



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.

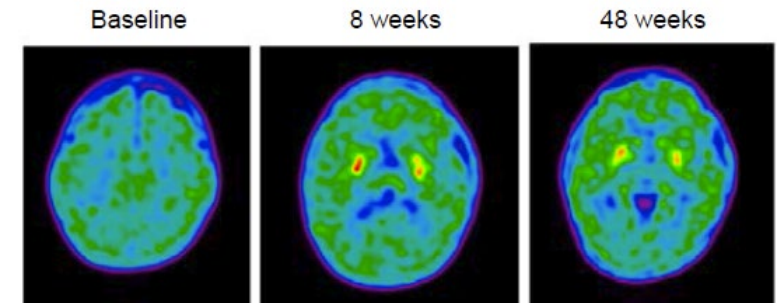
AADC Deficiency

- 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



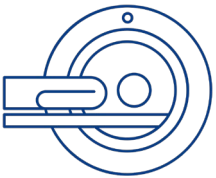
Gene Therapy (KEBILIDI) Administration: The ClearPoint® Neuro Pathway



- 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

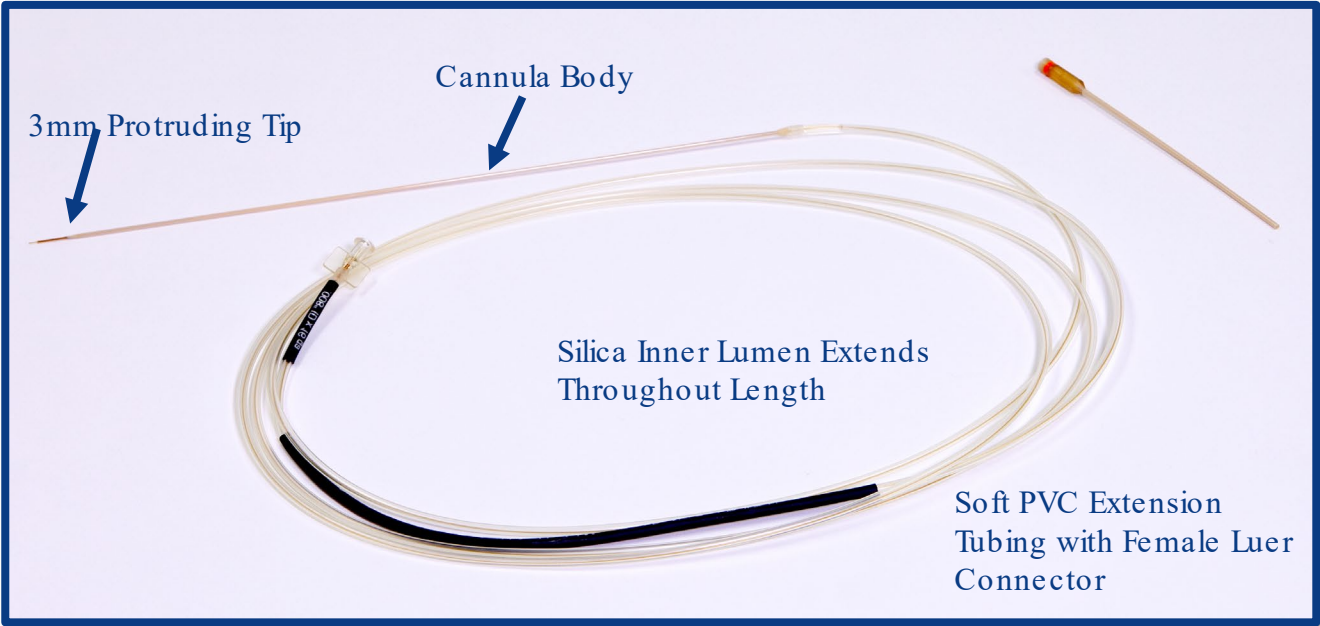


- KEBILIDI is expensive and in limited supply



- 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 μ m 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.)	(μ m)		(cc)	(mm)	(cm)	(cm)
NGS-NC-01-EE	16	0.65	1.65	.008"	200	4	0.04	18	26.8	30.0
NGS-NC-02-EE						10	0.10	18	26.8	30.0

**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
Intraputaminial 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



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 Grijalva-Perez³, Alex J. Fay³, Neha Seth⁴, Shannon M. Lundy⁵, Youngho Seo⁶, Miguel Pampaloni⁵, 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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ORIGINAL ARTICLE

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

Agathe Roubertie¹ | Thomas Opladen² | Heiko Brennenstuhl^{2,3} | Oya Kuseyri Hübschmann² | Lisa Flint⁴ | Michel A. Willemsen⁵ | Vincenzo Leuzzi⁶ | Angels Garcia Cazorla⁷ | Manju A. Kurian^{8,9} | Marie Céline François-Heude¹ | Paul Hwu¹⁰ | Bruria Ben Zeev^{11,12} | Karl Kiening¹³ | Thomas Roujeau¹⁴ | Roser Pons¹⁵ | Toni S. Pearson¹⁶

