Author: Raphaelle Beau-Lejdstrom, PhD
Contributor : Irene Fermont, MD, MSc
Published 31 January 2021

Male and female reproductive inclusion criteria in several Phase 3 vaccine trials

Question: In the BioNtech/Pfizer protocol C4591001 for the Phase 3 study of Comirnaty (below), the Appendix 4 describes strict male and female reproductive inclusion criteria.

Are all these precautions standard precautions in all vaccine trials?

Answer:

Strict criteria on male and female participants reproductive inclusion can be found in the three Covid19 vaccines protocols of Phase 3 that have been approved under emergency authorization worldwide (BioNtech/Pfizer, Moderna and AstraZeneca).

The most likely reason for such restrictive criteria can be found in the AstraZeneca AZD1222 - D8110C00001 protocol (ref protocol in the folder) p35:

"The study will exclude females who are pregnant or breast-feeding and individuals less than 18 years of age. Women who are pregnant or breast-feeding are excluded at this point as nonclinical developmental and reproductive toxicity studies to support vaccinating these individuals have yet to be performed."

In order to produce quality evidence on the efficacy and safety of these vaccines in a timely manner in the context of the current pandemic, reproductive toxicity studies were only conducted or completed after the start of Phase 3 trial. International (ICH) and FDA guidance on the conduction or trials in pregnant women (refs in the folder) recommend that these studies should be conducted **prior** to the start of the trial to allow the inclusion of pregnant women and in males without restriction on reproductive inclusion criteria.

The Risk Management Plan (EMA ref) for the Pfizer/BioNtech vaccine explains that "No vaccine-related effects on female fertility or the development of fetuses or offspring were observed in a DART study of BNT162b2 in rats" (DART= developmental and reproductive toxicity).

Some vaccine trials are less restrictive on male and female reproductive inclusion criteria as the reproductive toxicity studies in animals have been conducted previously.

To this day, a very limited amount of data is available for the use of covid19 vaccine in pregnant women and the drug manufacturers committed to collect more information on

the vaccination of pregnant women

However, because of the occurrence of several cases of severe forms of COVID-19 in pregnant women, some associations of gyneco-obstetricians have recommended vaccinating pregnant and breastfeeding women. This has led some regulatory authorities to adopt this advice. This is the case in the USA, Israel and WHO, after a preliminary contradictory position.

Male fertility is not a subject of concern raised in the FDA or EMA documents released on the evaluation of the Pfizer/BioNtech vaccine.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
     - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).