1 2 3 Innovation Initiative

Unlocking a new medicine's full potential by providing non-dilutive financial support combined with clinical trial experience and drug development expertise.

The Initiative at a glance

The 123 Innovation Initiative provides non-dilutive financing for conducting early-stage clinical trials that are more effective, more efficient, and more informative.

- **Non-dilutive financing** provides a loan to reach the next investment round while maintaining equity.

- **More effective,** as clinical trials performed at CHDR have a significantly higher likelihood of securing financing in the next round.

- **More efficient,** tackling the most critical issues by passing a series of micro-milestones before investing in subsequent trial phases.

Who is eligible?

- **Start-up biotech:** companies seeking to obtain early clinical data without diluting their equity

- **Academic programmes:** that need clinical data to establish spin-off businesses and/or establish partnerships with Pharma companies

- **Research programmes:** that have a promising approach but need to revise their strategy after encountering early roadblocks

Contents

Introduction

The 123 Innovation Initiative was established in order to provide non-dilutive financing and drug-development expertise to innovative young biotech companies.

We enable companies to perform early development experiments in human subjects more effectively and more efficiently. Importantly, the existing investors' equity is not diluted, as financing is provided in the form of venture debt. The Initiative provides a unique combination of venture lending and drug development expertise, including access to the full range of services provided by the Centre for Human Drug Research (CHDR), a translational drug development company located in Leiden, the Netherlands.

The challenges

Industry challenges

Relatively small biotech companies account for the majority of innovative first-in-class drugs; however, these companies often lack the early development expertise needed to perform focused experiments that enhance the project's value.

Changing market dynamics require increased discipline and improved methods for measuring performance. Traditional clinical trial development models generally fail to optimally profile new molecules, and they often fail to detect both risks and opportunities in the early stages.

- A **bottleneck** in the value chain is the **translation of preclinical potential into relevant clinical effects.** Clinical research expertise and disease knowledge – as well as the ability to develop well-designed and efficient clinical trials in early development – are essential for innovative breakthroughs.

- Typical pharmaceutical R&D suffers from an **innovation deficit.** The majority of products launched by large companies originate in biotech or academia, and many smaller companies **lack direct access** to world-class experts in early development.

- Poorly designed clinical trials increase **uncertainty,** as evaluating intermediate results does not lead to action or contingency planning.

Financial challenges

When an innovative programme reaches the stage in which the highest potential value is achieved, investors typically demand more assurances regarding the likelihood of finding a partner before providing additional funding. While companies are under increasing pressure to deliver short-term promising results, there is a recognised risk that less-informative experiments may be performed in order to prolong the existence of biotech companies without adding value.

- A **financing gap** often exists between initial discovery and clinical proof-of-concept results.

- Innovators often encounter **difficulty raising funds** for the initial development steps.

- Public funding is often available for basic research **but not for early development** or clinical activities.

Equity financing usually is not effective in this stage in the development of drug prototypes; in addition, equity financing is expensive and can carry significant risks. Nevertheless, the majority of venture financing in early R&D is equity-based, even though this financing model has been only marginally successful in terms of delivering new medicines to patients and delivering substantial financial returns. Despite rare spectacular successes (for example, a 1000-2000% return), the average return is only 1.68% in Europe and 5.86% in the US (based on a five-year horizon IRR in 2013 from the European Private Equity and Venture Capital Data), and equity financing carries significant risks to the investors and provides extremely long periods of illiquidity.

The solution

Bridge the investment gap in early development studies and key clinical studies in order to increase value and help secure future funding.

The 123 Innovation Initiative provides venture loans, expertise, and access to cutting-edge research facilities.

- Venture loans are short-term, non-dilutive, and complementary to venture capital.

- The Initiative increases cost-effectiveness and adds clear value by facilitating informative experiments and early, data-driven assessment of a product's feasibility.

- State-of-the-art clinical research facilities and a network of early development experts provide scientific, clinical, and economic benefits to the biotech company, the investors, and other stakeholders.

- By establishing micro-milestones, priorities are set at short intervals in order to effectively determine how the clinical trials will proceed. This approach significantly reduces risk and results in trials that are more efficient in terms of gathering information.

- CHDR has a proven track record for designing and managing clinical trials that have an extremely high likelihood of obtaining future financing in order to enter the next phase of development.

Combining financing and clinical research

The 123 Innovation Initiative is a unique approach in which financing supports research – and vice versa.

