WHAT ARE COMMUNITY ADVISORY BOARDS?

Patients and Developers engaged in a dialogue

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EURORDIS Membership Meeting, Bucharest, 18 May 2019

EURORDIS.ORG

In memoriam

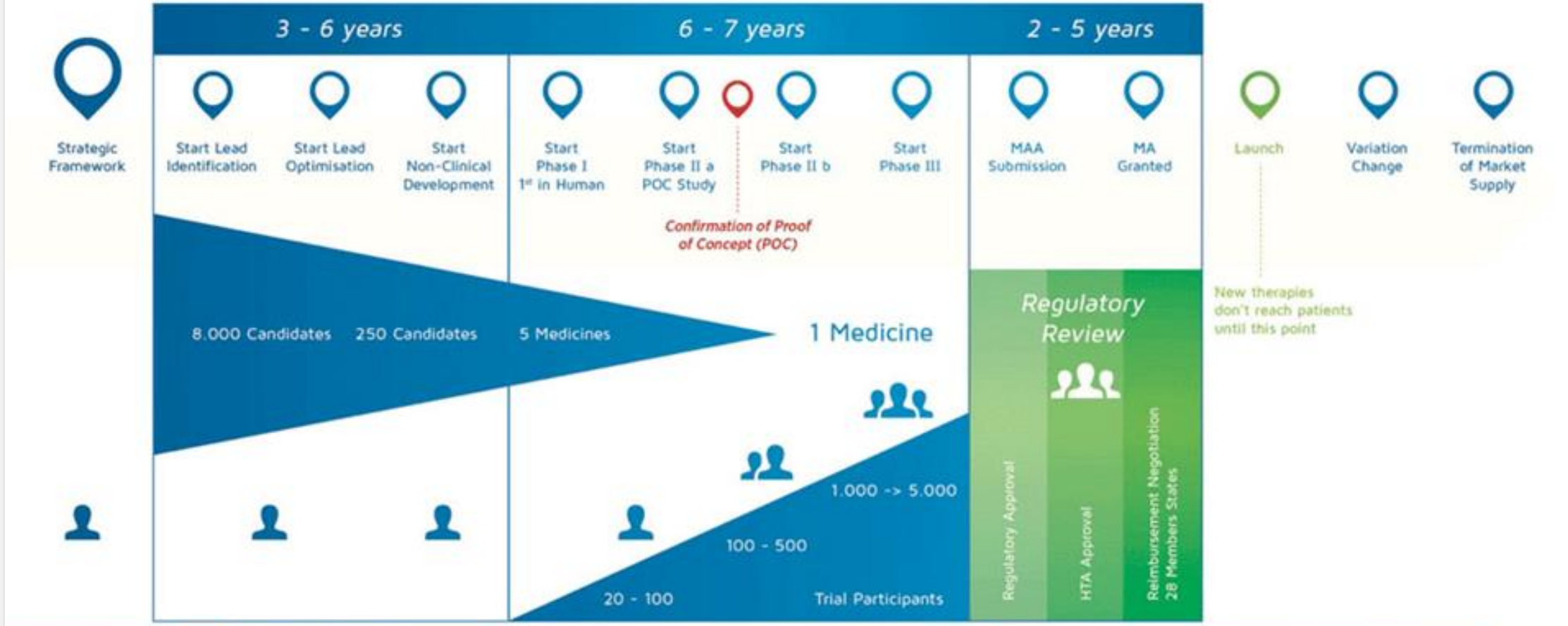
- Andy Velez
- Eric Abadie

Where and how can you make a difference?

