P0LICYI013 PREGNANCY AND SEXUAL HEALTH POLICY

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PURPOSE

To describe the requirements for the Protocol and Participant Information Sheet and Consent Form (PICF) in regard to pregnancy and sexual health.

Protocol

Further reference should be made to the ICH Guidance on Non Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals M3(R2) in relation to this Policy.

In accordance with ICH Guidance M3(R2), reproductive toxicity studies should be conducted as is appropriate for the population that is to be exposed. Consideration of the inclusion of Men, Women Not of Child Bearing Potential or Women of Childbearing Potential in trials will be based on these guidelines. The following sections related to these three groups are taken directly from the guidelines.

"Men

Men can be included in Phase I and II trials before the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated-dose toxicity studies.

A male fertility study should be completed before the initiation of large scale or long duration clinical trials (e.g., Phase III trials).

Women Not of Childbearing Potential

Women not of childbearing potential (i.e., permanently sterilised, postmenopausal) can be included in clinical trials without reproduction toxicity studies if the relevant repeated-dose toxicity studies (which include an evaluation of the female reproductive organs) have been conducted. Postmenopausal is defined as 12 months with no menses without an alternative medical cause."

The following extract from ICH Guideline M3(R2) will provide the basis for the consideration of the inclusion of WOCBP.

"Women of Child Bearing Potential (WOCBP)

For women of childbearing potential (WOCBP) there is a high level of concern for the unintentional exposure of an embryo or foetus before information is available concerning the potential benefits versus potential risks. The recommendations on timing of reproduction toxicity studies to support the inclusion of WOCBP in clinical trials are similar in all ICH regions.

It is important to characterize and minimize the risk of unintentional exposure of the embryo or foetus when including WOCBP in clinical trials. One approach to achieve this objective is to conduct reproduction toxicity studies to characterize the inherent risk of a drug and take appropriate precautions during exposure of WOCBP in clinical trials. A second approach is to limit the risk by taking precautions to prevent pregnancy during clinical trials. Precautions to prevent pregnancy include pregnancy testing (e.g., based on the β-subunit of HCG), use of highly effective methods of birth control, and study entry only after a confirmed menstrual period. Testing for pregnancy during the trial and subject education should be sufficient to ensure compliance with the measures designed to prevent pregnancy during the period of drug exposure (which could exceed the length of study). To support these approaches, informed consent should be based on any known pertinent information related to reproduction toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant reproductive

information is available, the potential for unidentified risks to the embryo or foetus should be communicated.

In all ICH regions, WOCBP can be included in early clinical trials without non-clinical developmental toxicity studies (e.g., embryo-foetal studies) in certain circumstances. One circumstance could be intensive control of pregnancy risk over short duration (e.g., 2 weeks) clinical trials. Another circumstance could be where there is a predominance of the disease in women and the objectives of the clinical trial cannot be effectively met without inclusion of WOCBP and there are sufficient precautions to prevent pregnancy.

Additional considerations for the conduct of studies in WOCBP without the non-clinical developmental toxicity studies include knowledge of the mechanism of action of the agent, the type of pharmaceutical agent, the extent of foetal exposure or the difficulty of conducting developmental toxicity studies in an appropriate animal model. For example, for monoclonal antibodies for which embryo-foetal exposure during organogenesis is understood to be low in humans based on current scientific knowledge, the developmental toxicity studies can be conducted during Phase III. The completed reports should be submitted with the marketing application.

Generally, where appropriate preliminary reproduction toxicity data are available from two species, and where precautions to prevent pregnancy in clinical trials (see above) are used, inclusion of WOCBP (up to 150) receiving investigational treatment for a relatively short duration (up to 3 months) can occur before conduct of definitive reproduction toxicity testing. This is based on the very low rate of pregnancy in controlled clinical trials of this size and duration, and the ability of adequately designed preliminary studies to detect most developmental toxicity findings that could raise concern for enrolment of WOCBP in clinical trials. The number of WOCBP and the duration of the study can be influenced by characteristics of the population that alter pregnancy rates (e.g., age, disease).

In the United States, assessment of embryo-foetal development can be deferred until before Phase III for WOCBP using precautions to prevent pregnancy in clinical trials (see above). In the EU and Japan, other than the situations described in the above paragraphs, definitive nonclinical developmental toxicity studies should be completed before exposure of WOCBP.

