

CLEARPOINT®
NEURO



Stereotactic -aided Intraoperative Neuronavigation System

ICD-10 Coordination and
Maintenance Committee Update
March 2025

Present Today



Daniel J Curry, MD **Texas Children's[®]**

- Director, Functional Neurosurgery and Epilepsy Surgery, Texas Children's Hospital
 - Professor, Pediatric Neurosurgery
Baylor College of Medicine
 - The John S. Dunn Foundation Endowed Chair for Minimally Invasive Epilepsy Surgery
-

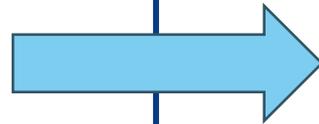


Jessica Anne Wilden MD

- BC Functional Neurosurgeon
- Director of Clinical Affairs, ClearPoint Neuro, Inc.

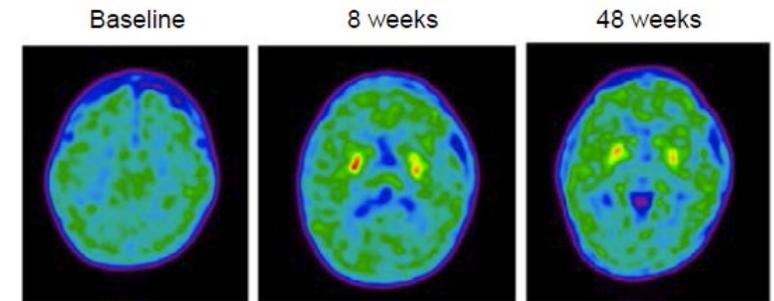
AADC Deficiency

- The tragedy of “kids with Parkinsons”
- **Severe** genetic disorder affecting mainly children that functionally results in catastrophic motor and behavior deficits
- Patients lack the **AADC enzyme** resulting in dysfunctional, low levels of dopamine in the putamen region of the brain
- BEDBOUND



New FDA approved gene therapy November 2024

Eladocagene exuparvovec-tneq (KEBILID) restores AADC enzyme function, which restores the deficient neurotransmitters (Figure 1; red-yellow regions show restored dopamine), which restores neurological function



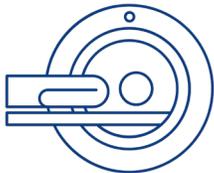
Gene Therapy (KEBILIDI) Administration: The ClearPoint® Neuro Pathway



- Advanced software/ hardware specializing in *computer-assisted* brain targeting (putamen), device/drug placement monitoring, and procedural success assessment



- Specialized delivery device, SmartFlow® Neuro Cannula



- Rigid and stable, capable of *percutaneous* brain infusions
- MRI compatible for live MRI monitoring of device placement/infusion
- Minimal priming volume/limited dead space preventing drug waste

