# Questions

Irbesartan

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

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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 irbesartan) 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 near-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?

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 poor 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?

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?

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?

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

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%).

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.

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.

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

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?

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?

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?

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

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

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?