

CHDR  
Centre for Human Drug Research

# Annual Report

2022

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# The year in perspective

With the world finally emerging from the global pandemic, 2022 was a year of renewed momentum for CHDR. Read our Executive Board's reflections on the past year and get an overview of 2022 in numbers.

# Message from the Executive Board

CEO Prof. Koos Burggraaf and CMO / CSO Prof. Geert Jan Groeneveld look back on 2022 and introduce the new format of this year's annual report.

In the course of 2022, it became clear that the problems caused by the COVID-19 pandemic were finally behind us. Whereas the first quarter of 2022 was still characterised by lockdowns and restrictions, in the following months we were able to gradually return to full capacity. In addition, our employees, who demonstrated so much resilience and resourcefulness amid all the difficulties of the pandemic, have now all returned to the office and are enjoying being able to work face-to-face with colleagues and external partners once again. With a full portfolio for the coming period, we therefore look to the future with optimism.

In October 2022, we celebrated CHDR's 35th anniversary with an event on the theme 'Creating value in an unpredictable world'. As an organisation, we strive to create value through the development of innovative drugs and research methods, as well as by championing personal and professional development through education and training. Unpredictability is an inescapable reality, with many ever-changing external factors at play: public health and infectious diseases, the economy, international current affairs, the energy transition, the labour market, and more. And of course, drug development itself is inherently unpredictable. Our scientific question-based approach and our data-rich methods are designed to tame that unpredictability at an early stage of the clinical drug development process, in turn augmenting the value that we create for the field.

The keen interest in our anniversary celebration in the Naturalis Biodiversity Center — both live and online— was uplifting. CHDR is still thriving after 35 years thanks to a network of collaborative partners in

industry, academia and healthcare, and that network continues to grow. We are pleased to announce a new collaboration with the Haga Hospital in The Hague, one of the major teaching hospitals in the region. Our work together will focus on oncology, pain, neurology and immunology, incorporating educational activities alongside research. Our long-established relationship with Leiden University Medical Center (LUMC) continues to flourish: we will open a new, dedicated unit for clinical drug development at the LUMC in 2023, expanding both our capacity and our capabilities.

To celebrate the renewed momentum of our organisation post-pandemic, this year we proudly present our annual report in this new online format. This format is not only more sustainable than the printed books of previous years, but will also enable us to reach many more readers.

This year's annual report is structured around our three strategic goals — developing drugs, developing methods and developing people — with a section dedicated to each of these three themes. Alongside this, we bring you a range of other stories from around the organisation, celebrating the diverse efforts of our operational and scientific staff. As usual, you can also find a full list of our publications from the past year, or see the year at a glance in 2022 in numbers.

We look forward to continued collaboration with our vibrant network of clients and partners — here's to creating value together for at least another 35 years!

*Prof. Koos Burggraaf, CEO*

*Prof. Geert Jan Groeneveld, CMO / CSO*



# 2022 in numbers

Despite lingering unpredictability following the global pandemic, in 2022 we continued to create value for clients, collaborative partners and patients. See the year's achievements at-a-glance in the infographics below.



**58**  
studies



**~41,000**  
volunteers available



**30**  
contracts signed



**~24,000**  
patients available



**81**  
articles published



**13**  
nationalities



**4**  
clinical pharmacology  
graduates



**32**  
birth countries



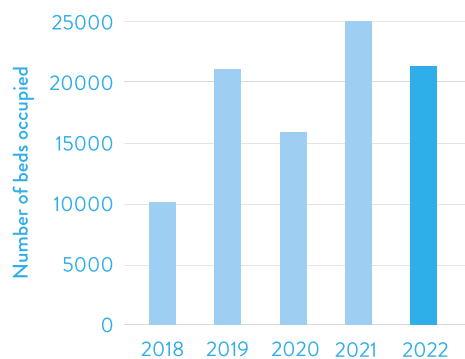
**5**  
PhDs graduated



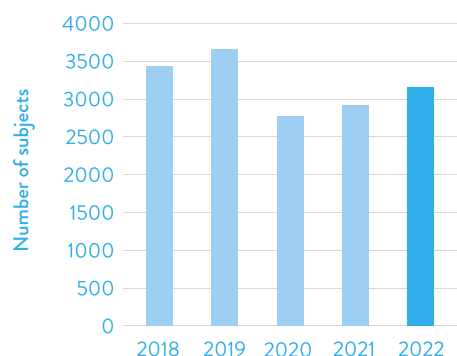
**10.2%**  
turnover of clinical  
research staff



## CRU OCCUPANCY



## SUBJECTS SCREENED

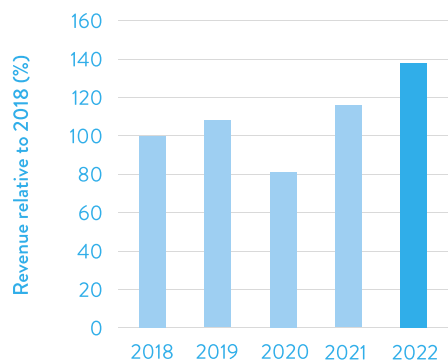


## OVERALL CLIENT SATISFACTION

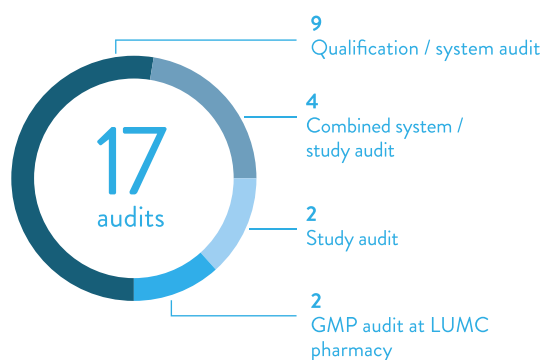
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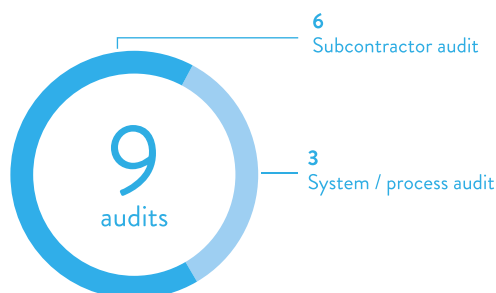
## CONTRACT REVENUE



## EXTERNAL AUDITS

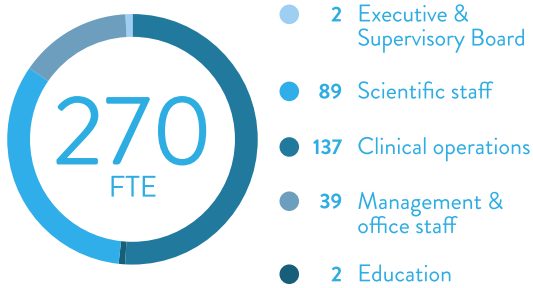


## INTERNAL AUDITS

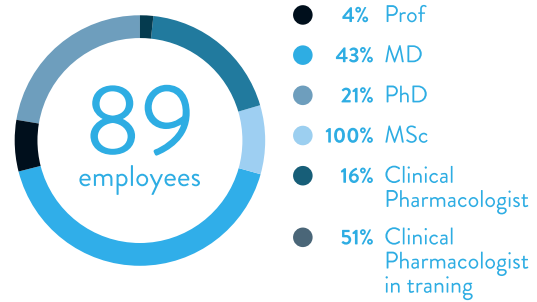




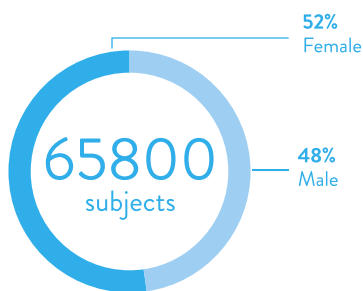
## EMPLOYEES BY DEPARTMENT



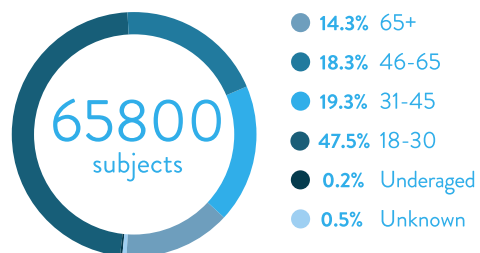
## CLINICAL RESEARCH STAFF



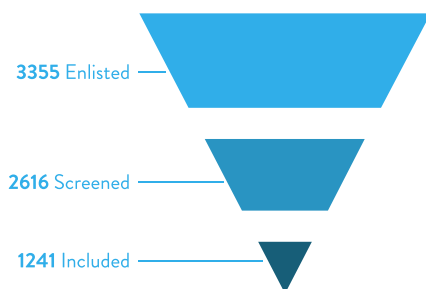
## SUBJECTS BY GENDER



## SUBJECTS BY AGE



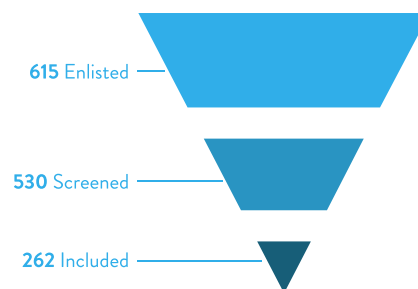
## HEALTHY VOLUNTEERS RECRUITED\*



\*including healthy elderly

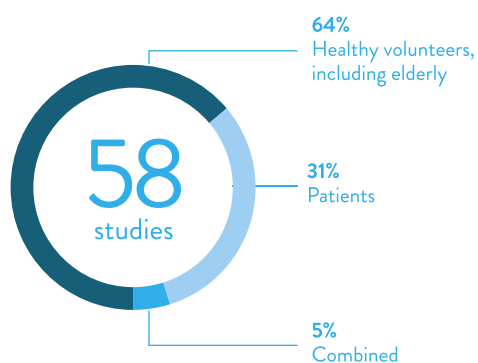


## PATIENTS RECRUITED

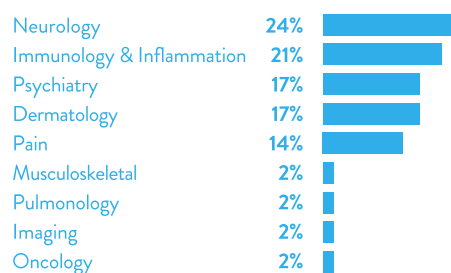




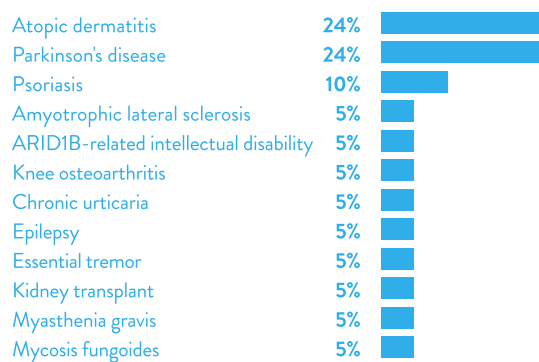
## STUDIES WITH SUBJECTS



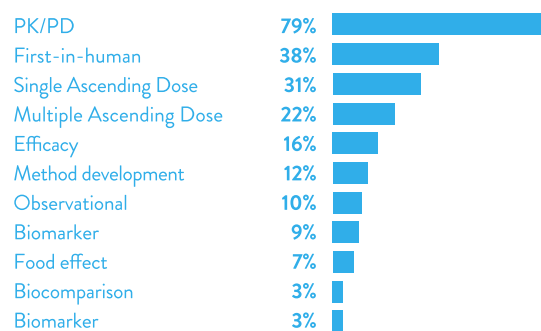
## STUDIES PER RESEARCH AREA



## TYPES OF PATIENTS



## TYPES OF STUDY





# Developing drugs

CHDR's research groups made vital contributions to the development of new drugs in 2022. In this we are proud to collaborate with a range of valued clients and partners, some of whom also share their stories below.

# Profiling novel GABA agonists

In recent years, the Psychiatry group has built up experience with a number of compounds that act relatively selectively via the  $\alpha 2$  and  $\alpha 3$  subunits of the GABA-A receptor. Using the NeuroCart® CNS test battery and quantitative EEG, data from healthy volunteer studies can provide evidence that a GABA-A  $\alpha 2/3$  subtype-selective agonist has the desired selectivity in humans.

‘Pharmacological activity at different subunits of the GABA-A receptor is responsible for the various clinical CNS effects of non-selective GABA agonists such as benzodiazepines,’ says Dr Gabriel Jacobs, Research Director in Psychiatry. ‘We know that the  $\alpha 1$  subunit mediates undesirable GABA-ergic effects, such as drowsiness and memory impairment. In contrast, converging evidence from preclinical and clinical experiments suggests that the  $\alpha 2$  and  $\alpha 3$  subunits might be implied in the anxiolytic and antiepileptic effects of GABA agonists.’

Several companies are currently developing compounds with selective activity at the  $\alpha 2$  and  $\alpha 3$  subunits of the GABA-A receptor. ‘We’ve had the opportunity to study a number of these compounds on behalf of various clients in recent years,’ says Dr Laura Borghans, neuropsychologist and Senior Clinical Scientist in the Psychiatry group. ‘It’s exciting to investigate whether novel subtype-selective GABA compounds live up to the promise shown in preclinical studies.’

