Clinical Trial Protocol

An Open Label, Multicenter, Retrospective, Pivotal Trial to Evaluate the Efficacy of Clinical Decision Support System-mPDia for Neurodegenerative Parkinsonism using MRI images

NCT04334902

Protocol Number	:	HR-MPD-01
Version (Date of Preparation)	:	3.4 (2020.10.06)

◈ Summary of Protocol

<table>
<tr><td>Title</td><td>An Open Label, Multicenter, Retrospective, Pivotal Trial to Evaluate the Efficacy of Clinical Decision Support System-mPDia for Neurodegenerative Parkinsonism using MRI images</td></tr>
<tr><td>Institution</td><td>10 hospitals consisting of Gachon University Gil hospital et. al (Gangnam Severance Hospital, Kyung Hee University Hospital, Korea University Guro Hospital, Korea University Ansan Hospital, Seoul St. Mary's Hospital, Seoul Asan Hospital, Hallym University Dongtan Sacred Heart Hospital, Hallym University Pyeongchon Sacred Heart Hospital, CHA Bundang Medical center)</td></tr>
<tr><td>Investigational Device</td><td>Product name: mPDia
Item Name: Clinical Decision Support System
Manufacturer: Heuron Co.,Ltd</td></tr>
<tr><td>Purpose</td><td>This trial is to check if the diagnosis results of mPDia would meet the success criteria, which is the lower limit of the 95% confidence interval satisfying 88.2% sensitivity and 70% specificity, while using final clinical diagnosis results of medical specialist groups as a golden standard. When the success criteria of mPDia, which is established based on prior reported sensitivity and specificity of neurodegenerative Parkinsonism diagnosis research, is satisfied, it is determined to have efficacy in assisting diagnosis of Parkinsonism.</td></tr>
<tr><td>Design</td><td>Open label, Multicenter, Retrospective, Pivotal clinical trial</td></tr>
<tr><td>Target case amount</td><td>Total of 221 cases

The sensitivity and specificity goal were set as 95% and 86%, respectively, and the lower limit of the 95% confidence interval, which is the success criteria of this study, was calculated as 88.2% and 70%, respectively. The necessary case (image) amount for calculation was 144 people and 56 people. Considering the 10% dropout rate, 159 people for the patient group and 62 people for the normal group, which is 221 people in total, was calculated.

<table>
<tr><td>Clinical performance target (P_1)</td><td>Least clinical performance (= lower limit of 95% confidence interval) (P_0)</td><td>N</td><td>+10% dropout rate</td><td>Total</td></tr>
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<tr><td>Sensitivity: 0.950</td><td>Sensitivity: 0.882</td><td>144</td><td>159</td><td rowspan="2">221</td></tr>
<tr><td>Specificity: 0.860</td><td>Specificity: 0.700</td><td>56</td><td>62</td></tr>
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<tr><td>Inclusion Criteria and Exclusion Criteria</td><td>
1. Inclusion Criteria
Normal group
1) Adult more than 19 years old
2) Person with confirmed 3T nigrosome 1 MRI image
3) Person with confirmed normal ^{18}F FP-CIT PET/CT image
4) Research participant who visited clinic with parkinsonian symptom as chief complaint that did not correspond to neurodegenerative parkinsonism or healthy participant.

Patient group
1) Adult more than 19 years old
2) Person with confirmed 3T nigrosome 1 MRI image
3) Person with confirmed abnormal ^{18}F FP-CIT PET/CT image
4) Person who visited clinic with parkinsonian symptom as chief complaint and was diagnosed as neurodegenerative parkinsonism (multiple system atrophy parkinsonian type, progressive supranuclear palsy).

