Navigating the Anatomical Maze:

Utilizing In-Silico Modelling for Targeted Deposition Analysis

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BEFORE WE BEGIN…

THIS PRESENTATION WILL COVER…

- The complexity of anatomical variability and its challenges in designing targeted delivery systems.
- A cost-effective approach that enables rapid testing of design parameters without extensive in-vivo experiments or physical prototypes
- How to simulate dynamic systems, while taking into consideration both biological and physical properties.
- Harnessing the power of supercomputers to optimize design parameters of delivery devices.
- Showcase ***Clexio's SPRACISE*** platform as a case study for targeted nasal drug delivery

CLEXIO AT A GLANCE

Solid foundations

Started in 2018 with strong financial backing and a broad network of partners worldwide

- ✓ Spin-off from Teva Pharmaceuticals
- ✓ Validated Mechanism of Actions
- ✓ De-risked clinical development pathways

Driven by the patients

Technological and therapeutic ingenuity to address patients' unmet needs

- ✓ Focus on CNS and Psychiatry
- ✓ Targeting significant unmet needs
- ✓ Developing Drug and Drug-Device Combination Products

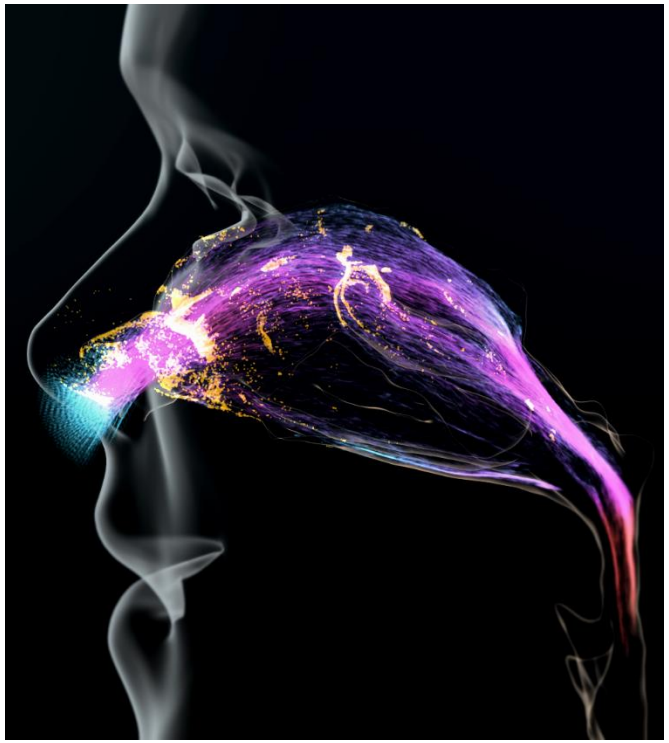
Multi-Asset Clinical Pipeline

Broad experience in Pharma & Biotech, from early innovation to clinical development & regulatory approvals

- ✓ 4 clinical stage programs
- ✓ Lead asset completed Phase 2
- ✓ Advanced preclinical pipeline
- ✓ 31 patent families, 22 granted in US

LOCALIZED DEEP NASAL DELIVERY OFFERS POTENTIAL KEY ADVANTAGES FOR APPLICATIONS REQUIRING TARGETED ACTION, AIMING TO *INCREASING EFFICACY* VS TRADITIONAL SPRAYS

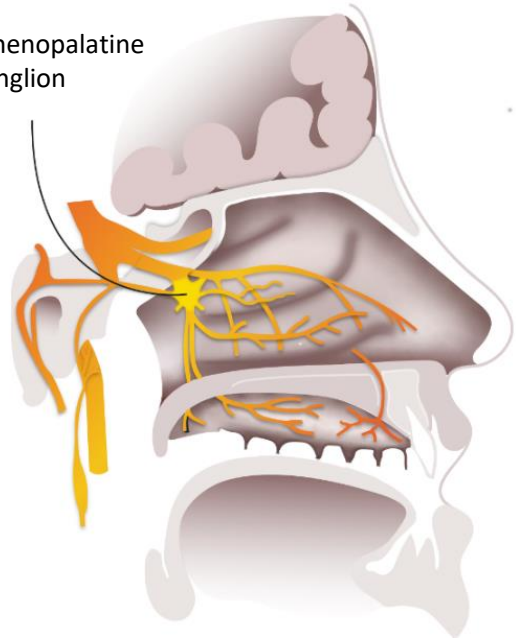
- Traditional Nasal Sprays dispense drugs broadly in the entire nasal cavity without focusing on a particular target
  - Broad dispensation and low specificity
  - High systemic exposure and increased risk of adverse effects
- Localized nasal delivery offers several potential key value points, making it an attractive option for drug delivery in certain therapeutic applications:
  - Enhanced targeting specificity and reduced systemic exposure
  - Higher local drug concentrations
  - Rapid onset of action
  - Minimized first-pass metabolism
  - Reduced Interactions with other medications



Specialized nozzles and propellant mechanisms have been developed to reach specific regions in the nasal cavity. However, most are focused on anterior targets and not deep posterior ones

CASE STUDY: SPG-TARGETED THERAPEUTICS FOR *"THE WORST PAIN KNOWN TO MAN"*

- **Cluster Headache** is a neurological disorder characterized by extremely severe recurrent headaches on one side of the head
- High Unmet Need: Patients currently have limited treatment options to prevent or stop attacks
- **SPG block** with local anesthetic is a clinically validated approach, targeting a specific nerve pathway at the Sphenopalatine Ganglion (SPG), a large extracranial parasympathetic ganglion involved in activation of the Trigemino-vascular system
- *Current* SPG block techniques are only intended for administration by a healthcare professional: Success is highly operator-dependent



