BOSTON BIOTECH
CLINICAL RESEARCH

BEST of CAMBRIDGE
Early Clinical Research &
Regulatory Consultants

Increasing Investor's Evaluation of SME Biotech in a Slumping Market.

12th Clinical Trials Strategic Summit 2023

May 10th- 11th 2023
Boston, USA

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The Biotech Industry Has Experienced a Decrease in Investments

1. Increased competition: More players entering the market, which has led to a saturation of the market and decreased investor interest.

2. High failure rate: With many drug candidates failing in clinical trials, leading to significant financial losses for investors.

3. Economic uncertainty: The COVID-19 pandemic and global economic downturns, has led to a decrease in investor confidence and a more cautious approach to investment.

4. Regulatory challenges: Drug approval process can be lengthy, complicated, and expensive, leading to increased costs and delays in bringing drugs to market.

5. Lack of attractive investment opportunities: With few promising drug candidates in the pipeline, and a limited number of potential blockbuster drugs.

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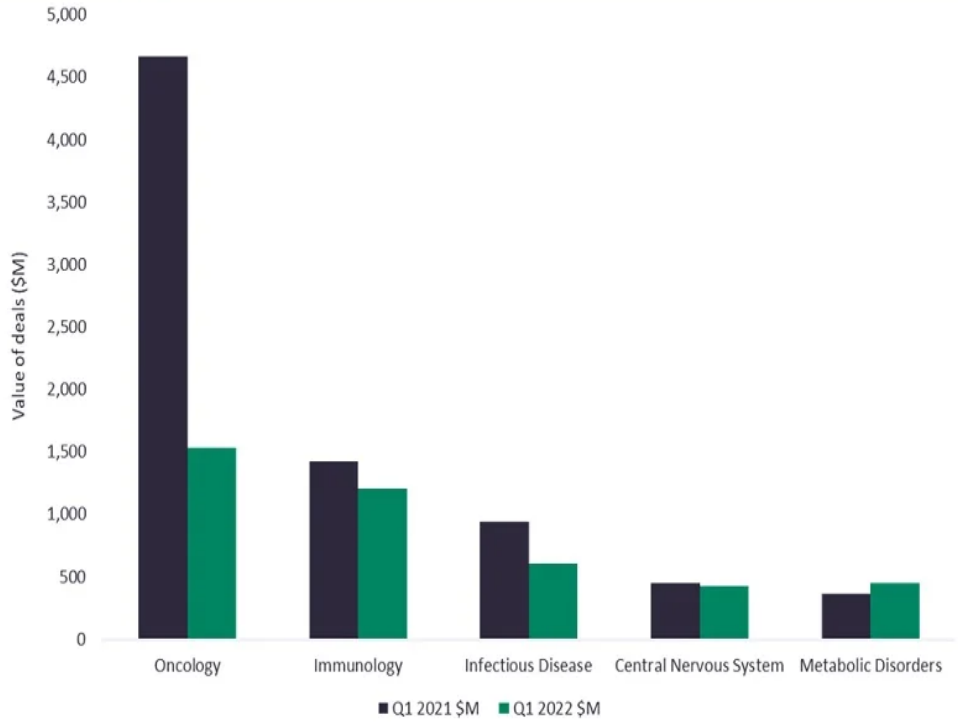
2022 Drop in Venture Financing

Figure 1: Venture Financing for US-Headquartered Biopharmaceutical Companies for Top Five Therapy Areas in Q1 2021 and Q1 2022



Source: GlobalData, Pharma Intelligence Centre Deals Database (Accessed 30 May 2022)

Notes: Includes deal values for all announced deals in Q1 2021 and Q1 2022.

Deals include innovator drugs only for marketed, pre-registration, Phase I, II, III, preclinical and discovery for US-headquartered target companies.

A deal can be tagged to more than one therapy area based on the therapy areas related to the drugs for that deal.

- A significant increase in venture financing in the biotech private sector was seen in 2021, entering a bull market where stock prices were on a continuous rise.
- This caused a biotech bubble that has since burst where stock declined, resulting in this year entering a bear market.
- A 46% drop in venture financing deal value for US-based biotech companies was seen, from $7.8bn in Q1 2021 to $4.2bn in Q1 2022.
  - Oncology received the largest total venture financing out of the top five therapy areas with $4.7bn in Q1 2021, but this decreased by 67% to only $1.5bn in Q1 2022.
  - Infectious diseases had the second largest decrease in venture financing by 36% from Q1 2021 to Q1 2022, with $0.9bn and $0.6bn, respectively.

Source: GlobalData's Pharma Intelligence Centre Deals Database.

