Lysosomal Storage Diseases (LSD)

October 4, 2022

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# AGENDA

## Today’s Topics

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<th>Topic</th>
<th>Speaker</th>
<th>Title</th>
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<td>1. Overview of Lysosomal Storage Diseases (LSD)</td>
<td>Gen Suzuki MD, PhD, FAHA</td>
<td>Medical Expert of Rare Disease, Japan Medical Office</td>
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<td>2. Gaucher Disease</td>
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<td>5. Q&amp;A Session</td>
<td>Q&amp;A Panelists</td>
<td></td>
</tr>
</tbody>
</table>
Overview of Lysosomal Storage Diseases
What is the lysosome?

The lysosome was discovered by Christian de Duve in Belgium in 1955.

- The lysosome is a 0.1 ~ 1.2 μm membrane-bound cell organelle.
- There are about 25 types of lysosomal membrane proteins.
- The lysosome uses endocytosis, autophagy, salvage, and nutrient sensing to control cellular metabolism and homeostasis.

In LSDs, the accumulation of undegraded substrates triggers pathogenetic cascades and induces clinical manifestations.

- Lysosomal diseases are a group of diseases caused by the congenital deficiency of hydrolytic enzymes, in which lysosomes accumulate intermediate metabolites (substrates) that should otherwise be metabolized.
Recognition of Lysosomal Storage Diseases (LSDs)

LSDs were identified more than 130 years ago
First in human Enzyme Replacement Therapy (ERT) treatment started more than 30 years ago

<table>
<thead>
<tr>
<th>Year</th>
<th>Reported by</th>
<th>Event</th>
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<tbody>
<tr>
<td>1882</td>
<td>Gaucher</td>
<td>First description of Gaucher Disease patient</td>
</tr>
<tr>
<td>1899</td>
<td>Anderson &amp; Fabry</td>
<td>First description of Fabry Disease patient</td>
</tr>
<tr>
<td>1917</td>
<td>Hunter</td>
<td>First description of Hunter Syndrome (Mucopolysaccharidosis II) patient</td>
</tr>
<tr>
<td>1955</td>
<td>de Duve</td>
<td>First description of the lysosome</td>
</tr>
<tr>
<td>1964</td>
<td>de Duve</td>
<td>Enzyme replacement therapy (ERT) proposed for LSDs</td>
</tr>
<tr>
<td>1965</td>
<td>Brady</td>
<td>Demonstration of the enzymatic defect in Gaucher Disease</td>
</tr>
<tr>
<td>1966</td>
<td>Brady</td>
<td>ERT proposed for the treatment of Gaucher Disease</td>
</tr>
<tr>
<td>1967</td>
<td>Brady</td>
<td>Demonstration of the enzymatic defect in Fabry Disease</td>
</tr>
<tr>
<td>1972</td>
<td>Johnson &amp; Brady</td>
<td>Purification of α-galactosidase A from human placenta</td>
</tr>
<tr>
<td>1973</td>
<td>Pentchev</td>
<td>Purification of glucocerebrosidase from human placenta</td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td>FDA approved to use ERT (placental derived Alglucerase) in Gaucher Disease type 1</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td>ERT for Fabry Disease (Agalsidase alfa and Agalsidase beta)</td>
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<tr>
<td>2010</td>
<td></td>
<td>FDA approved to use velaglucerase alfa in Gaucher Disease</td>
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</table>
Lysosomal Storage Diseases (LSDs) are inherited genetic diseases

Most LSDs are inherited in an autosomal recessive pattern, but there are also X-linked LSDs\(^1\)

There are over 50 different LSDs\(^2\). LSDs can be mapped to genetic variants, but correlations between genotype and phenotype are often difficult to establish due to the large number of variants. In some diseases, individuals with the same variant can have different clinical courses\(^3\).

**Autosomal recessive inheritance pattern**

- Majority of LSDs\(^4\)

- Parent A carrier
- Parent B carrier
- Child A unaffected
- Child B carrier
- Child C carrier
- Child D affected

**X-linked inheritance pattern**

- Fabry disease, Hunter syndrome, Danon disease\(^4\)

- Father unaffected
- Mother carrier
- Son A unaffected
- Daughter A carrier
- Son B affected
- Daughter B carrier

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## The List of Lysosomal Storage Diseases (LSDs)

31 LSDs are listed as designated intractable diseases in Japan. Takeda products contribute to three diseases enlisted here:

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher disease</td>
<td>Sialidosis</td>
</tr>
<tr>
<td>Niemann-Pick disease types A and B</td>
<td>Galactosialidosis</td>
</tr>
<tr>
<td>Niemann-Pick disease type C</td>
<td>Mucolipidosis type II and III</td>
</tr>
<tr>
<td>GM1 gangliosidosis</td>
<td>α-Mannosidosis</td>
</tr>
<tr>
<td>GM2 gangliosidosis</td>
<td>β-mannosidosis</td>
</tr>
<tr>
<td>Tay-Sachs disease, Sandhoff disease, type AB</td>
<td>Fucosidosis</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>Metachromatic leukodystrophy</td>
</tr>
<tr>
<td>Multiple sulfatase deficiency</td>
<td>Aspartylglucosaminuria</td>
</tr>
<tr>
<td>Farber's disease</td>
<td>Schindler disease/Kanzaki disease</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type I (Hurler/Scheie syndrome)</td>
<td>Acid lipase deficiency</td>
</tr>
<tr>
<td><strong>Mucopolysaccharidosis type II (Hunter syndrome)</strong></td>
<td>Danon disease</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type III (Sanfilippo syndrome)</td>
<td>Free sialic acid storage disease</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type IV (Morquio syndrome)</td>
<td>Ceroid lipofuscinosis</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)</td>
<td><strong>Fabry disease</strong></td>
</tr>
<tr>
<td>Mucopolysaccharidosis type VII (Sly disease)</td>
<td>Cystinosis</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type IX (hyaluronidase deficiency)</td>
<td></td>
</tr>
</tbody>
</table>
Intractable diseases are 1) diseases for which the mechanism of onset is not clear; 2) no treatment has been established; 3) rare diseases requiring long-term treatment expenses.

Specified pediatric chronic diseases meet the following requirements, and are applicable to children, etc. with the severity of diseases specified by the Minister of Health, Labour and Welfare. 1) A disease that chronically progresses, 2) is life-threatening for a long period of time, 3) is a disease for which symptoms or treatment deteriorate the quality of life for a long period of time, 4) is a disease for which the burden of medical expenses remains high for a long period of time.

Lysosomal Storage Diseases (LSDs) are supported by Japanese Goverment

Source: http://www.nanbyou.or.jp/
https://www.shouman.jp/
There are multiple treatment approaches for Lysosomal Storage Diseases (LSDs) that are approved or under investigation.

Treatments for LSDs are intended to correct enzyme activity reducing substrates and improving pathology. There are multiple approaches to achieving this goal.

Therapeutic options are disease-specific but may include one or more of the following:\(^1\):

1. **Enzyme-replacement therapy (ERT)**
   Direct administration of the deficient enzyme that can locate to the lysosome and degrade the substrate\(^1\).

2. **Hematopoietic stem cell transplantation (HSCT)**
   Implantation of hematopoietic stems cells from a donor that produce the deficient enzyme\(^1\).

3. **Substrate reduction therapy (SRT)**
   Therapeutic agent acting upstream that prevents substrate synthesis\(^1\).