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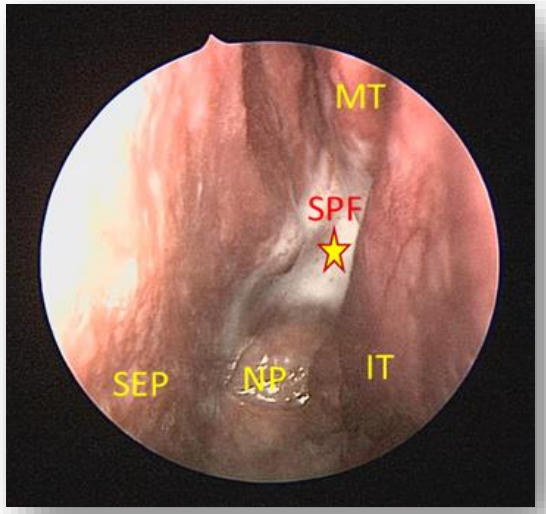
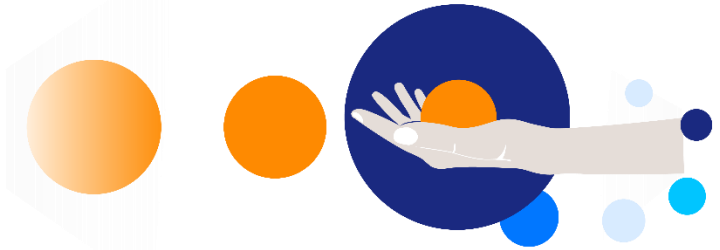
SPRACISE: THE DEVICE COMPONENT OF A FIRST-OF-ITS-KIND COMBINATION PRODUCT TO ACHIEVE RAPID RELIEF OF CLUSTER HEADACHE ATTACKS, BY *SELF-ADMINISTRATION*

- **SPRACISE*** aims to place the treatment in the hands of the patients such that it is conveniently portable and easy to use



- Prototype was tested successfully in **in-vitro & ex-vivo models**, confirming precise dosing to the target area in the tested models
- **3 Human Factor Studies** in Cluster Headache patients were performed, demonstrating usability and self administration
- **First-in-Human** Clinical Study ongoing



**SPRACISE is the device component of a new investigational drug-device combination under development and has not been approved for commercial distribution.*

ADDRESSING CHALLENGES INVOLVES A MIX OF INNOVATIVE FORMULATIONS, DEVICE ENGINEERING, AND CAREFULLY CONSIDERING USER NEEDS

- **Challenges**
  - Anatomical Variability between individuals (and within individuals)
  - Mucociliary clearance, swallowing, sneezing, dripping
  - Container Closure System compatibility
  - Specific delivery pattern and profile to achieve accuracy and focus
  - Patient compliance and competency during attack.

- **Success Strategies**
  - Computational Models to determine optimal Device Design Inputs
  - Physical properties of the drug formulation, to enhance retention time and local absorption
  - Constant collaboration between drug and device; optimizing tolerances
  - Controlling flow force and nozzle geometrical design; empirical testing
  - Human Factors of Self-Administration (asymptomatic) in the absence of a familiar mental model

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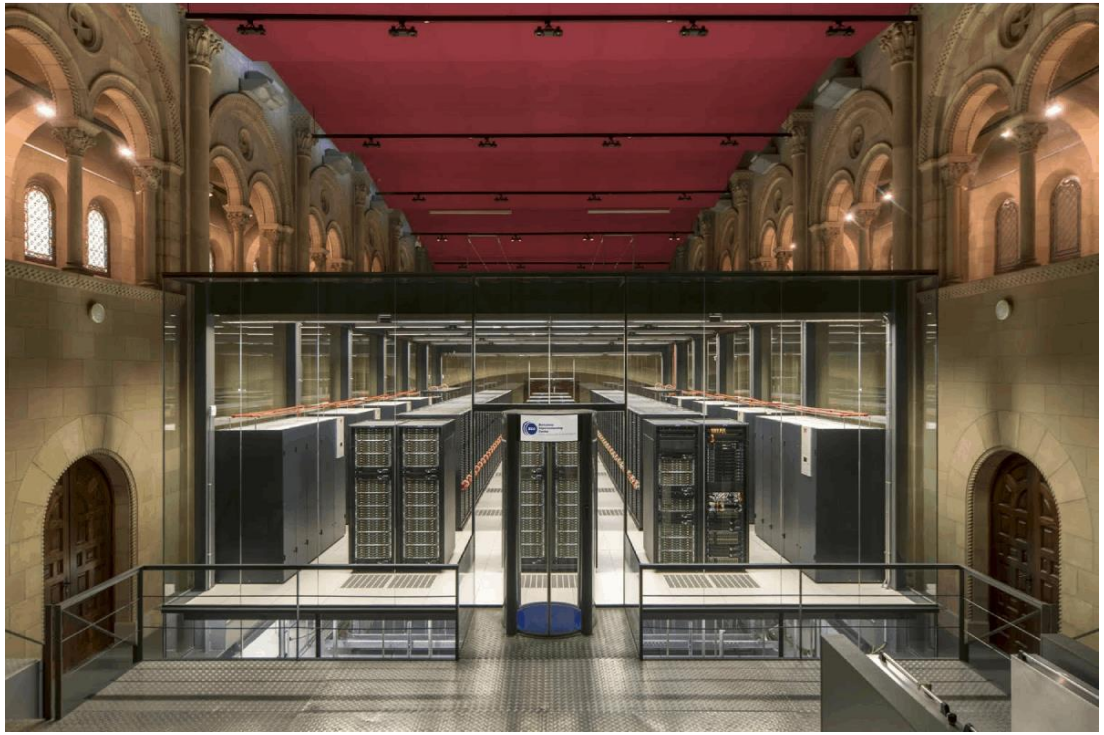
OBJECTIVE: SIMULATE SPRAY DEPOSITION IN THE NASAL CAVITY TO EVALUATE PARAMETERS' EFFECT ON TARGET ACCURACY AND COVERAGE - THEREBY DETERMINING *OPTIMAL DESIGN INPUTS*.

