EURORDIS
Rare Diseases Europe

Proposal for an Eurordis position on compassionate use of medicines

CNA & CEF meeting, 2-3 November 2016, Paris

Why do we need a position?

Advocating for compassionate use programmes (CUP), because:

- Negotiating a CUP is one of the most important actions a patient organisation may conduct
- They are a societal response to desperate situations
- Inequity by disease prevails
  - 100% of HIV and viral hepatitis product benefit from CUPs
  - As opposed to maybe 10% for OMPs?
- Inequity by country prevails
  - France: 73% of OMPs that are authorised are available in average 36 months before the marketing authorisation
  - UK: for many, only after NICE appraisal, and local trustees

REGULATION (EC) Nº 726/2004 art. 83

- *2. Running a 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.*
- *8. Where a compassionate use programme has been set up, the applicant shall ensure that patients taking part also have access to the new medicinal product during the period between authorisation and placing on the market*

A frequent situation

New drug being developed

New drug authorised

Marketing authorisation

Some patients have no more treatment options, their condition deteriorates. Some die.
They know trials are in progress

When the drug is authorised, patients can have access.

There is always one patient who will suffer the day before a drug is authorised and who knows the drug will be authorised next day

For all, this is a nightmare

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Compassionate use is a response

New drug being developed

New drug authorised

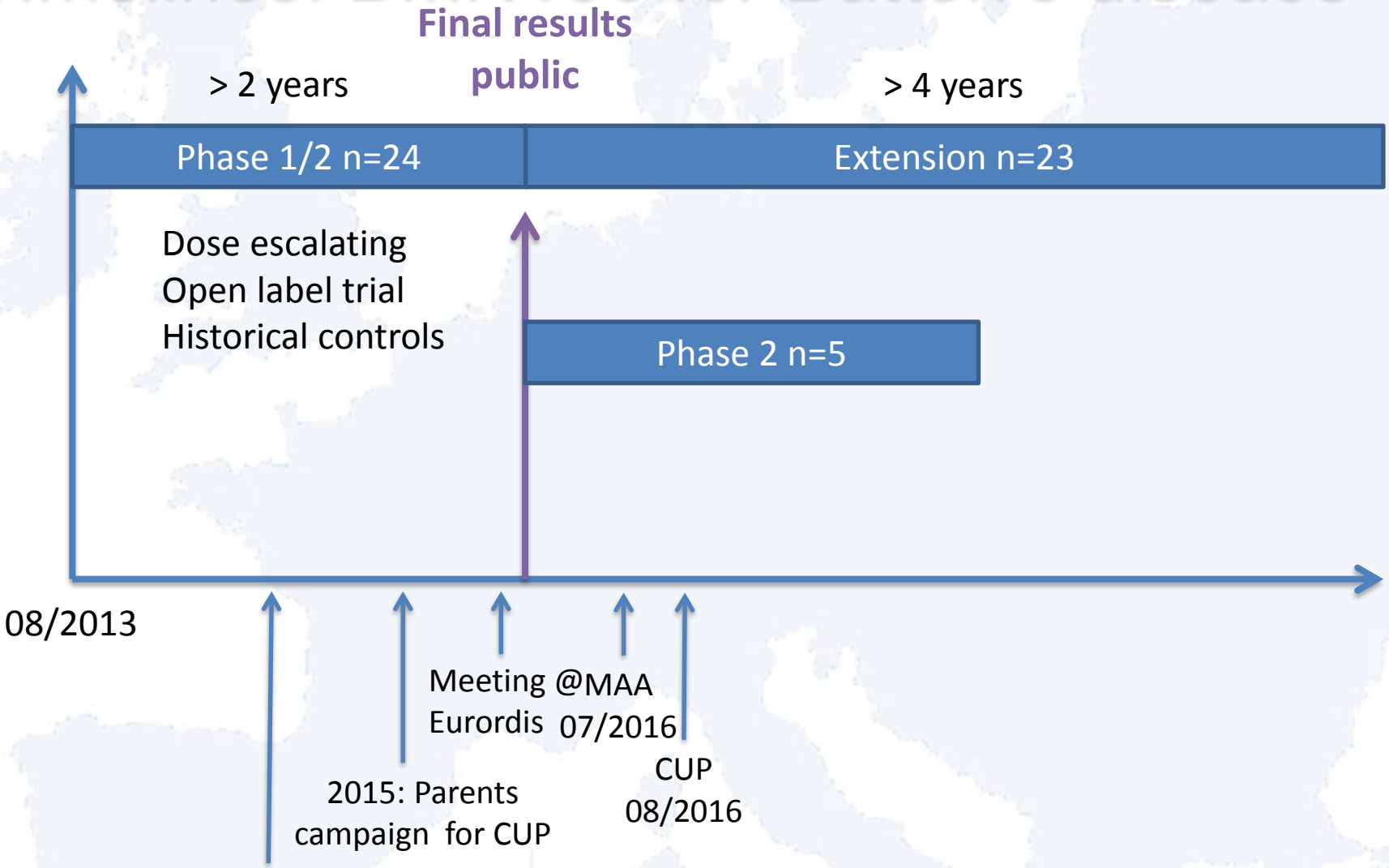
Compassionate use

Or adaptive licensing

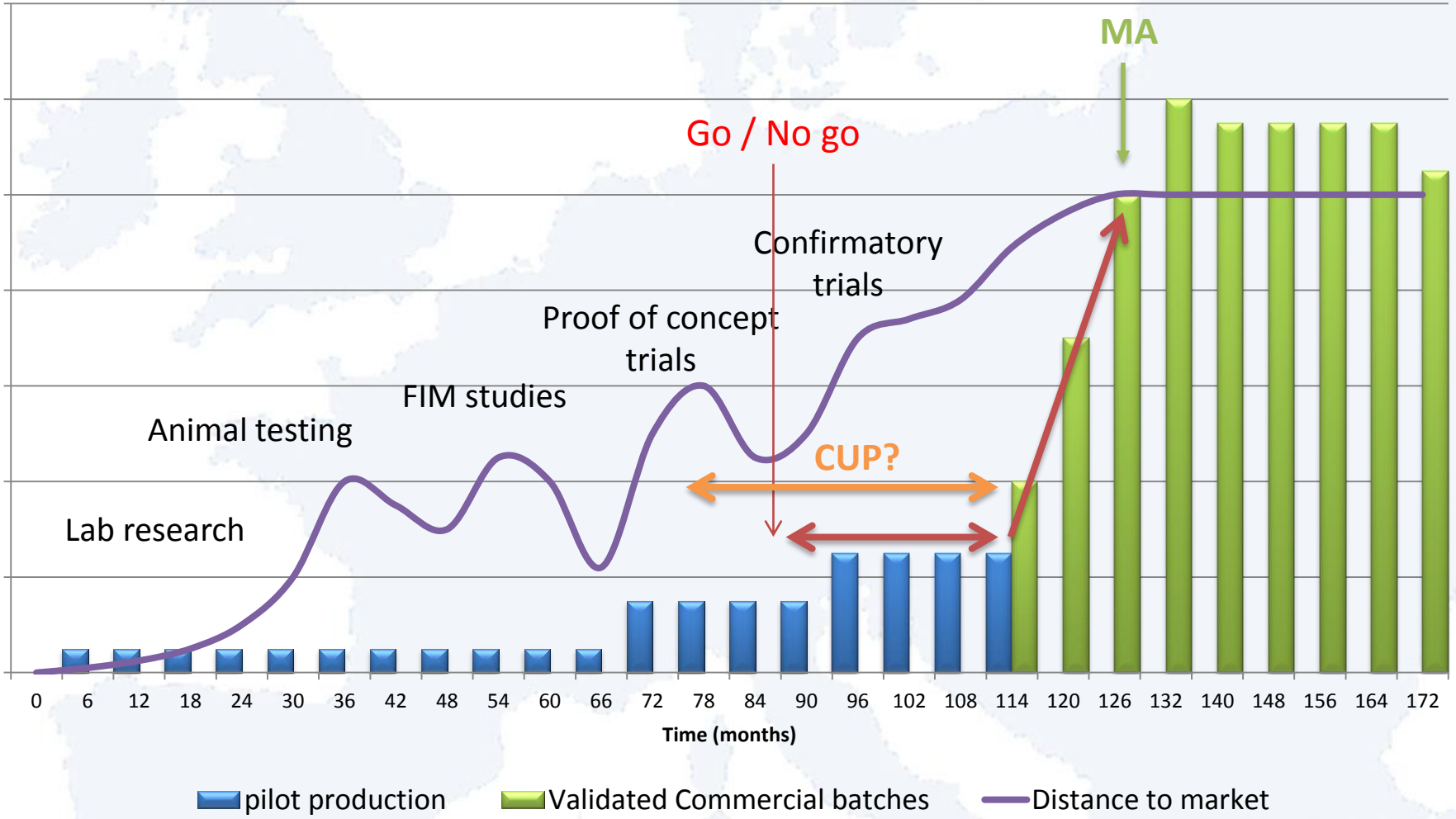
But whenever a compassionate use programme starts, there will always be patients for whom it will be too late.