4. **Chaperone therapy**
   Therapeutic agent that binds to degradative enzymes to support folding and increase stability\(^1\).

5. **Gene therapy**
   Introduction of a functional copy of the gene that enables endogenous production of the therapeutic protein\(^1\).

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LSDs are inherited metabolic disorders caused by deficient lysosomal enzymes characterized by the accumulation of substrates, which triggers diverse clinical manifestations. Gaucher disease, Fabry disease, and Hunter Syndrome are forms of lysosomal storage disease, and 31 LSDs are designated intractable diseases in Japan. LSDs were identified more than 130 years ago, and first-in-human ERT treatment started more than 30 years ago. Treatments for LSDs are intended to correct enzyme activity reducing substrates and improving pathology. There are multiple approaches to achieving this goal.

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5. Q&A Session
   - Q&A Panelists
What is Gaucher disease?

Gaucher disease is a rare inherited metabolic disorder

- Abnormally accumulated glycolipids: Inherited metabolic disorder caused by Glucocerebrosidase (GCase) Deficiency
  - First reported by Philippe Gaucher in 1882

- Inheritance Pattern
  - Autosomal recessive inheritance (GBA1 mutation on chromosome 1q21)

- Prevalence
  - Japanese: 1/330,000\(^1\); approximately 150 patients are diagnosed
  - Ashkenazi Jews: 1/800\(^2,3\)
  - 1/40,000 to 1/60,000 general population\(^2,3\)

A 4-year-old girl with type 1 Gaucher disease, showing marked distension of the abdomen due to hepatomegaly\(^4\)

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What is Autosomal recessive inheritance?

Mutations in both glucocerebrosidase genes cause symptoms of Gaucher disease
People with just one abnormal gene (carriers) usually show no symptoms

- Mother: One glucocerebrosidase gene altered

Carrier ➔ Child 25%

Healthy ➔ Carrier ➔ Child 25%

Carrier ➔ Child 25%

Gaucher disease ➔ Child 25%

Gaucher Terrace
https://www.gaucherterrace.jp/index.php/01_02/
Gaucher Disease Mechanism

Glucocerebrosidase GBA1 gene mutation

Glucocerebrosidase (GCase) activity decreased

Glucocerebroside (Gb1)
Accumulation in reticuloendothelial lysosomes
(Monocytes, macrophages)

Glucosylsphingosine (Lyso-Gb1)
Accumulation in the brain

deacylation

Hepatosplenomegaly

Accumulation in bone marrow

Angiotensin-converting enzyme,
Acid phosphatase level increased

Hypersplenism

Gaucher cell

Bone pain, pathologic fracture

Type I (non-neurologic)

Type II (acute) & III (subacute)

Anaemia, Thrombocytopenia

Central nervous system symptoms

MHLW website for Overcoming Intractable Diseases (http://www.japan-lsd-mhlw.jp/lsd_doctors_gaucher.html)
Primary Clinical Manifestations of Gaucher Disease

Dysfunction of glucocerebrosidase in Liver, Spleen, Bone and Neurons makes organs to become large and not to work correctly

**Neurologic symptoms**
- Wheezing
- Horizontal eye movement disorder
- Psychomotor development delayed
- Convulsion
- Myoclonus
- Hypertonia
- Opisthotonus
- Trismus
- Dysphagia
- Parkinsonian symptoms
- Epilepsy
  etc.

**Hematologic Abnormalities**
- Clotting abnormalities
- Anaemia
  etc.

**Liver**
- Hepatomegaly

Hepatomegaly: into reticuloendothelial cells (Kupffer cells, Ito cells)
Enlargement due to accumulation of glucocerebrosides

**Spleen**
- Splenomegaly

Splenomegaly: increased destruction of red blood cells, platelets – anemia, thrombocytopenia

**Bone symptoms**
- Bone density decreased
- Bone pain
- Bone deformity
- Necrosis of femoral head
- Distal femur deformity (Erlenmeyer flask deformation)
- Bone marrow infiltration
- Bone marrow infarction
- Bone crisis
  etc.

Bone symptoms in Gaucher disease

Tubularization of the distal metaphysis of the femur is impaired
Thinning of the bone cortex occurs, resulting in a flask-like appearance in the metaphyseal region
It causes a spreading Erlenmeyer flask deformity.

Written by the Editorial Board of the Handbook of Diagnosis and Treatment of Gaucher’s Disease.; Handbook of Diagnosis and Treatment of Gaucher Disease, 2nd ed. 2016, p. 9.
Tetsushi Abe, Orthopedic Therapies, Gaucher Disease UpDate, 1202016 Shindan To Chiryo Sha
Written by the Editorial Board of the Handbook of Diagnosis and Treatment of Gaucher’s Disease.; Handbook of Diagnosis and Treatment of Gaucher Disease, 2nd ed. 2016, p. 4 (modified)
Clinical Manifestation of Gaucher Disease

Gaucher disease is primarily classified by the absence (type 1) or presence and extent (type 2 or type 3) of neurological complications at diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>Type I (non-neurogenic)</th>
<th>Type II (acute neurologic)</th>
<th>Type III (subacute neural type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>Infants to adults</td>
<td>Neonatal/Infant</td>
<td>Infant to school child</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>(-)</td>
<td>(+++)</td>
<td>(+)(++)</td>
</tr>
<tr>
<td>(Convulsion, strabismus, abnormal eye movement, developmental delay, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>(-)(+++)</td>
<td>(+)</td>
<td>(+)(+++)</td>
</tr>
<tr>
<td>(Enlargement of the liver and spleen, calcification, anemia, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone symptoms</td>
<td>(-)(+++)</td>
<td>(-)</td>
<td>(-)(+++</td>
</tr>
<tr>
<td>(Bone pain, fracture, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Better</td>
<td>Poor</td>
<td>Vary by case</td>
</tr>
</tbody>
</table>

Gaucher disease is primarily classified by the absence (type 1) or presence and extent (type 2 or type 3) of neurological complications at diagnosis.
Distribution of Gaucher disease types: Japan vs. World-wide

In Japan Gaucher disease type is equally distributed. In contrast, globally, Type I is the majority of population.

Japanese (n=129)
- Type I: n=54 (41.8%)
- Type II: n=31 (24.0%)
- Type III: n=44 (34.1%)
  - III → III: n=28 (21.7%)
  - I → III: n=16 (12.4%)

Global: Gaucher Registry 2010 (n=5,458)
- Type I: n=5,005 (92%)
- Type II: n=62 (1%)
- Type III: n=391 (7%)
Changes in Disease Type of Japanese Gaucher Disease

Within Japanese Gaucher disease patients, some type I population shifted to Type III later\(^1\)

### At the first visit

- **Type I**
  - \(n=70\)
  - (54.2%)

- **Type II**
  - \(n=31\)
  - (24.0%)

- **Type III**
  - \(n=28\)
  - (21.7%)

### After assessment

- **Type I**
  - \(n=54\)
  - (41.8%)

- **Type II**
  - \(n=31\)
  - (24.0%)

- **Type III**
  - \(n=44\)
  - (34.1%)

Follow-up period:
- Mean 18 years and 9 months
- (2 to 40 years)

**Diagnosis of Gaucher disease (GD)**

**Clinical manifestations and measurement of reduced glucocerebrosidase (GCase) to determine GD**

● Clinical diagnosis

Hepatosplenomegaly, anaemia, thrombocytopenia, bone pain, pathological fracture, Central nervous symptoms (Developmental retardation, myoclonus, convolution, strabismus, etc.)