- The In-Silico model discussed here uses Alya, a simulation code for high performance computational mechanics, developed by ELEM, a biotech software spin-off from the Barcelona Supercomputing Center.

- Alya solves coupled Multiphysics problems using high performance computing techniques for distributed and shared memory supercomputers, together with vectorization and optimization at the node level.



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BSC Barcelona Supercomputing Center
Centro Nacional de Supercomputación

ELEM
THE VIRTUAL HUMANS FACTORY

TERMINOLOGY: CASES, CONFIGURATIONS & EXPERIMENTS

Cases **refer to the anatomical subjects and represent a single nasal cavity (either left or right) reconstructed from a real CT scan**

- For this scope of work, we selected 10 CT subjects, of which: 6 Standard + 2 Long + 2 Short
- 2 of the subjects were simulated on both sides
- **Total: 12 anatomical cases**

Configurations **refer to all possible combinations of the 4 design inputs (insertion depth, orientation angles, spray cone angle)**

- Fixed model parameters include Fluid-Dynamics information, approximated from Clexio's Engineering Verification and stability testing
- **Total: 450 spray configurations**

Experiment **refers to a distinct simulation of a spray event from a given** ***configuration*** **within a given** ***case***

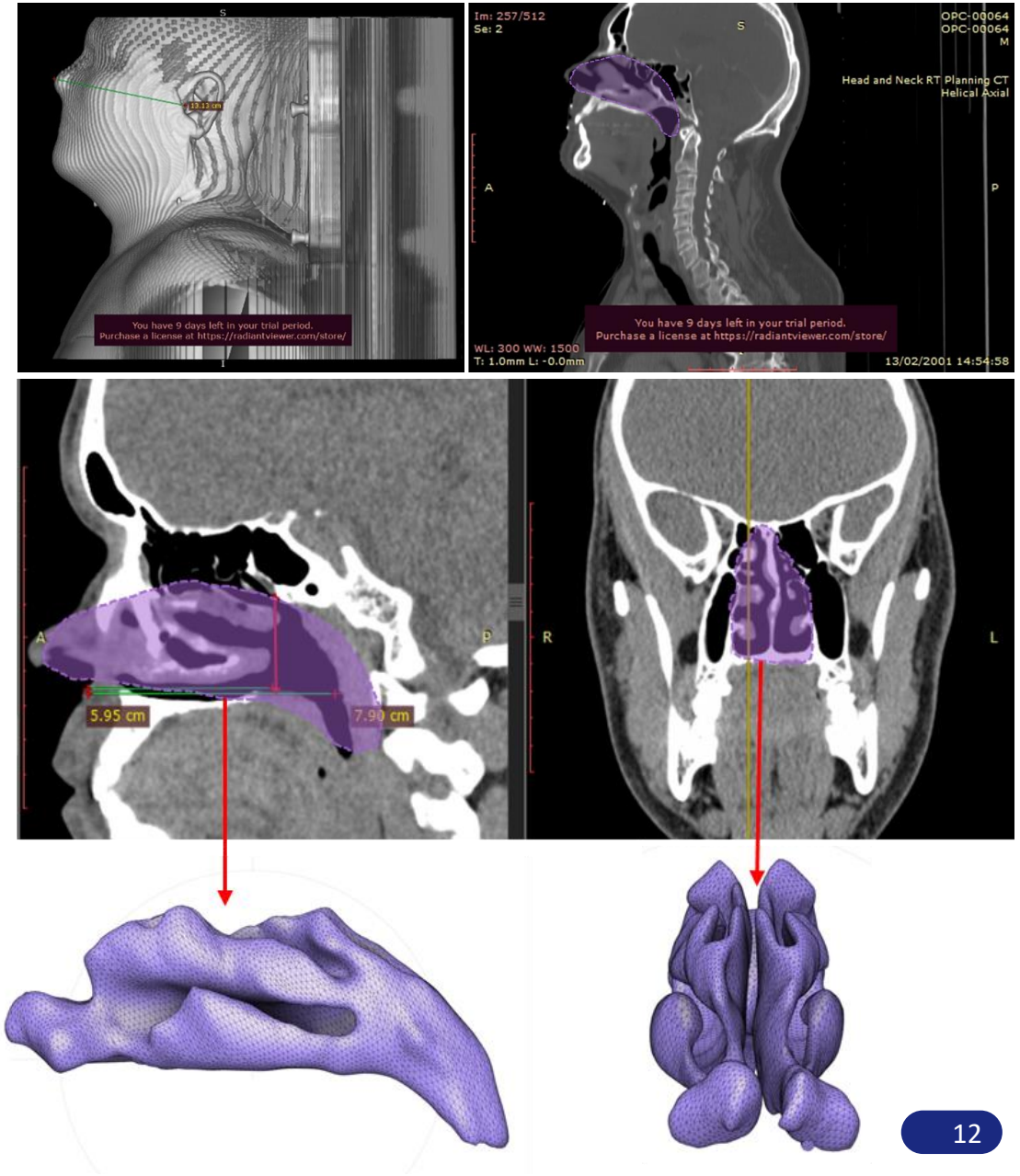
- **Total: 12 x 450 = 5,400 experiments**

PROCESS: 1. CASE SEGMENTATION

- 10 CT Cases selected for modeling from Clexio's database
  - of which: 6 "Standard" + 2 "Long" + 2 "Short"