Some 560 medicines for rare diseases currently in development

Timelines: BMN190 for Batten's disease



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



Compassionate use programmes

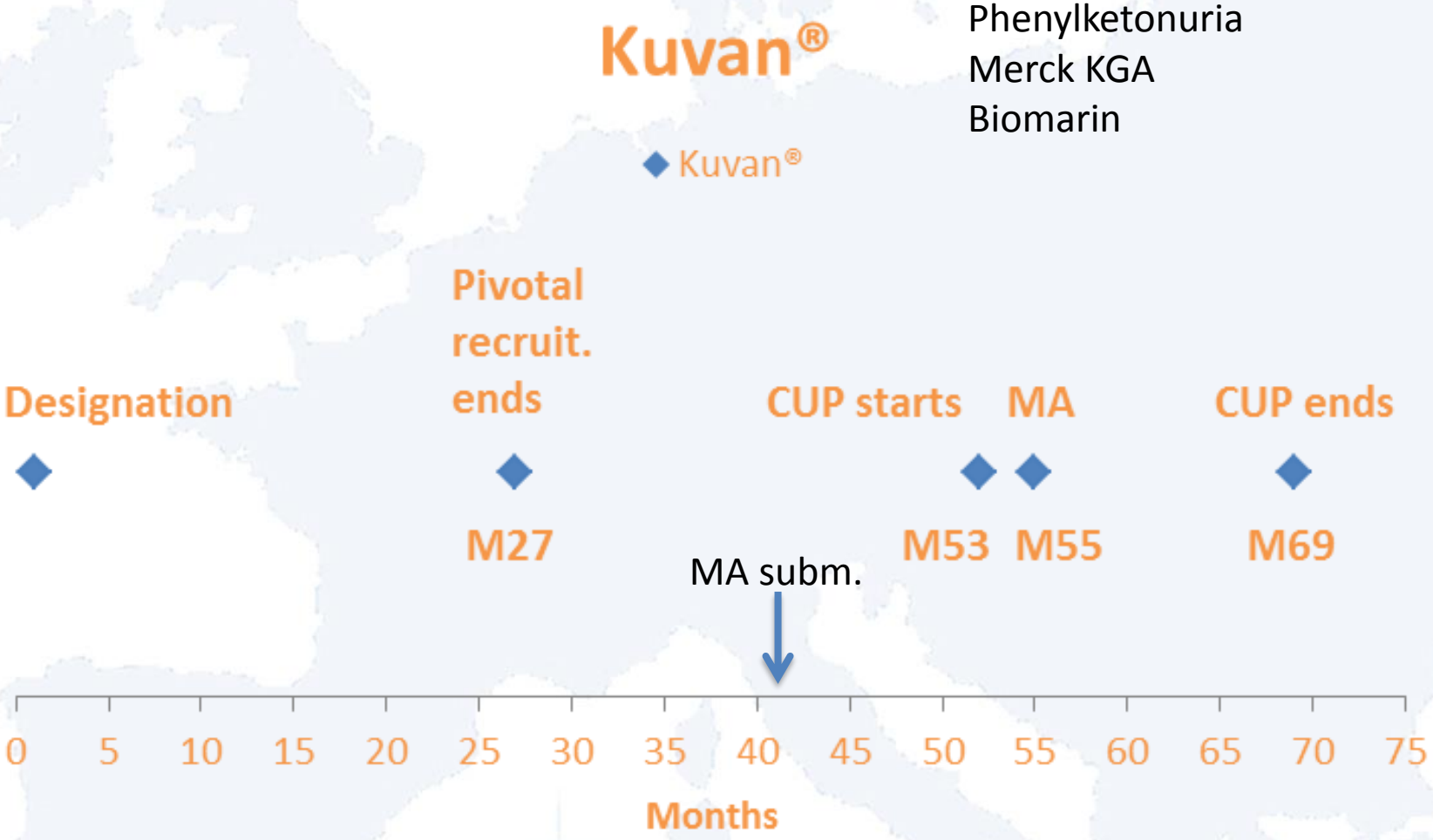
Completed programmes (1)