- In R&D

Your roles

Overview of Decision Points and Development Steps in Medicines R&D



Research & Discovery

Non-clinical Development

Clinical Development Phase I , II & III

Post-approval Life-cycle management & Pharmacovigilance

Patient Involvement

Decision Point

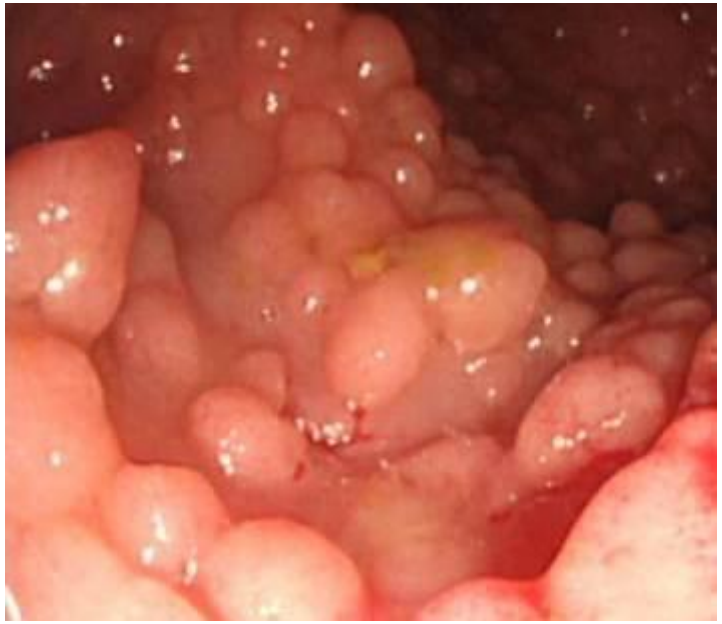
Credits: European Patients Academy EUPATI

Case 1

- Is the main evaluation criteria relevant?

Familial Adenomatous Polyposis (FAP) and celecoxib (Onsenal®)

- FAP develop hundreds to thousands of colon polyps, usually starting in the teens
- All patients will have colorectal cancer from the polyps usually by age 40



Developer did not discuss the project with patients!

Anti-inflammatory product proposed to reduce the numbers of polyps

Efficacy measured by Intestinal endoscopy: number of polyps decreased by 20%

But does this reduce the risk of cancer by 20%? Or fewer colectomies? No data → **conditional MA**

Medicine withdrawn as clinical efficacy could not be confirmed post-MA and new cardiovascular risk identified (Cox-2 inhib.)

- **How to attract investment for your disease?**
  - it takes a hundred Euros of drug revenue 17 years from now to motivate someone to invest one Euro today

- —Eric Vallabh Minikel
- http://www.cureffi.org/2019/04/29/financial-modeling-in-rare-disease/

To invest?

- Average duration of R&D: 17 years

• Discount rate

Assuming a 8% discount rate

one Euro next year is worth 92¢ today

one Euro in year 17, the year in which this hypothetical drug is approved, is worth only 26¢ today

• Failure rate

Only half of pre-clinical products enter clinical stage

Only 10% to 12% of drugs entering a Phase I clinical trial ultimately result in an approved New Drug Application (NDA)

Hay Nat Biotechnol. 2014 Jan;32(1):40-51

• Multiplying these together

The probability that a drug now in early preclinical development will actually result in an approved drug 17 years from now is only 5%

The net present value of a Euro's revenue in the first year of drug approval is one cent today

- One approach to lower the price of medicines

Is to decrease the risks for investors

de-risking

How? To be certain about the research hypothesis

• needs

- What do patients with the disease need the most?

• cause

- What causes the disease?
- What is the molecular target and the mechanism of action that you want a potential drug to have?

• benefit

- What benefit do you expect that mechanism of action to yield?
- In what group of patients at what disease stage after what duration of treatment?

