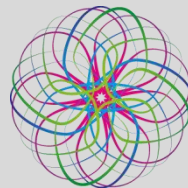


edenens

Expert Drug Evaluation Network
for CNS Drug Development

powered by



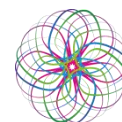
CHDR



TANGENT DATA

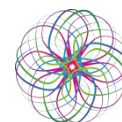
Accelerated POC in CNS

- Efficient route towards Proof of Concept in patients
- Starting with optimal FIM design
- Include PD measurements early on
- Establish Proof of Pharmacology in Phase I
- Use Phase I data for rational dose selection in first patient studies
- Fast start up of POC and other phase II trials



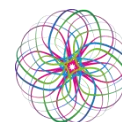
Accelerated POC in CNS

- Expertise in clinical pharmacology and neurology/psychiatry
- CNS biomarkers, including Neurocart and imaging techniques
- Collaboration with academic centers of excellence
- Proven patient recruitment in in common and rare disease areas

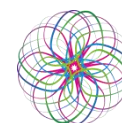


Accelerated POC in CNS

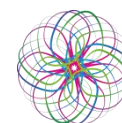
- Micro-milestones towards Proof of Concept
 - Early indication of pharmacological effects and side-effects
 - Dots the drug pass the BBB
 - Estimate effective window
- Allow rational go no-go decision after each step
- Saving resources and time before and during the POC



- Established in 1986 as a foundation
- Leiden University Medical Centre
- Leiden Amsterdam Centre for Drug Research
- Leiden Bio Science Park
- No shareholders, invest profit back into method and biomarker development

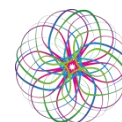


- Purpose built GCP licensed CRU
- GMP pharmacy (LUMC)
- Clinical chemistry/hematology (LUMC)
- Academic collaborations
- Large pool of healthy volunteers and patient volunteers



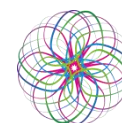
Tangent Data

- Established 2000
- CNS specilized POC
- Covering Estern Europe, US and India
- Investigator network of 70 sites in psychiatry and neurology
- Proven patient recruitment in schizophrenia , PD, AD, Bipolar Disorder



Full Service

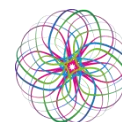
- Trial design, protocol development
- Study Execution
- Site management
- Biomarker labs
- Data management
- Monitoring
- Analysis
- Medical writing
- Regulatory Filings
- Archiving



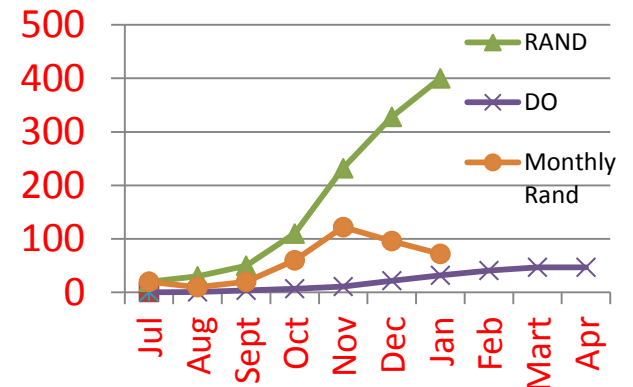
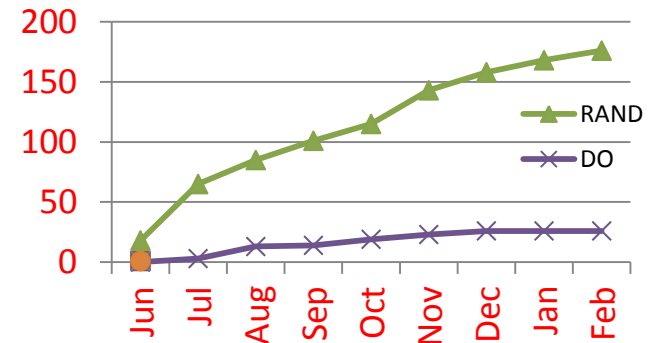
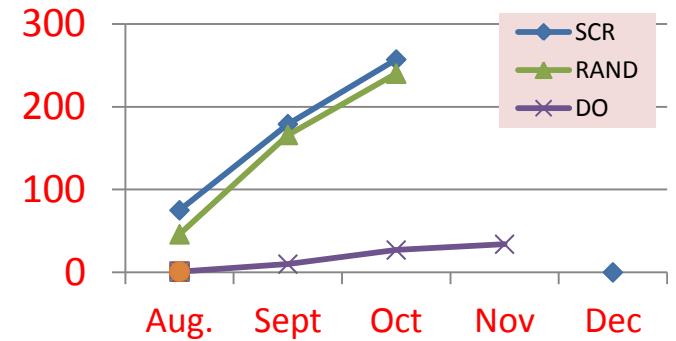
Volunteer recruitment

