CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019766/S027

MEDICAL REVIEW(S)

Medical Officer's Review
NDA 19-766/S-027
ZOCOR (simvastatin) tablets
Merck
Date of submission: August 12, 1997
Date of review: February 28, 1998
Materials reviewed
Proposed changes in labeling based on cerebrovascular disease outcome results of 4S

Introduction
The inclusion in labeling of a discussion of the cerebrovascular disease (CVD) outcome data from 4S was originally proposed by the sponsor in S-017. Proposed at that time was a brief summary statement in the Clinical Pharmacology section followed by a disclaimer, the gist of which was that prospective trials were needed to confirm the cited results of a post-hoc analysis of the trial data. In light of that position by the sponsor, the proposed changes to labeling were not approved. This was based in large part on the rather straightforward rationale that an efficacy result that must be so qualified clearly does not meet the standard of evidence for inclusion in labeling.

The current application proposes a discussion, without qualification, of the CVD event data in Clinical Pharmacology as well as a new indication to "Reduce the risk of stroke and transient ischemic attacks." The sponsor argues that the analyses are not really *post-hoc*. That is, fatal and hospital-verified non-fatal CVD events did constitute part of the combined tertiary endpoint of the trial. Ascertainment of CVD events was thus prospectively planned, and the approach to the adjudication of CVD events by the Endpoints Classification Committee (ECC) was delineated in the endpoint definition document for 4S. The relevant excerpts from these documents are included in the current application. In addition, at the request of this reviewer, the sponsor has also submitted a 4S blank case report form for cerebrovascular disease events. Insofar as this is clearly not a case of post-hoc "data dredging," the issue that must be resolved in coming to a decision on this application is whether the results for a tertiary endpoint of such a trial should support an indication. In such a trial, where all the disease endpoints share a common pathogenesis, the secondary and tertiary endpoint outcomes, if consistent with the primary endpoint results, serve to validate, internally, those primary trial results, and *vice versa*. Such is the case here.

Overview of 4S
Objective
The primary objective of the trial was to evaluate the effect of simvastatin therapy on overall mortality in patients with CHD and hypercholesterolemia.

General design
This was a clinical trial in which 4444 men and women, , with a previous MI (80%) or angina alone (20%), and total cholesterol (average LDL-C 192 m/dL) were randomized to treatment with either simvastatin or matching placebo.

Simvastatin dosage was titrated from the starting dose of 20 mg in order to reduce total-C to goal of . For each simvastatin patient that was titrated up or down, a matching placebo patient had an "adjustment" of his dose, in order to maintain the blind. The median follow up was 5.4 years.

Endpoints

For the purposes of this review, only those aspects of the protocol relevant to the proposed changes in labeling will be addressed.

In the current submission, the sponsor has provided excerpts from several 4S documents. These support the contention that, while the study was not designed primarily to investigate the effects of simvastatin therapy on CVD event rates, nevertheless, the implementation of the trial clearly involved ascertainment, recording, and adjudication of these events, definitions of which were provided in the protocol. Excerpts from the protocol follow:

MK-733 protocol dated March 1994

"Tertiary objectives 1) To investigate whether chronic treatment with simvastatin in patients with coronary heart disease (CHD) and hypercholesterolemia will reduce the incidence of hospitalization because of acute events ascribed to CHD, cerebrovascular disease, or other atherosclerotic diseases."

MK-733 protocol dated March 1994, excerpt from Appendix 5, Data Analysis Plan

This contains a similar statement to that above regarding the tertiary objectives. In addition, it addresses the role of the ECC with specific regard to the adjudication of suspected MIs and causes of death, including cerebrovascular disease related. Finally, it addresses the data analysis plan regarding the various endpoints, including "atherosclerosis-related event-free survival," which was to include cerebrovascular disease events.

Endpoint definition document dated 26 August 1994

This document is entitled "4S Endpoints: Definitions, criteria for events, data collection and classification procedures." Again, CVD events are included in the tertiary endpoint definition. In addition, cerebrovascular disease death, subdivided into non-embolic and embolic infarction, intracerebral hemorrhage, unclassified stroke, and subarachnoid hemorrhage is listed as a primary endpoint event category. The same five subcategories with the addition of TIA are listed for the tertiary endpoint category of non-fatal, hospital-verified, acute cerebrovascular disease events. The procedures and practical arrangements for data collection and events classification are described in the endpoint definition document and include a discussion of the use of the reporting forms for fatal and non-fatal events, as well as the use of hospital records, autopsy reports, police records, and information obtained from relatives and witnesses. As an aside, the sponsor has provided the reviewer with a copy of the case report form for cerebrovascular disease events (CRF E3). While the primary focus of the endpoint definition document is on CHD event definitions and classification, nevertheless, it is clear that information on cerebrovascular

disease-related events was to be collected for the purposes of analyses, albeit (at least for the non-fatal events) as a non-primary endpoint of the trial.

Disposition/Implementation

This trial accomplished ascertainment of vital and clinical status at trial closure for all of the randomized patients. Dropout rates were constant for the period of follow up and approximately equal in the two treatment groups.