● Definitive diagnosis

Enzymatic diagnosis
(Skin fibroblasts, Blood;Dried Blood Spot, bone marrow aspirate,
Check glucocerebrosidase activity: <10% of normal)
Lyso-Gb11,2,3 (Reflects disease progression and response to treatment) increased – under investigation in Japan and in some regions

● Ancillary Diagnosis

Angiotensin converting enzyme (ACE) 4, serum acid phosphatase (ACP) 5,6, chitotriosidase8, ferritin9 increased, Liver biopsy or examination of bone marrow for Gaucher cells genetic analysis

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Delayed diagnosis is thought to be due to lack of awareness of the disease or misdiagnosis

Mean years of delay in diagnosis in patients with type I Gaucher disease is 4.0 (± 10) years\(^1\)
Average number of doctors you see before definitive diagnosis is 3.0 (± 1.2) \(^1\)

### The specialty of the diagnosing physician\(^2\)

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Number of sites (response: 41 sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>9</td>
</tr>
<tr>
<td>Hematology Oncology</td>
<td>8</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>7</td>
</tr>
<tr>
<td>Primary care physician</td>
<td>5</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>4</td>
</tr>
<tr>
<td>general practice</td>
<td></td>
</tr>
<tr>
<td>Hepatology</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>3</td>
</tr>
<tr>
<td>Genetics</td>
<td>3</td>
</tr>
<tr>
<td>Orthopedics / Rheumatology</td>
<td>2</td>
</tr>
<tr>
<td>Radiology</td>
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</table>

### Major symptoms\(^2\)

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>Splenomegaly</td>
<td>11</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
</tr>
<tr>
<td>Anaemia</td>
<td>10</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>9</td>
</tr>
<tr>
<td>Bone/joint pain/growth pain</td>
<td>9</td>
</tr>
<tr>
<td>Contusion/epistaxis/bleeding tendency</td>
<td>8</td>
</tr>
<tr>
<td>Simple fracture</td>
<td>5</td>
</tr>
<tr>
<td>Aseptic necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Growth retardation/Delayed puberty</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal X-ray findings</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
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</tr>
</tbody>
</table>

### Causes of Delayed Diagnosis\(^2\)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number of sites (response: 13 sites)</th>
</tr>
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<tbody>
<tr>
<td>Lack of Awareness/Misdiagnosis</td>
<td>7</td>
</tr>
<tr>
<td>Phenotypic heterogeneity</td>
<td>3</td>
</tr>
<tr>
<td>Nonspecific symptoms</td>
<td></td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Outsourcing of testing</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
</tr>
</tbody>
</table>

[Subjects and Methods]
An internet survey was conducted in 16 specialists of Gaucher disease (Physicians who are involved in treatment, and physicians who have published reports on patient findings) about patient characteristics, symptoms before diagnosis, and delayed diagnosis.

Example of early diagnosis effort in Japan: Neonatal mass screening

Neonatal mass screening system is created by Japanese government

Newborn/Parents

Informed consent

OB/GYN Neonatal center

(Dried Blood Spots)

Regional Analysis Center

Phenylketonuria, Homocystinuria, Maple syrup urine disease, Galactosemia, Congenital hypothyroidism, Congenital adrenal hyperplasia
Urea cycle disorder
Organic acid metabolism disorder
Fatty acid metabolism disorder
Fatty acid metabolism disorder

*LSDs are tested additionally by local government

Stein RA, Genetic engineering and Biotechnology News, 2014
## Treatment for Gaucher Disease (GD)

### Enzyme Replacement Therapy (ERT) and Substrate Reduction Therapy (SRT) are major therapies for Gaucher disease

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drug name</th>
<th>Brand Name</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Enzyme Replacement Therapy (ERT, iv)</td>
<td>Velaglucerase alfa</td>
<td>VPRIV</td>
<td>Available (e.g. GD; Japan, GD1; EU/US, GD1&amp;3; Turkey, etc.)</td>
</tr>
<tr>
<td></td>
<td>Imiglucerase or, β-glucocerebrosidase</td>
<td>Cerezyme</td>
<td>Available (e.g. GD; Japan, GD1; US, GD 1&amp;3 EU, etc.)</td>
</tr>
<tr>
<td></td>
<td>Taliglucerase alfa*</td>
<td>Elelyso</td>
<td>Available (e.g. GD1; US/Brazil, GD; Canada, etc.)</td>
</tr>
<tr>
<td><strong>2</strong> Substrate Reduction Therapy (SRT, Inhibition of synthesis of Gb1)</td>
<td>Eliglustat**</td>
<td>Cerdelga</td>
<td>Available (e.g. GD; Japan, GD1; US/EU, etc.)</td>
</tr>
<tr>
<td></td>
<td>Miglustat**</td>
<td>Zavesca</td>
<td>Available (e.g. GD1; US/EU/Canada, etc.)</td>
</tr>
<tr>
<td></td>
<td>Venglustat</td>
<td>N/A</td>
<td>Under investigation (Phase1: GD3, other LSDs)</td>
</tr>
<tr>
<td><strong>3</strong> Hematopoietic stem cell transplant</td>
<td>N/A</td>
<td>N/A</td>
<td>Inhibiting progression or improvement of neurological symptoms, Risk of life-threatening complications, 4 patients in Japan, approximately 50 in global</td>
</tr>
<tr>
<td><strong>4</strong> Chaperone therapy*: Chemical chemotherapy (po)</td>
<td>Ambroxol*</td>
<td>N/A</td>
<td>Under investigation</td>
</tr>
<tr>
<td></td>
<td>N-octyl-β-valienamine*</td>
<td>N/A</td>
<td>Under investigation</td>
</tr>
<tr>
<td></td>
<td>N-(n-nonyl) deoxynojirimycin (NN-DNJ), isofagomine (IFG)</td>
<td>N/A</td>
<td>Under investigation</td>
</tr>
</tbody>
</table>

*Including information not approved in Japan and information under research
**Since it is degraded by CYP2D6, the blood concentration may increase depending on CYP2D6 genotype.

In addition, drugs that inhibit CYP3A co-administration may be contraindicated.

GD: Gaucher Disease, LSD: Lysosomal Storage Disease, N/A: Not Applicable

---

Package insert of Vpriv, 400 units for intravenous infusion, revised in October 2016 (Version 4)
Package insert of Cerezyme®, for Intravenous Injection 400 units, revised in February 2017 (Version 5). Japanese.
## Other therapies

New therapies including gene therapies and others are being investigated

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drug name</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Gene Therapy</td>
<td>AAV9 vector (GBAgene→β-glucocerebrosidase)</td>
<td>Phase 1/2: Infants With Type 2 GD (intraventricular; intracisternally), Phase1/2: Children with Type3 GD</td>
</tr>
<tr>
<td></td>
<td>Lentiviral vectors (GCase)</td>
<td>Phase1/2: Adult with Type 1 GD, autologous CD34+HSCs overexpressing Gcase</td>
</tr>
<tr>
<td>6 Nanoparticles</td>
<td>SapC-DOPS-GCase nanovesicles for nGD mouse model (able to cross BBB)</td>
<td>Saposin C+phospholipid dioleoylphosphatidylserine+acid b-glucosidase</td>
</tr>
<tr>
<td>7 in utero enzyme replacement therapy (IUERT)</td>
<td>Administering ERT during pregnancy</td>
<td>Drug can cross an immature, incomplete BBB Individual case studies reported recently (Feb 2022- WORLD symposium)</td>
</tr>
</tbody>
</table>

AAV: Adeno-associated Virus, GD: Gaucher Disease, GCase: glucocerebrosidase, HSC: Hematopoietic Stem Cell

ClinicalTrials.gov Identifier: NCT04411654, NCT04145037
Velaglucerase alfa (VPRIV) - Mechanism of Action of Enzyme Replacement Therapy

Enzymatic products administered intravenously (with mannose glycans added) bind to mannose receptors on the surface of macrophages, are taken up by cells by endocytosis, and are ultimately transported to lysosomes for action.

