



Phase 1 in the Netherlands

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Leiden, 2005: a first dose that did not happen

The proposal

A German biotech
A novel biological affecting T-cell
function
First-in-human in healthy volunteers

The scientific question was not only: can we dose?
It was: should we dose this, here, now, in healthy people?



The result

CHDR did not get the study

Reason: asking too many difficult questions?

Risk signals to interrogate:

- immune target biology
- relevance of animal data
- healthy-volunteer setting
- possibility of human-cell testing

In Phase I, saying “no” can be a safety intervention.

Independent judgement is part of the infrastructure.

THE STUDY PROCEEDS ELSEWHERE

Harrow, 13 March 2006: the first cohort

Parexel Clinical Pharmacology Research Unit · Northwick Park Hospital site

First cohort

8 healthy men

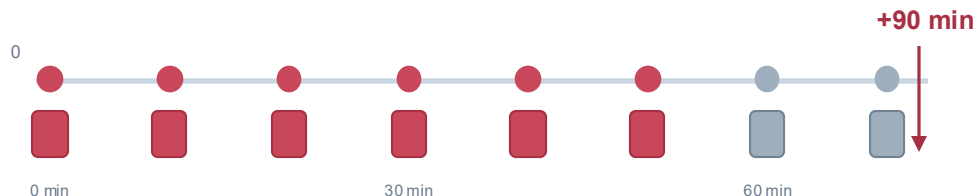
6 active

2 placebo

Dosed at ten-minute intervals

The molecule is still not named.

Then the clock starts



All six active recipients develop a systemic inflammatory response

headache · myalgias · nausea · diarrhoea · erythema · vasodilatation · hypotension

Within 12–16 hours: critically ill.

Pulmonary infiltrates, lung injury, renal failure and DIC were reported in the clinical course.

Drug was TGN1412

YouTube — *The Drug Trial That Went Horribly Wrong*
https://www.youtube.com/watch?v=a9_sX93RHOk

TeGenero's anti-CD28 superagonist monoclonal antibody

TGN1412

CD28 superagonist
first-in-human trial
March 2006

TeGenero

What happened to the six active recipients?

All six transferred to intensive care
Two developed prolonged cardiovascular shock and ARDS
All six survived, after intensive cardiopulmonary support



ICU

The product of Phase I is not the first dose. It is the first reliable decision.



Adam Cohen



Jan Jonkman

Phase I tradition

and hospital-based early-phase capability, 1985–2026

CHDR
1987–present

PBR → PRA → ICON
1980s–present

e → Kendle
1989–2011

Xendo → QPS clinical unit
≈2000–2024

CTC

Delphinium

AVL-NKI early oncology
specialised RH/RP oncology

UMC-U CRU
2022–present



Several independent early-phase ecosystems — not just one or two successful units.

Approximate operational lineages. Some start dates indicate organisational predecessors rather than exact legal entities.

A Dutch Phase I tradition: active capability today

From historical breadth to four visible early-phase pillars

Current visible ecosystem

L

CHDR

Leiden

Independent human pharmacology; healthy-volunteer and patient studies

N

ICON

North Netherlands

Industrial Phase I lineage: PBR → PRA → ICON

G

CTC & Delphinium

Groningen

QPS expertise continued in new early-phase organisations

A

NKI-AVL

Amsterdam

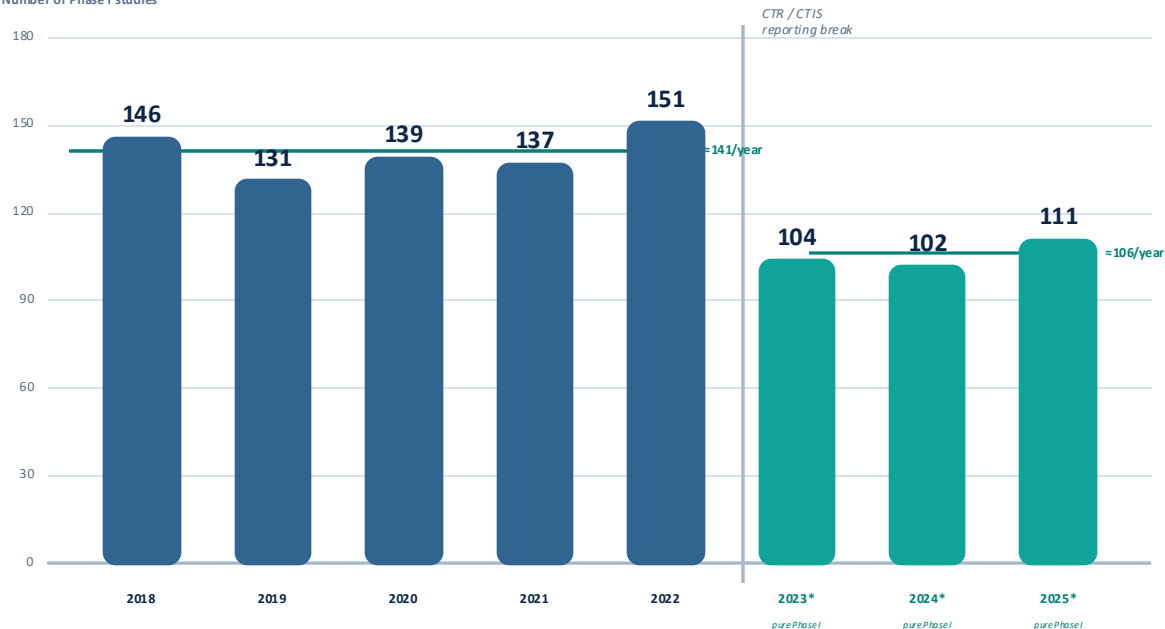
Specialised first-in-patient oncology and translational research