- Recruitment department 6 FTE
- Healthy Volunteers
 - Database
 - Males: 8000, Female: 6500, Elderly: 650
 - Non-smokers 65%, occasional 20%, smokers 15%
 - Website: www.proefpersoon.nl
 - Advertisements, posters, stands, events
- Patient Volunteers
 - Database
 - Asthmatics 1000, Diabetics 350 and many more
 - Advertisements in local and national newspapers, internet
 - GP and Specialists: Neurology, Pulmonology, Oncology, Rheumatoid Arthritis
 - Patient Support Groups

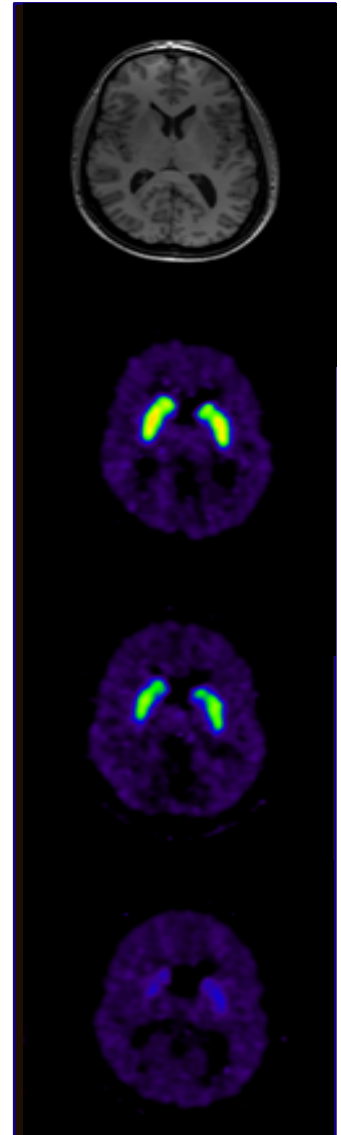
proefpersoon.nl



- >40 Hospital sites
 - >150 investigators
 - >7 academic groups
- 4 Countries
 - Romania
 - Moldava
 - Bulgaria
 - Netherlands
- Patient groups
 - Schizophrenia
 - Depression
 - Dementia



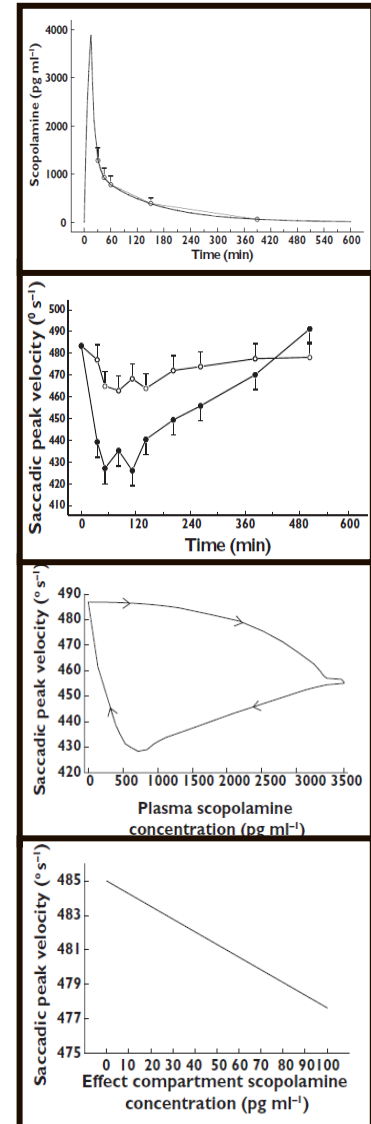
- LUMC, Leiden
 - GCP accredited CRU
 - GMP licensed Pharmacy
 - Clinical chemical lab
 - Dedicated techniques such as imaging tools
- Erasmus MC, Rotterdam
 - Pulmonary collaboration
- VUMC, Amsterdam
 - Four-bed CRU in the neurology department
 - PET Centre
- AMC, Amsterdam