Principles of ERT for Gaucher disease.

Enzymatic products administered intravenously (with mannose glycans added) bind to mannose receptors on the surface of macrophages, are taken up by cells by endocytosis, and are ultimately transported to lysosomes for action.
Multicenter, open-label extension, global phase 3 clinical study: Long-term treatment study in adult and pediatric patients

Core Clinical Studies

032 Study
Treatment-naive patients (adults/children) (n = 25)
- velaglucerase alfa 60 U/kg (n=12)
- velaglucerase alfa 45 U/kg (n=13)
Duration of treatment: 12 months

039 Study
Treatment-naive patients (adults/children) (n = 34)
- velaglucerase alfa 60 U/kg (n=17)
- Imiglucerase 60 units/kg (n=17)
Duration of treatment: 9 months

034 Study
Previously treated patients (adults/children) (n = 40)
- velaglucerase alfa 15 ~ 60 U/kg (n=38)
Duration of treatment: 12 months

Extension study

Studies 032, 039, and 034 Participating patients (n = 95)
Assessed 24 months after start of core clinical study\(^a\)
Duration of treatment: Up to 66 months cumulative

- < Velaglucerase alfa group > (n = 39\(^b\))
  - velaglucerase alfa 60 U/kg

- < Imiglucerase → velaglucerase alfa group > (n = 16)
  - velaglucerase alfa 60 U/kg

- < Switch treatment group > (n = 38)
  - velaglucerase alfa 15 ~ 60 U/kg

\(^a\): Imiglucerase → velaglucerase alfa group was evaluated at 15 months after the first administration of velaglucerase alfa.
\(^b\): ITT population (2 patients included in safety analysis are not included)
Clinical parameters were outside the reference ranges among untreated patients with Gaucher disease\(^1\)

In comparison to healthy individuals, patients with Gaucher disease demonstrate greater volume of spleen and liver and lower hemoglobin concentration and platelet count.

---

**Spleen and liver\(^1\)**

<table>
<thead>
<tr>
<th>Volume (MN)</th>
<th>Female 12-59 years</th>
<th>Male 12-59 years</th>
<th>Female ≥59 years</th>
<th>Male ≥59 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 13.6 MN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median 1.5 MN (treatment-naive patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Haemoglobin\(^1\)**

<table>
<thead>
<tr>
<th>Haemoglobin (g/dL)</th>
<th>6-12 years</th>
<th>Female 12-59 years</th>
<th>Male 12-59 years</th>
<th>Female ≥59 years</th>
<th>Male ≥59 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 10.9 g/dL (treatment-naive patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Platelets\(^1\)**

<table>
<thead>
<tr>
<th>Platelets (x10(^9)/L)</th>
<th>6-12 years</th>
<th>12-59 years</th>
<th>≥60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 82.5 x 10(^9)/L (treatment-naive patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

MN: multiples of normal

Achievement rate of treatment goal after administration of velaglucerase alfa (Study HGT-GCB-044: Pooled Analysis)

Hemoglobin, platelets, liver volume and spleen volume were improved at 1-year and maintained at 4 years follow-up

**Hemoglobin**
- Female >11 g/dl: 97% (15/36 patients) at 1 year, 97% (29/30 patients) after 4 years
- Male >12 g/dl: 33% (12/36 patients) at baseline, 71% (24/34 patients) at 1 year, 100% (29/29 patients) after 4 years

**Platelets**
- >120x10⁹/L: 100% (20/20 patients) after 4 years

**Liver volume**
- >20% decrease: 80% (31/35 patients) at 1 year, 96% (126/130 patients) after 4 years

**Spleen volume**
- >30% decrease: 96% (27/28 patients) at 1 year, 100% (119/119 patients) after 4 years

**Lumbar spine BMD**
- Z score change >0: 96% (26/27 patients) at 1 year, 87% (20/23 patients) after 4 years

**Femur BMD**
- Z score change >0: 71% (24/34 patients) at 1 year, 70% (16/23 patients) after 4 years

*Patients who could be evaluated at baseline, 1 year and/or 4 years after administration of velaglucerase alfa (BMD after 3 years and/or 4 years) were included.

[Subjects and Methods]
The subjects were 39 patients with type I Gaucher disease who participated in Study HGT-GCB-044 to evaluate the long-term safety and efficacy of velaglucerase alfa. Velaglucerase alfa was continuously administered to the subjects, and the status of treatment goal achievement, normalization/abnormal rate, etc. were investigated.

BMD: bone mineral density

Velaglucerase alfa was Associated with Improvements Over 5 Years in Bone Health Among Patients with Gaucher Disease (Exploratory Data)

Velaglucerase alfa was associated with benefits for bone health in treatment-naïve and previously treated patients.\(^1,2\)

- Numbers of patients declined during the period of follow-up because they transitioned to commercial VPRIV, making results at later time points less reliable.\(^2\)

BMD: bone mineral density, CI: confidence interval.

Change in clinical parameters over 5 years among patients switching from imiglucerase to velaglucerase alfa\(^1\)

Following switch from imiglucerase to velaglucerase alfa, clinical parameters were maintained\(^1\)

\[\text{Haemoglobin Concentration} \]

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>-1.0</td>
<td>0</td>
<td>-2.0</td>
<td>-1.0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>(n=36)</td>
<td>(n=36)</td>
<td>(n=36)</td>
<td>(n=40)</td>
<td>(n=36)</td>
<td>(n=36)</td>
<td>(n=36)</td>
</tr>
</tbody>
</table>

\[\text{Normalized Spleen Volume} \]

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>39</th>
<th>51</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>0</td>
<td>-20</td>
<td>-40</td>
<td>0</td>
<td>-20</td>
<td>0</td>
</tr>
<tr>
<td>(n=36)</td>
<td>(n=34)</td>
<td>(n=34)</td>
<td>(n=34)</td>
<td>(n=13)</td>
<td>(n=5)</td>
<td>(n=4)</td>
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</table>

\[\text{Platelet Count} \]

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>(n=36)</td>
<td>(n=35)</td>
<td>(n=16)</td>
<td>(n=6)</td>
<td>(n=6)</td>
<td>(n=6)</td>
<td></td>
</tr>
</tbody>
</table>

\[\text{Normalized Liver Volume} \]

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>39</th>
<th>51</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>0</td>
<td>-20</td>
<td>-40</td>
<td>0</td>
<td>-20</td>
<td>0</td>
</tr>
<tr>
<td>(n=37)</td>
<td>(n=37)</td>
<td>(n=19)</td>
<td>(n=6)</td>
<td>(n=6)</td>
<td>(n=6)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Baseline n values calculated from Zimran A, et al. (2013)\(^2\)\(^3\) Patients started to transition to commercial VPRIV, and were no longer eligible to participate, after 24 months\(^1\)