¹CHU Montpellier, Département de Neuropédiatrie, INM, Univ Montpellier, INSERM U 1298, Montpellier, France
²Division of Child Neurology and Metabolic Medicine, University Children's Hospital Heidelberg, Germany
³Institute Human Genetics, University Children's Hospital Heidelberg, Germany
⁴AADC Research Trust, Caterham, UK
⁵Department of Pediatric Neurology, Donders Institute for Brain, Cognition, and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands
⁶Department of Human Neuroscience—Unit of Child Neurology and Psychiatry, University of Rome La Sapienza
⁷Neurometabolism Unit, Department of Neurology, CIBERER and MetabERN, Hospital Sant Joan de Déu, Barcelona, Spain
⁸Developmental Neurosciences, Zayed Centre for Research into Rare Disease in Children, Great Ormond Street Institute of Child Health, University College London, London, UK
⁹Department of Neurology, Great Ormond Street Hospital for Children, London, UK
¹⁰Department of Pediatrics and Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan
¹¹Pediatric Neurology Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel
¹²Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
¹³Division of Stereotactic Neurosurgery, University Hospital Heidelberg, Germany
¹⁴CHU Montpellier, Département de Neurochirurgie, Montpellier, France
¹⁵First Department of Pediatrics, National and Kapodistrian University of Athens, Aghia Sofia Hospital, Athens, Greece
¹⁶Division of Neurology, Nationwide Children's Hospital, Columbus, Ohio, USA

Correspondence

Thomas Opladen, Division of Child Neurology and Metabolic Medicine, University Children's Hospital Heidelberg, Im Neuenheimer Feld 430, Heidelberg, Germany.
Email: thomas.opladen@med.uni-heidelberg.de

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

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

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J Inher Metab Dis. 2024;47:463–475.



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

Paul Muth-Linnemann^{1,2}, Donald L. Gilbert³, Bruria Ben-Zeev⁴, Daniel J Curry⁵, Seelie Stone⁶, Matthew Vestic⁷, Christian Werner⁸, Alexia Krolsch⁹, Vinay Penevatsa¹⁰, Antonia Wang¹, Lee Golden¹ and Philipp L. Pearl¹

¹Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan; ²Proton Medical Center, Chongqing Children's Hospital Medical Center, Chongqing, China; ³Center for Pediatric Neurology, Department of Neurology, Baylor College of Medicine, Houston, TX, USA; ⁴Neonatal Intensive Care Unit, Harvard Medical School, Boston, MA, USA; ⁵Duke Department of Neurosurgery, Duke University School of Medicine, Durham, NC, USA; ⁶NYC Therapeutics Company GmbH, Frankfurt, Germany; ⁷NYC Therapeutics Inc., Irvine, CA, USA

1 Introduction

AADC deficiency is an autosomal recessive disorder that presents in infancy and often necessitates lifelong care.^{1–4} Pathogenic CAC gene variants lead to impaired AADC enzyme activity, resulting in deficient production of dopamine and other monoamine neurotransmitters.^{1–4} This can lead to a wide range of debilitating symptoms, including movement disorders, developmental delay, and autonomic dysfunction.^{1–4}

Eladocogene exuparvovec is a recombinant AAV1 that contains the human CAC gene and is designed to restore AADC production, regardless of the underlying pathogenic variant(s) in the native CAC gene (Figure 1).^{1–4}

Figure 1. Eladocogene exuparvovec gene construct.^{1–4}

Eladocogene exuparvovec gene therapy was granted marketing authorization in 2022 as the first disease-modifying treatment for AADC deficiency.^{1–4} It is indicated for the treatment of patients aged ≥ 18 months with AADC deficiency with a severe phenotype in the European Member States, Great Britain, Iceland, Israel, Luxembourg, Norway, Northern Ireland and Taiwan.^{1–4} Marketing authorization was granted based on the findings from three clinical trials (AAV2-010 (NCT02355441), AAV2-011 (NCT02355442), and AAV2-012 (NCT02355443)) and the long-term follow-up study (AAV2-013).^{1–4} However, the clinical use for the bilateral intracranial infusion of eladocogene exuparvovec in these studies is not suitable for commercial use in the USA. Therefore, this study is being conducted using the SmartFlow MR-compatible ventricular cannula, which has been approved for use in the EU and USA.^{1–4}

2 Objectives

To assess the pharmacodynamics of eladocogene exuparvovec gene therapy and the safety of intracranial administration using the SmartFlow MR-compatible ventricular cannula in paediatric patients with AADC deficiency.^{1–4}

3 Methods

Study 01-403 is an ongoing, phase 2, open-label, multicentre trial in paediatric patients aged ≥ 1 year (NCT04503288).

