Fase1 srl

CLINICAL RESEARCH AND TRIALS IN SARDINIA

REGIONE AUTONOMA DELLA SARDEGNA

Fase1 srl

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REGIONE AUTONOMA DELLA SARDEGNA

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ABOUT US

FASE 1 s.r.l. is a company fully owned by the Regional Administration of Sardinia. Its corporate goal is to develop - through clinical research - new drugs and new indications for existing diagnostic preparations and treatment drugs.

Its corporate objects include:

- Pre-and post-patenting selection of new diagnostic and treatment agents, optimisation and preparation for industrial development.
- Clinical development of medicinal drugs and new therapeutic formulations and applications.
- Development of procedures and services supporting diagnosis, prognosis and treatment.

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- Assistance in the development, production and marketing of biotechnology and pharmaceutical products.

FASE 1 provides the following services:

- Pre-patenting assistance up to creation of an appropriate intellectual property framework.

- Assessment of current intellectual protection status and possible extension of existing national and/or international PCT and/or European applications, and/or their continuation and maintenance.

- Assessment of the adequacy of the technical-scientific and regulatory dossier for new procedures or diagnostic tests and assistance in their completion.

- Design of preclinical and clinical development plans.

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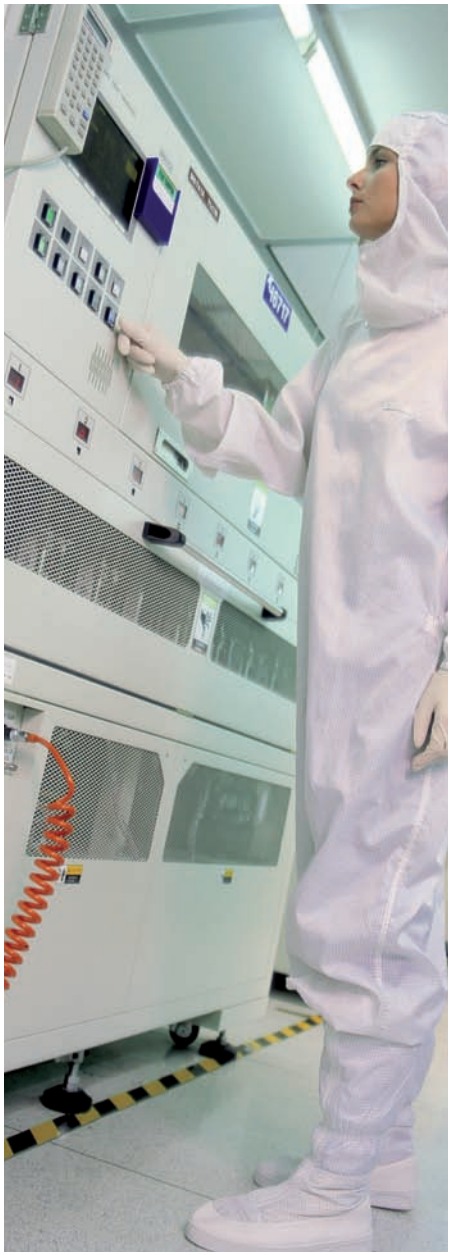

- Implementation of preclinical validation studies.
- Execution of clinical trials on healthy volunteers and patients at our Clinical research unit.

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OUR ACTIVITIES

■ CLINICAL TRIALS

Fase 1 performs clinical trials on healthy volunteers and patients at its Clinical Research Centre which consists of two operational units with full functional integration:

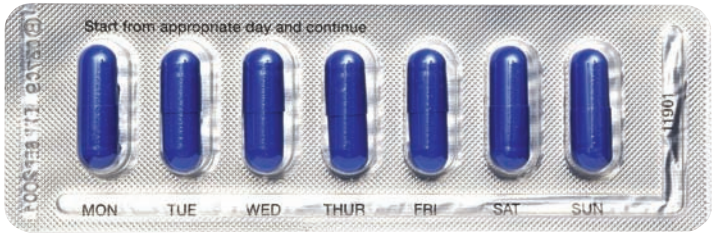
- Clinical Trial Management Unit, tasked with registration, validation, data analysis and issue of the final medical report, based in Pula (CA) at Polaris - the Regional Science and Technology Park.
- Phase 1 Clinical Research Unit, in Cagliari, on the 11th floor of G. Brotzu Hospital, ranked as a national-level, high specialisation hospital by Decree of the Prime Minister dated 8/04/1993 and delivering first-rate healthcare to Sardinian citizens especially in specialised areas, such as heart surgery and organ transplants.

