COMPASSIONATE USE

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Summer school 2017

EURORDIS.ORG

Introduction

Batten disease

- NCL2 = neuronal ceroid lipofuscinosis type 2
- Lysosomal storage disorder primarily affecting the brain
- NCL 2 is a debilitating and life-threatening disease that usually leads to death between the ages of 8 and 12
  - Children loose their cognitive functions one after the other
  - Rapidly evolving: a child can walk, 6 months later he can't. Same for speech, and all other functions
- Symptoms usually begin between 2 and 4 years of age, and include delayed speech, inability to coordinate muscle movements, fits, loss of vision and mental deterioration

Prevalence (SOP) (12/03/2013): 15,000

- On its web site, BioMarin estimated the number of children ranging from 1,200 to 1,600 in their "commercial territories" (Biomarin, 2016)

- But in its annual report year 2014, BioMarin estimated that 400-600 cases exist worldwide

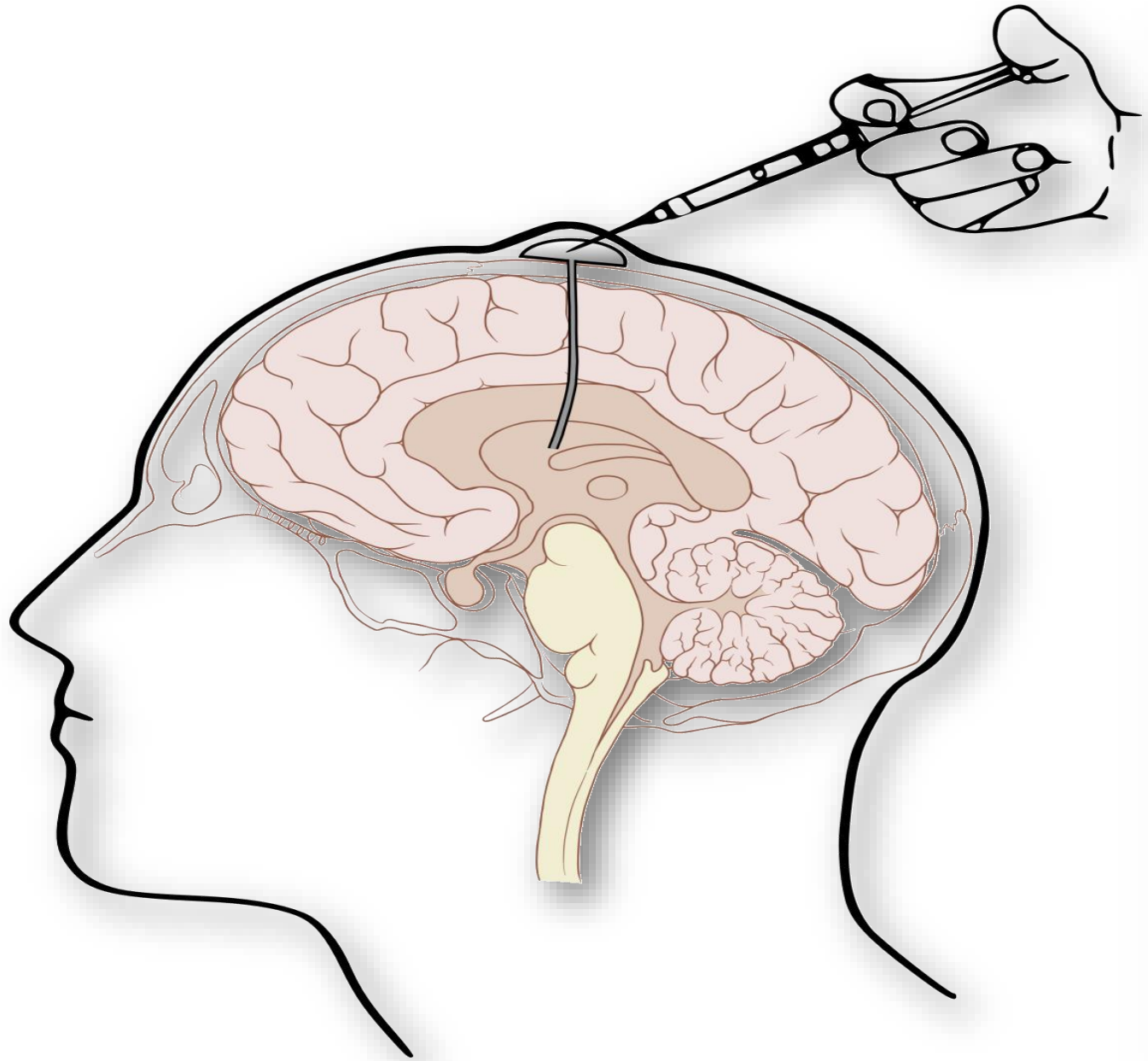
"BioMarin is expecting 500 Mio$ revenues per year with BMN 190"

