NUVISAN

The Science CRO

About NUVISAN

NUVISAN is the Science Contract Research Organization (CRO)

with its headquarters in Neu-Ulm, Germany, six sites in total across Germany and France as well as offices in Argentina, Peru, and Brazil.

NUVISAN offers integrated services and solutions along the drug development value chain from target identification to proof of concept in patients with all supporting services (DMPK, GMP synthesis, formulation development and analysis, bioanalysis, Phase 1 CPU, clinical study supplies and monitoring).

NUVISAN's 40 years of service is a testimony to our operational excellence and the depth and breadth of our +1.000 employees.

WHY NUVISAN?

The trend of outsourcing in pharma R&D

Key factors

Flexible cost structures

Flexible resource allocation

Flexible models of partnering

Creative models for venture capital

On-demand incorporation of dedicated expertise

"Fresh pair of eyes" problem solving skills

NUVISAN AT A GLANCE

NUVISAN is one of the fastest growing scientific CROs

We pride ourselves in our ability to collaborate and jointly develop strategic solutions for venture capitals, start-ups, biotechs, and the pharmaceutical industry at large

Fully integrated services to drive **your project**

ONE TEAM

Seamless transition of projects along the drug discovery value chain

Quick turnaround through close cooperation

Unified data and compound handling standards

ONE PARTNER

Fully aligned drug discovery team along the value chain

Partially or fully integrated programs can be accommodated

ONE SOLUTION

Highly experienced drug discovery team available to drive challenging programs

Long term drug discovery experience and knowledge in a harmonized environment

High-end technology and competence portfolio to deliver on challenging tasks

NUVISAN BUSINESS UNITS

Early drug discovery & research

Non-clinical studies

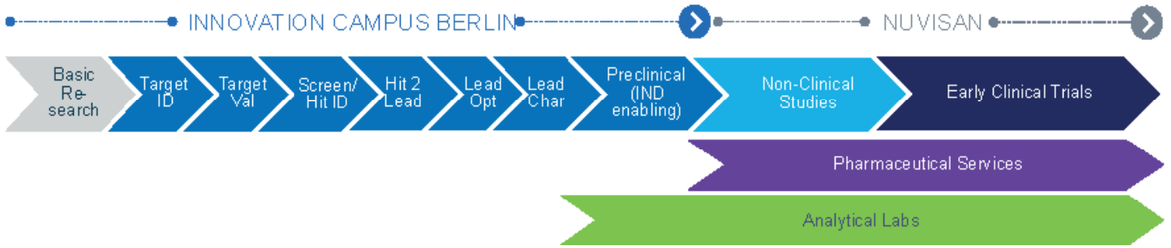
Clinical studies

Pharmaceutical services

Bioanalytical labs

THE **NUVISAN** CONCEPT

Delivering all services and solutions along the value chain



NUVISAN
INNOVATION CAMPUS BERLIN

Since July 2020 NUVISAN has supported early discovery through the acquisition of a research unit which brings new dynamics to the NUVISAN group and includes approximately 400 additional scientists. The early discovery service expansion empowers NUVISAN to further enforce our strategy to deliver "all from a single source" solutions from early discovery and pre-clinical services (including lead structure development, medicinal chemistry, pharmacology, drug metabolism and pharmacokinetics and as well as toxicology) to clinical Phase 1 and Phase 2/3 development.

With the Innovation Campus Berlin, NUVISAN expands its capabilities into early drug discovery