The G. Brotzu Hospital collaborates with Fase 1 srl in the implementation of clinical trials, by providing:

- a clinical facility fully integrated within the hospital, sized for the performance of phase 1 clinical trials on human subjects;
- ward facilities for inpatients and associated services;
- specialised lab and pharmacy services and other specialised services;
- medical and nursing staff;
- general medical services such as ICU, emergency room, stroke unit, coronary care unit and other on-demand services.

All the above services have the following characteristics:

- Specific procedures (Standard Operating



Procedures or SOPs) for managing the standard processes of all trials (relations with the Ethics Committee, definition of protocols and operational processes, regulatory compliance, management of operational relations with labs, quality control, etc.).

- Specific non-standard procedures for each type of application as required (administering to human subjects, doses, different trial designs, etc.).

PRECLINICAL DEVELOPMENT

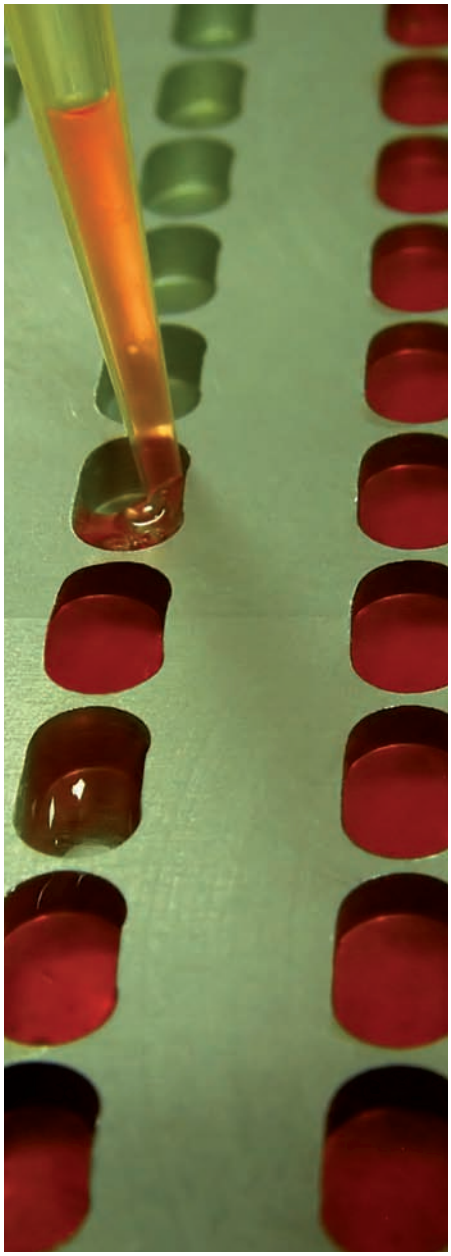
The company designs and implements preclinical studies for testing the pharmacological and clinical effects of any new drug by means of several steps aimed at gradually collecting evidence on drug efficacy and tolerability.

Preclinical development can be of four different types, all or part of which may be carried out according to the project's prior de-

velopment and studies already performed: these activities - many of which are carried out in parallel - are conducted on the basis of a detailed development programme:

1. Preparation of Chemical-Pharmaceutical Documentation (Active Principle and Commercial Formulation): this involves selection of active principle and commercial formulation manufacturers, able to supply the product for animal trials and for the first phases of clinical trials, in accordance with the principles of good manufacturing practices (GMP).
   A key phase is the passage from laboratory scale to semi-industrial scale manufacturing technology, and associated validation of manufacturing and testing methods.

