ANNEXURE: 05 **AF/IEC/05/08/V-8.3**

Guide to Placebo Justification

Name of the PI:

Protocol Version and Date:

IEC meeting Date:

Background conditions, such as benefits of standard treatment, risk of using placebo, risk management and disclosure should be considered. The followings are some guides to ease Board decision.

I. Benefits of standard treatment (Yes/No)

1) Is there a standard treatment?
2) Is the standard treatment widely accepted?
3) Has the efficacy of the treatment been consistently proven?
4) Are all newly diagnosed patients with this condition put in standard treatment (versus observed or other)?
5) Does the treatment act on the basic mechanism of the disease (vs. symptoms)?
6) Are most (85%) of the patients with this condition responsive to standard treatment alternatives (vs. resistant or refractory)?

If the answer of (1) to (6) are "yes", placebo is not recommended.

If any one or more answers are "no", placebo may be possible.

II. Risks of placebo

1) Is the risk of using placebo instead of treatment life threatening?
   If yes, placebo is not acceptable.
2) Is the use of placebo instead of treatment likely to lead to permanent damage?
   If yes, placebo is not acceptable
3) Is the risk of using placebo instead of treatment likely to cause irreversible disease progression?
   If yes, placebo is not acceptable.
4) Can the use of placebo instead of treatment lead to an acute emergency?
5) Is the risk of using placebo instead of treatment the persistence of distressing symptoms?
6) Is the risk of using placebo instead of treatment severe physical discomfort or pain?
   If the answer of (4) to (6) are"yes", placebo is not acceptable unless risk management is adequate.

III. Risk management

1) Is there benefit in the overall management of the subject?
   □ Yes, consider placebo

□ No, placebo not recommended.

2) Will the discontinuation of previous treatment put the participant in danger of acute relapse when transferred to placebo?

□ No, consider placebo

□ Yes, placebo not recommended.

3) Are subjects at high risk for the use of placebo excluded?

□ Yes, consider placebo

□ No, placebo not recommended.

4) Is the duration of the study the minimum necessary in relation to the action of the drug?

□ Yes, consider placebo

□ No, placebo not recommended.

5) Are there clearly defined stopping rules to withdraw the subject in case he/she does not improve?

□ Yes, consider placebo

□ No, placebo not recommended.

6) Is risk monitoring adequate to identify the progression of the disease before the subject experience severe consequences?

□ Not applicable.

□ Yes, consider placebo

□ No, placebo not recommended.

7) Are there clearly defined stopping rules to withdraw the subject before the advent of severe disease progression?

□ Yes, consider placebo

□ No, placebo not recommended.

8) If the risk of placebo is an acute emergency, are rescue medication and emergency treatment available?

□ Not applicable.

□ Yes, consider placebo

□ No, placebo not recommended.

IV. Risk disclosure in the consent form

1) Are the risks of getting placebo instead of active treatment fully disclosed?

□ Yes, consider placebo.

2) Are the risks of the test drug disclosed?

□ Yes, consider placebo.

2) Are the advantages of alternative treatments explained?

□ Yes, consider placebo.

Conclusions:

1. The use of placebo is ethically acceptable because:

□ Subjects are not exposed to severe or permanent harm by the use of placebo.

□ Subjects under placebo will benefit from the overall treatment of the disease.

□ Risks of the use of placebo are minimized.

□ Risks are adequately disclosed in the consent form.

2. The use of placebo in this study could be reconsidered if the following conditions are met:

……..…

3. The use of placebo in this study is ethically unacceptable because:

□ Subjects are exposed to severe or permanent harm by the use of placebo instead of active treatment.

□ Due to the nature of the disease, the risks of placebo cannot be minimized.

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