Phase I-IIa: Redefining Early Phase Clinical Services

Syneos Health® is a Global Professional Services Organization Designed to Help the Biopharmaceutical Industry Accelerate the Delivery of Much-Needed Therapies to Market

Our combined Contract Research Organization (CRO) and Contract Commercial Organization (CCO) offer a differentiated suite of services, processes and integrated solutions that improve customer performance. We have the ability to support customers in more than 110 countries, our global scale and deep therapeutic expertise enable Syneos Health to help customers successfully navigate an increasingly complex environment.

Syneos Health Clinical Solutions is dedicated to providing customers with a comprehensive range of Phase I-IV clinical development services. These include the conduct of clinical studies, biostatistics, data management, analysis of samples, project management, study monitoring, patient recruitment, safety and pharmacovigilance.

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Overview

Phase I-IIa Services
At Syneos Health, we strive to expedite clinical programs and build the foundation for continued development of the product. With more than 20 years of experience in Phase I-IIa services, we provide our customers with the appropriate talent, experience, processes and infrastructure to conduct their clinical studies successfully.

We meet the objectives of each study through our flexible approach to translational research and creative solutions tailored to our customers’ specific needs.

We offer a full range of services—from protocol development to report generation—to help our customers reduce costs, shorten their development timelines and obtain quality data. Our extensive experience, streamlined processes and state-of-the art facilities help mitigate risk in your Phase I-IIa services.

Outstanding Project Management
A dedicated project manager is assigned to each study, supported by a team of experts, including physicians and specialists in patient recruitment, clinical operations, quality assurance, biostatistics and clinical pharmacology. These experts work with sponsors to minimize risk and establish contingency plans, providing robust quality and regulatory controls to ensure protocol compliance and patient safety.

Tools and Methodologies in Phase I-IIa Studies
Through our strategic partnerships with universities, hospitals, private clinics, and our extensive central database, we have broad access to a significant population of potential participants, including special populations. This, along with our ability to develop efficient processes across the study, means that we can expedite the conduct of any study, regardless of its size or complexity. To help in this regard, we employ advanced technology to streamline the collection of real-time data.
Diverse Experience

We have broad experience in various study designs in all major therapeutic areas, along with a wide range of dosage forms to facilitate study and protocol development for efficient regulatory submissions.

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<thead>
<tr>
<th>Study Types</th>
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<tr>
<td>Age/Gender</td>
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<td>Bioavailability</td>
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<td>Drug-drug interactions</td>
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<td>Hormone therapy</td>
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<td>Neuroscience</td>
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<td>Dose Proportionality</td>
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<td>Respiratory Depression</td>
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Clinical Operations

State-of-the-Art Facilities
We operate modern clinics in North America: Quebec City, Canada and Miami, Florida. Additionally, we have a Virtual Clinic Model (VCM) in place to effectively run studies in Australia and throughout the APAC region. Both focus on inpatient treatment and translational medicine.

At our sites, doctors, nurses, medical technicians and experienced project coordinators are available to monitor the study and ensure the safety of participants. We also provide access to experienced staff in cardiac safety and drug interactions for more complex trials. Sample analyses can be performed at our two North American bioanalytical labs: Quebec City, Canada, and Princeton, New Jersey.

Safe Drug Handling
Each of our clinics maintains an on-site, state-of-the-art pharmacy that provides a range of delivery methods and special storage conditions, including those required for controlled substances. Drug product storage is controlled by a medication team comprised of a pharmacist and medication technicians who also assist with dispensing tablets and capsules, preparing suspensions and filling syringes. Dose preparation and drug dispensing—including IV bolus, IV infusion, subcutaneous and intramuscular delivery—is performed under aseptic conditions.