2. Preparation of Non-clinical Documentation (Pharmacology and Toxicology): based on the therapeutic indications of the product under development, appro-



priate 'in vitro' and especially 'in vivo' studies must be carried out to demonstrate its efficacy and safety, in accordance with good laboratory practice (GLP) rules.

3. Clinical Information (Protocol Drafting).

4. Requests for Authorisations (National Health Institute and Ethics Committee): the requests for authorisations will contain a summary of the information provided under points a), b) and c), presented in a specific format.

EDUCATION AND TRAINING

In order to complement its core activities with appropriate supporting initiatives, Fase 1, also in collaboration with the local universities, promotes the development of scientific know-how and advanced knowledge in the field of clinical trials and drug development.

In this area, Fase 1 plans and implements the following initiatives:

EDUCATION AND INFORMATION

- Seminars and conferences on industrial property, preclinical activities, clinical trials and reference legislation etc.

TRAINING

- Scholarships for degree dissertations on clinical trial issues
- Scholarships for young researchers (who have published articles on relevant themes)
- PhD scholarships
- Master course in clinical trials
- Professional placements at the Clinical Trial Centre.

DEDICATED PROFESSIONAL DEVELOPMENT PATHS

- Creation of professional development

paths within universities and the public health system

- Organisation of advanced specialisation master courses.

SCIENTIFIC COLLABORATION

- Development of joint initiatives with clinical and scientific research centres and with enterprises.

HOW WE OPERATE

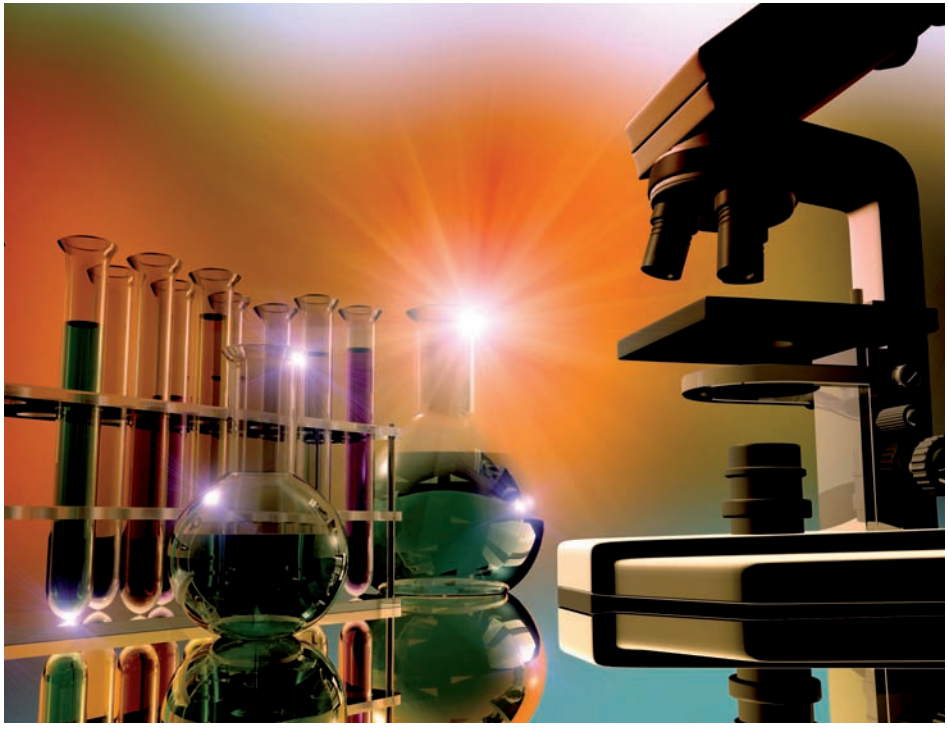
Fase 1 has two operational lines:

1. Technical-financial investment in innovative projects to bring new potential diagnostic and treatment agents to a more advanced stage of preclinical and clinical industrial development (Development Line).

2. Organisation and delivery of high-quality services for attracting national and international I and IIA clinical trials (Clinical Trial Line).