• tools

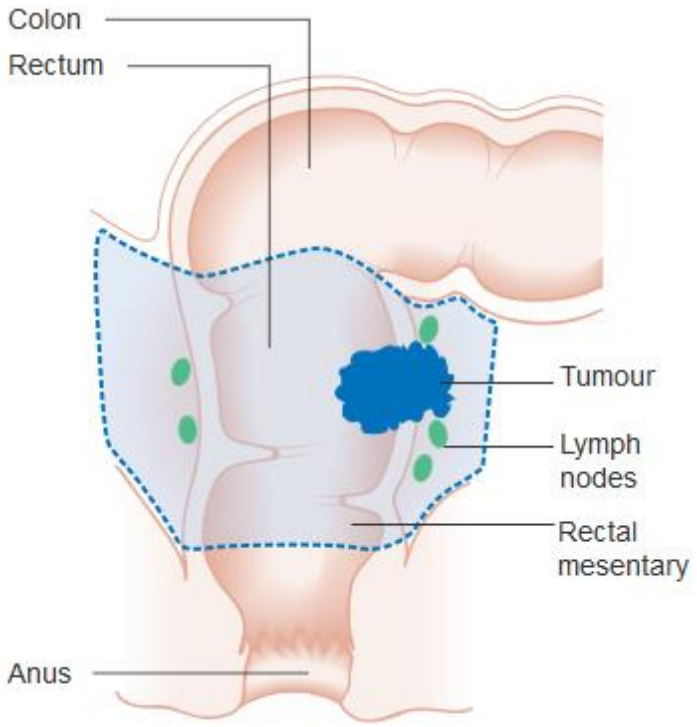
- registries and good clinical trial sites
- clinical tools like biomarkers
- clinical outcome assessments
- CAB

• history

- natural history datasets
- Placebo data
- Previous research / Access to data

Case 2

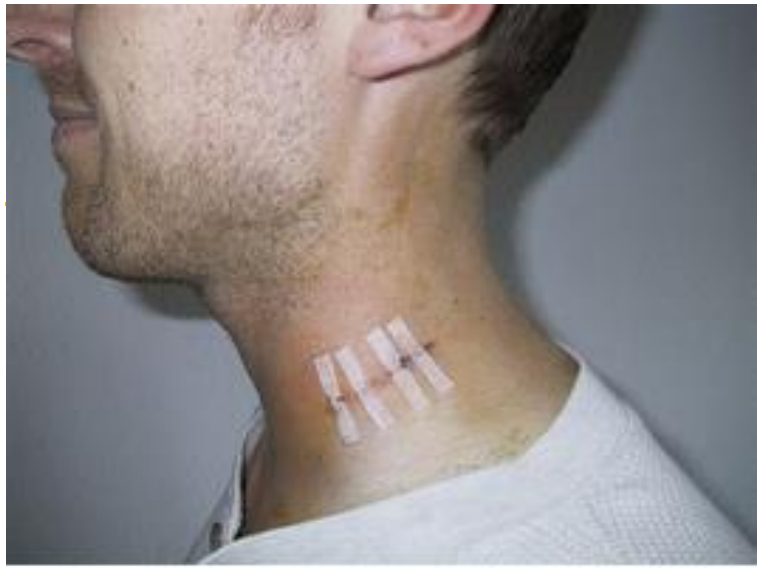
- Interleukin-2 trial | immune system recovery, HIV infection | The INSIGHT–ESPRIT Study Group and SILCAAT Scientific Committee



- If you don't ask patients, how do you decide?

Wrong choice and your study fails

The contribution from CAB members depends on how well they're connected to the patient community, more than their own knowledge.



What do trial participants prefer?