## Recruitment strategies

‘In 2022, we conducted studies with two different selective GABA-A  $\alpha 2,3,5$  positive allosteric modulators (PAMs),’ says Pauline Nettesheim, Clinical Scientist and Research Physician. ‘Engrail Therapeutics, the client developing these compounds, was keen to know more about their clinical CNS profile in humans and

whether this would turn out to be much different from the non-selective GABA PAMs.’ Drawing on previous experience with GABA PAMs, such as TPA023, NS11821, AZD7325/6280 and darigabat, the team was able to set up studies to profile both agents.

‘We followed a very similar protocol for both agents, which meant that we could compare the results,’ says Borghans. In addition to a thorough investigation of pharmacokinetics, the team used EEG and NeuroCart® measures to gain additional insight into drug effects. EEG measurements can provide useful information about the CNS characteristics of a compound. In addition, the NeuroCart offers several measures that can be used to identify desired and undesired effects. For example, body sway can indicate drowsiness and reduced psychomotor control (fall risk). In addition, saccadic eye movements can indicate an anxiolytic effect — especially in the absence of drowsiness, as measured using visual analogue scales.

In both studies, the drug was administered over several days, reaching a plateau in blood levels. ‘This approach is expected to correspond to the potential indication of each compound as maintenance treatment for anxiety disorders and/or epilepsy,’ says Borghans. EEG and NeuroCart measurements were performed prior to administration of the drug, on the first day of treatment, and at plasma steady state. ‘We’re currently interpreting the results of the two studies. Although we can’t draw definitive conclusions yet, it’s



clear that we've been successful in characterising these compounds, providing the client with valuable insight.'

### Carbon dioxide inhalation challenge

Moving into patient populations requires significant financial investment. As a result, clients are often seeking additional confidence in the potential efficacy of novel CNS drugs in the earlier phases of development. CHDR supports clients by offering experimental medicine models to demonstrate relevant drug effects in healthy volunteers. One such model is the carbon dioxide (CO<sub>2</sub>) inhalation challenge. In combination with EEG and NeuroCart measures, this challenge model can shed light on the anxiolytic efficacy of a compound in healthy volunteers, and can be used to derisk compounds with regard to unwanted effects.

'The principle is rather straightforward,' explains Koshar Safai Pour, Clinical Scientist and Research Physician. 'In approximately 50% of people without a personal or family history of anxiety or depression, inhaling air with a relatively high ratio of CO<sub>2</sub> to oxygen will trigger symptoms resembling those of a panic attack. In our clinical studies, we can use this to compare the

occurrence and the intensity of CO<sub>2</sub>-induced panic under placebo to its occurrence following administration of an active drug.' The model is most informative if the compound has reached steady state plasma concentrations. Therefore, subjects are asked to take the medication for a certain period of time to achieve steady state before the challenge test.

'Ideally, we compare novel compounds not only with placebo, but also with a relevant active control. In the case of darigabat, a GABA-A  $\alpha$ 2/3 subtype-selective agonist developed by Cerevel Therapeutics, we used the benzodiazepine alprazolam as an active control. That enabled us to show that darigabat was more effective in reducing CO<sub>2</sub>-induced panic than alprazolam. Additionally, by assessing effects at steady state using EEG and NeuroCart measures, we demonstrated fewer unwanted CNS effects compared with alprazolam. These findings were crucial for the client in moving darigabat forward to phase 2.' Read more about the story of darigabat in the interview with Dr Rachel Gurrell.

# ‘I really enjoyed brainstorming with the CHDR team’

— Dr Beate Rohde, Bayer

Dr Beate Rohde and her team at Bayer Research and Development approached CHDR to help with the clinical development of a promising immunomodulatory agent. In close consultation with CHDR’s Dermatology and Immunology groups, a study was conducted in healthy volunteers, yielding new insights into the compound. ‘The information we’ve gained from this study has even enabled us to explore development opportunities in other indication areas.’

‘What initially attracted me to CHDR was their experience with human challenge models for studying the innate immune response,’ says Rohde. ‘Once we started talking, I found I really enjoyed the discussions with Robert Rissmann, Matthijs Moerland and colleagues. We brainstormed together, trying to come up with the best approach to answer our questions. I was impressed by how solutions-oriented they were, and by the depth of their scientific expertise. So our initial idea for the study evolved into something much more advanced, ultimately yielding much more meaningful information.’

## Challenge models

The team decided to study the immunomodulatory compound both topically and systemically, using CHDR’s topical imiquimod challenge and the systemic bacterial lipopolysaccharide (LPS) challenge. To

complement this, imiquimod and LPS challenges were also applied ex vivo. Both imiquimod and LPS trigger the innate immune response, but through different pathways: imiquimod binds to toll-like receptors (TLR) 7 and 8, while LPS activates TLR4.

Rohde and her colleagues at Bayer also wanted to get an impression of their compound’s pharmacokinetics within the skin. After discussing the possibility of conducting invasive procedures such as microdialysis, the team decided it was preferable to use suction blisters. ‘A major reason not to use microdialysis was that we wanted to avoid an unnecessary burden on participants, as this was already quite a complex study,’ says Rohde. ‘While creating this innovative study design, the CHDR team always kept the study participants’ comfort in mind.’



A protocol was agreed upon and given the green light by the medical ethics committee. But then, the team hit an unexpected roadblock: there were difficulties obtaining LPS. Rohde: 'CHDR handled this challenge very professionally and got things back on track as soon as possible.' Once the results were analysed, Rohde and her team could benefit from new insights into their compound. 'The results confirmed our expectations, which made us more confident about our plans for the compound. But we also gained a wealth of additional information, which opened up discussions about other possible indication areas.'

### Constructive collaboration

'I have more than 20 years of experience in this industry and I've worked with many contract research organisations, including ones that specialise in early phase studies. What I appreciate about CHDR is that they are really curious and really want to advance

the field. That's not just something they put on their website — it genuinely underpins the way they work. And while they have a strong research background, they also understand the constraints of the commercial context, with its budgets and timelines.

'All in all, this was a very constructive collaboration. I'd like to congratulate Robert Rissmann on his grant award and the academic network that he has managed to build. With the vast and varied expertise that this network can offer, we look forward to more opportunities to collaborate with CHDR in the future.'

# Patients and healthy volunteers in an integrative approach to drug development in oncology

Until recently, healthy volunteers had no place in the clinical development of cancer drugs: classical therapeutics, such as chemotherapy, are simply too toxic. However, things have changed with the development of molecular targeted and immunomodulatory drugs in oncology. In collaboration with academic, clinical and industry partners, CHDR is breaking new ground with an integrative oncology drug development programme that aims to use the same biomarkers in both healthy volunteers and patients.

‘Through my discussions with clinical and academic cancer experts from across the Netherlands, it’s become clear to me that there’s a great need for a new approach to cancer drug development,’ says Dr Jacobus (Co) Bosch, Research Director in Oncology. ‘During the COVID-19 pandemic, we all witnessed how an integrative approach enabled rapid vaccine development. We think an integrative approach can speed up the drug development process in oncology as well.’

In an integrative approach, the classical phases of drug development interact more closely and may even be partly combined. For this to succeed, it is pivotal to have an interdisciplinary team. ‘We’re currently in the process of building a collaborative network of clinical specialists from various fields of oncology, along with hospital-based clinical research units in the region and beyond,’ says Bosch.

## Healthy volunteers in oncology

In 2022, CHDR’s Oncology group published a study showing that immuno-oncological drugs can be safely studied in healthy volunteers. This systematic literature review, undertaken by Clinical Scientist Igor Radanovic, showed how involving healthy volunteers may be beneficial for early-stage oncological drug development. ‘In the absence of confounding factors mediated by malignant disease, dose finding is more efficient. This avoids inefficient dose-finding studies in the target population as well as the inclusion of patients in studies with pharmacologically inactive doses,’ says Bosch. ‘Overall, an integrative approach has the potential to accelerate the drug development process in oncology and make early assessment of proof-of-pharmacology more efficient.’



The challenge is to discover relevant biomarkers that can facilitate early pharmacodynamic assessment in both healthy volunteers and patients. This is where CHDR's extensive track record in developing biomarkers and challenge models comes into play. Bosch: 'Obviously, not all new drugs in oncology lend themselves equally well to studies with healthy volunteers. For example, immune checkpoint inhibitors have an increased risk of inducing strong autoimmunity.' With this in mind, novel PK/PD modelling and further development of CHDR's derisking strategies, such as the IB-Derisk tool, will be important.

'It's clear that healthy volunteers can play a valuable role in drug development in oncology. Of course, as with any drug, a thorough risk assessment is essential. But the potential is enormous,' says Bosch. 'We're encouraged by the growing demand and support for this approach among oncologists. We're now actively pursuing a strategic programme, designing novel study protocols as well as setting up interdisciplinary collaborations with both industry and academia. We look forward to further developing our integrative approach for oncology together with our partners.'

# ‘It’s been a fantastic journey’

— Thomas Holm Pedersen, NMD pharma

NMD Pharma is developing a promising compound for the treatment of neuromuscular diseases, for which the first human trials have been conducted at CHDR. Over the last two years, the team has conducted studies both in healthy volunteers and in patients with myasthenia gravis. These studies have yielded promising results which open up new opportunities for the compound.

‘Our company has its origins in the research I did for my PhD,’ says Thomas Holm Pedersen, CEO of NMD Pharma, based in Aarhus, Denmark. ‘We’re developing a small molecule that inhibits a particular ion channel called CIC-1, a chloride ion channel that is only expressed in skeletal muscle. When you inhibit this ion channel, you enhance neuromuscular transmission.’ While setting up the company, Pedersen and colleagues came into contact with Prof. Geert Jan Groeneveld from CHDR, then head of the Neurology group. ‘Since then, we’ve been discussing with Geert Jan and his team how best to investigate this promising compound in humans.’

## Myasthenia gravis

The CIC-1 channel plays a role in balancing muscle strength and relaxation. When the motor nerve signals to a muscle to contract, this is accompanied by an influx of positively charged sodium ions at the interface between the nerve and the muscle fibre — the neuromuscular junction. In contrast, CIC-1 causes the

influx of negatively charged chloride ions, and therefore has the opposite effect. Inhibiting the CIC-1 channel may be beneficial in conditions where the muscle does not contract hard enough because the muscle fibres fail to become activated at the neuromuscular junction.

Pedersen: ‘We chose myasthenia gravis as the first indication to investigate. It’s an area of significant unmet medical need, and recent therapeutic advances in this indication provide clear criteria to gauge the success of novel treatments, which in turn helps to guide the design of our development programme. In addition, the animal models of myasthenia gravis translate well to humans.’

Following single and multiple ascending dose studies in healthy volunteers, NMD Pharma and CHDR’s Neurology group (now headed by Dr Philip Kremer) started a crossover placebo-controlled single dose study in patients with myasthenia gravis. Hand grip strength was chosen as the main outcome measure. Additionally, patients were assessed using the quantitative myasthenia gravis (QMG) scale, which is



a well validated instrument for quantifying the severity of muscle weakness. Pedersen: 'The outcomes of the patient study were good — beyond expectations, in fact. Both hand grip and QMG scores visibly improved after a single dose of our drug, and compared well to placebo.'

### Experimental biomarker

The first studies in healthy volunteers had already produced indications of a possible effect. 'One of the volunteers experienced muscle stiffness at the highest dose level tested. For me, that was clear evidence that our drug had an effect,' says Pedersen. 'We know, for example, that people who lack a functional CIC-1 channel due to an inherited mutation are more likely to experience muscle stiffness.'

Corroborating evidence came from an experimental biomarker deployed by CHDR, called muscle velocity recovery cycles (MVRC). This technique, which uses electromyography (EMG), shows how easily the muscle can be excited again after a contraction. Pedersen: 'The

MVRC measurements, too, showed a clear difference between placebo and active compound in the first studies with healthy volunteers, and this finding was confirmed in the patient study.'

### New indications

'So it's been a fantastic journey, but at the same time, the results also bring our company to a whole new chapter,' says Pedersen. 'We now see opportunities in a number of other neuromuscular indications, especially some rare diseases for which there are still few or no resources available. In the near future we want to investigate the efficacy of our compound in spinal muscular atrophy and Charcot-Marie-Tooth disease, in addition to myasthenia gravis. We're all very curious to pursue these possibilities further and see what we can achieve in the coming years.'

# Unlocking the potential of psychedelic compounds in psychiatry

Rediscovering the therapeutic potential of psychedelic drugs has been one of the most promising recent developments in the treatment of mood, anxiety, trauma-related and substance abuse disorders. The Psychiatry group is currently conducting a series of studies to characterise the pharmacology of various psychedelic compounds, as well as substances that aim to target similar pathways without inducing hallucinogenic effects.

‘We’ve further expanded our experience with ketamine and gained new experience studying DMT,’ says Dr Gabriel Jacobs, Research Director in Psychiatry. ‘Although psychedelics have been around for a long time, there is still much we don’t know about their human pharmacology. At CHDR, we have an array of methods to systematically characterise the pharmacodynamic effects of psychedelic compounds, such as the NeuroCart®, quantitative EEG with or without event-related potentials, and TMS-EEG. We use both subjective and neurocircuitry-based CNS biomarkers, and relate the effects to the compounds’ pharmacokinetics.’