Cost per patient
300 k$ to 1 Mio$/year/pt

If 15,000: 33,000 $/pt/y

BMN 190: not an easy product

- Enzyme replacement therapy
- Biological: large protein produced in Chinese hamster ovary cells
- Administration mode is
  - every other week
  - Via Intraventricular infusions (implanted intra-cerebro-ventricular (ICV) reservoir and cannula)
- Needs to be transported frozen (brain infusion = no preservatives)
- By a trained neuro-paediatrician in specialised centres
- Risk of brain infection: 1 per 46 patient-year (mini)
- Doesn't pass the retina



Context for BioMarin

An active company in RD

Commercial Products	Indication	Orphan Drug Exclusivity Expiration U.S.	Orphan Drug Exclusivity Expiration EU	2014 Total Net Product Revenues (in millions)	2014 Research & Development Expense (in millions)
Vimizim	MPS IV A (1)	2021	2024	$ 77.3	$ 63.6
Naglazyme	MPS VI (2)	Expired	September 2015	$ 334.4	$ 12.1
Kuvan	PKU (3)	June 2015	NA (4)	$ 203.0	$ 13.5
Aldurazyme (5)	MPS I (6)	Expired	Expired	$ 105.6	$ 1.6
Firdapse	LEMS (7)	NA (8)	2019	$ 18.1	$ 4.6

(1) Morquio disease or Mucopolysaccharidosis type IV ORPHA582
(2) Maroteaux-Lamy disease or Mucopolysaccharidosis type VI ORPHA583
(3) Phenylalanine hydroxylase deficiency ORPHA716
(4) Mercks-Serono markets Kuvan in the EU. Court case in progress against generic manufacturer
(5) Agreement with Genzyme Corporation
(6) Hurler syndrome Mucopolysaccharidosis type I ORPHA579
(7) Lambert-Eaton myasthenic syndrome ORPHA43393

An ambitious R&D in RD

Products in Development	Target Indication	Orphan Designation US	Orphan Designation EU	Stage	2014 Research & Development Expense (in millions)
Drisapersen	DMD [9]	Yes	Yes	Clinical Phase 3	N/A
BMN 044 (PRO 044)	DMD [9]	Yes	Yes	Clinical Phase 2	N/A
BMN 045 (PRO 045)	DMD [9]	Yes	Yes	Clinical Phase 2	N/A
BMN 053 (PRO 053)	DMD [9]	Yes	Yes	Clinical Phase 1/2	N/A
Pegvaliase (PEG PAL)	PKU	Yes	Yes	Clinical Phase 3	$ 70.5
Reveglucosidase alfa (BMN 701)	Pompe [10]	Yes	Yes	Clinical Phase 2/3	$ 51.1
Talazoparib (BMN 673) [11]	BRCA breast cancer	No	No	Clinical Phase 3	$ 59.8
BMN 111	Achondroplasia	Yes	Yes	Clinical Phase 2	$ 22.5
Cerliponase alfa (BMN 190)	CLN2 [12]	Yes	Yes	Clinical Phase 1/2	$ 39.5