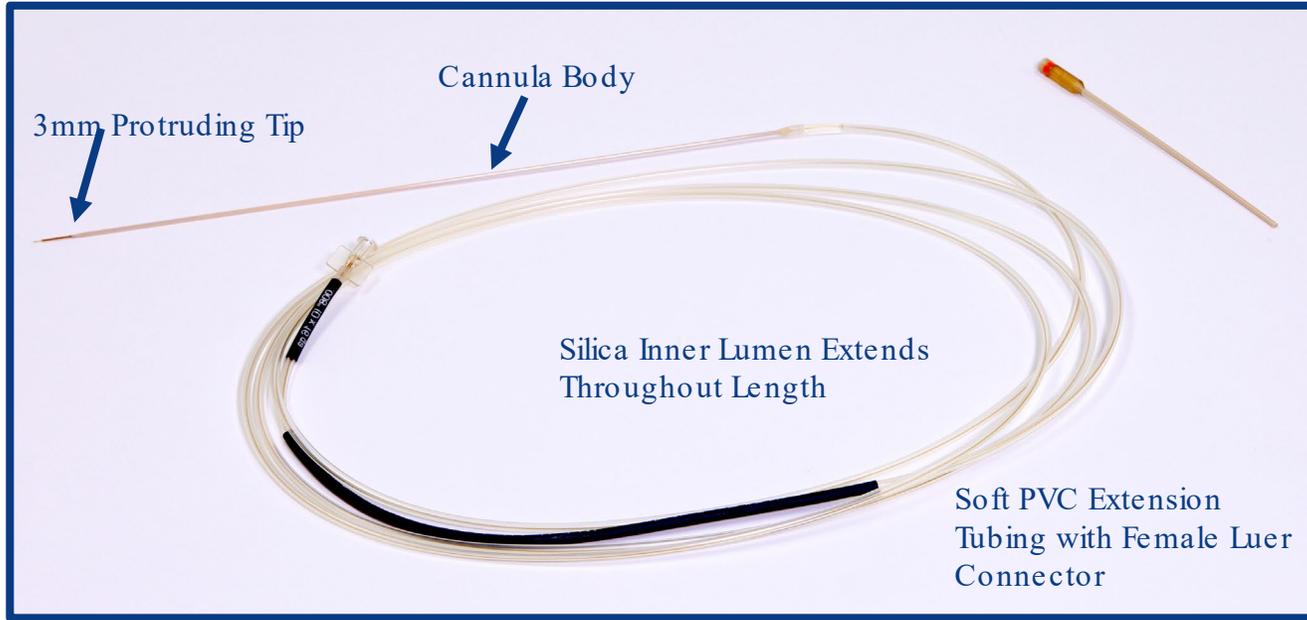


- KEBILIDI is expensive and in limited supply



- Cannula tubing/length(s) capable of accommodating various operative settings

SmartFlow® Neuro Cannula Distinctive Attributes



- **RIGID** for precise, accurate placement
- **CONTINUOUS INNER LUMEN** for avoiding leaks
- **200 μm INNER LUMEN** for minimal dead space
- **STEPPED TIP** for Convection Enhanced Delivery*
- **4- & 10-FT TUBING** for enabling diverse OR settings
- **MRI SAFE** for live MRI monitoring of device and drug placement if desired
- **WIDELY COMPATIBLE** with different brain targeting platforms, though designed for best use with ClearPoint's Navigation System/Products

Header: Catalog Number	Header: Outside Diameter			Header: Inner Diameter		Header: Length Overall	Header: Priming Volume	Header: Tip Length	Header: Usable Body Length	Header: Bore Length
	(ga)	(in.)	(mm)	(in.)	(μm)					
NGS-NC-01-EE	16	0.65	1.65	.008"	200	4	0.04	18	26.8	30.0
NGS-NC-02-EE						10				

* Convection enhanced delivery describes how the SFC delivers its payload more effectively than other devices due to the stepped tip creating a pressure gradient which pushes the drug from the tip into surrounding tissue.

Regulatory Status

- **Smartflow[®] Neuro Cannula** - received FDA De Novo clearance on November 13, 2024
Intrapataminal administration of eladocagene exuparvovegtneq (KEBILIDI) for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.*
- **ClearPoint[®] Neuro Navigation System** - received FDA 510(k) clearance on November 27, 2013
Accurate, precise guidance and placement of devices into the brain within an MRI environment and in conjunction with MR imaging.*
- **ClearPoint SmartFrame[®] OR** - received FDA 510(k) clearance on January 12, 2024
Accurate, precise guidance and placement of devices into the brain with the use of a compatible optical navigation system and MRI and/or CT imaging in an operating room (OR) environment.*

**Indications are paraphrased for brevity and clarity.*

Documentation

- **Device & Methodology Documentation**
 - Operative report dictated by surgeon
 - May include the following terms
 - Smartflow[®] Neuro Cannula
 - SmartFlow[®] cannula
 - SFC
 - SmartFlow[®] drug delivery device
 - ClearPoint[®] Neuro Navigation System
 - ClearPoint[®] system
 - ClearPoint SmartFrame[®] OR
 - Stereotactic system
 - Stereotactic frame

nature COMMUNICATIONS

ARTICLE

<https://doi.org/10.1038/s41467-021-24524-8> OPEN

Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons

Toni S. Pearson^{1,2,12}, Nalin Gupta^{1,12}, Wally San Sebastian¹, Jill Imamura-Ching¹, Amy Viehoever³, Ana Grijalvo-Perez³, Alex J. Fay³, Neha Seth⁴, Shannon M. Lundy⁵, Youngho Seo⁶, Miguel Pampaloni⁶, Keith Hyland⁷, Erin Smith⁸, Gardenia de Oliveira Barbosa⁹, Jill C. Heathcock⁹, Amy Minnema¹⁰, Russell Lonser¹⁰, J. Bradley Elder¹⁰, Jeffrey Leonard^{10,11}, Paul Larson¹ & Krystof S. Bankiewicz^{1,10,13}

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare genetic disorder characterized by deficient synthesis of dopamine and serotonin. It presents in early infancy, and causes severe developmental disability and lifelong motor, behavioral, and autonomic symptoms including oculogyric crises (OGC), sleep disorder, and mood disturbance. We investigated the safety and efficacy of delivery of a viral vector expressing AADC (AAV2-hAADC) to the midbrain in children with AADC deficiency (ClinicalTrials.gov Identifier NCT02852213). Seven (7) children, aged 4–9 years underwent convection-enhanced delivery (CED) of AAV2-hAADC to the bilateral substantia nigra (SN) and ventral tegmental area (VTA) (total infusion volume: 80 µl per hemisphere) in 2 dose cohorts: 1.3 × 10¹¹ vg (n = 3), and 4.2 × 10¹¹ vg (n = 4). Primary aims were to demonstrate the safety of the procedure and document biomarker evidence of restoration of brain AADC activity. Secondary aims were to assess clinical improvement in symptoms and motor function. Direct bilateral infusion of AAV2-hAADC was safe, well-tolerated and achieved target coverage of 98% and 70% of the SN and VTA, respectively. Dopamine metabolism was increased in all subjects and FDOPA uptake was enhanced within the midbrain and the striatum. OGC resolved completely in 6 of 7 subjects by Month 3 post-surgery. Twelve (12) months after surgery, 6/7 subjects gained normal head control and 4/7 could sit independently. At 18 months, 2 subjects could walk with 2-hand support. Both the primary and secondary endpoints of the study were met. Midbrain gene delivery in children with AADC deficiency is feasible and safe, and leads to clinical improvements in symptoms and motor function.

