ISPOR EUROPE 2023

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RWD From Patient Registry for Rare Diseases and Its Uses in HTA Process in Brazil

Session Information

Rare Disease Case Studies

Wednesday, 15 November 2023

Time: 10:00 - 11:00

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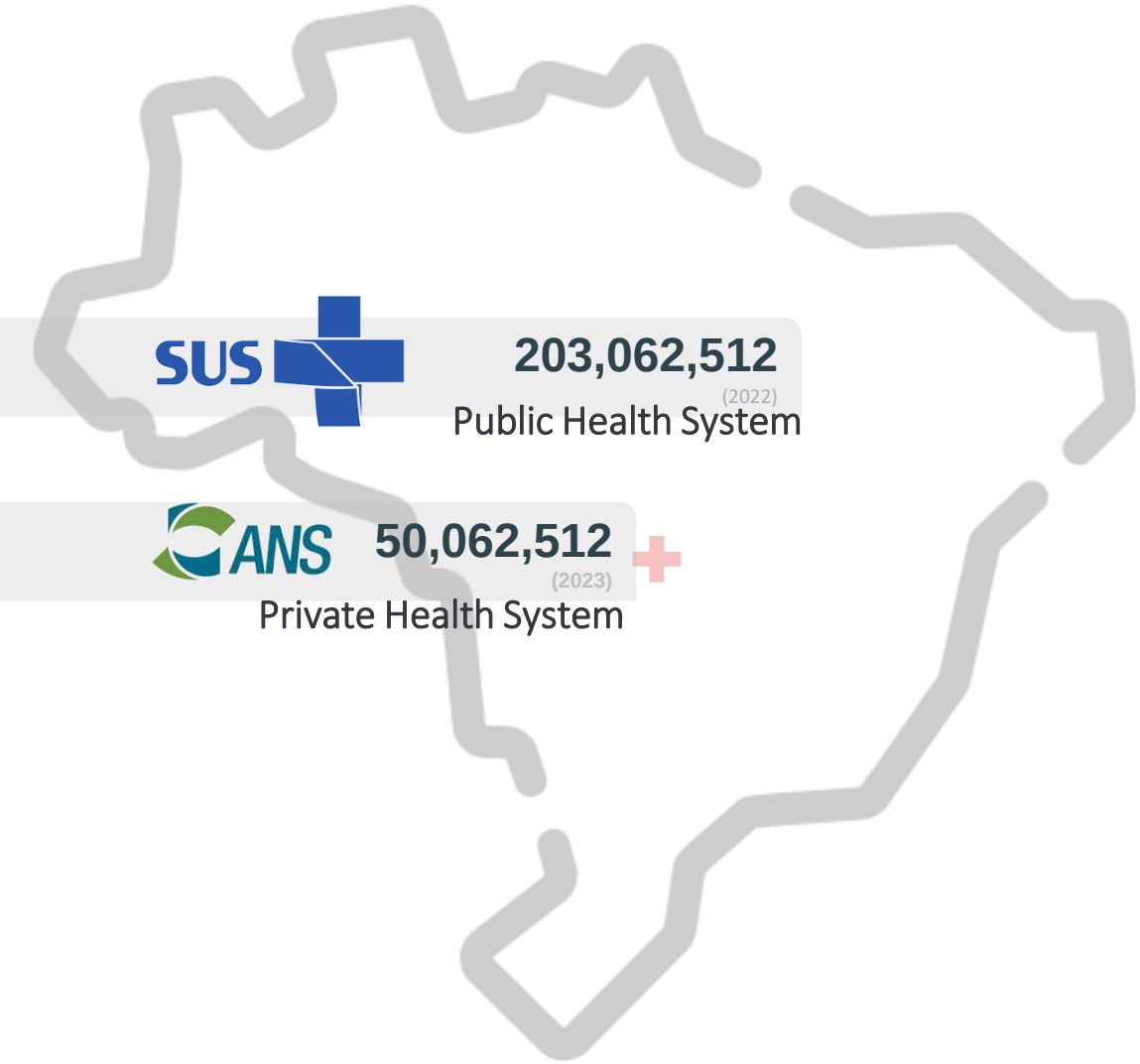
Brazil healthcare system overview