Discovery & early research at

INNOVATION CAMPUS BERLIN

Drug discovery team with extensive expertise in pharma R&D

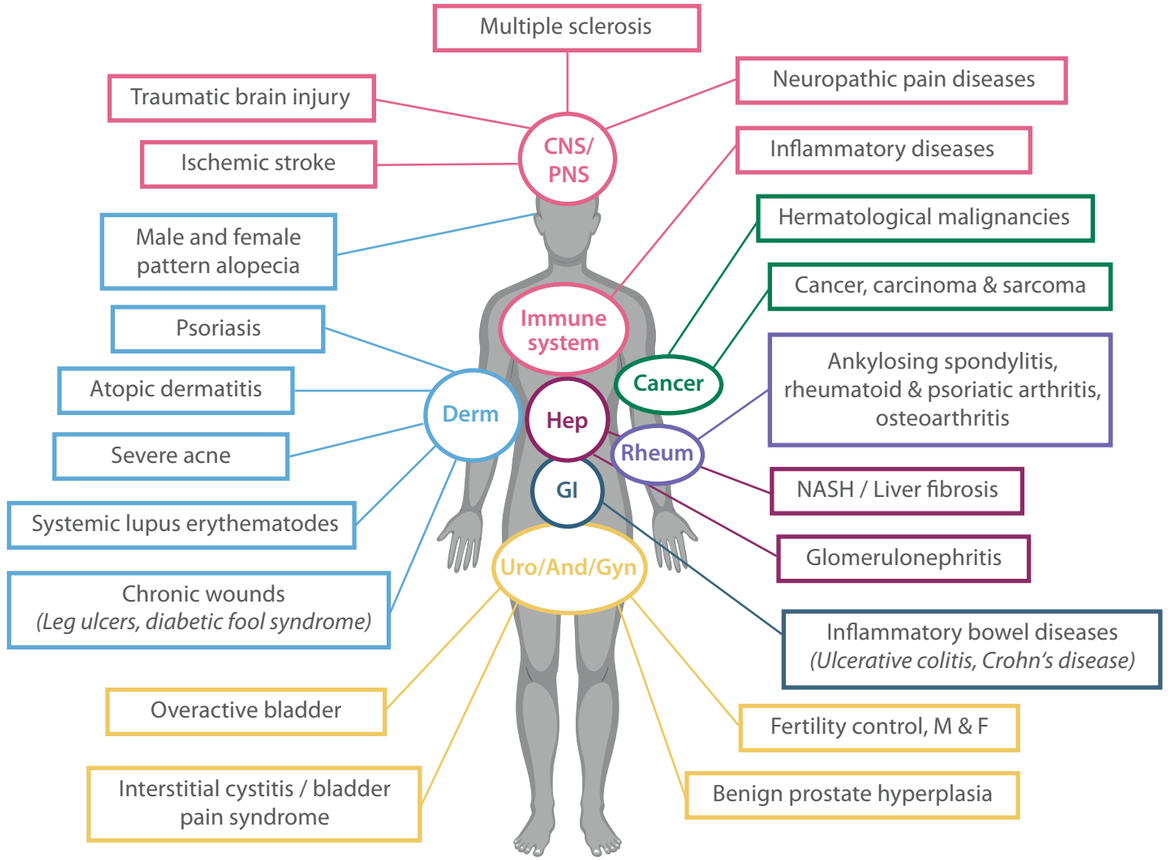
Fully integrated research functions across the whole discovery value chain

Broad coverage for indication / disease areas including focus on oncology

Molecule research with strong foothold for small molecules and access to a high quality compound library

Dedicated site across all research functions with fit-for-purpose infrastructure and state-of-the-art laboratory equipment

Fields of expertise



LEAD DISCOVERY

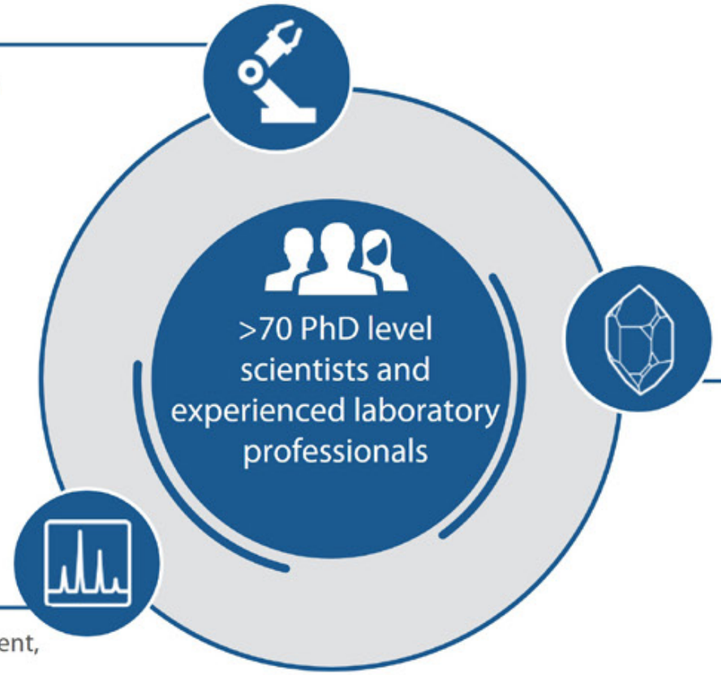
Find the right molecule and study it in detail to transform your idea into an asset

Screening

Assay development, lead identification, and lead optimization support with a broad technology and target-based biology