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Agathe Roubertie, Thomas Opladen, Roser Pons and Toni S. Pearson contributed equally.

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ORIGINAL ARTICLE

Gene therapy for aromatic L-amino acid decarboxylase deficiency: Requirements for safe application and knowledge-generating follow-up

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Abstract
The autosomal recessive defect of aromatic L-amino acid decarboxylase (AADC) leads to a severe neurological disorder with manifestation in infancy due to a pronounced, combined deficiency of dopamine, serotonin and catecholamines. The success of conventional drug treatment is very limited, especially in patients with a severe phenotype. The development of an intracerebral

Introduction

- AADC deficiency is an autosomal recessive disorder that presents in infancy and often necessitates life-long care.
- Pathogenic DDC gene variants lead to impaired AADC enzyme activity, leading to deficient production of dopamine and other monoamine neurotransmitters. This can lead to a wide range of debilitating symptoms, including movement disorders, developmental delay and autonomic dysfunction.
- Exogenous exogenous dopamine is a recombinant AAV2 that contains the human DDC gene and is designed to restore AADC production, regardless of the underlying pathogenic variant(s) in the native DDC gene (Figure 1).

Objectives

- To assess the pharmacodynamics of exogenous exogenous gene therapy and the safety of intracranial administration using the SmartFlow MR-compatible ventricular cannula in pediatric participants with AADC deficiency.

Methods

Study 01-463 is an ongoing phase 2, open-label, multicenter trial in pediatric participants aged 4–9 years (NCT04502388).

- Participants received exogenous exogenous at 1.8 × 10¹¹ vector genomes by bilateral infusion into the putamen via SmartFlow MR-compatible ventricular cannula in a single operative session.
- The primary endpoints were:
 - the pharmacodynamics of exogenous exogenous gene therapy, assessed by the change from baseline in CSF HVA levels at 8 weeks;
 - TEAEs associated with the SmartFlow MR-compatible ventricular cannula used for gene therapy delivery in the weeks after administration;
 - Scan the MR code for the study design (Figure 1), ongoing criteria and secondary endpoints.

Results

Overall, 13 participants aged 10–122 months with AADC deficiency received exogenous exogenous using the SmartFlow MR-compatible ventricular cannula (Table 1).

Table 1 Baseline demographics and general characteristics of the 13 participants.

Parameter	All participants (n = 13)
Age at gene therapy, months	46.2 (28.8)
Height (cm)	33.0 (16.0, 128.0)
Sex, n (%)	6 (46.2)
Female	6 (46.2)
Male	6 (46.2)
Mean (SD) height, cm	50.4 (16.3)
Mean (SD) weight, kg	12.4 (4.2)

Table 2 AADC deficiency (DDC) CSF HVA level of 22.5 (SD 3.3) nmol/l was observed at baseline, consistent with a diagnosis of AADC deficiency.

Conclusions
In pediatric participants with AADC deficiency, CSF HVA levels and ¹⁸F-DOPA uptake increased significantly at 8 weeks and 48 weeks after administration of exogenous exogenous gene therapy compared with baseline, indicating de novo dopamine production. Pharmacodynamic evidence of increased AADC expression and production of dopamine also consistent with the acquisition of key motor milestones, consistent with results from previous clinical trials. No TEAEs were deemed to be related to the SmartFlow MR-compatible ventricular cannula, which suggests it has a favourable safety profile and is well tolerated. This study also added to the body of evidence for the favourable safety profile of exogenous exogenous in pediatric participants with AADC deficiency.

An open-label study of eladocogene exuparvovec administered using the SmartFlow magnetic resonance-compatible ventricular cannula in paediatric participants: 48-week interim analysis

David Mikhlin, Lisa Mikhlin, Donald I. Gilbert, Bruria Ben-Zeev, Daniel J. Curry, Scott Stone, Matthew Vestal, Christian Werner, Alexis Krolsch, Vinay Penevatski, Antonia Wang, Lee Golden and Phillip L. Pearl

Introduction

- A significant mean increase in CSF HVA levels from baseline was observed at 8 weeks and sustained up to 48 weeks after administration of eladocogene exuparvovec gene therapy, suggestive of increased expression and activity of AADC (Figure 3).

Results (continued)

Figure 3. CSF HVA levels for individual participants at baseline and 8 weeks and 48 weeks after gene therapy.

Figure 4. Acquisition of key motor milestones was observed after administration of eladocogene exuparvovec gene therapy in participants who had achieved fewer motor developmental delay at baseline (Figure 4).

Figure 5. CSF HVA levels for individual participants at baseline and 8 weeks and 48 weeks after gene therapy.

Figure 6. CSF HVA levels for individual participants at baseline and 8 weeks and 48 weeks after gene therapy.

Figure 7. CSF HVA levels for individual participants at baseline and 8 weeks and 48 weeks after gene therapy.

Figure 8. Most common TEAEs (recorded in 50% of participants) in the 48 weeks after gene therapy.