rejected

Prosensa

(9) Duchenne Muscular Dystrophy ORPHA98896

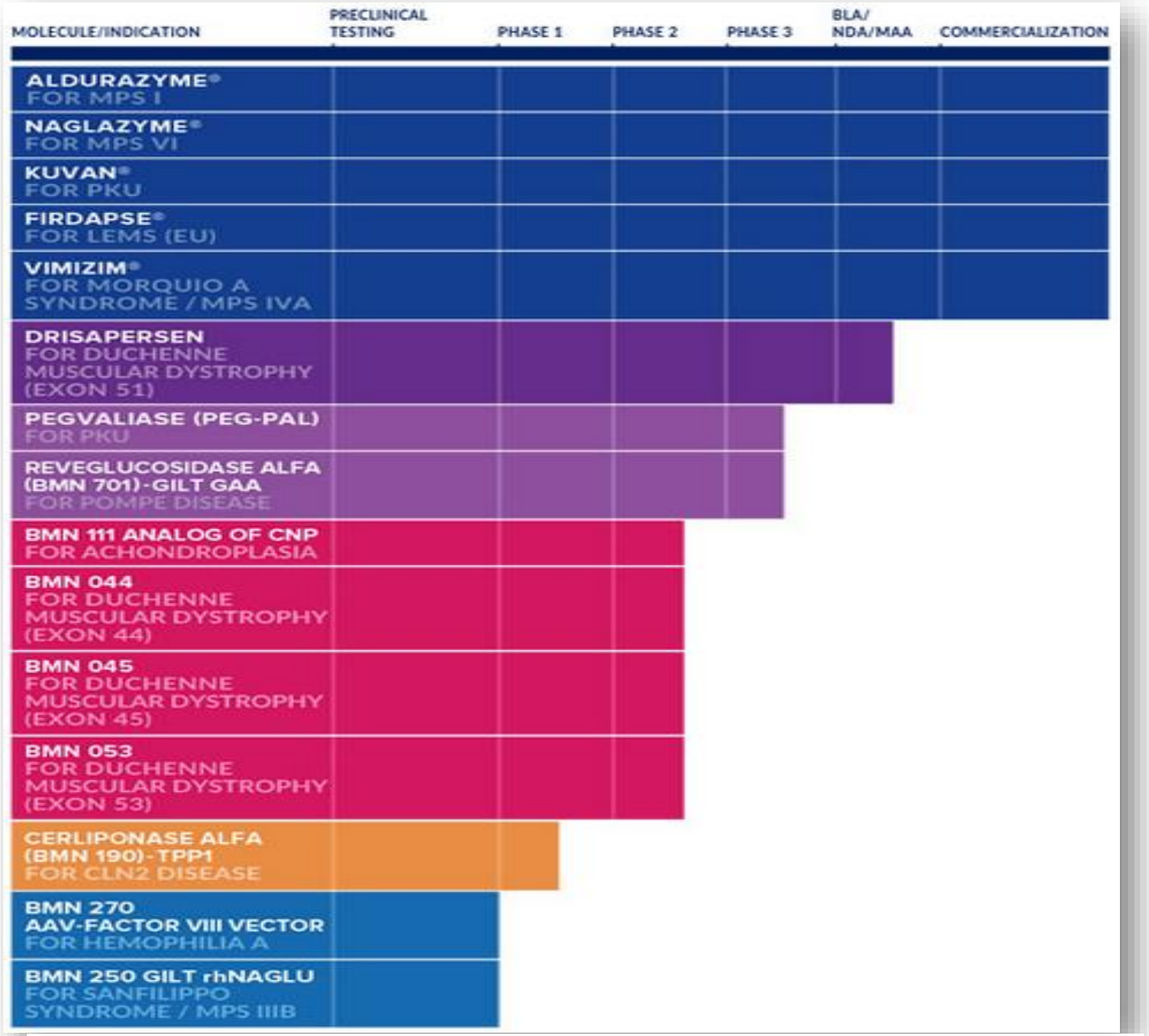


Figure 1: BioMarin's Pipeline as of January 2016

Financial situation

	Years Ended December 31,		
	2014	2013	2012
Total net product revenues	$ 738.4	$ 538.4	$ 496.5
Cost of sales	129.8	95.7	91.8
Research & Development (R&D) expense	461.5	354.8	302.2
Selling, general and administrative (SG&A) expense	302.2	235.4	198.2
Net loss	(134.0)	(176.4)	(114.3)
Stock-based compensation expense	86.4	64.4	48.0

Mr. Bienaimé joined BioMarin in May 2005 as Chief Executive Officer

Under his leadership, the market capitalization of BioMarin went from around $450 million in May 2005 to approximately $9 billion in May 2014

http://frenchtechhub.com/fr/2014/06/interview-jean-jacques-bienaime-biomarins-ceo-nominated-as-the-years-personality-for-the-french-american-business-award/