BW: body weight, CI: confidence interval

Overall safety profile of velaglucerase alfa

The most serious AE was hypersensitivity reactions (2.1%)  
The most commonly reported AE was infusion-related reactions (39.4%)

- The most serious adverse reactions in patients in clinical studies were hypersensitivity reactions (2.1%)
- In velaglucerase alfa clinical trials, infusion-related reactions were the most commonly reported AEs in patients (incidence of 39.4%)
- Very commonly reported AEs (reported in ≥1/10 patients) include headache, dizziness, abdominal pain, bone pain, and arthralgia
- Other commonly reported AEs (reported in >1/100 patients) include hypersensitivity reactions, tachycardia, dyspnoea, flushing, rash, and chest discomfort
- In the clinical studies for Marketing Authorization one of 94 (1%) patients developed IgG-class antibodies to velaglucerase alfa

AE: Adverse Event

In Gaucher disease
- The activity of glucocerebrosidase is decreased
- Inheritance is autosomal recessive

In Japan, the prevalence is 1 in 330,000
- Type 1 (chronic non-neurologic), Type 2 (acute neurologic), and Type 3 (subacute neurologic) are almost equally occurred

World-wide, the prevalence is 1/800 in Ashkenazi Jews, 1/40,000 to 1/60,000 non-Jews
- Type 1 & type 3 are major populations

Enzyme Replacement Therapy (ERT) is a standard care of Gaucher disease. Velaglucerase alfa improves hepatosplenomegaly, anemia and thrombocytopenia, and bone health in Gaucher disease patients.
# AGENDA

## Today’s Topics

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overview of Lysosomal Storage Diseases (LSD)</td>
<td>Gen Suzuki MD, PhD, FAHA</td>
</tr>
<tr>
<td></td>
<td>Medical Expert of Rare Disease, Japan Medical Office</td>
</tr>
<tr>
<td>2. Gaucher Disease</td>
<td>Gen Suzuki MD, PhD, FAHA</td>
</tr>
<tr>
<td></td>
<td>Medical Expert of Rare Disease, Japan Medical Office</td>
</tr>
<tr>
<td>3. Fabry Disease</td>
<td>Sanghun Iwashiro MD</td>
</tr>
<tr>
<td></td>
<td>Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office</td>
</tr>
<tr>
<td>4. Hunter Syndrome (Mucopolysaccharidosis II)</td>
<td>Sanghun Iwashiro MD</td>
</tr>
<tr>
<td></td>
<td>Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office</td>
</tr>
<tr>
<td>5. Q&amp;A Session</td>
<td>Q&amp;A Panelists</td>
</tr>
</tbody>
</table>
Fabry disease is caused by variants in the α-galactosidase A gene (GLA), located on the X chromosome
- First reported by Anderson & Fabry in 1898
- α-galactosidase A enzyme deficiency leads to progressive accumulation of the glycolipid Gb3 in lysosomes
- Causes widespread organ damage and early death

Inheritance Pattern
- X chromosome latent (recessive) inheritance

Reported incidence and prevalence of Fabry disease

1:336,000 (males)\(^1\)
1:339,000 (female heterozygotes)\(^2\)

UK (2001)

1:468,000\(^3\)
Netherlands (1999)

1:3,100 (males)\(^4\)
1:9,000\(^5\)

Italy (2006\(^4\), 2018\(^5\))

1:7,683 (including VUS)\(^9\)
1:11,854 (excluding VUS)\(^9\)

Japan (2020)

1:3,500\(^8\)
USA (Missouri state only; 2015)

1:117,000\(^7\)
Taiwan (2009)

1:1,250 (males)\(^6\)
1:40,840 (females)\(^6\)

Australia (1999)

• Reported incidence and prevalence of Fabry disease vary, reflecting differences in study designs and populations\(^1–9\)
• Reported incidence and prevalence may be underestimated\(^10,11\)
• True incidence and prevalence are unknown, due to the existence of atypical or oligosymptomatic forms\(^11\)

VUS: variants of unknown significance

Fabry disease: X-linked recessive inheritance

Fabry disease is an X-linked recessive condition that can be inherited from either parent.¹⁻³

1. No male-to-male transmission of the defective gene variant.¹

2. All hemizygous men transmit the defective gene to all daughters who are heterozygous.¹

3. Heterozygous women with the defective gene have a 50% chance of passing it on to each child.¹

Figure adapted from Vanier MT, Caillaud C. In: Saudubray et al., editors. Inborn metabolic diseases. 5th ed. Berlin, Heidelberg: Springer, 2012:555–77.

Fabry disease is a multisystemic disorder

<table>
<thead>
<tr>
<th>Dermatological¹</th>
<th>Neurological²</th>
<th>Other organs and systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiokeratomas</td>
<td>Sweating problems (hypohidrosis)¹,²</td>
<td>GI issues (e.g., diarrhea, pain, early satiety)²</td>
</tr>
<tr>
<td>(typically on lower trunk)</td>
<td>Hearing loss, vertigo, tinnitus²,³</td>
<td>Airflow limitation⁵</td>
</tr>
<tr>
<td></td>
<td>Acroparesthesia (e.g., tingling, chronic burning or nagging pain in the hands/feet)²</td>
<td>Joint pain,² osteopenia⁴,⁵</td>
</tr>
<tr>
<td></td>
<td>Neuropsychiatric issues (e.g., depression)²</td>
<td>Fatigue²</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy²</td>
<td>Low exercise tolerance²</td>
</tr>
<tr>
<td></td>
<td>Vasculopathy, stroke, white matter lesions²</td>
<td>Lymphedema²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ophthalmological²</th>
<th>Cardiac²</th>
<th>Renal²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea verticillata</td>
<td>Left ventricular hypertrophy</td>
<td>Impaired renal function, albuminuria/proteinuria, hematuria</td>
</tr>
<tr>
<td>Retinal vessel tortuosity</td>
<td></td>
<td>Specific biopsy findings (e.g., intracellular accumulation of glycosphingolipids)</td>
</tr>
</tbody>
</table>

GI: gastrointestinal

Natural course of Fabry disease by gender

Male - Multiple organ dysfunction, with the number of organs involved rising with age. Female - Patients can exhibit significant signs and symptoms of Fabry disease.


