### Trial Description

**Title**


**Trial Acronym**

TNF-α Blocker in Pregnancy

**URL of the trial**

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**Brief Summary in Lay Language**

The safety in pregnancy of the five licensed TNF-α inhibitors adalimumab, certolizumab pegol, etanercept, golimumab and infliximab has been insufficiently examined. Part 1 of the study compares frequency and cluster of malformations and the risk of spontaneous abortion of exposed fetuses/children (during the first trimester or longer) with a suitable comparison group.

Part 2 focuses on infections, reactions to vaccines, allergies and the development of intrauterine exposed children during the first year of life. It is known that at least some of the TNF-alpha inhibitors have a high placental transfer beginning in week 20. It will be distinguished between early (<20 weeks of gestation) and late exposure (>20 weeks of gestation). All exposed children will also be compared to suitable control children.

**Brief Summary in Scientific Language**

The five TNF-alpha inhibitors adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are not labeled for use in pregnancy. However, inadvertent exposure occurs and in certain patients they might be the best treatment option. Existing experience during pregnancy does not suggest teratogenicity, but varies between the different substances and altogether is still limited. There are concerns against the use of TNF-α inhibitors in late pregnancy (> gestational week 20), because at least some of them exhibit an increasing placental transfer during the course of pregnancy. This results in therapeutic fetal/neonatal plasma concentrations. A case report of an infant raises concern. The mother was treated with infliximab throughout pregnancy. The 3-months old infant received BCG live-vaccination resulting in disseminated BCG infection and ultimately in the death of the child (Cheent 2010). Our prospective multicenter cohort study enrolls pregnant women who have spontaneously contacted a teratology information service (TIS) within the European Network (ENTIS). The sample of exposed includes women who have been treated with a TNF-alpha inhibitor during the first trimester (part 1). Part 2 consists of intrauterine exposed children (either till week 20 or longer than week 20) aged one year (part 2). The comparison groups consist of non-exposed women/children matched for year of enrollment and TIS. Cases exposed to major teratogens or fetotoxicants are excluded from all groups. The focus of part 1 lies on the risk of major
malformations, spontaneous abortion, and low birth weight. Part 2 will evaluate potential impacts on the infant’s development and immune system. Infants of part 2 will be compared to non-exposed children and matched for sex, gestational week at birth, birth weight, and year of birth. Excluded are children born with major birth defects having an impact on infant development.

Organizational Data

- DRKS-ID: DRKS00005036
- Date of Registration in DRKS: 2013/05/31
- Date of Registration in Partner Registry or other Primary Registry: [---]*
- Investigator Sponsored/Initiated Trial (IST/IIT): yes
- Ethics Approval/Approval of the Ethics Committee: Approved
- (leading) Ethics Committee Nr.: EA4/013/13, Ethik-Kommission der Charité - Universitätsmedizin Berlin-

Secondary IDs

- ICD10: P04.1 - Fetus and newborn affected by other maternal medication
- Free text: Malformation rate, rate of spontaneous abortion, both after first trimester exposure. Frequency and severity of infections, allergies, developmental delay, weight gain after exposure in late pregnancy.

Health condition or Problem studied

- Arm 1: Study part 1: maternal exposure to TNF-α blockers; prospectively ascertained; exposure time meets any time from last menstrual period (LMP) until week 12+0 after LMP. Exposure may have started earlier than LMP and can have continued beyond week 12.

Study part 2: maternal exposure to TNF-α blockers; exposure time either took place before the 20th week of gestation or meets any time beyond week 20 after LMP. Exposure may have started earlier in pregnancy; at least one injection after week 20+0 and before delivery is obligatory. The pregnancy may have been included in the study part 1, but need not and can be retrospectively ascertained shortly after birth as long as long-term follow-up up to at least 1 year of age is ascertained prospectively.

- Arm 2: Study part 1: prospectively ascertained pregnancies without TNF-alpha blocker therapy or other biologics; randomly chosen from the same data pool as the exposed.

Study part 2: prospective long-term follow-up; noTNF-alpha blocker therapy or other biologics. Per exposed two control children matched for infant's sex,
gestational week at birth, birth weight (+/-100g) and year of birth.

