EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory perspectives on Duchenne muscular dystrophy (DMD) therapies

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Chairman of the Committee of Orphan Medicinal Products (COMP)
Member of the Committee of Human Medicinal Products (CHMP)

EU Charter of Fundamental Rights

Why an orphan regulation?

- Rare diseases → developing and marketing cost would not be recovered by the expected sales

(products are called orphans, they do not have “developers”)

- Persons suffering from rare conditions deserve same quality of treatment as other patients

- Pharmaceutical industry does not develop medicines for rare diseases under normal market conditions

Legal references in the EU

Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999

- Criteria for designation
- Committee (COMP)
- Procedure
- Incentives

Commission Regulation (EC) No 847/2000 of 27 April 2000

Commission communication July 2003 (2003/C 178/02)

Commission communication on Art 8(1) and (3) (C(2008) 4077)

Principles on orphan designation

Objective of Regulation (EC) No 141/2000

- provide incentives that stimulate research and development
- modify market conditions
- set up system of recognition for orphan medicines to be eligible for incentives:
  - Rarity (not more than 5 in 10,000)
  - Seriousness (life threatening / chronically debilitating)
  - Existence of alternative methods of treatment (significant benefit?)

Main characteristics orphan designation

- For medicinal products for human use
- Procedure free of charge
- Can be requested at any stage of development
- Sponsor can be either company or individual
- Established in the Community (EU, Ice, Liech, Nor)
- European Commission Decision gives access to incentives

First lessons learned with the Orphan Regulation

Stakeholders & Development of orphan drugs in the EU

2000

Patients: few drugs

Industry: major 'Big Pharma' & development of *blockbusters*

Health care professionals / Academia: not involved

Regulators: at least 27 different procedures for MA

2010

Patients: 68 'active' OD, > 800 products designations

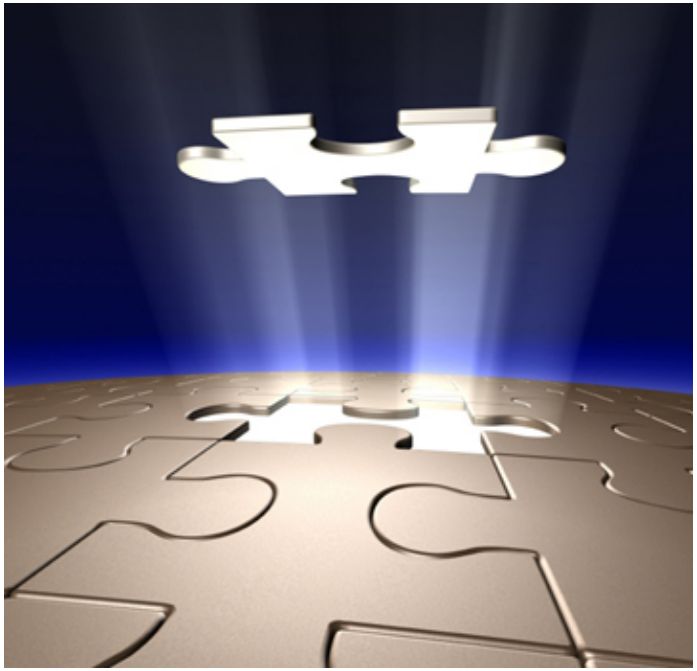
Industry: major 'small Pharma'involvement – 2/3 of designations

Health care professionals / Academia: Sponsors of designations / some are MAH

Regulators: 1 procedure – centralised

Opportunities for patients

- Benefits for more than 30 millions of patients' in the EU
- Potential benefits for neglected diseases
- Model of other geographic areas
- Study model for other more prevalent diseases



Stimulation of innovation

- Fusion proteins
- Monoclonal Antibodies
- Gene and cell therapy
- Oligonucleotides
- Tissue engineering
- etc.

Committee for Orphan Medicines (COMP)

Committee for Orphan Medicines (COMP)

- 1 elected Chair + EMA Scientific Secretariat
- 1 Representative per Member State
- 3 Patients' Representatives appointed by Eur. Commission
- 3 Members appointed by European Commission on proposal from Agency
- 1 Member for Norway and 1 for Iceland

Total: 33 members + 2 non voting

COMP Mission

- Give opinions on designation
- Advise Commission on establishment and development of a policy on orphan medicinal products
- Assist Commission in international liaison
- Assist on guidelines
- Contribute to Protocol Assistance (esp. Significant Benefit)

COMP advisory role

Regular exchange of information with EC to identify high level research needs

Access to information on development

Regulators have direct contact experience with successes and failures

Direct access to a wealth of information

International collaboration between regulators (USA, Japan, Canada)

COMP responsibilities

"Dreamworks"

COMP

CHMP

Idea

Hypothesis

Assumption or viable hypothesis

Proof / Evidence

COMP

- Designates at any stage of development
- Resubmission is user friendly
- *Occasionally might encourage dreams*

"Gate opener"

CHMP

- Interrogative
- Adversarial
- If in doubt, negative
- Prudent and cautious
- Quality, Security and Efficacy

"Gate keeper"

Main characteristics orphan designation

For medicinal products for human use

Procedure free of charge

Can be requested at any stage of development

Sponsor can be either company or individual

- Established in the EEA (EU, Iceland, Liechtenstein, Norway)

European Commission Decision gives access to incentives

Designation criteria

RARITY (prevalence) / RETURN OF INVESTMENT

- Medical condition affecting not more than 5 in 10,000 in the EU (around 250,000 people)
- Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment

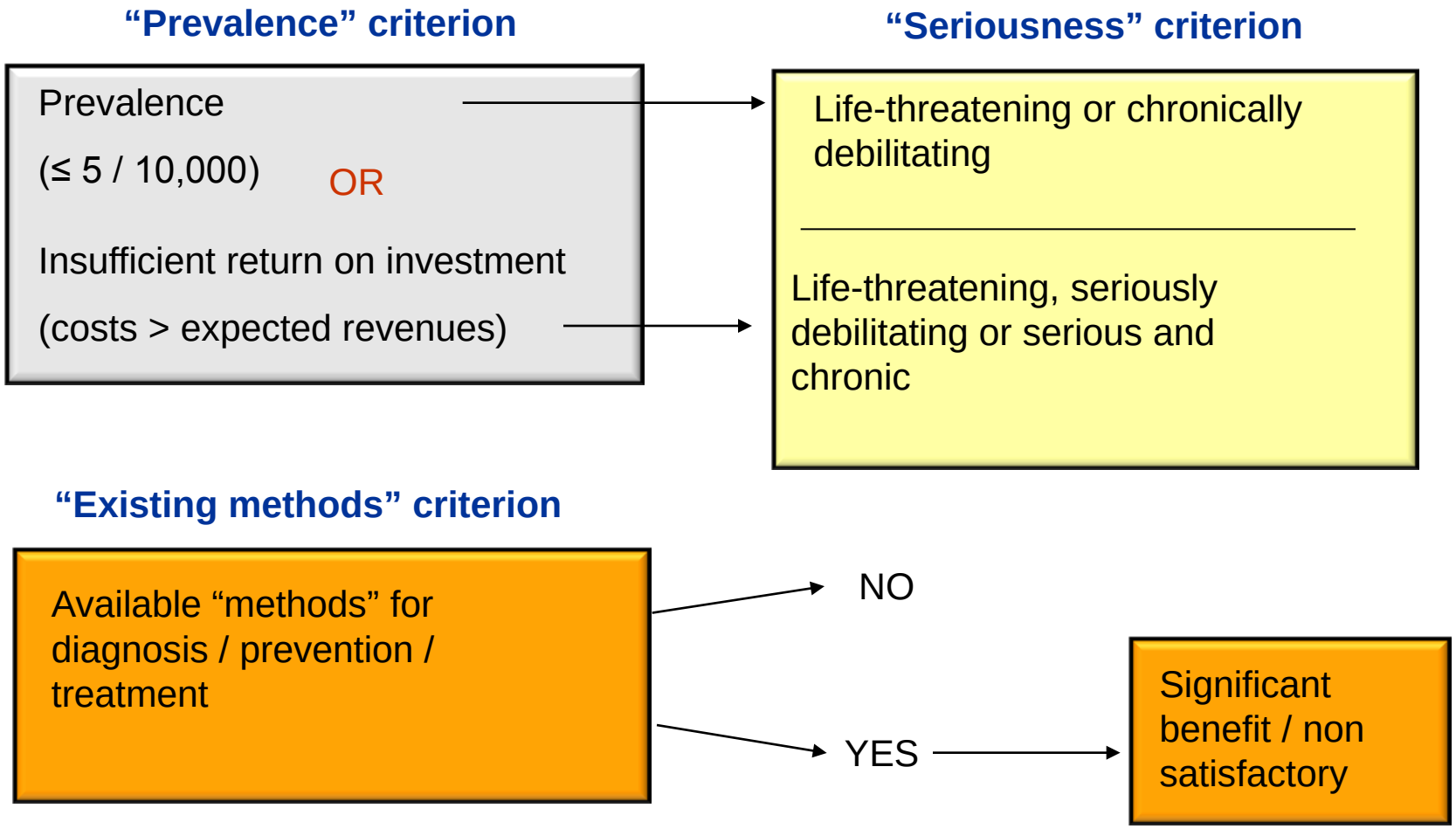
SERIOUSNESS

- Life –threatening or chronically debilitating

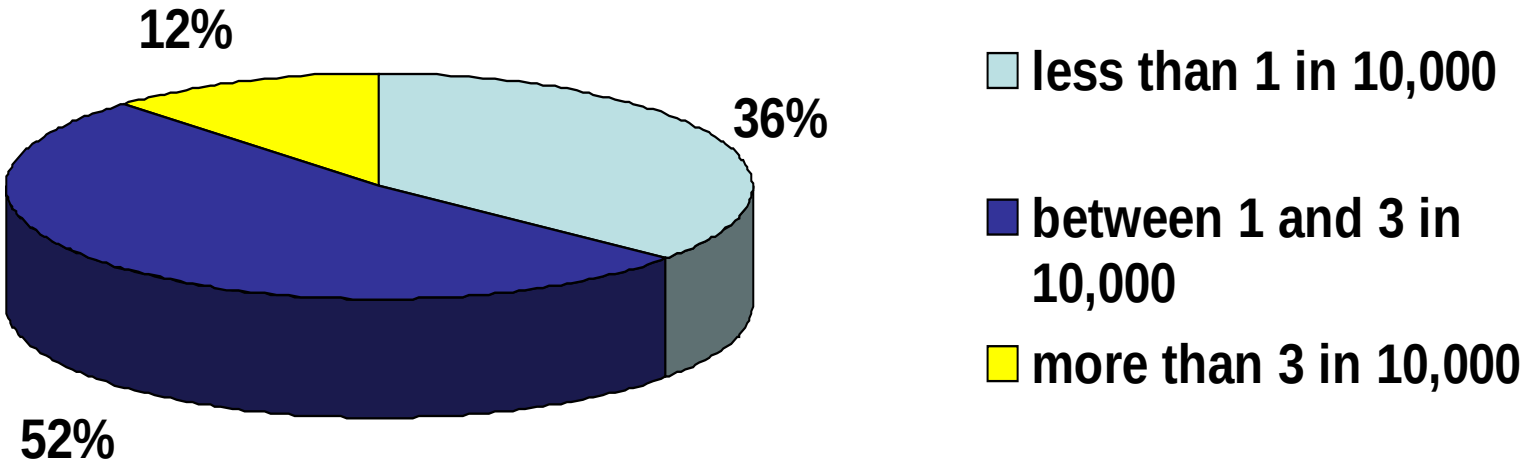
ALTERNATIVE METHODS AUTHORISED

EXCLUSIVE for EU

- If satisfactory method exist the sponsor should establish that the product will be of significant benefit


"Prevalence" criterion
"Seriousness" criterion
Prevalence
(≤ 5 / 10,000)
OR
Insufficient return on investment
(costs > expected revenues)
Life-threatening or chronically debilitating
Life-threatening, seriously debilitating or serious and chronic
"Existing methods" criterion
Available "methods" for diagnosis / prevention / treatment
NO
YES
Significant benefit / non satisfactory

Prevalence of Designated Conditions



Incentives (I)

- Fee reduction / exemption
  - Extended incentives for Small and Medium Sized Enterprises (SMEs)
- Market exclusivity (10 years)
- Protocol assistance
- Community marketing authorisation
- National incentives (inventory from European Commission)

Fee reductions

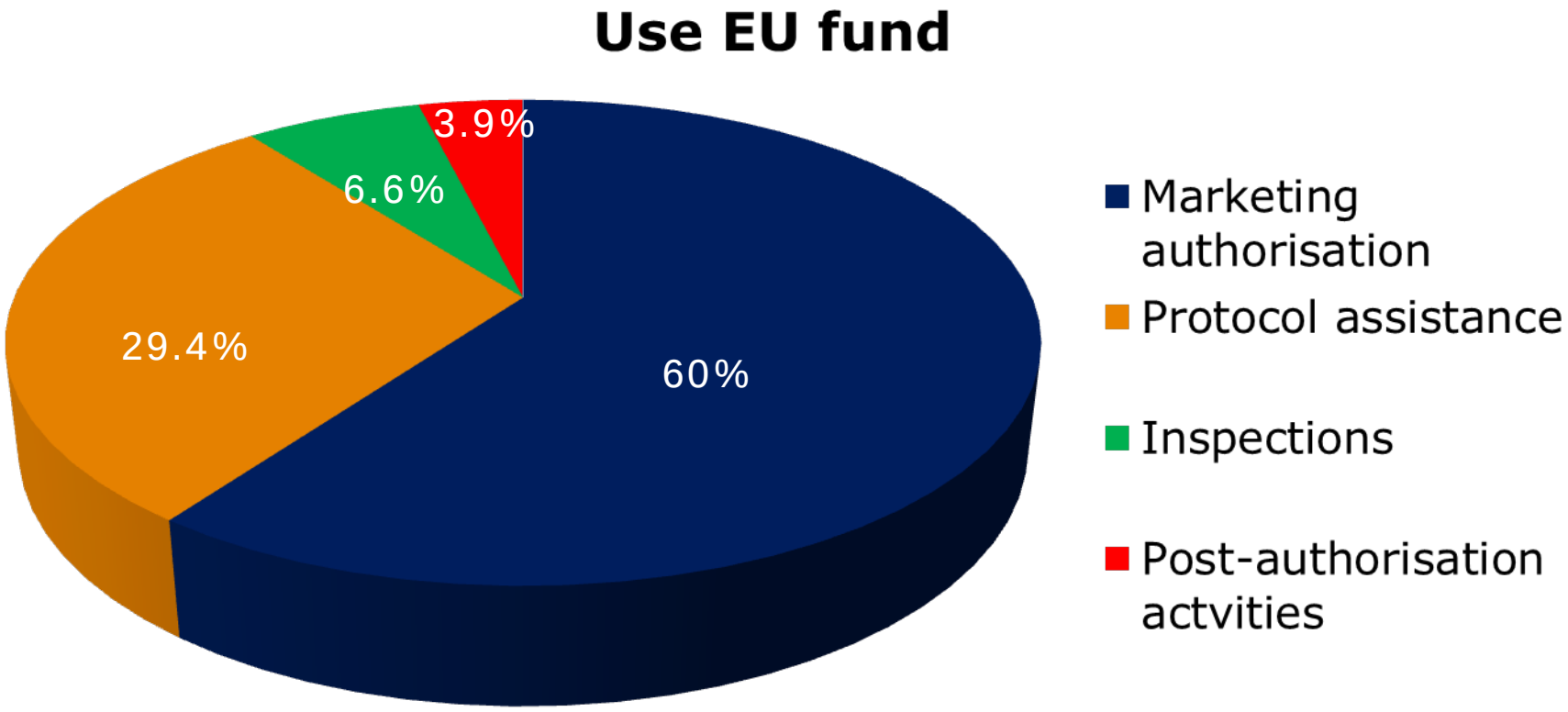
Annually EU allocated special fund to cover fee reductions (approx. 6 million Euro)