## DMT

Jacobs and his team are currently conducting a study with DMT in a group of volunteers who are experienced in the recreational use of psychedelics. DMT is a short-acting drug that, like other classic psychedelics, acts via the 5-HT<sub>2A</sub> receptor in the brain. In this study, the team is investigating the relationship between pharmacokinetics, subjective effects and various CNS-

based biomarkers. Jacobs: ‘We carefully select and prepare the participants for the study. We then guide them through the psychedelic experience, and debrief them afterwards. In this regard, we’ve benefited greatly from the expertise of Chris Timmermann of Imperial College London, who is an expert in the field of DMT research.’

Cybin, the sponsor of this study, is planning to characterise a DMT derivative (CYB004) in future studies, which will be developed for people suffering from generalised anxiety disorder. A key challenge is that DMT is rapidly broken down by the enzyme monoamine oxidase both centrally in the brain and peripherally in plasma. This leads to significant variability between individuals, both in plasma levels of DMT and in the corresponding psychedelic effects.

Jacobs: ‘There is a lack of published data regarding the pharmacokinetics of DMT, which are quite variable. Moreover, there is no “standard” dosing approach for the drug, and other research groups have previously employed different dosing paradigms and formulations, which makes it difficult to draw appropriate



comparisons. Therefore, in this study we aim to identify an optimum dose and dosing approach that results in pharmacodynamic effects which are expected to translate into therapeutic benefits in patients with mental health disorders.'

### Non-psychedelic alternatives

Psychedelic substances can be remarkably safe and effective in the treatment of several psychiatric disorders. However, the therapeutic application of psychedelics is very demanding compared to regular pharmacotherapy. 'Not only do patients need to be screened for various risk factors, they must also be given careful guidance before, during and after a psychedelic session,' says Jacobs. 'The session itself can also be quite an intense experience for the patient.'

Currently, there are efforts underway to develop compounds that have the same therapeutic effect but with fewer or no 'psychedelic' effects such as loss of psychological integrity or hallucinations. 'This is down to

molecular changes that render such compounds more selective for receptor subtypes or different populations of 5-HT and NMDA receptors,' explains Jacobs.

'We're currently performing a number of studies for Gilgamesh Pharmaceuticals, who are at the forefront of developing such compounds. For us, this is a new challenge. The aim of these studies is to demonstrate pharmacological effects in healthy volunteers. This should enable us to characterise the clinical differences and similarities of such compounds compared to drugs we've already characterised, such as ketamine and DMT.' The team will combine established methodologies with more experimental new ones, such as measures of reward based on the Research Domain Criteria of the US National Institute of Mental Health. 'This is really exciting because it's still uncharted territory. However, we've already invested quite a lot of work in identifying and validating reliable assessments of this kind, and we're keen to see how they shed light on the effects of these compounds.'

# ‘It’s exciting when the pieces of the puzzle fall into place’

— Dr Rachel Gurrell, Noema Pharma

The journey of a compound from lab to clinic is often challenging. Pharmacologist Dr Rachel Gurrell, Head of Research and Early Development at Noema Pharma, describes how CHDR provided crucial data in the clinical development of darigabat. This compound, a selective GABA-A receptor positive allosteric modulator (PAM), is currently in a phase 2 trial in adults with drug-resistant focal seizures and will shortly enter a phase 2 trial in panic disorder at Cerevel Therapeutics.

The story of the molecule now known as darigabat began at Pfizer, where Gurrell and her colleagues initially explored its potential in treating epilepsy, anxiety states and chronic pain. ‘It is selective for the  $\alpha 2/3/5$  subunits of the GABA-A receptor. These are the subunits that are believed to modulate seizures and anxiety in particular. And it avoids the  $\alpha 1$  subunit, which is implicated in the sedative properties of benzodiazepines,’ says Gurrell. ‘However, similar compounds still showed sedative effects when they were first tested in humans. So we went to CHDR, because of their experience with biomarkers for selective GABA-A modulators. Specifically, we wanted to verify the EEG profile, which showed a wave pattern distinct from classical benzodiazepines in preclinical animal models.’

## Pharmacological insight

Trials with healthy volunteers were conducted at CHDR using the NeuroCart® CNS test battery. These trials confirmed what Gurrell and her colleagues had seen in the lab: both EEG and other NeuroCart parameters such as body sway and saccadic eye

movements indicated that the compound was active at the GABA-A receptor without sedating the trial participants. Gurrell: ‘In science, it’s exciting when the pieces of the puzzle start to fall into place and reveal the picture that you were expecting to see. Everything we hypothesised was basically borne out. In addition, we gained clear insight into the pharmacology as well as the safety profile. This was key for the further development of the molecule.’

Further development focused on epilepsy and lower back pain. ‘On my initiative, we conducted a trial using CHDR’s PainCart® — in fact, ours was one of the first sponsored trials to use it. Pfizer subsequently did several PainCart trials at CHDR.’ The compound turned out not to be viable as a pain medication, but did proceed to phase 2 trials for epilepsy.

Around the same time, Pfizer decided to spin out much of its activities in neuroscience. The clinical development of the compound was continued at Cerevel Therapeutics. It was Cerevel who gave the compound its current name — darigabat — and decided to explore its potential for the treatment of both seizures and panic disorder. Gurrell also moved to



Cerevel, where she headed the darigabat programme, as well as the Translational Medicine and Biomarker department.

### CO<sub>2</sub> challenge

To explore the effects of darigabat on panic, Gurrell once again turned to CHDR. 'Gabriel Jacobs and his team had just added a promising model to their repertoire: the CO<sub>2</sub> challenge,' says Gurrell. 'We needed to bridge the gap between our preclinical and phase 1 data and trials in patients. So I researched which models would be able to identify the compound's effect on panic in healthy volunteers. The CO<sub>2</sub> challenge model came out on top, also in terms of the drugs that had already been tested with it. And it turned out that CHDR had just concluded a trial with another compound, using a benzodiazepine as active control, which was the perfect preparation for the trial we wanted to perform.'

'We collaborated on the trial design, and also drew on input from Prof. Koen Schruers of Maastricht University who has years of experience working with the CO<sub>2</sub> challenge model,' says Gurrell. 'When the

results came in, we were really pleased. We knew we had a solid basis to continue developing darigabat for this indication.' CHDR's Clinical Scientist Koshar Safai Pour, who was project leader for this trial, will write a PhD thesis based on these trials. 'That's something really valuable that CHDR does — offering opportunities for people to develop themselves through their work.'

Cerevel has announced that darigabat will enter a phase 2 trial in patients suffering from panic disorder. If the compound successfully makes it to market, it will contribute to the quality of life of patients with this debilitating condition. In the meantime, Gurrell has moved to Noema Pharma, where she is Senior Vice President, Head of Research and Early Development, as well as programme lead for a novel therapeutic for major depressive disorder with atypical features.

# ‘CHDR is an active and innovative research partner’

— Dr Peter van der Ark, Janssen

Over the years, CHDR has regularly collaborated with Dr Peter van der Ark from Janssen’s Neuroscience group, based in Belgium. Van der Ark, who retired in 2022, reflects on the dynamic relationship that has grown between his team and CHDR’s Psychiatry group.

‘We used to joke that we were the ones who saved the company lots of money,’ says Van der Ark. Within Janssen Neuroscience, he headed a team responsible for the early clinical phases of drug development — an area of focus similar to that of CHDR. ‘Compared to phase 2b and phase 3 trials, first-in-human studies and initial small-scale patient trials are relatively cheap. That means that if you can detect potential issues with a compound early on in clinical development, you can save a lot of unnecessary expense.’

## Brainstorming and innovation

‘We always approached study design as a team. We would often go to Leiden to brainstorm with the neuropsychiatry experts at CHDR: Gabriel Jacobs, Joop van Gerven and Rob Zuiker,’ says Van der Ark. ‘These were open-ended conversations about the pharmacology of novel compounds with little-known targets. We discussed the relation of such targets to CNS function, trying to define potential human biomarkers to reliably demonstrate pharmacological effects in both healthy volunteers and patients. We also shared ideas about the potential indications of such compounds in neuropsychiatry. I often asked them: what path would you take in developing this new compound? And regardless of whether we agreed or not, those were always interesting conversations.’

‘CHDR’s CNS researchers have extensive experience with a wide range of both novel and registered CNS active compounds, so they were able to identify similarities and differences between our new compounds and other molecules that they had studied previously. Our brainstorming sessions were informed not only by scientific expertise but also by experience, which added a great deal of value in the design process.’

‘Something I really appreciate about CHDR is their constant quest for new methodologies to demonstrate drug effects. Their repertoire has really evolved over the years — for example, we’ve seen the NeuroCart® grow from simply a set of measurements into a sophisticated computer-driven testing suite. During our collaborative exchanges, our team also suggested methods that have since become part of CHDR’s regular repertoire, such as the CO2 challenge for investigating anxiolytic effects of novel compounds in healthy volunteers.’

## Challenging times

Around a decade ago, the development of new compounds in neuroscience almost ground to a halt. Some pharmaceutical companies even decided to divest or spin out their neuroscience divisions. Van der Ark: ‘For Janssen, that was never an option. Neuroscience has always been one of the main pillars of our company, ever since the development of haloperidol in the



1950s. We also saw it as a moral duty, given the great unmet medical need in psychiatry. But of course these were difficult times for us as well, with very few new compounds being developed.'

Things changed around 2018, when a few promising compounds started to emerge with the potential to contribute to safer and more effective treatments for mood, anxiety and trauma-related disorders, particularly depression. 'These are agents with a completely new pharmacological mechanism of action, not just an extension of existing agents that target the serotonin and noradrenaline systems,' says Van der Ark. 'There has been very little progress in the treatment of depression in the past half century since the development of SSRIs and SNRIs. Meanwhile, the prevalence of depression has risen, and there's a significant proportion of patients who don't respond adequately to treatment.'

'One of our new compounds, which we also worked on together with CHDR, acts on the orexin-2 receptor. Orexins are involved in sleep, but I think there is a strong interrelation between psychiatric disorders such as depression and disorders in sleep and biological rhythms. We may see some interesting developments in those areas in the coming years.'

### Proactive patient recruitment

'It's important to involve patients even in the early phases of drug research, particularly when targeting novel mechanisms of action. Some compounds won't lead to a detectable signal in healthy volunteers, even though they do address the pathological mechanism in patients,' says Van der Ark. 'I always advised the CROs I worked with to take a proactive approach to recruiting patients. CHDR has been quite active in that regard, and as a result, they can provide better continuity between research with healthy volunteers and research in patients.'

New drugs increasingly target specific subgroups of patients with a specific clinical or genetic profile. Van der Ark: 'Genetic tests are becoming cheaper all the time, so I expect that in the future we'll also use genetic information to help decide which drugs to prescribe. We're already seeing the first steps in that direction. Drug development will always be a dynamic field, and CHDR, with its innovative approach, is one of the drivers of progress.'



# Developing methods

Developing precise, data-rich methods for early clinical drug research is one of the unique aspects of CHDR's work. 2022 saw new developments in methods for neurology, immunology, dermatology, oncology, and more.

# Deep phenotyping mycosis fungoides: profiling an orphan malignancy

As part of an ongoing collaboration with the Dermatology department of the Leiden University Medical Center (LUMC), CHDR's Dermatology group has built an in-depth profile of mycosis fungoides, the most common form of cutaneous T-cell lymphoma. The project, which made use of CHDR's DermaToolbox and the suction blister technique, also aimed to find predictive biomarkers for the therapeutic effect of chlormethine gel in this rare malignant skin condition.

'The LUMC Dermatology department has a strong record of research into mycosis fungoides (MF) and keeps a central registry of patients with the disease,' says Selinde Wind, Clinical Scientist at both CHDR and the LUMC. 'MF patients from all over the Netherlands come to Leiden for diagnostics and treatment. In fact, the LUMC is one of the leading centres of expertise worldwide.'

Despite the impressive body of research, much is still unknown about this disease, which appears to be very heterogeneous on both a clinical and a molecular level. For example, it is not yet possible to predict whether a treatment will work in a particular patient. Wind: 'In this project, which was supported by CHDR's R&D Fund and co-funded by Recordati Rare Diseases and Helsinn, we therefore aimed to better phenotype MF. For this, we used the DermaToolbox, CHDR's comprehensive dermatological testing suite.'

## Initial findings

Preparations for this study already began back in 2020. Although MF is a rare diagnosis made only a few dozen times a year in the Netherlands, Wind was able to enrol 21 patients within five months, along with 10 matched healthy individuals. They were studied for about 6 months, which was extended to 12 months in a follow-up study. Wind: 'I was working as a doctor in the outpatient clinic for MF patients at LUMC, so I could approach patients directly. This enabled us to include the required number of people in a very short time. In fact, it was a world record for a monocentre study of an orphan disease!'

The team used a range of techniques to profile both the MF lesions and healthy skin of patients, as well as the skin of the matched healthy volunteers. This included imaging the blood flow and microvasculature and measuring the barrier function of the skin. 'One technique we've used extensively here at CHDR is the suction blister. By drawing a blister locally on a



lesion or on a healthy piece of skin and then sampling the interstitial fluid, you can get a good impression of the cells and proteins in the various layers of the skin,' says Wind. 'In MF, there is strong evidence that the tumour microenvironment is very important for the development of the disease. The suction blister technique allowed us to map that environment in detail.'

In addition to the 'deep phenotyping' of MF lesions, the DermaToolbox was also used to map the effect of treatment with chlormethine gel, a topical alkylating agent. Wind: 'We wanted to investigate whether it's possible to predict which patients will respond to treatment with chlormethine gel. This treatment can be effective in many patients, but there are also non-responders.'