Case 3

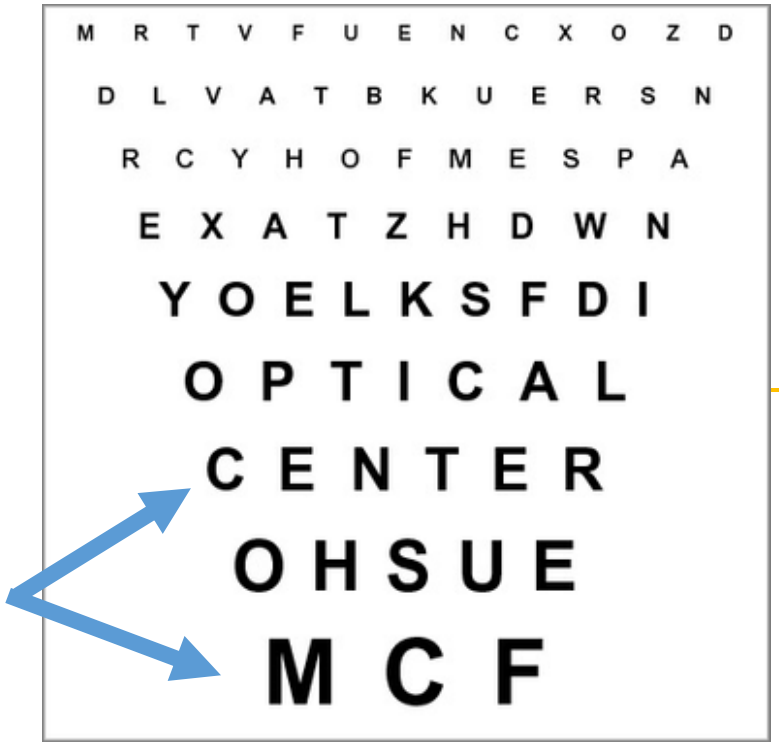
- A treatment to help slow down disease progression?

Leber Hereditary Optic Neuropathy

An experimental product with some improvement in vision

Ok, but does it help?

- What can be measured that confirms the eye chart?
- % who can go on the street unaccompanied?



•?

- Same with industry?

"With a high quality dialogue, patients and regulators can only agree."

Jean-Michel Alexandre

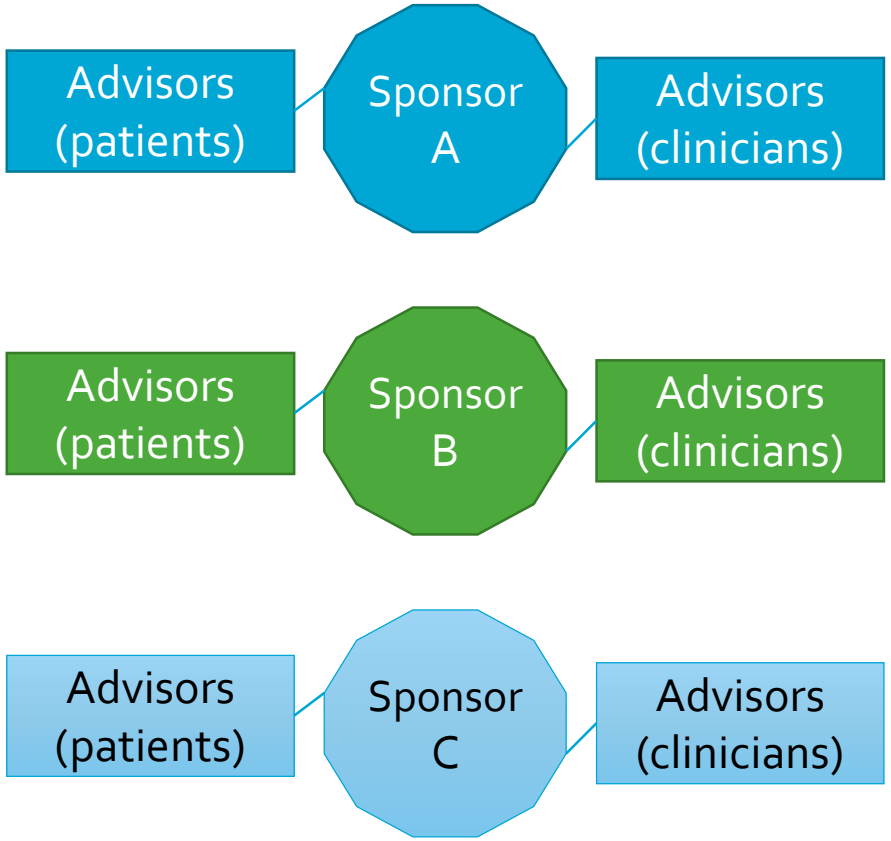
Former CHMP chair, EMA

What is a CAB? How do they operate?