Xyrem®

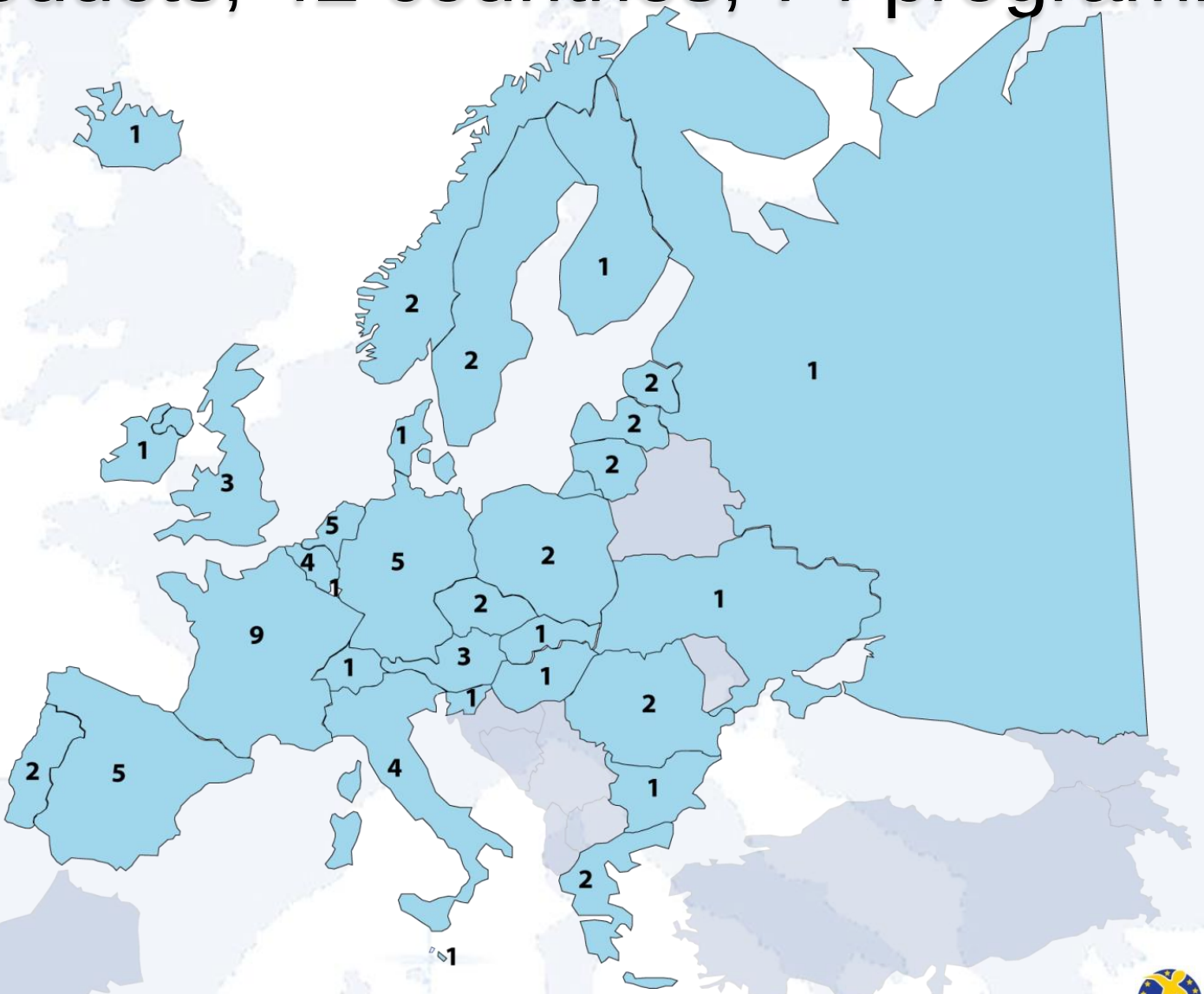
narcolepsy
UCB

Completed programmes (2)

Phenylketonuria
Merck KGA
Biomarin



9 products, 42 countries, 74 programmes



What we are asking for

Policy options

Promote the French ATU system

Or **adopt an EU Regulation**

and/or **apply the Directive on Patients' Rights in Cross-Border Healthcare**

Or Generalise the Medicines Adaptive Pathways to Patients

and/or **Amend the EMA guidelines for compassionate use**

Recommendations

To patients' organisations

To industry

To Member States

To European Authorities (EC, EMA, HMA)

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

Still in discussion: should the company set up its own ethics committee ? Right to Try Act

- Named patient basis
- No clear criteria, no clear information on how much product
- Companies doesn't want to choose patients
- They set up an ad hoc committee, the committee selects eligible patients
- Officially it's not the company's responsibility

- Our concerns:
  - First come first served: not ethical, favours first informed
  - No public scrutiny, not accountable to patients
  - Easy fix to escape responsibilities
  - Committee members appointed by company, arrangements unknown
  - Company and patients connected
  - Cohort programmes preferred
- But if not?

Another hot topic: when supply is limited

- Equity:
  - Members of patients' organisations should not be advantaged compared to non-members (no advantage for the best informed)
  - Medical criteria: doesn't work, doctors write what they want
  - If extremely limited supply: random draw to enrol patients

- French Ethics Council Opinions 1996