EMA has consistently kept maximum coverage for SMEs

Academia and SME responsible for 79% development of advanced therapies

Policy reviewed annually, needed revision in 2013 according to current budget

Allocation funds for fee reductions (2012)



Incentives (II)

10-year market exclusivity (+ 2 if paediatric indication – completion investigation plan)

- Protection against
  - similar products
    - Molecular structure
    - mechanism of action
    - for same indication
  - Three derogations (➔access to market even if similar)
    - Sponsor's consent
    - Lack of supply
    - Clinical superiority

Fostering orphan drug development

Medicines development

- Orphan designation and protocol assistance

Economic incentives

- Fee reductions and market exclusivity

Support to research

- COMP advisory role to EC on policy for orphan medicines

Regulation (EC) No 141/2000

Fostering orphan drug development

Medicines development

- Orphan designation and protocol assistance
- Scientific validation / guided development

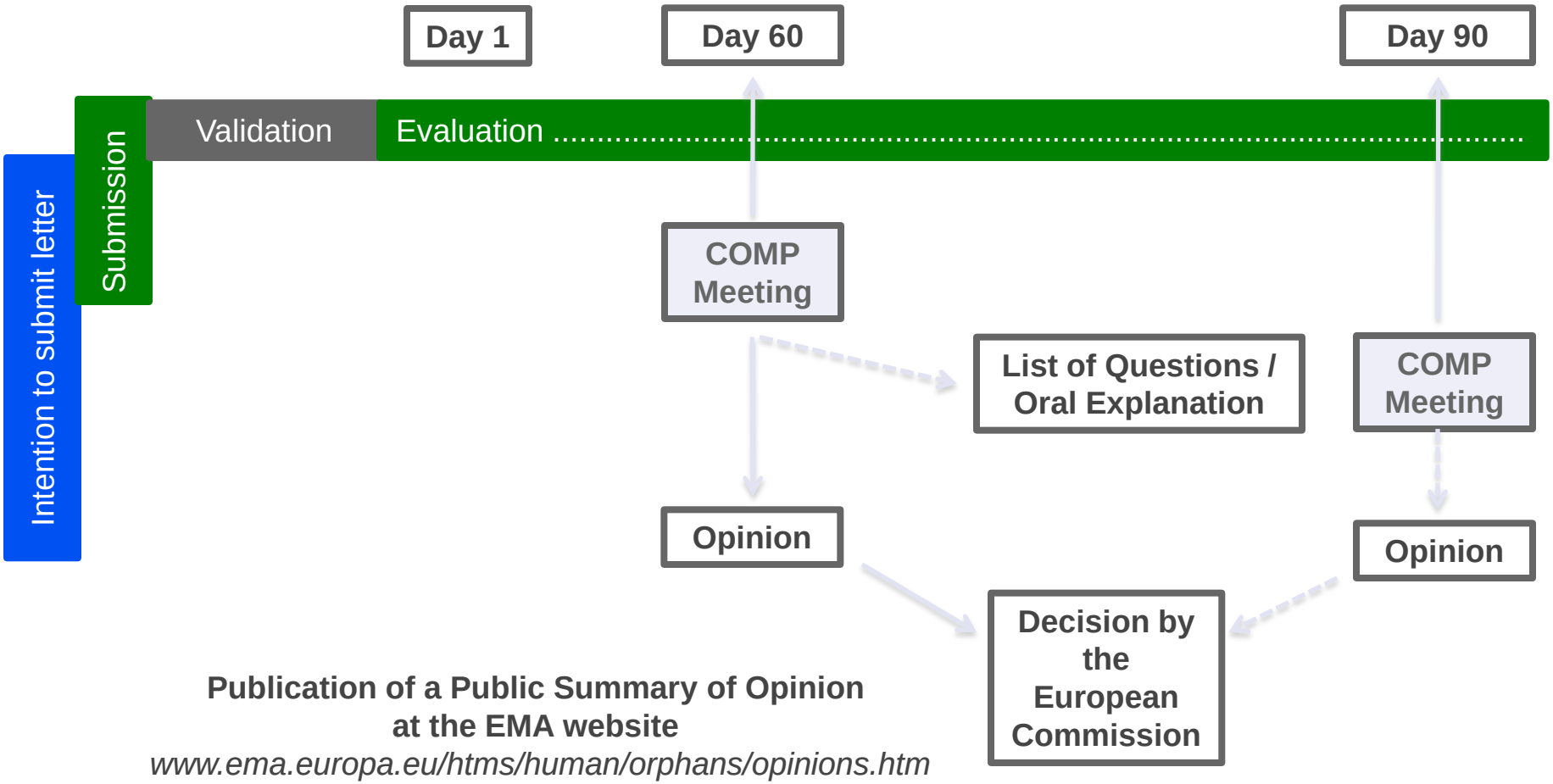
Economic incentives

- Fee reductions and market exclusivity
- Economic viability

Support to research

- COMP advisory role to EC on policy for orphan medicines
- Knowledge “repository” and target identification – public regulatory intelligence