The tradition is not one organisation — it is a distributed capability across complementary early-phase settings.

Dutch Phase I activity: stable pre-CTR; lower but steady in CTIS

Official CMO Phase I series, 2018–2022; CTIS pure Phase I shown separately, 2023–2025

Number of Phase I studies



WHAT THIS SERIES SAYS

131–151

Phase I studies/year, 2018–2022

103–111

pure Phase I/year, 2023–2025
CTIS basis; integrated I/II excluded

No pre-2023 downward trend

After 2022, the counting basis changed. The 2023–2025 bars answer the obvious question, but they should not be treated as a direct continuation of the older CMO phase table.

KEY MESSAGE

The old official Phase I series was stable; CTIS-era pure Phase I counts remain substantial, but sit on a different counting basis.

*2023–2025: purePhase I only, based on CTIS extraction; integrated Phase I/II excluded. Different counting basis from CMO 2018–2022 phase table. Sources: CMO annual report 2022 five-year phase table; CMO 2025 reporting explanation; CTIS public data extraction.

The Netherlands combines scale with high Phase I intensity

2025 activity | selected high-activity EU markets; Australia shown as external benchmark

DUTCH MEDICINE DAYS 2026

Country / source		All trials / submissions	Pure Phase I	Phase I per 1M	Phase I share
Belgium	CTIS	389	92	7.8	23.6%
Netherlands		414	111	6.2	26.8% highest share of the selected EU markets
Spain	CTIS	839	172	3.5	20.5%

