POLICY STATEMENT
ON
RESEARCH INVOLVING THE USE OF
THALIDOMIDE, LENALIDOMIDE OR ANALOGS THEREOF

10/11/2006

The Duke University Health System Institutional Review Board (DUHS IRB) has adopted the following policy for the review of research that involves the administration of thalidomide, lenalidomide, or analogs thereof, to human subjects. For the purposes of this policy, analogs shall mean any compounds that contain the basic indolyl-piperidine-dione structure common to thalidomide and lenalidomide and exhibit the same chemical properties as these drugs.

This policy is based primarily upon information from the following websites:
Thalidomide:

http://www.fda.gov/medwatch/safety/2006/May_PIs/Thalomid_PI.pdf

http://www.fda.gov/cder/news/thalinfo/thalfaq.htm

Lenalidomide:

http://www.fda.gov/cder/drug/infopage/lenalidomide/qa.htm

I. Summary of Risks and Precautions:

The DUHS IRB recognizes that thalidomide has been extensively characterized regarding its effects on humans and presents significant risks to fetuses conceived or carried during the term of exposure to the drug. Although lenalidomide and its analogs have not been completely characterized in humans, they share the same basic structure as thalidomide and must be treated with the same caution as thalidomide until data are available to the contrary. When there is a difference among the drugs regarding safety precautions to be taken, the DUHS IRB requires that the strictest standard be used for all of these drugs, as outlined in this combined policy. In the policy, thalidomide, lenalidomide, or analogs thereof will be referred to collectively as “thalidomide-related drugs.”

All research studies involving the direct administration of thalidomide-related drugs pose a greater than minimal risk to research subjects and must be reviewed by a convened IRB at intervals of no greater than one year, as specified by 45CFR46 and 21CFR50/56.

Before DUHS IRB approval will be granted, the research protocol must contain at a minimum all of the provisions listed below.

A. Female Subjects:

(i) Exclusion of pregnant or breast-feeding females;
(ii) A minimum of four (4) weeks using no less than two (2) contraceptive measures prior to initial drug administration, unless continuous abstinence from sexual intercourse is the chosen method;
(iii) A negative serum pregnancy test 7-10 days prior to initial drug administration followed by a second negative serum pregnancy test no greater than 24 hours prior to initial drug administration;
(iv) Maintenance of no less than two (2) contraceptive measures for the duration of drug administration and for four (4) weeks after the final administration of drug, unless continuous abstinence from sexual intercourse is the chosen method;
(v) Negative serum or urine pregnancy tests weekly for the first four (4) weeks of drug administration. Thereafter, a negative serum or urine pregnancy test must be obtained every four (4) weeks for female subjects with regular menstrual cycles and every two (2) weeks for female subjects with irregular menstrual cycles for the duration of drug administration. A final serum or urine pregnancy test will be obtained four (4) weeks after the last administration of drug.

Note: All pregnancy tests must have a sensitivity of at least 50mIU/mL.

B. Male Subjects:

Use of a latex condom every time a male subject has intercourse with a woman of childbearing potential for the duration of drug administration and for four (4) weeks after the last administration of drug.

C. All Subjects:

All subjects will be consented with both the consent form for the research study and a separate safety consent form required by the FDA describing the risks of the specific thalidomide-related drug and required contraceptive measures.

All studies using thalidomide-related drugs must contain in the consent form for the research study the wording provided in Section III below. Any exceptions or modifications to this language must be specifically approved by a convened IRB.

II. Principal Investigator Responsibilities

The Principal Investigator is responsible for ensuring that all subjects are adequately apprised of the risks of the specific thalidomide-related study drug before participating in the study. In addition, the Principal Investigator must determine, to the best of his/her ability, that a potential subject, male or female, is capable of complying with the contraceptive measures in this policy. If a potential subject is younger than 18 years, the Principal Investigator must ensure that the parent/legal guardian: (i) is involved in the consent process; (ii) has access to all educational materials provided to subjects regarding the specific

thalidomide-related study drug; and (iii) will try to ensure the compliance of the minor subject with the contraceptive measures in this policy. Thalidomide and lenalidomide increase the risk of DVT. Some hormonal forms of birth control also increase the risk of DVT. Clinical trials that are sponsored by Celgene Corporation, the manufacturer of both drugs, are increasingly using low-dose aspirin (81mg/day) to reduce this risk. The Principal Investigator should consider the additive potential risk for DVT and the benefit/risks of using low-dose aspirin with specific protocols or patient populations.