The problem

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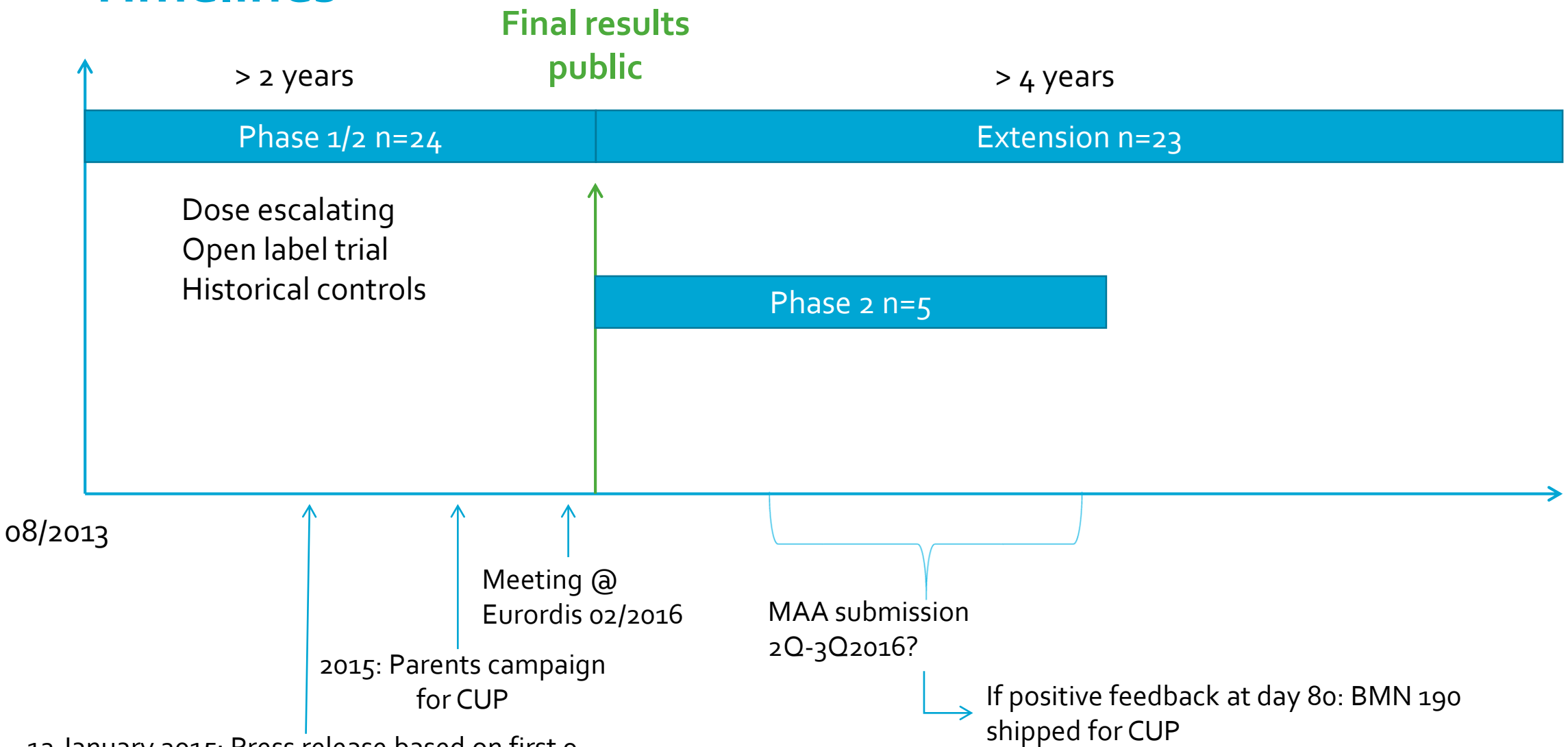
Timelines