Figure 9. CSF HVA levels for individual participants at baseline and 8 weeks and 48 weeks after gene therapy.

Figure 10. CSF HVA levels for individual participants at baseline and 8 weeks and 48 weeks after gene therapy.

Conclusions
In pediatric participants with AADC deficiency, CSF HVA levels and ¹⁸F-DOPA uptake increased significantly at 8 weeks and 48 weeks after administration of eladocogene exuparvovec gene therapy compared with baseline, indicating de novo dopamine production. Pharmacodynamic evidence of increased AADC expression and production of dopamine also consistent with the acquisition of key motor milestones, consistent with results from previous clinical trials. No TEAEs were deemed to be related to the SmartFlow MR-compatible ventricular cannula, which suggests it has a favourable safety profile and is well tolerated. This study also added to the body of evidence for the favourable safety profile of eladocogene exuparvovec in pediatric participants with AADC deficiency.

Procedure Overview

- Plan brain targets on software
- Identify entry points on skull
- Fixate the stereotactic aiming frame(s) onto the skull over entry points
- Aim the frame(s) appropriately toward the brain targets
- Make incisions at entry points
- Drill holes in the skull at the entry points
- Prime and measure the SmartFlow[®] Cannula(s) appropriately
- Insert the SmartFlow[®] Cannula(s)
- Infuse KEBILIDI into targets
 - Simultaneous or sequential
- Remove the SmartFlow[®] Cannula(s) from the brain
- Remove the aiming frame(s) off the skull and close the incisions
- Obtain postoperative imaging to confirm final infusion distribution

Use of Magnetic Resonance Imaging for KEBILIDI Administration

Diagnostic Setup



Compatible with Siemens, GE, and Philips diagnostic -only scanners

Intraoperative Setup

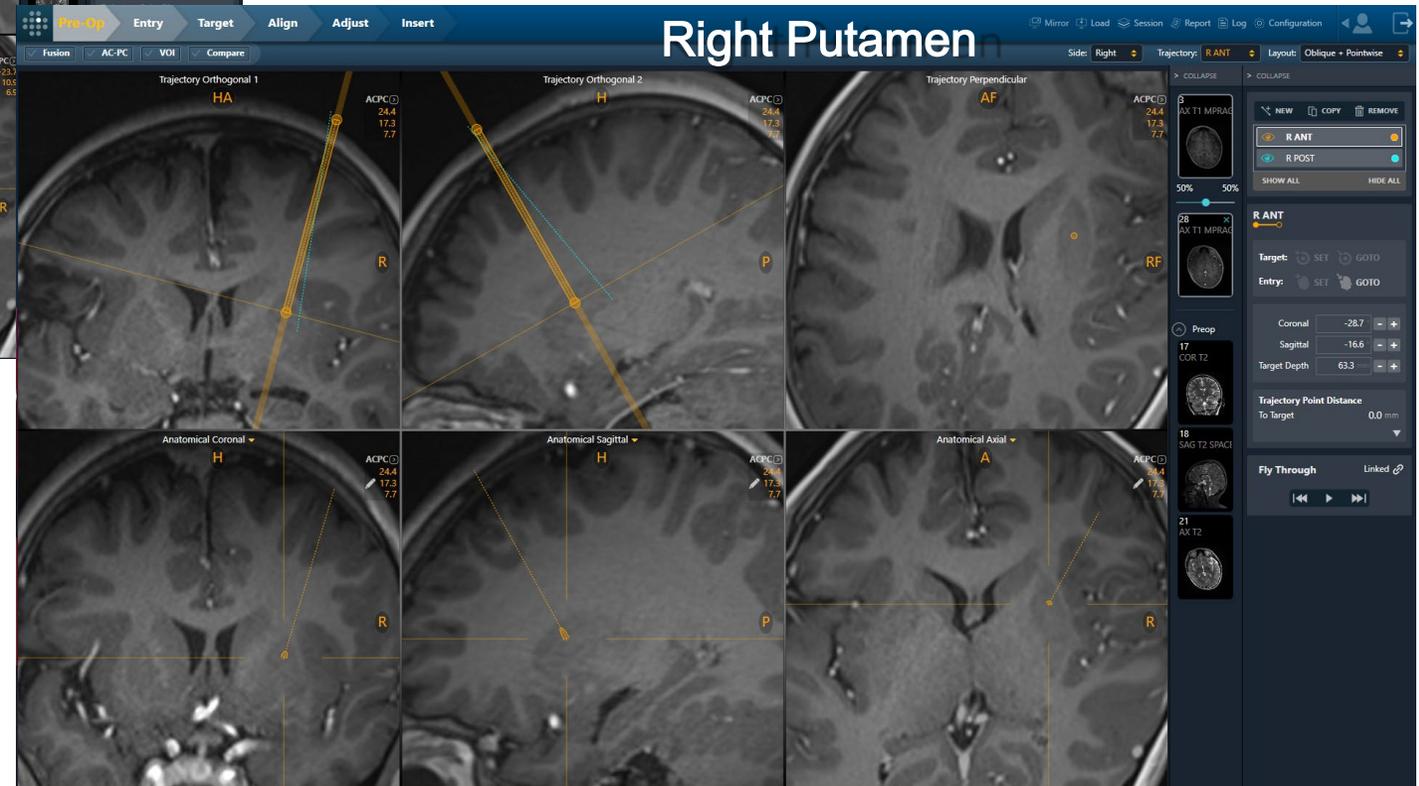
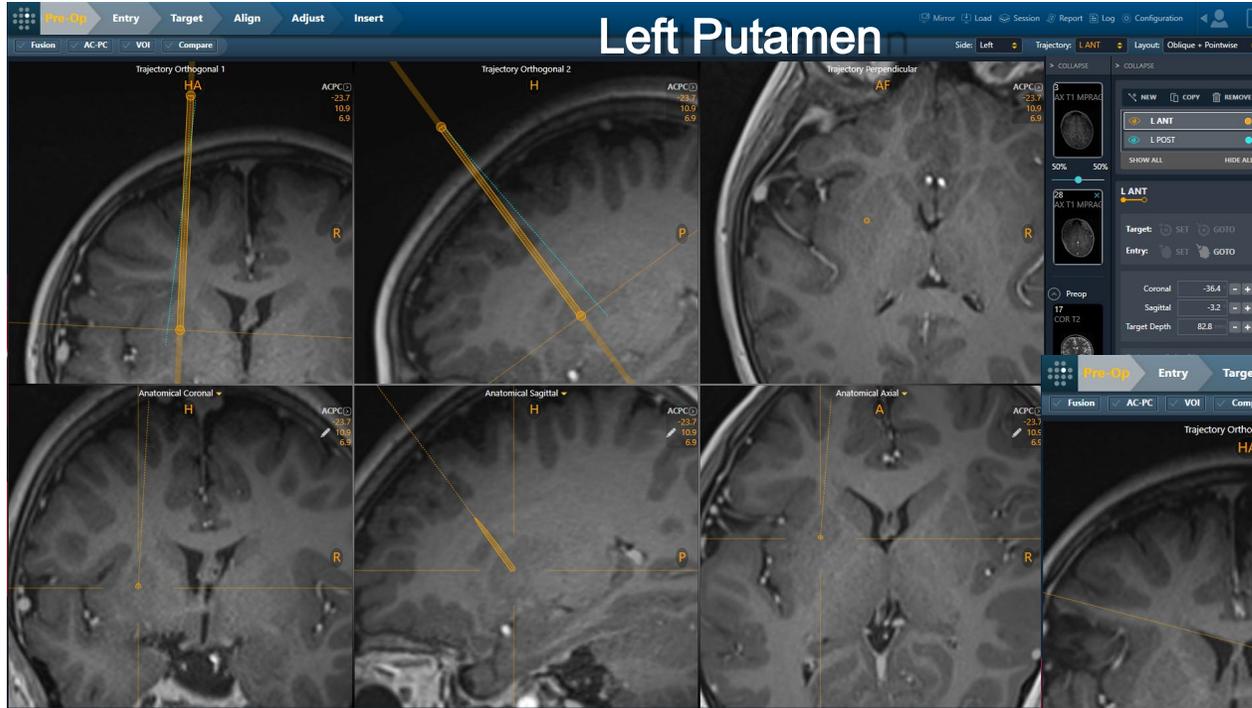