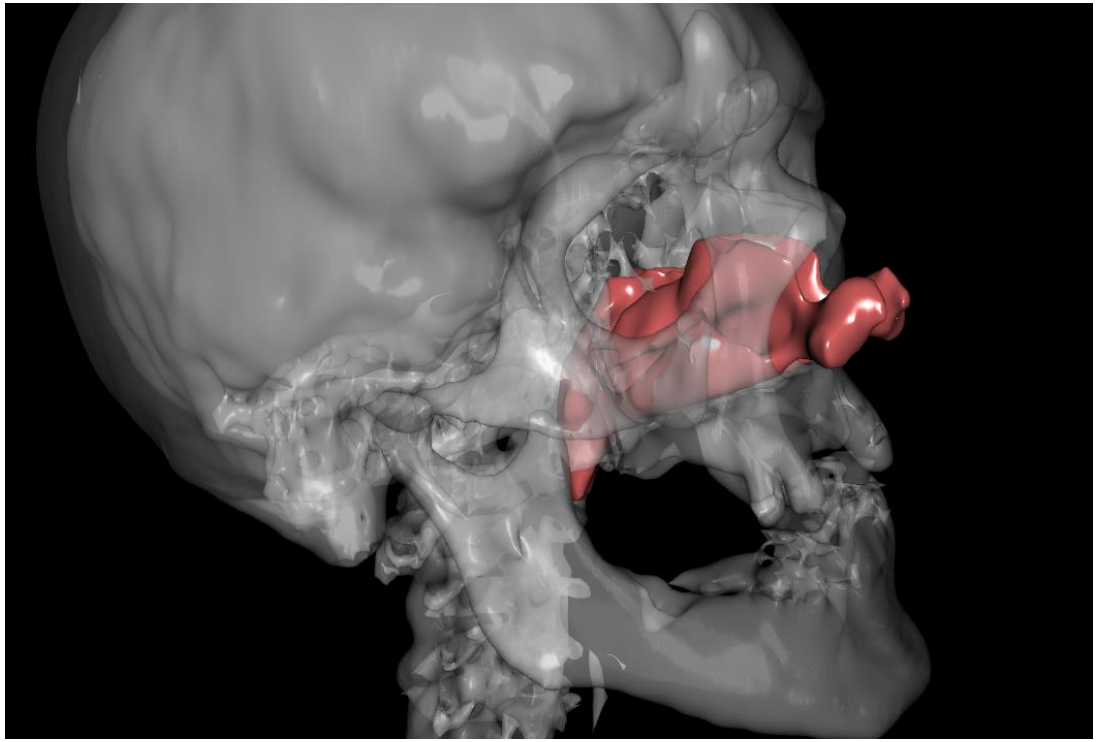
- Segmentation: The nasal cavity of the selected cases are segmented into a 3D Mesh

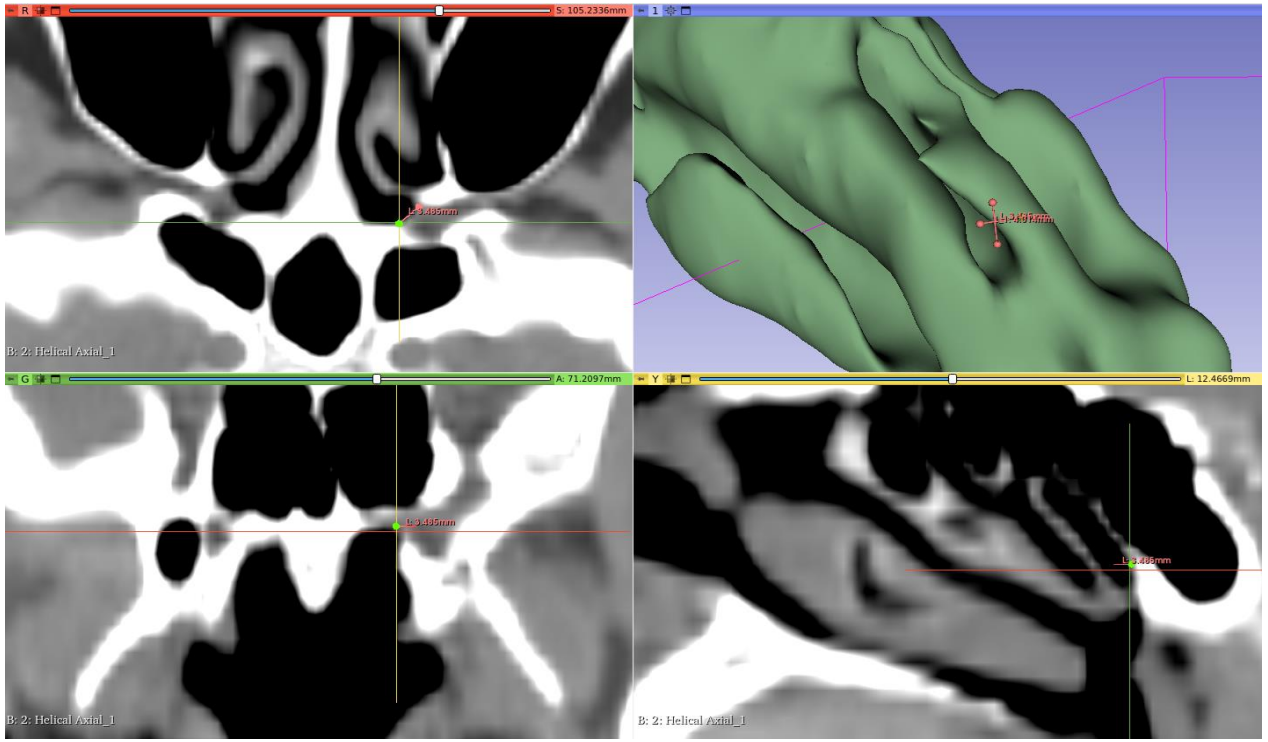
- Output is a 'negative' solid of the nasal airway (shell of open space within the cavity)