NETHERLANDS

111 Phase I trials

6.2 per million

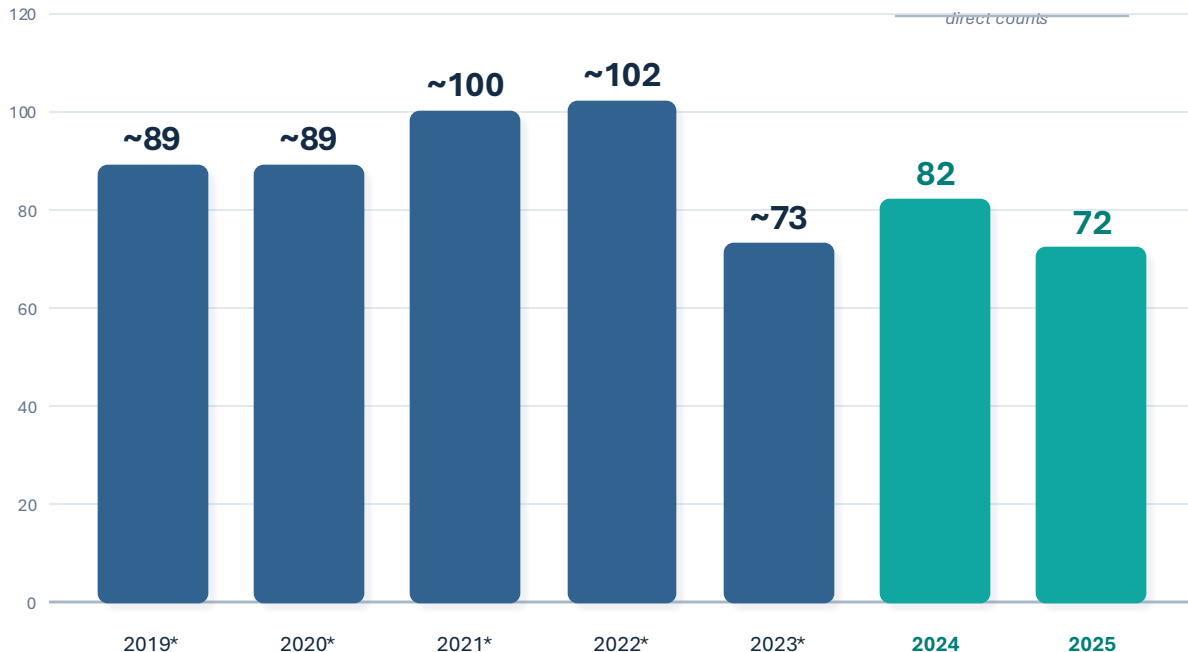
26.8% of national CTIS portfolio

*EU countries: CTIS public-data extract, 2025, pure Phase I only; integrated Phase I/II excluded. Countries shown are selected high-activity/high-intensity markets, not a complete EU ranking. Australia: 738 interventional studies with a 2025 start date in ClinicalTrials.gov; 40.1% classified as Phase I. Use as an external benchmark, not a head-to-head CTIS comparison.

BEBO – Phase 1 expertise

BEBO-reviewed Phase I protocols in the Netherlands, 2019–2025

Number of BEBO-reviewed Phase I protocols



Repeated exposure creates specialist review expertise in early-phase risk assessment.

*2019–2023 are approximate estimates from BEBO phase-share data; 2024–2025 are reported counts. National share is shown only for pre-CTR years with comparable public CCMO phase-I data.

Sources: BEBO annual reports 2019–2025; CCMO annual reporting 2019–2021.

WHAT THIS ADDS

~70–100

Phase I protocols reviewed
by BEBO in a typical year

Share of all Dutch Phase I protocols



Roughly two-thirds to three-quarters
of Dutch Phase I protocols before CTR/CTIS.

Colour coding

IB-derisk

	100	Study without clinical observations			
	103	Desirable effect			
	104	Undesirable but acceptable effects			
	105	More severe adverse effects			
	106	Serious irreversible toxicity and/or death			
	102	Intended human dose			

Pre-clinical data

MABEL (~1 ng/mL)

Starting dose

ATD (~100 ng/mL)

Adverse effects
(~ 5000 ng/mL)

EMA sentinel dosing guidance: principle, not a prescription

The EMA establishes a safety principle — but leaves the operational decision largely risk-based

EMA 2017 — key wording

“It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP (often known as sentinel dosing).”

“Flexibility in this approach is allowed but should be on a risk-proportionate basis with a clear scientific rationale for any proposals not to use this strategy.”

— EMA/CHMP/SWP/28367/07 Rev. 1, §8.2.6 (2017)

When placebo is included

“...one subject on active and one on placebo [may be] dosed simultaneously prior to dosing the remaining subjects in the cohort.”

EMA then says this approach is “expected for all single and multiple dosing cohorts” — yet does not specify a cohort-by-cohort decision rule.

The operational gap

- Which SAD cohorts need a sentinel?
- Which MAD cohorts / doses need it?
- How much observation is enough?
- When is omission sufficiently “risk-proportionate”?

IN PRACTICE

Protocol-by-protocol EC interpretation → unpredictable approval timelines

“Pre-competitive collaboration” among Dutch Phase 1 CRO’s

ORIGINAL ARTICLE



Sentinel dosing: A proposed algorithm to guide decision making on which cohorts in early phase clinical pharmacology trials should use this approach

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Wim Tamminga³ | Pieter de Graeff⁴ | Geert Jan Groeneveld^{1,5} 

Br J Clin Pharmacol. 2025;91:2705–2710.



Nederlandse Associatie van Fase Een Klinieken (NAFEK)



NAFEK

Nederlandse
Associatie van
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Questions?