Compatible with IMRIS and other iMRI suites, which allow surgeons to conduct MR imaging while the patient is undergoing neurosurgery

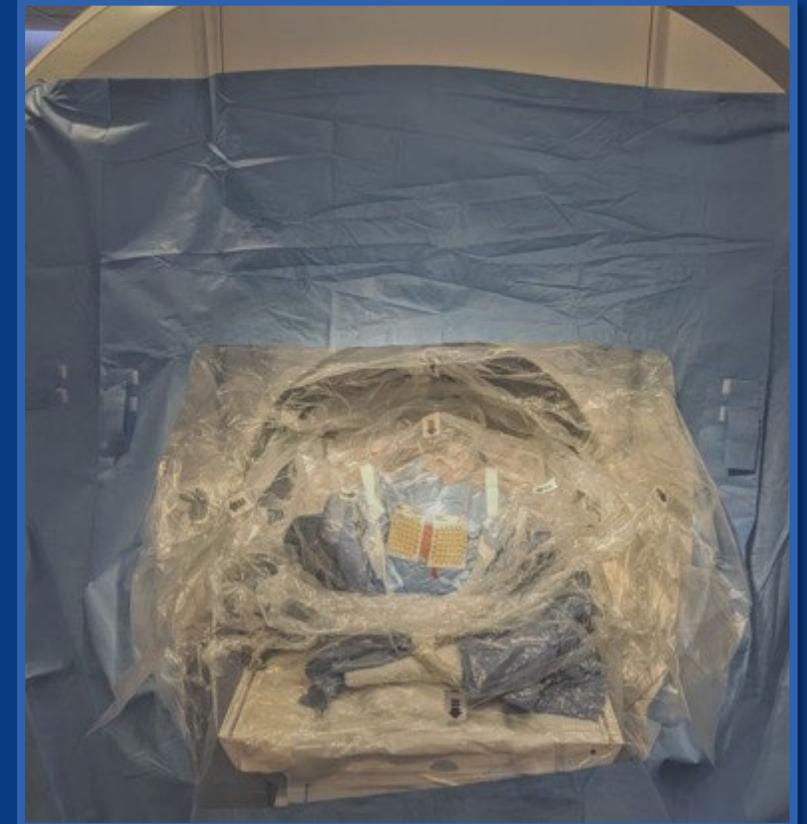
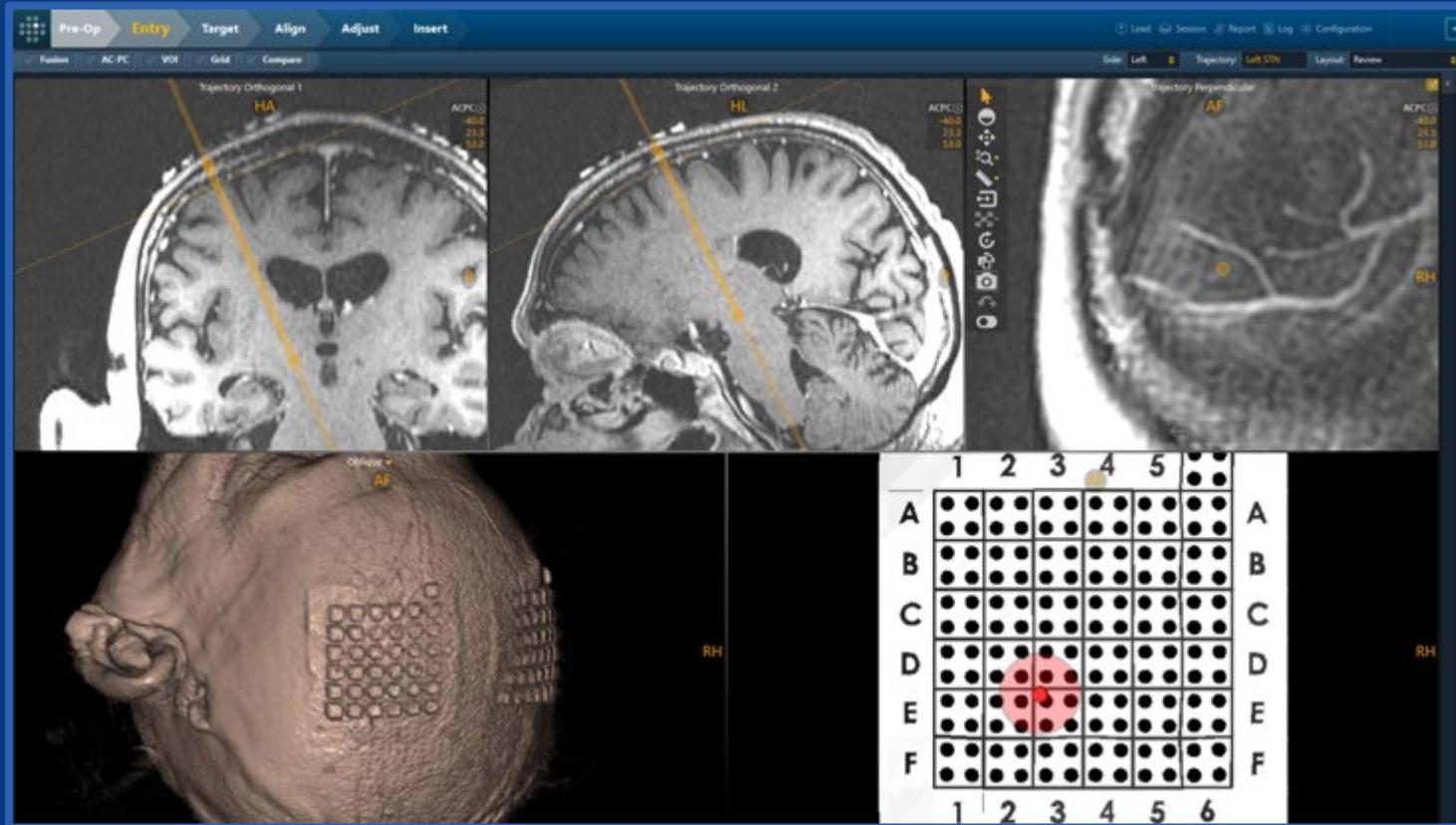
- ClearPoint® enables surgical procedures in **both** diagnostic-only and intraoperative scanners.
- MRI is the best for visualizing the brain structures *without radiation exposure to patient*.
- The ClearPoint® Navigation System + Smartflow® Neuro Cannula enables surgeons to image the device and the drug via MRI scanner while the patient is undergoing surgery for KEBILIDI administration into the putamen for optimal results.