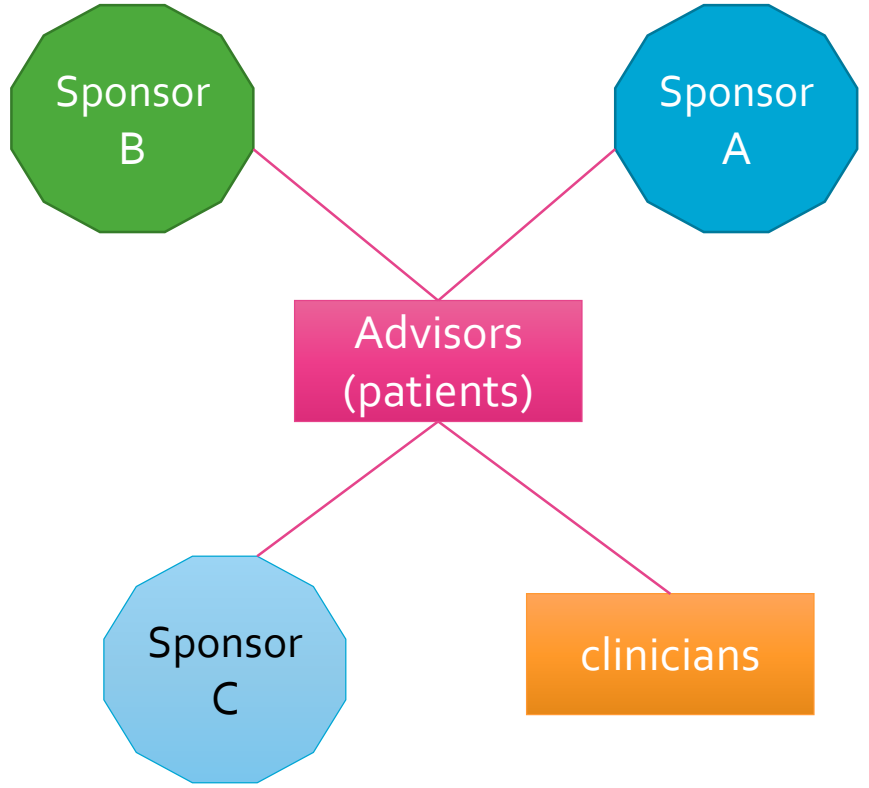
Community Advisory Board

Same disease area, different sponsors

Sponsor-dependant model: you rarely know who's in



CAB model Consistency, transparency



EUROCAB in practice: the "patient investigator"

- Group of 7 - 16 trained patients (same disease or similar) committed to follow up the research over time
- Meet at regular intervals (from twice a year to 6 times a year or more)
- Mentor to help with the organisation, governance
- Costs borne by company/sponsor
- Charter / Memorandum of Understanding (Scope, commitment…)
- Agendas are public (transparency), names of CAB members are public

15

4-day meeting example: 3 sponsors

Wednesday

- Arrival
- Preparation of 2 meetings to come

Thursday

- First time meeting with sponsor A

Friday

- Meeting with Sponsor B
- Meeting with sponsor C

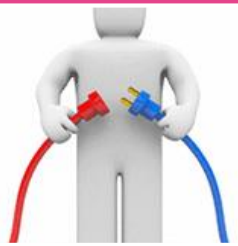
Saturday

- Training on horizon scanning
- Organisational matters
- Departure

The EUROCAB programme: incubator, mentor, advisor

Identification of areas where CABs are needed

- Call to Members
- Feedback from experts (COMP, PRIME…), scanning the horizon
- Webinars to patient networks, meetings, preparatory phase (6-9 months)



Matchmaking with industry

- Contact or help contacting developers /sponsors in relation to horizon scanning
- Receives direct requests from developers

Mentoring (EURORDIS staff and others)

- Help preparing and running CAB meetings
- Keeping guidelines up-to-date, developing policies
- Back-end office, "treatment activist advice"

Issues addressed at a conference about CABs, Bergen, 1997 (haemophilia, cancers, HIV)

- Dependency on pharmaceutical companies
- Operating procedures (Recruitment, training needs, representative character…)
- Outcomes, evaluation
- Attitudes of physicians
- Conflicts of Interest (financial, intellectual, participatory)
- Long-term commitment
- Transparency, confidentiality

18

Guidelines and GPEP (Good Patient Engagement Practices)

How to create and operate a CAB

Travel, subsistence and compensation of time spent

Code of Conduct for CAB members

Declaration of interest

Charter

Confidentiality undertaking

Insider Trading prevention

(industry working group)

How to evaluate your CAB?