High-throughput compound testing (more than 150.000 experiments per day)

Best-in-class high content screening platform



Structural biology

Structural biology with focus on X-ray structure determination including fragment screening

NMR methods for fragment screening

High-throughput workbench enabling multi-target crystallization

CryoEM in collaboration with external partners

Protein technologies

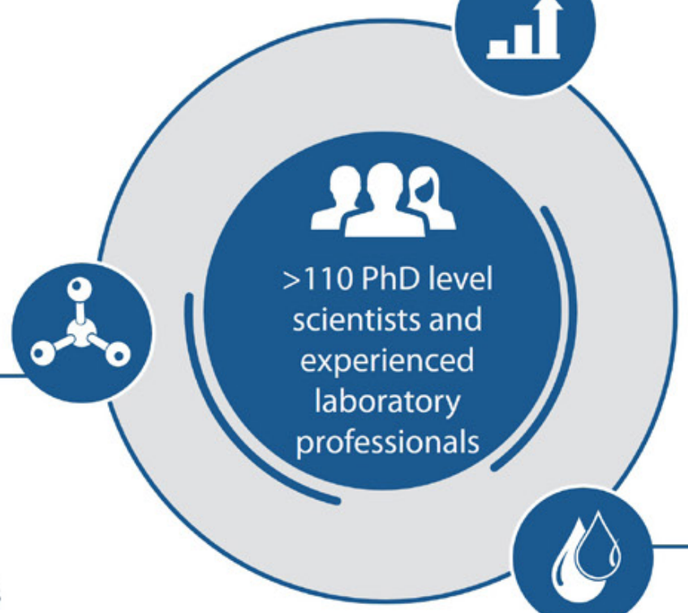
High quality tool protein production to enable assay development, protein structure determination, and biophysics analysis

Extensive biophysics platform

Fragment screening platform

LIFE SCIENCE CHEMISTRY

From library to new chemical matter: designing the right molecule for a specific disease



Design and synthesis: medicinal chemistry

Translational expertise from library to clinic

Finding new leads for challenging targets

Optimizing molecules towards clinical development

SMOLs, probes, and new modalities, including PROTACs

Access to library and legacy dataset

Microbiological chemistry, upscaling, and special technologies

Metabolite synthesis (fermentation)

Biotransformation, protein production

Upscaling, carbonylation, photochemistry

Purification, analytics, and PhysChem

High-throughput purification labs

Chiral separation capabilities

NMR, LC-MS, optical methods, structure elucidation

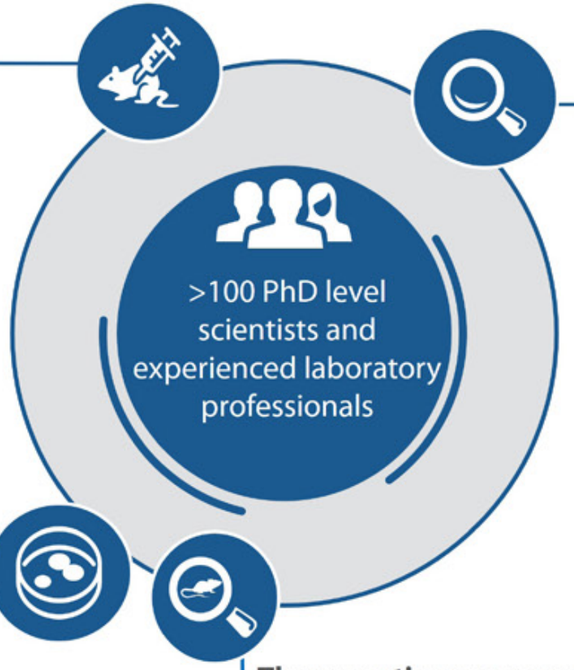
Solubility, lipophilicity, and stability

THERAPEUTIC RESEARCH

Empowering translation to the clinic

Oncology

Experience from target validation to pre-clinical fields, comprising: cellular stress / hypoxia / angiogenesis / hormone-dependencies / chromatin modulation / epigenetics, tumor stem cells / oncogenic signaling / antibody drug conjugates / tumor metabolism / proteases / metastasis



Cross indication platform

Broad understanding to familiarize with patho-mechanism of new indications

Identification of best suited patho-mechanisms

in vitro and *in vivo* pharmacological characterization

Life-cycle-management: additional indications for a given compound

Characterization of compounds in a disease relevant *in vivo* model of pre-defined indication