Characteristics

- **Study Type:** **Non-interventional**
- **Study Type Non-Interventional:** **Observational study**
- **Allocation:** **Non-randomized controlled trial**
- **Blinding:** [---]*
- **Who is blinded:** [---]*
- **Control:** **Other**
- **Purpose:** **Prognosis**
- **Assignment:** **Parallel**
- **Phase:** **N/A**
- **Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels):** **Yes**

**Primary Outcome**

Part 1: Eight weeks after the estimated date of birth a structured questionnaire is sent to the mother/physician. Primary endpoints are delivery of the child with/without anomalies, spontaneous abortion, and elective termination of pregnancy.

Part 2: For children being one year or older, an extra questionnaire designed for this study, will be sent to the mothers dealing with infant development within the first year of life. Primary objectives are frequency and severity of infections, allergies and reactions to vaccines.

**Secondary Outcome**

Part 1: prematurity, birth weight
Part 2: infant's weight gain, achievement of developmental milestones

**Countries of recruitment**

- DE Germany
- FR France
- FI Finland
- IT Italy
- NL Netherlands
- UK United Kingdom
- CH Switzerland
- AU Australia
Locations of Recruitment

- University Medical Center Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie, Berlin
- Medical Center Centre Régional de Pharmacovigilance, Lyon
- Medical Center Centre de Référence sur les Agents Tératogènes (CRAT), Paris
- University Medical Center Teratology Information Service, Helsinki
- University Medical Center Centro di Riferimento Regionale di Tossicologia Perinatale, Florenz
- Medical Center Department of Clinical Pharmacology, Bergamo
- other Netherlands Pharmacovigilance Centre Lareb, Teratology Information Service, MH ’s Hertogenbosch
- other UK Teratology Information Service (UKTIS), Newcastle
- University Medical Center STIS and Division of Clinical Pharmacology and Toxicology, Lausanne
- Medical Center Mothersafe; teratology information service, Sydney
- University Medical Center Department of Pharmacology, Trabzon

Recruitment

- Planned/Actual: Actual
- (Anticipated or Actual) Date of First Enrollment: 2013/09/02
- Target Sample Size: 1837
- Monocenter/Multicenter trial: Multicenter trial
- National/International: International

Inclusion Criteria

- Gender: Both, male and female
- Minimum Age: no minimum age
- Maximum Age: no maximum age

Additional Inclusion Criteria

Part 1: Prospectively ascertained pregnancies with first trimester exposure to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab. Maternal therapy might have started earlier and can last longer. Comparison group: prospectively ascertained pregnancies without exposure to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab (or other biologics).

Part 2: Prospective ascertainment of long-term follow-up of children being at least
1-year-old or older. They must have been exposed in utero to at least one maternal injection of the named TNF-alpha blockers. Comparison children: Prospective ascertainment of long-term follow-up of children being at least 1-year-old or older matched for sex, gestational week at birth, birth weight and year of birth. No TNF-alpha blockers (or other biologics) during pregnancy.

Exclusion criteria

Excluded from all cohorts are pregnancies with: major teratogens (acitretin, isotretinoin, mycophenolate, thalidomide, valproic acid) or/and major fetotoxic agents (ACE-inhibitors or sartans when used in 2nd and/or 3rd trimester) or/and acute malignancies. For study part 2: Excluded are children with malformations having an impact on normal development and preterms born before week 34 0/7.

Addresses

- **Primary Sponsor**
  
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Sources of Monetary or Material Support

- Public funding institutions financed by tax money/Government funding body
  (German Research Foundation (DFG), Federal Ministry of Education and
  Research (BMBF), etc.)

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- Public funding institutions financed by tax money/Government funding body
  (German Research Foundation (DFG), Federal Ministry of Education and
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  53175 Bonn
  Germany

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  E-mail: [---]*
  URL: http://www.bfarm.de/cln_103/DE/Home/home_node.html

Status

- Recruitment Status: Recruiting complete, follow-up continuing
- Study Closing (LPLV): [---]*

Paper Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: a prospective multicentre cohort study

* This entry means the parameter is not applicable or has not been set.
*** This entry means that data is not displayed due to insufficient data privacy clearing.