In all ICH regions, WOCBP can be included in repeated-dose Phase I and II trials before conduct of the female fertility study since an evaluation of the female reproductive organs is performed in the repeated-dose toxicity studies. Nonclinical studies that specifically address female fertility should be completed to support inclusion of WOCBP in large-scale or long-duration clinical trials (e.g., Phase III trials).
In all ICH regions, the pre-postnatal development study should be submitted for marketing approval.

All female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed before inclusion, in any clinical trial, of WOCBP not using highly effective birth control or whose pregnancy status is unknown."

Participant Information Sheet and Consent Form (PICF)

To support these approaches, informed consent should be based on any known pertinent information related to reproduction toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant reproductive information is available, the potential for unidentified risks to the embryo or fetus should be communicated.

PICF Requirements for Children and Adolescents

- A separate PICF for children and adolescents is required.
- Please be aware that certain disclosures by children about abuse or neglect, or any suspicion formed by the PI or their staff about abuse or neglect, may invoke mandatory reporting obligations under children's protection legislation. A statement to this effect must be included in the PICF and participants and/or guardian must be informed as part of the consent discussion.
- Where appropriate, the following clause is recommended:
    - For children: The study drug could cause bad birth defects in babies. If you are a girl and have started your periods, pregnancy testing will be done. You must not become pregnant during the study. If you think you may be pregnant you must tell your study doctor straight away. You must not take part in this study if you become pregnant.

- For adolescents: The effects of the study drug are unknown. Therefore there are unknown risks to the unborn child if you become pregnant during this study. You must not participate if you are pregnant, plan to become pregnant or are breastfeeding a child during the study. The study doctor must discuss with you effective methods of avoiding pregnancy during the study. Regular pregnancy testing will be done during the study.

PICF - Sample Clause for Participants and Partners of Participants

The effect of *[Name of investigational product]* on your fertility, including future fertility, may not be known.

The effects of *[Name of investigational product]* on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least *[number]* months after the last dose of study drug.

Both male and female participants must avoid pregnancy during the course of the research and for a period of *[number]* months after completion of the research project, as there is potential risk for an abnormal child being born. The study doctor must discuss effective methods of avoiding pregnancy with you.

[For female participants] If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

[For male participants] It is highly recommended that you inform your partner of your participation in the study and the need to avoid pregnancy. You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

[Where appropriate] The study drug may cause harm to your partner through the absorption of the study drug from seminal fluid. You should discuss with your study doctor effective methods of avoiding this.

Note: Appendix A provides further information for Investigators to use as appropriate when discussing with study participants fertility risks, mutagenic risks and avoiding pregnancy.

Pregnancy/Pregnant Partner Data Release Form

The Pregnancy/Pregnant partner Data Release Form is to be used to request consent for follow up on the progress of a pregnancy and the birth and health of a child when the participant or participant's partner becomes pregnant. The Principal Investigator is required to nominate and justify a follow up time, but this is expected to be not less than 12 months following birth.

Where the form is used for the pregnant partner of a study participant, information about the trial, such as drugs used, risks etc. must be included in the data release form along with an explanation of why [Sponsors Name] is seeking data with regard to the outcome of the pregnancy, birth and health of the child. This may be achieved, for example, by attaching a copy of the trial Participant Information Sheet.

This form can either be included with the original submission to Bellberry HREC, or approval can be sought if/when a pregnancy occurs and the form is required.

SAMPLE PREGNANCY/PREGNANT PARTNER DATA RELEASE FORM

Study Title:

Protocol Number:

Principal Investigator:

Co-Investigators:

Name of Participant/Pregnant Partner:_____

Participant Study Number: _____

PURPOSE OF THE FORM

The purpose of this form is to request your consent to follow the progress of your pregnancy and the birth and health of your child. Signing this form is voluntary; it is up to you to decide whether to agree to the collection of this information or not.

[For pregnant partner] Provide a brief explanation of the study including details about the drug/s used, risks etc.

The reason for this request is that the risk to your unborn child is unknown and you:

- became pregnant while participating in the above study, or
- you became pregnant while your partner was participating in the above study, or
- you became pregnant …. days after you or your partner completed the study.

We ask for your permission to review your and your child's medical records relating to your pregnancy, the delivery of your child and the health of your child up to …. [insert and justify length of time as stated in the protocol] of age.