Establishment of various new animal models for several indications

Functional genomics

Expertise in functional genomics (RNAi, CRISPR / Cas9) as well as RNASeq

Solid background in oncology, cardiology, women´s health

Identification and validation of biomarker targets and elucidation of mode-of-action of compounds

Therapeutic compound research - translational / biomarker

Broad experience in translational and biomarker research across the value chain

Planning / coordination IND enabling tailored research activities

Research and biomarker expertise in global projects during clinical development of new therapeutics

PRE-CLINICAL COMPOUND PROFILING

Providing guidance regarding PK, DDI potential, and tolerability for compound selection

In vitro assay platform

Comprehensive *in vitro* ADMET assay panel incl. 2D culture and genotoxicity assays

High-throughput *in vitro* assays (CYP inh, CL_{int}, Caco-2)

In vitro panel suited for IND-enabling PK characterization

DDI profiling (victim & perpetrator) and assessment on transporters and metabolizing enzymes in the project context

In vivo profiling & toxicology

In vivo rodent and non-rodent PK and tolerability studies & micronucleus testing

Single compound and cassette dosing, different administration routes incl. basic compound formulation

Special PK studies in rodents (e.g. BDC, GIT, portal, lymph, femoralis administration)

Necropsy, advanced histopathology, clinical chemistry incl. hematology & endogenous biomarker

PK/TK analysis (experience up to FiM for dose recommendation)

Animal management & infrastructure services

§11 Husbandry license for all relevant laboratory animal species (rodents, rabbits, mini pigs)

Automated cage cleaning, supply organization, and disposal services

Animal welfare and supervision of legal compliance

Animal care service for DMPK, toxicology, and pharmacology

Structure & sample analytics

Metabolite identification, structure elucidation & confirmation in various matrices

Quantification of compounds, metabolites, and endogenous biomarkers in accordance to bioanalytical standards

Broad experience using high-resolution HPLC-MS^n devices

Strong expertise in Mass Spectrometry Imaging (MSI)

FORMULATION DEVELOPMENT AT **NUVISAN**

We are specialized in R&D of topical formulations for pharmaceutical and OTC dermatological treatments as well as complementary consumer products

We support your formulation conception and creation from preformulation to formulation selection and transition into scale up, clinical development, and QbD

Compositions are customized to meet the specific physicochemical characteristics of each active and disease state / skin condition

Innovative formulas are created with pragmatism that facilitate scale up and clinical development

Solubility, stability, delivery, local tolerance, and cosmetic elegance are optimized to maximize safety, compliance and efficacy

FORMULATION SCIENCE & TECHNOLOGY

Preformulation

Solubility and compatibility profiling in single solvents and solvent blends

Accelerated degradation:
extreme pH, UV, oxidation

Rational residual composition design to optimize solubility and skin delivery

Capacities

300 m^2 R&D state-of-the-art laboratory

100 g - 50 kg batch capacity

Handling of highly potent API up to HHB5 (OEL > 0.1 µg/m^3)

Formulation & process

Excipient selection & function justification

Prototyping to ensure optimized formulation parameters: stability / API release & skin delivery/ tolerance customized to disease / sensory profile / microstructure characterization

Technology development

Technology assessment

IP creation

Patent strategy

Strategic life-cycle management

CHEMICAL DEVELOPMENT

Chemistry

API route scouting & process research

Process development combined with GMP manufacturing

Custom synthesis of advanced intermediates

Package ready to transfer to CMO

Capacities

200 m^2 non-GMP facility with 40 L reactor capacity

200 m^2 GMP facility with 266 L reactor capacity

State-of-the-art laboratory

Handling of highly potent API up to HHB5 (OEL > 0.1 µg/m^3)

Solid form characterization

Crystal 16, XRPD, DSC, and microscopic observations for polymorph screening, salt screening, solubility curves, and filtration assessments

Impurities

Preparative HPLC / SFC systems

High-resolution mass spectrometry equipment and 400 MHz NMR for identification and characterization of small molecules

Bridging the gap between CRO & CDMO

We support API manufacturing from route scouting up to Phase 2a

Infrastructure is optimized to support process development from mg to kg scale

GMP compliant

Toxicology & GMP batch manufacturing up to 10 kg

BIOANALYTICAL CONTINUUM AT **NUVISAN**

For your drug discovery and development efforts, bioanalytical testing provides valuable information to assess the exposure, safety, and efficacy of therapeutic agents. From candidate selection through regulatory package development, our scientists guide fit-for-purpose assay development, transfer, and validation throughout the drug development continuum as well as bioanalysis of biological samples from in-house (non-clinical and clinical) and external studies.