■ DEVELOPMENT LINE

Under this line, the company, tapping into key public funding from regional, national and/or community sources, provides financial and technical support for the development by researchers, universities, public research and experimentation centres, start-ups, spin-offs, micro-enterprises and



SMEs, of new diagnostic and treatment agents (new compounds that show promise for becoming medicinal drugs and new therapeutic formulations and applications) from the last preclinical research phases to the early human clinical trials.

This activity is carried out through national notices, addressed to both non-profit organisations and SMEs, in order to source, select, develop and bring to the clinical trial stage the most promising diagnostic and treatment agents.

The ultimate goal is to create added value by accompanying especially promising patents to a further development level, preferably to Phase 1.

Fase 1 srl selects the proposals showing the greatest promise from the scientific and medical viewpoint and as to application potential, and supports their implementation.

Each intervention usually comprises the following steps, which can be adjusted according to type of call:

1. PUBLICATION OF A CALL FOR EXPRESSIONS OF INTEREST

   Interested parties respond to the call, and may submit proposals in line with the specifications set out in the call.

2. ASSESSMENT OF THE EXPRESSIONS OF INTEREST

   Fase 1 srl assesses the expressions of interest received on the basis of criteria set out in the call.

3. INVITATION TO SUBMIT A DETAILED PROJECT

   After initial selection of the expressions of interest received, taking into account the public funding available at the time, the applicants who have passed the initial screening are invited by Fase 1 to submit a detailed project for review and final comparative assessment.

4. WORK PLAN

   Working together with successful applicants, Fase 1 srl then prepares an operational and financial plan covering intended development and trial activities.

5. CONCLUSION OF CONTRACT

   Once the work plan has been completed, Fase 1 srl and the successful applicant sign an agreement for implementation of the planned activities.

6. START AND IMPLEMENTATION OF PROJECT ACTIVITIES.

CLINICAL TRIAL LINE

Under this operational line, Fase 1, through its Clinical Research Unit, promotes, supports and coordinates drug trials, carrying out phase 1 and 2A clinical trials either on behalf of third parties, or as direct promoter as per its "Development Line" activities.

GOALS AND OBJECTIVES

- **Towards Pharma companies (sponsors)**: offer top-rate services in phase 1 and 2 trials in terms of quality and productivity.

- **Towards trial participants (healthy volunteers and patients)**: guarantee

competency, respect, courtesy and kindness.

- **For the inhabitants of Sardinia**: foster the creation of a local pool of expertise in the field of clinical research and drug production, professional development in the biomedical field, and generate high-level employment for medical and technical staff.

RESOURCES

- Staff with extensive experience in the performance of clinical trials.
- Ongoing training and updating programmes.
- Extensive database of healthy volunteers for phase 1 clinical trials.
- Large pool of patients for selecting participants in phase 2A trials and specific phase 1 trials.
- Adoption of Standard Operating Procedures (SOPs) in compliance with international regulatory standards, for managing the standard processes of all trials (relations with the Ethics Committee, definition of protocols and approval processes, regulatory compliance, management of operational relations with labs, quality control).
- Specific non-standard procedures for each type of application as necessary (administering to human subjects, doses, different trial designs).

FACILITIES AND SERVICES

The Clinical Research Unit (CRU) of Fase 1 srl has a floor area of about 300 m2 on the 11th floor of Brotzu Hospital, and meets the structural, utility and equipment requirements set out in the Presidential Decree of 14.01.1997 and the criteria for authorisation of Centres conducting clinical drug trials (Ministerial Decree 19.03.1998).

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The Unit is equipped with:

- Access control and alarm system.
- Twelve beds with 6 continuous patient monitoring stations (ECG, arterial pressure, heart rate, body temperature and arterial oxygen saturation) also enabling centralised real-time visualisation of vital parameters.
- Patient leisure area with satellite TV including pay TV channels, videogame console, computer with free Internet access, DVD players, book and video collection, newspapers and magazines and board games;
- Medical examination/treatment room with ECG machine and stress test machine, Holter monitor and emergency cart with defibrillator, aspirator and emergency medications.

- Testing lab with countertop centrifuge -80° C freezer, -20°C freezer and drug refrigerator with graphic temperature recorder and security key.

