CTX

Delivery new medicine to the patient faster

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Japan Clinical Trial Transformation Research Society

- For Delivering New Medicines To Patients Faster -

Introduction of Examples of Initiatives for Enhancing the Potential for Case Accumulation

Mitsubishi Research Institute

Introduction of examples

- 01. Use and application of RWD and a registry
- 02. Utilization of a clinical trial network (NW)

Registry-linked medical institution selection | Takeda Pharmaceutical Co Ltd × CIRCLe(1/2)

Achieve the target number of cases quickly by implementing a feasibility survey (questionnaire survey) of the institutions participating in the registry (consent from 15 patients in four months)

Registry name, etc.	CIRCLe*1 (Comprehensive and Informative Registry system for Childhood Liver Disease) • Established in 2020 • 105 institutions in 40 prefectures are participating(2025/8/29) - Gathers clinical information and biological samples - Provides specialized tests for diagnose - Selected to be an implementing institution C under the FY2023 Real-World Data Utilization Promotion Project of the MHLW and PMDA
Representative	Hisamitsu Hayashi, Laboratory of Molecular Pharmacokinetics , Graduate School of Pharmaceutical Sciences , The University of Tokyo
Target diseases	• Patients who have/had cholestasis or liver disorder in childhood (up to 18 years old) • Patients who were diagnosed with “cholestasis or liver disorder” when 18 years old or older, in the case that there is a suspected relationship to a hereditary liver disease of childhood • Childhood liver disease of unknown cause

- **Takeda Pharmaceutical Co Ltd acquired manufacturing and marketing approval on Mar 27, 2025 based on the results of the TAK-625 clinical trials*2**
  - Livmarli® Oral Solution 10mg/mL (generic name: Maralixibat Chloride)
  - Indications: pruritus associated with cholestasis in the following diseases
    - Alagille Syndrome (ALGS)
    - Progressive Familial Intrahepatic Cholestasis (PFIC)
- **It was announced in the March 2025 meeting of the Japan Society of Clinical Trials and Research that Takeda Pharmaceutical Company Limited had succeeded in streamlining clinical trials in collaboration with a disease registry**
  - P-19 “Clinical Trial Center Selection and Short-Term Case Registration for Maralixibat Chloride in Collaboration with the Disease Registry CIRCLe” Presenter: Junichi Tanogashira of Takeda Pharmaceutical Co Ltd

Existing registry utilization of the purpose of extracting medical institutions with patients

Registry-linked medical institution selection | Takeda Pharmaceutical Co Ltd × CIRCLe(2/2)

After selecting the institutions based on a feasibility study, patient consent is obtained*3

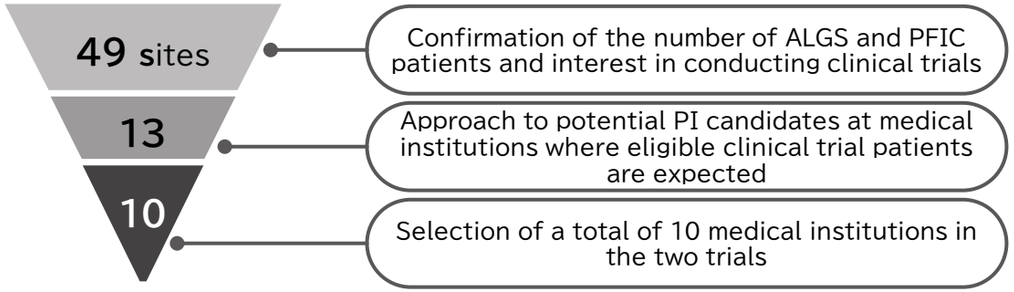
① Alagille Syndrome (ALGS)

- Intrahepatic cholestasis taking the autosomal dominant inheritance form with JAG1 or NOTCH2 as the responsible gene
- Incidence: overseas, one person in every 30,000 to 70,000 births
- About 200-300 patients in a nationwide survey of Japan
- Included within specific pediatric chronic diseases (new registrations are about ten cases per year)
- Certified a designated intractable disease in Jul. 2015

② Progressive Familial Intrahepatic Cholestasis (PIFC)

- A disease taking the autosomal recessive inheritance form
- Incidence: overseas, one person in every 50,000 to 100,000 births
- A disease included within specific pediatric chronic diseases (2 to 8 new cases are registered per year)
- Certified a designated intractable disease in Oct. 2021

- **Purpose of collaboration: rapid clinical trial execution and case registration**
- **Clinical trials**
  - For ALGS: TAK-625-3001 trial
  - For PIFC: TAK-625-3002 trial
- **Feasibility survey (questionnaire survey) for selecting the medical institutions**
  - Regarding the data held by CIRCLe, there was a limit to ascertaining the number of patients in the medical institutions participating in CIRCLe overall, so a feasibility survey was conducted



- **15 patients consented to participation in the clinical trial over four months**
  → administered to 12 patients

New construction construction of a new registry aiming for patient recruitment

Recruitment of patients with rare diseases | Multiple System Atrophy Registry(1/2)