With an in-depth knowledge of international regulatory agency requirements and a strong pharmaceutical industry background, we ensure that the data provided meets the quality demanded for each step of development, leading to successful submissions.

Highlights

More than 1.200 molecules analyzed in discovery and development since 2016

More than 250 projects reported on an annual basis (clinical / non-clinical)

Small and large molecule bioanalysis from a single source with direct access to our clinical Phase 1 unit

Our bioanalytical laboratories in Neu Ulm (DE), Grafing (DE), and Sophia-Antipolis (FR) are GLP accredited

METHOD DEVELOPMENT & VALIDATION

- Method development
- Method transfer and cross-validation
- Bioanalytical method validation
  - Bioanalysis in support of PK and/or immunogenicity (including cell-based assays)
  - Biomarkers (from exploratory to decision making)
  - Biosimilars (comparative assay validation)
- Fit-for-purpose validation based on context of use

SAMPLE ANALYSIS

- We have a wide range of techniques available for proof of exposure:
  - LC/MS bioanalysis
  - Immunoassays
  - Immunogenicity (incl. cell-based assays)
  - Biomarkers
- Capacity and throughput: from investigative studies with only a few samples to complete Phase 3 supportive programs

PROJECT MANAGEMENT

A single project manager is assigned to the client as a key contact, responsible for project coordination with all technical experts and liaising with the client through conduct of regular project meetings.

PHARMACEUTICAL ANALYTICAL SERVICES

Method development, validation and transfer

Complex matrixes

Design of experiment

Compliant with ICH

Oral dosage forms with small molecules and peptides

Capacities

2.400 m^2 GMP facility, incl. 800 m^2

GMP laboratory

80 analytical experts

State-of-the-art laboratory & 20 high-performance liquid chromatography

Laboratory Information Management System (LIMS)

Highlights

Microbiological testing

Microstructure characterization

Semi-solid expertise

GMP certified since 1989

Handling of highly potent API up to HHB5

Quality control

Stability management, ICH guidelines compliant

Challenge and microbial limit tests

Packaging safety and performance

Cleaning validation

CLINICAL TRIAL SUPPLIES

Services

Powders, capsules, over encapsulation, liquid, semi-solid, tablets manufacturing

Comparator sourcing

Global distribution & depot management

Label design & printing

Capacities

Laboratory Information Management System (LIMS)

Team

49 CTS employees (FTE) supported by

4 heads of production

6 heads of quality control

3 responsible persons GDP

6 qualified persons

Highlights

Significant capacity of -20° and -80°C storage and labelling areas

CMC support

Randomization lists/ code breaking envelops

Just-in-time and direct-to-patient shipments

State-of-the art topical formulation lab

Rapid entry into Phase 1 for first-in-man studies

We conduct all steps for sourcing, importation, manufacturing, labeling, handling, and distribution of clinical supplies

With a powder-in-bottle approach, the sponsor could save up to 6 month development time

Just-in-time labeling for immediate service to our clients

Expertise in cold chain supplies for biologics, vaccines, and other temperature critical products

IN VIVO DMPK

Discovery

Fast turnover discovery

In vivo screening PK

Blood brain barrier assay

Single, multiple, and cassette dosing

Microsampling

Infusion studies

Capacities

Headcount: 21 (35 % academics)