Biotech's Market Outlook in 2023

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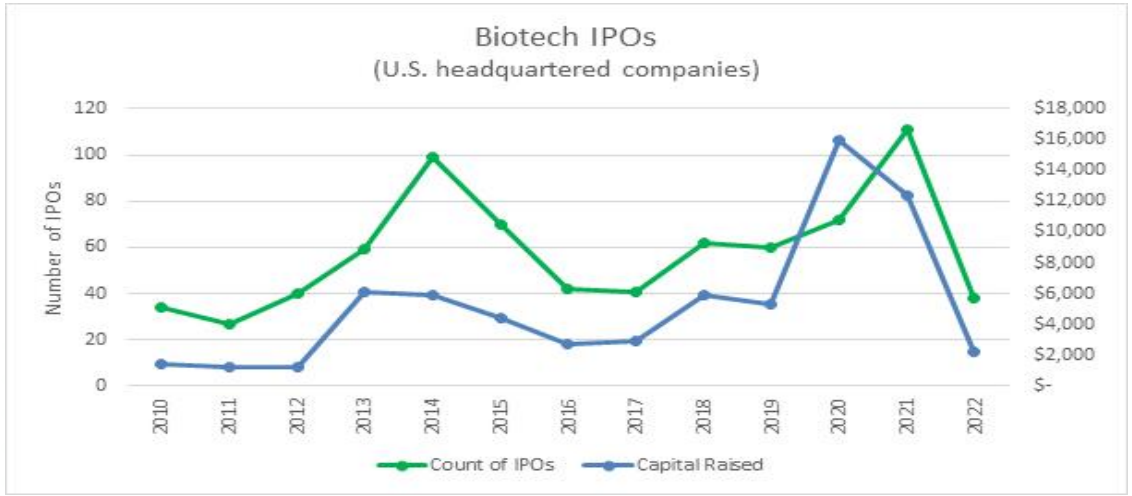
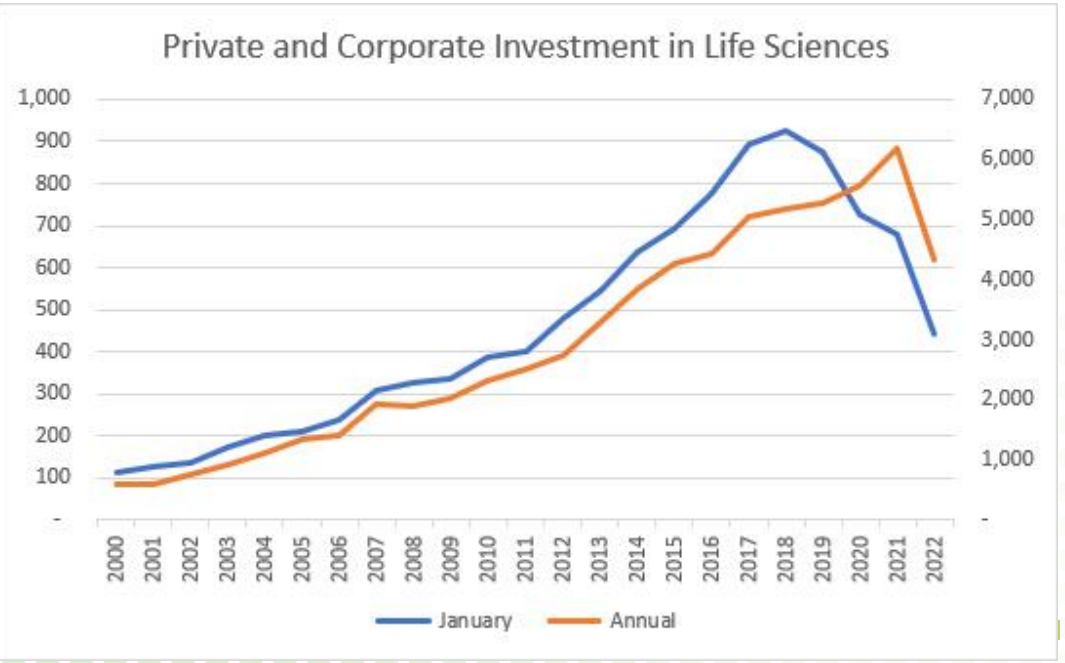
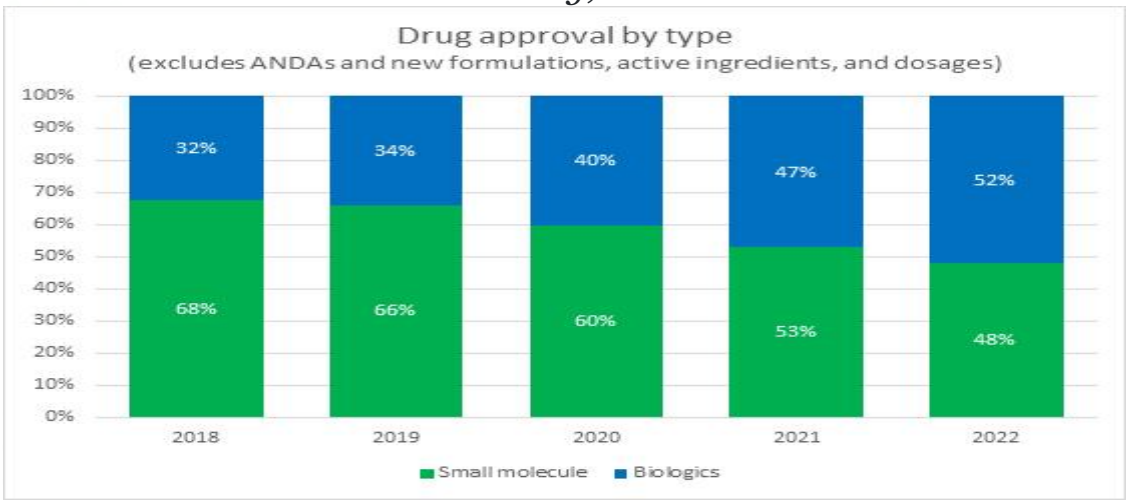


