eden CNS
Expert Drug Evaluation Network for CNS Drug Development
powered by CHDR TANGENT DATA
Accellerated 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 common and rare disease areas
Accellerated 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 specialized POC
- Covering Eastern Europe, US and India
- Investigator network of 70 sites in psychiatry and neurology
- Proven patient recruitment in schizophrenia, PD, AD, Bipolar Disorder
• 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
- >40 Hospital sites
  - >150 investigators
  - >7 academic groups
- 4 Countries
  - Romania
  - Moldava
  - Bulgaria
  - Netherlands
- Patient groups
  - Schizophrenia
  - Depression
  - Dementia
Academic Partners

- 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
Pharmacometrics

- 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