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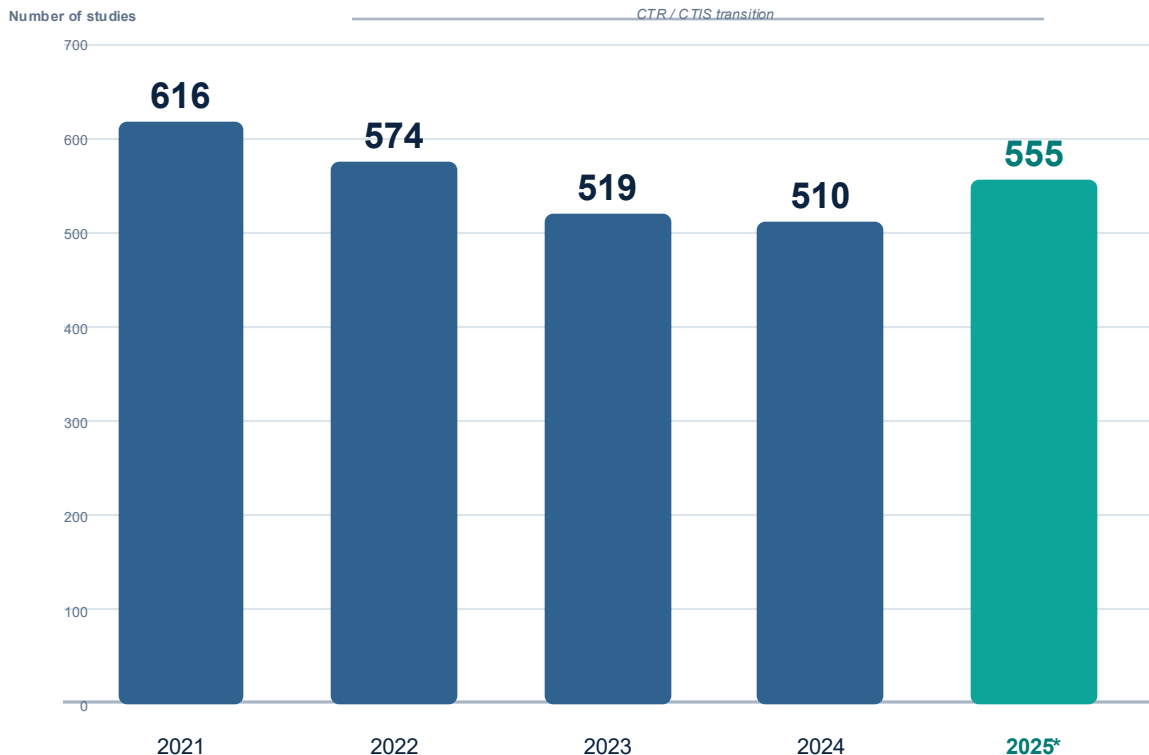
Farma kiest vaker voor snel China voor testen nieuw medicijn: 'In Nederland heeft ieder ziekenhuis eigen procedures, dat kost veel tijd'

in 2021 to 19.6 in 2025, placing the Netherlands among the sharper declines in Western Europe. (71) Recent EFPIA analysis quantifies what is at stake domestically: attracting 11% more clinical research could translate into up to €138 million in additional annual economic value for the Netherlands, highlighting the upside of restoring competitiveness in trial set-up and predictability. (20)

translating innovation into timely market access and commercial uptake remains a relative weakness.

Number of clinical drug studies in NL 2021–2025

CCMO-reported medicinal-product studies in the Netherlands, 2021–2025



WHAT THE OFFICIAL
SERIES SHOWS

616 → 555

No near-halving

A gradual decline through
2024, followed by a reported
increase in 2025.

In 2025 CCMO reports
primary submissions, not
necessarily studies that
started recruitment.

*In 2025, CCMO changed from reporting by assessment date to reporting by submission date; 2025 is therefore not fully comparable with earlier years. The 2024 bar follows CCMO's retrospective primary-submission series.

Source: CCMO annual reporting, 2021–2025.

Sentinel algorithm

Is this the first time the IMP* is administered in humans (first-in-human trial)?

* Answer "no" for biosimilars or new formulations of a known active substance

‡ Major risks and/or uncertainties include:

- Unpredictable translation to humans
- Poorly predictable exposure or response
- Narrow therapeutic window, steep dose-(adverse) effect curve
- Potential major effect on immune system, on- or off- target

Are the doses and predicted systemic exposures being considered in this trial already covered by previous clinical trials with the IMP and were these safe?

Is the IMP a first-in-class drug?

Is the effect that can be expected from the mechanism of action predictable or is the pathway well known?

Are there major risks and/or uncertainties‡ at the intended doses and/or predicted exposures based on the available (pre-)clinical data?

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Can these uncertainties be linked to specific exposures or dosing regimen?

Are exposure and/or response/toxicity likely to change on continued exposure, or time-dependent?

No sentinel required in any of the cohorts

A sentinel is required only in the first cohort of the SAD

A sentinel is required in the first cohort of the SAD and specific exposures /dose levels of the SAD and/or MAD

A sentinel is required in all SAD cohorts

A sentinel is required in all SAD and in at least the 1st MAD cohort, and/or at specific exposures in the MAD