Source: Bloomberg, RSM US LLP



Source: Pitchbook, RSM US LLP



Source: FDA, RSM US LLP

VC funding will rebound by the end of 2023

Gene Frantz, General Partner, Capital G

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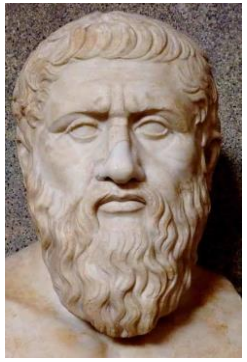

"The beginning is the most important part of the work."

Plato

Even in Good Times, Nothing is Assured

Demand early, solid planning on clinical pathway and end points to increase your success

- Only **1 out of 10** drugs that enter the clinical testing obtains market approval.
- The cost of clinical trials has increased significantly over the past decade, and costs continue to grow.
- According to clinicaltrials.gov, there were approximately 26,000 new clinical trials registered in 2020.
- Small biotech companies face reduced access to funding due to investors risk-averse during uncertain economic times and market competition.

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What Investors Look For in BioTech Companies?

Clinical trial progress: The number of patients enrolled in trials, the phase of the trial, and any regulatory milestones that have been achieved or are upcoming.

Pipeline development: This includes compounds or products in development, as well as their potential for revenue or commercialization.

Product development: Status on the development of a product, including the progress of preclinical studies, clinical studies, and regulators comments and concerns.

Regulatory: Progress of regulatory approvals and submissions, including FDA, EMA, and other regulatory authorities.

Market size and potential for growth: The size of the target market for a product and its potential for growth, as well as the competition in the market.

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An Early Development Strategy in the Pitch Deck to Win

Early Development Strategy

- Unmet Medical Need definition
- Product Presentation
  - Swot Analysis Indications
  - Clinical Landscape
  - Regulatory Strategy
  - Clinical Program & Trial Design
  - Biomarkers & Endpoints
  - Road Map & Clear Goals
- Competition
- Market Size

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Start by working on the Asset Strategy Development

- **Indication/s Identification:** Evaluate indications in orphan and no orphan diseases based on the product's specificity and biomarkers, genes, and target organ
- **Indication/s Standard of Care:** Available treatments adopted accordingly to line of therapy and treatment guideline if available
- **Unmet Medical Needs**: Based on treatment success rate and safety profile explore unmet medical needs
- **Risk/Benefit of Indication/s:** Ways to address potential contingencies or mitigate challenges, with options for modified or alternative development scenarios.
- **Swot Analysis:** for each indication
- **KOLs engagement :** Indication insight, medical comments, and advice.
- **Back-bone Clinical Plan** including:
  - **Phase I Synopsis**
  - **Regulatory Strategy and Requirements Alinement**
  - **Target Population & Objectives:** for POC and Pivotal studies

Clinical Program & Trial Design

Rare and Non-Rare Diseases Clinical Studies

- Real World Data (RWD): Routine & SOC treatments
- Real World Evidence (RWE): Observational trial
- N-of-1 trials: Example of Cystic Fibrosis (Vertex)
- Synthetic Control Arms: RWD from multiple sources
- Pediatric study: 2012 FDA; Safety and Innovation Act
- Basket Trial: Multiple Disease Type
- Umbrella Trial: Multiple Targeted Therapies
- Platform Trial: Multi therapy arms compared a common control
- MOT Trial: Hybrid of biomarker based interventional trial and RWD

Regulators showed an increased flexibility to use accelerated approval programs and external (RWD) control arms.