  Since patients will be selected randomly by computer, there will be no conscious or unconscious emotional preference or pressure. Drawing lots will relieve doctors of the responsibility of choice and preserve patients' trust in their attending physicians. Lots will be drawn each time supplementary drug doses are made available, with the aim of including all eligible patients.

But who should organise the lottery?

- Local hospitals?
- National authorities?
- The sponsor of the clinical trials/ developer of the product?
- The clinical research organisation?
- The patients' organisation?

- *The view of prominent patients' advocates is that the pharmaceutical company that is responsible for the communication on "promising results" should be responsible for monitoring the consequences of this communication*

Another point to clarify

- Advance medicinal products
- Should they have a compassionate use programme?
  - E.g. ADA-SCID gene therapy product Theleton Italia/GSK
- Or should we favour clinical trials above all?
  - French ATU scheme: AMP excluded for this reason

Other considerations for CUPs

- Compassionate use programme for all, as open as possible
- Inclusion criteria mirror the exclusion criteria of the CT
  - No conflict between clinical trial enrolment and enrolment in the compassionate use programme
  - In rare diseases, this is not always possible
- Information
  - EURORDIS resources: http://www.eurordis.org/content/links-national-authorities-websites
  - NCAs that publish guidance on their compassionate use programs within their Member States (HMAs): http://www.hma.eu/fileadmin/dateien/HMA_joint/02-_HMA_Strategy_Annual_Reports/08_HMA_Publications/2016_05_HMA_Compassionate_use_program.pdf