Mice, rats, dogs, and minipigs

Pharmacokinetic studies for discovery & development programs

GLP and non-GLP DMPK studies

Radiolabeled and "cold compound" studies

Development

Absorption, metabolism, excretion

Quantitative tissue distribution

Juvenile PK

Lactation studies

Placental transfer

Mechanistic studies

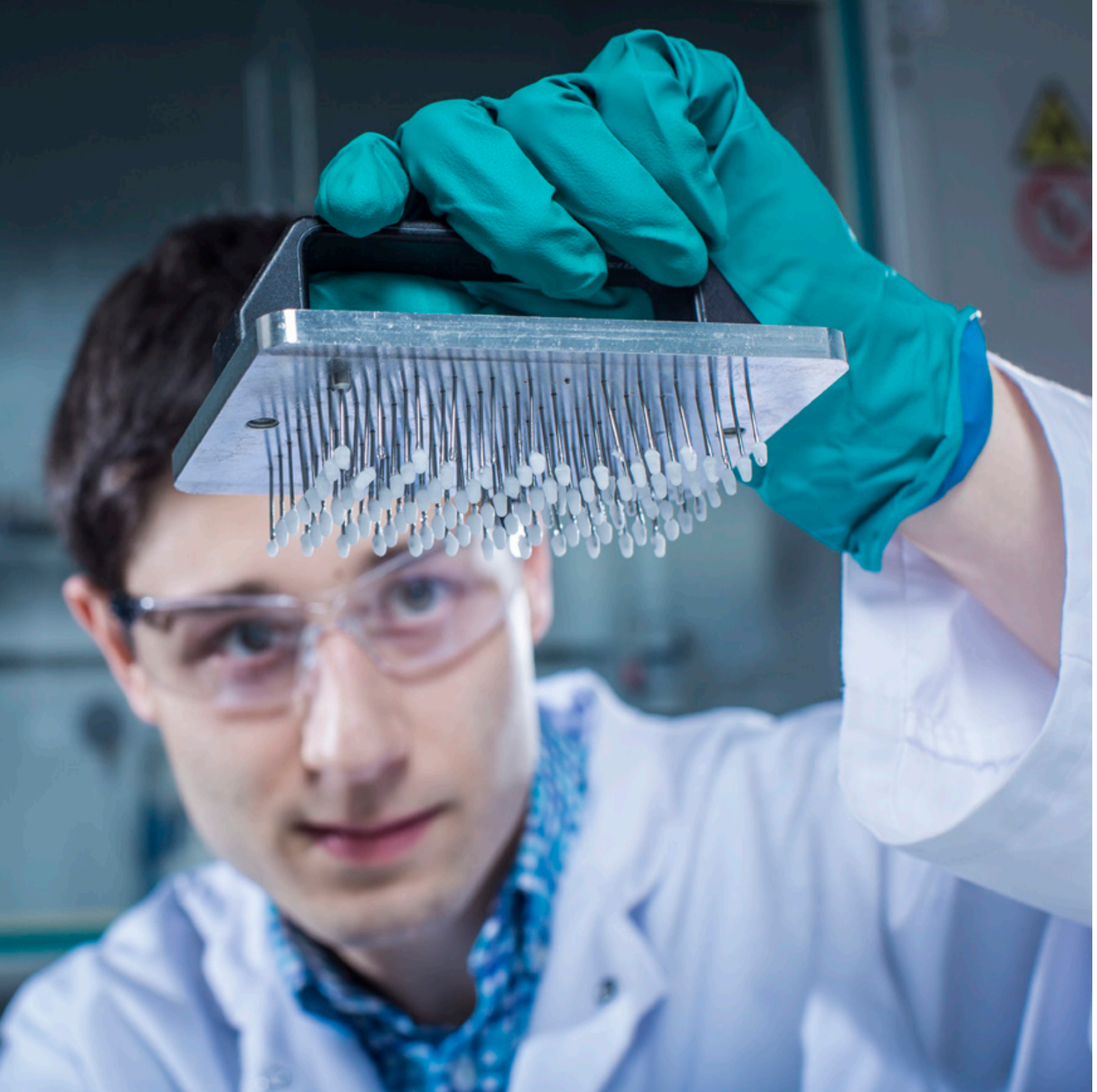
Quality

AAALAC accreditation

State-of-the-art animal welfare standards

Strong focus on 3R principles

GLP audited



We contribute to the optimization of compounds by *in vivo* DMPK

Full AAALAC accreditation (Grafing)

Strong focus on 3R-principles

Fast turnover: your timelines are our priority

Tailored study designs to meet requirements of each individual client

BIOTRANSFORMATION & *IN VITRO* PK AT **NUVISAN**

Our experts guide pharmaceutical clients throughout all R&D phases starting from discovery to clinical development and marketing authorization

Our mission: generate PK data to enable the safe administration of NCEs at the right dose and regimen to maximize the benefit for patients

Standardized or tailor-made high quality DMPK studies and complete packages enabling IND / IMPD, start of first-in-man (FIM) and / or large clinical studies

Project management and scientific consultancy

All studies will be performed in compliance with FDA and EMA requirements as described in the respective guidelines

ISOTOPE CHEMISTRY

Synthesis of radiolabeled NCEs or Peptides and stable isotope labeled compounds

CAPACITIES & WORKING FIELDS

Headcount: 7 (71% Academics)

5 state-of-the-art labs (200 m^2)