FOS: Fabry Outcome Survey - a global, multicenter, observational registry, sponsored by Shire/Takeda; GI: gastrointestinal; SD: standard deviation

gray vertical lines denote mean age of onset and red bars indicate SD
Schematic model of the progression of Fabry disease

Fabry disease has a progressive pathology

**Early symptoms**
- Pain
- GI symptoms
- Hypohidrosis
- Cold/heat intolerance

**Late complications**
- Renal failure
- Cardiovascular complications
- CNS complications

Irreversible damage, poorest treatment outcomes

Optimal time to intervene

Intervention useful but may not be optimal

Organ failure

Tissue involvement

Gb₃ storage

**Disease burden**

Time

Childhood ≤18 years

Young adulthood >18 years to ≤30 years

Later adulthood Third to fourth decades of life

**Early symptoms**

**Late complications**

QoL is impaired in patients with Fabry disease\textsuperscript{1,2}

Depression is common and underdiagnosed\textsuperscript{3} - need for correct assessment of symptoms of depression

Pooled SF-36 subdomain scores in treated and untreated male and female patients with Fabry disease (n=599)\textsuperscript{3}

Error bars show standard error of the mean (SEM). Figure adapted from Arends M et al. Orphanet J Rare Dis 2015;10:77
QoL: Quality of Life,
SF-36: 36-item short-form health survey for measuring health status and QoL. (Scale scores range from 0 to 100, with higher scores representing better perceived health)

Current methods for diagnosing Fabry disease and assessing patients¹⁻⁵

Diagnosis method is different between male and female

**Family member with Fabry disease or signs or symptoms suggestive of Fabry disease (e.g., angiokeratoma, acroparesthesia)**¹

**Male patients – biochemical diagnosis**

**Definitive diagnosis in male patients: enzyme assay** (measurement of plasma α-Gal A activity) – little or no α-Gal A activity is observed in classic male patients²⁻³

*α-Gal A enzymatic activity in DBS samples widely used for screening purposes*⁴

Plasma or urinary Gb₃ or lyso-Gb₃

Confirmation of Fabry disease and identification of the GLA variant can be made by genetic analysis of the GLA gene

**Female patients – genetic diagnosis**

**Definitive diagnosis in female patients: DNA testing**²⁻³

Many female patients have α-Gal A enzyme levels within the normal range⁵

Lyso-Gb₃ levels can assist in diagnosis but confirmation requires genetic analysis of the GLA gene²

---


A delay often occurs between disease onset and diagnosis\textsuperscript{1–3}

Patients with Fabry disease often undergo a long diagnostic odyssey\textsuperscript{1}

The clinical course of Fabry disease is highly variable, with a broad range of possible differential diagnoses\textsuperscript{1}

<table>
<thead>
<tr>
<th>Time between disease onset and diagnosis</th>
<th>2001–2006 vs 2007–2013\textsuperscript{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>14.0 (95% CI: 9.0, 20.0)</td>
</tr>
<tr>
<td>Children</td>
<td>10.5 (95% CI: 8.0, 13.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Misdiagnoses of Fabry disease in patients in FOS\textsuperscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatological disease/rheumatic fever</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Enzymopathies</td>
</tr>
<tr>
<td>Osteo's disease</td>
</tr>
<tr>
<td>Neuropsychological disease</td>
</tr>
<tr>
<td>Ménière's disease</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Figure adapted from Reisin R et al. Int J Clin Pract 2017;71

CI: confidence interval, FOS: Fabry Outcome Survey - a global, multicenter, observational registry, sponsored by Shire/Takeda, NS: not significant

Treatments for Fabry disease

**ERT and Chaperone therapy are standard care of Fabry disease**

| **ERT** | • Corrects the underlying enzyme deficiency and can slow disease progression  
• Indicated for long-term use in patients with a confirmed diagnosis of Fabry disease\(^1,2\)  
• Can be used at home by patients who tolerate the infusion well\(^1\) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chaperone therapy</strong></td>
<td>• Reversibly binds to certain variant forms of (\alpha)-Gal A, facilitating trafficking of these variant forms of (\alpha)-Gal A to lysosomes and increasing enzyme activity(^4)</td>
</tr>
</tbody>
</table>
| **Under investigation** | • Substrate reduction therapy, inhibits synthesis of glycosphingolipids\(^6\)  
• Gene therapy\(^5,7-10\) |
| **Supportive care** | • Supportive therapies can help to treat the complications of Fabry disease\(^11-13\) |

\(\alpha\)-Gal A: \(\alpha\)-galactosidase A, ERT: enzyme replacement therapy

Phase 2/3 clinical trial: agalsidase alfa reduced neuropathic pain scores and stabilized renal function

TKT003 – registration trial

- Adult males with Fabry disease and neuropathic pain (n=26) were randomized to receive agalsidase alfa 0.2 mg/kg EOW or placebo for 6 months\(^1\)

- Agalsidase alfa was associated with progressive decline in neuropathic pain scores (BPI) for ‘pain at its worst in the last week’ (primary endpoint; \(P=0.02\))\(^1\)

- In an open-label extension study (n=25), treatment with agalsidase alfa over 48–54 months was associated with stabilization of eGFR in patients with normal GFR or mild to moderate renal dysfunction\(^2\)

- Agalsidase alfa was generally well tolerated in both studies\(^1,2\)

\(\text{BPI: Brief Pain Inventory, CKD: chronic kidney disease, eGFR: estimated GFR, EOW: every other week, GFR: glomerular filtration rate, SD: standard deviation}\)


Open label extension: Agalsidase alfa reduced myocardial Gb₃ content and left ventricular mass

TKT007 – registration trial

- Adult males with Fabry disease and left ventricular hypertrophy (LVH; n=15) were randomized to receive agalsidase alfa 0.2 mg/kg EOW or placebo for 6 months

- Agalsidase alfa:
  - saw a 20% reduction in myocardial Gb₃ content (primary efficacy endpoint) compared with a 10% increase with placebo ($P=0.42$)
  - significantly reduced left ventricular mass (LVM) (secondary efficacy endpoint) compared with placebo ($P=0.041$)

- In an open-label extension study, treatment with agalsidase alfa over 24–36 months was associated with a significant reduction in LVM compared with baseline

- Agalsidase alfa was generally well tolerated
  - No SAEs related to agalsidase alfa

EOW: every other week, Gb₃: globotriaosylceramide, LVH: left ventricular hypertrophy, LVM: left ventricular mass, SAEs: serious adverse events

20–year Fabry Outcome Survey data

Agalsidase alpha has been used for renal and cardiac protection that leads to survival improvement

Fabry Outcome Survey: a global, multicenter, observational registry, sponsored by Shire/Takeda
In agalsidase alfa clinical trials, infusion-related reactions were the most commonly reported AEs in adult patients (incidence of 13.7%)\(^1\)

- Very commonly reported AEs (reported in \(\geq 1/10\) patients) include chills, headache, nausea, pyrexia, tiredness, difficulty breathing, shaking, cough and vomiting\(^1\)

- Other commonly reported AEs (reported in \(>1/100\) patients) include dysgeusia, increased lacrimation, flushing, abdominal discomfort, hypersensitivity, aggravated fatigue\(^1\)

- Most of the undesirable effects were mild to moderate in severity\(^1\)

In the long-term FOS analysis of 555 patients receiving agalsidase alfa 0.2 mg/kg EOW, 188 (34%) patients experienced 826 AEs over 5 years of observation, with infusion-associated reactions being the most common (occurring in 35 patients)\(^2\)

- Low-titre IgG responses have been observed in \(~24\%\) of male patients treated with agalsidase alfa 0.2 mg/kg EOW\(^1\)

AE: Adverse Event, FOS: Fabry Outcome Survey - a global, multicenter, observational registry, sponsored by Shire/Takeda

Fabry disease is an X-linked genetic disease that is caused by pathogenic variants of the GLA gene.

The classical form of Fabry disease is characterized by multisystemic damage and symptoms including heart failure and kidney disease.

It is important to diagnose correctly as early as possible to provide specific treatment.

Enzyme replacement therapies (ERT) and chaperone treatment are standard care of Fabry disease. Agalsidase alpha has been used for renal and cardiac protection that leads to survival improvement.

