DRAFT MINUTES

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

January 17 & 18, 2002

NDA 20-757/S-021, Avapro® (irbesartan), Sanofi-Synthelabo c/o Bristol-Myers Squibb), for the treatment of hypertensive patients with type 2 diabetic renal disease.

Questions to the committee were:

The Cardio-Renal Advisory Committee is asked to opine on the benefits and risks of irbesartan, an angiotensin II receptor antagonist, for the treatment of nephropathy in type 2 diabetes. Reviews of chemistry, pharmacology, toxicology, biopharmaceutics, biometrics, and clinical safety present no apparent barriers to its approval.

The Committee is asked if it believes the strength of evidence for a treatment benefit supports approval.

The direct evidence is derived from two studies. IDNT enrolled 1715 subjects with type 2 diabetes, hypertension, proteinuria >900 mg/d, and serum creatinine between 1 and 3 mg/dL. Subjects were randomized to placebo, amlodipine 10 mg, or irbesartan 300 mg and followed for a mean of about 2 years. The primary end point was a time to first event comparison of irbesartan and placebo for death, end stage renal disease, or doubling of serum creatinine. The result was an estimated risk reduction of 20% (p=0.023), with treatment groups diverging only after about 18 months.

1. There were 411 total end point events in the placebo and irbesartan groups, 33 fewer in the irbesartan group than on placebo. One of the characteristics of a none-too-small p-value is that the result is sensitive to the handling of subjects with incomplete data.
   - 1.1 Sixteen subjects (8 on placebo or irbesartan) never received any treatment.
     - 1.1.1 How were they handled?
     - 1.1.2 How should they have been handled?
   - 1.2 Four hundred and eight subjects (275 on placebo or irbesaztan) discontinued study drug.
     - 1.2.1 How were they handled?
     - 1.2.2 How should they have been handled?
   - 1.3 Nineteen subjects (13 on placebo or irbesartan) were lost to follow-up. Mortal status is known for 11/19 (7/13 on placebo or irbesartan).
     - 1.3.1 How were they handled?
     - 1.3.2 How should they have been handled?
   - 1.4 Two placebo group subjects (see page 28 of MOR) were credited with end point events for near-doubling of serum creatinine.
     - 1.4.1 How were they handled?
     - 1.4.2 How should they have been handled?
     - 1.4.3 How many other neaz-doubling events were *not* counted as events?
   - 1.5 In summary, what effect have the sponsor's rules for handling these situations on the credibility of the principal finding?

   See *discussion in the transcripts.*

2. Of the 411 primary end point events on placebo or irbesartan, 58% were creatinine elevation and 42% were death or need for dialysis. All of the apparent treatment benefit was the effect on creatinine.
   2.1 Was this a statistical anomaly?
   2.2 Was this because there were just so few clinical outcome events?
   2.3 Was this because the effects on clinical outcome would not be expected over 57 months of follow-up?
   2.4 Was this because an effect on serum creatinine is a or predictor of clinical outcome? 2.5 Subjects who experienced doubling of serum creatinine could later have end-stage renal disease or die. When these events are counted, the relative risk of death on irbesartan was 0.92 (95% CI 0.69-1.23) and the risk of needing dialysis was 0.80 (95% CI 0.59-1.10). Are these data supportive of an effect on clinical outcome?

See discussion in the transcripts.

3. Irbesartan reduced the composite event rate compared with amlodipine by 23%. 3.1 Considering the low nominal p-value (0.006), is this as good as a second study? 3.2 This p-value is smaller than for the comparison between irbesartan and placebo because amlodipine did worse than placebo. How does that confirm a benefit of irbesartan?

See discussion in the transcripts.

4. Comment on other secondary end points in IDNT.
   4.1 There was a prespecified analysis of time to first cardiovascular death, non-fatal MI, CHF hospitalization, disabling stroke, or amputation. There were 416 such events, with no significant difference in the distribution among groups.
      4.1.1 Is this further evidence of a lack of clinical benefit?
      4.1.2 Is it comforting that there is a lack of apparent harm?
      4.1.3 Were there simply too few events to show a meaningful effect?
   4.2 There was a prespecified analysis of time to first cardiovascular death, non-fatal MI, coronary revascularization, CHF hospitalization, need for ACE inhibitor or ARB for heart failure, disabling stroke, amputation, or peripheral revascularization. There were 518 such events, with no significant difference in the distribution among groups.
      4.2.1 Is this further evidence of a lack of clinical benefit?
      4.2.2 Is it comforting that there is a lack of apparent harm?
      4.2.3 Were there simply too few events to show a meaningful effect?

See discussion in the transcripts.

5. Are the results of IDNT *alone an* adequate basis for approval of irbesartan for the treatment of type-2 diabetic nephropathy?

The committee vote was 11 NO.

IRMA-2 randomized 611 subjects with type 2 diabetes and microalbuminuria (28 to 288 mg/day) to placebo or irbesartan 150 or 300 mg for 2 years. The primary end point was time to progression to overt proteinuria (>300 mg/day) and the analysis plan compared each active arm to placebo. The results ordered by dose, but only the 300-mg dose group was statistically significantly different from placebo.