Planning on ClearPoint® Neuro Navigation Software

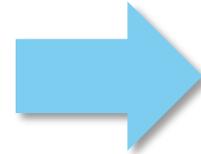
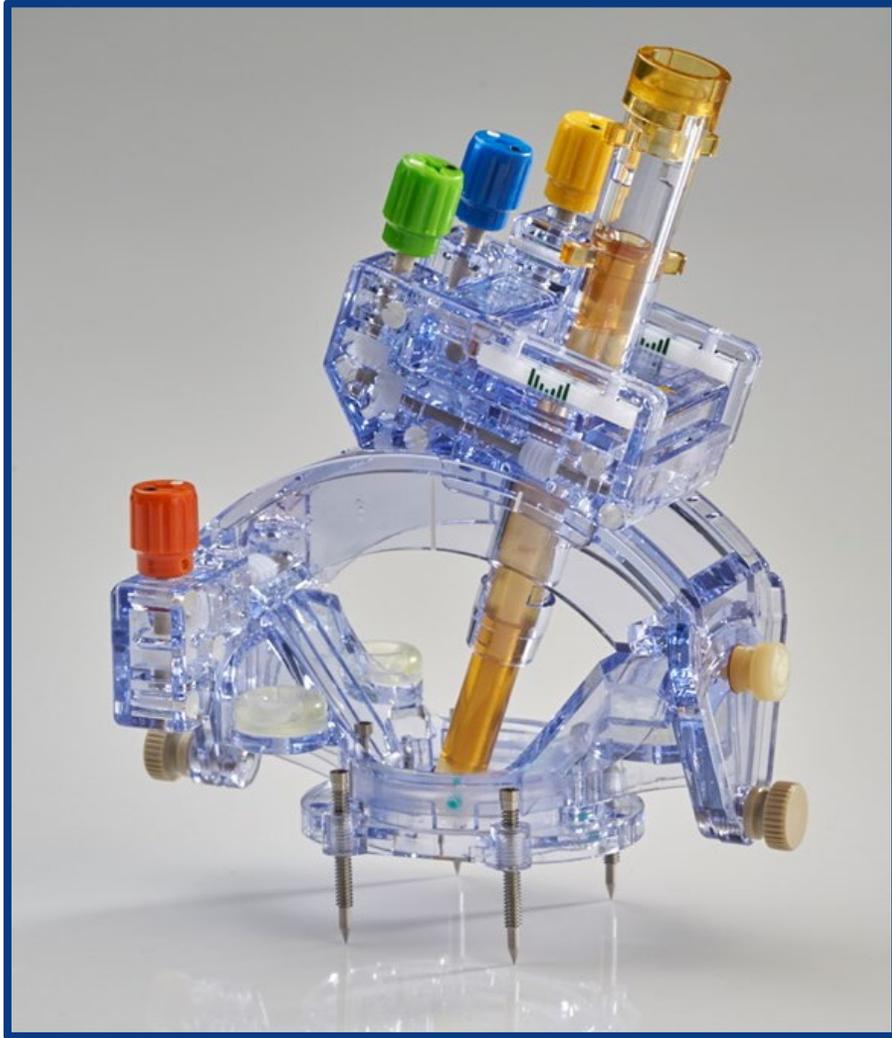
Treatment Trajectory to the Left and Right Putamen