Regulatory Strategy to aligns Clinical Program with Regulatory Requirements

1.Regulatory Intelligence: Identify the specific regulations and guidelines

2. Authority Interactions: Early interactions can help seek regulatory advice, clarify requirements, and obtain scientific guidance on trial design, endpoints, and safety assessments

3.Submissions and Approvals (pre-IND, IND): Prepare and submit regulatory filings, applications, or notifications to regulatory authorities.

4.Clinical Trial Design and Endpoints: Ensure that the trial design supports the intended product claims and provides meaningful data.

5.Target Product Profile (TPP): Early TPP for the investigational product.

6. Risk Management: Integration into the regulatory strategy

7. Ethical and Safety Considerations: Address ethical considerations related to the protection of human subjects participating in the clinical trials

8.Safety Reporting and Pharmacovigilance

9.Regulatory Strategy Iteration: Remain flexible and adaptable to adjust the strategy as new information becomes available.

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Road Map for Adaptable & Achievable Clear Goals

1. Strategic Planning: help prioritize initiatives, allocate resources effectively, and make informed decisions about investments, resource allocation, and timelines.

2. Stakeholder Engagement: Facilitate engagement and alignment with stakeholders, including investors, and partners.

3. Transparency and Accountability: Enables tracking progress, identifying delays or bottlenecks, and taking corrective actions as needed.

4. Risk Mitigation: Reducing the likelihood of project delays or failures

5. Flexibility and Adaptability: Reflect the evolving and priorities of the program.

6. Resource Optimization: Resource allocation by initiatives, timelines, and available resources.

7. Clear Goals: Ensure that goals are specific, measurable, attainable, relevant, and time-bound (SMART).

8. Continual Improvement: Evaluating progress and incorporating new ideas or technologies into future iterations.

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Early Development Strategy can help **Minimize the Risks and Costs** associated with drug development while **Maximizing the Chances of Success** by enabling early identification of safety and efficacy concerns, early **Engagement with Regulatory Authorities**, and early **Identification of the Patient Population**.

Invest in an Early Strategy for Your Pitch Deck

Early Development Strategy has several advantages, including:

1. **Identification of safety profile:** Early strategy helps identify any safety concerns associated with the drug candidate, allowing for modifications

2. **Early identification of efficacy:** Early strategy provides early signals of efficacy, allowing for early decision-making.

3. **Time and cost savings:** Early strategy optimizes ph1-2 studies, which save significant resources in late studies.

4. **Early engagement with regulatory authorities:** enabling sponsors to address any regulatory concerns or issues before advancing the drug candidate.

5. **Early identification of patient population:** identify the patient population that is most likely to benefit from the drug candidate, allowing for more targeted recruitment in later-stage clinical trials.

Building a Compelling Story for Investors

BBCR Builds Successful Early Clinical Strategy With Investor's Package

Partnering with BBCR includes:

- Scientific and medical rationale supporting the program development plan
- Indication selection with genetic, molecular, and clinical-related data
- Development of the asset strategy, backbone clinical plan & study synopsis
- KOLs engagement and recommendations
- Regulatory strategy and early regulators' engagement & recommendations
- Development of a Clear & Compelling Story of your Product Development
- Investor package development and regulatory engagement activities are to be run in parallel to obtain the best results for the program advancement and a timely manner.

The FDA recommendations significantly impact investors concerning:

- Asset Strategy Validation
- Confidence in the program success rate

Who We Are

BBCR consulting dedicated to small/medium size biotech, pharmaceutical, and device companies with 20-year experience in oncology, inflammation, rare diseases and orphan program development.

- We provide regulatory, clinical, and biomarkers strategies for the growth of pharmaceutical innovators and to nurture their products' strength.
- We are committed to increasing trial success rate, reducing costs and time, and maintaining the highest standards of integrity and professionalism.
- We aspire to become your committed partner in early regulatory, translational and clinical research.