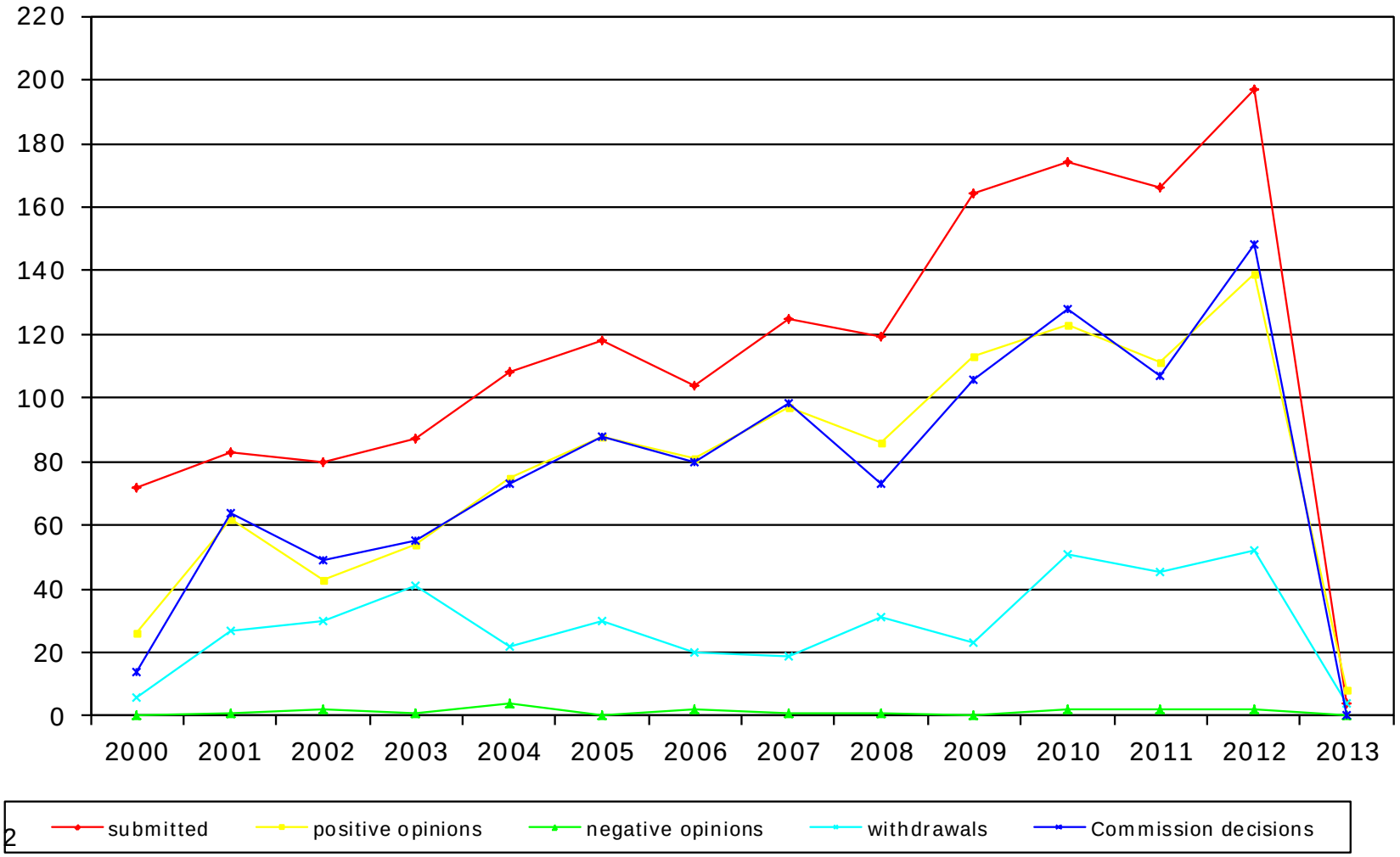
The designation process in the EU



Status of Orphan Applications

	2000 2005	2006 2010	2011	2012	2013	Total
Applications submitted	548	686	166	197	4	1601
Positive COMP Opinions	348	500	111	139	8	1106
Negative COMP Opinions	8	6	2	2	0	18
EC Designations	343	485	107	148	0	1083
Withdrawals	156	144	45	52	4	401

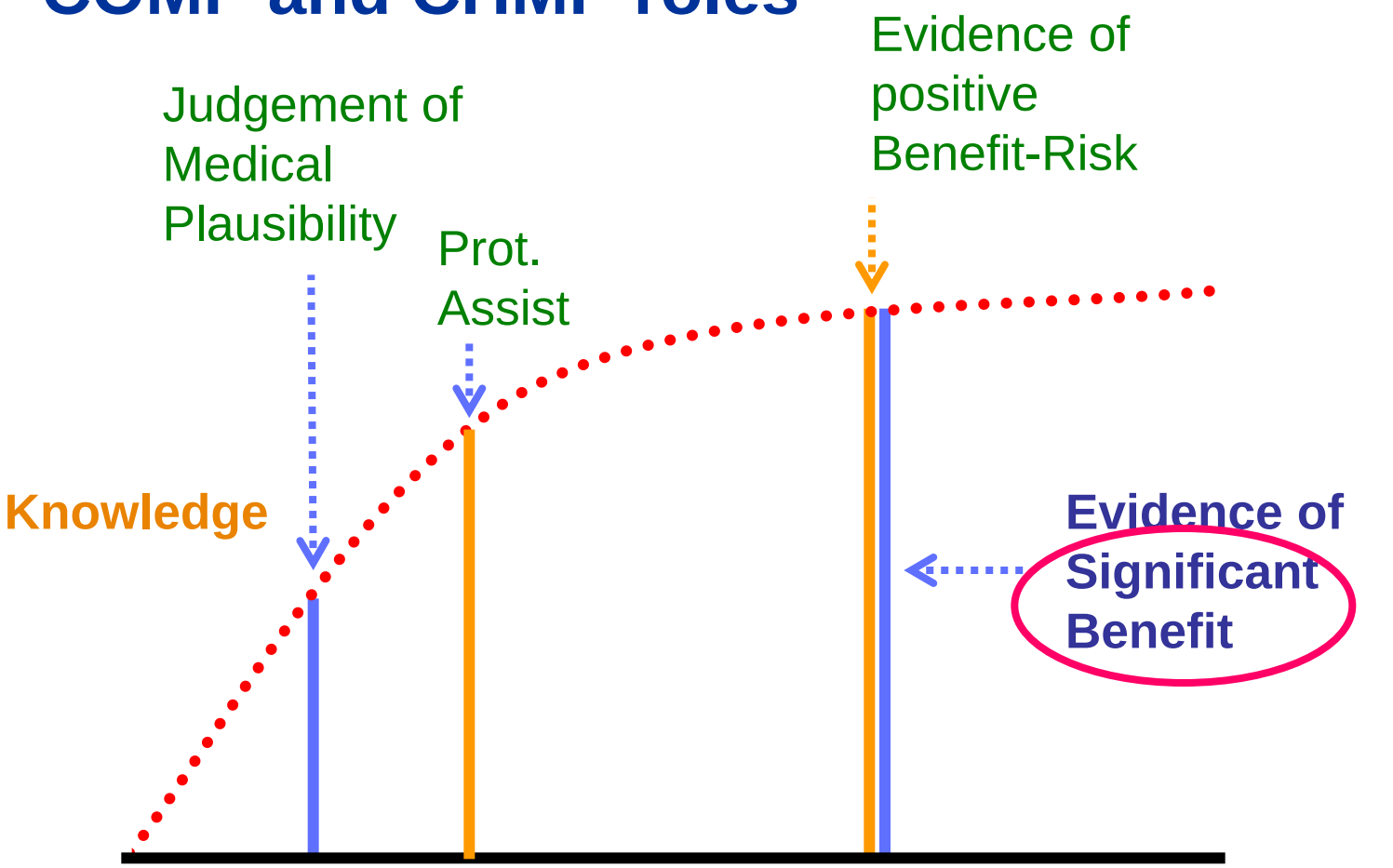
Status of Orphan Applications



Oprhan drug designations for DMD

Active Substance	Disease / condition	Date of decision	Decision
2'-O-methyl-phosphorothioate oligonucleotide	Treatment of Duchenne muscular dystrophy	15/02/2006	Withdrawn
2-(4-(Diethylamino) phenyl)-6-methyl-2H-benzo[d][1,2,3] triazol-5-amine	Treatment of Duchenne muscular dystrophy	25/07/2006	Withdrawn
3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid	Treatment of Duchenne muscular dystrophy	27/05/2005	Positive
5-(Ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole	Treatment of Duchenne muscular dystrophy	04/12/2008	Positive
Adeno-associated viral vector containing a modified U7 snRNA gene	Treatment of Duchenne muscular dystrophy	27/07/2005	Positive
Adeno-associated viral vector containing modified U1 snRNA	Treatment of Duchenne muscular dystrophy	08/10/2009	Positive
Exon 44 specific phosphorothioate oligonucleotide	Treatment of Duchenne muscular dystrophy	26/02/2009	Positive
Exon 45 specific phosphorothioate oligonucleotide	Treatment of Duchenne muscular dystrophy	26/04/2012	Positive
Exon 51 specific phosphorothioate oligonucleotide	Treatment of Duchenne muscular dystrophy	27/02/2009	Positive
Exon 53 specific phosphorothioate oligonucleotide	Treatment of Duchenne muscular dystrophy	26/04/2012	Positive
Exon-52-specific phosphorothioate oligonucleotide	Treatment of Duchenne muscular dystrophy	06/12/2012	Positive
Exon-55-specific phosphorothioate oligonucleotide	Treatment of Duchenne muscular dystrophy	06/12/2012	Positive
Givinostat	Treatment of Duchenne muscular dystrophy	04/07/2012	Positive
Halofuginone hydrobromide	Treatment of Duchenne muscular dystrophy	26/04/2012	Positive
Humanised monoclonal antibody against myostatin	Treatment of Duchenne muscular dystrophy	08/02/2013	Positive
Idebenone	Treatment of Duchenne muscular dystrophy	19/03/2007	Positive
Recombinant fusion protein consisting of the extracellular portion of human activin receptor IIB linked to the human IgG1 Fc domain	Treatment of Duchenne muscular dystrophy	26/11/2010	Positive
RNA, [P-deoxy-P-(dimethylamino)] (2',3'-dideoxy-2',3'-imino-2',3'-seco) (2'a5') (C-m5U-m5U-A-C-A-G-G-C-m5U-C-C-A-A-m5U-A-G-m5U-G-G-m5U-C-A-G-m5U), 5' [P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]carbonyl]-1-piperazinyl]-N,N-dimethylaminophosphonamidate], 3'-[2'a-[N2-acetyl-L-arginyl-6-aminohexanoyl-L-arginyl-L-arginyl--alanyl-L-arginyl-L-arginyl-6-aminohexanoyl-L-arginyl-L-arginyl--alanyl-L-arginyl-6-aminohexanoyl--alanyl], octahydrochloride	Treatment of Duchenne muscular dystrophy	02/02/2010	Positive
RNA, [P-deoxy-P-(dimethylamino)] (2',3'-dideoxy-2',3'-imino-2',3'-seco) (2'a?5') (C-m5U-C-C-A-A-C-A-m5U-C-A-A-G-G-A-A-G-A-m5U-G-G-C-A-m5U-m5U-m5U-C-m5U-A-G), P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]carbonyl]-1-piperazinyl] N,N-dimethylaminophosphonamid	Treatment of Duchenne muscular dystrophy	02/12/2008	Positive