2. Exclusion Criteria
1) Patient with encephalopathy besides parkinsonism.
2) Person with anatomic abnormality confirmed by MRI etc.
3) Person with other causative disease in advance. (ex: thyroid disease)
4) Patient with lesion in basal ganglia such as in Vascular Parkinsonism, Hydrocephalus, Wilson’s disease.
5) Other cases that the researcher determines to be unsuitable for this clinical trial.
* Specific reason will be documented in the case report form
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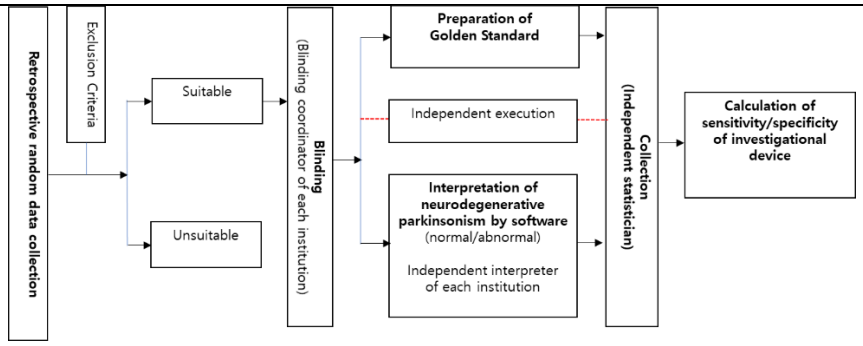
Data collecting method	The following data will be collected retrospectively from person whose past 3T nigrosome 1 MRI image, ^{18}F FP-CIT PET/CT image, image interpretation, and neurologic exam results are confirmed by medical records, and those whose diagnosis as neurodegenerative parkinsonism is confirmed. Data collecting must be executed following the protocol 10.2 random collection. Only the verified researcher who is registered in this study will have access to medical records. Data collected for this study will be as follows: - Demographic information - Environmental factor and medical history/past history - Family history - MDS-UPDRS assessment results - Check Red Flag signs suggestive of PD plus syndrome - Non-motor symptom assessment scale results of Parkinson's disease - REM sleep behavior disorder screening results - Check of any pain - Cognitive function test (K-MMSE, K-MoCA) results - S&E ADL test results - Hoehn & Yahr stage test results - ^{18}F FP-CIT PET/CT image and interpretation results - Results of neurologic exam and decision of neurodegenerative parkinsonism - Confirmed 3T nigrosome 1 MRI image Data used in this study have been collected by the 10 participating institutions from May 1st, 2018 to the starting period of the clinical trial. Data used for the education of the investigational device were collected from November 1st, 2014 to April 30th, 2018 by one institution (Gachon University Gil Hospital), making it mutually independent.

Study Method	 **1. Image blinding** The blinding coordinator will select 3T nigrosome 1 MRI image from data collected by the 10.1 data collection method and blind all non-image information such as the belonging group or demographic information. **2. Interpretation using mPDia** The blinded image will be delivered to an independent interpreter and the interpreter will sequentially upload the image on mPDia according to the image number, check the result, and save it. The saved results will be printed to be used as source document. The results should be blinded, so the saved and printed results should have separate passwords or be in a locked space so that researchers other than the independent interpreter have no access. The independent interpreter should be a neurologist or radiologist of each site who is not participating in this study and should be educated of mPDia usage for this study. Interpretation using mPDia should be performed independently from golden standard creation, and an independent statistician of the sponsor collects the mPDia interpretation data. **3. Golden Standard** Professor Sung Yunghee, a neurologist of Gachon University Gil Hospital, Kim Eung Yup, a radiologist of Gachon University Gil Hospital, will check the collected medical records, provide final diagnosis to the registered candidate based on protocol 10.5.1 neurodegenerative parkinsonism diagnosis checklist and check on the following

	neurodegenerative parkinsonism classification chart. Cases corresponding to Parkinson's disease or atypical Parkinsonian syndromes are defined as neurodegenerative parkinsonism diagnosis. Besides such cases, it is defined not to be neurodegenerative parkinsonism. Only when corresponding to neurodegenerative parkinsonism can the positive response of mPDia regarding neurodegenerative parkinsonism be confirmed. The following diagnosis results will be used as a golden standard in this study. 1) Positive in neurodegenerative parkinsonism 2) Negative in neurodegenerative parkinsonism When opinions of two specialists are different, the two will discuss to reach a consensus and record it on the final diagnosis result. All discussed contents will be documented on the Note to file. Golden standard creation must be performed independently from mPDia interpretation, and the golden standard data will be collected by an independent statistician of the sponsor. **4. Independent statistician** The independent statistician of this study will be Doctor Lee Donghyuk of Heuron Co.,Inc. Without participating in this study, the independent statistician will collect mPDia interpretation results and golden standard and save them in a separate hardware which only the independent statistician can have access to. The independent statistician cannot open the interpretation results or golden standard before statistical analysis is finished.
Study Period	12 months from IRB approval date
Endpoint	**1. Efficacy endpoint** Sensitivity and specificity of mPDia for diagnosis of neurodegenerative parkinsonism using final diagnosis results of the specialist group as a golden standard **2. Efficacy endpoint assessment method**

With the following calculation methods, sensitivity and specificity are calculated, and the 95% confidence interval is provided and evaluated to assess whether the lower limit of the 95% confidence interval reaches 88.2% sensitivity and 70% specificity, which is the success criteria of mPDia, in comparison to the golden standard, which is the final clinical diagnosis result of the specialist group for diagnosis of neurodegenerative parkinsonism.

< Sensitivity and specificity calculation method >

Results		Golden standard		
		Positive	Negative	Total
Investigational Device (mPDia)	Positive	True positive (TP)	False positive (FP)	True positive + False positive
	Negative	False negative (FN)	True negative (FN)	False negative + True negative
	Total	True positive + False negative	False positive + True negative	N

- Sensitivity: 100 x True positive (TP)/[True positive (TP) + False negative (FN)] (%)
- Specificity: 100 x True negative (TN)/[False positive (FP) + True negative (TN)] (%)