### Pioneering research

Currently, Wind is processing all the results of the project. Her first impressions are positive: 'The fluid collected from the suction blisters has turned out to be a rich source of different types of cells. Besides tumour cells, we also found regulatory and cytotoxic T cells,' says Wind. 'The full analysis is still pending, but so far it seems that those different cell types may also be predictive of the treatment outcome. Maybe in the future we could even use the suction blister in the clinic, to select patients for this treatment.'

Whatever the exact outcomes will be, it is already clear that the approach used in this project will set an example for future therapy development in dermatology. 'MF is one of six conditions that will be investigated further by the Next Generation ImmunoDermatology consortium, which is based on our deep phenotyping approach,' says Wind. 'It's been really exciting to be involved in such a landmark research project.'

# Developing biomarkers to study drugs for neurodegenerative diseases

Many new drugs for neurodegenerative diseases target the function of lysosomes. CHDR has a growing arsenal of tests to demonstrate the effects of such drugs at early stages of clinical development, using white blood cells from healthy volunteers.

‘Biotech companies looking for a suitable target for inhibiting neurodegeneration often come up with compounds that affect lysosomal function,’ says Dr Philip Kremer, Research Director in Neurology. Lysosomes, small membrane-covered compartments within the cell, play a crucial role in the cell’s metabolism and ‘waste disposal’ processes. When lysosomes malfunction, defective proteins or other molecules accumulate in the cell. In brain cells, this accumulation likely plays a role in a variety of neurodegenerative diseases, such as Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and various forms of dementia.

alpha-synuclein proteins,’ says Kremer. ‘Other synucleinopathies include Lewy body dementia and multiple system atrophy. With a group of biochemically related disorders like this, it’s possible that a drug will be developed that is effective in more than one disorder.’

In other neurodegenerative diseases, different proteins are involved. ALS, for example, is linked to aggregates of a protein known as TDP-43. The same protein plays a role in some patients with frontotemporal dementia. Meanwhile, in Alzheimer’s disease — the most common form of dementia — there is accumulation of beta amyloid and tau protein.

## Parkinson’s and similar diseases

CHDR has conducted several studies with such drugs in recent years. In one study, researchers investigated the efficacy of a compound that stimulates the activity of the lysosomal enzyme glucocerebrosidase. This study focused specifically on patients with a variant of the gene for this enzyme, who were selected through a large-scale screening of PD patients. Another recent study looked at a PD drug that inhibits the lysosomal enzyme LRRK2.

‘PD belongs to a group of diseases that we now know are associated with accumulation of so-called

## Biomarkers for lysosomal pathways

Researchers at CHDR are always on the hunt for new ways to study the pharmacodynamics of novel compounds in the early stages of clinical development. CNS compounds that directly affect neurophysiology can be studied using the NeuroCart® test battery. To study compounds that primarily influence cellular functions, however, the researchers need a proxy for brain cells.

In the Research & Development lab, Dr Matthijs Moerland and his colleagues are developing assays that



target white blood cells, particularly peripheral blood mononuclear cells (PBMCs). These easily accessible cells contain an active lysosomal apparatus, offering a proxy to test the effects of new compounds for treating neurodegenerative diseases.

‘Which tests we need depends on the compound and the mechanism of action,’ says Moerland. ‘Sometimes you can see an immediate effect of an agent, and sometimes you have to stress the cells a bit first, for example with bacterial lipopolysaccharides (LPS). We’ve developed tests for different lysosomal pathways in recent years and we’re continuing to develop our cellular test battery. With these biomarkers, we can assess drug effects in the blood of healthy volunteers. Specifically, we can see if a drug does indeed affect the target pathway at the dose we administered.’

Kremer: ‘By also measuring drug concentrations in the cerebrospinal fluid, we can model the concentration in the target areas in the brain. Together, these measurements reveal pharmacodynamic action at the cellular level in healthy volunteers, as well as in early clinical studies with patients. This kind of qualitative and quantitative information is highly valuable for the further clinical development of a compound.’

# Laying the foundations for faster vaccine development

CHDR is part of the European Inno4Vac consortium, in which academic researchers and companies collaborate on faster vaccine development. ‘We contribute by developing clinical models to evaluate future vaccines for RSV and influenza,’ says Dr Ingrid de Visser-Kamerling, Associate Research Director in Infectious Diseases.

The importance of rapid vaccine development has become abundantly clear thanks to the COVID-19 pandemic. ‘Different partners within Inno4Vac focus on different aspects of this process,’ says De Visser. ‘At CHDR, we focus on the early stages of clinical development. Our pharmacological expertise is complemented by the expertise of Meta Roestenberg, professor of infectious diseases and models of controlled human infection at the Leiden University Medical Center (LUMC).’

The collaboration between CHDR and LUMC in the field of infectious diseases intensified during the COVID-19 pandemic, when the two groups worked closely together to develop drugs and vaccines for SARS-CoV-2. Now that society has more or less gone back to normal, De Visser and Roestenberg once again have time to focus on their long-term strategic goals. These mainly concern developing controlled human infection models (CHIMs) for common infections such as respiratory syncytial virus (RSV) and influenza.

## Controlled human infection models

The first controlled infections of healthy volunteers with RSV and influenza at CHDR are expected to take place in 2024. However, no vaccine or drug will be tested yet. ‘We want to use clinical and immunological readouts to carefully chart the course of the infection. Then, once we’ve validated our CHIMs for these infections, we’ll be ready for clinical trials with vaccines or drugs,’ says De Visser. ‘We know that pharma and biotech companies have a great need for CHIM research. The fact that Inno4Vac is a public-private partnership reflects our common goals.’

Before the clinical study can start, there is still a lot of groundwork for CHDR and its European partners. The selection of virus strains, for example, requires careful consideration. De Visser: ‘Influenza and RSV are common infectious diseases, so every individual has some immunity to these viruses. That makes some strains less suitable for inducing infection. Of course we



don't want our study participants to get too sick, but it's important that some symptoms of illness do occur — this is what gives us the opportunity to see if a vaccine makes any difference.'

### Challenges and rewards

Deliberately infecting healthy volunteers is ethically justified, provided that strict conditions are met. A key condition, of course, is that the volunteers are in good health and do not have any conditions that compromise their immunity. 'For this reason, we'll pay extra attention to the immunological health of the participants during screening. In addition, participants will need to be prepared to stay quarantined in the unit during the study,' says De Visser. 'Overall, this is an exciting area of research with its own particular challenges and rewards. Together with Prof. Roestenberg, we look forward to the journey ahead.'

# The search for human complement challenge models

The complement system plays an important role in both useful and pathological immune responses. Many new compounds are currently being developed that modulate complement activation. Clinical Scientist Juliette van den Noort is searching for in vivo and ex vivo methods that can demonstrate activation of the various complement pathways in study participants.

During my pharmacy studies I did an internship at CHDR, working with Matthijs Moerland's group,' Van den Noort explains. 'At the time, the team was working on an assay to predict infusion reactions. These are rare reactions that may occur after the injection of a drug, due to complement activation — for example, a drop in blood pressure, or a skin rash. Back then, we were looking for an in vitro test: if you add the drug to blood from the participant in a test tube, can you predict who will get an infusion reaction?'

Partly due to the rarity of infusion reactions, this search did not yield definitive answers. After gaining her master's degree, Van den Noort returned to CHDR to begin her PhD research on complement. Meanwhile, the scope of the question had broadened. It was no longer just about predicting infusion reactions, but also about developing an in vivo challenge model to measure complement activation.

## Innate immunity

The complement system is part of the innate immune system. It consists of dozens of proteins, which can successively activate each other in three different cascades. The end products of these pathways are capable of killing bacteria and disabling viruses, attracting phagocytes, or triggering inflammatory responses. Recent research shows that complement activation may play a role in unwanted immune responses, such as autoimmune diseases and neurodegeneration. There are also compounds being developed to activate complement in the context of cancer immunotherapy. Van den Noort: 'Complement is hot right now. For almost every component of the complement system, there's currently a compound in development.'

In recent years, CHDR has developed many challenge tests to map activation of the innate immune system. Various LPS challenges have been developed in-house



that activate the innate immune system via the TLR4 receptor, whether in blood (in vitro or ex vivo), in vivo in the skin, or systemically. Another model uses imiquimod, which triggers an innate immune response via the TLR7 receptor. In combination with skin biopsies and suction blisters, these challenge models offer detailed insight into the innate immune response. Van den Noort: 'Equipped with these validated challenge models, we are looking to contribute to the in vivo measurement of complement activation.'

### Detecting complement activation

Demonstrating complement activation is no easy task, and the team's attempts to detect activated complement in the blood or in skin biopsies have not yet been unequivocally successful. Van den Noort: 'Evolutionarily, the complement system is the oldest part of our immune system, but it's also the part we know the least about. For instance, we don't yet know

how long the different components of the cascade are detectable for. On the other hand, we do know that some components only exist for a short time. That makes it difficult to design assays: if you don't detect any activation, is there really no activation, or did you just biopsy a minute too late to find the activated protein?'

Van den Noort does not know whether she will succeed in finding an in vivo model that will allow her to detect complement activation in the skin or blood of study participants. But she is optimistic, thanks to CHDR's previous successes in measuring innate immunity. 'I know it's a search for a needle in a haystack. But luckily, it's a haystack that we already know pretty well!'

# Assessing the pharmacokinetics of large molecules in the CNS

Supported by CHDR's R&D Fund, the Neurology group plans to investigate the pharmacokinetics of large molecules in the brain and spinal cord. With a better understanding of how these molecules reach their targets, the team will be able to provide more detailed advice on treatments administered intrathecally, such as antisense oligonucleotides (ASOs).

'There are some interesting new treatment approaches in neurology that involve the administration of large molecules, such as antibodies and ASOs,' says Dr Philip Kremer, Research Director in Neurology. However, how such antibodies pass from the blood or cerebrospinal fluid (CSF) to the interstitial fluid around brain cells and into brain cells themselves is still only partially known. 'At CHDR, we live by our philosophy of question-based drug development. The first question in developing a new drug should always be: does the compound reach the target? The answer to that question is often more complex — and more enlightening — than it might seem.'

## Reaching the target

Unlike classical small molecules, antibodies and nucleotides do not reach the brain easily after intravenous administration. The first big hurdle they have to overcome is the blood-brain barrier. To achieve this, some antibodies — for example, those being developed as a possible treatment for Alzheimer's

disease — are administered in very high concentrations, of which a mere 0.1~0.2% pass into the CSF.

Meanwhile, ASOs and some other large molecules are administered intrathecally, bypassing the blood-brain barrier. But they still have to make the long journey from the cauda equina at the base of the spinal cord to their target areas in the brain. Kremer: 'Monkeys like macaques are often considered to be a reliable preclinical model for this approach. But macaques are much smaller than humans. As the oligonucleotide has to travel to its target area via diffusion, physical distance is an important factor.'

## Vibrating vest

There are several possible ways to try and accelerate the transport of large molecules through the space containing the CSF. One promising approach is a vibrating vest, which causes fluctuations in pressure that set the CSF in motion. However, this fluctuating pressure on the CSF may also lead to increased leakage



of the compound through nerve roots. To assess the amount of leakage, Kremer and his team will start by focusing on naturally occurring proteins, such as tau protein.

‘We’ll measure the concentration of these proteins in the CSF and in the blood while the study participant is at rest. Then we’ll ask the participant to put on the vibrating vest and see if those concentrations change,’ says Kremer. ‘Assuming that the production of proteins remains constant, this way we can see if there are shifts between the two compartments, indicating leakage.’

### Imaging techniques

To track the fate of large molecules that are administered intrathecally, the team plans to use imaging. ‘We could, for example, use a gadolinium-based contrast agent to make the compound visible to MRI. Or we could use radioactive tracers and PET

scanning. In any case, the aim is to find out how these molecules move through the CSF,’ says Kremer. ‘This is exploratory research, but with clear practical implications. By gaining an understanding of the kinetics of such molecules within the CNS, we can contribute to the development of these exciting new therapeutic approaches.’

# Bone marrow puncture procedure opens up new opportunities for early phase immuno-oncology trials

CHDR now offers an in-house procedure for bone marrow sampling in early phase clinical trials, expanding the possibilities for a wide range of therapeutic areas, particularly immuno-oncology. The newly implemented procedure was validated in a study performed in 2022, which showed that healthy volunteers tolerated the procedure well and most would be willing to undergo it again as part of a future study.

In recent years, the field of oncology has seen a growing interest in immunomodulatory drugs. For the clinical development of these drugs, it is important to study immune cells in different immunological compartments. CHDR already has broad experience researching immune cells in skin and peripheral blood, whether in vitro, ex vivo or in vivo. Now a central compartment has been added: bone marrow.

Dr Jacobus (Co) Bosch, Research Director in Oncology: ‘Access to bone marrow can provide important novel insights into drug effects on the haematopoiesis and differentiation of immune cells. This is instrumental in haemato-oncology and the development of oncological treatments for solid tumours, as well as in the study and treatment of autoimmune diseases.’

## Validation study

‘We’ve established a procedure for bone marrow puncture for use in early phase clinical drug research, which we recently validated in a proof-of-concept study. This procedure involves both the aspiration of bone marrow and the associated biopsy,’ says Bosch. ‘The whole pipeline of bone marrow sample processing and analysis has also been validated. For the purposes of the study, we performed the cellular analysis in our Research & Development lab, but in future it’ll be done in our operational laboratory as a standard procedure.’ The histopathological analysis of the bone marrow biopsy and the cytomorphological analysis of the bone marrow smear are performed at the Pathology and Haematology departments of the Leiden University Medical Center.