Bilateral MR-Visible SmartGrid[®] to Localize SmartFlow[®] Neuro Cannula Entries



SmartFrame® Base and Tower Assembly for Aiming to Target



Confirmed Device Placement in Right Putamen

Pre-Op > Entry > Mount > Target > Align > Adjust > **Insert**

Fusion VOI Compare

FRAME: **RIGHT** TRAJECTORY: **right posterior** LAYOUT: **Insertion**

Trajectory Orthogonal 1
HA

Device Coronal
HR

Device Sagittal
HA

Device Axial
AF

38 AX T1 MPRAC
4 AX T2 SPACE
3 AX T1 MPRAC
2 AX T1 MPRAC
13 AX T2 SPACE
15 COR T2
16 AX T2

INSERTION SUMMARY

Frame: **RIGHT**
Trajectory: **right posterior**
Depth: **220.3 mm (22.03 cm)**

SCAN PLANE PARAMETERS

Orthogonal 1 Orthogonal 2
Target

INSERTION REVIEW

Set Tip Go To Tip
Detect Device Go To Target

ERROR MEASUREMENTS

Plane: Trajectory Axial

Frame X: **0.0 mm**
Frame Y: **-0.2 mm**
Radial: **0.2 mm**
Depth: **-1.3 mm**

OVERLAYS

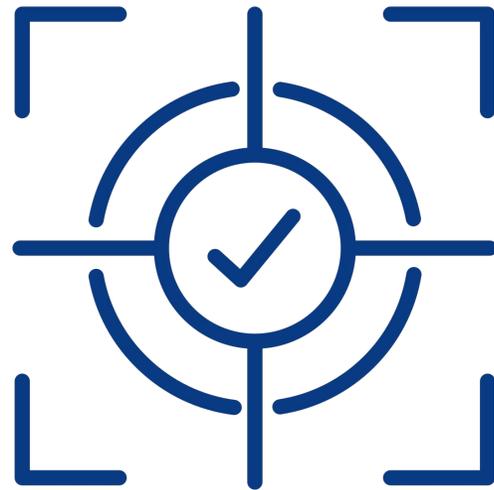
Trajectory
Device

Re-Adjust

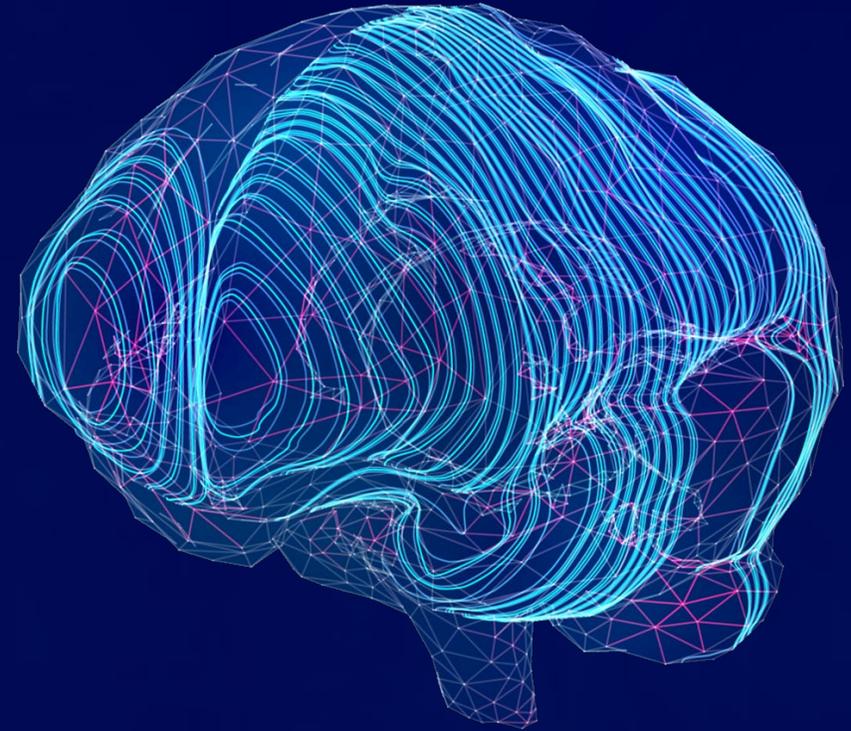
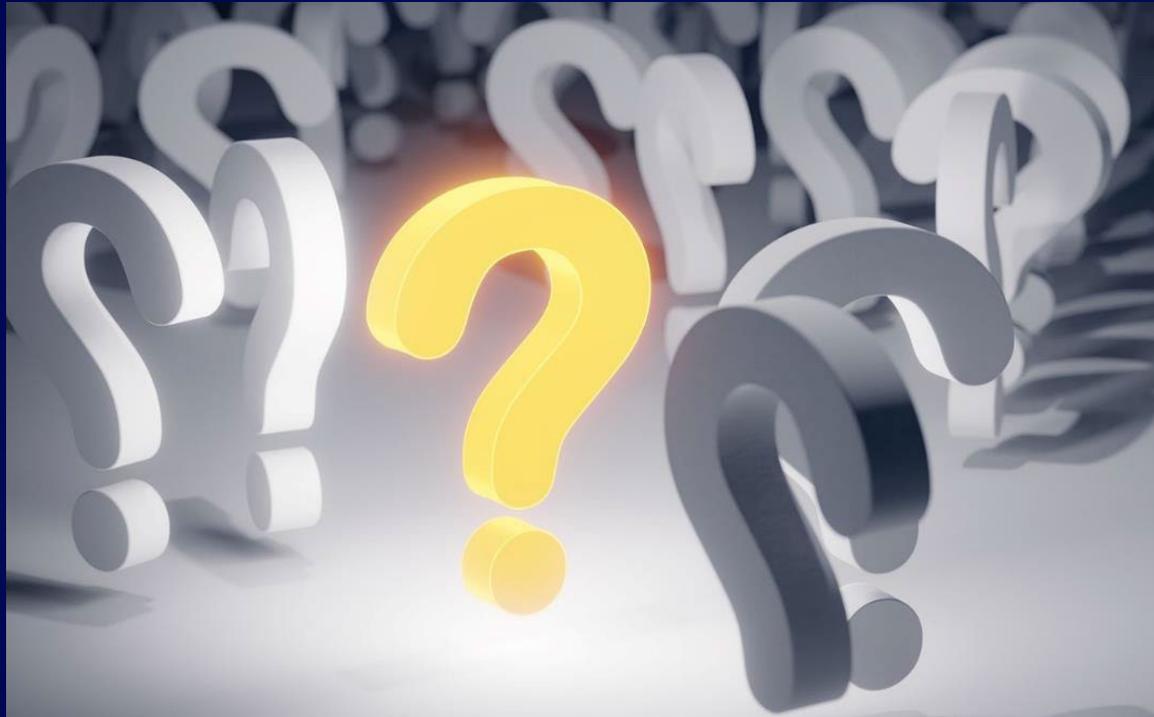
Minimally Invasive. Computer-Guided. Accurate.

Approximate Procedure Times

- Trajectory planning, Frame mounting, Percutaneous SmartFlow[®] Cannula insertion: 4 to 5 hours
- KEBILIDI infusion: 30 minutes



Thank You Questions?




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