CHDR provides the ideal clinical research conditions

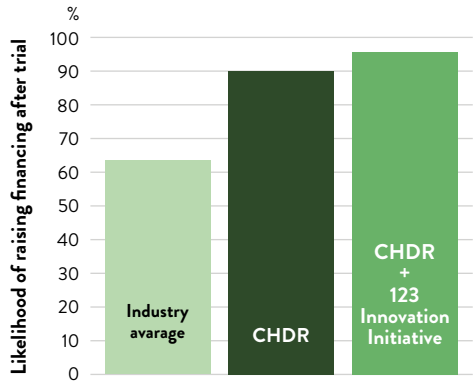
CHDR is a leading clinical research facility located in the heart of the biotech cluster in Leiden, the Netherlands. CHDR performs clinical trials that yield high-quality, reliable data. Importantly, CHDR is a unique bridge between academic clinical pharmacology research and commercial drug development.

CHDR has a solid track record for helping early-stage clients obtain financing for subsequent phases of research. Companies that perform their early trials at CHDR have a refinancing rate that greatly exceeds the industry average. In addition, the Netherlands has one of the most flexible regulatory systems in the world. Importantly, CHDR is a non-profit foundation with no internal shareholder interests, a healthy balance sheet, and a 30-year record of steady, consistent growth.

- CHDR performs clinical pharmacology trials using state-of-the-art research facilities.
- CHDR optimises the key aspects of successful innovative early drug development using question-based drug approaches.
- CHDR maintains close ties with academic facilities, providing open access to large international knowledge bases and patient populations. CHDR is affiliated with four leading Dutch academic medical centres, providing access to more than ten million potential research subjects and patients.

Securing future funding

Ninety percent of all early-stage clinical trials performed at CHDR secure the subsequent funding needed for the next stages of development and research. With the addition of the 123 Innovation Initiative, this number is expected to increase to 99%.



‘Venture debt lowers the cost of financing without diluting equity’

Financial advantages

Venture debt provides early-stage, high-growth companies with non-dilutive financing that complements venture capital.

Venture debt is a valuable tool that can accelerate a company's growth by helping achieve critical milestones in product development. Venture debt is well-suited for shareholders who are looking to significantly increase the company's value without diluting equity.

Venture debt is also well-suited for companies that lack the assets and/or cash flow needed for obtaining traditional debt financing. For example, many of the companies that receive venture debt have a negative cash-flow situation.

As a source of capital, venture debt is complementary to venture capital in early-stage, high-growth companies. In 2007, venture debt accounted for more than 10% to the total venture capital market, and venture debt has played an important role in the growth and long-term success of many companies.

How does venture debt differ from venture capital?

Venture debt is a tool that maximises a company's valuation for current shareholders by protecting shareholders from significant equity dilution. Following a large increase in value (for example, when a clinical trial yields promising results), shareholders benefit by raising equity after the increase and using venture debt. It is important to note that the company still must repay the loan, with interest, and a small amount of equity dilution is unavoidable due to warrants issued as partial remuneration to the venture lender.

Tailored to meet the needs of early-stage clinical trials.

Funding is essential for early-stage companies. Therefore, the 123 Innovation Initiative provides this much-needed funding and helps design optimal clinical trials, resulting in a more cost-effective project. Historically, such trials have a significantly higher likelihood of raising funds in the next round of financing.

Funding from the Initiative is provided in the form of venture debt (rather than in the form of equity) and is complementary to the equity provided by traditional venture capital. Venture debt typically includes interest and has a small pledge of warrants, options, shares, and/or exit fees. With the Initiative, loans are offered for a period of 1–2 years and are used to fund a clinical trial. The advantage of this approach is that the cost of venture debt is generally lower than the cost of venture capital, and venture debt is simpler to manage, can increase ROI for existing shareholders, and closely matches the specific financing requirements of clinical trials.

Although the cost of venture lending is usually higher than a bank loan, the cost is generally lower than equity provided through venture capital. Because processing, negotiating, and documenting a venture loan is less complex than equity financing, venture debt can be obtained relatively quickly. In most cases, the clinical trial is specified while the terms of the venture loan are established, thereby streamlining the entire process.

The 123 Innovation Initiative versus traditional venture capital

	123 Innovation	Venture Capital
Dilution of equity	minimal	high
Cost of financing	marginal	high
Fundraising timeline	weeks	months
Duration of financing	1 - 2 years	until exit (5 - 10 years)
Processing	simple	complex
Board seat	no	yes
Improves trial quality	yes	not always
Likelihood of raising future financing	high	low

The process

Step 1: **Develop a question-based drug development programme**

A question-based drug development programme is established in collaboration with the Initiative in order to define the critical questions to be addressed, including micro-milestones and critical go/no-go criteria.

Step 2: **Obtain venture lending**

After agreeing upon the most effective, informative, and value-generating clinical study design, a venture loan is offered to the biotech company. The venture loan is matched to the milestones and criteria established in Step 1.

Step 3: **Initiate the research programme**

The most cost-effective and most informative experiments in the clinical trial are performed first, allowing the study to reach the first micro-milestone as early as possible. At critical junctures, go/no-go decisions are made, and depending on the decision, the study proceeds to the next stage.