OUR CORE TEAM

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Candida Fratazzi, MD

- Founder and President
- Clinical Senior Advisor
- SFDA Advisor
- Former Shire Clinical Lead

Federico Goodsaid, PhD

- Regulatory Senior Advisor
- Former FDA Director

Claudio Carini, MD PhD

- Biomarker Senior Advisor
- Biomarker Senior Advisor NIH (Oncology, Inflammation)
- Biomarker Senior Advisor King's College (UK)
- Former Pfizer Global Head of Biomarkers
- Former Biomarker Advisor NIH (CNS)

Market Approved Drug

1. CASIMERSEN™ (**Sarepta**): DMD
2. ZINBRYTA™ (**Biogen**): Multiple Sclerosis
3. TAZVERIK® (**Epizyme**): Epitheliod Sarcoma
4. TECFIDERA™ (**Biogen**): *Multiple Sclerosis*
5. VPRIV™ (**Shire**): *Type 1 Gaucher Disease*
6. REPLAGAL® (**Shire**): *Fabry Disease*
7. Tygacil ® (**Pfizer**): Infectious Disease
8. Ezetimibe (**Scheing-Plough**): Atherosclerosis
9. Ivacaftor (**Vertex**): Cystic Fibrosis
10. Mabthera (**Roche**): Rheumatoid Arthritis
11. Tocilizumab (**Roche**): Rheumatoid Arthritis
12. Briakinumab (Abbott) Psoriasis
13. Gilenya (**Novartis**) Multiple Sclerosis
14. Daptomycin (**Cubist**): Infectious Disease
15. Anavex2-73 (**Anavex Corp**.): Parkinsons
16. MBQ-167 (**MBQ pharma**): Metastatic Cancer

Approved Diagnostics

1. AxSYM Diagnostic System (**Abbott** Diagnostics)
2. 130-gene NGS oncology panel (**TOMA** biosciences)
3. Invision First-lung (**Inivata**)

EXPERIENCE & EXPERTISE

OUR SERVICE & METHOD

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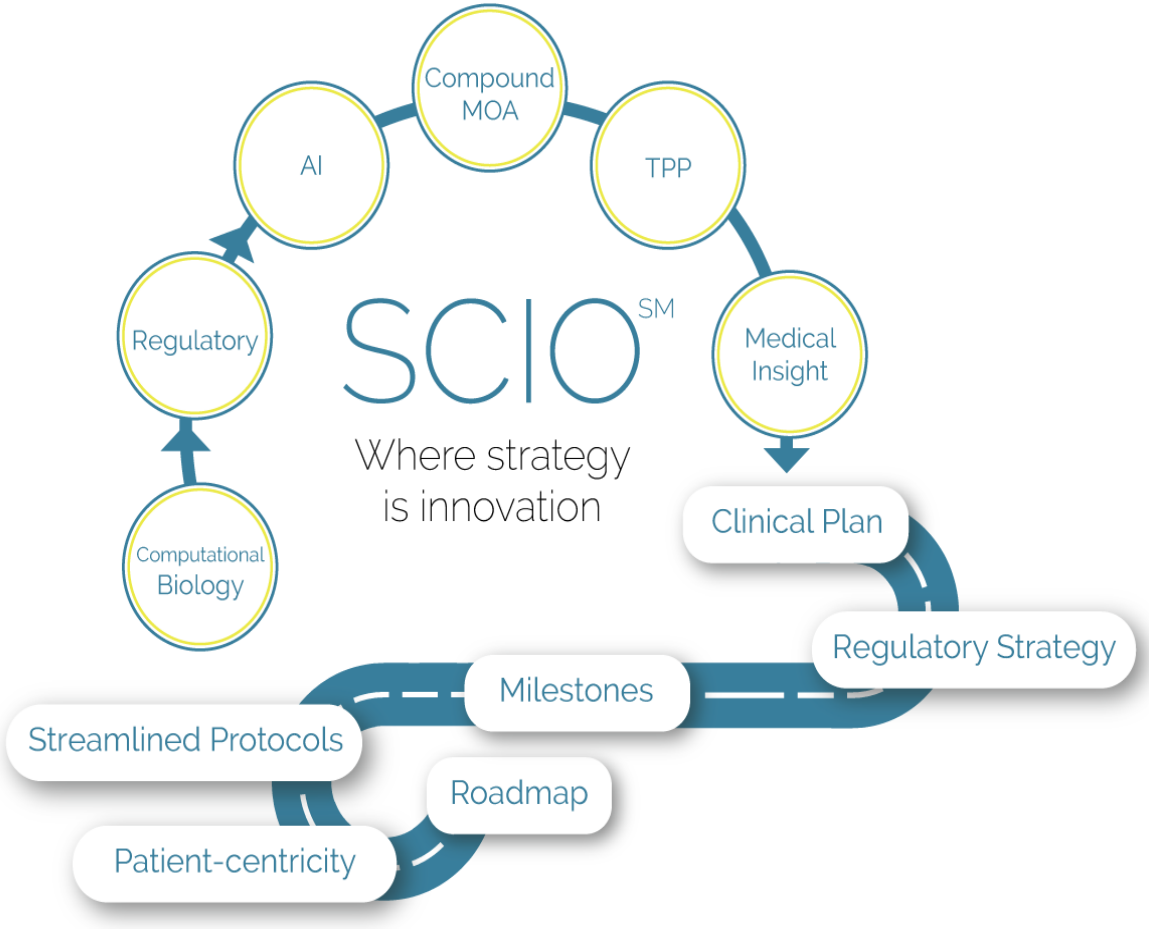
SCIO$_{SM}$

The BBCR proprietary SCIO$_{SM}$ method generates a product-specific early-development regulatory strategy and clinical plan taking advantage of appropriate source knowledge such as AI and computational biology.