Dosage form preparation and dispensing is tightly controlled and monitored through the following measures:

- Limited restricted access
- Monitoring by a security alarm system, 24/7
- Temperature and humidity controls (15-25 °C and 30-60% H)
- Licensed for controlled drugs
- Laminar flow hoods for aseptic preparation techniques
- Ambient, refrigerated, -20 °C and -80 °C storage capabilities

Patient Safety and Data Integrity
We are a member of an inter-CRO data exchange of clinical trial participants. This exchange protects both study participants and data integrity by preventing simultaneous enrollment in multiple clinical trials and by alerting us when individuals are still within a washout interval.
Quality Management

Project Management Professionals
For each study, we assign a dedicated project manager as a primary point of contact and assemble a knowledgeable team of professionals in development, clinical operations, medical affairs, quality assurance, IT and clinical pharmacology. We believe this cross-functional approach is key to mitigating risk in clinical studies. By providing the necessary resources, solving problems and managing milestones, our project management team ensures that studies stay on track, on budget and on time.

Quality Assurance
Providing robust quality and regulatory controls throughout the entire study promotes compliance. To ensure the success of every study, our quality assurance processes include internal training programs, auditing vendors, validating software and establishing Standard Operating Procedures (SOPs). All of our departments and business processes are compliant with Good Laboratory Practices (GLP), Good Clinical Practices (GCP) and/or International Council for Harmonization (ICH) standards, and employees are given extensive training to ensure they are kept current. An independent Quality Assurance unit validates study data and reports, providing the basis for regulatory success. Our facilities have been successfully audited by major regulatory agencies, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada and several European agencies.

In addition, our external collaborators (hospitals and investigator sites) are audited to ensure that our quality standards are met.

Scientific and Regulatory Affairs Specialists
Scientific and regulatory affairs experts are available to collaborate throughout the study in assessing the bio-analytical and clinical feasibility, developing the protocol, presenting to the Institutional Review Board (IRB) and preparing the regulatory submission.

Effective study design starts with the development of a protocol that covers all of the study parameters and focuses on improved study efficiency. Working closely with sponsors, our Phase I-IIa experts can help develop the initial protocol, creating innovative study designs.

In addition, our team consults with sponsors who provide their own study design. We conduct a thorough feasibility study and assess inclusion/exclusion criteria to ensure successful program execution and patient safety. We then build a project plan to make certain we meet all critical milestones.
Access to Comprehensive Resources:

Project Manager
- Primary point of contact
  - Ensures expectations are met
  - Timely communication and reporting

Clinical Operations
- Participant/patient recruitment and screening
- On-site physicians and medical professionals
  - Monitor study
  - Ensure participant safety

Clinical Pharmacology
- Protocol
- Regulatory submission
- Biostatistics and pharmacometrics
- Data management
- Medical writing

Quality Assurance and Information Technologies
- Support services
  - Deliverables meet specifications

Rapid Recruiting
Our extensive, centralized database and strategic partnerships with local hospitals and independent investigators offer access to a large pool of potential participants, including a diverse set of healthy volunteers, special populations and patients. Selected hospitals and investigators can participate in a partnership model for specific study needs and even act as a clinical site for the realization of a project.

We customize recruitment strategies to suit the patient population and the therapeutic area. For complex studies, we can employ a number of strategies—from traditional print ads to social media—which are tailored to meet the objectives of each study. Our experience in executing marketing initiatives helps to ensure that we fill study panels quickly. In addition, we have successfully launched online incentive programs that have expanded access to healthy participants and special populations.
Quality Management (continued)

Clinical Pharmacology

Syneos Health clinical pharmacology team includes experts in pharmacokinetics, pharmacometrics, biostatistics and data management, backed up by experienced Quality Management specialists. Working together with the sponsor, we analyze the data using automated and validated systems for rapid compilation of the clinical study report.