CONFIDENTIALITY OF RECORDS

All information collected with regard to your pregnancy, the delivery of your child and the health of your child is confidential to the limit allowed by law. Your data will be coded to hide your identity and the identity of your baby. In particular, your name and your child's name will not be reproduced on any other paper or electronic document.

These data will not be disclosed voluntarily by [Sponsors name and co-sponsor(s) (if applicable)]. However, regulatory agencies may have to examine these data to ensure that the study is done properly.

Please be aware that if you are the pregnant partner of a study participant and you do not wish to provide such information, this will not prevent your partner from continuing with the study.

In most cases, privacy legislation allows you the right to access personal information collected from you and request corrections of any such information that is incorrect.

PARTICIPANT/PREGNANT PARTNER STATEMENT AND SIGNATURE

- I have had the reasons explained to me as to why data with regard to the pregnancy, the delivery and the health of the child are required.
- I have had an opportunity to discuss this with my partner's study doctor and I have had my questions answered to my satisfaction.
- I freely agree to allow the data concerning the pregnancy and the outcome of this pregnancy to be held on the [Sponsors Name] Drug Safety Database and being forwarded to regulatory agencies as necessary.

Participant/Pregnant Partner's printed name

_____

Participant/Pregnant Partner's signature

____/____/_____
DATE (to be personally dated)

_____

A verbal explanation of the research project, including drugs involved, risks and reasons why [Sponsors Name] is seeking data with regard to the outcome of the pregnancy, has been given to the person named above and I believe they understood that explanation. A copy of this signed and dated Pregnancy Data Release Form will be provided to the above named for their record.

INVESTIGATOR NAME (print)	INVESTIGATOR SIGNATURE	DATE (to be personally dated)
_____	_____	___/___/_____

ATTACHMENT A

The following information is provided as a guide for Investigators when discussing with participants fertility risks, mutagenic risks and avoiding pregnancy.

For women

The effect the drug has on your fertility, including future fertility, may not be known.

Because the experimental agents in this study may affect an unborn baby, and there is potential risk for an abnormal child being born, you should not be pregnant or become pregnant while on this study and for …… months following the end of the study.

You must confirm to the investigator that, to the best of your knowledge, you are not pregnant now, and that you do not intend to become pregnant during the study.

You must use a highly effective method of contraception/birth control (methods which result in low failure rate, i.e. less than 1% per year, when used consistently and correctly) and if currently lactating, you should not breast feed your baby while on this study and for 3 months after the last dose of study drug has been taken.

Examples of acceptable forms of highly effective contraception include:

1. Established use of oral, injected or implanted hormonal methods of contraception.
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
3. Sterilised male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
4. True abstinence: When this is in line with your preferred and usual lifestyle

Examples of non-acceptable methods of contraception include:

- Condoms alone or double barrier
- Periodic abstinence (e.g. calendar, ovulation, sympthothermal, post ovulation)
- Withdrawal
- Spermicide (as it is not approved as a method of contraception in Australia)

If you are uncertain of what form of contraception is acceptable for use during the study, then please ask your study doctor.

If you suspect that you have become pregnant during the study, you must notify your study doctor immediately. You will not be able to continue participation in the study if you become pregnant. In the event you do become pregnant the Sponsor will request that you sign a separate consent form to allow monitoring of your pregnancy and the birth and the health of your child up to ……..years of age.

It is recommended that a condom be worn for all sexual intercourse as the study drug may cause harm to a sexual partner through absorption of the study drug from seminal fluid.

For men

The effect the drug has on your fertility, including future fertility, may not be known.

Because the experimental agents in this study may affect an unborn baby, you should not father a baby while on this study and for …… months following the end of the study.

It is recommended that a condom be worn for all sexual intercourse. The study drug may cause harm to your partner through the absorption of the study drug from the seminal fluid. The study drug may also affect your sperm risking the potential for an abnormal child being born

It is also highly recommended that you inform your partner of your participation in the study and that highly effective methods of contraception (as detailed above) is strongly recommended.

Further, you must agree that if your partner becomes pregnant while you are on the study, you will advise the study doctor who will then provide you with an authorisation form to present to your partner. If she is in agreement, that authorisation will function as consent to approve the study doctor's access to medical information to allow monitoring of the pregnancy, and the birth and the health of the child up to ……years of age.