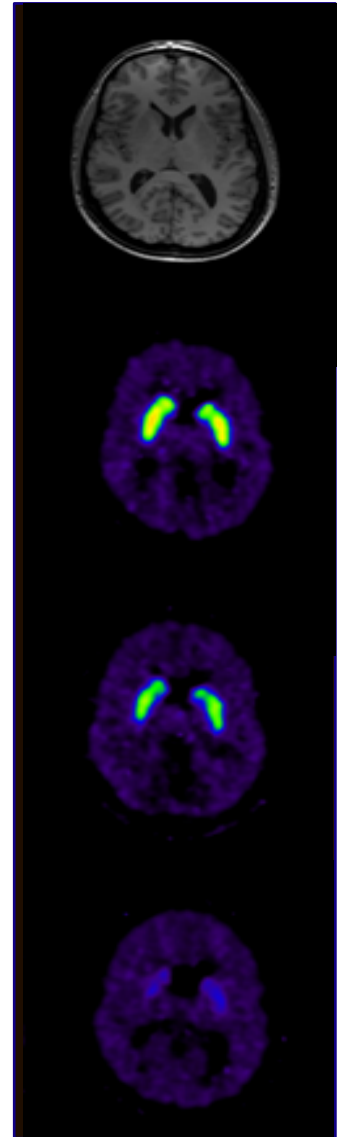
- Early phase clinical trials
 - First-in-human
 - SAD, MAD
 - Food interaction
 - Proof-of-pharmacology
 - Human Models
 - Imaging: PET, MRI
 - Proof-of-concept
 - Psychiatry
 - Neurology
 - Pain
- Clinical pharmacology
 - QTc
 - Drug interactions



- Safety and tolerability
 - MRSD based on the NOAEL
- PK-profile of parent drug and/or metabolites
 - In vitro ADME properties and in vivo animal PK
 - Allometric scaling
 - Physiologically based pharmacokinetic modeling
- PK-PD modeling
 - Proof of Mechanism
 - Proof of Principle
 - Study optimisation



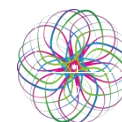
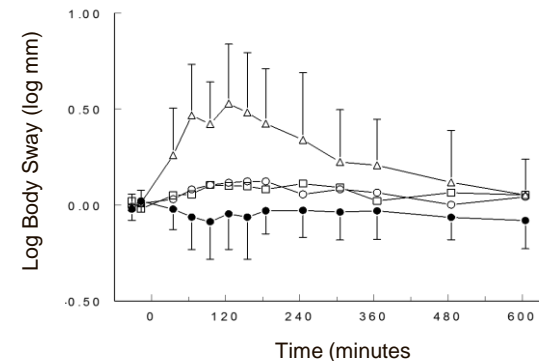
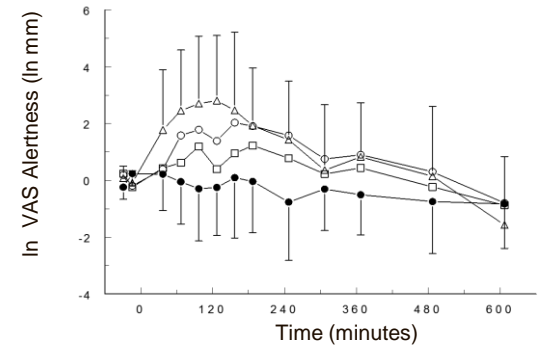
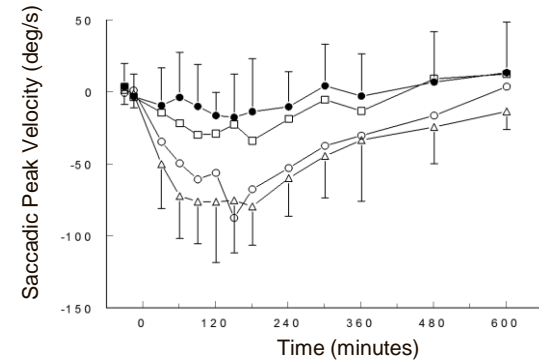
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- CNS
 - Psychiatry
 - Neurology
 - Pain
- Vascular Medicine
 - Inflammation - Immunology
 - Cardiovascular - Hematology
 - Metabolism
 - Women's health
- Pulmonary diseases
 - Asthma
 - Allergy
- Nutrition