Participants received eladocogene exuparvovec at 1.8 × 10¹¹ vector genomes by bilateral infusion into the putamen via SmartFlow MR-compatible ventricular cannula in a single operative session.^{1–4}

The primary endpoints were:^{1–4}

- the pharmacodynamics of eladocogene exuparvovec 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 8 weeks after administration;
- Scan the UK code for the study design (Figure 1), eligibility criteria and secondary endpoints.

4 Results

Overall, 13 participants aged 10–128 months with AADC deficiency received eladocogene exuparvovec using the SmartFlow MR-compatible ventricular cannula (Table 1).

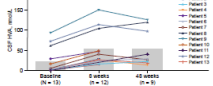
Table 1. Baseline demographics and clinical characteristics of the 13 participants.

Variable	All participants (n = 13)
Median age at gene therapy, months (range)	46.2 (28.6–128.6)
Median (mm, range)	33.0 (18.0–128.0)
Sex, n (%)	
Female	7 (53.8)
Male	6 (46.2)
Mean (SD) height, cm	92.4 (16.3)
Mean (SD) weight, kg	12.4 (4.2)
A low mean (SD) CSF HVA level of 22.5 (32.3) nmol was observed at baseline, consistent with a diagnosis of AADC deficiency. ^{1–4}	

4 Results (continued)

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 in participants who had achieved severe motor developmental delay at baseline (Figure 2).

Figure 2. CSF HVA levels for individual participants at baseline and 8 weeks and 48 weeks after gene therapy.



Mean (SD) CSF HVA levels were reported as < 2.0 nmol, and sustained from an < 2.0 nmol, CSF HVA level at baseline (SD: 32.3 nmol), 8 weeks (SD: 32.4 nmol), and 48 weeks (SD: 32.4 nmol), respectively. CSF HVA levels were significantly increased at 8 weeks (p = 0.0001, n = 13) and 48 weeks (p = 0.0001, n = 13) compared to baseline (p = 0.0001, n = 13).

A significant mean increase in bilateral putamen-specific uptake of ¹¹C-DOPA from baseline was observed at 8 weeks and 48 weeks after administration of eladocogene exuparvovec gene therapy (Figure 3).

Figure 3. De novo dopamine production in the putamen, visualized as increased ¹¹C-DOPA uptake from baseline on PET images, at 8 weeks and 48 weeks after gene therapy.

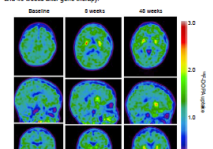


Figure 4. Acquisition of key motor milestones at baseline and 24 weeks and 48 weeks after gene therapy.

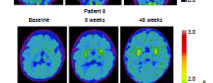


Figure 5. Motor common TEAEs (recorded in ≥ 50% of participants) at 48 weeks after gene therapy.

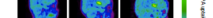


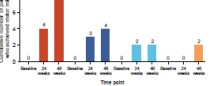
Figure 6. The median time to the first episode of dyskinesia was 27.5 days after gene therapy and the median duration of dyskinesia episodes was 104.5 days.

Of the 240 TEAEs reported, most were mild (n = 192/240) or moderate (n = 48/240). In severity, and determined to be unrelated or unlikely to be related to gene therapy (n = 170/240 and n = 42/240, respectively) or the neurosurgical procedure (n = 2/240 and n = 2/240, respectively).

4 Results (continued)

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

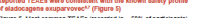
Figure 4. Acquisition of key motor milestones at baseline and 24 weeks and 48 weeks after gene therapy.



In total, 240 TEAEs were reported in 13 participants, of which 239 were deemed unrelated (n = 13) and one deemed unlikely to be related (n = 1) to the SmartFlow MR-compatible ventricular cannula.

Reported TEAEs were consistent with the known safety profile of eladocogene exuparvovec.^{1–4}

Figure 5. Motor common TEAEs (recorded in ≥ 50% of participants) at 48 weeks after gene therapy.



Dystonia is an expected TEAE owing to increased dopamine sensitivity in AADC-deficient patients.^{1–4}

The median time to the first episode of dyskinesia was 27.5 days after gene therapy and the median duration of dyskinesia episodes was 104.5 days.

Of the 240 TEAEs reported, most were mild (n = 192/240) or moderate (n = 48/240). In severity, and determined to be unrelated or unlikely to be related to gene therapy (n = 170/240 and n = 42/240, respectively) or the neurosurgical procedure (n = 2/240 and n = 2/240, respectively).

5 Conclusions

In paediatric patients with AADC deficiency, CSF HVA levels and ¹¹C-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 coincided with the acquisition of key motor milestones, consistent with results from previous clinical trials.^{1–4}

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 paediatric patients with AADC deficiency.

