

White Paper

Early Phase Clinical Research in Italy





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1. Introduction

The development of a new compound starts by studying a target molecule which researchers believe might modulate symptoms or alter the natural course of a specific disease. Phase 1 clinical research represents an exploratory phase in the entire drug development process in which the compound is studied for the time in humans. Subjects in these studies are not usually patients suffering from the disease in question, but rather healthy volunteers.

According to definition provided by EMA¹:

“Phase 1 starts with the initial administration of an investigational new drug into humans... Studies conducted in Phase I typically involve one or a combination of the following aspects: a) Estimation of Initial Safety and Tolerability... b) Pharmacokinetics c) Assessment of Pharmacodynamics d) Early measurement of drug activity.”

Because this is the first time the compound has been administered to humans, the starting doses used in Phase 1 are very low. The parameters suggested by EMA Guidelines² to identify the starting dose in Phase 1 studies are the NOAEL (No Observable Adverse Effect Level) in the most sensitive animal species in which the compound has been tested and the MABEL (Minimal Anticipated Biological Effect Level). MABEL is the anticipated dose level leading to a minimal biological effect level in humans².

The results of early phase studies drive the further development of a new compound and can suggest new strategies to maximize the potential of the new drug.

Recently the number of Sponsors who decide to carry out Phase 1 studies in Italy has increased, especially for oncology trials.

2. Italian Legislation Governing Phase 1 Clinical Research

In recent years, the legislation in Italy which governs clinical research activity has undergone important changes. These revisions also affected the conduct of early phase clinical research, including Phase 1. Specifically, legislation introduced in 1998, 2001, 2003, 2007 and 2012 introduced changes which are relevant to the conduct of Phase I studies in Italy.

The first of these pieces of legislation was a Decree published in 1998. This decree detailed the minimal requirements relating to, for example facilities, equipment and staff which must be present in a privately operated Phase 1 facility in Italy³.

In 2001 the decree DPR 4394 was published, in which the definition of phase 1 studies was described. In the same decree the application process by which regulatory approval for Phase I studies was achieved prior to commencement of a Phase I study was defined. According to the decree, applicants have to achieve approval by Istituto Superiore di Sanità (ISS), an institution which is part of Italian Ministry of Health. In the same decree the

Commission of Experts for Eligibility for the Clinical Trial Phase I at ISS was defined (art. 7)⁴, which met for the first time in March 2002. In 2004, with the publication of D.L.vo 211/2003 (art. 2)⁵, ISS became the Competent Authority (CA) for authorization of First in Human (FiH) Studies.

In 2007 with publication of D.L.vo 6 Nov 2007 (art.35)⁶, the role of ISS as the CA was expanded to include authorization of not only FiH trials, but also of all Phase 1 studies. In the same year DM 21 Dec 2007⁷ was published requiring all applicants to complete and submit a Clinical Trial Application Form (CTA form), as for other European Countries. This aspect has been better defined with “determina AIFA 7 March 2011”⁸, where the CTA form was present in the list of essential documents required for ISS study submission. The publication of “DM 21 Dec 2007”⁷ (Attachment 2 Paragraph 6.1.2.8 and Appendix 13) also defined aspects of compensation paid to healthy volunteers and of travel reimbursement expenses for patients involved in Phase 1 studies.

In 2012, “law 8.11.2012 n.189”⁹, also known as the “Balduzzi Decree” was published with the aim of centralizing the role of CA in Italy. The Balduzzi Decree made AIFA, the CA for all clinical trials to be carried out in Italy; this law will be adopted by a Decree. The transfer of functions of CA to AIFA has been an important change in clinical research in Italy at all phases, including Phase 1. In the same law it is also specified that AIFA uses ISS to execute this function in accordance with the mode established with the Decree to be published.

Since September 2012, AIFA has published further documents to update or better specify changes introduced by “law 8.11.2012 n.189”⁹. At the beginning of 2013, an official document “Determina AIFA n. 1/2013”¹⁰ was published to define how to manage the submission of clinical trials until the publication of the Decree and, in the meantime, the Ministry of Health database (OsSC) was also under technical renovation. Indeed, another change introduced by “law 8.11.2012 n.189” is the implementation of “e-submission” procedure (no more both paper and electronic submission) of all clinical studies to be carried out in Italy. This new procedure will be feasible through the utilization of “new Ministry of Health database, delivered on 15th July 2014, but active to be used starting on 1st Oct 2014.