Other issues to be addressed at EU level

- There are important differences between Member States policies (authorisation of the CUP, documentation required, assessment time, validity, follow up, reporting…)
- Liability risks need to be clarified
- Transparency of the programmes
- Interference with the marketing authorisation procedure and whether or not the data collected in a programme can be part of the dossier submitted to regulatory authorities
- Free of charge or paid for programmes

Revise EMA guidelines on CUP, as proposed in ComCom on RD in 2008

- EMA guidelines: very restrictive interpretation of the Regulation
  - CHMP adopt opinions on the conditions for use, the conditions for distribution and the patients targeted
- EMA interprets conditions for distribution only as
  - medicinal product is subject to medical prescription, or whether it is subject to special or restricted medical prescription.

- What should be addressed
  - Anticipation of the programme during early SA
  - Estimates on how many patients could benefit from the CUP in the EU
  - Criteria to increase the number of patients when more product is available
  - Measures when the demand exceeds available supply
  - Measures to ensure a fair distribution of available stock among Member States

To conclude: from here

- 2 key questions need to be answered
- Internal consultation with EPAC
- Formal adoption by BOD / General Assembly
- Advocacy: Access initiatives, EMA, EP, EC
- Community Advisory Boards are the place to discuss CUPs

To patients' organisations

1. Patients' organisations should be aware of the importance of compassionate use programmes;
2. Patients' organisations should be aware when the clinical development of a new product, and engage discussions with the developer at an early stage to agree on if and when a compassionate use programme could be relevant, and for which patients
3. Patient organisations and clinicians should consult each other about all practical aspects of the compassionate use programme

To Member States

1. Member States should respect article 83 of Regulation (EC) Nº 726/2004 and notify the EMA of compassionate-use programmes that they authorise, so that clinicians and patients are aware of which programmes are run in which countries and how to join them;
2. Member States should create a compassionate use programme Facilitation Group in order to exchange information and build upon common experiences to set up harmonised procedures and create a network which can facilitate future changes in the legislation

To industry (1)

1. Discuss the relevance and timing of a compassionate use with patients' advocates and doctors early in the development of a medicine;
2. Define inclusion criteria for the compassionate use with patients and clinicians;
3. Set up clear rules between compassionate-use and clinical trials.
4. Accept information on compassionate-use programmes cannot be considered as confidential;
5. Collect information from the compassionate-use programme, in particular toxicity data and special populations;

To industry (2)

1. Plan an adequate supply of the product. If tensions occur, the responsibility lies with the company and a company should not ask patients or doctors to make decisions;

And avoid:

1. Interrupting the programme in an abrupt manner, rather discuss the programme-end modalities with patients, doctors and regulators in the first place;
2. Presenting the programme to clinicians as a gift to high inclusion rates in clinical trials;
3. Mixing compassionate-use programmes with humanitarian or financial support programmes.