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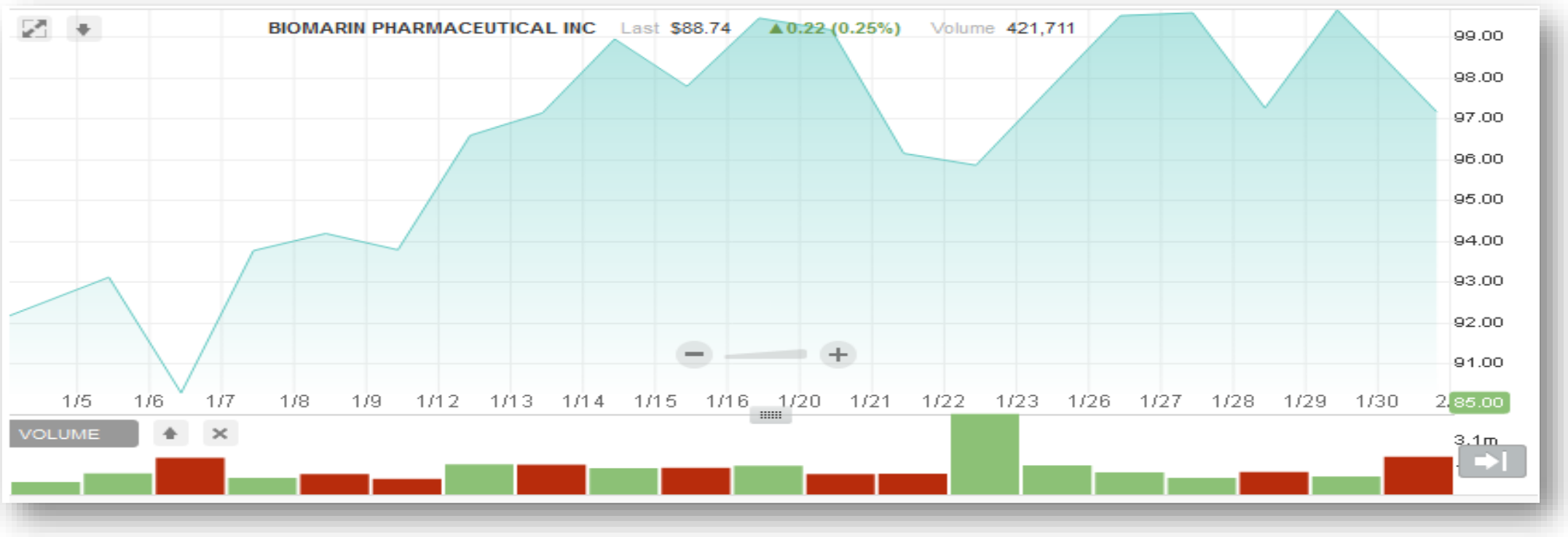
Sequence of events

- Some patients consulted on the clinical trial in 2013
  - Who? Transparency?
- When first 9 patients reached 6 months of treatment, press release "promising results" (January 2015)
- Immediately: parents asked for compassionate use
  - Large media campaign in Germany
- BioMarin refused on "ethical grounds"
- 5/02/2016 "reconciliation meeting" @ EURORDIS
- 03/03/2016 final results announced at World conf.

Impact of press release

We now include a 40% probability of approval for BMN-190 in Batten disease (up from 20%). Early data for BMN-190 was positive.



Participants @ EURORDIS meeting

Parents and advocates	Representing
Ms Iris Dyck	NCL-Gruppe Deutschland e.V., Germany
Mr Michael Vogel	Parent, Germany
Mr. Paul Marshall	Accompanying person
Mr Saverio Bisceglia	Asso. Nazionale CeroidoLipofuscinosi, Italy
Mr Stratigakis Charalambos	Accompanying person
Ms Inge Schwerzens	DGM, Germany
Ms Bojana Mirosavijevic	Child RD support and research asso., Serbia
Ms Andrea West	Batten Disease Family Asso., UK
Mr Caroll	Batten Disease Family Asso., UK
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Ms Małgorzata Skweres-Kuchta	Parent, Poland
Ms Monika Kuchta	Accompanying person
Mr François Houÿez	EURORDIS
Ms Anja Helm	EURORDIS
Ms Virginie Hivert	EURORDIS
Ms Jill Bonjean	EURORDIS

Clinicians	
Dr Angela Schulz	University Hospital Hamburg
Dr Marina Trivisano	Bambino Gesu Roma

Biomarin	
Camilla Simpson	Group Vice Pdt, Regulatory Affairs
James Lennertz	Group Vice Pdt, Commercial Operations
Jessica Cohen Pfeffer	MD, Senior Medical Director, Medical Affairs
Chay Morgan	Vice Pdt, Regulatory Affairs, EU
Paul Humphrey	Associate Director, BioMarin Patient Advocacy