6. Comment on the handling and implications of premature withdrawal of 166 subjects (27%).

See discussion in the transcripts.

7. There was a trend toward *a greater* increase in the rate of change in serum creatinine on irbesartan than on placebo. Comment on the hypothesized relationship between proteinuria and renal function as evidenced by creatinine clearance.

See discussion in the transcripts.

8. A 133-subject subgroup was randomized to have GFR measured at 3 months, at the end of active treatments, and then 4 weeks after the last dose. At month 3 and at the end of active treatment, there were no statistically significant differences in GFR between placebo and either dose of irbesartan. Four weeks after the last dose, GFR *increased* in all 3 treatment groups; differences from placebo were again statistically non-significant. Comment on the hypothesized relationship between proteinuria and renal function as evidenced by GFR.

See discussion in the transcripts.

9. Are the results of IDNT *plus IRMA-2 an* adequate basis for approval of irbesartan for the treatment of type-2 diabetic nephropathy?

The committee vote was 1 YES and 10 NO.

A drug with a related mechanism of action, captopril, has an indication for diabetic nephropathy in patients with type 1 diabetes. The primary basis of that approval was the demonstration, in a 409-subject, 2-year study, of 51% reduction (p=0.004) in risk of doubling serum creatinine, and a 50% reduction (p=0.006) in risk of mortality or end-stage renal disease. Both effects were manifest in the first few months of treatment. Captopril also reduces the progression for microalbuminuria to overt proteinuria.

10. Are the results with captopril germane to a discussion of irbesartan? In particular...
    10.1 ... is nephropathy in type 1 diabetes enough like nephropathy in type 2 diabetes?
    10.2 ...are the phamarmacological effects of captopril and irbesartan adequately similar?

The committee vote was 9 YES and 2 NO.

11. If the results with captopril are relevant to irbesartan...
    11.1 ... are the results on protein excretion similar with respect to direction and magnitude for captopril and irbesartan?
    11.2 ... are the results on doubling of creatinine similar with respect to direction and magnitude for captopril and irbesartan?
    11.3 ... are the results on death or ESRD similar with respect to direction and magnitude for captopril and irbesartan?

See discussion in the transcripts.

12. Are the results of IDNT, IRMA-2, *and prior expectations derived from the captopril database an* adequate basis for approval of irbesartan for the treatment of type-2 diabetic nephropathy?

The committee vote was 4 YES and 7 NO.

13. Are there results from other development programs that impact on approval of irbesartan for the treatment of type-2 diabetic nephropathy?

See discussion in the transcripts.

14. Should irbesartan be approved for the treatment of nephropathy in type 2

diabetes? *The committee vote was 5 YES and 6 NO.*

15. Do the results of the irbesartan development program in type 2 diabetic nephropathy support the use of proteinuria as a surrogate for clinical benefit?

The committee vote was 1 YES, 8 NO, and 2 ABSTAIN.

On January 18, the committee discussed:

the risk of death, nonfatal myocardial infarction, myocardial revascularization procedures, and ischemic stroke in patients with clinically evident coronary heart disease.

Questions to the committee were:

The Cardio-Renal Advisory Committee is asked to opine on the benefits and risks of a fixed-dose combination product consisting of pravastatin and aspirin for use in patients who are prescribed these two products as individual entities. It is common knowledge that FDA will accept applications for fixed-dose combination products when 2 (or more) approved drugs are commonly prescribed together, for convenience (and perhaps for better compliance).

In discussions of such products, we have said that availability of such convenience formulations should not alter health care provider's prescribing practices (e.g. by not providing a full range of useful doses). Generally that means that a full range of dosing strengths of each individual entity should be available for the combination product, thereby providing convenience but not influencing selection of doses or dosing regimens of individual entities.

Further, the Division has asserted that it should be well established that both entities should be taken concomitantly, since the existence of a fixed-dose combination product implies that they **should** be taken together not just that they **can** be taken together. Generally speaking, the Division has required for fixed dose combination antihypertensive products that the effects of the combination (A + B) be greater than the effects of either one one (A or B). Moreover, the effects of several doses of A in combination with several doses B be evaluated (often in a factorial trial) so that some description of the use of A+B can be compared with either A or B alone.

The sponsor has chosen a single dose of pravastatin (40 mg) and two doses of buffered aspirin (81 and 325 mg) to combine. Thus there will be two formulations of the fixed-dose combination marketed, 40 mg pravastatin/81 mg buffered aspirin and 40 mg pravastatin/325 mg buffered aspirin. Although initial marketing will be accomplished by co-packaging, formulations of fixed-dose combinations have been prepared and are awaiting completion of stability studies. The fixed-dose combinations will be marketed as soon as data are available. Although the application is for a co-packaged product, the Advisory Committee is asked to consider the issue the same as that of marketing of a fixed-dose combination product.