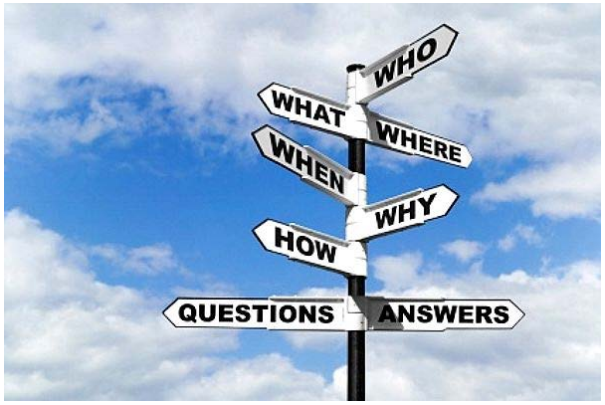
COMP and CHMP roles



Protocol assistance

Protocol assistance ≅ scientific advice

- Questions on quality-efficacy-safety
- Questions on significant benefit
- Company position required
- SAWP provides answers



- CHMP adopts answers
- COMP involved if issues on significant benefit arise

Protocol assistance

Provides Agency (EU Wide) advice on drug development

- clinical (90%; 51% exclusively)
- preclinical (44%)
- quality (27%)

Dedicated procedure for biomarker qualification

Following advice increases chances of marketing authorisation (RR 1.48; failure rate non compliant 70%; compliant 2%)

Significant benefit

Significant benefit: “A clinically relevant advantage or a major contribution to patient care”

- Based on **assumptions** at the time of orphan designation
- Significant benefit over “satisfactory methods”
- COMP to assess whether or not assumptions are supported by available data/evidence supplied by applicant
- Sign benefit to be **confirmed** prior to marketing authorisation to maintain orphan status
- Recommendation document on data for SB and plausibility

Examples assumption for significant benefit

Clinically relevant advantage

- Drug has a new mechanism of action: clinically relevant advantage to be justified/demonstrated
- Opens possibilities for drug combination
- Alternative therapeutic option
- “complementary / better” safety profile

Major contribution to patient care

- Improvement quality of life (e.g. alternative to dietary restrictions)
- More “convenient” administration route
- Age adjusted formulation

Protocol Assistance - Procedure

40 or 70-day procedure (maximum)

- Pre-submission meeting highly recommended
- Discussion meetings with SAWP (in 50%)
  - Major disagreement
  - Need for additional information

Final advice letter adopted by CHMP

COMP involved if issues on significant benefit

Possibility of EMEA-FDA parallel advice

Type of requests

SA or PA requests can address different aspects (Quality, Safety, and/or Efficacy)

90% include clinical questions

- 51% related to clinical efficacy issues only

44% include pre clinical questions

27% include quality questions

Question on significant benefit almost always present if orphan drug and clinical questions

“Emerging” topics

Adaptive designs

- Modification of CT design at interim analysis, WITH control of type I error

Demonstration of positive benefit/risk with preliminary evidence (for a conditional marketing authorisation)

- Data necessary for authorisation
- Interim analysis, surrogate endpoints

Interim analyses

- Blinding
- Stopping rules
- Type I error control

Similarity issues

Biomarker qualification (!!)

Critical issues about SA/PA

Sponsor

Ask question if

- Deviation from guidelines
- Uncertainty

Ask at the appropriate time

- Early
- Transition

Come back if necessary

Follow the advice !!

Agency

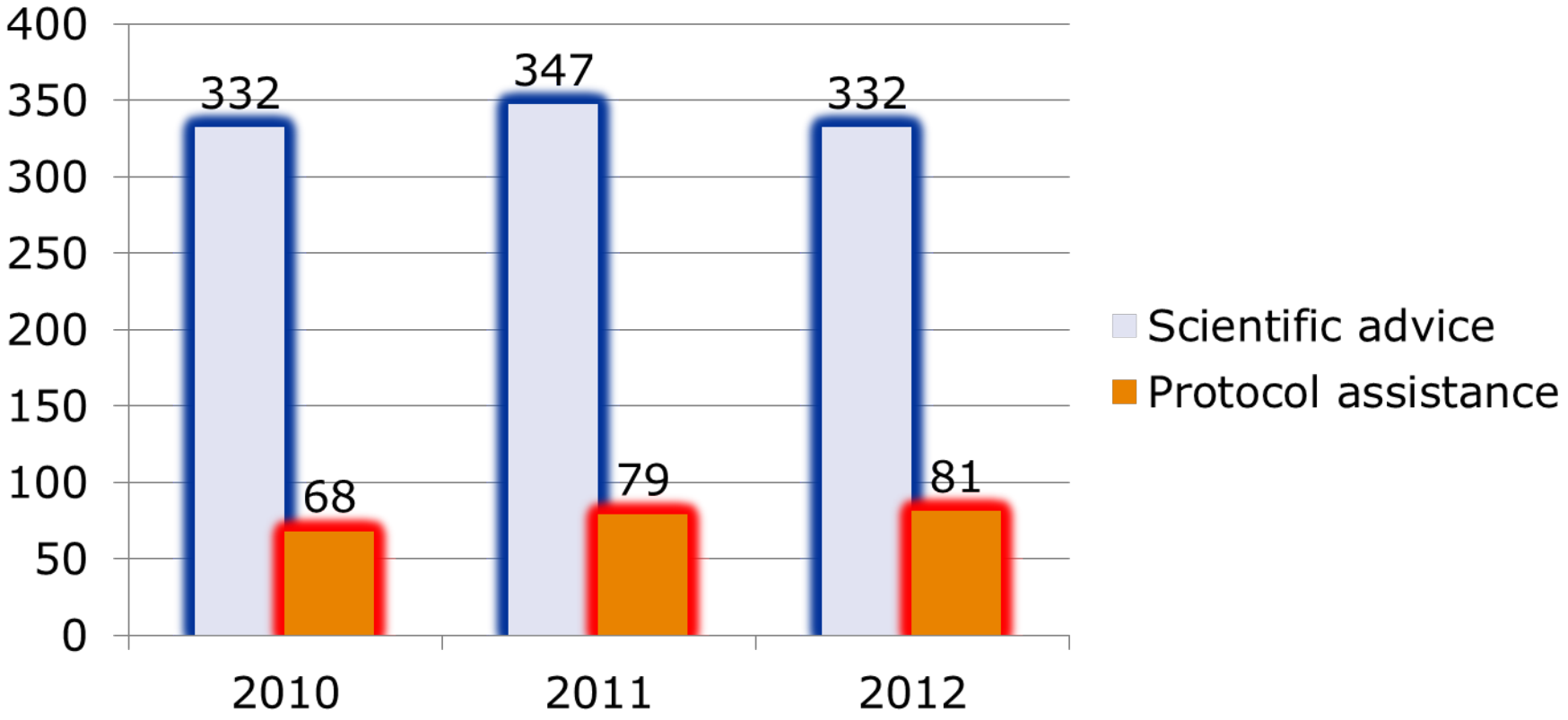
Involve experts if necessary (including patients) … conflicts of interest!