SUS **203,062,512** (2022)
Public Health System

ANS **50,062,512** (2023)
Private Health System

National HTA process

Public Health System (SUS)

Conitec

National Commission for Health Technology Incorporation

Private Health System

ANS

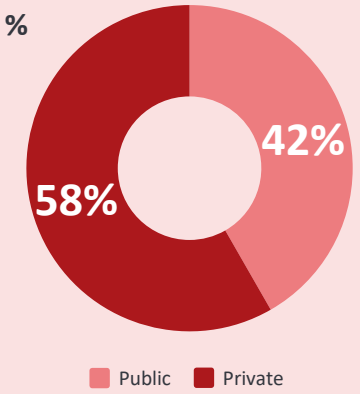
National Supplementary Healthcare Agency

National Health GDP

Total health expenditure as a % of the GDP (public + private)

9.5%

USA	16.8%
GER	11.7%
ARG	9.5%
MEX	5.4%



49Mn

4.6x higher per capita

BRASIL. IBGE. Data From 2023. Sala de Sutuação. ANS. Data from 2023.

HTA process in Brazil is well established

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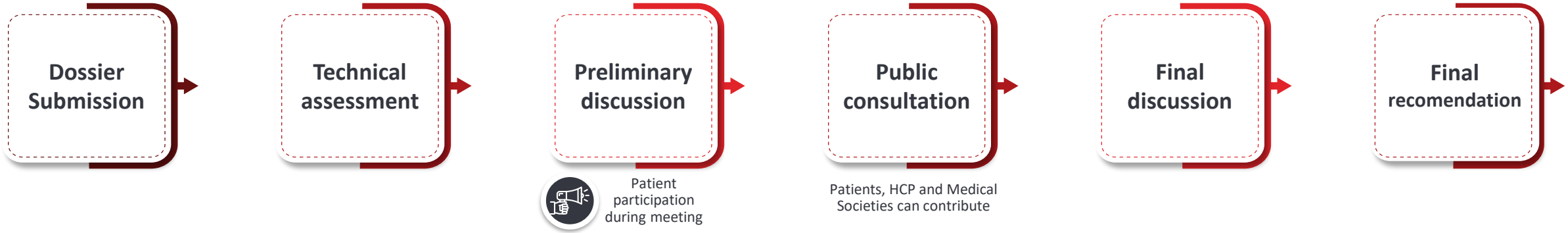
Simplified HTA process for mandatory Public health care system coverage



Conitec dossier main documents:

- Clinical evidence
- Full economic analysis
- Budget impact analysis

Clinical evidence (systematic review)

- Important part of a HTA dossier (preferably Head-to-head RCT)

GRADE framework to assess certainty of evidence

- Real world evidence might add information of: effectiveness, long term outcomes (safety/effectiveness), special population data, etc

Conitec. Diretrizes de submissão. Available https://www.gov.br/conitec/pt-br

Current scenario of rare diseases

Worldwide

Rare diseases are an heterogeneous group of disorders that can affect any part of the body[2]

→ Associated with **decreased quality of life** and neglected for a long time[3]

→ **5,000 to 8,000 rare diseases** according to WHO[4]

→ **Differentiated HTA criteria have been discussed** to evaluate orphan drugs for rare diseases, in addition to classic cost-effectiveness based and budgetary impact methodologies[6]

Brazil

2014 **National Policy for People with Rare Diseases**

→ aim to reduce mortality

→ improving people's quality of life, through early detection, timely treatment, disability reduction and palliative care

→ **Prevalence of 65 / 100,000 (same as WHO)**

2022 **Cost-effectiveness thresholds – Conitec**

→ **8K USD per QALY – flexible to 24K per QALY in rare diaseases**

→ Discussion are flexible during the Conitec plenary considering clinical outcomes, safety, social, economic and organizational aspects

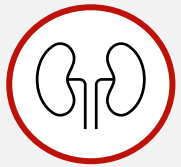
Brasil. Ministério da Saúde (MS). *Política Nacional de Atenção Integral às Pessoas com Doenças Raras.* Portaria GM nº 199, de 30 de janeiro de 2014.
WHO. Rare diseases data.