GLA: α-galactosidase A
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<tr>
<th>Today’s Topics</th>
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<td>1. Overview of Lysosomal Storage Diseases (LSD)</td>
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<td>4. Hunter Syndrome (Mucopolysaccharidosis II)</td>
<td>Sanghun Iwashiro</td>
<td>MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office</td>
</tr>
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<td>5. Q&amp;A Session</td>
<td>Q&amp;A Panelists</td>
<td></td>
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</table>
What is Hunter Syndrome (Mucopolysaccharidosis II)?

Hunter Syndrome is a type of LSD first described by Charles Hunter in 1917, who examined two brothers with the disorder.\(^1\)

- Hunter Syndrome is caused by deficiency in or absence of iduronate-2-sulfatase (I2S)\(^2-3\)
  - Causes widespread pathological lysosomal storage of glycosaminoglycans (GAGs), which leads to progressive damage and dysfunction in cells, tissues and organs throughout the body.\(^3\)
  - First reported by Charles Hunter in 1917

- Inheritance Pattern
  - X-linked recessive

- Incidence
  - \(~0.38-2.16/100,000\) live births\(^4-5\)

---

Hunter Syndrome is an X-linked disorder present almost exclusively in male patients

It is an X-linked recessive genetic disorder\(^1\) affecting approximately \(~0.38-2.16/100,000\) live births\(^2,3\), almost exclusively males\(^1\)

---

**Heterozygous woman passes IDS variant on to affected son and daughter who becomes a carrier\(^4,5\)**

**Man with Hunter Syndrome passes IDS variant on to daughter\(^5,6\)**

---

IDS: iduronate-2-sulfatase gene

Symptoms of Hunter Syndrome

Symptoms of Hunter Syndrome are systemic and affects QoL and prognosis of patients.

Cognitive manifestation in two-thirds of patients with Hunter Syndrome (neuronopathic form)

Somatic manifestations in all patients with Hunter Syndrome

Respiratory

Abdominal

Craniofacial

Cardiac

Musculoskeletal

CNS

Daily life

QoL

Mortality: life expectancy of 10–15 years (median 11.7 years) for patients with cognitive impairment

CNS: central nervous system, QoL: quality of life

## The clinical spectrum of Hunter Syndrome

### Patients usually appear healthy at birth$^1$

**Phenotype spectrum ranges from non-neuronopathic (attenuated) to neuronopathic (severe) forms$^1$**

- **Presence/absence of neurological involvement$^1$** mainly distinguishes the two phenotypes
- The clinical manifestation of Hunter Syndrome appears to be similar in female and male patients$^2$–$^6$

### Disease spectrum continuum

<table>
<thead>
<tr>
<th>Non-neuronopathic</th>
<th>Neuronopathic</th>
</tr>
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<tbody>
<tr>
<td>Proportion of patients with Hunter Syndrome affected</td>
<td>One-third$^7$</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>3.7–6.8 years$^8$</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td>Somatic manifestations predominate$^9,10$ Commonly start between 2 and 4 years of age$^1$</td>
</tr>
<tr>
<td>Prognosis</td>
<td>• Survival into adulthood is common$^9,12$ • Death typically from cardiac or respiratory disease occurs between 20 and 30 years of age (although some patients might survive into their 50s and 60s)$^9,12$</td>
</tr>
</tbody>
</table>

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Disease progression in non-neuronopathic Hunter Syndrome

The most common causes of death in patients with Hunter Syndrome are airway involvement (65%) and cardiac involvement (16%)\(^1\)


Symptoms in the first few months of life are usually respiratory\(^1\)

Delays in ossification cause progressive pathophysiological musculoskeletal effects\(^2,3\)

Progressive arthropathy leads to stiffness and contracture of joints\(^4\)

Growth retardation usually begins between 3 and 4 years of age\(^6\)

A significant burden on the cardiovascular system with anatomical and functional changes\(^5,6\)

Somatic manifestations can result in secondary effects on cognitive function and behavior\(^5,7\)

Cardiovascular and respiratory disease are risks of death for patients surviving into adulthood\(^6,9\)

Age

Neuronal Hunter Syndrome manifestations are associated with a high burden of disease

- **Neurological manifestations** are debilitating, affecting day-to-day activities and the QoL of both patients and caregivers.
  - Symptoms include:
    - cognitive impairment
    - developmental delay
    - Seizures
    - gross and fine motor function problems
    - Hydrocephalus
    - spinal cord compression
    - hearing loss and severe language disturbance
    - carpal tunnel syndrome

- **Behavioral problems** start in the second year of life, are serious and severely affect home life.
  - Symptoms include:
    - hyperactivity, restlessness, excitability
    - aggression, obstinacy
    - biting, chewing behavior
    - impulsivity, sensory seeking
    - sleep disorders, poor attention span
    - social function, emotional function

QoL: quality of life

Effective management of Hunter Syndrome requires a multidisciplinary team

Keys to effective management of Hunter Syndrome are greater awareness among HCPs of:
• the early signs and symptoms
• the available tools and guidelines for assessing and monitoring cognitive impairment

• A wide range of symptoms of Hunter Syndrome can be severe in nature, requiring a large proportion of patients substantial medical and surgical support from a multidisciplinary team\textsuperscript{1,2}

• Input from the following HCPs is often required:
  – Pediatricians
  – Specialist nurses
  – Otorhinolaryngologists
  – Orthopedic surgeons
  – Ophthalmologists
  – Cardiologists
  – Pneumologists
  – Anesthesiologists
  – Neurologists
  – Physiotherapists
  – Occupational therapists
  – Speech therapists
  – Psychologists
  – Social workers
  – Homecare patient societies
  – Dental services
  – Behavioral therapists

HCP: healthcare professional

Current gold standard laboratory testing pathway for Hunter Syndrome diagnosis

Following clinical suspicion of disease

A suspected diagnosis of Hunter Syndrome should be confirmed by biochemical and/or genetic analysis

Clinical suspicion of Hunter Syndrome (early clinical signs observed) → Check for alternative diagnosis

Assessment of urinary GAG excretion

Urinary excretion of DS and HS increased → Normal DS and HS excretion

Enzyme assay of blood samples

I2S low → Exclude multiple sulfatase deficiency

I2S within normal range → Check for other MPS/LSDs

Genetic analysis of IDS (if available)

Gene variant identified → Second enzyme test (e.g., leukocytes)

Gene variant not identified → Genetic analysis not available

Hunter Syndrome confirmed

Red stars indicate the three major categories of confirmatory testing for Hunter Syndrome following clinical suspicion that are required for a definitive diagnosis:


Early diagnosis of Hunter Syndrome is challenging and remains an unmet need

Early diagnosis is critical for optimal patient management, with emerging treatments on the horizon\textsuperscript{3,7,8,10}

Keys for early diagnosis: clinical suspicion of very early symptoms and symptom clusters indicative of Hunter Syndrome\textsuperscript{2,11}

**Hunter Syndrome diagnosis is challenging**

- Patients usually appear **healthy at birth**
- Initial signs and symptoms are **heterogeneous and non-specific**\textsuperscript{1,3}
- Many symptoms **overlap with common childhood complaints**\textsuperscript{2}

- Delays between disease onset and diagnosis\textsuperscript{1} without family history
- **Around 2–4.5 years of delayed diagnosis**\textsuperscript{4–6} experienced by most patients
- **Early diagnosis is important** for early treatment, anticipation of complications, carrier identification and family genetic counseling\textsuperscript{3,7–9}

Universal implementation of NBS programs will aid early diagnosis and access to early treatment\textsuperscript{7,9,12–14}

ERT: enzyme replacement therapy, IV: intravenous, NBS: newborn screening

Available treatments for patients with Hunter Syndrome

ERT and HSCT are available for non-neuronopathic Hunter Syndrome but requires supportive treatment to manage overall symptoms. Pabinafusp alfa is newly introduced in Japan as a therapy that addresses neuronopathic symptoms.