The validation study also included the extraction of genomic material from the sampled bone marrow cells. ‘This enables us to conduct cytogenetic and molecular analysis as well,’ says Bosch. ‘In short, we can now offer the full spectrum of bone marrow analysis.’



### Well tolerated procedure

A bone marrow puncture is generally known to be a stressful procedure. The team sought to minimise the burden as much as possible through the training of medical and nursing staff, the efficient application of local anaesthesia, and the information provided to the healthy volunteers. 'The volunteers tolerated the procedure well. Most said they would be willing to undergo it again, which is encouraging and always a good sign,' says Bosch. 'Bone marrow sampling is increasingly in demand for early drug development, so it's great that we're now able to offer this procedure in-house.'

# Developing and validating a finger tapping test for Parkinson's disease

Over the past three years, the Biomarker Engineering and Analytics (BEA) group has developed and validated a tool to assess medication effects in patients with Parkinson's disease (PD), financed by CHDR's R&D Fund.

'The Neurology group conducts many studies in patients with PD,' says Dr Robert-Jan Doll, Associate Director and head of the BEA group. 'So they were seeking an objective measurement of motor symptoms that would be straightforward to apply and could be frequently repeated.' Such a measure would provide a more versatile alternative to the Movement Disorder Society's Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III), which requires systematic evaluation by a clinician. The team decided to develop a finger tapping task, in which the patient is asked to press two buttons alternately. Parameters relating to the speed, accuracy and rhythm of taps can yield insight into the severity of motor symptoms.

The first prototype used physical buttons. However, this approach did not produce sufficiently consistent results. 'Pressing the buttons takes some force, which comes at the expense of speed and accuracy,' says Jeremy Cicilia, Clinical Research Engineer in the BEA group. The team therefore developed an alternative method using a touchscreen. 'An additional advantage of touchscreens is that you can collect more forms of data — for example, the number of taps that miss the target,' says Cicilia.

## Initial testing in healthy volunteers

Soma Makai-Bölöni, Clinical Scientist in the BEA group, was responsible for the first exploratory study using touchscreens. 'Various finger tapping tasks can be found in the literature, but they are often only described in general terms,' says Makai-Bölöni. He conducted a study with 14 healthy volunteers to map out the different possibilities and determine which to take forward in patient studies.

Makai-Bölöni: 'We looked at alternate finger tapping (AFT), in which the patient taps with their index and middle finger, and alternate side tapping (AST), where the index finger is used to tap targets which are further apart. We tested both options with and without visual cueing.' In terms of endpoints, the initial study revealed that the total number of taps and spatial error had the highest repeatability and sensitivity. Meanwhile, a simpler setup without visual cueing is preferred, to maximise the ability of the test to detect medication effects.

As part of this initial phase, it was also necessary to describe the technicalities of the setup in detail. Abdes Maatoug, Validation Engineer in the BEA group: 'To use a task in clinical drug development, it has to be very precisely defined in terms of standard operating



procedures and technical validation procedures. We work through each procedure to verify functionality before a method or tool is clinically validated.'

### Placebo-controlled trial in PD patients

The next step in the development was a study in 20 PD patients. Eva Thijssen, Experienced Clinical Scientist: 'To ascertain whether finger tapping is suitable for measuring drug effects, we did a placebo-controlled crossover study with the most commonly used Parkinson's medication: a combination of levodopa and carbidopa.' Patients participating in this study were given placebo or levodopa/carbidopa after a one-night withdrawal from their own PD medication.

AFT and AST were then applied without visual cues. A thumb-index finger tapping task was used as an additional source of data, with a goniometer to measure index finger flexion. An MDS-UPDRS III score was recorded pre-dose and up to three-and-a-half hours post-dose. Thijssen: 'Based on the data, we can conclude that the AST and thumb-index finger tapping

tasks provide short, rater-independent measurements that are sensitive to dopaminergic drug effects, with an effect size similar to the MDS-UPDRS III.'

### Composite biomarker

The data from this study were then further analysed by Ahnjili Zhuparris, Data Scientist in the BEA group. Zhuparris: 'The end goal was to have an objective and repeatable measurement of PD motor symptoms which is sensitive to drug effects. To this end, we applied machine learning to develop a composite finger tapping biomarker.' A composite biomarker would reflect co-occurring manifestations of motor function impairment in PD patients, and could subsequently be used to monitor or predict differential longitudinal treatment effects. Zhuparris' work demonstrates that the AST composite biomarker may detect treatment effects earlier and more accurately than the MDS-UPDRS III. 'This provides evidence in favour of adopting the AST as a composite biomarker for monitoring anti-Parkinsonian drug effects in clinical trials,' says Zhuparris.



# Developing people

Education remains one of CHDR's core activities, from primary school to postgraduate training and professional development. In 2022, the organisation celebrated five new PhD graduates and two new professorships.

# Leaders in pharmacology education: from primary school to professional training

CHDR is increasingly approached by external organisations asking for input on education or seeking to participate in the organisation's educational activities. In recent years, CHDR's work in this area has expanded to include creating materials for primary schools as well as teaching university students and professionals.

'Developing people is one of our core strategic goals as an organisation, so it's rewarding to see that our educational expertise is in demand,' says Dr Jeroen van Smeden, Education Director. 'Many CHDR staff members are involved in teaching activities, and our Teaching Resource Centre is used worldwide by students and professionals as a learning resource for pharmacology.'

CHDR's teaching activities often coincide with the organisation's other two strategic goals: developing drugs and developing methods. 'Pursuing these goals requires us to attract and develop talented people,' says Van Smeden. 'The certified clinical pharmacology training we provide is followed by many of our own staff members. In addition, student internships offer an opportunity to spot upcoming talent.' But developing people is also a goal in itself for CHDR. This is realised not only through university teaching and professional training, but also by the contribution CHDR makes to primary education.

## Pharmacology for primary school students

'ICLON, Leiden University's Graduate School of Teaching, develops educational content from primary school to university level. Several primary schools had asked ICLON to develop learning resources on medicine, and so ICLON turned to us for help. A couple of years ago we organised a summer programme for kids to learn about the journey of a pill through the body, and now they asked us to develop that into a curricular programme for the oldest primary school year groups,' says Van Smeden.

The programme describes the journey of medicines from four perspectives: the journey through time (from the ancient Egyptians and the Middle Ages to the present day), the journey through nature (with a variety of medicinal substances, from pitch and honey to various plants), the journey through the body (pharmacokinetics, but in simple terms), and the journey from lab to patient (drug development). Van Smeden: 'It's great fun to tell those stories in a way that engages children.'



### Central medical ethics committee

CHDR's education team was also approached last year by the Netherlands' Central Committee on Research Involving Human Subjects (CCMO). 'Following the introduction of the new EU Clinical Trials Regulation in 2022, the CCMO is growing, and so is their need for expertise in clinical pharmacology,' says Van Smeden. 'So they were seeking clinical pharmacology training for their staff. Of all the institutes in the Netherlands that offer this training, they chose us, which is quite an honour I think!'

Other institutes in the field of drug development and pharmacology in the Netherlands also regularly contact CHDR to train staff or develop teaching modules. 'It's our ambition to be a key opinion leader for drug development not only from a research perspective, but also with respect to education,' says Van Smeden. 'And we know that becoming a leader is not just about challenging yourself, but also earning that recognition from others.'

# Collaborating to grow the human resources potential of the Leiden Bio Science Park

CHDR is situated at the heart of the Leiden Bio Science Park (LBSP), a dynamic hub for business and innovation in the field of life sciences. The LBSP's ambition is to become the leading 'innovation quarter' in the Netherlands. However, achieving this relies on future-focused human resources strategies aimed at growing and attracting talent. CHDR collaborates with partner companies and educational institutions in the LBSP to create the conditions for success.

'We need each other,' says Human Resources Director Yvette Akkermans. 'In the coming years, we need to collaborate to create a climate that is attractive to a range of young talent: nurses, researchers, laboratory staff, quality assurance staff, IT specialists, statisticians, and so on. Not just academics, but also people with applied sciences or vocational qualifications.'

## Great ambitions

CHDR moved to the LBSP in 1995, having outgrown its first premises close to the Leiden University Medical Center. It was one of the first companies to establish a facility in the LBSP. Since then, the LBSP has grown into a thriving campus where numerous start-ups and supporting companies are located side-by-side with departments of Leiden University and the Leiden University of Applied Sciences, as well as large companies such as Janssen and Hal Allergy/Halix.

Currently, more than 70 drug development companies

and services are located in the LBSP, and more companies are moving in all the time. The most recent of these is Bristol Myers Squibb, which will establish a production facility specialising in CAR T-cell therapy. Building on the synergy between companies, research facilities and educational institutions, the LBSP aims to become a focal point for bioscience innovation. 'Human resources is one of the key issues involved in achieving this,' says Akkermans. 'To grow, we need sufficient talent, at all different levels.'

## 'Triple helix'

Attracting and retaining talent is not easy, exacerbated by recent population trends that mean fewer young people entering the job market. Akkermans: 'We hope to make a difference through cooperation. We call this the "triple helix": the interaction between companies, educational institutions and local government. By working together in this triple helix, we can create optimal conditions to attract the talent of the future.'



For instance, we can stimulate vocational colleges and the University of Applied Sciences to align their programmes with the needs of employers, and companies can offer internships and opportunities for practical experience. The local government also has a role to play, for instance by ensuring sufficient housing.'

Akkermans regularly consults with her HR counterparts from other companies in the LBSP and actively participates in a working group focusing on future developments. CHDR also supports joint activities, such as when the LBSP participates in job fairs in the region. Another important new development is that, in addition to university students, CHDR also offers internships for students from secondary and higher vocational education. 'This concerns a range of careers, from lab technicians and nurses to logistics staff,' says Akkermans. 'In this way, we contribute to the cooperation with educational institutions, while also making ourselves more visible as an employer. It's important to invest not only in our own future, but also in that of the LBSP ecosystem.'

# Prof. Geert-Jan Groeneveld: the revolution in neuropharmacology is underway

On 11 March 2022, Geert-Jan Groeneveld, CHDR's CMO / CSO, delivered his inaugural lecture as professor of Clinical Neuropharmacology at Leiden University. In his address, titled 'The importance of the biomarker', he explained that neuropharmacological research will yield several medical breakthroughs in the coming years, as targeted treatment is developed for subgroups of patients with neurodegenerative diseases and neuropathic pain. Watch the video below (in Dutch) or scroll down for a summary.

Neurodegenerative diseases will become increasingly important in the coming years due to decreasing mortality from cardiovascular diseases and cancer. The good news is that (genetic) research into these diseases is yielding more and more targets for therapy. As Groeneveld puts it: 'It's becoming increasingly clear that the non-hereditary forms of these neurodegenerative diseases are also caused — or partly caused — by genetic defects. The speed at which new genetic mutations are being discovered is increasing and shows no signs of slowing down.'

## Biomarkers and neurodegeneration

The lecture focused largely on clinical drug development in neuropharmacology, driven by a central question: how can we demonstrate that a novel drug for a very slowly progressing neurodegenerative disease actually works, and that it affects a process that we may have only recently come to understand and which has

never before been measured in humans? As already revealed by the title of the lecture, biomarkers provide the answer.

Groeneveld illustrated his point with research conducted by CHDR's Neurology group, which he led for many years. This research was conducted in a subgroup of patients with Parkinson's disease (PD) in whom the activity of the enzyme glucocerebrosidase is reduced due to a genetic mutation. The compound the team investigated aimed to increase glucocerebrosidase activity.

To demonstrate a pharmacological effect of the drug, the team used a measure of glucocerebrosidase activity in white blood cells. However, before they could use this measurement as a pharmacological biomarker, a lot of preliminary research first had to be carried out by CHDR's Research & Development lab, for instance on the natural fluctuation in the activity of glucocerebrosidase in white blood cells. In addition, it



was necessary to screen a large group of PD patients in order to select the subgroup with the genetic mutation. Thanks to all this groundwork, the pharmacological effect could be demonstrated, and the compound is now in the next stage of development.

### Ongoing research

Groeneveld also spoke about the pain research he conducts at CHDR, partly in collaboration with the Leiden University Medical Center. This research is also concerned with developing biomarkers to map the pharmacological action of new drugs, as well as thoroughly defining subgroups of patients. In conditions such as neuropathic pain, the focus is not so much on genetic differences, but rather on defining subgroups through better phenotyping.

In the booklet published to accompany the lecture, Groeneveld further argued for a 'leaner' version of Good Clinical Practice (GCP) requirements, which could reduce the cost of drug development. 'I think it's feasible to provide scientific evidence that a lean GCP interpretation is not inferior to the current "fat" version. This may encourage regulators to change. I foresee potential for a collaboration between regulators and academics to carry out these studies,' says Groeneveld.

# On the right path: career development at CHDR

In 2018, Dr Manon Jansen was looking for a new challenge after completing her PhD research in immunology. She recounts how she became a Senior Clinical Scientist in CHDR's Immunology group, led by Research Director Dr Matthijs Moerland.