Abbreviations

AADC: aromatic L-amino acid decarboxylase; AAV2: adeno-associated virus 2; CSF: cerebrospinal fluid; HVA: homovanillic acid; MR: magnetic resonance; PET: positron emission tomography; TEAE: treatment-emergent adverse event; VTA: ventral tegmental area.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Correspondence

Paul Muth-Linnemann, Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan. Email: paul.muth-linnemann@ntu.edu.tw

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A full list of author affiliations appears at the end of the paper.

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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

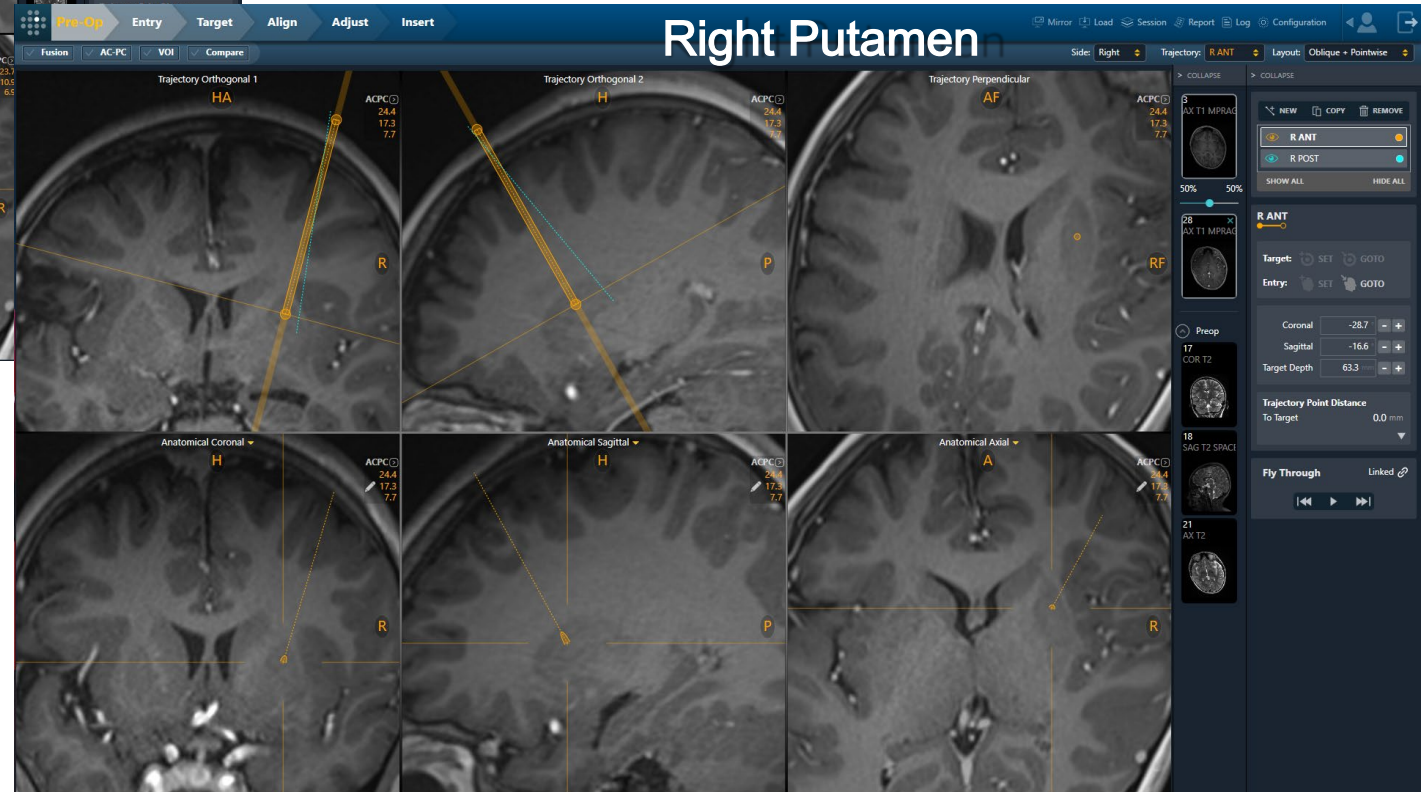
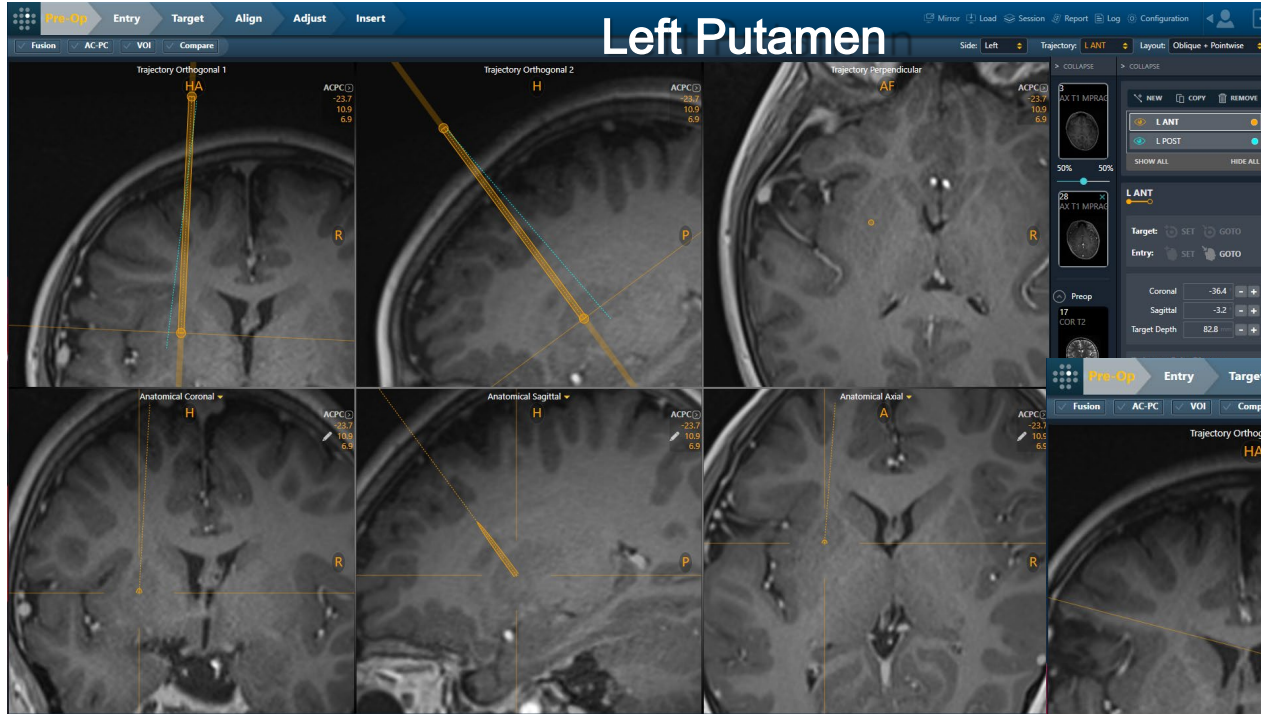