Clinical Pharmacology Services

- **Biostatistics and Pharmacometrics**
  - Bioequivalence/bioavailability studies
  - Phase I-IIa clinical trials
  - Pharmacokinetics (PK) for preclinical studies
  - Toxicokinetics (TK) studies
  - Pharsight Knowledge Server (PKS) to effectively and securely manage PK/PD data and associated analyses
  - Derived data set creation
  - Model fitting
  - Statistical analysis plan preparation and writing
  - Tables, Figures and Listings (TFLs) programming
  - Population PK modeling and assessments
  - PK/PD and virtual patient modeling
  - Study design and Phase I Program strategy
  - Phase I Regulatory consulting and Agency meetings

- **Data Management**
  - Medical coding
  - Case Report Form (CRF) design and mapping
  - Database design and build
  - Data review
  - Submission-ready Clinical Data Interchange Standards Consortium (CDISC)-compliant data set production, Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)

- **Medical Writing**
  - Clinical study reports and summaries
  - Investigator brochures
  - Participation to Statistical Analysis Plan (SAP)
  - Safety, efficacy and PD data interpretation

Our Wide Range of Patient Populations Include:

- Asthma
- Cardiovascular disease
- Chronic Obstructive Pulmonary Disease (COPD)
- Diabetes
- Gastrointestinal diseases
  - Peptic ulcer disease (PUD) and/or gastroesophageal reflux disease (GERD)
- Geriatrics
- Hyperlipidemia
- Hypertension
- Hypogonadism
- Metabolic disorders
  - Extensive/poor metabolizers
- Obesity
- Renal impaired
- Rheumatoid arthritis
- Women’s health-related conditions
  - Healthy premenopausal women with regular menstrual cycles taking or not taking hormonal contraceptives
  - Surgically sterile women
  - Postmenopausal women

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Data Management

Our e-source Clinical Trial Management System (CTMS) reduces data verification time and the possibility of errors and eliminates the need for data transcription onto Case Report Forms. The system is specifically designed for Phase I clinical trials and allows for rapid study set-up (a standard study can be set up in a matter of hours). Front-end checks that are incorporated directly into e-source data capture include time and range tolerances, required fields and response-driven fields. We are able to further reduce the possibility of source-code errors through the use of data/time stamps, medical instrument interfaces and study-specific codes. Bar codes for identification of subjects, study medications, collected samples, processed samples and instruments ensure seamless tracking and data reliability. Our CTMS provides real-time access to accurate data, ensures source data integrity and improves study timelines.

Our team can provide clinical monitoring services during multi-center trials. For each study, we develop a rigorous monitoring plan to ensure that all customer requirements and timelines are met. All necessary monitoring tools are created based on the customer needs and protocol specifications.

Regulatory Support and Consulting

Ever-changing regulations set by regulatory agencies around the world represent a complex environment. To help sponsors navigate successfully, we have assembled an exceptional team of former senior-level FDA and EMA officials, in addition to other international regulatory and pharmaceutical experts. We provide comprehensive support services to help sponsors navigate the 505(b)(2) regulatory pathway. Whether sponsors are considering brand extensions, new indications, formulations, active ingredients (e.g., new salt), dosage forms or a combination of new entities, we have the strategic and scientific expertise to help them develop and introduce new and improved products and invigorate their brands.

We typically file more than 180 clinical trial applications each year. This high volume of work, along with our lengthy relationships with authorities, facilitates rapid study approval. During the last three years, the average review time for the bioequivalence studies we manage was six days, and for Phase I studies, it was just 20 days.
Study Types

First-in-Human
First-in-human clinical trials require detailed preparation and care, recognition of ethical and safety responsibilities to study participants, and a deep understanding of the critical role these studies play in moving a compound forward. Our experienced, specialized operational teams, as well as our access to special populations, ensure a smooth transition into ascending dose studies. Drug concentrations and biomarkers of interest can be measured on site in our bioanalytical laboratories and then integrated into study reports.

We have extensive experience in both small molecules and biological compounds and have the capability to manage all aspects of the study process. Our team also executes combination study designs, such as SAD/MAD, as a means to reach proof-of-concept faster, safer and more economically. Our in-house bioanalytical capabilities provide timely dose-escalation information based on safety and PK data.

Proof-of-Concept
Proof-of-concept studies explore the relationship between the dose and desired outcome, and establish the safety of drug candidates in the target population. Our scientific team works closely with sponsors to design proof-of-concept studies to reduce risk and avoid costly, late-stage clinical development failures. In addition, because of our knowledge across a wide range of therapeutic indications and collaboration with local hospitals established through our Patient Access Model, we can provide sponsors with enhanced access to study participants with special conditions and diseases.