'I did my bachelor's degree in Biomedical Sciences at Utrecht University,' says Jansen. 'After that, I stayed in Utrecht to do an MSc in Biology of Disease, in which I focused on immunology. I then did my PhD research in translational immunology, focusing on restoring immune tolerance in rheumatoid arthritis. I worked a lot in the lab and with animal models.' After her PhD, Jansen was looking for a change. 'I heard about CHDR through a friend, and had an introductory meeting with Matthijs Moerland. I hoped to work in his Research & Development lab, but there wasn't a vacancy. However, Matthijs was looking for a Senior Clinical Scientist to help lead clinical trials. And so that's how I ended up joining!'

Jansen worked as a project leader for over a year, gaining experience by supervising various projects in immunology and dermatology. 'There was a steep learning curve at the beginning, and I had some educational experiences with a rather demanding client. But I knew that I had chosen the right path: in my PhD research, I missed the direct connection with clinical application. I also wanted to work in a more dynamic environment, engaging and collaborating with other people — and that's exactly what I found at CHDR.'

## Brainstorming with clients

With that intensive first year under her belt, Jansen quickly grew into her position as Senior Clinical Scientist. Around the same time, Moerland established his Immunology group to perform clinical studies involving in vivo immune challenges and drugs that target the immune system. Jansen is currently the group's only Senior Clinical Scientist. Together with Moerland, she supervises seven Clinical Scientists who are responsible for the day-to-day running of trials.

'I am one of the few immunologists here at CHDR, which means I'm regularly called on to brainstorm with scientists from the companies we work with — something I really enjoy. And I have plenty of opportunity to keep developing my career: I'm currently training to become a clinical pharmacologist, gaining expertise which will add a lot of value to my day-to-day work here.'



# Prof. Robert Rissmann: the golden hour of dermatology is just beginning

On 8 July 2022, Robert Rissmann, CHDR's Research Director in Dermatology, delivered his inaugural lecture as professor of Translational Dermatology at the Leiden Academic Centre for Drug Research, Leiden University. In his address, titled 'The golden hour of skin', Rissmann spoke persuasively about the importance of dermatology for patients' quality of life, and urged a multifaceted approach to therapy development in this field.

Rissmann began his lecture by drawing attention to the heavy burden that patients with skin diseases must bear, which results not only in low quality of life, but also high social costs due to absenteeism and the need for frequent and long-term medical treatment. Given the impact that skin diseases can have, it is vital that effective treatments are developed. In this regard, translating in vitro results and animal models to humans is a major hurdle. In Rissmann's words, 'there is a big discrepancy between laboratory findings and results in patients.'

Rissmann then introduced his area of expertise, translational dermatology (with a humorous nod to the role of translation in his own life, as a German with a French wife, working in the Netherlands and using English most of the time). The field of translational dermatology is concerned with how the results of laboratory studies are translated into clinical practice. At the same time, Rissmann's work also includes systematic laboratory investigation of mechanisms identified through findings in the clinic — a kind of back-translation.

## Precision medicine

To bridge the gap between preclinical and clinical research, it is essential to consider skin diseases from different perspectives. Rissmann refers to this as 'deep phenotyping'. This is a multimodal approach, bringing together a range of measurement methods, the patient's experience, and the clinical view of the dermatologist. This multifaceted perspective is also of great value when evaluating novel treatments. As Rissmann emphasised in his lecture, the measurements used in this approach need to be objective and highly precise in nature.

In closing, Rissmann outlined a vision of personalised dermatological disease profiling via rapid pattern recognition, using technology akin to the algorithms used for machine translation and face recognition. 'We are getting closer and closer to therapies that are tailored to subtypes of diseases instead of the classical "one size fits all" approach.'

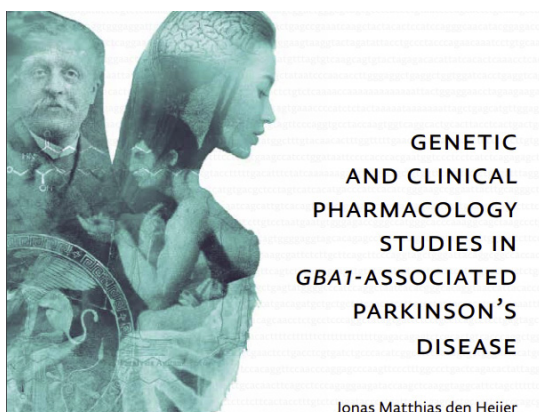


Thanks to CHDR's catalysing role and through his advocacy of 'deep phenotyping', Rissmann has been successful in building a national consortium in the field of immunodermatology, which was recently awarded an €11 million grant from the Netherlands' national research fund. 'The time is ripe for such a nationwide, collaborative approach connecting all university medical centres,' says Rissmann. 'If the vision of the new consortium becomes a reality, dermatology's golden hour has only just begun.'

# Five new PhD graduates in 2022

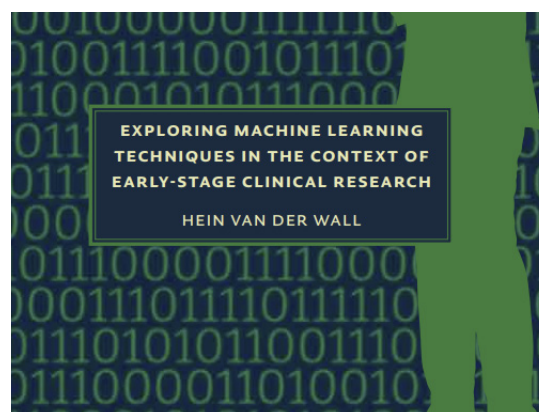
At CHDR, educating students and professionals is one of our core values. Through our Clinical Research Programme we offer ambitious young researchers and clinicians a well-defined career development path. In this rigorous five-year PhD programme, participants design and conduct several research projects while being coached by Senior Clinical Scientists and Research Directors. Throughout the programme, participants develop key skills and competencies in project management, clinical pharmacology, and scientific research. The programme usually culminates in the completion of a PhD thesis.

In 2022, five PhD candidates successfully defended their theses at CHDR. Click on each of the book covers below to read more.



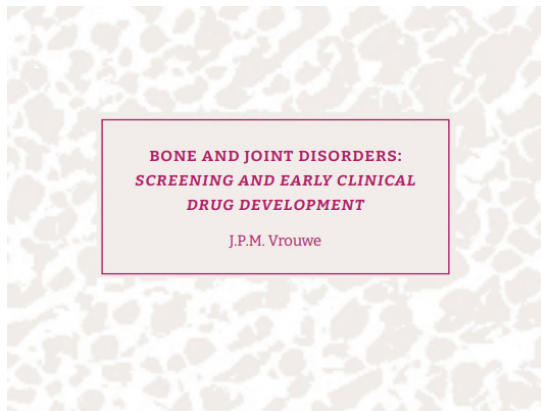
## Thesis Jonas den Heijer

Genetic and Clinical Pharmacology Studies in GBA1-associated Parkinson's Disease



## Thesis Hein van der Wall

Exploring machine learning techniques in the context of early-stage clinical research



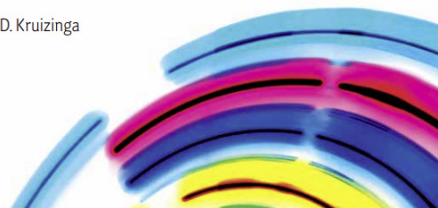
### Thesis Josine Vrouwe

Bone and joint disorders: sceening and early clinical drug development

### Trial@home for children

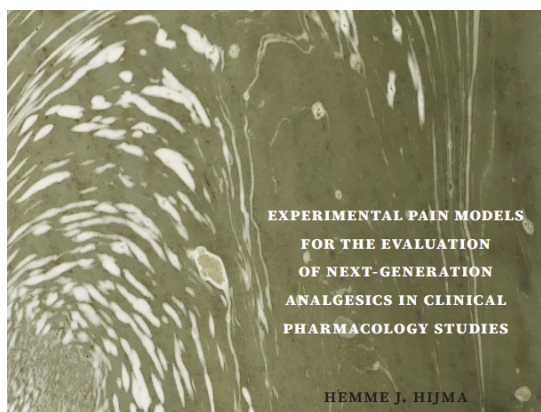
Novel non-invasive methodology for the pediatric clinical trial of the future

Matthijs D. Kruizinga



### Thesis Matthijs Kruizinga

Trial@home for children - novel non-invasive methodology for the pediatric clinical trial of the future



### Thesis Hemme Hijma

Experimental pain models for the evaluation of next-generation analgesics in clinical pharmacology studies



# 2022 stories

CHDR strives to create value for patients, professionals and the wider population, both leading and responding to new developments in the field. Read about how we adapted to change and launched novel projects of our own in 2022.

# 35 years of creating value in an unpredictable world

On 7 October 2022, CHDR celebrated its 35th anniversary with an event titled ‘Creating value in an unpredictable world’. This festive occasion involved a symposium and celebration at the Naturalis Biodiversity Center, just around the corner from CHDR’s main facility in the Leiden Bio Science Park.

In his opening address, CEO Prof. Koos Burggraaf briefly sketched the evolution of CHDR over the past 35 years, from its origins as a government-funded initiative with a single employee to the dynamic organisation it is today. CMO / CSO Prof. Geert Jan Groeneveld reflected on the fact that unpredictability is inevitable, and yet biological systems tend to evolve towards more order, culminating in the human need to create meaning and value in the midst of change.

Creating value underpins CHDR’s three strategic goals — to develop drugs, develop methods, and develop people. In collaboration with partners and clients, CHDR creates value by developing drugs that alleviate symptoms of disease and prolong life. By developing better methods and cultivating the potential of talented people, the value is amplified even further.

In the symposium, three renowned scientists spoke about their experiences in creating value. Prof. Dinko Valerio described several new developments in biotechnology that he has been involved in realising. Prof. René Bernards explained how the fundamental oncology research of recent decades is now giving rise to ever better therapies. And Prof. Meta Roestenberg gave a personal account of how her team, in collaboration with CHDR, worked amid all the unpredictability of the pandemic to develop treatments and a vaccine for COVID-19.

During interludes between the lectures at the symposium, musicians Eric Vloeimans and Juan Pablo Dobal underlined with their lucid improvisations how human creativity can turn the inherent unpredictability of the world into value and beauty.

Watch the presentations [here](#).



# Fully prepared for the European Clinical Trials Regulation

On 31 January 2022, the Clinical Trials Regulation (CTR) entered into application in the European Union. For many companies, complying with this new legislation is still quite a challenge, but CHDR is fully prepared and ready to support clients and partners too. In May 2022, CHDR was the first Dutch research organisation to have an application approved under the CTR, using the Clinical Trial Information System (CTIS) online platform.

‘We started preparing for the CTR as soon as we knew what was required,’ says Tanja Grobben of the Quality Assurance team. ‘We immediately started taking stock of the implications for our own processes and what would change for our clients.’ ‘The whole procedure for submitting a study protocol has changed,’ adds Kristy-Cheryll Riley. As CHDR’s regulatory submission specialist, she is the point of contact for the Clinical Trial Assistants who have to submit protocols. ‘Until now, submitting a protocol was our job as CRO. Once our client had agreed to the protocol content, we could do the rest. Now, the client needs create an account for the study in CTIS and authorise us to enter information. And timing is key: everything has to be completed within a limited timeframe, otherwise the application has to be resubmitted.’

## Adjusting procedures and templates

The scientific, operational and administrative processes surrounding a clinical trial are complex and intertwined, so the implementation of the CTR at CHDR affects almost all aspects of the organisation. This was already evident from the initial exploration that Grobben, Riley and colleagues undertook back in 2020. In February 2021, they set up a working group to navigate the transition. February 2022 saw the start of an EU-wide transition period in which applications could be submitted either in the new way via CTIS or in the old way. Already in May, CHDR submitted its first protocol under the new system, which was approved a month later.



‘We had to start in good time to get everything in order. There were a lot of standard operating procedures and templates that had to be adapted,’ says Riley. ‘But it was also fun to do. I felt a lot of support from the organisation — everyone was very interested, and the information meetings we organised were very well attended.’ Staff directly involved in developing and submitting research protocols also received targeted training, based on European Medicines Agency (EMA) materials.

### Supporting clients and partners

The working group not only addressed the internal challenges related to the introduction of the CTR, but also optimised the support that CHDR can provide to clients and partners. Riley: ‘The new CTR represents a big change, which is quite a challenge for

our clients. Companies that have sponsored many drug development studies in the past now have to get used to a completely new way of doing things. We can facilitate this by guiding them through what they need to do.’

Collaboration partners such as the Leiden University Medical Center also stand to benefit from CHDR’s thorough preparations. ‘Because we’re already experienced with the CTR and CTIS, we were asked to help put together a webinar for researchers in academia and healthcare,’ says Riley. ‘The CTR is a challenge for anyone doing drug research, not least because of technical problems with CTIS, which regularly shuts down partially or completely. But we were already using other EMA systems, such as EudraCT, which also had their share of technical problems. And any new system takes some getting used to. We can’t eliminate all the obstacles, but we can support our clients and partners to make things as smooth as possible.’

# New compensation guidelines improve study recruitment

In 2022, CHDR and other early phase CROs in the Netherlands drew up new guidelines on compensation for participants in early phase drug development. In particular, these guidelines adjust the level of compensation to better reflect the actual burden on the study subject. The Recruitment department is already seeing positive effects on the recruitment of participants.