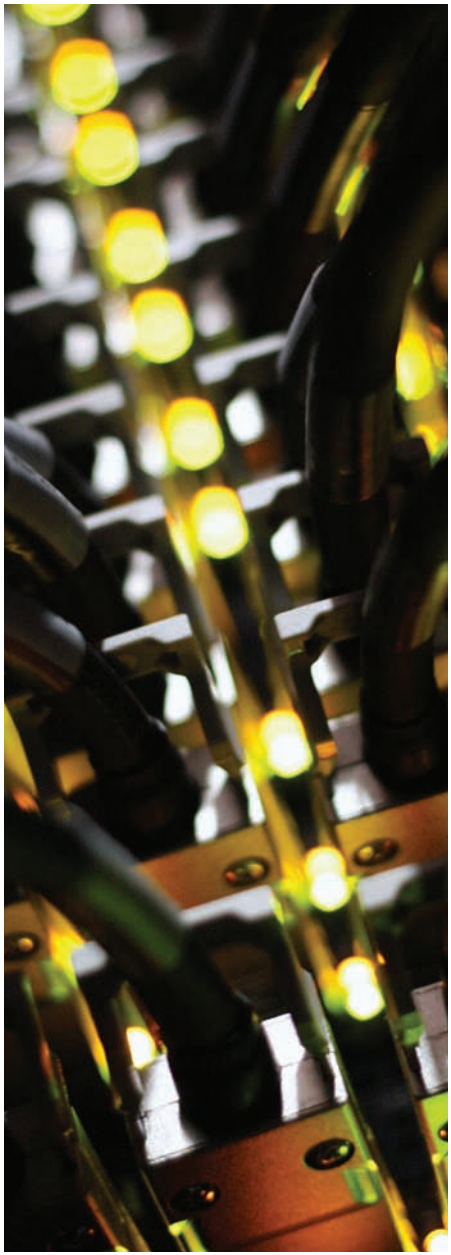
IT SYSTEM

Fase 1 srl has a state-of-the-art IT system. The Research Unit's IT network is based at the Brotzu Hospital in Cagliari and is linked to the Hospital's facilities (Library, Radiology, Testing Lab and Pharmacy) through the hospital's Intranet. It also has broadband Internet connection.

Great attention has been paid to IT security. The IT network located within the hospital has its own firewall and all communications on the hospital's Intranet and with the Internet are regulated by specific company policies.

All sensitive information and related communication protocols are encrypted and are stored on servers that are inaccessible from the Internet.

The whole IT system has been installed in



accordance with advanced data protection and disaster recovery criteria, using virtualisation technologies.

Again at the hospital, we offer broadband Internet connection, by cable or WIFI, to the volunteers enrolled in the trials, to enable them to pursue their work and leisure activities during the time spent in the ward. For security reasons, the public portion of the network is physically separate from the research network, with no communication between the two structures.

WHERE WE OPERATE

Fase 1 srl has been established and operates in a favourable regional context, marked by the presence of important elements, such as the technology cluster "Sardegna Biovalley", the Polaris Technology Park with its infrastructure and high-tech tenant enterprises, by the existence of a number of strategic R&D projects for medicine, and finally, a health service system which is achieving major medical, scientific and technology advances.

THE BIOMEDICINE AND HEALTH TECHNOLOGY CLUSTER

The Biomedicine and Health Technology cluster is located in the geographical axis Cagliari-Pula and was set up on the initiative of the Region of Sardinia and the Italian Ministry of the University and Research, with the following aims:

- Create a critical mass of highly competitive resources, activities, projects and initiatives
- Attract and enhance top-level scientific and technological expertise
- Define research priorities, focusing on product and process development
- Foster integration between enterprises, research centres and universities.

The Cluster aims in particular to foster local collaboration among researchers, companies and the health service on projects for the conception, testing, validation, development and implementation of new diagnostic and treatment procedures based on the principles of advanced and personalised medicine; the underlying objective is to raise the international profile of the cluster and attract external investment to create a biomedicine and biotechnology pole (Biovalley).