EuroCAB Register

Developed

In development

Guidelines headlines - How to start (20 pages)

- Finding volunteers, CAB composition / task description
- Deciding which developers to work with
- Preparing the first meeting / all questions you need to address before
- CAB Scientific Secretariat, CAB liaison with sponsor
- Budget planning
- Declarations of interests and consequences advising sponsors / companies (level 2 Conflict of Interest as for clinical investigators? As more difficult to influence people in a group than isolated ones?
  - the "patient investigator"

EURORDIS RARE DISEASES EUROPE

EuroCAB Seal criteria

- Mandatory
  - Open Call for volunteers (among European patient groups and social networks)
  - Agendas and composition made public (members' names)
  - Work with different developers in the field (when applicable)
  - Memorandum of Understanding for each development / research project / study
  - Minutes and follow-up of each meeting
  - EuroCAB contract signed between CAB and EURORDIS
  - Elected CAB chair
- Important to have
  - Scientific secretariat
  - Certification that CAB members followed the e-learning (Open Academy)…
  - Horizon scanning activities

EURORDIS RARE DISEASES EUROPE

EuroCAB

- Plans for 2019 – 2020: 20 CABs

5 CABs

- Active in 2019

- Duchenne MD
- Cystic Fibrosis
- Hered. Haemorr. Telangiec.
- Lymphoma
- Cystinosis

10 CABs soon to start

- Coming soon

- Ataxias
- Retinopathies
- (Multiple Sclerosis)
- Spinal Muscular Dystrophy
- Osteogenesis imperfecta
- Pituitary syndrome
- Myasthenia Gravis
- Fabry disease
- (Thalassaemia & sickle cell)
- (Pompe disease)

5 prospects

- Discussions

- Head and Neck K
- Myelodysplastic syndromes
- Tuberous Sclerosis Complex
- Scleroderma
- (Psoriasis)

- CABs gives consistent substance to term “Engagement”
- Moving away from "have to find a drug” to “have to enable a drug” (Eric Vallabh Minikel)
- A comprehensive programme with guidance
- EuroCAB provides a solid framework in rare diseases

Thank you for your attention

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One more word from the investor's perspective

Table 3: The results from the base case analysis.

Disease	Drugs	Price	Break-even price	Mark-up*	
		Annual	Annual	Absolute	%
Paroxysmal nocturnal hemoglobinuria (PNH)	Eculizumab	€358,000	€458,870	-€100,870	-22%
Hunter syndrome	Idursulfase	€600,000	€1,076,579	-€476,579	-44%
Cystic fibrosis (CF)	Lumacaftor/ivacaftor	€169,386	€65,861	€103,525	157%
Cystic fibrosis (CF)	Ataluren	€270,000	€254,464	€15,536	6%
Primary biliary cholangitis (PBC)	Obeticholic acid	€38,021	€46,652	-€8,631	-19%
Spinal Muscular Atrophy (SMA)	Nusinersen	€240,000	€95,860	€144,140	150%
Neuronal ceroid lipofuscinosis, late infantile type 2 (CLN2)	Cerliponase alpha	€595,971	€799,744	-€203,773	-25%
Metabolic disease - alpha-mannosidosis lysosomal disease	Velmanase alpha	€800,000	€799,744	€256	0.1%
Congenital or acquired lipodystrophy	Metreleptin	€480,000	€509,623	-€29,623	-6%

*A positive difference indicates that actual prices are higher than break-even prices and a negative difference indicates that actual prices are lower than break-even prices.

Nuijten et al. Int J Rare Dis Disord 2018, 1:005