Isotopes: ^{3}H, ^{14}C, ^{177}Lu, ^{32}P

Current license allows handling of up to 78 GBq ^{14}C and 41 GBq ^{3}H

Dedicated storage for radioactive APIs up to 120 GBq ^{14}C and 20 GBq ^{3}H

RADIOACTIVE SYNTHESIS

Isotopes: ^{14}C, ^{3}H

Experience in isotope chemistry from >50 years as a part of a big pharma company

Custom (multistep) radioactive synthesis of APIs for e.g. DMPK studies

Detailed synthesis reports and comprehensive certificates of analysis:
Identification and (radio-)chemical, enantiomeric purity by H/UPLC,
NMR, (radio-)TLC, LC-MS

SYNTHESIS OF STABLE LABELED COMPOUNDS

Isotopes of choice: D, ^{13}C, ^{15}N

Mainly required as internal standard for bioanalysis (mass spectrometry)

Dedicated equipment, glassware, and laboratory space for stable
label and radioactive synthesis

FURTHER SERVICES

Re-analysis and re-purification of APIs

Stability Investigations

24/7 access and temperature-controlled storage (-80 °C – RT)

Worldwide shipment of radioactive compounds

Formulation for *in vivo* studies

We support the development program of our clients offering synthesis of stable isotope labeled compounds as bioanalytical standards for mass spectrometry and radioactive labeled NCEs (^{3}H, ^{14}C) for e.g. DMPK studies

Proposal of optimal labeling position

Permission to work with radioactivity is regularly adapted to the needs of client projects (recent addition of ^{177}Lu and ^{32}P)

Storage of radioactive samples before routine analysis

CLINICAL SERVICES

Study conduct

Staff

6 physicians

6 part-time physicians

11 study coordinators

40 part-time staff

Network of specialists

Facilities

~4.000 m^2

140 bed capacity

Functional rooms

Cafeteria (incl. special diets)

Laminar flow

Recruitment

4 recruiters

5 call center agents

Services

4 decades of experience in PK/PD trials

Broad experience with NCE, NBE & biosimilars

Possibility for combined study designs
e.g. SAD, MAD, FDI, DDI, patient PK/PD

PROJECT MANAGEMENT

Planning and coordination of the project

Main contact for the sponsor

Surveillance of the project regarding regulatory, time, and quality

STAFF

10 project managers with scientific education

3 clinical trial assistants

1 regulatory affairs manager

2 regulatory start-up coordinators

REGULATORY AFFAIRS

Preparation of investigational medicinal product dossier

Organization of scientific advice meetings

Submission for approval from ethics committee
and competent authority

MEDICAL MONITORING / DRUG SAFETY

Independent evaluation of safety aspects

SAFETY LABORATORY

STAFF

24/7 availability

3 lab technicians

2 data specialists

1 support staff

FACILITIES

Lab area of ~100 m^2

Roche Diagnostics equipment

IN-HOUSE TRIALS

Door-to-door with CPU

Turnaround of 4 to 6 hours

Continuous safety assessments

DATA MANAGEMENT

6 data managers / 2 data coordinators

Preparation of paper CRF or eCRF according to CDASH

Setup and validation of database (Clintrial, Inform) / data cleaning

Data provision in SDTM data file structure

BIOSTATISTICS

1 statistician

4 data programmers / 2 data analysts

Analysis of study data (SAS, WinNonlin) in ADaM dataset structure

MEDICAL WRITING

3 medical writers (EMWA certified)
Preparation of study protocols, investigator's brochure
and clinical study reports in eCTD format for submission for registration

MONITORING

1 lead CRA & 4 monitors in Europe

1 lead CRA & 4 monitors in Latin America

NUVISAN

YOUR SCIENTIFIC CRO / CDMO PARTNER

NUVISAN is a fully integrated CRO / CDMO offering all solutions from drug discovery to proof of concept in patients including: target identification, high-throughput screening, compound profiling, pre-clinical DMPK, toxicology, API synthesis, formulation development, pharmaceutical analysis, and clinical trials in healthy volunteers and patient populations.

With capabilities distributed over 6 locations in Europe, a presence in Latin America, and more than 40 years of experience, we deliver high-quality solutions certified by various accreditations and inspections (e.g. BfArM, EMA, FDA, ANVISA, ANSES, AAALAC, GLP, GMP, CIR).