Other important changes introduced by “law 8.11.2012 n.189”⁸ were a significant reduction of the number of Ethical Committees (EC) in each of the Italian Regions and the submission of all study docs to Region Representative further to EC and CA.

3. Our Experience

The Centro Ricerche Cliniche (CRC) is the CROMSOURCE early phase facility. In our experience, the regulatory changes which have occurred during the last years have not increased the number of days needed to obtain regulatory approval.

Table 1, below, provides some examples of timings with regard to Phase 1 study submissions made by CRC during these recent when the regulatory environment was changing.

Table 1: Examples of CRC Phase 1 study submissions to ISS

Study Code	Date of Submission to ISS	Date of Final CA Approval	Days Required
A	19/4/10	19/5/10	30
B	3/4/12	31/5/12	58
C	10/4/13	20/5/13	40
D	04/03/2014 Answers sent to ISS: 09/05/2014	13/05/2014	70

The duration of process to get final approval corresponds to a medium value of 50,75 days, between a range of 35 days as minimum to 70 as maximum (in this case included answers to ISS requests). It is important to underline that one of the submission processes performed, after implementation of “Balduzzi decree” changes, has been faster than previous ones. For the last one the answers to ISS requests were sent on 09th May 2014 for the ISS meeting scheduled on 12th May 2014 and the final AC approval was received on the day after.

With respect to submission of substantial amendments the process is even shorter. Usually it takes between 10 to 30 days to receive approval.

Helpfully, the shipment of the hard copy of the final approval is performed almost immediately after the meeting and the ISS Secretariat is very keen to provide clarifications or to manage issues. The contacts at ISS have not been changed to date, and CRC staff has established a very good relationship with them.

With this in mind, CRC has received very positive feedback from Sponsors about the submission process, including the time required to obtain final regulatory approvals for their studies to commence.

4. About the Author

Cristina Costantin, Pharm. D., PhD, Head of Operation Department, Pharmacist/Senior Project Manager, Centro Ricerche Cliniche (CROMSOURCE Early Phase)

Cristina has a Chemistry and Pharmaceutical Technologies Degree and attained the Certificate of Pharmacist, both from the University of





Padua. In 2011 she completed a Doctorate in “Translational Biomedicine” at University of Verona.

From March 2002 to December 2005 Cristina worked in the GlaxoSmithKline (GSK) Research Center in Verona as a Pharmacist and Study Team Leader, acquiring great experience in Early Phase clinical trials. In 2006, Cristina joined CRC as a pharmacist and project manager and became Head of Operation Department in 2013. She is also a fellow of AFI “Associazione Farmaceutici Industria”, a scientific society.

5. About CROMSOURCE Early Phase

When choosing a partner for your early phase clinical projects, you need an expert. For many years the CROMSOURCE Early Phase facility, Centro Ricerche Cliniche (CRC), formed the Phase I unit of a top 10 global pharmaceutical company. When this company disinvested in the facility, it moved location to the nearby teaching hospital, taking the expert team and cutting edge equipment with it. In 2012, CRC became the CROMSOURCE Early Phase facility. Our sponsors can therefore be certain that the quality and expertise of our facility is second to none.

The strategic location of our facility in Verona, Italy ensures that EU-wide regulatory timelines and procedures are also adhered to whilst project costs are significantly lower than in most EU countries.

CROMSOURCE is a high quality ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

Operating through Pharmaceutical, Medical Device, and Staffing Solutions teams with offices across all regions of Europe and North America CROMSOURCE delivers a comprehensive breadth of services. We seamlessly move biopharmaceutical products from first in human conducted in our exceptional early phase unit, through all subsequent phases of pre and post-approval research internationally. Our Medical Device experts oversee projects through regulatory strategy and submission, to pilot and pivotal clinical investigations in Europe and North America. Our Staffing Solutions Team ensures that high quality professionals are available to support your work whenever you need more resources.



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