Feasibility

Flexibility (as much as possible)

Clear and comprehensive

Protocol assistance



Authorisation of an orphan drug

Based on same standards as for non orphan products (quality / safety / efficacy)

Authorisation only centralised procedure

CHMP responsible for assessment

Authorisation within designated condition

More than one designation possible per product (independent incentives)

Specific requirements MAA (I)

Assessment of similarity (WHEN ORPHAN IS ON MARKET)

- Applies if other orphan medicines authorised for same designated condition
- Need to submit report in module 1.7
  - Molecular structure
  - Mechanism of action
  - Similarity of indication (“significant overlap of populations”?)
- Assessment by CHMP competent working party
- Final opinion by CHMP
- Similarity can be triggered any time before EC decision
- Proactive publication on going procedures

Specific requirements MAA (II)

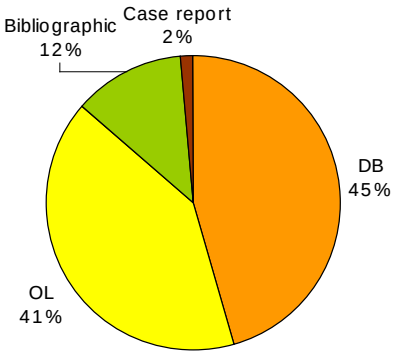
Maintenance designation criteria

- Report to orphan medicines section
  - At time of submission MA
  - Possible to update
- Need to address all designation criteria
- Standard set at time of authorisation
- Assessment by COMP; opinion after MA opinion by CHMP

Level of evidence

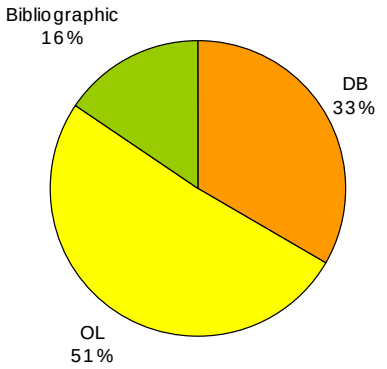
Of the granted marketing authorisations:

- 30 (45%) MAAs included double blinded randomised studies
- 27 (41%) MAAs included open label studies
- 8 (12%) MAAs were based on bibliographical data
- 1 (2%) MAAs were based on case reports



Of the rejected marketing authorisations:

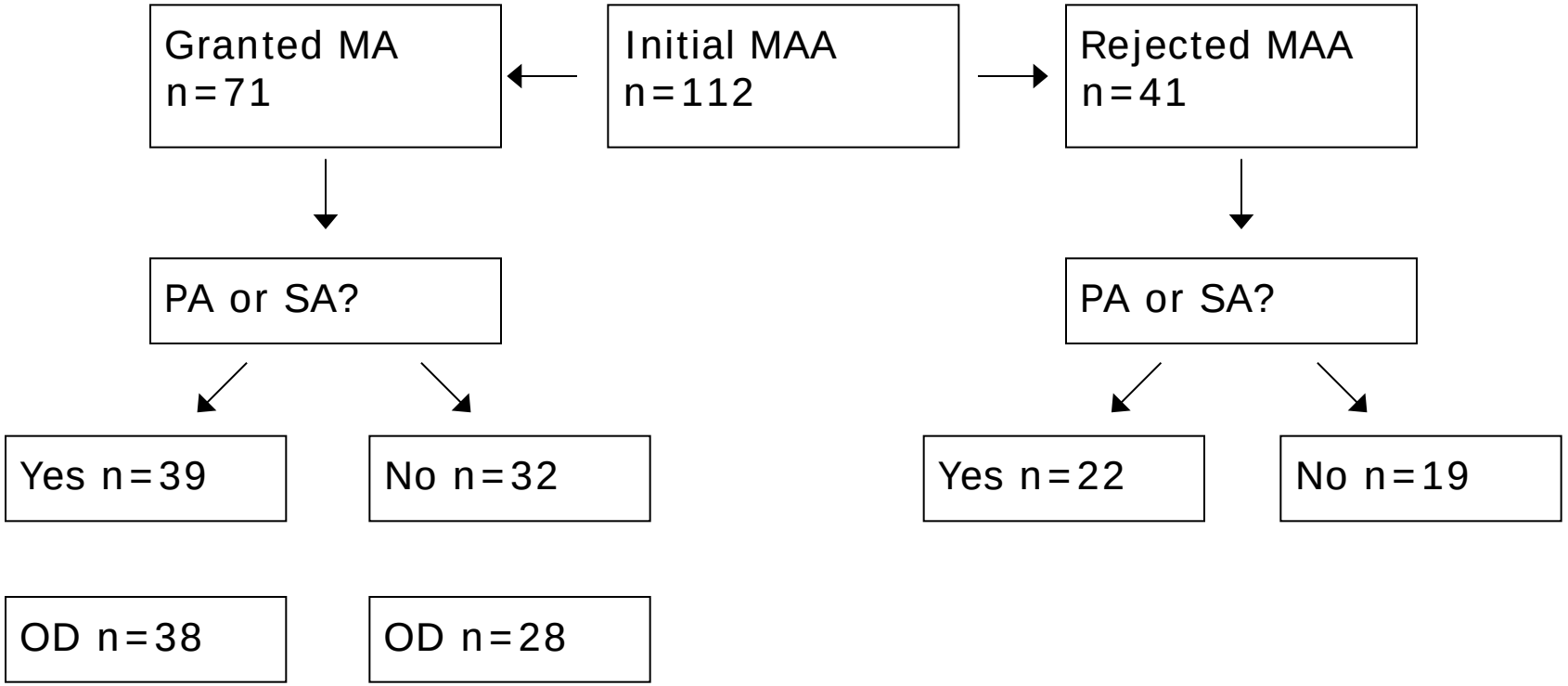
- 15 (37%) MAAs included double blinded randomised studies
- 23 (56%) MAAs included open label studies
- 3 (7%) MAAs were based on bibliographical data



Significant benefit

- 49 (74%) of the granted MAs had to show significant benefit
- 27 (66%) of the rejected MAs would have had to show significant benefit

Protocol assistance and scientific advice



Authorised products not showing SB

Product	SB at orphan designation	At marketing authorisation
Ruconest (R. Human C1 inhibitor) MA 28/10/2010 Treatment of angioedema	Availability	Berinert (plasma derived C1 inhibitor) approved in 22 member states through mutual recognition
Votrient (Pazopanib) MA 14/06/2010 Treatment of renal cell carcinoma	New mechanism of action and improved efficacy (preclinical data)	Pazopanib was unable to show a relevant clinical advantage compared to sunitinib or sorafenib
Teysuno (Tegafur, gimeracil, oteracil) MA 14/03/2011 Treatment of gastric cancer	Improved effect	Teysuno+cisplatin not shown to be superior to 5-FU+cisplatin. Improved safety claimed could not be supported by data
Cinryze (Human C1 inhibitor) MA 15/06/2011 Treatment of angioedema	Availability and longer duration	Availability; Berinert see above. The pharmacokinetic characteristics has not been translated to a relevant clinical advantage
Ixario		Prevalence criteria re-evaluated at marketing authorisation