Results

The original 4S CVD event data analyses combining fatal and non-fatal events were in error as a result of a typographical error in programming. Corrections were submitted to FDA on January 31, 1997. The error resulted in the combination of "nonfatal CVD events" with "fatal other cardiovascular events" rather than with "fatal CVD events." This resulted in an additional 5 patients with events in the simvastatin group and an additional 4 patients with events in the placebo group.

The following table is reproduced from the submission and summarizes the revised data.

Summary table of fatal and non-fatal cerebrovascular events: All patients

		Simvastatin N=2221		Placebo N=2223	
		Events	Patients	Events	Patients
Primary: CVD deaths					
	intervention	3	3	2	2
	non-embolic	3	3	3	3
	embolic	0	0	2	2
	intracereb hem	4	4	1	1
	unclassif stroke	3	3	4	4
	subarach hem	1	1	0	0
Primary subtotal		14	14	12	12
Tertiary: NF CVD events					
	intervention	3	3	10	10
	non-embolic	17	16	33	33
	embolic	13	13	16	16
	intracereb hem	0	0	2	2
	unclassif stroke	14	14	12	12
	subarach hem	1	1	1	1
	TIA	19	19	31	29
Tertiary subtotal		67	61	105	95
TOTAL		81	75	117	102

In this table, patients experiencing more than one non-fatal event are counted only once in the tertiary subtotal, and patients experiencing one or more nonfatal events followed by a fatal CVD event are likewise counted only once in the overall total. As such, the overall totals are not always the sums of the primary and tertiary subtotals.

The crude rates of patients affected follow:
simvastatin 75/2221 3.4%
placebo 102/2223 4.6%

relative risk (95%CI) 0.723 (0.537, 0.975)
P= 0.033

Discussion

This was a well-conducted trial. The data integrity in 4S were confirmed at the time of the original review on the basis of clinical records inspections by the Division of Scientific Investigations. The ascertainment of cerebrovascular disease events was prospectively planned as a component of this clinical investigation. The protocol contained definitions for fatal and non-fatal CVD events and provided for adjudication of these events by the ECC as part of the original data analysis. Finally, this trial accomplished 100% ascertainment of vital and clinical status at closure. The data regarding CVD events, therefore, would appear to be as reliable as those for the overall primary and secondary endpoints of the study. The analysis of the effect of simvastatin therapy on CVD events is not an example of *post-hoc* data dredging.

A meta-analysis of 16 statin trials, in primary and secondary prevention, involving approximately 29,000 patients followed for an average of 3.3 years, and including 4S, has recently been published (**Hebert, PR, et. al., JAMA 1997;278:313-321**). With a total of 454 strokes, it confirms the stroke outcomes from the individual large-scale trials (4S, CARE, WOSCOPS) by showing a 29% reduction in risk of stroke (fatal and non-fatal) among the statin-treated groups. This is significant particularly in light of the lack of a clear relationship, based on epidemiological data, between cholesterol levels and stroke incidence. Based on the finding that in these interventional trials risk reduction for stroke and MI parallel each other and because of the known increase in risk for stroke post-MI (perhaps due to cerebral embolism of cardiac mural thrombi), the authors suggest that reducing the incidence of MI thus reduces the risk of embolic stroke. An alternative or additional mechanism is that statin therapy ameliorates atherosclerosis and endothelial function in the extracranial arteries as it does in the coronaries.

It is also worth pointing out that although the numbers were small, there was a small increase in the incidence of fatal strokes seen across the 16 trials. This is perhaps significant in light of epidemiologic evidence of an association between lower cholesterol levels and hemorrhagic strokes, which constitute the majority of fatal strokes. Although the data are inadequate to reach any firm conclusions, it is therefore reasonable to hypothesize that the overall reduction in stroke risk in the statin groups is due to a favorable impact on the majority non-fatal events but counterbalanced by an increased incidence of relatively rare fatal hemorrhagic strokes.

Conclusion

In 4S, simvastatin therapy was associated with a statistically significant reduction in risk for combined stroke (non-fatal plus fatal) and TIA relative to placebo. This finding is supported by a meta-analysis of 16 statins trials and likewise consistent with the data from CARE and WOSCOPS.

APPEARS THIS WAY
ON ORIGINAL

Labeling review

Clinical Pharmacology, Clinical Studies

The sentence describing the 4S CVD event outcome should read as follows:

Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 patients vs. 102 patients).

APPEARS THIS WAY
ON ORIGINAL

Indications and Usage

The sponsor proposes to eliminate the first sentence of the section to eliminate redundancy. This sentence reads: "Therapy with lipid altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia."

I do not consider this to be redundant. However, in light of recent clinical trial evidence, I think it should be replaced with the following, all by way of conveying the first principle of the use of lipid altering agents.

Therapy with lipid-altering agents should be considered 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.

Coronary Heart Disease

The new bulleted indication based on the 4S CVD data should read as follows:

- Reduce the risk of stroke or transient ischemic attack

APPEARS THIS WAY
ON ORIGINAL

Recommendation

Contingent on the changes to proposed labeling above, this supplement may be approved.

APPEARS THIS WAY
ON ORIGINAL

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DMEDP/CDER/FDA

/S/ 3-24-98

Recommendation code: AE

cc:
NDA 19-766 Arch
HFD-510
HFD-510 Sobel/Orloff/Simoneau

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