Context of agalsidase-alfa for Fabry disease in Brazil

BUT WHAT IS FABRY DISEASE?

- Rare genetic disease that affects **1 in every 117,000 live births** characterized by reduced or absent activity of the enzyme (α-galactosidase A (α-Gal A)
- This absent or reduced activity results in the progressive accumulation of a substance (Gb3) within cells, **causing cell dysfunction and death**
- Around **45.9%** of patients have severe multisystem disease with target **organ involvement**, the classic form of the disease:

HEART FAILURE, ACUTE MYOCARDIAL INFARCTION AND LEFT VENTRICULAR HYPERTROPHY



CHRONIC KIDNEY DISEASE AND KIDNEY FAILURE

DISABLING NEUROPATHIC PAIN, STROKE AND HEARING LOSS

2009 Market Authorization (ANVISA)

2014 Prioritized in the Rare Disease National Policy

2017 2019 Two negative recommendations from Conitec (HTA agency)

2022 TAKEDA's resubmission

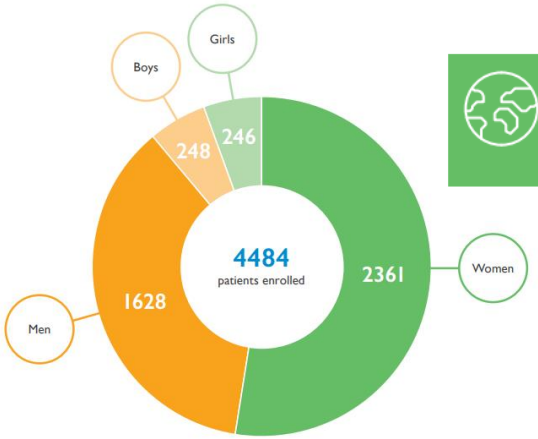
DATA FROM FOS (Fabry Outcomes Survey) Diseases registry sponsored by Takeda for 20 years

RCT UNCERTAINTY
HIGH BUDGET IMPACT
LIMITED SCIENTIFIC DATA

	RTCs	Study objective	Study design	Population	Intervention	Control arm	FUP
1	Schiffmann 2001 (FOS)	To evaluate the safety and efficacy of intravenous a-gal A for Fabry disease	RCT, double blind, placebo-controlled trial	Adult male patients with classic phenotype N=26	Agalsidase-alfa 0,2 mg/kg, IV, every 2 weeks N=14	Placebo, IV, every 2 weeks N=12	6 months
2	Hughes, 2008	to assess the safety and efficacy of a-gal A on the cardiac manifestations of Fabry disease	RCT, double blind, placebo-controlled trial	Adult male patients with classic phenotype N=15	Agalsidase-alfa 0,2 mg/kg, IV, every 2 weeks N=7	Placebo, IV, every 2 weeks N=8	6 months

Germain DP. Orphanet J Rare Dis. 2010;5:30
Laredo, F. et al. CHARACTERISTICS OF FABRY DISEASE PATIENTS IN BRAZIL: A PATIENT REGISTRY ANALYSIS. Value in Health. May, 2020.
Silva, CA. COMDORA
Meikle PJ,. Prevalence of lysosomal storage disorders. JAMA. 1999 Jan;281(3):249–54.
Schiffmann R, *et al.* Enzyme Replacement Therapy in Fabry Disease: A Randomized Controlled Trial. *JAMA* 2001;285.
Hughes DA,. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: A randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. *Heart* 2008;2:153-158.

