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How to avoid risks for patients in minimal-access trials: Avoiding complications in clinical first-in-human studies by example of the ADBEE study

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A clinical trial is a prospective study designed to establish the safety and efficacy of investigational devices in humans, in accordance with the strict guidelines of the Food and Drug Administration (FDA; USA) or European Medicines Agency (EMA; Europe). Before a clinical first-in-human study is initiated, preclinical studies of the investigational product are mandatory, and the results should be sufficient to indicate that the investigational device is acceptably safe for the proposed evaluation in human subjects. The present paper describes an experience of clinical trials, highlighting ways of avoiding possible complications in clinical first-in-human studies. For a better approach to our aim, we exemplified a prospective, randomized, single-blind study, ADBEE. The primary

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objective was to assess the safety of the ADBLOCK system when used as an adjunct to laparoscopic primary removal of myomas in women wishing to improve pregnancy outcomes.

Introduction

The clinical trials are conducted in a series of stages, called phases, with each phase being designed to answer a separate research aspect.

I. Preclinical, nonclinical studies. These include studies with a duration of 2–3 years on different models such as cultured tissue and animals. The safety examination includes the study of toxicology, pharmacology, biochemistry, mutagenicity, and pharmacokinetics (absorption, drug distribution, metabolism, and excretion). For the first-in-human studies, the early nonclinical examinations should provide sufficient information on the initial human dose and safe duration of exposure as well as produce data on the physiological and toxicological effects of the investigational device [1].

Preclinical phase for ADBLOCK System

Preclinical studies for ADBEE were undertaken in accordance with standards issued by the International Organization for Standardization (ISO), harmonized European standards (EN) [2], and the Food and Drug Administration (FDA) Guidance for Resorbable Adhesions Barrier Devices (FDA, US Food and Drug) [3]. These studies have provided evidence of both the safety and efficacy of the ADBLOCK system in reducing adhesions in standard animal models [4]. Although novel compounds, the constituent elements are well-established agents for use in clinical practice.

The safety and efficacy of ADBLOCK is based on the results obtained from the biocompatibility and pharmacokinetic studies, in vitro testing, manufacturing and control data, in vivo testing, sterilization validation, and stability testing. A comprehensive risk review for ADBLOCK has also been performed in accordance with EN ISO 14971. The details of the risk management review are described in a risk management report. This concluded that all known possible risks associated with the materials, design, manufacturing process, and clinical use of the system have been considered and made acceptable by taking into account requirements stipulated in applicable harmonized standards or international standards during design, production, and testing, or by putting in place the necessary precautions, warnings, or contraindications in the information provided with the device.

Biochemical safety

ADBLOCK Adhesion Barrier is an experimental site-specific sprayable adhesion barrier gel based on a dextrin polymer, which is currently being investigated as an adhesion-reducing agent for use in patients undergoing abdominopelvic surgery as an adjunct to surgery, with the aim of reducing the incidence, severity, and extent of adhesion formation postoperatively.

A similar existing dextrin polymer (icodextrin) has recently been approved in Europe and the USA as an anti-adhesion solution (Adept®), with an excellent long-term safety record from its global use as an intraperitoneal dialysate as well as an anti-adhesion agent. The anti-adhesion solution Adept is currently the most widely used anti-adhesion agent available. Although it has been shown to be safe and effective in reducing adhesions [5], recent research suggests other advantages offered by site-specific gels such as ADBLOCK [6].

The polymer system in ADBLOCK is a novel compound based on existing and established agents. It contains one precursor comprising an NHS (N-hydroxysuccinimide)-modified carboxymethyl dextrin polymer with trehalose (alpha linked disaccharide), which has been used in various pharmaceutical biopharmaceutical agents (including the monoclonal antibody formulations trastuzumab and bevacizumab – Herceptin® and Avastin®) [7] and is being investigated for its anti-adhesion potential in ocular surgery. The other precursor is a standard alkaline sodium hydrogen

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