Efficacy of certolizumab in women with unexplained recurrent implantation failure: a double-blind randomized controlled trial; essai CERTIFy

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<td>Sponsor</td>
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<td>Scientific justification</td>
<td>Recurrent implantation failure (RIF), defined as the absence of clinical pregnancy after the transfer of three good-quality embryos, concerns up to 40% of IVF couples and is associated with a low success rate. The etiologic remains unexplained in over 50% of cases. Various dysimmune changes (related to immune T cells profiles, pro-inflammatory cytokines levels) have been described in unexplained RIF as compared to fertile controls, and it has been estimated that such dysimmunity may occur in 50% of unexplained RIFs. Previous data on a benefit of general immune modulation by steroids or immunoglobulins remain heterogeneous and failed to demonstrate clinically significant benefit. The proinflammatory cytokine Tumor Necrosis Factor (TNF) α participates in the regulation of the immune balance of the endometrium, its peripheral blood and endometrial concentrations are increased in RIF patients as compared to fertile controls. In 2009, a pilot placebo controlled study showed that TNF-α antagonist treatment allowed a 56% live birth rate (versus 13% in controls) in 13 women with unexplained RIF. Due to the lack of maternal and fetal tolerance data, TNF-α antagonists were not further evaluated. Today, safety data issued from 1200 pregnancies are reassuring allowing the use of TNF-α antagonists during pregnancy (<a href="http://www.lecrat.org">www.lecrat.org</a>). In addition the TNF-α antagonist certolizumab does not cross the placental barrier. We hypothesize that certolizumab may improve clinical pregnancy rates in women with unexplained RIF with a good safety profile.</td>
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| Main objective and primary endpoint | **Main objective:** To evaluate the efficacy of certolizumab compared to placebo on clinical pregnancy rate in women with unexplained recurrent implantation failure.  
**Primary endpoint:** Clinical pregnancy defined as the presence of cardiac activity on ultrasound scan at 5 weeks + 6 days of gestation |
| Design of the study | Phase III multicenter double blind randomized controlled trial with parallel groups. |
| Population of study participants | Adult women with recurrent implantation failures (RIF) |
| Inclusion criteria | - Women aged 18-40 years  
- Idiopathic, male or tubal factor infertility  
- Unexplained consecutive failure to obtain clinical pregnancy after at least transfers of 3 good-quality embryos (Istanbul criteria) |
| Exclusion criteria | Known cause of RIF among the following:  
- Genetic parental anomalies  
- Non-gestational diabetes mellitus of type I and II,  
- Infectious disease  
- Antiphospholipid syndrome  
- Sickle cell disease  
- Extensive adenomyosis |
| Contraindication to certolizumab: | |
| **Investigational medicinal product(s)** | Certolizumab (TNF-α antagonist) 400 mg injected subcutaneously monthly from 5 weeks before embryo transfer until 7 weeks of gestation (injections at 5 and 1 week before embryo transfer, 3 and 7 weeks after embryo transfer) for a total of 4 injections in case of ongoing intrauterine pregnancy. |
| **Comparator treatment** | Placebo of similar appearance injected subcutaneously at the same frequency |