Global registry that started in 2001: long term data from patients with Fabry disease



Total number of countries: 26

Total number of study sites: 144

Total number of patients: 4484

Who was eligible to take part in FOS?

- All patients (adults and children) with a diagnosis of Fabry disease who:
  - were untreated
  - were receiving or had previously received any approved treatment for Fabry disease.[a]
- Patients continued to be assessed and treated as determined by their own healthcare provider while enrolled in FOS.

FOS manuscripts

As of September 2022, a total of 61 articles containing information from FOS have been published in scientific journals, including two in 2022 (Cybulla M and co-authors, and Beck M and co-authors).

Articles published in the past 10 years are arranged by topic in the table below and on the following pages. Links provide access to the articles via Open Access from the journal website.

FOS FABRY OUTCOME SURVEY

Key results

In total, 560 patients had information available for analysis of heart size at the start of treatment

Of these, 306 patients had an enlarged heart and 254 patients did not have an enlarged heart at the start of treatment.

Patients with an enlarged heart at the start of treatment had a higher risk of developing heart or kidney conditions during follow-up than those with normal heart size.

- The risk of developing a heart condition was 57% higher in patients with an enlarged heart at the start of treatment than in those without.

In total, 1093 patients had information available for the analysis of kidney function at the start of treatment

Of these, 433 patients had poor kidney function and 660 patients had healthy kidney function at the start of treatment.

Patients with poor kidney function at the start of treatment had a higher risk of developing heart or kidney conditions during follow-up than those with healthy kidney function.

- The risk of developing a heart condition was 33% higher in patients with poor kidney function at treatment start than in those with healthy kidney function.
- The risk of developing a kidney condition was more than five times higher in those with poor kidney function than in those with healthy kidney function.

FOS. 2020 annual update for patient organizations. https://www.fabrynetwork.org/new/wp-content/uploads/2021/09/FOS-Patient-Report_30Jul21_.pdf

New HTA evaluation: data from FOS were essential for the positive recommendation of Conitec

CLINICAL TRIALS

RTCs	Study design	Population	Intervention	Control arm	FUP
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Cochrane Library

Cochrane Database of Systematic Reviews

Enzyme replacement therapy for Anderson-Fabry disease (Review)

El Dib R, Gomaa H, Carvalho RP, Camargo SE, Bazan R, Barretti P, Barreto FC

"ERT demonstrates significant improvement of microvascular Gb3 deposits and pain-related quality of life."

"The long-term influence of enzyme replacement therapy on the risk of Fabry disease-related morbidity and mortality has not yet been established."