Compatible with IMRIS and other iMRI suites, which allow surgeons to conduct MR imaging while the patient is undergoing neurosurgery

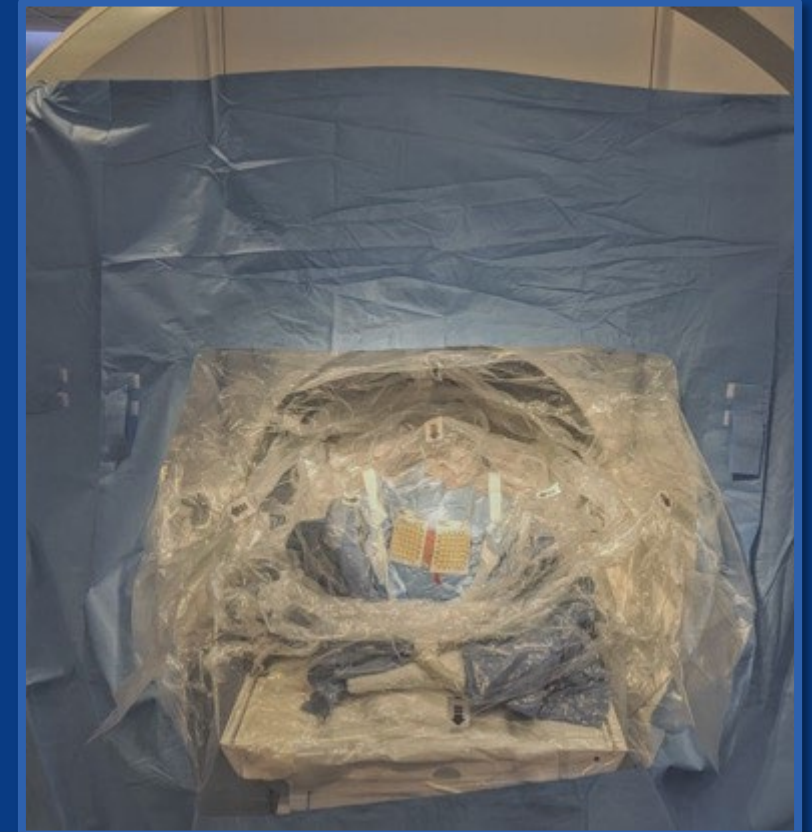
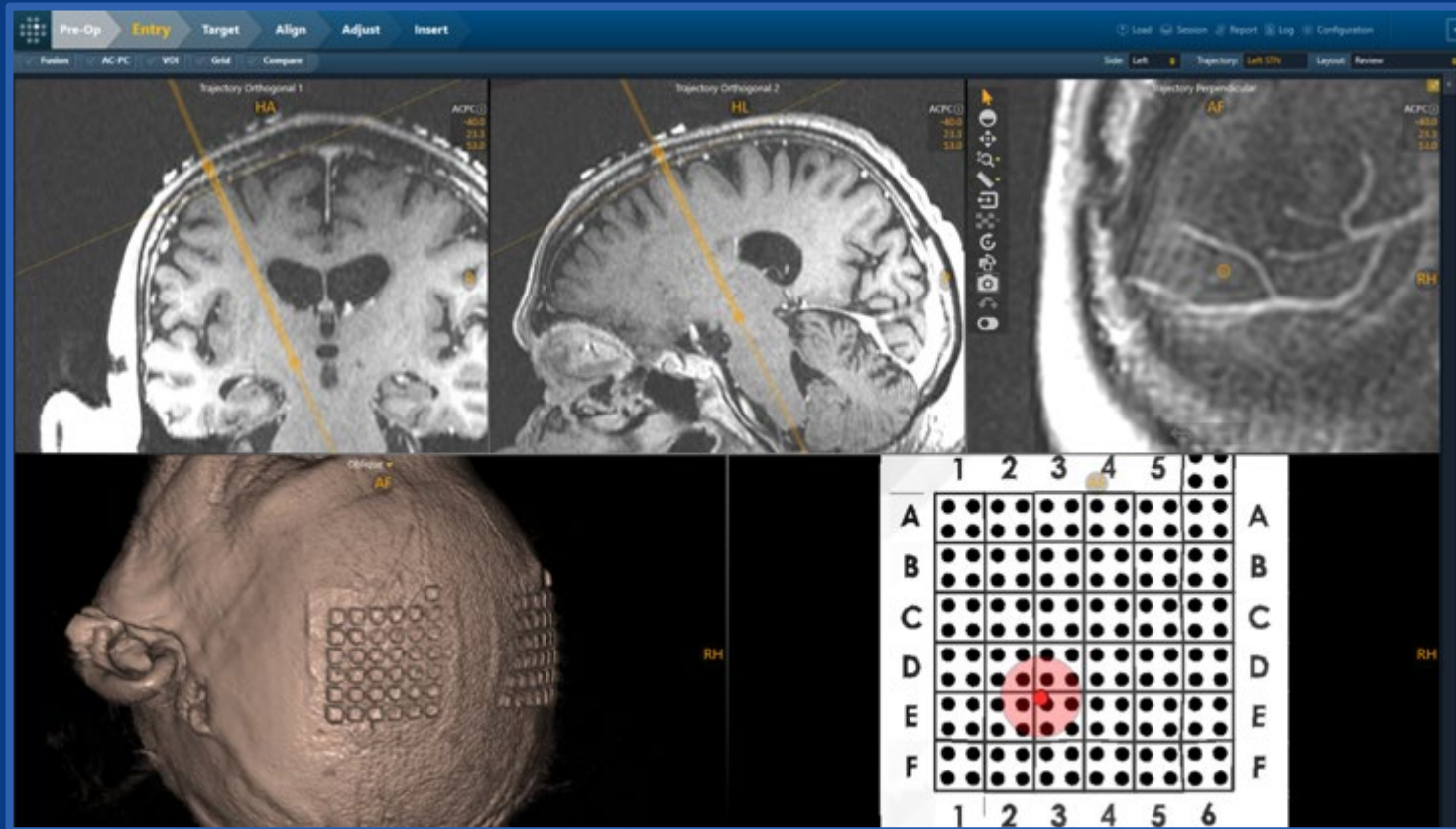
- ClearPoint® enables surgical procedures in **both** diagnostic-only and intraoperative scanners.
- MRI is the best for visualizing the brain structures *without radiation exposure to patient*.
- The ClearPoint® Navigation System + Smartflow® Neuro Cannula enables surgeons to image the device and the 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