PROCESS: 2. ANNOTATION

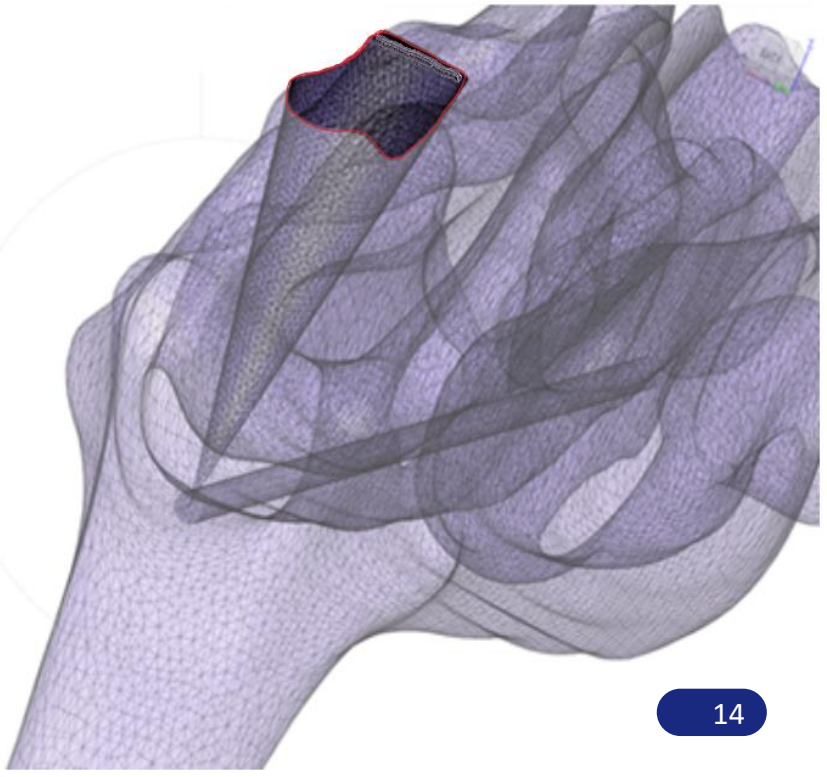
- Target Labeling: Identify the target location in all CT views – Sagittal, Coronal, Axial - and marking it on the model





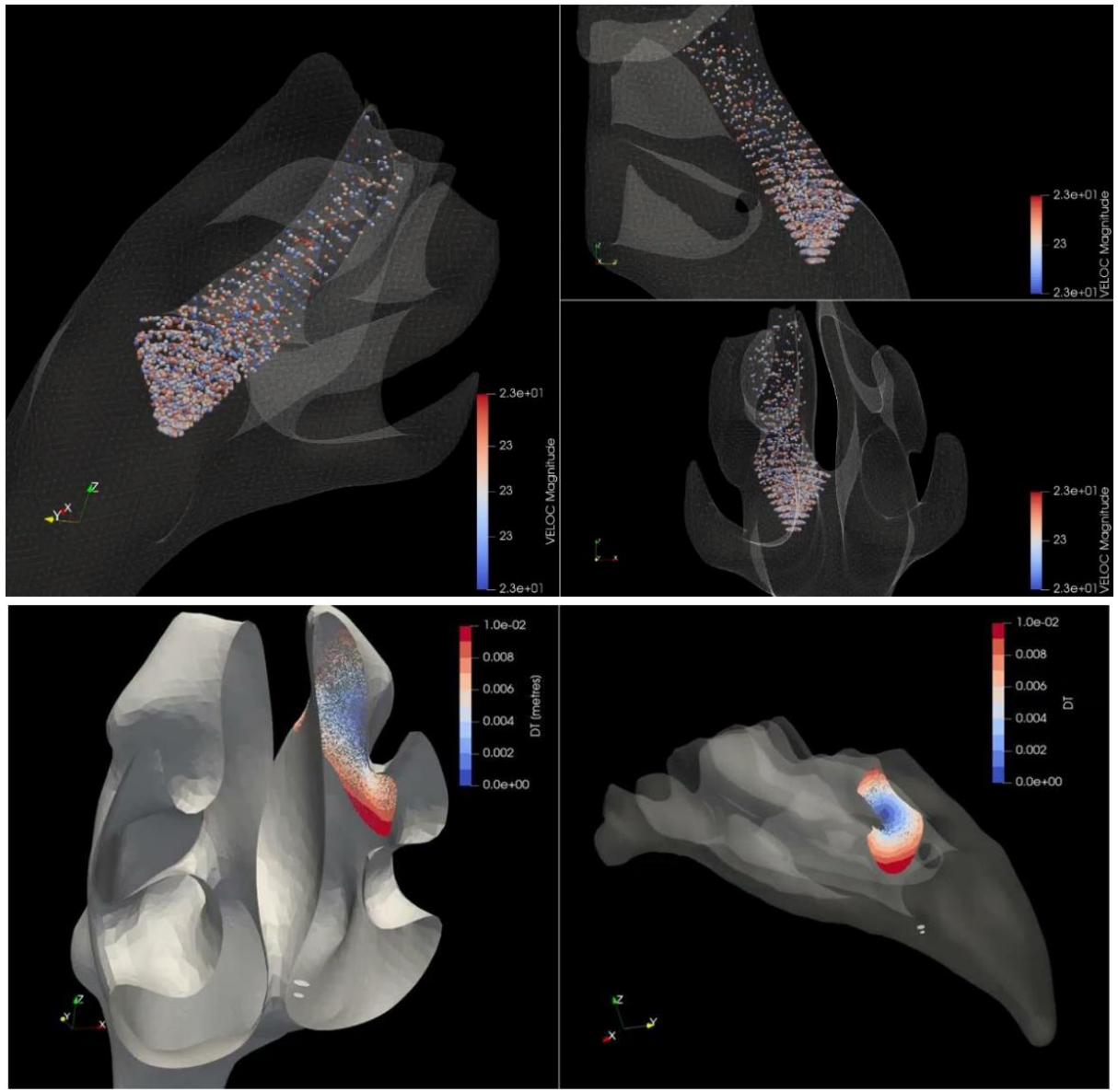
PROCESS: 3. SPRAYING CONFIGURATION SETUP