‘When deciding how much compensation a trial participant should get for a particular study, we go by a set of national guidelines,’ says Dr Rob Zuiker, Associate Director. ‘Every few years, together with the two other Dutch CROs who conduct early phase clinical drug trials, we make a proposal to update the guidelines. This proposal is reviewed by the medical research ethics committee that assesses most early phase drug studies in the Netherlands.’

In 2022, a new proposal was agreed on. ‘The last time the guidelines were revised was in 2019 — so, before the COVID-19 pandemic,’ says Zuiker. ‘This time, apart from adjusting for inflation, we also looked closely at the balance between compensation for attendance and compensation for activities. It’s important that participants are compensated for each time they have to attend the Clinical Research Unit. Meanwhile, participants should also get extra compensation if the testing they have to undergo at the unit is particularly intensive, as it is in some of our studies using the NeuroCart® CNS test battery. In the new guidelines, we’ve improved the balance between these two factors.’

## Improvements in recruitment

CHDR’s recruiters noticed the effect of the new agreement immediately. ‘Since the pandemic, it had been more challenging to find enough volunteers,’ says Afke Mevius, Recruitment and Screening Manager. ‘But from the moment we introduced the new compensation rates, things started to pick up.’

An increase in compensation was clearly needed in the current economic situation. ‘On the other hand, we don’t want individual participants to be tempted to join too many studies,’ says Zuiker. ‘It would be both an ethical and a methodological problem if people started becoming “professional” study subjects. Therefore, individuals are limited to participating in studies a maximum of three times per year within Europe. What’s more, there should be a break of at least three months between consecutive studies. All European CROs keep records, so we can draw on an independent database to enforce these rules.’



# Prestigious grant awarded to national immunodermatology consortium

The Next Generation ImmunoDermatology (NGID) consortium, a network of researchers, clinicians and industry partners in the field of (immuno) dermatology, has been awarded over €10 million from the Dutch Research Council. Established on the initiative of Prof. Robert Rissmann, CHDR's Research Director in Dermatology, the consortium will focus on 'deep phenotyping' and personalised therapy development in six skin diseases.

'I am very happy and humbled by the success of this application — first of all for all the patients whose quality of life is affected tremendously by skin diseases, and also for our own research which aims to resolve this unmet clinical need,' says Rissmann. 'Dermatology research in the Netherlands has never before received a grant of this size. It's a huge boost for the under-researched field of inflammatory skin diseases, both in the Netherlands and abroad. And thanks to the involvement of pharmaceutical and tech companies, who will invest an additional €1.5 million, we should see more impetus for translational studies.'

For the first time, all Dermatology departments at Dutch university medical centres (UMCs) are brought together within one consortium. Together with consortium partners, the UMCs will build a unique infrastructure to facilitate research, involving nationwide standardisation of outcome measures and methodology. Rissmann: 'This consortium is a really exciting development for CHDR Dermatology too. We already have very fruitful collaborations with the UMCs of Leiden and Rotterdam, and now we'll have the

opportunity to collaborate with more dermatologists in a wider range of UMCs, each with their own specific areas of expertise and highly specialised patient care.'

## Deep phenotyping

For Rissmann, the award means recognition for the efforts of the many partners who have aligned and engaged with one another to make this consortium possible. The award also represents further endorsement for the approach Rissmann calls 'deep phenotyping': using a range of different measurement methods to develop objective biomarkers to map disease progression and recovery accurately at very high resolution. As part of the consortium, deep phenotyping will be carried out in six key diseases: cutaneous T-cell lymphoma, atopic dermatitis, plaque psoriasis, urticaria, hidradenitis suppurativa, and cutaneous lupus erythematosus.



CHDR's DermaToolbox, a suite of precise, objective dermatological measures, is dedicated to deep phenotyping for application in clinical drug trials. 'We have already been using the DermaToolbox extensively to study cutaneous T-cell lymphoma, vulvar diseases, psoriasis and wound healing. We look forward to deploying it to study the additional diseases selected by the consortium.' This thorough and harmonised in-depth characterisation of patient cohorts promises to yield enormous benefits, not only for evaluating novel treatments, but also for informing clinical practice.

### Focus on inflammation

The grant comes at a time of innovation, as a variety of new treatments are being developed for inflammatory skin diseases. The NGID, too, has a strong emphasis on inflammation. Of the six diseases under investigation by the consortium, five are inflammatory skin diseases. Rissmann: 'In recent years, our Dermatology group has developed challenge models for studying inflammatory skin diseases, in collaboration with Dr

Matthijs Moerland's Immunology group. With the DermaToolbox and our suction blister technique, we're able to objectively evaluate skin characteristics and examine inflammatory cytokines and various immune cells following the application of a challenge.

'Inflammatory skin diseases can also serve as a useful model to study treatments for other inflammatory disorders: on the skin, most compounds can be administered locally and the effects are easy to see and measure,' says Rissmann. 'In the coming years, I expect to see several breakthroughs in the treatment of inflammatory diseases in the skin and elsewhere in the body. With the NGID consortium in place, we are ready to play our part in driving those developments.'

# 1,000th patient with atopic dermatitis recruited

Over the past seven years, CHDR has conducted eleven studies in the field of atopic dermatitis (eczema). In 2022, a special milestone was reached: the recruitment of the 1,000th patient with this skin condition.

‘We have been very successful in recruiting this group of patients,’ says Prof. Robert Rissmann, Research Director in Dermatology. ‘This is due to a team effort by our in-house recruiters and physicians, along with our strong national network of dermatologists, CONNECTED.’ In multicentre trials, CHDR often manages to recruit the largest numbers of patients with atopic dermatitis. ‘In our most recent multicentre trial, we were the top recruiter out of 20 sites. In addition, we were much more efficient in terms of the inclusion rate,’ notes Rissmann. Of the eczema patients that CHDR recruits for trials, on average more than a third are actually able to go on and participate in a study.

‘The treatment options for atopic dermatitis have greatly improved in recent times,’ says Rissmann. ‘Patients with moderate to severe eczema can access effective treatments in a clinical setting. As a result, however, most of them aren’t willing to interrupt their regular treatment to participate in a placebo-controlled study. Therefore, we often focus our recruitment efforts on people with mild to moderate eczema. They can be reached by our media campaigns, and there are also a number of such individuals in our extensive database of study volunteers.’

## High throughput

According to Rissmann, the relatively low screening failure rate is due to effective pre-screening by CHDR’s recruiters, who contact each prospective participant by phone. ‘Our recruiters are very adept at pre-screening by phone. Besides carefully addressing the questions that have been pre-defined and approved by our team, they also know how to put people at ease. That way, we not only attract people to participate, but also filter effectively to find the right people to invite for screening.’

Once the right patients are included in a study, Rissmann and his team can begin with the clinical work. ‘Our Dermatology group has a great track record with high-throughput clinical trials. In some multicentre studies, the clients are surprised by the amount of data we can generate in quite a short period of time. And we get great satisfaction from being able to deliver above expectations!’





# Scientific output

In 2022 CHDR continued to contribute to the progress of the field with over 80 peer-reviewed papers on a wide variety of topics. Click the tile below to open the full list including links to view each individual publication.

# Our publications in 2022

Aulin LBS, Kleijburg A, Moerland M, et al. Characterizing the kinetics of presepsin and associated inflammatory biomarkers in human endotoxemia. *Inflamm Res*. 2022; 71(9):999-1001.

Baakman AC, Gavan C, van Doeselaar L, et al. Acute response to cholinergic challenge predicts long-term response to galantamine treatment in patients with Alzheimer's disease. *Br J Clin Pharmacol*. 2022; 88(6):2814-2829.

Bakkum MJ, Loobeek BJ, Richir MC, et al. Teaching resources for the European Open Platform for Prescribing Education - a nominal group technique study. *NPJ Sci Learn*. 2022; 7(1):23.

Bakkum MJ, Verdonk P, Thomas EG, et al. A Clinical Pharmacology and Therapeutics Teacher's Guide to Race-Based Medicine, Inclusivity, and Diversity. *Clin Pharmacol Ther*. Published online 2022.

Balak DMW, Rissmann R. Anti-interleukin-17A for pityriasis rubra pilaris: catching the psoriasis biologic wave. *Br J Dermatol*. 2022; 187(5):633-634.

Berfelo T, Doll RJ, Krabbenbos IP, et al. Observing Altered Nociceptive Detection Thresholds in Patients With Persistent Spinal Pain Syndrome Type 2 With a Dorsal Root Ganglion Stimulator. *Neuromodulation*. 2022; 25(7):1006-1014

Buters TP, Hameeteman PW, Jansen IME, et al. Intradermal lipopolysaccharide challenge as an acute in vivo inflammatory model in healthy volunteers. *Br J Clin Pharmacol*. 2022; 88(2):680-690.

Buters TP, Hameeteman PW, Jansen IME, et al. Clinical, Cellular, and Molecular Effects of Corticosteroids on the Response to Intradermal Lipopolysaccharide Administration in Healthy Volunteers. *Clin Pharmacol Ther*. 2022; 111(4):964-971.

Cohen AF, van Smeden J, Webb DJ. De-risking Clinical Trials: The BIAL Phase I Trial in Foresight. *Clin Pharmacol Ther*. 2022; 111(2):362-365.

Damman J, Mooyaart AL, Bosch TPPVD, et al. Lectin and alternative complement pathway activation in cutaneous manifestations of IgA-vasculitis: A new target for therapy? *Mol Immunol*. 2022; 143:114-121.

Dankers M, Nelissen-Vrancken HMJMG, Berger MY, et al. Recente en toekomstige behandelingen bij covid-19 [Current and future therapeutic options for COVID-19]. *Ned Tijdschr Geneesk*. 2022; 166:D6675.

de Boer M, Gosselt HR, Jansen J, et al. Analysis and visualization of the course and burden over time of adverse drug reactions (ADRs) attributed to TNF $\alpha$ -inhibitors in patients with inflammatory rheumatic diseases (IRDs). *Expert Opin Drug Saf*. Published online 2022.

de Jong LM, Klomp SD, Treijtel N, et al. A systematic review on disease-drug-drug interactions with immunomodulating drugs: A critical appraisal of risk assessment and drug labelling. *Br J Clin Pharmacol*. 2022; 88(10):4387-4402.

de Las Heras B, Bouyoucef-Cherchalli D, Reeve L, et al. Healthy volunteers in first-in-human oncology drug development for small molecules. *Br J Clin Pharmacol*. 2022; 88(4):1773-1784.

Dijkstra F, O'Donnell P, Klaassen E, et al. Central nervous system effects of TAK-653, an investigational alpha-amino-3-hydroxy-5-methyl-4-isoxazole receptor (AMPA) positive allosteric modulator in healthy volunteers. *Transl Psychiatry*. 2022; 12(1):408.

Dijkstra FM, van de Loo AJ, Abdulahad S, et al. The effects of intranasal esketamine on on-road driving performance in patients with major depressive disorder or persistent depressive disorder. *J Psychopharmacol.* 2022; 36(5):614-625.

Dijkstra FM, Zuiker RGJA, Siebenga PS, et al. Pharmacological profile of ALKS 7119, an investigational compound evaluated for the treatment of neuropsychiatric disorders, in healthy volunteers. *Br J Clin Pharmacol.* 2022; 88(6):2909-2925.

Donker EM, Brinkman DJ, van Rosse F, et al. Do we become better prescribers after graduation: A 1-year international follow-up study among junior doctors. *Br J Clin Pharmacol.* 2022; 88(12):5218-5226.

Donker EM, Pandit R, Poleij MCS, et al. The Dutch list of essential drugs for undergraduate medical education: A modified Delphi study. *Br J Clin Pharmacol.* Published online 2022.

Eveleens Maarse BC, Graff C, Kanters JK, et al. Effect of hydroxychloroquine on the cardiac ventricular repolarization: A randomized clinical trial. *Br J Clin Pharmacol.* 2022; 88(3):1054-1062.

Galema HA, Meijer RPJ, Lauwerends LJ, et al. Fluorescence-guided surgery in colorectal cancer; A review on clinical results and future perspectives. *Eur J Surg Oncol.* 2022; 48(4):810-821.

Grievink HW, Smit V, Huisman BW, et al. Cardiovascular risk factors: The effects of ageing and smoking on the immune system, an observational clinical study. *Front Immunol.* 2022; 13:968815.

Harrison SA, Manghi FP, Smith WB, et al. Licogliflozin for nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a study. *Nat Med.* 2022; 28(7):1432-1438.

Hassing GJ, van Esdonk MJ, van Westen GJP, et al. Dose escalations in phase I studies: Feasibility of interpreting blinded pharmacodynamic data. *Br J Clin Pharmacol.* 2022; 88(12):5412-5419.

Heck J, Rath AK, Wons K, et al. Students' guide to documentation in clinical trials. *Eur J Clin Pharmacol.* 2022; 78(11):1861-1862.

Heuberger JAAC, Henning A, Cohen AF, et al. Dealing with doping. A plea for better science, governance and education. *Br J Clin Pharmacol.* 2022; 88(2):566-578.

Hijma H, Koopmans I, Klaassen E, et al. A crossover study evaluating the sex-dependent and sensitizing effects of sleep deprivation using a nociceptive test battery in healthy subjects. *Br J Clin Pharmacol.* 2023; 89(1):361-371.