The SCIO$_{SM}$ method provides the following:

- Investors' package
- A clear, actionable, and sustainable road-map
- Risks management and challenge solutions
- Up to 30% saving in the clinical trial



EARLY DEVELOPMENT SERVICES

Regulatory Affairs

- Regulatory strategy
- Assessment of nonclinical and toxicology studies
- Protocol assistance, scientific advice, pIND, IND
- Pediatric Investigational Plan
- Orphan drug designation (FDA and EMA)

Clinical Research

- Orphan drug clinical research consultant
- Data-driven evidence, streamlined clinical plan
- Study design optimization with patient enrichment and endpoints considerations
- Study Synopsis, design and protocol development

Biomarkers

- Biomarker strategy and plan
- Data driven surrogate endpoint/s
- Surrogate endpoint determination and qualification

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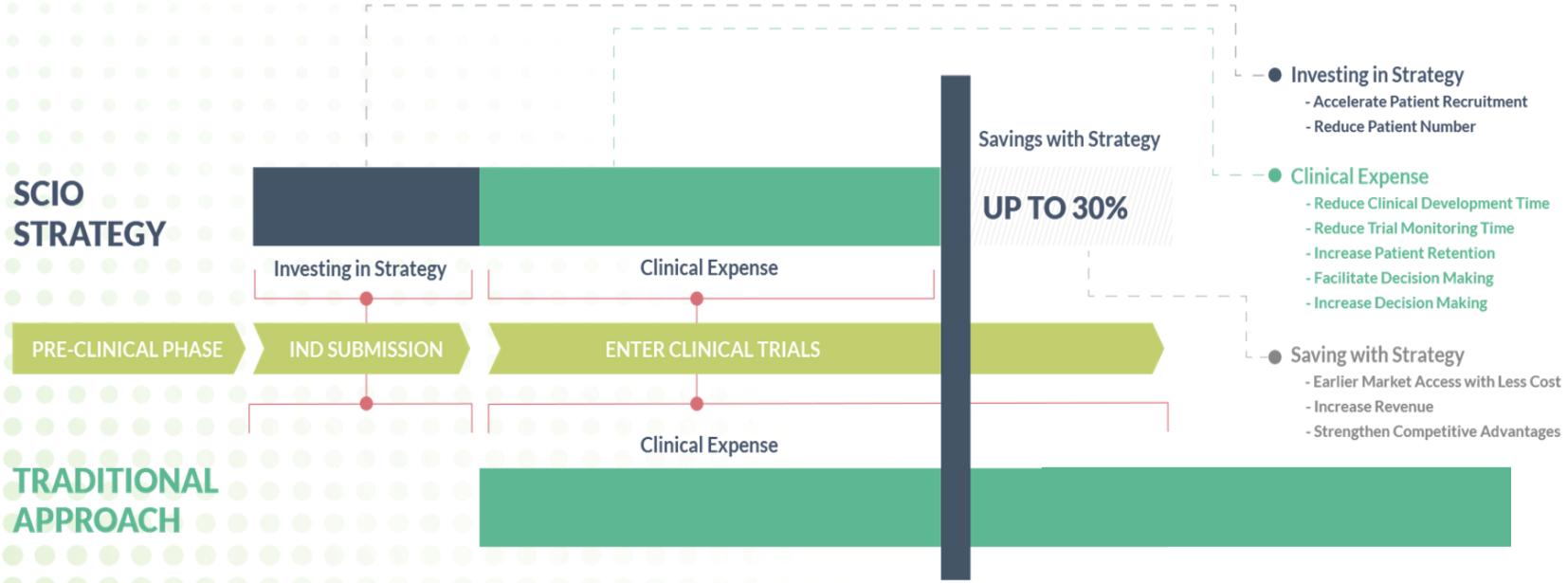
COMPARISON OF TOTAL EXPENSE AND TIME