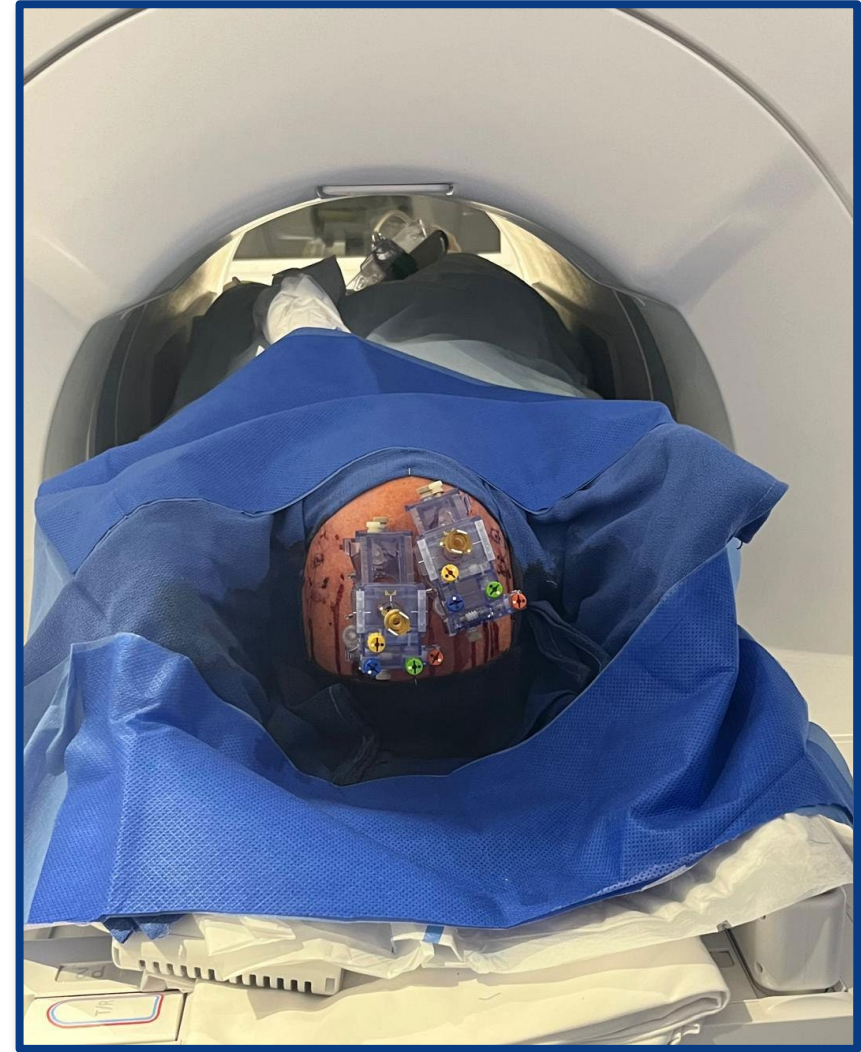
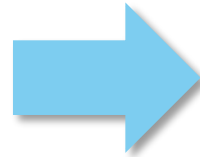
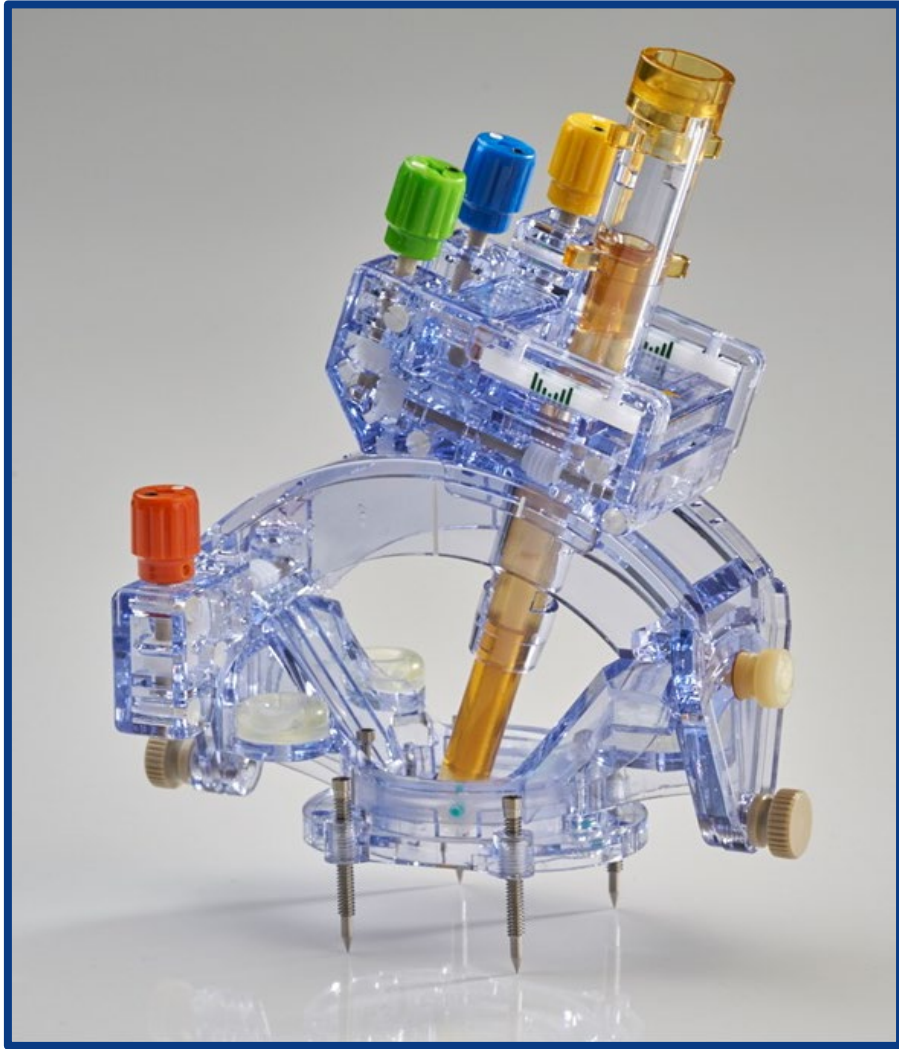
Treatment Trajectory to the Left and Right Putamen