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

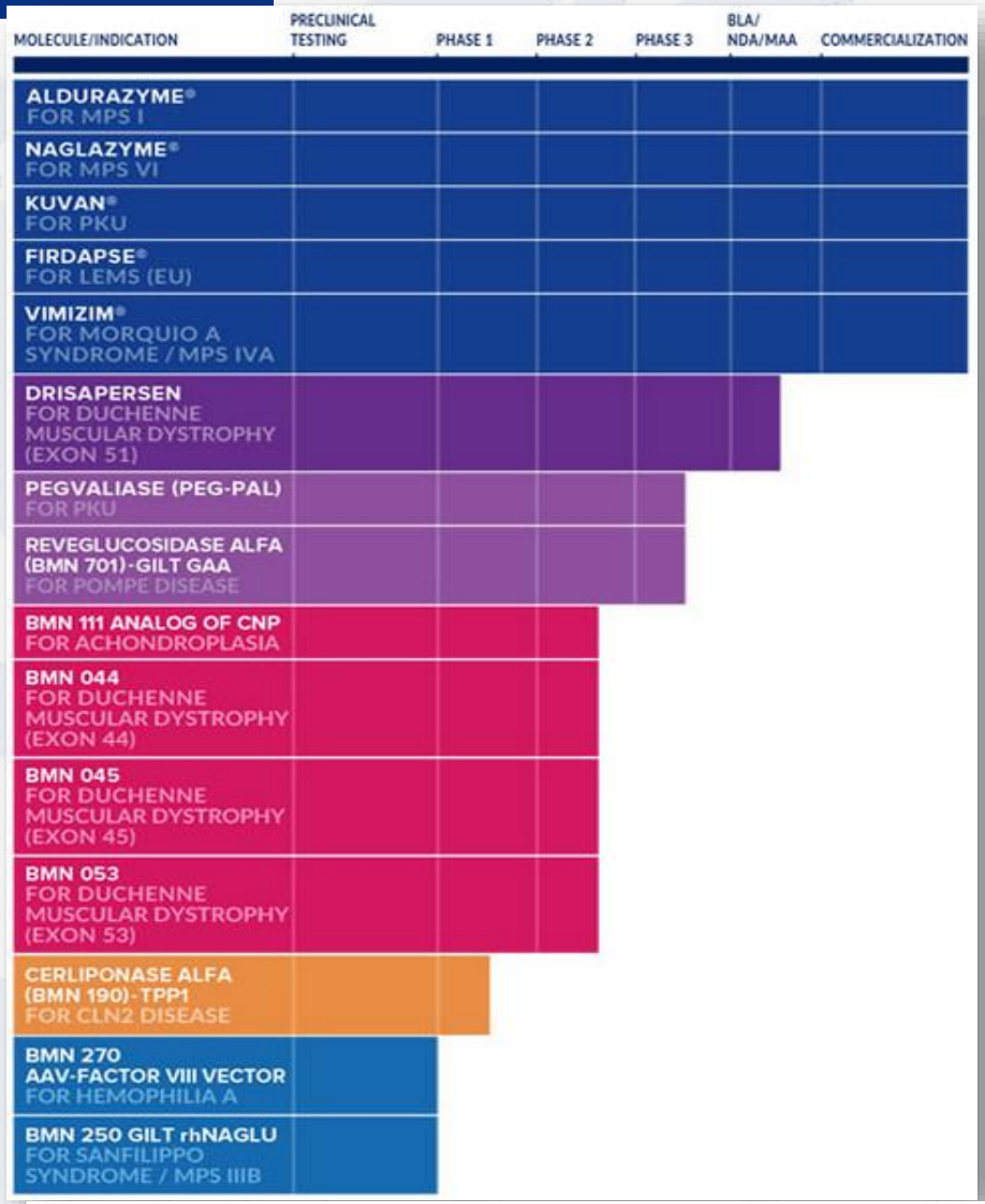


Figure 1: BioMarin's Pipeline as of January 2016

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

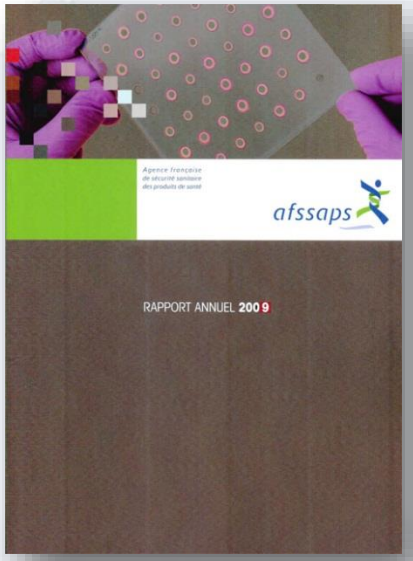
Under his leadership, the market capitalization of BioMarin went from around $450 million in May 2005 to approximately $9 billion in May 2014

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

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