

FDA SUMMARY

Cordis Checkmate™ System
Cordis Corporation
P990036

FDA SUMMARY

- FDA Review Team
- Nonclinical Evaluation
- Clinical Evaluation

FDA Review Team

Office	Individuals
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Nonclinical Evaluation

Nonclinical Evaluation

- *In Vitro* testing
- Biocompatibility testing
- *In Vivo* (Animal) testing
- Source dosimetry

Clinical Evaluation

Clinical Data Provided in Panel Pack

- SCRIPPS-I
- GAMMA-I
- WRIST
- SCRIPPS-III
- WRIST Plus
- Pooled Analysis

SCRIPPS-I Study

- Feasibility study
- 60 patients enrolled
- Stratified randomization in 8 subgroups:
 - Lesion length in mm (<15, >15 and ≤ 30)
 - Type of restenosis (instent, S/P PTCA)
 - Type of vessel (native, SVG)
- IVUS based dose prescription

SCRIPPS-I Study

- Clinical and angiographic follow-up at 4-6 months
- 2 cases of stent thrombosis
 - 17 and 39 days post-procedure
- Post-procedure anticoagulation
 - Initially 14 days
 - Extended to 8 weeks

SCRIPPS-I Report

- **Outstanding Issues**
 - Poolability of data across 8 subgroups
 - Interpretation of pooled analysis of 6-month and 3-year angiograms

GAMMA-I Study

- **Pivotal study**
- **252 patients enrolled**
- **Enrollment limited to instent restenosis**
- **Lesion lengths evaluated (mm)**
 - ≤ 15 , > 15 and ≤ 30 , > 30 and ≤ 45

GAMMA-I Study

- **Angiographic follow-up at 6 months**
- **Clinical follow-up at 9 months**
- **IVUS based dose prescription**
- **Post-procedure anticoagulation**
 - 8 weeks duration

GAMMA-I Study

- **Primary study endpoint**
 - **Composite clinical endpoint at 9-months**
 - **Death**
 - **Myocardial infarction (MI)**
 - **Q-wave and non-Q-wave**
 - **Target lesion revascularization (TLR)**

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GAMMA-I Report

- **Modified definitions**
 - **Myocardial Infarction**
 - **Target lesion revascularization**
- **Clinical follow-up preceded angiographic follow-up at 6-months**

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Definitions of Myocardial Infarction

- **Original definition**
 - **Clinical symptoms**
 - **EKG changes**
 - **Enzyme changes**
- **Modified definition**
 - **EKG changes**
 - **Enzyme changes**

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Definition of TLR

Clinically-Driven

- Positive functional study in the distribution of the target vessel
- Ischemic symptoms at rest in the distribution of the target vessel
- Ischemic symptoms with an in-lesion diameter stenosis $\geq 50\%$ by quantitative coronary angiography (QCA)
- No ischemic symptoms with an in-lesion diameter stenosis $\geq 70\%$ by QCA

Definition of TLR

Non-clinically Driven

- Non-emergent revascularization for a diameter stenosis $\leq 50\%$ by QCA
- Non-emergent TLR for a diameter stenosis $< 70\%$ by QCA without either a positive functional study or angina

Composite Clinical Endpoints

- Group of individual clinical endpoints that form a single clinical endpoint
- Factors contributing to use:
 - Statistical
 - Evaluation of one or more nonfatal clinical endpoints in addition to mortality
 - Broader view of net clinical benefit

Composite Clinical Endpoints

- Major Adverse Cardiac Event (MACE) rate typically incorporates:
 - Death
 - MI
 - TLR
- Commonly used in evaluating investigational device studies

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Limitations of Composite Clinical Endpoints

- May be under-powered to allow statistical evaluation of individual study endpoints
- Uniform weighting of individual clinical endpoints does not take into account differences in patient outcome
- Statistical significance can be achieved for the composite event rate with discordant changes in individual clinical event rates

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Evaluation of Safety and Effectiveness

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**Evaluation of Effectiveness
GAMMA-I Study**

	Treatment Arm	Control Arm
MACE	28.2%	43.8%
Death	3.1%	0.8%
MI	11.7%	5.8%
TLR	24.4%	42.1%

Clinical follow-up at 9 months

Evaluation of Safety: GAMMA-I Study

Evaluation of Individual Study Endpoints

- Death
- Myocardial infarction
- Late total occlusion
- Late stent thrombosis
- Edge effect

Late Total Occlusion

- Multiple definitions
- Symptomatic
 - Late stent thrombosis
- Asymptomatic
- Differentiation from late stent thrombosis

Late Stent Thrombosis

- Multiple definitions
- Concerns
 - Establish definition
 - Capture clinical events
 - Identification and evaluation of risk factors

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Late Stent Thrombosis

- Current definition excludes Patient 57 in SCRIPPS-I Study
- Stent thrombosis demonstrated on surgical pathology
- Surgical pathology considered "gold standard"

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Edge Effect: GAMMA-I Study

Restenosis Rate	Treatment Arm	Control Arm
In-lesion	32.4%	55.3%
In-stent	21.6%	50.5%
Edge effect	10.8%	4.8%

Angiographic follow-up at 6 months

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Summary of Safety: GAMMA-I Study

	Treatment Arm	Control Arm
Death	3.1%	0.8%
Myocardial infarction	12.2%	6.6%
Late total occlusion	11.7%	5.8%
Late stent thrombosis	6.1%	0.0%
Edge effect	10.8%	4.8%

Summary of Clinical Benefit versus Risk: GAMMA-I Study

	Treatment Arm	Control Arm
MACE	28.2%	43.8%
TLR	24.4%	42.1%
Death	3.1%	0.8%
Myocardial infarction	12.2%	6.6%
Late total Occlusion	11.7%	5.8%
Late stent thrombosis	6.1%	0.0%
Edge effect	10.8%	4.8%

Panel Questions

Panel Question 1

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.

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Panel Question 2

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.

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Panel Question 3

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

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

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Panel Question 4

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

Panel Question 5

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.

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

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

Panel Question 6

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.

Panel Question 7

Please comment on the **INDICATIONS FOR USE** section as to whether it identifies the appropriate patient population for treatment with the device.

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.

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Panel Question 7 (cont.)

Please comment on the **WARNINGS** and **PRECAUTIONS** sections as to whether they identify all potential hazards regarding device use.

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).

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

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Panel Question 8

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

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

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Panel Question 9

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?