Step 4: **Future planning**

Using the results of the question-based clinical trial, the company can now make informed decisions regarding further drug development and future investments without the need to compromise equity in an early stage.

How do stakeholders benefit?

With the 123 Innovation Initiative, all stakeholders benefit, including the biotech company, the shareholders, investors in the Initiative, licensors, and venture capitalists.

Biotech companies
- Have easy access to complementary financing
- Have access to leading-edge scientific expertise
- Have access to Europe's best clinical facilities within a flexible regulatory environment

Licensors and potential partners
- Acquire a well-documented product
- Avoid costly repetition and delays in early development programmes
- Receive high-quality, reliable clinical trial data

Venture capitalists
- Increase the likelihood of obtaining financing in the next round
- Create value in the company with minimal equity dilution due to the low cost of capital versus equity

Investors
- Receive an attractive, risk-adjusted return
- Invest with confidence thanks to expertise provided by leading researchers
- Obtain low-risk access to new drug development

Shareholders
- Have an extended runway for product development
- Have a minimal amount of equity dilution
- Receive capital at a lower cost

‘Venture debt enables companies to grow while minimising equity dilution’

Eligibility

Biotech companies with a compound that is currently in – or is currently being prepared for – early-stage clinical studies (e.g. pre-GLP, GLP, or Phase 1) are eligible for the Initiative. Companies with a compound before the GLP-tox stage or before (or in) the clinical stage have preference; in this case, the Initiative can optimally utilise the expertise needed in order to reach proof-of-concept.

The 123 Innovation Initiative maximally benefits:

- Start-up biotech companies looking to obtain early clinical data without diluting shareholder equity;

- Academic projects that require clinical data in order to launch a spin-off company and/or establish a partnership with a pharmaceutical company; and

- Programmes with a promising, innovative approach to refocussing after encountering an early roadblock.

Investment criteria

Suitable companies are determined based on financial and/or medical criteria.

Financial criteria
The financial strength of the current venture capitalists or angel investors is considered when determining whether a company is eligible for venture debt. The risk of failure, default and recovery rates, the IPO, new equity rounds, and liquidation value are all taken into consideration.

Medical criteria
The drug's target pathway and mechanism of action should have a sound scientific basis. Completing the trial within one year should be feasible, and each milestone must provide key information that significantly increases the project's value. Suitable clinical measurements, validated clinical endpoints, and/or biomarkers for predicting outcome must be available.

Suitable companies will be selected by the 123 Innovation Initiative, which consists of industry and academic experts.