Status of Orphan Marketing Authorisation Applications: 78 granted to date

Adopted positive opinion

- 1 awaiting decision

On-going applications in review process

- 27 applications in review process

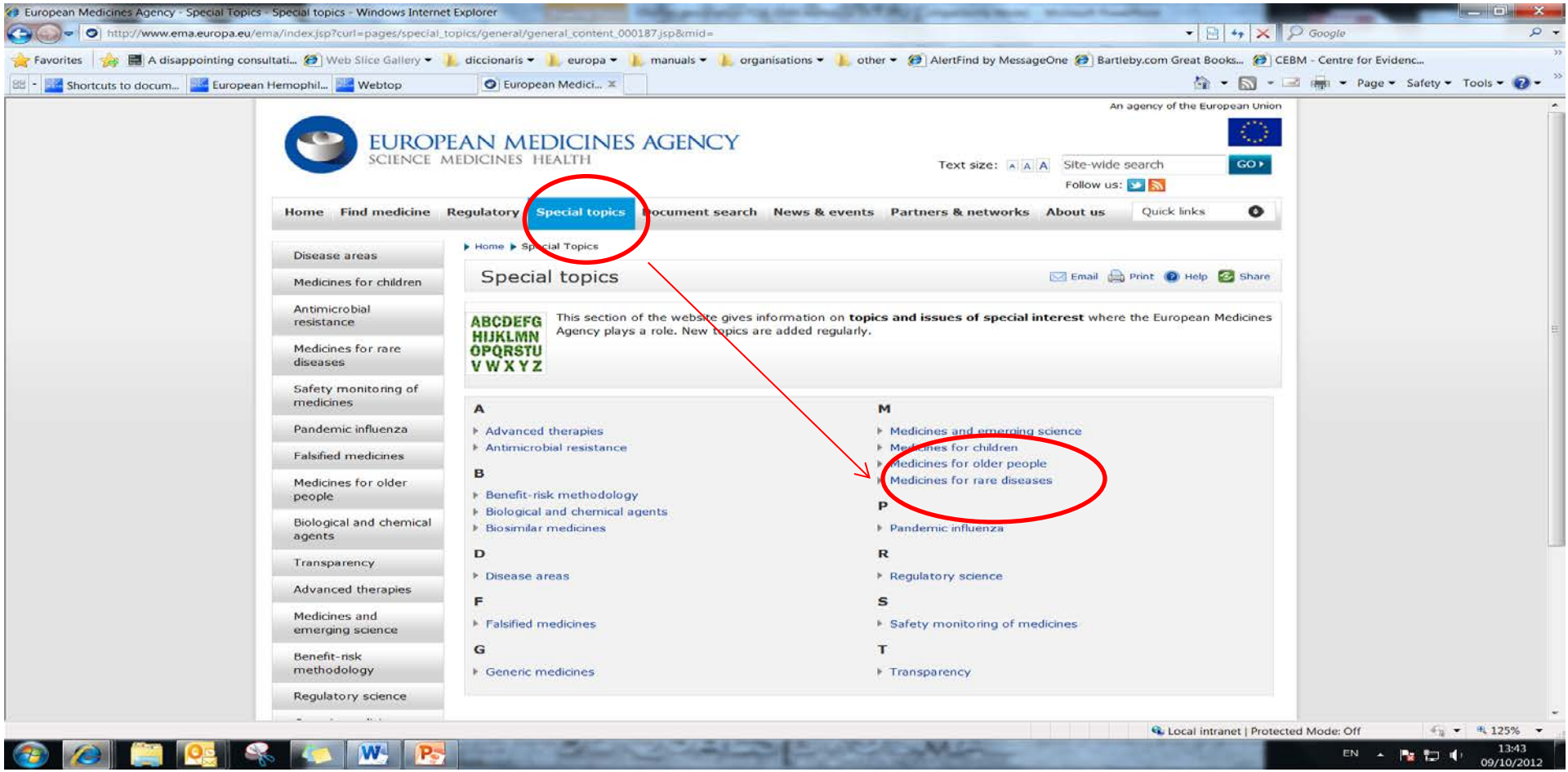
Variations / Line Extensions in review process

