

# Circulatory System Devices Panel Questions for Discussion

## Cordis CHECKMATE™ System P990036

June 19, 2000

### Evaluation of Safety and Effectiveness

#### Question #1

A composite clinical endpoint consisting of death, Q-wave and non-Q-wave myocardial infarction (MI) and target lesion revascularization (TLR) at 270-days post procedure was the primary endpoint for the pivotal GAMMA-I study. This composite endpoint of major adverse cardiac events is commonly referred to as MACE.

**Q: The definitions for myocardial infarction and target lesion revascularization in the GAMMA-I trial are provided on pages 0005-0298 and 0005-0299. Please discuss whether you believe these definitions are adequate to assess the clinical performance of the device.**

---

---

#### Question #2

In the GAMMA-I Study, patients were scheduled to complete angiographic follow-up at 6 months and clinical follow-up at 9 months. FDA infers from information provided by the sponsor on page 0005-0733 that all patients completed clinical follow-up preceding angiographic follow-up at 6 months.

**Q: Please discuss whether you believe any conclusions can be reached regarding patient outcome at 9 months since it appears that patients completed both angiographic and clinical follow-up at 6 months.**

---

---

**Question #3**

Late total occlusion was observed at a higher rate in the treatment arm of the GAMMA-I trial. Late total occlusions were comprised of late stent thrombosis leading to MI or asymptomatic total occlusions. Although stent thrombosis has previously been recognized as an acute adverse event occurring < 30 days post stent implantation, the GAMMA-I study showed that the incidence of late stent thrombosis (>30 days) was higher in the treatment arm compared to the placebo arm. Please reference pages 0005-0094 through 0005-0096 of pack for thrombosis/occlusion definitions and results as you address the following questions:

**Q: Please discuss which definitions of [late] thrombosis and occlusion are adequate to assess the clinical performance of the device.**

**Q: Please discuss whether the definitions employed by the sponsor are clinically meaningful and whether they adequately differentiate late stent thrombosis from late total occlusion.**

---

---

**Question #4**

Intracoronary radiation may stimulate neointimal hyperplasia at the lesion edge. This phenomenon has been termed the "edge effect." In the GAMMA-I report, edge effect is defined as the in-lesion restenosis rate minus the in-stent restenosis rate. Information on edge effect is located on pages 0005-0727 through 0005-0732 and 0005-0773 through 0005-0822 of the panel pack.

**Q: Please discuss the adequacy of the sponsor's definition and methodology used to quantify edge effect.**

---

---

**Question #5**

The sponsor provided a retrospective analysis in November 1999 that contained pooled data for patients from SCRIPPS-I, GAMMA-I and WRIST studies with native coronary artery in-stent restenosis who did not receive an additional stent. The sponsor has proposed the hypothesis that additional stenting is a risk factor for late stent thrombosis and should be avoided. The sponsor has also provided preliminary information from the SCRIPPS-III and WRIST-Plus studies regarding the effect of extended antiplatelet therapy on the late stent thrombosis rate in patients treated with intravascular radiation with and without placement of an additional stent. The sponsor has proposed the following boxed warning in the labeling based on the above analyses:

**WARNING:**

**Placement of a new stent during the radiation procedure has been associated with a higher rate of late thrombosis in comparison to the placebo arm. Every attempt should be made to avoid new stent placement in the irradiated area. However, if placement of a new stent was necessary, it is recommended that the patient be placed on antiplatelet therapy for 12 months.**

**Q: Please discuss whether the study data and analyses provided support the information contained in this warning.**

**Q: Please comment on whether any other information should be included in the labeling regarding late thrombosis.**

---

**Question #6**

A statistically significant reduction in MACE was demonstrated for the active treatment arm compared to placebo [28.2% vs.43.8%, respectively] as reported in the non-hierarchical analysis of complications in Table 11 [page 0005-0320] of panel pack. This reduction in MACE was principally driven by the lower TLR rate in the treatment arm [24.4% vs. 42.1%] given that the rates of death [3.1% vs. 0.8%] and MI [12.2% vs. 6.6%] were higher in the treatment arm. Also, as discussed above, other secondary safety measures such as late total occlusion, late stent thrombosis, and edge effect occurred at a higher rate in the radiation treatment arm compared to placebo.

**Q: Please discuss whether you believe the probable clinical benefit of the radiation treatment (i.e., reduction in TLR) outweighs the probable risks of death, MI, late total occlusion, late stent thrombosis, and edge effect posed by the device in the intended patient population.**

---

## **Product Labeling**

### **Question #7**

One aspect of the premarketing evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the products potential adverse events, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling:

**Q: Please comment on the INDICATIONS FOR USE section as to whether they identify the appropriate patient population for treatment with the device.**

**Q: Please comment on the CONTRAINDICATIONS section as to whether it identifies all conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.**

**Q: Please comment on the WARNINGS and PRECAUTIONS sections as to whether it identifies all potential hazards regarding device use.**

**Q: Please comment on the remainder of the product labeling as to whether it adequately describes how the product should be used to maximize benefits and minimize adverse events (e.g., late thrombosis, late occlusion, edge effects).**

**Q: Does the panel have any other recommendations regarding the labeling of the device?**

---

---

## **Training Program**

### **Question #8**

Use of the Cordis CHECKMATE™ System during the investigational studies required the collaboration of a cardiologist, radiation oncologist, and radiation physicist.

**Q: Please discuss what important elements should be contained in a physicians' training program for this product.**

---

## Post-Market Evaluation

### Question #9

Published literature on radiation-induced heart disease is primarily related to late effects on normal tissue in which the heart is irradiated as part of the treatment of intrathoracic neoplasms. There is generally a long latent period between the index treatment and the development of coronary artery disease.

**Q: Based on the literature, do you believe that additional clinical follow-up is necessary to evaluate the chronic effects of intravascular radiation administration? If so, how long should patients be followed and what endpoints and adverse events should be measured?**

---