Biosimilars
Despite an evolving regulatory landscape and increasing complexity in proving safety/efficacy on par with existing treatments, opportunities in the global biosimilars market continue to grow. At Syneos Health, our world-renowned clinical research and commercialization capabilities work hand-in-hand to accelerate our customers’ success in this challenging environment. With a fully integrated range of capabilities from clinical development, regulatory consulting, in-house ligand-binding and immunogenicity services to industry-leading market access and commercialization support, we are ready to help our customers through any challenge faced in the development of their biosimilar product.

Bioavailability/Bioequivalence
Our considerable experience in conducting a full range of bioavailability and bioequivalence clinical trials has given us a thorough understanding of the generic development process. Customers can have confidence that their projects will be completed professionally and on time.

QT/Thorough QT
We conduct investigational drug studies to assess risk as early as possible and evaluate the drug's effect on the cardiovascular system. QT/TQT studies are conducted at one of our own facilities, with an experienced team of trained staff and nurses supporting each study. We maintain close relationships with electrocardiogram (ECG) core laboratories and can monitor as many as 49 participants simultaneously on our cardiac telemetry system—an ideal use of technology for first-in-human studies of drug candidates with potential cardiac liability.

Drug-Drug Interaction
As required by regulatory agencies, how an investigational drug is metabolized must be defined during early drug development, and its interaction with other drugs must be explored as part of an adequate assessment of safety and effectiveness. Our professionals evaluate the safety profile of the compound under co-administration regimes while ensuring the well-being of study participants. Because not every drug-drug interaction is metabolism-based, but may arise from changes in pharmacokinetics caused by absorption, distribution and excretion interactions, we offer a full range of studies, including the evaluation of pharmacodynamic effects.
Validated Assays for Compounds with Potential Drug-Interaction or Co-Administration Studies

<table>
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<tr>
<th>Miscellaneous</th>
<th>Oral Hypoglycemic Agents</th>
<th>3A4,5,7 Macrolide Antibiotics</th>
<th>Miscellaneous</th>
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<tr>
<td>Digoxin</td>
<td>Glipizide</td>
<td>Clarithromycin</td>
<td>Aripiprazole</td>
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<td>Docetaxel</td>
<td>Angiotensin II blockers</td>
<td>Erythromycin</td>
<td>Buspirone (m)</td>
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<td>Torsemide</td>
<td>Diazepam</td>
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<td>Hydrochlorothiazide</td>
<td>Warfarin</td>
<td>Midazolam (m)</td>
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With our broad range of clinical development and commercialization services, we can tailor our offerings to your company’s specific needs.

From a comprehensive strategic relationship to specific services, we commit to the same level of drive, passion and expertise to accelerate your success.

We create better, smarter, faster ways to help biopharmaceutical customers accelerate performance to address modern market realities.

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<tr>
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<th>Address</th>
<th>Square Feet</th>
<th>Beds</th>
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<tr>
<td>Miami, FL</td>
<td>+1 305 547 5800</td>
<td>Phase I-IIa Clinic</td>
<td>23,000 sq. ft.</td>
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<tr>
<td>Montreal, QC</td>
<td>+1 800 831 4001</td>
<td>Offices and Screening Center</td>
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<tr>
<td>Princeton, NJ</td>
<td>+1 609 951 0005</td>
<td>Laboratory</td>
<td>40,000 sq. ft.</td>
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</tbody>
</table>

Quebec City, QC

+1 800 831 4001

Phase I Clinic and Laboratory
- 151,700 sq. ft.
- 248 beds

Contact us:
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About Syneos Health

Syneos Health® (Nasdaq:SYNH) is the only fully integrated biopharmaceutical solutions organization. The Company, including a Contract Research Organization (CRO) and Contract Commercial Organization (CCO), is purpose-built to accelerate customer performance to address modern market realities. Learn more about how we are shortening the distance from lab to life® at syneoshealth.com.