- Eye movement
- Memory testing
- Adaptive tracking
- Finger tapping
- Body sway
- Electroencephalography
- Visual analogue scales
- Psychometric questionnaires
- Autonomic function tests
- Polysomnography
- Other CNS function tests
 - Symbol Digit Substitution Test
 - Critical Flicker Fusion
 - Stroop conflict task



Pharmacological Challenges

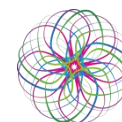
- Alcohol clamping
 - interaction studies
 - ethnic and patient studies
- Cholinergic challenge
 - scopolamine
- Cannabinoid challenge
 - THC*
- Serotonergic challenges
 - tryptophan depletion
 - 5-hydroxy-tryptamine†
 - vasopressin†
- Glutamatergic challenges
 - ketamine*

Physiological Challenges

- Cognitive impairment models
 - hypoxaemia model
 - sleep deprivation models
- Anxiety models
 - mental stress test †
 - fear potentiated startle
- PainCart
 - thermal, electrical, chemical, mechanical
 - phasic & tonic pain
 - inhibitory control

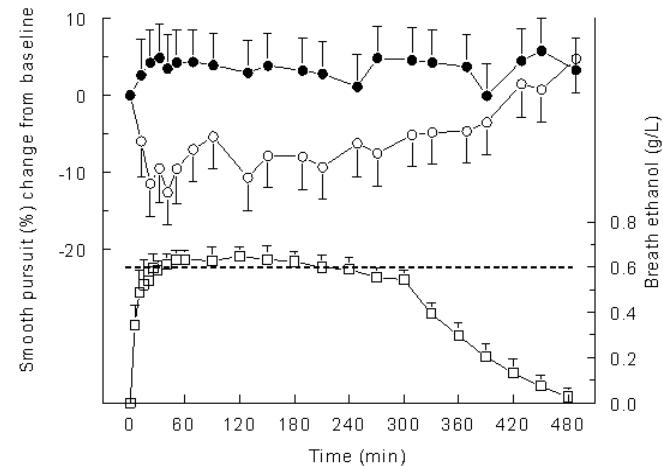
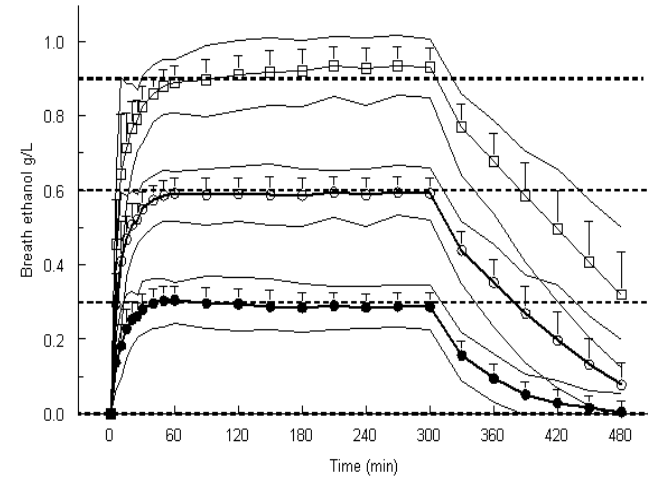
*validated psychosis models

†validated HPA axis models

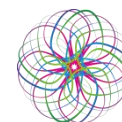


Alcohol Clamping

- Interaction studies
- Therapeutic effect in Essential Tremor



Zoethout et al. BJCP (2009) 68; 524–534



Nociceptive Pain Tests

- Cold pain test
- Electrical pain test
- Heat pain test
- Pressure pain test
- UVB inflammatory pain model
- Heat-Capsaicin neuropathic pain model
- Conditioned pain modulation (DNIC) paradigm

