes were all classified as vascular.

Clopidogrel was associated with a lower incidence of outcome events of every kind. The overall risk reduction was 8.7%, P=0.045. Clopidogrel was also associated with somewhat lower rates of vascular deaths (3.6% vs 3.9%), all cause mortality (5.8% vs 6.0%); composite endpoints that counted all-cause mortality and all-cause vascular strokes instead of vascular mortality and ischemic strokes; and all types of non-first outcome events in patients who had survived an in-study stroke or myocardial infarction.

Efficacy of clopidogrel relative to aspirin was heterogeneous across the population studied (P=0.043). The relative benefits of clopidogrel appeared strongest in patients who were enrolled because of peripheral vascular disease and who had experienced myocardial infarction; weaker in other peripheral-vascular-disease patients; and weaker still in stroke patients.

Dr. Lloyd Fisher presented a theoretical comparison of clopidogrel vs. placebo. He used both historical controls and the Antiplatelet Trialist's Collaboration Meta-Analysis for his calculations. He said that clopidogrel clearly beat theoretical placebo. Dr. Fisher also addressed the variation in effect seen across qualifying subgroups. He concluded that from a statistical standpoint there was little evidence for qualitative interaction, if there is interaction it is more likely to be quantitative.

Dr. Alison Pilgrim continued on this topic. She said that the qualifying condition criteria was driven mainly by trial design; that there was considerable overlap in medical history between the subgroups and there was a greater convergence of treatment effects when the overall medical condition of the patients was taken into account. Superior efficacy of clopidogrel in the prevention of vascular events was both statistically significant and clinically meaningful.

At the conclusion of this presentation the committee began to answer questions that had been developed by the FDA. A copy of these questions is attached to theses minutes. Prior to question 1, Dr. Packer reminded the committee of FDA's introduction that "for clopidogrel to be approved the demonstration that it is superior to placebo must be as convincing as those which, in other clinical settings, have usually been provided by two or more successful trials . . . before permitting comparative claims in any drug's labeling, FDA has generally insisted on the evidentiary equivalent of two or more successful trials. Additionally, FDA has required that the comparator regimen has not been handicapped by inadequate dosage or other unfair burden. " Drs. Moye and Graboys left some absentee ballots which would be entered into the vote tally when appropriate.

In response to question 1, they voted 8-3 for 1(C), that the CAPRIE finding that aspirin appeared to be superior to aspirin was a plausible finding but weaker than that of typical successful trial. They voted 5-2A, 5-2B, 1-2C, that the heterogeneity of effect among the three enrollment groups (MI, stroke and PAD) was either attributable to chance or a plausible but weak finding. Questions 3 and 4 were omitted. The committee voted 10-1 that CAPRIE data could be meaningfully combined with data that compared aspirin to placebo.

With respect to the pooled aspirin/placebo trials, the committee voted 8-6E, 2-6C and 1-6D, that the finding that aspirin was superior to placebo was as persuasive as a package of two or more typical, successful trials. They voted 6-7B, 2-7A, 2-abstentions, aspirin being indistinguishable from placebo in the PAD group was a plausible finding but weakened by sample size.