REAL WORLD DATA - FOS

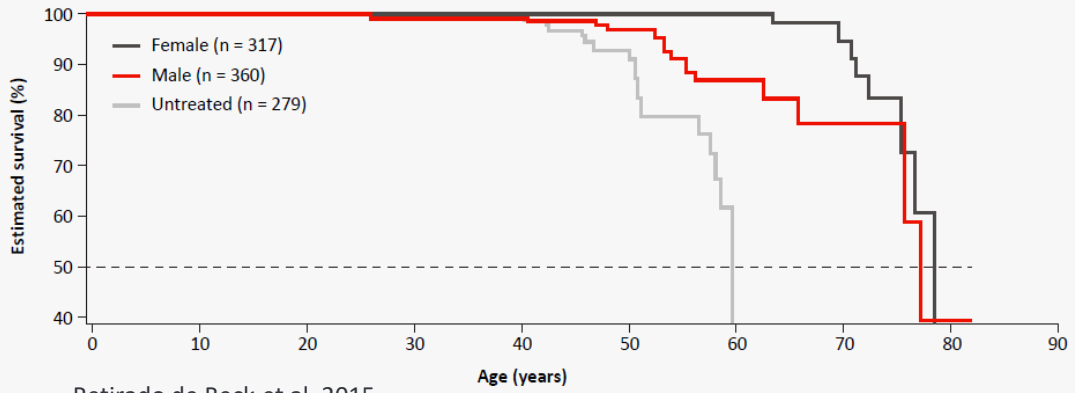
FOS started in 2001

4.484 PATIENTS Jan - **2021**

144 CENTERS IN **26** COUNTRIES Including Brazil

FOS HAS GENERATED **60** PUBLICATIONS ABOUT FABRY DISEASE

Kaplan-Meier survival analyzes for treated FOS patients and untreated patients (matched historical control).



Retirado de Beck et al, 2015.

The estimated median survival was 77.5 years for male patients with FOS compared to 60 years in male patients without ERT, indicating a reduced risk of mortality for those who received alfagalsidase.

Germain DP. Orphanet J Rare Dis. 2010;5:30
Laredo, F. et al. CHARACTERISTICS OF FABRY DISEASE PATIENTS IN BRAZIL: A PATIENT REGISTRY ANALYSIS. Value in Health. May, 2020.
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Icatibant clinical trials overview

Study	FAST 3 (Trial 1)[1]	FAST 1 (Trial 2)[2]	FAST 2 (Trial 3)[2]
Study objective	Phase 3: To evaluate clinical efficacy and safety of icatibant in the treatment of acute attacks of HAE type I and type II		
Study design	Randomized, placebo-controlled, double-blinded	Randomized, placebo- controlled, double-blinded	Randomized and comparator- controlled, double-blind study
Number of patients	98	56	74
Location	Multicenter (11 countries)	Multicenter (United States, Canada, Australia, and South America)	Multicenter (11 European countries and Israel)
Dose regimen	Icatibant 30 mg SC (one injection) or placebo	Icatibant 30 mg SC (one injection) or placebo	Icatibant 30 mg SC (one injection) or oral TA 3 g daily for 2 days
Primary endpoint	FAST 3 • Cutaneous/abdominal attacks: subject-assessed median time to 50% reduction in symptom severity of cutaneous and/or abdominal attack by VAS from pretreatment score in the 3-symptom composite VAS* • Laryngeal attacks: subject-assessed median time to 50% reduction in symptom severity of laryngeal attacks from pre-treatment score in the 5-symptom composite VAS† FAST 1 and FAST 2 • Median time to clinically significant relief of index symptom‡		
Outcome	• FAST 2 and FAST 3: icatibant is an effective treatment for acute HAE attacks in adults, including cutaneous, abdominal, and laryngeal attacks, as shown by consistent efficacy across multiple endpoints • Icatibant 30 mg SC had a consistent safety profile across all 3 clinical studies		

*Defined as a 50% reduction from pretreatment score in the 3-symptom composite VAS score (mean of scores for skin swelling, skin pain and abdominal pain, VAS-3) maintained at three consecutive timepoints. The first of those three timepoints was then determined retrospectively to be the time of onset of response.
†Defined as a 50% reduction from pretreatment score in the 5-symptom composite VAS score (mean of scores for skin swelling, skin pain, abdominal pain, difficulty swallowing and voice change, VAS-5) for a mild-to-moderate laryngeal attack. Median time to onset of symptom relief for a single primary symptom was as defined for cutaneous and/or abdominal attacks.
‡Based on the highest score on the VAS before study-drug administration, one of the three main symptoms (cutaneous swelling, cutaneous pain, or abdominal pain) was defined in each patient as the index symptom for purposes of assessing the primary end point. For attacks with a combination of these symptoms, abdominal pain was considered the index symptom. Clinically significant symptom relief was defined as a minimum decrease in the score on the VAS of 20–30 mm, depending on the initial symptom severity. Decrease in severity to achieve the primary endpoint was ≥30% (30 mm decrease from a baseline score of 100 mm). This decrease had to have been sustained for three consecutive VAS measurements, with the first measurement being the time point at which clinically significant relief was achieved.
FAST, For Angioedema Subcutaneous Treatment; HAE, hereditary angioedema; SC, subcutaneous; TA, tranexamic acid; VAS, visual-analogue scale