- Spray configurations programmed into AYLA as a solid 3D cone and catheter with different parameters (*Design Inputs*)
- Range of interest is defined for each input parameter
- Fixed model parameters include CFD information, approximated from Clexio's EVT and stability testing
  - The number of particles per spray event is calculated
- Assumptions made on different forces criticality (e.g. drag and gravitational forces, particle rotation, airflow effects etc. considered; some determined to be negligible enough and omitted)



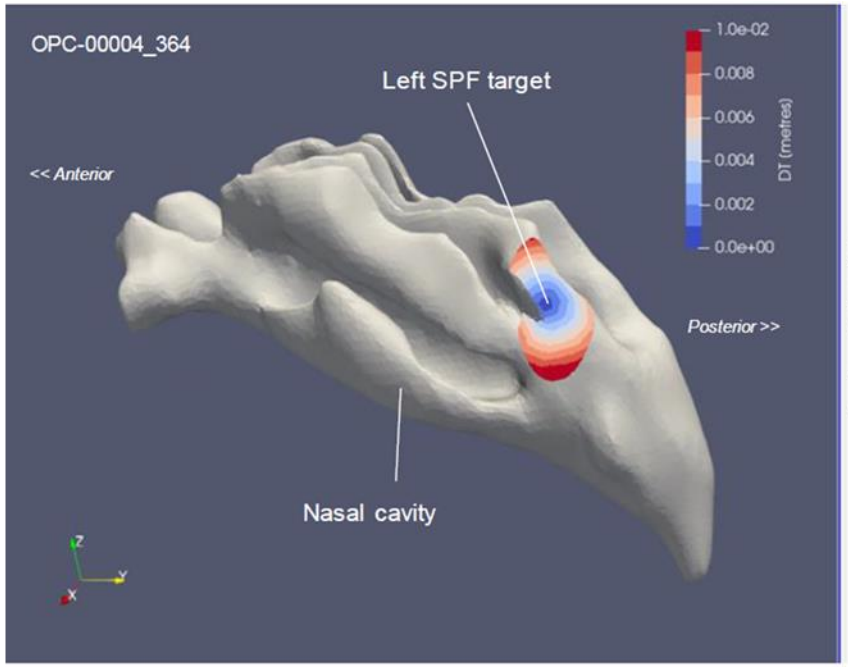
PROCESS: 4. SIMULATION

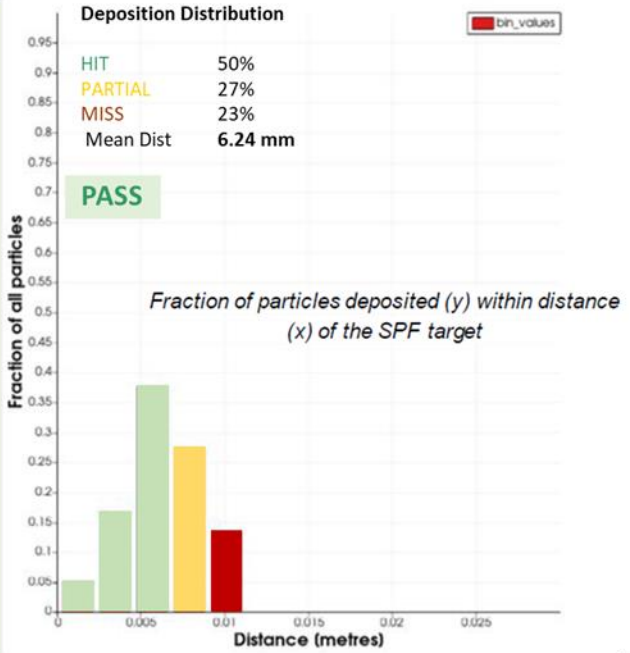
- Simulation of the spray droplets deposition in the segmented model
- Each droplet is classified into a category – HIT / Partial / MISS - according to its geodesic distance from the center of the SPF target
- Ultimately, each distinctive experiment yields a ‘heat map’ of the deposition in respect to the geodesic distance from the center of the target
- Heat map → Hit map: quantitative analysis based on proximity of the formulation droplets to the SPF area