Hijma HJ, van Brummelen EMJ, Siebenga PS, et al. A phase I, randomized, double-blind, placebo-controlled, single- and multiple dose escalation study evaluating the safety, pharmacokinetics and pharmacodynamics of VX-128, a highly selective Nav 1.8 inhibitor, in healthy adults. *Clin Transl Sci.* 2022; 15(4):981-993.

Huisman BW, Nené LEH, Linders FLL, et al. No effect of topical digoxin and furosemide for patients with actinic keratosis. *J Eur Acad Dermatol Venereol.* Published online 2022.

In 't Veld AE, Jansen MAA, Huisman BW, et al. Monitoring of Ex Vivo Cyclosporin a Activity in Healthy Volunteers Using T Cell Function Assays in Relation to Whole Blood and Cellular Pharmacokinetics. *Pharmaceutics.* 2022; 14(9):1958.

Kanhai KMS, Goulouze SC, van der Grond J, et al. Kinetics of myelin breakdown products: A labeling study in patients with progressive multiple sclerosis. *Clin Transl Sci.* 2022; 15(3):638-648.

Klomp SD, Meziyerh S, Vissers MFJM, et al. Increased Tacrolimus Exposure in Kidney Transplant Recipients With COVID-19: Inflammation-Driven Downregulation of Metabolism as a Potential Mechanism. *Transpl Int*. 2022; 35:10269.

Knijff JM, Houdijk ECAM, van der Kaay DCM, et al. Objective Home-Monitoring of Physical Activity, Cardiovascular Parameters, and Sleep in Pediatric Obesity. *Digit Biomark*. 2022; 6(1):19-29.

Kolkhir P, Lares PA, Salameh P, et al. The benefit of complete response to treatment in patients with chronic spontaneous urticaria - CURE results. *J Allergy Clin Immunol Pract*. Published online 2022.

Kruizinga MD, Essers E, Stuurman FE, et al. Clinical validation of digital biomarkers for paediatric patients with asthma and cystic fibrosis: potential for clinical trials and clinical care. *Eur Respir J*. 2022; 59(6):2100208.

Kruizinga MD, Zhuparris A, Dessing E, et al. Development and technical validation of a smartphone-based pediatric cough detection algorithm. *Pediatr Pulmonol*. 2022; 57(3):761-767.

Kruizinga MD, Zuiker RGJA, Bergmann KR, et al. Population pharmacokinetics of clonazepam in saliva and plasma: Steps towards noninvasive pharmacokinetic studies in vulnerable populations. *Br J Clin Pharmacol*. 2022; 88(5):2236-2245.

Kwee CM, van Gerven JM, Bongaerts FL, et al. Cannabidiol in clinical and preclinical anxiety research. A systematic review into concentration-effect relations using the IB-de-risk tool. *J Psychopharmacol*. 2022; 36(12):1299-1314.

Leijenaar JF, Ingala S, Sudre CH, et al. Decreased integrity of the monoaminergic tract is associated with a positive response to MPH in patients with vascular cognitive impairment - proof of principle study STREAM-VCI. *Cereb Circ Cogn Behav*. 2022; 3:100128.

Linders DGJ, Bijlstra OD, Fallert LC, et al. Cysteine Cathepsins in Breast Cancer: Promising Targets for Fluorescence-Guided Surgery. *Mol Imaging Biol*. Published online 2022.

Liu F, Aulin LBS, Guo T, et al. Modelling inflammatory biomarker dynamics in a human lipopolysaccharide (LPS) challenge study using delay differential equations. *Br J Clin Pharmacol*. 2022; 88(12):5420-5427.

Liu F, Aulin LBS, Kossen SSA, et al. A system pharmacology Boolean network model for the TLR4-mediated inflammatory response in early sepsis. *J Pharmacokinet Pharmacodyn*. 2022; 49(6):645-655.

Maleki G, Zhuparris A, Koopmans I, et al. Objective Monitoring of Facioscapulohumeral Dystrophy During Clinical Trials Using a Smartphone App and Wearables: Observational Study. *JMIR Form Res*. 2022; 6(9):e31775.

Marcec R, Dodig VM, Radanovic I, et al. Intravenous immunoglobulin (IVIg) therapy in hospitalised adult COVID-19 patients: A systematic review and meta-analysis. *Rev Med Virol*. 2022; 32(6):e2397.

Meijer RPJ, Faber RA, Bijlstra OD, et al. AVOID; a phase III, randomised controlled trial using indocyanine green for the prevention of anastomotic leakage in colorectal surgery. *BMJ Open*. 2022; 12(4):e051144.

Meijer RPJ, Neijenhuis LKA, Zeilstra AP, et al. Data-Driven Identification of Targets for Fluorescence-Guided Surgery in Non-Small Cell Lung Cancer. *Mol Imaging Biol*. Published online 2022.

Mieog JSD, Achterberg FB, Zlitni A, et al. Fundamentals and developments in fluorescence-guided cancer surgery. *Nat Rev Clin Oncol*. 2022; 19(1):9-22.

Moss LM, Algera MH, Dobbins R, et al. Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: A placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients. *PLoS One*. 2022; 17(1):e0256752.

Moss LM, Berends CL, van Brummelen EMJ, et al. First-in-human trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of STR-324, a dual enkephalinase inhibitor for pain management. *Br J Clin Pharmacol*. 2022; 88(1):103-114.

Muehlan C, Brooks S, Vaillant C, et al. Driving Performance after Bedtime Administration of Daridorexant, Assessed in a Sensitive Simulator. *Clin Pharmacol Ther*. 2022; 111(6):1334-1342.

Neijenhuis LKA, de Myunck LDAN, Bijlstra OD, et al. Near-Infrared Fluorescence Tumor-Targeted Imaging in Lung Cancer: A Systematic Review. *Life (Basel)*. 2022; 12(3):446.

Niemeyer-van der Kolk T, Buters TP, Krouwels L, et al. Topical antimicrobial peptide omiganan recovers cutaneous dysbiosis but does not improve clinical symptoms in patients with mild to moderate atopic dermatitis in a phase 2 randomized controlled trial. *J Am Acad Dermatol*. 2022; 86(4):854-862.

Olofsen E, Algera MH, Moss L, et al. Modeling buprenorphine reduction of fentanyl-induced respiratory depression. *JCI Insight*. 2022; 7(9):e156973.

Pagan L, Yfanti C, Rijnveld R, et al. Results of a randomized, placebo-controlled, first-in-human trial of topical CY-002 in patients with cutaneous warts. *J Eur Acad Dermatol Venereol*. 2022; 36(10):e773-e775.

Prins MLM, van der Plas JL, Vissers MFJM, et al. Viral clearance, pharmacokinetics and tolerability of ensovibep in patients with mild to moderate COVID-19: A phase 2a, open-label, single-dose escalation study. *Br J Clin Pharmacol*. Published online 2022.

Prins S, de Kam ML, Teunissen CE, et al. Inflammatory plasma biomarkers in subjects with preclinical Alzheimer's disease. *Alzheimers Res Ther*. 2022; 14(1):106.

Radanovic I, Klarenbeek NB, Rissmann R, et al. Integration of healthy volunteers in early phase clinical trials with immuno-oncological compounds. *Front Oncol*. 2022; 12:954806.

Rozen GVT, Prins MLM, van Binnendijk R, et al. Safety and Immunogenicity of Intradermal Fractional Dose Administration of the mRNA-1273 Vaccine: A Proof-of-Concept Study. *Ann Intern Med*. 2022; 175(12):1771-1774.

Ruijs TQ, Heuberger JAAC, de Goede AA, et al. Transcranial magnetic stimulation as biomarker of excitability in drug development: A randomized, double-blind, placebo-controlled, cross-over study. *Br J Clin Pharmacol*. 2022; 88(6):2926-2937.

Ruijs TQ, Koopmans IW, de Kam ML, et al. Muscle velocity recovery cycles as pharmacodynamic biomarker: Effects of mexiletine in a randomized double-blind placebo-controlled cross-over study. *Clin Transl Sci*. 2022; 15(12):2971-2981.

Ruijs TQ, Koopmans IW, de Kam ML, et al. Effects of Mexiletine and Lacosamide on Nerve Excitability in Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study. *Clin Pharmacol Ther.* 2022; 112(5):1008-1019.

Saghari M, Gal P, Gilbert S, Yateman M, et al. OX40L Inhibition Suppresses KLH-driven Immune Responses in Healthy Volunteers: A Randomized Controlled Trial Demonstrating Proof-of-Pharmacology for KY1005. *Clin Pharmacol Ther.* 2022; 111(5):1121-1132.

Saghari M, Gal P, Grievink HW, et al. Impact of oral administration of single strain *Lactococcus lactis* cremoris on immune responses to keyhole limpet hemocyanin immunization and gut microbiota: A randomized placebo-controlled trial in healthy volunteers. *Front Immunol.* 2022; 13:1009304.

Samb A, Kruizinga M, Tallahi Y, et al. Saliva as a sampling matrix for therapeutic drug monitoring of gentamicin in neonates: A prospective population pharmacokinetic and simulation study. *Br J Clin Pharmacol.* 2022; 88(4):1845-1855.

Schröder S, Heck J, Groh A, et al. White Blood Cell and Platelet Counts Are Not Suitable as Biomarkers in the Differential Diagnostics of Dementia. *Brain Sci.* 2022; 12(11):1424.

Stibbe JA, Hoogland P, Achterberg FB, et al. Highlighting the Undetectable - Fluorescence Molecular Imaging in Gastrointestinal Endoscopy. *Mol Imaging Biol.* Published online 2022.

Stuijt DG, Exadaktylos V, Bins AD, et al. Potential Role of Smartphone-Based Passive Sensing in Remote Monitoring of Patients With Cancer. *JCO Clin Cancer Inform.* 2022; 6:e2200079.

Te Beek ET, Burggraaf J, Teunissen JJM, et al. Clinical Pharmacology of Radiotheranostics in Oncology. *Clin Pharmacol Ther.* Published online 2022.

Thiboutot DM, Craft N, Rissmann R, et al. Anti-IL-17A blockade did not significantly reduce inflammatory lesions in a placebo-controlled pilot study in adult patients with moderate to severe acne. *J Dermatolog Treat.* Published online 2022.

Thijssen E, den Heijer JM, Puibert D, et al. A Randomized Trial Assessing the Safety, Pharmacokinetics, and Efficacy During Morning Off of AZ-009. *Mov Disord.* 2022; 37(4):790-798.

Thijssen E, den Heijer JM, Puibert D, et al. Safety and pharmacokinetics of multiple dosing with inhalable apomorphine (AZ-009), and its efficacy in a randomized crossover study in Parkinson's disease patients. *Parkinsonism Relat Disord.* 2022; 97:84-90.

Thijssen E, Makai-Bölöni S, van Brummelen EMJ, et al. A Placebo-Controlled Study to Assess the Sensitivity of Finger Tapping to Medication Effects in Parkinson's Disease. *Mov Disord Clin Pract.* 2022; 9(8):1074-1084.

van den Berg B, Hijma HJ, Koopmans I, et al. Simultaneous measurement of intra-epidermal electric detection thresholds and evoked potentials for observation of nociceptive processing following sleep deprivation. *Exp Brain Res.* 2022; 240(2):631-649.

van der Wall HEC, Hassing GJ, Doll RJ, et al. Cardiac age detected by machine learning applied to the surface ECG of healthy subjects: Creation of a benchmark. *J Electrocardiol.* 2022; 72:49-55.

van Diemen MPJ, Ziagkos D, Kruizinga MD, et al. Mitochondrial function, grip strength, and activity are related to recovery of mobility after a total knee arthroplasty. *Clin Transl Sci.* Published online 2022.

van Schie P, van der Lelij TJN, Gerritsen M, et al. Intra-operative assessment of the vascularisation of a cross section of the meniscus using near-infrared fluorescence imaging. *Knee Surg Sports Traumatol Arthrosc.* 2022; 30(5):1629-1638.

Vissers MFJM, Heuberger JAAC, Groeneveld GJ, et al. Safety, pharmacokinetics and target engagement of novel RIPK1 inhibitor SAR443060 (DNL747) for neurodegenerative disorders: Randomized, placebo-controlled, double-blind phase I/Ib studies in healthy subjects and patients. *Clin Transl Sci.* 2022; 15(8):2010-2023.

Vrouwe JPM, Hennus PML, Hamdy NAT, et al. Risk of osteoporosis in testicular germ cell tumour survivors: A systematic review of the literature. *BJUI Compass.* 2022; 4(1):24-43.

Vrouwe JPM, Meulenberg JJM, Klarenbeek NB, et al. Administration of an adeno-associated viral vector expressing interferon- $\beta$  in patients with inflammatory hand arthritis, results of a phase I/II study. *Osteoarthritis Cartilage.* 2022; 30(1):52-60.

Wind S, Jansen MAA, Rijsbergen M, et al. Topical Bimimalisib Shows Meaningful Cutaneous Drug Levels in Healthy Volunteers and Mycosis Fungoides Patients but No Clinical Activity in a First-in-Human, Randomized Controlled Trial. *Cancers (Basel).* 2022; 14(6):1510.

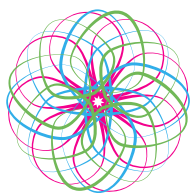
Yu HJ, Thijssen E, van Brummelen EMJ, et al. A Randomized First-in-Human Study With UB-312, a UBITH®  $\alpha$ -Synuclein Peptide Vaccine. *Mov Disord.* 2022; 37(7):1416-1424.

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