III. Required Language for the Risks Section of the Consent Form

The Risk section of the consent form must include the following:

Reproductive Risks

[The following paragraph is to be used for studies using Thalidomide:] Thalidomide causes severe birth defects. Even a single dose of thalidomide may cause birth defects. Any unborn baby will almost certainly have serious birth defects and can even die if a woman is pregnant or becomes pregnant while taking thalidomide. Major birth defects caused by taking thalidomide during pregnancy include the absence of limbs, shortened limbs, failure of bones to develop, absence of bones, spinal cord defects, external ear abnormalities, eye abnormalities, heart, kidney and/or genital abnormalities, abnormal formation of the digestive system, and congenital heart defects. Death at the time of, or shortly after, birth has been reported in about 40% of infants.

[The following paragraph is to be used for studies using lenalidomide or analogs thereof:] Although the risks to an unborn fetus or nursing child from [name of study drug] are unknown, the drug is similar to thalidomide, which is known to cause severe birth defects. Therefore, the risks for [name of study drug] may be the same as the risks for thalidomide. Any unborn baby will almost certainly have serious birth defects and can even die if a woman is pregnant or becomes pregnant while taking thalidomide. Major birth defects caused by taking thalidomide during pregnancy include the absence of limbs, shortened limbs, failure of bones to develop, absence of bones, spinal cord defects, external ear abnormalities, eye abnormalities, heart, kidney and/or genital abnormalities, abnormal formation of the digestive system, and congenital heart defects. Death at the time of, or shortly after, birth has been reported in about 40% of infants.

For Women of Childbearing Potential

Because of the risks of birth defects caused by [Name of study drug], pregnant women will be excluded from participation in this study. Women who are currently breast-feeding will also be excluded from participation in this study. Women of childbearing potential must have two blood pregnancy tests (using 1 teaspoon of blood drawn from a vein by needlestick), and both must be negative before they can receive the drug. The first test will be done 7-10 days before the first dose of [Name of study drug], and the second test will be done no more than 24 hours before the first dose of the drug. A blood or urine pregnancy test will be

done every week during the first 4 weeks of taking [Name of study drug]. After that, women with regular menstrual cycles will have blood or urine pregnancy tests every 4 weeks; women with irregular menstrual cycles will have blood or urine pregnancy tests every 2 weeks for the time they are taking the drug. All women of childbearing potential will have a final blood or urine pregnancy test 4 weeks after taking the last dose of [Name of study drug].

Pregnancy Prevention During the Study

Because of the risks of birth defects caused by [Name of study drug], females of childbearing potential must agree to use the following contraceptive measures, unless they choose not to have sexual intercourse. In order to prevent pregnancy during exposure to [Name of study drug], women of childbearing potential must always use **two methods of birth control at the same time** at least 4 weeks prior to the first dose of [Name of study drug], during the entire time they are taking the drug, and for 4 weeks after the last dose. Females of childbearing potential must use one method from column A **and** one method from column B at all times:

Column A	Column B
Some types of birth control pills, injections, patches, or implants	Latex condom used by partner
Tubal ligation	Diaphragm
Intrauterine device (IUD)	Cervical cap
Partner's vasectomy	

NOTE: The following types of birth control are NOT allowed:

Progesterone-only "mini-pills," for example: Ortho Micronor® Tablets and Ovrette® Tablets
IUD Progesterone T
Female condoms
Cervical shield (not the same as a cervical cap)
Withdrawal during intercourse
Natural family planning (rhythm method)
Breastfeeding
Fertility awareness

These contraceptive methods must be used even if a female has a history of infertility. However, females who have had a hysterectomy, bilateral oophorectomy, or who are menopausal and have not had a menstrual period for at least 24 consecutive months are not subject to these requirements.

Important Information for Male Subjects

Male subjects must be aware that [Name of study drug] may be present in semen. A male subject, regardless of age, must use a latex condom every time he has sexual intercourse with a woman of childbearing potential for the entire time he is taking [Name of study drug] and for 4 weeks after his last dose of the drug **even if he has had a successful vasectomy**.

Information for All Subjects

All male and female subjects will be asked to sign a separate consent form explaining the risks of birth defects and the appropriate birth control measures that must be used when taking [Name of study drug].

[Name of study drug] given as part of this research study is for individual use only and must be stored out of the reach of others. It cannot be shared with anyone. It must be kept out of the reach of children and cannot be given to women outside of this study who are potentially able to become pregnant.

It is extremely important that female subjects avoid becoming pregnant and that male subjects avoid fathering a child during this study. However, any female subject who thinks she has become pregnant while taking [Name of study drug] or during the 4 weeks after the last dose, must notify the study doctor immediately. Likewise, any male subject who thinks he has fathered a child while taking [Name of study drug], or during the 4 weeks after the last dose, must notify the study doctor immediately.

Donation of Blood, Eggs or Semen

Females taking [Name of study drug] must not donate blood or eggs for the duration of drug administration and for 4 weeks after the last dose. Males taking [Name of study drug] must not donate blood or semen for the duration of drug administration and for 4 weeks after the last dose.