40 **A trusted scientific partner**
With a 40-year track record of customer satisfaction

A wide range of expertise
A unique, comprehensive and, integrated offer from target identification to clinical trials

A data-focused expert
Our top priority is to ensure accurate, reliable, and consistent data quality

A flexible service provider
Fast turnaround ability and strong responsiveness to change

Enquire now

Whether you need support in specific areas only or need a more comprehensive offer, NUVISAN can tailor a solution to fit your specific requirements.

If you have any questions or need more information, please reach out to us:

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Web: www.nuvisan.com

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LIST OF ACRONYMS / ABBREVIATIONS

Acronym / abbreviation	Definition
3R Principles	Replace, Reduce, Refine
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International
ADaM	Analysis Dataset Model
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicity
And	Andrology
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
ANVISA	Brazilian Health Regulatory Agency
API	Active Pharmaceutical Ingredient
BA	Bioanalysis
BDC	Bile Duct Cannulation
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
Caco-2	Cell line of human colorectal adenocarcinoma cells
CAD	Charged Aerosol Detection
Cas9	CRISPR-associated protein 9
CDASH	Clinical Data Acquisition Standards Harmonization
CDMO	Contract Development and Manufacturing Organization
CIR	Credit Impot Recherche
Cl int	Intrinsic Clearance
CMO	Contract Manufacturing Organization
CNS	Central Nervous System

LIST OF ACRONYMS / ABBREVIATIONS

Acronym / abbreviation	Definition
cpm	Compound
CPU	Clinical Pharmacology Unit
CRA	Clinical Research Associate
CRF	Case Report Form
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRO	Contract Research Organization
CryoEM	Cryogenic Electron Microscopy
CTA	Clinical Trial Application
CTS	Clinical Trial Supplies
CYP inh	Cytochrome P-450 inhibition
DDI	Drug-Drug Interactions
Derm	Dermatology
DMPK	Drug Metabolism and Pharmacokinetics
DSC	Differential Scanning Calorimetry
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EMWA	European Medical Writers Association
FDA	Food and Drug Administration
FDI	Food Drug Interaction

Acronym / abbreviation	Definition
FiM	First in Man / First in Human
FTE	Full Time Equivalent
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GIT	Gastrointestinal Transit
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Gyn	Gynecology
HCA	High-Content Analysis
Hep	Hepatic
HHB4	Health Hazard Band 4
HHB5	Health Hazard Band 5
HPLC	High Performance Liquid Chromatography
HPLC-MS	High Performance Liquid Chromatography Mass Spectrometry
ICB	Innovation Campus Berlin
ICH	International Conference on Harmonization
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IP	Intellectual Property
Kg	Kilogram

LIST OF ACRONYMS / ABBREVIATIONS

Acronym / abbreviation	Definition
LC	Liquid Chromatography
LC-MS	Liquid Chromatography - Mass Spectrometry
Lead Char	Lead Characterization
Lead Opt	Lead Optimization
LIMS	Laboratory Information Management System
M & F	Male and Female
MAD	Multiple Ascending Dose
Metabolite ID	Metabolite identification
microHVLD	Micro High Voltage Leak Detection
MNT	Micronucleus Test
MS	Mass Spectrometry
MSI	Mass Spectrometry Imaging
NASH	Nonalcoholic Steatohepatitis
NBE	New Biological Entity
NCEs	New Chemical Entities
NMR	Nuclear Magnetic Resonance
Non-GLP	Non-Good Laboratory Practice
Non-GMP	Non-Good Manufacturing Practice
OEB5	Occupational Exposure Band 5
OEL	Occupational Exposure Limit
OTC	Over The Counter
PD	Pharmacodynamic
pH	Power of hydrogen
PK	Pharmacokinetics
PNS	Peripheral Nervous System
PROTACs	Proteolysis Targeting Chimeras
QbD	Quality by Design
R&D	Research and Development
Rheum	Rheumatology
RNA	Ribonucleic Acid
RNASeq	Ribonucleic Acid Sequencing
SAD	Single Ascending Dose
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SFC	Supercritical Fluid Chromatography
SMOL	Small-Molecule
Target ID	Target Identification / Identificator
Target Val	Target Validation
TK	Toxicokinetics
TLC	Thin-layer chromatography
Tox	Toxicology
UPLC	Ultra-Performance Liquid Chromatography

LIST OF ACRONYMS / ABBREVIATIONS

Acronym / abbreviation	Definition
Uro	Urology
UV	Ultraviolet
WinNonlin	Name of Pharmacokinetic Software Package
XRPD	X-Ray Powder Diffraction

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