Comparison of Total Expense and Time

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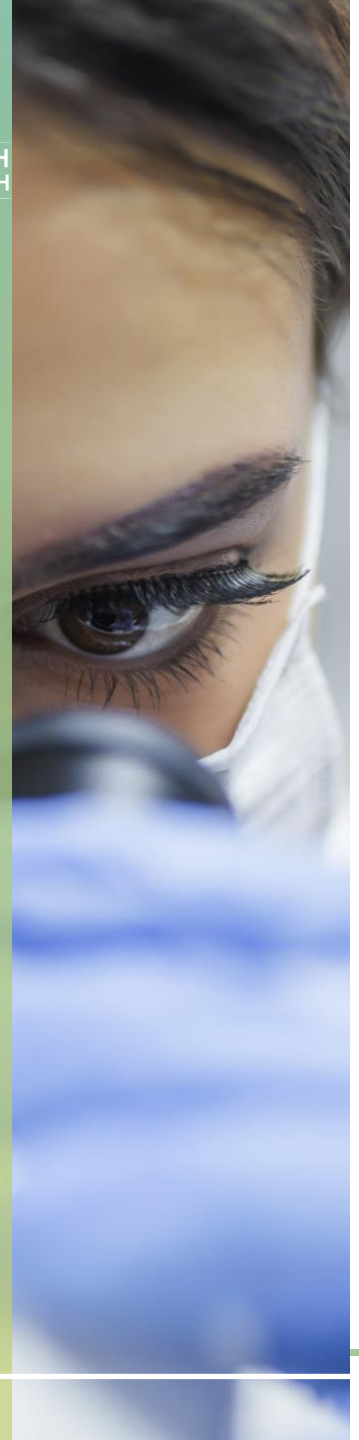
Solid Tumor
- Prostate Cancer
- Breast Cancer
- Lung Cancer (NSLC)
- Head&Neck Cancer
- INI1-Negative Tumors
- Plexiform Neurofibromas
- Synovial Sarcoma
- Paraganglioma
- Pancreatic Cancer
- Renal Cell Carcinoma
- Synovial Sarcoma

Hematologic Tumor
- Acute Lymphoblastic Leukemia
- Multiple Myeloma
- Peripheral T-Cell Lymphoma (PTCL)
- Acute Myeloid Leukemia
- Non-Hodgkin lymphoma (NHL)

Inflammatory Disease
- Rheumatoid Arthritis
- Ulcerative Colitis
- Crohn’s Disease
- Lupus (SLE)



ONCOLOGY & INFLAMMATION
SERVICE & EXPERIENCE

KOLs meetings	CRO selection
Development clinical plan	CRO and study management
Pre-IND and IND briefing books and meetings	Safety monitor
Development regulatory strategy	Trial rescue
Trial design and protocol	Data analysis and CSR
CMO and Medical Monitor	Due Diligence

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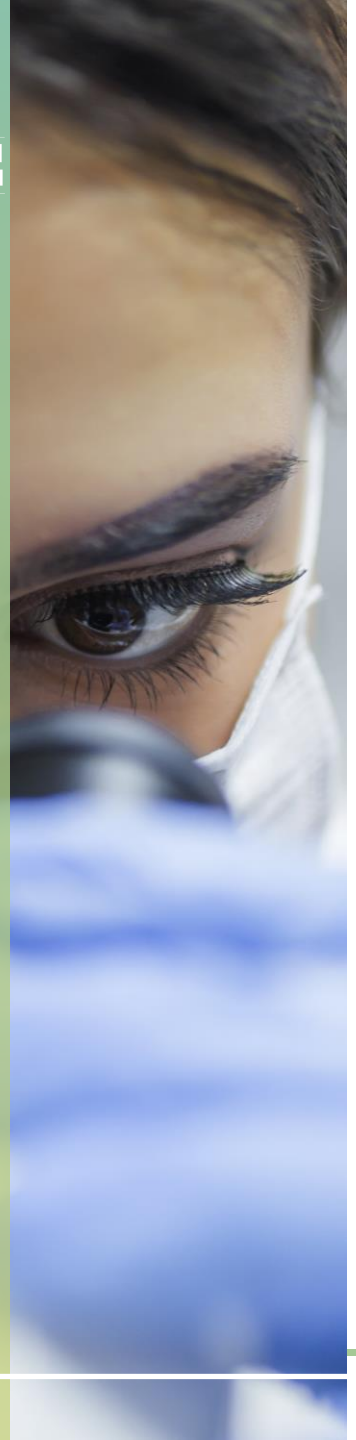
Rare Diseases

- Pemphigus
- INI1-Negative Tumors
- Plexiform Neurofibromas
- GCDs
- Sickle Cell Disease
- Synovial Sarcoma
- Acute Lymphoblastic Leukemia
- DMD
- Fabry Disease
- Hyperoxaluria
- Multiple Myeloma
- ALS
- WHIM
- Peripheral T-Cell Lymphoma (PTCL)
- Cystic Fibrosis
- Phenylketonuria
- Beta-Thalassemia
- Paraganglioma
- Pancreatic Cancer
- Acute Myeloid Leukemia
- Gaucher Disease
- Hereditary Angioedema
- Renal Cell Carcinoma
- Multiple Sclerosis



RARE DISEASE
SERVICE & EXPERIENCE

Orphan Petitions	CRO selection
Development regulatory strategy	CRO and study management
Pre-IND and IND briefing books and meetings	Safety monitor
Patients identification and awareness	Development clinical plan
Trial design and protocol	Data analysis and CSR
CMO and Medical Monitor	Due Diligences

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CLIFF NOTES

→ Funding Access

Developing an Investors' Package that wins Due Diligence.