In six months, recruit approximately 150 patients with diseases which only affect about 10,000 people in Japan, by building a registry which also includes genetic information

Registry name, etc.	**Multiple System Atrophy Registry** • Construction of the registry using Japan Agency for AMED research funding • Joint research with 13 medical institutions in Japan • “Streamlining clinical trial recruitment” is included in the purpose of construction - In particular, streamlining of recruitment for comparing the carriers and non-carriers of genetic mutations is necessary - Includes genetic information and information about severity gained from regular follow-ups - Implement genetic tests using the research funding
Representative	Shoji Tsuji , Hospital Physician, Department of Neurology , The University of Tokyo Hospital (Contact person: Jun Mitsui , The University of Tokyo)
Target diseases	Multiple System Atrophy (MSA) • A progressive neurodegenerative disease • Only symptomatic treatment is available; no definitive treatment has been established • As of the end of FY2019, the number of patients is about 11,387 nationwide, so it has been certified as a designated intractable disease[*4]

Achievements in investigator-initiated clinical trials

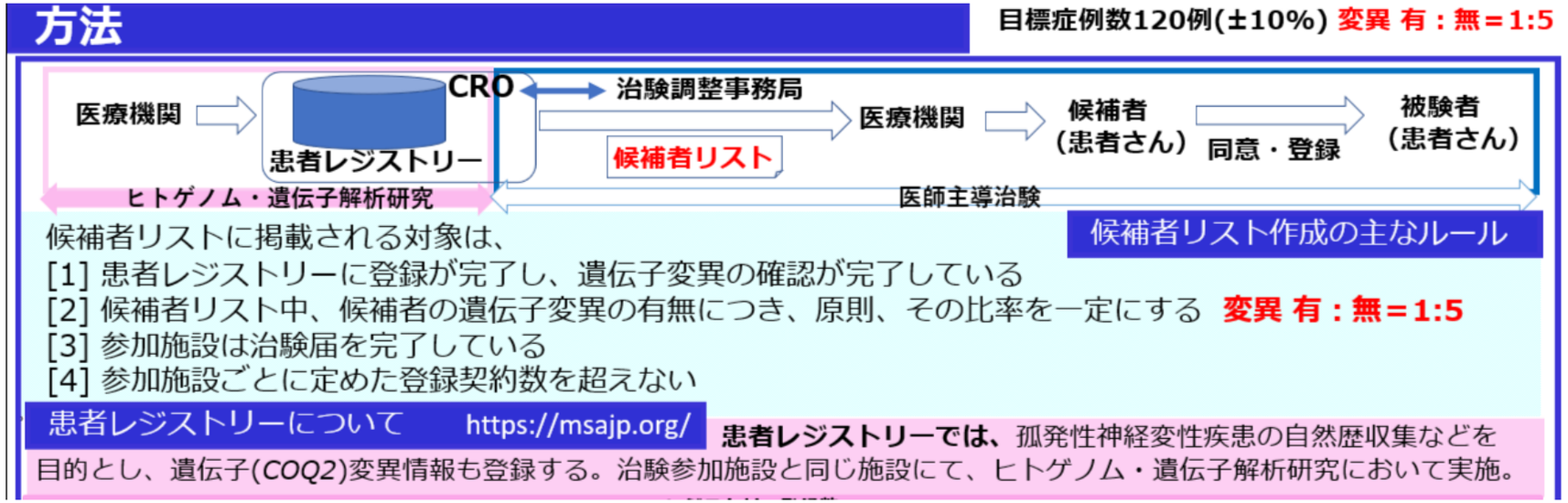
- **Presented the potential for a medical treatment to slow progression in an investigator-initiated P2 trial**[*5]
  - Obtained results in a multicenter, randomized, double-blind, placebo-controlled trial supporting the effectiveness of ubiquinol (reduced coenzyme Q10)
  - Designated as eligible for support as an orphan drug in Jun. 2024
- **Recruited approximately 150 patients in six months**
  - Moreover, succeeded in securing the target number of cases for gene mutation carriers, who account for only about 8% of all patients

New construction construction of a new registry aiming for patient recruitment

Recruitment of patients with rare diseases | Multiple System Atrophy Registry(2/2)

Candidate patients are extracted from the registry information and put into a list, and the individual medical institutions obtain their consent based on the list

- **Recruitment flow**[*6]
  - Patient data from 13 medical institutions is registered in the registry (including the results of genetic tests)
  - CROs select patients from the registry who are candidates for clinical trial participation
  - The candidate list is shared with the cooperating medical institutions
  - Clinical trial information is shared with the patients through the doctors at the cooperating medical institutions and the consent of the patients is obtained



Empirical study using an app for communication among medical professionals | National Cancer Center Hospital Japan (NCCJ)

Hospital visits for eligibility confirmation are reduced in order to streamline clinical trial recruitment from a patient perspective*7

- 90% of patients referred from other hospitals do not satisfy the eligibility criteria and cannot participate in the trial even if they visit the hospital
  - Many reasons can be determined before visiting the hospital
- Transmit patient information to the NCC via an app for online communication among medical professionals
- The NCC reviews the information and responds on the app regarding the possibility of participating in clinical trials in the hospital and the applicable clinical trials