Current therapies are based on a ‘cross-correction’ principle: lysosomal enzymes produced in one cell travel to and degrade GAG storage material in the lysosomes of neighboring cells.

ERT

- **Regular IV infusions of Idursulfase**, an enzyme replacement therapy, is the current standard of care, which treats somatic aspects of disease.
  - Approved therapies include: **Eaprase** (idursulfase), **Hunterase** (idursulfase beta)
  - Generally reduces urinary GAG levels and liver/spleen volume, but evidence for other long-term outcomes is less clear.

HSCT

- **One-time surgical treatment** to transplant donor blood stem cells to provide a source of functional enzymes.
  - Previously used to treat other mucopolysaccharidoses; applied to Hunter Syndrome in the 1980s.
  - Limited experience with few clinical benefits.
  - Can be associated with a serious risk of morbidity and mortality.

Novel Agent

- **IZCARGO®** (pabinafusp alfa) is a recombinant iduronate-2-sulfatase ERT available in Japan (as of September 2022).
  - Developed with J-Brain Cargo® technology (JCR Pharma) that delivers therapeutics across the blood-brain barrier (BBB).
  - Expected to treat not only somatic symptoms but also neurological complications which had been an unmet need.
  - Currently a global phase 3 trial is ongoing.


TKT024 study: Phase 2/3 study design

Baseline
(disease score recorded and patients stratified by age and disease severity)

n=96

Placebo (n = 32)

Idursulfase 0.5 mg/kg i.v. weekly (n = 32)

Idursulfase 0.5 mg/kg i.v. EOW, alternating with placebo (n = 32)

53 weeks of treatment

- Double-blind, placebo-controlled multicenter study
- Stratification followed by randomization to one of three groups
- All treatments administered via 3-hour intravenous infusions

<Primary Efficacy Endpoint>

Comparison between placebo and weekly idursulfase groups in change from baseline to study end in two-component composite score

- Respiratory function (per cent predicted FVC)
- Physical functional capacity (6MWT)

BL: baseline, EOW: every other week, i.v.: intravenously, 6MWT: 6-minute walk test, FVC: forced vital capacity

TKT024 study results: Idursulfase significantly improved the primary endpoint composite score compared with placebo at week 53

The recommended dose regimen of idursulfase is 0.5 mg per kg of BW administered once weekly as an intravenous infusion. Data are shown as mean + SEM. Analysis of covariance for comparison of adjusted mean change versus placebo at the end of the study. 6MWT: 6-minute walk test, BW: body weight, EOW: every other week, FVC: forced vital capacity, SEM: standard error of the mean.

*P=0.0131 versus placebo at week 53

†P=0.065 versus placebo at week 53

‡P=0.953 versus placebo at week 53
• 59.6% of patients had at least one drug-related AE
• 28.7% of patients had at least one severe or life-threatening AE
  - bacteremia (n=2), chronic otitis media (n=2), carpal tunnel syndrome (n=6), sleep apnea (n=2), abdominal strangulated hernia (n=2), obstructive airway disorder (n=2; one of these cases was a life-threatening AE)
• 53.2% of patients had at least one IRR
  - Most common IRRs were headache (16.0%), urticaria (11.7%) and pyrexia (8.5%)
  - Incidence of IRRs declined with continued treatment
• Median survival based on Kaplan–Meier estimates (95% confidence interval [CI]) in treated and untreated patients was 33.0 (30.4, 38.4) years and 21.2 (16.1, 31.5) years, respectively.

• Cox regression modeling (below figure) estimated the risk of death to be 54% lower in patients receiving treatment with IV idursulfase than in untreated patients (hazard ratio, 0.46; 95% CI: 0.29, 0.72)

Comparison of the survival times: untreated and treated patients with Hunter Syndrome

Idursulfase treatment may improve survival probability in patients with Hunter Syndrome

CI: confidence interval, IV: intravenous

Hunter Syndrome is an X-linked genetic disease with deficiency in or absence of iduronate-2-sulfatase (I2S) that leads to GAG accumulation.

Hunter Syndrome is characterized by multisystemic damage and symptoms. Neuropathic Hunter Syndrome shows CNS symptoms.

Early diagnosis of Hunter Syndrome is challenging and remains an unmet need.

ERT is a standard of care for non-neuronopathic Hunter Syndrome patients, of which idursulfase is effective against somatic symptoms and improves prognosis by 11.8 years\(^1\).

CNS: Central Nervous System, ERT: Enzyme Replacement Therapy
Today’s Summary - Lysosomal Storage Diseases (LSDs)

LSDs are inherited metabolic disorders caused by deficient lysosomal enzymes; they are characterized by the accumulation of undegraded materials (substrates), which results in lysosomal dysfunction and diverse pathologies.

- LSDs differ in their molecular etiologies depending on which enzymes are affected and are grouped based on the substrate involved.
- The cumulative incidence of all LSDs is reported to be 1 in 7,000 live births.
- Typical clinical symptoms of LSDs include hepatosplenomegaly, pulmonary and cardiac problems, bone abnormalities, dementia, deafness, blindness and movement problems.
  - Two-thirds of LSDs involve neurological effects.

<table>
<thead>
<tr>
<th>Affected Enzyme (Cause)</th>
<th>Gaucher Disease</th>
<th>Fabry Disease</th>
<th>Hunter Syndrome (Mucopolysaccharidosis II)</th>
</tr>
</thead>
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<tr>
<td>Current Standard of Care</td>
<td>ERT, SRT</td>
<td>ERT, Chaperone therapy</td>
<td>ERT, HSCT</td>
</tr>
</tbody>
</table>

ERT: enzyme replacement therapy, SRT: substrate reduction therapy, HSCT: hematopoietic stem cell transplantation

# AGENDA

## Today’s Topics

1. **Overview of Lysosomal Storage Diseases (LSD)**  
   - **Gen Suzuki**  
     - MD, PhD, FAHA  
     - Medical Expert of Rare Disease, Japan Medical Office

2. **Gaucher Disease**  
   - **Gen Suzuki**  
     - MD, PhD, FAHA  
     - Medical Expert of Rare Disease, Japan Medical Office

3. **Fabry Disease**  
   - **Sanghun Iwashiro**  
     - MD  
     - Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office

4. **Hunter Syndrome (Mucopolysaccharidosis II)**  
   - **Sanghun Iwashiro**  
     - MD  
     - Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office

5. **Q&A Session**  
   - **Q&A Panelists**
# Q&A Session

## Q&A Panelists

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<tr>
<th>Gen Suzuki</th>
<th>Sanghun Iwashiro</th>
<th>Sachiko Yoshimoto</th>
<th>Emiko Koumura</th>
<th>Kazuaki Enya</th>
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<td>MD Head, Medical Franchise Rare Disease, Japan Medical Office</td>
<td>MD, PhD Japan Site Head, Marketed Products Development</td>
<td>Head, Therapeutic Area Strategy Unit (Rare Genetic and Hematology)</td>
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