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

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Scientific justification	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 heteregenous 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 (www.lecrat.org). 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
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