BioMarin regulatory approach

- Submission of a marketing authorisation application to EMA
  - 2Q or 3Q 2016 (between May-September 2016)
  - With results from the 201 trial (23 patients only)
  - With accelerated review (150 not 210 days)
  - For a full approval
- In parallel: start arrangements for CUPs in Ger, Ita, UK and USA
  - But will ship product only if positive feedback from regulators (day 80, August-December 2016)
  - In theory they could ship it at anytime, independently from regulators' feedback

The unknowns

BioMarin

- Current production
  - 800 L every 6 months, enough for 500 pts?
  - New site under construction in Shanbally, Ire, for 2500 L
    - But no recipe for the last 3 years
- Acquiring Prosensa knowing drisapersen had failed
  - Regulatory approach failed ("rescue approach")
  - For next product (BMN 190): can't take the risk anymore
- If CUP starts now but regulatory approach rejected
  - Then CUP can last for many years – out of control

Hell is in the details

Germany

- CUP to be initiated by the company, not by clinicians
- CUP must be for free
- CUP must use commercial batches of highest quality
- Unclear who pays for other expenses (surgery…)

France

- CUP can be on doctor's request
- CUP can be free of charge or paid for
- CUP can use pilot batches
- Healthcare system pays for all related expenses

Compassionate use programmes

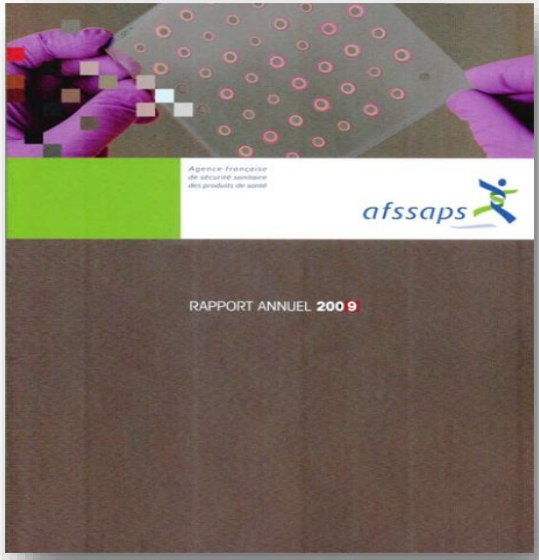
REGULATION (EC) Nº 726/2004 art. 83.2

- *Running a Compassionate Use Programme (CUP) consists in making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product.*
- *The medicinal product concerned must either be the subject of an application for a marketing authorisation or must be undergoing clinical trials.*