→ Product Development Success

Adopting an Early Development Strategy including Swot Analysis Indications, Clinical Landscape, Regulatory Strategy, Road Map & Clear Goals

→ Partnering Opportunities

Investing in a unique product profile.

Invest in the Investor's Package Success

- **Clinical Landscape,** current and future.
- **Swot Analysis** for each target disease
- **Regulatory Strategy** enabling to address regulatory concerns
- **Flexible Road Map** actionable and sustainable
- **Clear Goals** to pre-empt challenges and manage risks
- **Cost-effective** for up to 30% saving in clinical trial
- **Robust clinical data** for Decision-Makings

CASE STUDY

Strategy to Avoid Market "Me Too" in Rare Disease

PROJECT Develop the product avoiding a "me too" treatment in an orphan population when a very similar product had a market monopoly for 15 years.

PROPOSAL Created a clinical innovative strategy and trial designs that avoided the obvious head to head design, which would had required an unfeasible number of patients, and be at high risk to prove efficacy and safety in the rare disease population. The FDA at the IND meeting approved the proposed clinical plan with no modification.

RESULTS The proposed clinical plan was successful, and the product approved in many countries.

Carla Epps, M.D., at the FDA/CDER/OND described this clinical plan:

- Well planned
- Clinically meaningful endpoints
- Each trial had a distinct purpose

Fast Value Growth of an Ultra-Rare Disease Start-up Biotech

PROJECT A start-up biotech asked Dr. C. Fratazzi to act as a CMO and to BBCR to provide support with pre-IND clinical strategy for the three compounds in the pipeline each of which for the treatment of an ultra rare disease.

PROPOSAL **T**he FDA was engaged in pre-IND meetings to discuss pre-clinical data needed for the FIM study, adoption of Real-World Evidence (RWE) as a comparator arm for Phase III pivotal studies, and the agreement for the 505(b)(2) NDA approval process.

RESULTS The FDA approved the use of RWE as comparator arm in the Phase 3 pivotal study and the clinical development plan proposed.

The start-up was sold for $26.6M, with only 9 months of regulatory and clinical planning work

OUR CUSTOMERS

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WHO WE WORK FOR

- Small and Medium Sized Pharmaceutical and Biotech Companies
- Venture Capitalists and Investors
- Diagnostic and Device Companies

FujiFilm, Nimbus Therapeutics, X4 Pharma, Sarepta Therapeutics, Aquinox, Alnara Pharma, Marquet, Chiesi, Biogen, Ichorion Therapeutics, Nimbus Therapeutics, Erytech, UV Technologies, Corfo, Excemed, Taligen Therapeutics, Probiomed, GLG, Mallinckrodt, Epizyme, Akrivis Technologies, Momenta, PCUT, Madvisors, Dinsmore, EMD Serono, TLG Pharmaceutical, Kyowa Kirin, Mexico Conacyt, Foreign Affair Canada, Remiges Ventures.

WHAT THEY SAY ABOUT US

"..strong track record experience developing treatments for rare diseases. ..ability to effectively build clinical development programs and provide unique support for regulatory interactions."

Ichorion Therapeutics, CEO

" ..have the vision to see through the details of complex clinical and regulatory strategy issues and comes up with practical
and innovative solutions."

Shire, Global Lead Neurogenetics and Rare Diseases

"...brings a track record of success...that made BBCR the perfect fit for our pharmaceutical licensing platform."

FujiFilm Pharma USA, Head of Operations

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OUR SUCCESS STORIES

Industry Recognition

369 Scientific Publications

152 Products Developed

143 Years of Experience Combined

30% Reduction in Clinical Trial Cost

2011 FDA defined our rare disease program: as "well-planned and clinically meaningful endpoints."

2016 OPPD granted for a "subpopulation of NSCLC patients."

2018 BBCR's effective pre-IND strategy: start-up bought within nine months.

2020 Patients' enrolment was triplicated during the COVID pandemic with 2/3 site reduction.

2023 BEST of CAMBRIDGE Award for Early-Clinical Research & Regulatory Consultant

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