Lumry WR, *et al. Ann Allergy Asthma Immunol* 2011;107:529–537; 2. Cicardi M, *et al. N Engl J Med* 2010;363:532–541 and supplementary appendix

RWE for iOS patient registry – study design and objective

Design

Ongoing, international (>14 COUNTRIES), prospective, observational disease registry to document routine clinical outcomes over time in patients with angioedema, including HAE, treated with icatibant in countries where it is currently approved.

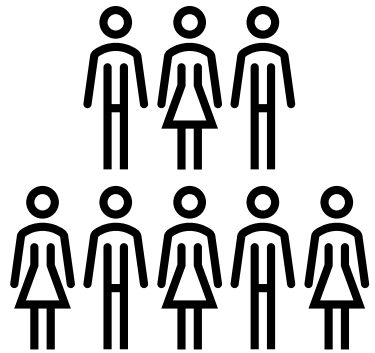
Objective

Evaluate FIRAZYR in routine clinical practice, according to the following primary outcome measures:

FIRAZYR

- Incidence of AEs, SAEs, ADRs
- Incidence of cardiac ischemia events in patients predisposed to such events
- Generalized reactions such as hypotension, swelling of mucous membranes, bronchoconstriction, and aggravation of pain
- Level of sexual hormones (Tanner Staging)
- Time to complete resolution of laryngeal attacks
- Incidence of pregnancy and lactation events

Secondary outcome measures include time to treatment for attack, time to complete resolution of attack, total duration of attack, and the frequency, severity and affected sites of treated attacks



As of 2021†, 961 patients are enrolled in the IOS registry

ADR, adverse drug reactions; AE, adverse event; HAE, hereditary angioedema; IOS, Icatibant Outcome Survey; SAE, serious adverse events
ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/study/NCT01034969 (accessed February 2022)

iOS data added important information for Conitec

LONG TERM FOLLOW UP (10 YEARS)

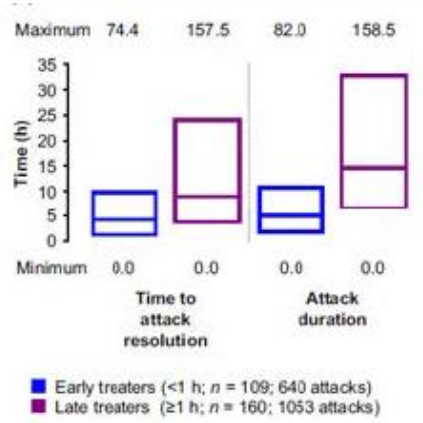
Maurer (2022) [n=549]
2009 a 2019
Total 5995 attacks treated with icatibant

Time to complete resolution of attack = 6 h

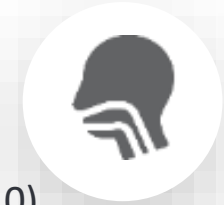
Total duration of attack = 9 h

PATIENT-IMPORTANT OUTCOME DATA

Rapid treatment of attacks is linked to better health outcomes



LIFE-THREATENING ATTACK DATA



Longhurst (2022) [n=42]

Analysis of laryngeal attack (2008 to 2013)
Median time to first injection = 2 hours (IQR: 1.0-8.0)
Median duration of attack = 8.5 hours (IQR: 4.5-19.8)
Median time to complete resolution of symptoms = 6.0 hours (IQR: 2.0-21.0)

LOCAL DATA

Grumarch (2021) [n=42 – n=26 Tipo I e II]
Brazilian data corroborate with general data

Time to complete resolution of attack = 5,5 h;
Time of attack onset = 1h

PEDIATRIC DATA