A.T.U and orphan drugs

- Afssaps, annual report 2009

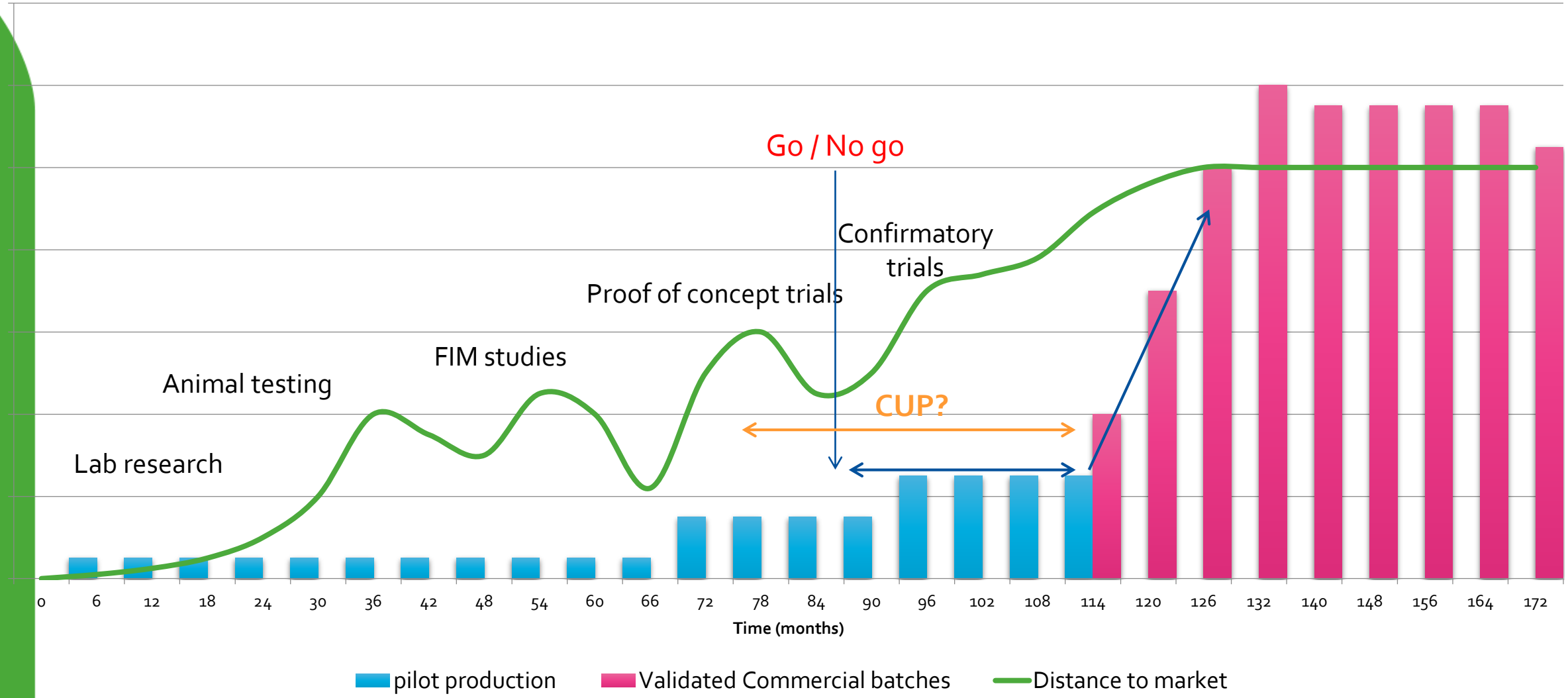
> Le plus souvent, ces médicaments sont mis à la disposition des patients de façon précoce par des Autorisations temporaires d'utilisation (ATU) nominatives ou de cohorte, délivrées par l'Afssaps. Ainsi, 72% des médicaments orphelins pour lesquels une AMM a été accordée, ont été administrés aux patients, par le biais des ATU, 34 mois en moyenne avant l'obtention de leur AMM.



- 72% of authorised orphan drugs received ATU* status
- In average 34 months before authorisation

* Temporary Use Authorisation

CUP initiation is a matter of manufacturing capacity, proof of concept and willingness



Usual difficulties for companies / CUP

- Differences in the local legislation across countries caused products to be available earlier in some MS than in others
- The sites where the CUPs are run cannot be selected: any request needs to be honoured, for any patient that meets the criteria for use of the product
- In emergency situations, administrative constraints are difficult to manage; even in countries with sophisticated CUP schemes, emergency situations remains difficult to respond to
- EURORDIS resources: http://www.eurordis.org/content/links-national-authorities-websites

What to do in this case?

- Regulators can only act if a procedure is initiated
  - At national level for compassionate use
  - At EU level MAA submission or opinion requested for CUP
- Letters from doctors and patients to BioMarin?
  - And so what? It's BioMarin choice
  - Patients missed the only opportunity they had to negotiate
- Media campaign / Public statement
  - "BioMarin promising results are patients false hopes / delusion"?
  - "BioMarin unable to manufacture product and yet ready to submit MAA?"
  - Maybe no effect, but parents will feel supported

What can EURORDIS do in general?

- Explain members what they can do and when
  - More "know-how" and less "know" in trainings?
  - Systematic information when product designated on their role in R&D and evaluation?
- EURORDIS Position on CUP
  - Adopted by MB March 2017
  - Sent to all national competent authorities in the EU
  - To be presented at STAMP on 27 / 06
  - EMA session on CUP end 2017

EURORDIS proposes to

1. Promote the French ATU system
2. Adopt European legislative measures which would confer a greater role in the organisation of CUPs upon the EMA
3. and/or apply the Directive on Patients' Rights in Cross-Border Healthcare to include compassionate use as part of the care basket
4. and/or apply the Medicines Adaptive Pathways to Patients to all medicines
5. And amend the EMA guidelines for compassionate use

Together with recommendations to

- Patients' organisations
- Industry
- Member States
- European Authorities

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Thank you!

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