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



SmartFrame® Base and Tower Assembly for Aiming to Target



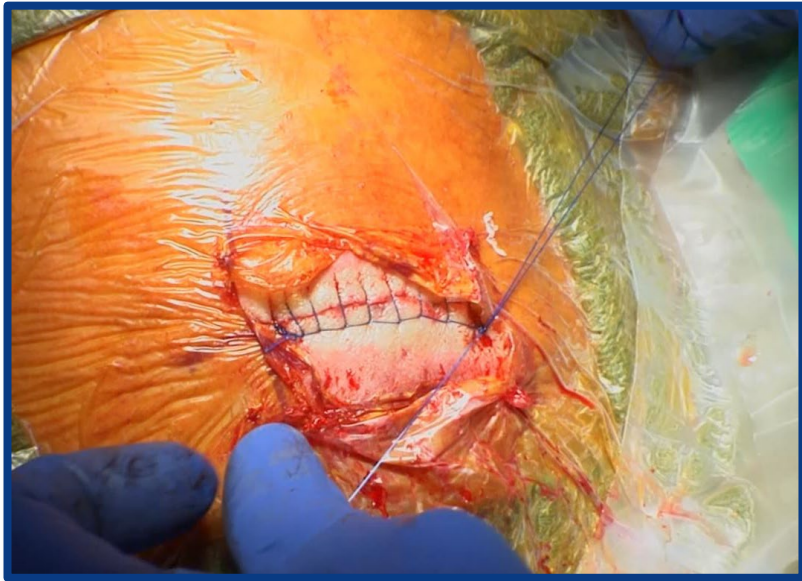
Confirmed Device Placement in Right Putamen



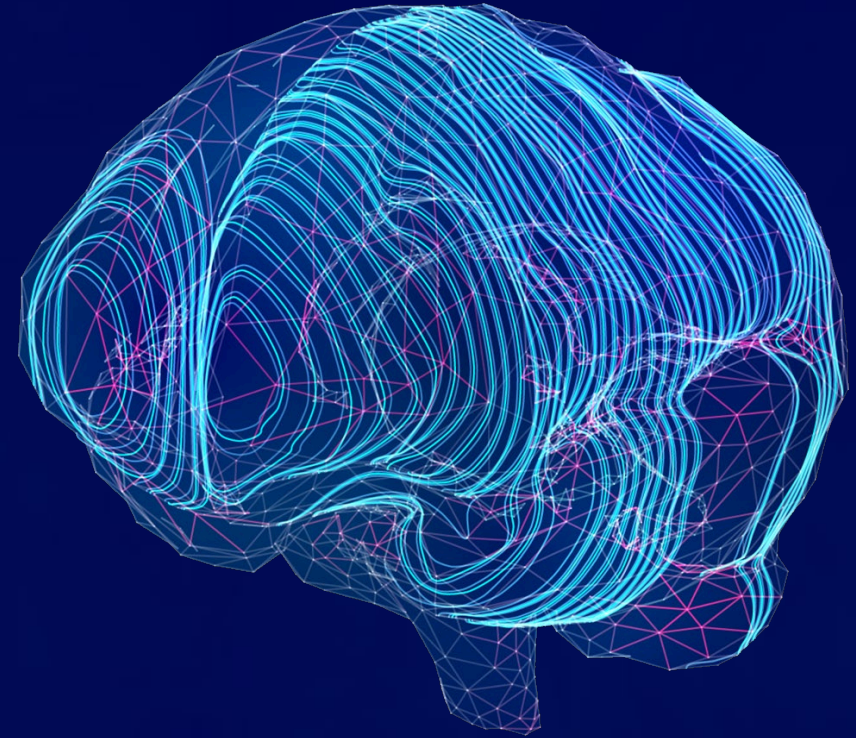
Minimally Invasive. Computer-Guided. Accurate.

Approximate Procedure Times

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



Thank You Questions?




CLEARPOINT®
NEURO