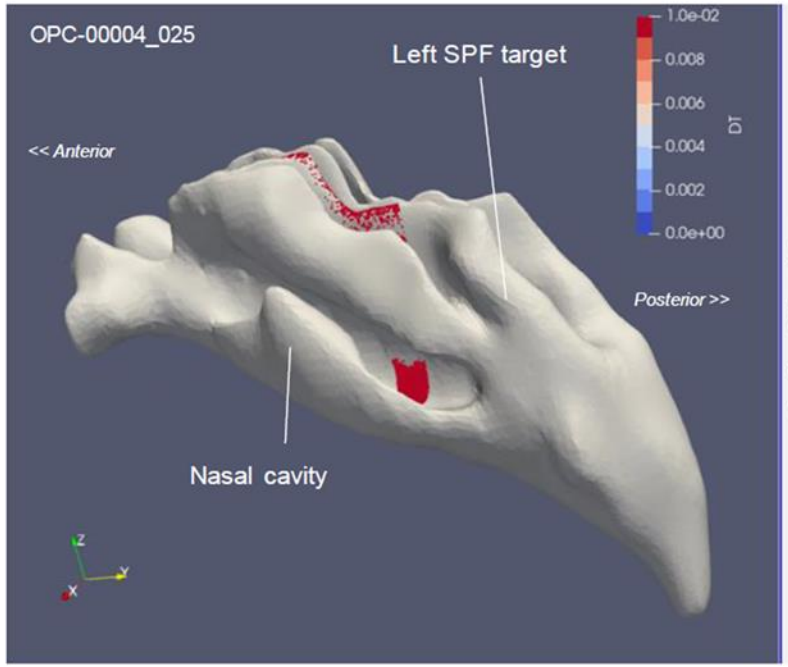


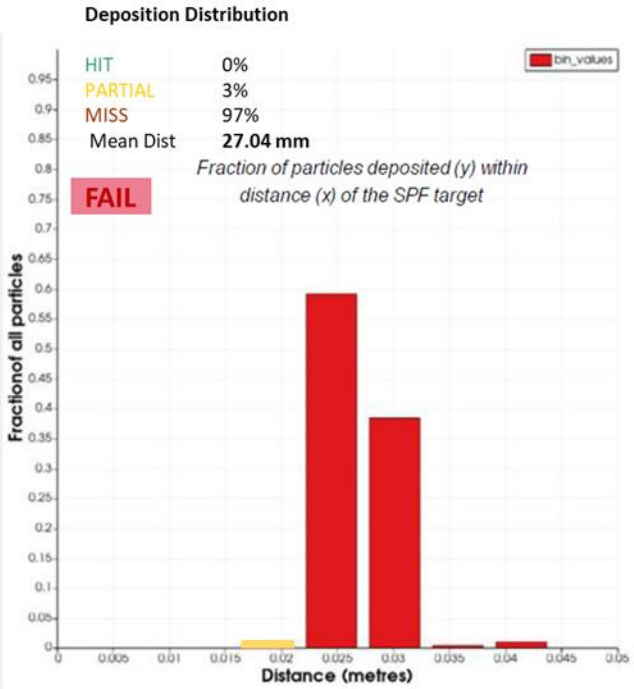
EXAMPLES

- Spray Configurations sorted per individual and by group to rank the best performing device design option









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SUMMARY: *LOCALIZED DELIVERY* IS AN ATTRACTIVE OPTION FOR A RANGE OF MEDICAL CONDITIONS

- **Clexio** has developed a **technology to deliver precise quantities of drugs to specific locations** of the nasal cavity. The device is intended to be small, portable, easy and convenient for use and suitable for self administration.
- To overcome the complexity of anatomical variability, we turn to In-Silico modeling to simulate dynamic systems, taking into consideration both the biological environment and the physical properties of the delivery method.
- This cost-effective approach enables rapid testing of different designs and parameters without the need for extensive in-vivo experiments or physical prototypes of multiple configurations, thus accelerating the development process.
- Two methods were used to define success: by smallest geodesic mean distance or by largest coverage (HIT and Partial areas).
- Optimal configurations were found for different device presentation options (e.g. single-size applicator vs. multiple applicators) and Design Inputs specified.

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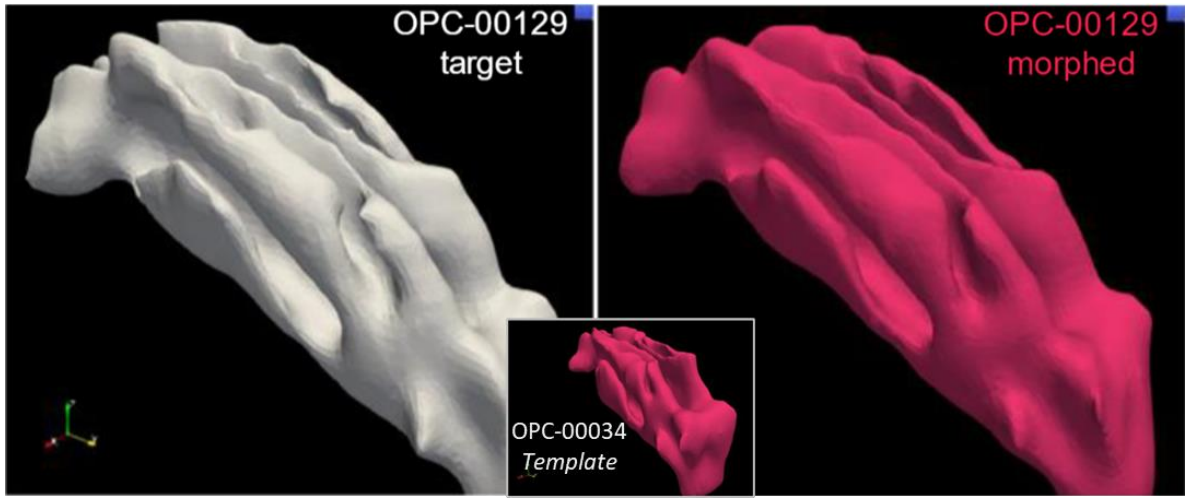
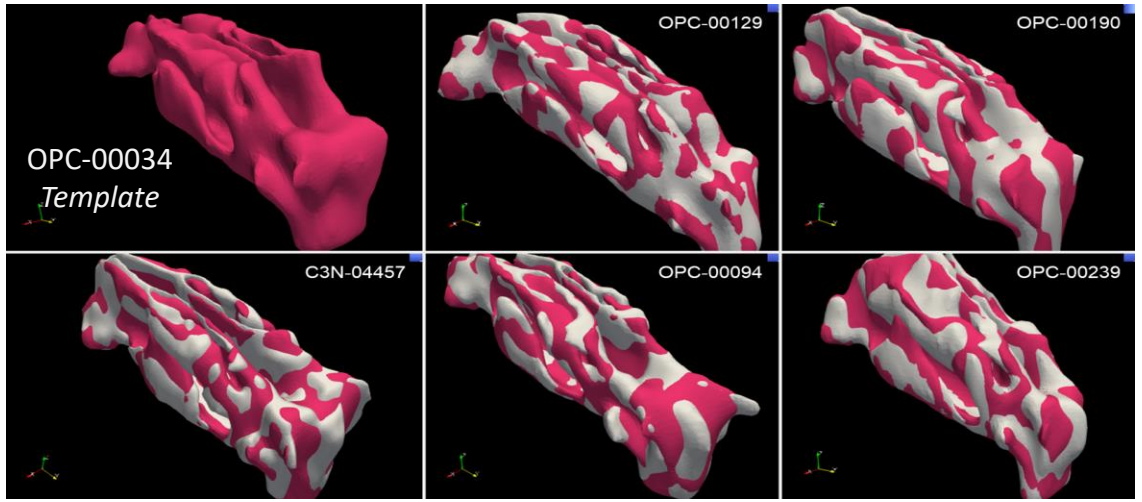
SCALE UP BY VIRTUAL POPULATION