Dr. Map/Disease Map | CMA-Okayama clinical trial and clinical research network

Publish a Dr Map/Disease Map on the council's website to streamline information gathering by clinical trial sponsors*8

Dr. Map

- The clinical trial achievements of medical institutions participating in the CMA are published in a list
- It is possible to view the achievements for each disease using the small classifications in the ICD-10

疾患	ICD-10	医療機関	診療科	治験責任医師数	実施中 2022年4月以降も継続している試験		終了/中止 2022年3月末時点で終了または中止した試験		
					試験数	目標症例数（合計）	試験数	目標症例数（合計）	実施症例数（合計）
感染症									
肺炎球菌感染症	A491	福山市民病院	小児科	1	—	—	1	29	26
帯状疱疹	B029	姫路赤十字病院	麻酔科	1	1	3	—	—	—
B型肝炎ウイルス感染	B169	福山市民病院	内科	1	—	—	1	3	1
サイトメガロウイルス感染症	B258	岡山大学病院	血液・腫瘍内科	1	1	3	—	—	—
			肝・胆・膵外科	1	1	1	—	—	—
			泌尿器科	1	1	2	—	—	—
RSウイルス感染症	B348	岡山医療センター	新生児科	1	1	10	—	—	—
		岡山市立市民病院	小児科	1	1	10	—	—	—
			救急センター	1	—	—	1	1	0
		福山医療センター	小児科	1	—	—	1	1	0
		福山市民病院	小児科	1	—	—	3	15	10
新生物＜腫瘍＞									
食道癌	C159	岡山大学病院	消化器内科	3	2	7	1	4	0
胃癌	C169	岡山大学病院	消化管外科	1	2	6	1	1	2
		福山市民病院	外科	1	—	—	1	4	4
結腸癌/大腸癌/直腸癌	C189	岡山大学病院	消化管外科	1	—	—	1	2	0
		福山市民病院	外科	1	—	—	1	2	0
肝癌	C220	岡山大学病院	消化器内科	1	2	5	2	4	0

Disease Map

- The number of patients for each disease in the medical institutions participating in the CMA are published in a list
- Patient numbers by disease (ICD-10 subcategories) and by medical institution are also viewable.

ICD-10 中分類 疾患分類名をクリックすると医療機関ごとでの患者数の表が展開します		ネットワーク10病院合計		
		外来 小計	入院 小計	総計
感染症				
クロストリジウム・ディフィシル腸炎	A047	144	22	166
インフルエンザ菌感染症	A492	5	2	7
帯状疱疹	B020-023/B027-029	6,117	235	6,352
B型肝炎	B162/B169/B181	9,672	442	10,114
C型肝炎	B171/B182	5,146	385	5,531
サイトメガロウイルス感染症	B250-251/B258-259/B271	1,373	40	1,413
RSウイルス感染症	B348	285	141	426
新生物＜腫瘍＞				
食道癌	C150-155/C158-159	3,496	503	3,999
胃癌	C160-166/C169	13,923	1,248	15,171
結腸癌/大腸癌/直腸癌	C182-187/C189/C19/C20	13,750	1,719	15,469
肝癌	C220-224/C227/C229	5,294	850	6,144
胆道癌	C23/C240-241/C248-249	1,650	319	1,969
膵癌	C250-254/C257-259	4,579	731	5,310

Sources

1. CIRCLe website https://www.circle-registry.org/ (View date: July 7, 2025)
2. Takeda Pharmaceutical Company Limited press release of March 27, 2025: “Takeda Announces Approval of “LIVMARLI® Oral Solution 10 mg/mL” for the Treatment of Pruritus Associated with Cholestasis in Alagille Syndrome and Progressive Familial Intrahepatic Cholestasis in Japan ” https://www.takeda.com/jp/newsroom/local-newsreleases/2025/takeda-announces-approval-of-livmarli-oral-solution/ (View date: July 8, 2025)
3. Japan Society of Clinical Trials and Research, 16th Annual Meeting Poster Presentation by Junichi Tanokashira of Takeda Pharmaceutical Company Limited, P-19 “Clinical Trial Center Selection and Short-Term Case Registration for Maralixibat Chloride in Collaboration with the Disease Registry CIRCLe”
4. Japan Intractable Diseases Information Center , Multiple System Atrophy (1) Striatonigral Degeneration (Designated Intractable Disease 17) (View date: 2025/07/31)
5. The University of Tokyo press release: “Development of the world’s first treatment for Multiple System Atrophy, an intractable neurological disease,” 2023/04/14 (View date: 2025/07/31)
6. Excerpted from the materials provided by the registry operator
7. National Cancer Center press release of March 3, 2025: “Commencement of a “clinical trial DX” empirical study applying an app for communication among medical professionals” (View date: March 10, 2025)
8. Council for Medical Alliance, Okayama website https://www.cma-o.jp/research/client/doctor/ https://www.cma-o.jp/research/client/disease/ (View date: July 31, 2025)

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