Pravastatin is approved for use in a) Primary Prevention in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of coronary heart disease, and other risk factors, b) Secondary Prevention of cardiovascular events, total mortality and stroke, and c) for the treatment of Hyperlipidemia.

Aspirin is for use in the following patient populations: a) Secondary Prevention of death and stroke in patients who have had Transient Ischemic Attacks, or stroke (all CNS indications related to thrombotic events), b) Secondary Prevention in patients who have survived a myocardial infarction, and c) patients who are suspected of having an acute myocardial infarction, patients with unstable angina, and patients who are having revascularization procedures (coronary or carotid) who have underlying occlusive vascular disease. Aspirin is given for life, according to the dosing and administration section for patients who have had unstable angina or PICA.

1.0 Can you define a patient population for whom pravastatin plus buffered aspirin would be indicated?

1.1 If yes, please define the population; this would be the population named in the indications section for the combination product.

1.2 Are there patient populations where there might be net harm from giving both pravastatin and buffered aspirin together?

1.2.1 If so, please define some of these populations.

See discussion in the transcripts.

2.0 There are no data from any trial prospectively-designed to test the hypothesis that pravastatin (at any dose) **plus** buffered aspirin (at any dose) produced a better clinical outcome (measured by any clinical end-point) than either pravastatin or buffered aspirin **alone.**

2.1 Is that sufficient reason to **cease** consideration of approval of the fixed dose combination product? In other words, is it necessary to have the results of specifically designed controlled clinical trials to consider approval of this fixed dose combination product?

2.2 If not, what might be sufficient?

See discussion in the transcripts.

3.0 One could argue that, for the patient population you have defined, since the purported mechanisms of action for the demonstrated clinical benefit of each agent are very different (something to do with lipids for pravastatin and something to do with platelets for aspirin), showing that there were no important pharmacokinetic or pharmacodynamic interactions (using surrogates) would be an adequate basis for approval of the fixed dose combination product.

3.1 Do you agree with this? If so,

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3.1.1 Are there sufficient data present to support the presence of or lack of significant pharmacokinetic interaction?

3.1.2 Are there sufficient data present to support the presence of or lack of significant pharmacodynamic drug interaction?

The committee vote was unanimous NO.

4.0 The sponsor has provided 3 different meta-analyses (data from 5 placebo-controlled trials, the total number of randomized patients being 14,617) that address whether or not administration of pravastatin **plus** buffered aspirin has a greater effect than either buffered aspirin or pravastatin alone. Some of the selected trials required that patients have greater than normal levels of serum cholesterol; others did not.

4.1 Do these 14,617 randomized patients represent a reasonable approximation of the patients for whom this combination product would be indicated?

4.2 From the results of the meta-analyses, do you conclude that the data show that pravastatin **plus** buffered aspirin has a greater effect than either buffered aspirin or pravastatin alone;

4.2.1 Using as a standard of 2 trials at a $p < 0.05$, is the strength of evidence from the meta-analyis as strong as this standard?

4.2.2 Using as a standard of one trial at a $p < 0.05$, is the strength of evidence from the meta-analysis as strong as this standard?

4.3 Which of the models offered by the sponsor (Cox Proportional Hazard, Bayesian hierarchical Cox proportional hazards, or Model 3) is most supportive, are they all equally supportive, or are they equally non-supportive?

See discussion in the transcripts.

5.0 Upon what basis was the dose of buffered aspirin chosen, for use in the fixed-dose combination product?

5.1 Do you considef this reasonable?

5.2 What alternative doses can you recommend?

5.3 Should one wait, prior to approval, on settling the question of buffered aspirin dose?

See discussion in the transcripts.

6.0 Upon what basis was the dose of pravastatin chosen, for use in the fixed-dose combination product?

- 6.1 Do you consider this reasonable?
- 6.2 What alternatives can you recommend?
- 6.3 Should one wait, prior to approval, on settling the question of pravastatin dose?

See discussion in the transcripts.

7.0 Assuming that you have concluded something about the strength of evidence that pravastatin and buffered aspirin should be taken together and that the doses to be available in the fixed- dose combination product are appropriate, what is the strength of evidence that a fixed-dose combination product (taking a single pill), has increased clinical benefit with respect to taking two pills (not necessarily together)?

- 7.1 Should we require better demonstration of additional benefit provided by "convenience"?
- 7.2 at kind of demonstration would be better?

See discussion in the transcripts.

8.0 How likely is it that the availability of the fixed dose combination product would encourage:

- 8.1 Inappropriate use of buffered aspirin for primary prevention?
- 8.2 Inappropriate use of a dose of 40 mg pravastatin?
- 8.3 Inappropriate use of a dose of 325 mg buffered aspirin?
- 8.4 Inappropriate use of a dose of 81 mg buffered aspirin?

See discussion in the transcripts.

9.0 Do you recommend approval of the fixed-dose combination of product of pravastatin plus buffered aspirin?

The committee vote was I YES, 7 NO, and I ABSTAIN.

The following question was added: If a broader range of pravastatin were available, how would you vote? The committee vote was 3 YES, 5 NO, and /ABSTAIN.