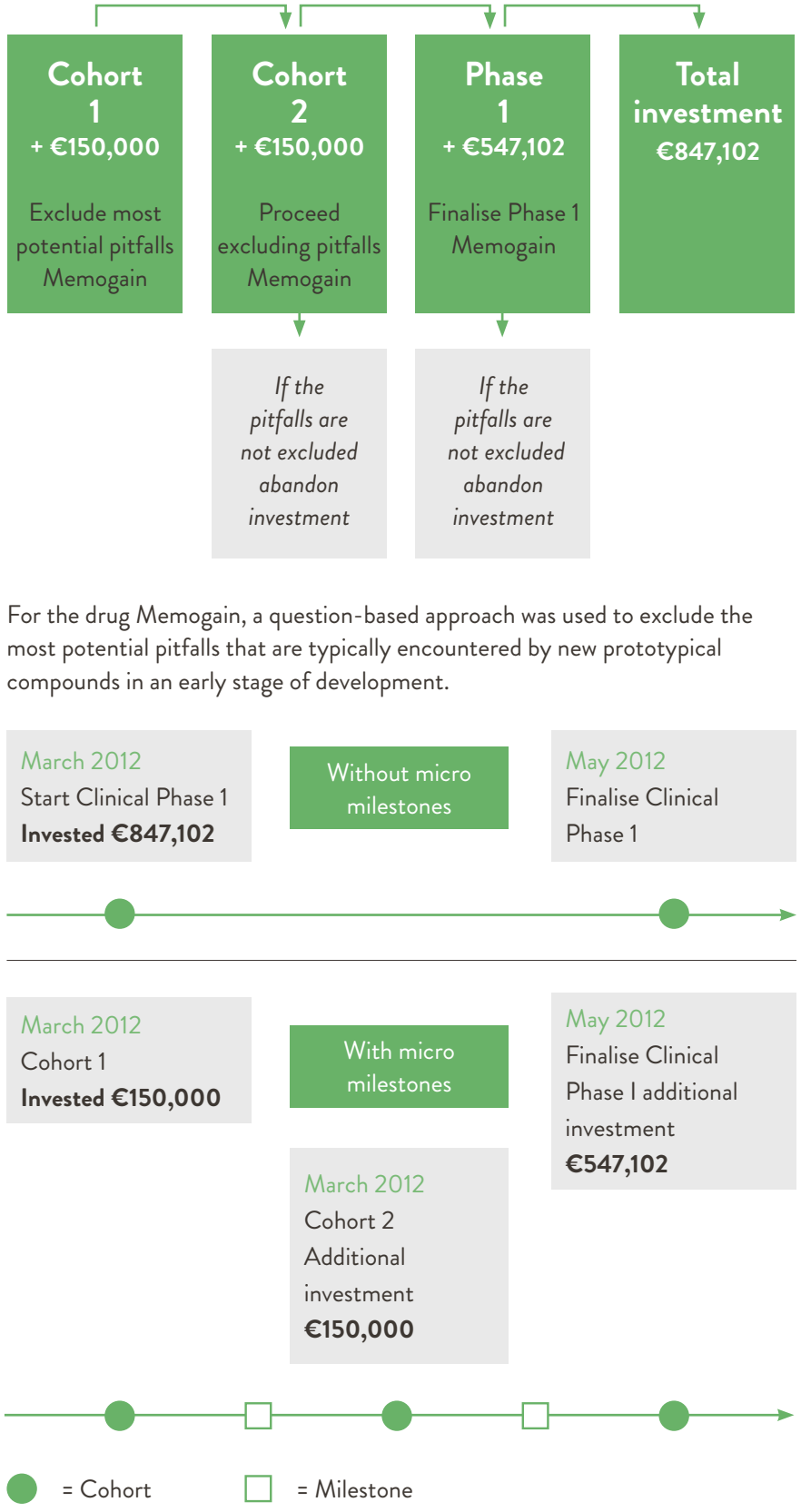
A success story: Memogain®

This example illustrates how using micro-milestones can optimise decision-making while minimising risk. The experiments are divided into a series of predetermined milestones.

Phase 1 testing is then performed in several cohorts, thereby splitting the financial loans and minimising risk. If phase 1 is not successful, the investment is abandoned; if it is successful, the project proceeds towards the next milestone.

This unique approach has several clear advantages:

- Early checkpoints in the clinical study, after which go/no-go decisions can be made;
- Less risk to the investor;
- Minimal loss of time; and
- Minimal waste of money.



About us

Adam Cohen

CEO, Centre for Human Drug Research

Adam Cohen has more than 35 years of experience in the field of early drug development. Since 1987, Dr Cohen has served as CEO at the Centre for Human Drug Research in Leiden, a company that provides consulting services and performs early-phase research for large pharma companies and biotech firms around the globe. Dr Cohen is also a Professor of Clinical Pharmacology at Leiden University Medical Center, Editor-in-Chief of the British Journal of Clinical Pharmacology, and has co-authored more than 300 scientific publications. From 1999 to 2011, Dr Cohen was Vice-Chair of the Netherlands Competent Authority for Clinical Trials. He holds several non-executive board positions in the Netherlands and USA.

Hans van Swaay

Private equity partner at Lyrique

Hans van Swaay is a partner of Lyrique and has been active for more than twenty years in private equity as cofounder of Lyrique, as Head of Private Equity at Pictet & Cie, as Managing Director of UBS Capital, as Managing Director of Merifin and as partner of Lowe Finance. Lyrique invests in private equity for family offices, private wealth institutions and institutional investors. Lyrique makes fund investments in the world's best private equity and venture capital funds. It also co-invests with these funds and in specific situations Lyrique makes direct investments. Hans is a co-author of the book Private Equity 4.0, Reinventing Value Creation, published by Wiley in February 2015.

Andreas Wallnoefer

Senior Pharma Expert and Former Head of Roche Clinical Research & Exploratory Development

A clinical pharmacologist by training, with a PhD in pharmacology and additional degrees in Pharmaceutical Medicine and an EMBA from IMD Lausanne, Andreas joined F. Hoffmann-La Roche after his fellowship at Leiden University. At Roche, he became Global Head of Clinical Research & Exploratory Development and successfully built this newly formed function. Under his leadership Discovery Research and Clinical Research became better connected and translational medicine became a key driver to implement the Personalized Healthcar e strategy of Roche. As a Senior Vice President, Andreas became the task force leader for the integration of the clinical development departments of Roche and Genentech after the Genentech acquisition and was subsequently appointed as the new Head of Roche pRED Development. In 2012 he took on, in addition, the role of the Acting Head of the Cardiovascular & Metabolism (CVM) Disease Therapeutic Area. After Roche's strategic decision to exit CVM, Andreas decided to leave Roche in 2015. He founded a Life Sciences Consulting company and advises boards and management of several biotech companies strategically and operationally. In 2016, he became partner at BioMedPartners, a leading European VC company.

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