Goal: Create different cohorts of Virtual Populations to explore the performance of the optimized device at different anatomical features.

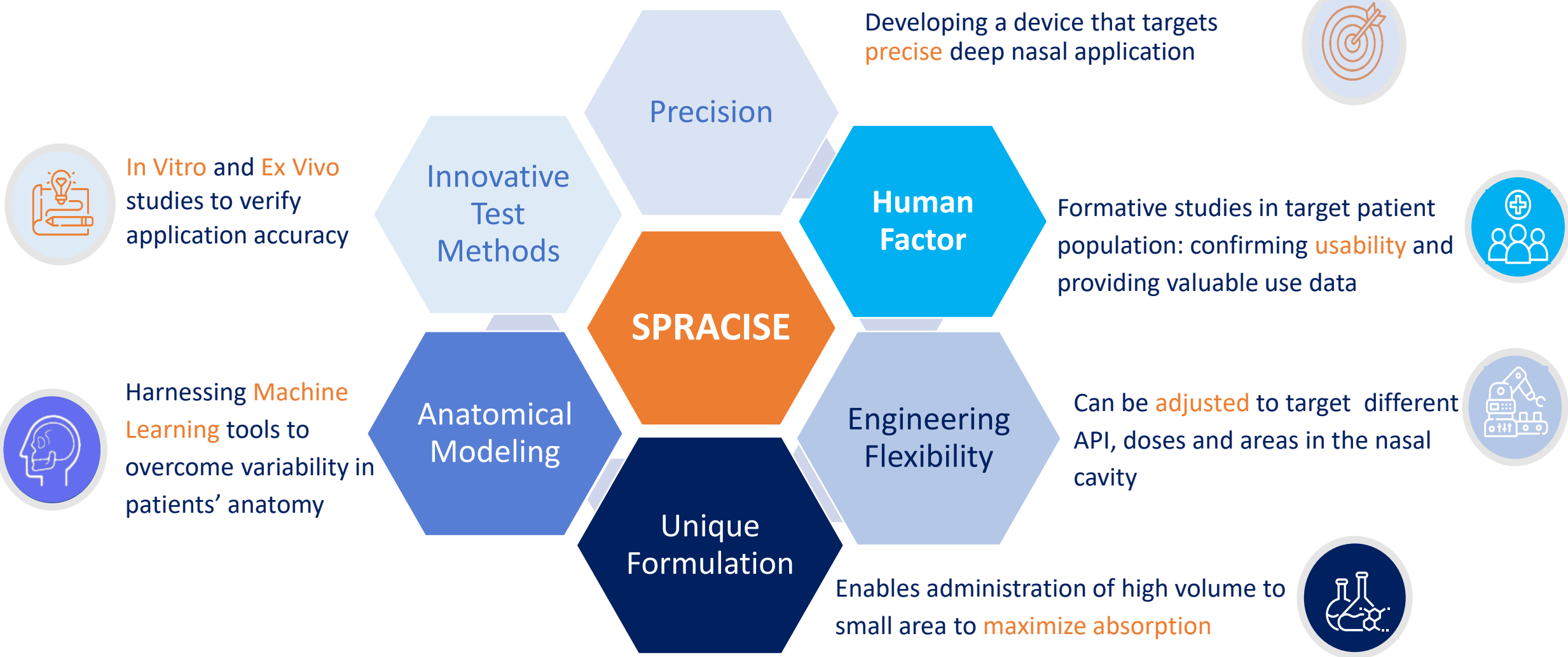
Process:

- The template geometry is morphed to each individual target case.
- Showcasing here an overlay between the morphed and the target geometry for each case
- Finally the result is a morphed geometry from the template to a specific target.





CLEXIO'S EXPERTISE IN DEEP NASAL LOCALIZED APPLICATIONS



Developing a device that targets precise deep nasal application

In Vitro and Ex Vivo studies to verify application accuracy

Formative studies in target patient population: confirming usability and providing valuable use data

Harnessing Machine Learning tools to overcome variability in patients' anatomy

Can be adjusted to target different API, doses and areas in the nasal cavity

Enables administration of high volume to small area to maximize absorption

THANK YOU!

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For more information visit our website: **https://www.clexio.com/**

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