SARDEGNA BIO VALLEY

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POLARIS

POLARIS THE REGIONAL TECHNOLOGY PARK

Polaris, the Technology Park of Sardinia is a research and development facility providing optimum conditions for fostering technology R&D and industrial application capacity.

Operational setup includes:

- A system of advanced infrastructure for the location of innovative companies and R&D activities
- A system of services and tools for innovation, research and technology development.

The Park's main campus at Pula (CA), specialises in biomedicine, ICTs and bioinformatics: it hosts a community of more than 50 enterprises with about 400 researchers and engineers, and is equipped with advanced innovation services and state-

of-the art technology platforms.

THE STRATEGIC PROJECTS

The Technology Cluster and the Science and Technology Park, through close collaboration between business, research and health systems are implementing major R&D projects aimed at strengthening the biomedicine sector on the island, with a focus on the research areas targeted by Fase 1 srl.

HUMAN SIMULATOR HUMAN PROJECT

This project aims at setting up and operating a bioinformatic platform for developing a software to simulate Phase 1 clinical trials (dose finding, pharmacokinetics etc.) able to predict possible side effects and efficacy limits.

PHARMACEUTICAL LAB

Sardegna Ricerche plans to support the further evolution of the biomedicine and advanced biomedical devices sector in col-

laboration with Fase 1 srl by setting up pre-clinical testing laboratories based on GLP (Good Laboratory Practice) and GMP (Good Manufacturing Practice) criteria, and by favouring prototype and pilot productions in the Park (of both advanced medical systems and of drugs and supplements) and small-scale commercial productions (mostly supplements, nutraceutics, body care products, etc.).

GENOTYPING OF A HEALTHY CONTROL POPULATION

This project targets the individual genetic mapping of a large anonymised population of healthy Sardinians (about 3000 individuals).

This large number of genetic profiles, which will be processed and stored by means of dedicated bioinformatics procedures, will provide the basis and essential reference for effective study of the predisposing genetic profiles of individuals suffering from diseases with a strong genetic component and high prevalence in the region (e.g. type I diabetes, multiple sclerosis, etc.).

GENOME SEQUENCING IN AN INFORMATIVE NUMBER OF SARDINIAN INDIVIDUALS

This project aims at sequencing the entire genome of 10 persons from Sardinia or of Sardinian origin, using the Illumina-Solexa platform.

With the data thus collected it will be possible to define the common genetic variants typical of the Sardinian population (and absent from genotyping panels obtained by sequencing non-Sardinian individuals) and to develop systems for verification and large-scale use.

THE REGIONAL HEALTH PLAN

The Regional Administration of Sardinia has adopted a Regional Health Plan.

The Plan focuses on the treatment of certain diseases that are particularly widespread in the Sardinian population, defines the objectives for the Island's health service and identifies the tools for healthcare delivery.

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CORPORATE PROFILE

■ ORGANISATION CHART

DEVELOPMENT LINE

- General coordinator
- Project manager
- Technical-scientific expert
- Technical-economic expert
- Staff manager
- Administration officer
- Organisational secretariat officer

CLINICAL TRIAL LINE

- Director
- Principal investigator
- Co-investigators
- Quality control
- Head nurse
- Nurses
- Pharmacist
- Medical social worker

SCIENTIFIC AND STEERING COMMITTEE

The Scientific and Steering Committee, consisting of seven members, defines the company's technical and scientific priorities, selects the projects to be submitted to management, and checks the progress of financed projects.

Current Committee membership:

- GIOVANNI BIGGIO
  President, Full Professor of Pharmacology at Cagliari University, President of the Italian Society of Pharmacology
- ANTONIO CAO
  Director of the Institute of Neurogenetics and Neuropharmacology of the National Research Council (CNR), Cagliari
- ENRICO GARACI
  President of the National Health Institute (ISS)
- GIANFRANCO GENSINI
  Dean of the University of Florence Medical School
- GUIDO RASI
  General Director of the Italian Drug Regulatory Agency (AIFA)
- LUCA PANI
  Director of Research at the Institute for Biomedical Technologies (Milan) of the Italian National Research Council
- CARLO TOMINO
  Clinical Trials Unit Director at the Italian Drug Regulatory Agency