- 3 applications in review process

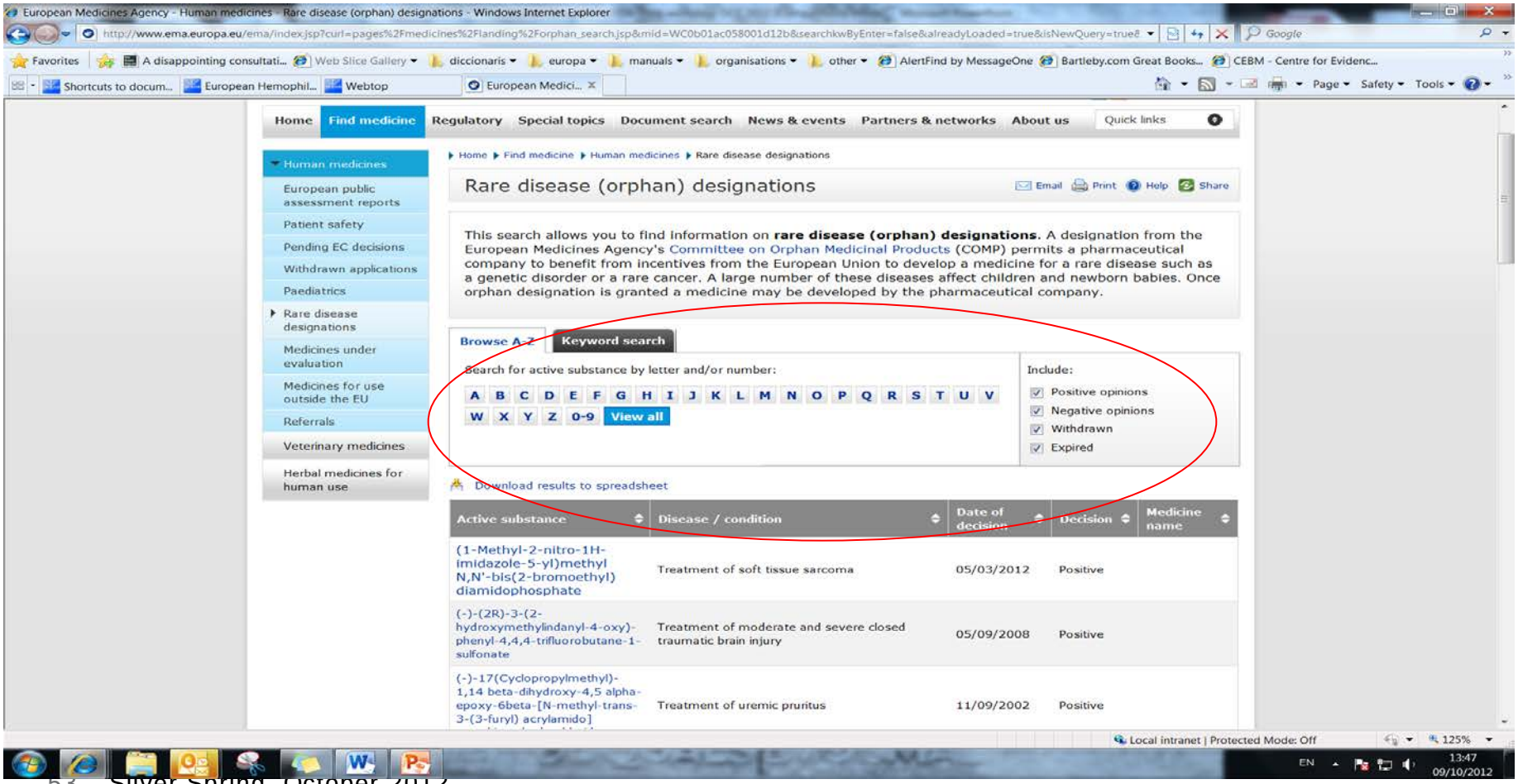
Negative outcomes for orphan MAA

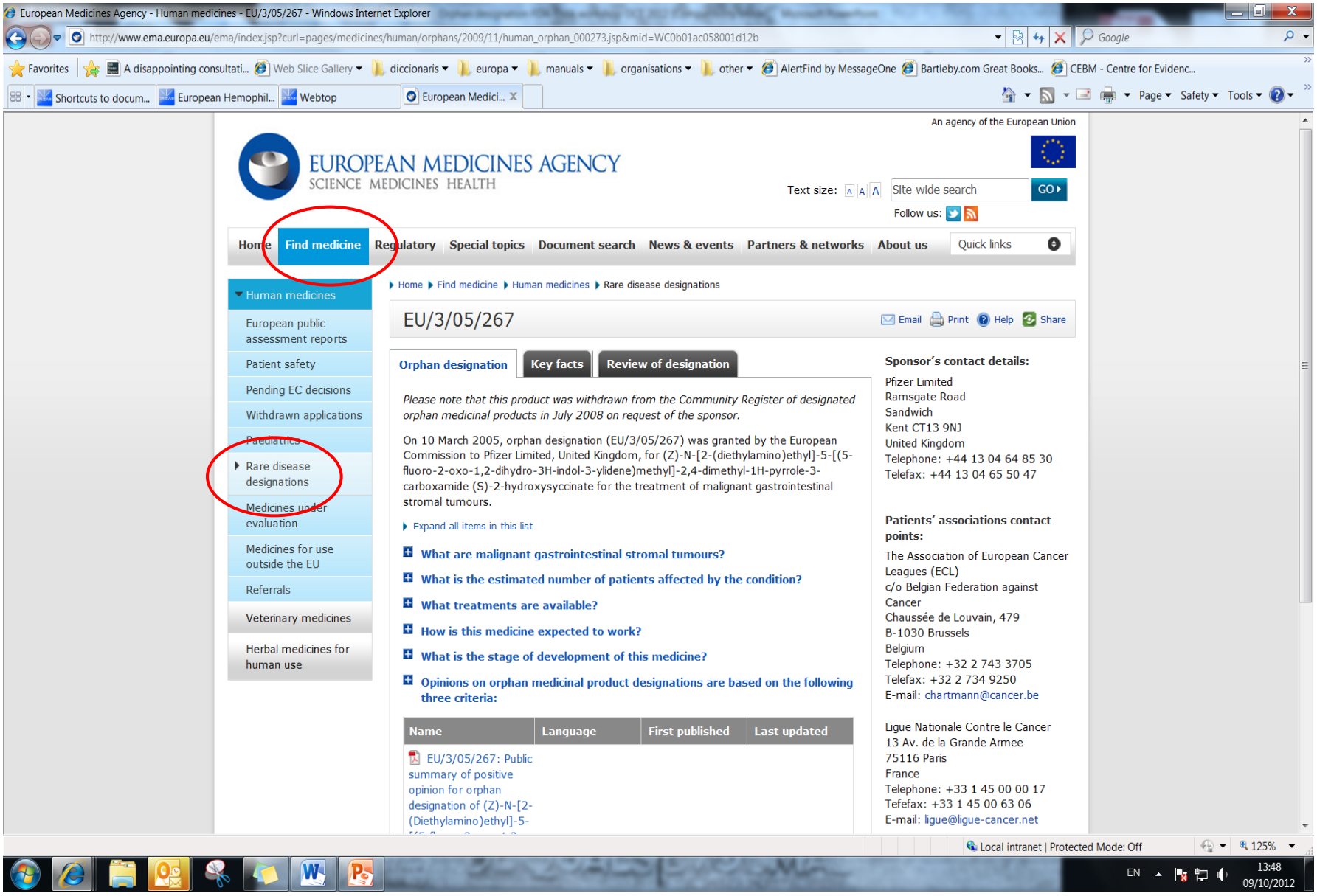
- 56 applications withdrawn
- 10 negative decisions/refusals

Where to have more information



Where to have more information




European Medicines Agency - Human medicines - EU/3/05/267 - Windows Internet Explorer
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Shortcuts to docum...
European Hemophil...
Webtop
European Medici...
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EUROPEAN MEDICINES AGENCY
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Patient safety
Pending EC decisions
Withdrawn applications
Paediatrics
Rare disease designations
Medicines under evaluation
Medicines for use outside the EU
Referrals
Veterinary medicines
Herbal medicines for human use
Home ▸ Find medicine ▸ Human medicines ▸ Rare disease designations
EU/3/05/267
Email
Print
Help
Share
Orphan designation
Key facts
Review of designation
Please note that this product was withdrawn from the Community Register of designated orphan medicinal products in July 2008 on request of the sponsor.
On 10 March 2005, orphan designation (EU/3/05/267) was granted by the European Commission to Pfizer Limited, United Kingdom, for (Z)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysyccinate for the treatment of malignant gastrointestinal stromal tumours.
Expand all items in this list
What are malignant gastrointestinal stromal tumours?
What is the estimated number of patients affected by the condition?
What treatments are available?
How is this medicine expected to work?
What is the stage of development of this medicine?
Opinions on orphan medicinal product designations are based on the following three criteria:
Name
Language
First published
Last updated
EU/3/05/267: Public summary of positive opinion for orphan designation of (Z)-N-[2-(Diethylamino)ethyl]-5-
Sponsor's contact details:
Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom
Telephone: +44 13 04 64 85 30
Telefax: +44 13 04 65 50 47
Patients' associations contact points:
The Association of European Cancer Leagues (ECL)
c/o Belgian Federation against Cancer
Chaussée de Louvain, 479
B-1030 Brussels
Belgium
Telephone: +32 2 743 3705
Telefax: +32 2 734 9250
E-mail: chartmann@cancer.be
Ligue Nationale Contre le Cancer
13 Av. de la Grande Armee
75116 Paris
France
Telephone: +33 1 45 00 00 17
Tefefax: +33 1 45 00 63 06
E-mail: ligue@ligue-cancer.net
Local intranet | Protected Mode: Off
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09/10/2012

Draft guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy

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Email address for submissions cnswpsecretariat@ema.europa.eu

Summary

Recent advances in basic and clinical research have opened new perspectives for future therapeutic options in Duchenne and Becker muscular dystrophy. This guideline is intended to provide guidance for the evaluation of medicinal products in the treatment of these diseases, including study design, the choice of appropriate efficacy endpoints and the definition of reliable surrogate outcome measures.

Therapeutic approaches

- Limited to symptomatic treatment
- Medical and physical therapies to improve cardiac and respiratory functions
- Corticosteroids to improve muscle strength and function
- Other standards of care apply (multi-disciplinary teams)
- Therapies exist for orthopedic corrections

Currently no curative treatments for DMD exist.

Other therapies *(none registered)*

Corticosteroids	Standard of care
Myostatin inhibition	Block the myostatin break-down of muscle cells
Exon skipping AON	Shorter dystrophin so transform into less severe form, Mutation specific
Exon skipping AON in rAAV vector	Shorter dystrophin so transform into less severe form, Mutation specific
Reading through stop codon	Mutation specific, Small molecule, Oral medication, Full length protein
Gene therapy	rAAV vector (shorter dystrophin), Adeno virus / HSV (full length dystrophin)
Stem cell : myoblast mesoangioblast transplantation	Low efficiency, immune suppression required
Utrophin upregulation	Transform into less severe form
Myostatin inhibition	Block the myostatin break-down of muscle cells

Therapeutic advances in DMD

- **Gene therapy**

Introduction of a transgene coding for full-length or a truncated version of dystrophin complementary DNA (cDNA) in muscles

- **Pharmacological therapy**

With the objective of restoring dystrophin expression or alleviate the DMD phenotype

- the stop codon read-through approach
- the exon skipping approach

Specific considerations when developing products for the treatment of DMD

- Improvement of symptoms and improvement of disability in affected patients

- Modification of the natural course of the disease or increasing survival

Conclusions

- Orphan designation is centralised in the EU → EMA Committee (COMP); Applications to be submitted to EMA and assessed by COMP; designations by European Commission
- Free of charge; requirement: Sponsor is established in EU
- 99% agreement FDA-EMA regarding conditions
- Significant benefit exclusive to EU: justifications to support claims (even at early stage)
- Orphan drugs for DMD have been designated
- The review process for MA has started for some on the pipeline but still not concluded
- After first DMD orphan drug approval, significant benefit will take this into account

*There is no disease so **rare**, that it does not deserve attention*

Committee of Orphan Medicinal Products

bruno.sepodes@ema.europa.eu

EMA website: http://www.ema.europa.eu