RARE DISEASES AND ORPHAN DRUGS

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

SILVIO GARATTINI

Bologna 7th March 2018

WHY RARE DISEASES SHOULD BE STUDIED?

- All the patients independently from the type of their disease have the right to be cured
- They furnish information useful also for common diseases
- They represent the future: an example of personalized medicine

1983

U.S.A. GOVERNMENT APPROVES

“ORPHAN DRUGS ACT”

TO BOOST THERAPIES FOR

RARE DISEASE

PREVALENCE < 200.000 PEOPLE

1992

THE MARIO NEGRI INSTITUTE ESTABLISHES A CLINICAL RESEARCH CENTER FOR RARE DISEASES

LE SEDI

Mario Negri MILANO

Mario Negri BERGAMO

Centro per le Malattie Rare
"Aldo e Cele Daccò"
RANICA (BG)

Centro Ricerche Trapianti
RANICA (BG)

ISTITUTO DI RICERCHE FARMACOLOGICHE
MARIO NEGRI
IRCCS

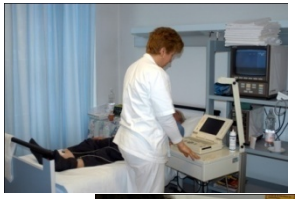
THE CLINICAL RESEARCH CENTRE FOR RARE DISEASES

Since 1992

INFORMATION
DOCUMENTATION

EDUCATION

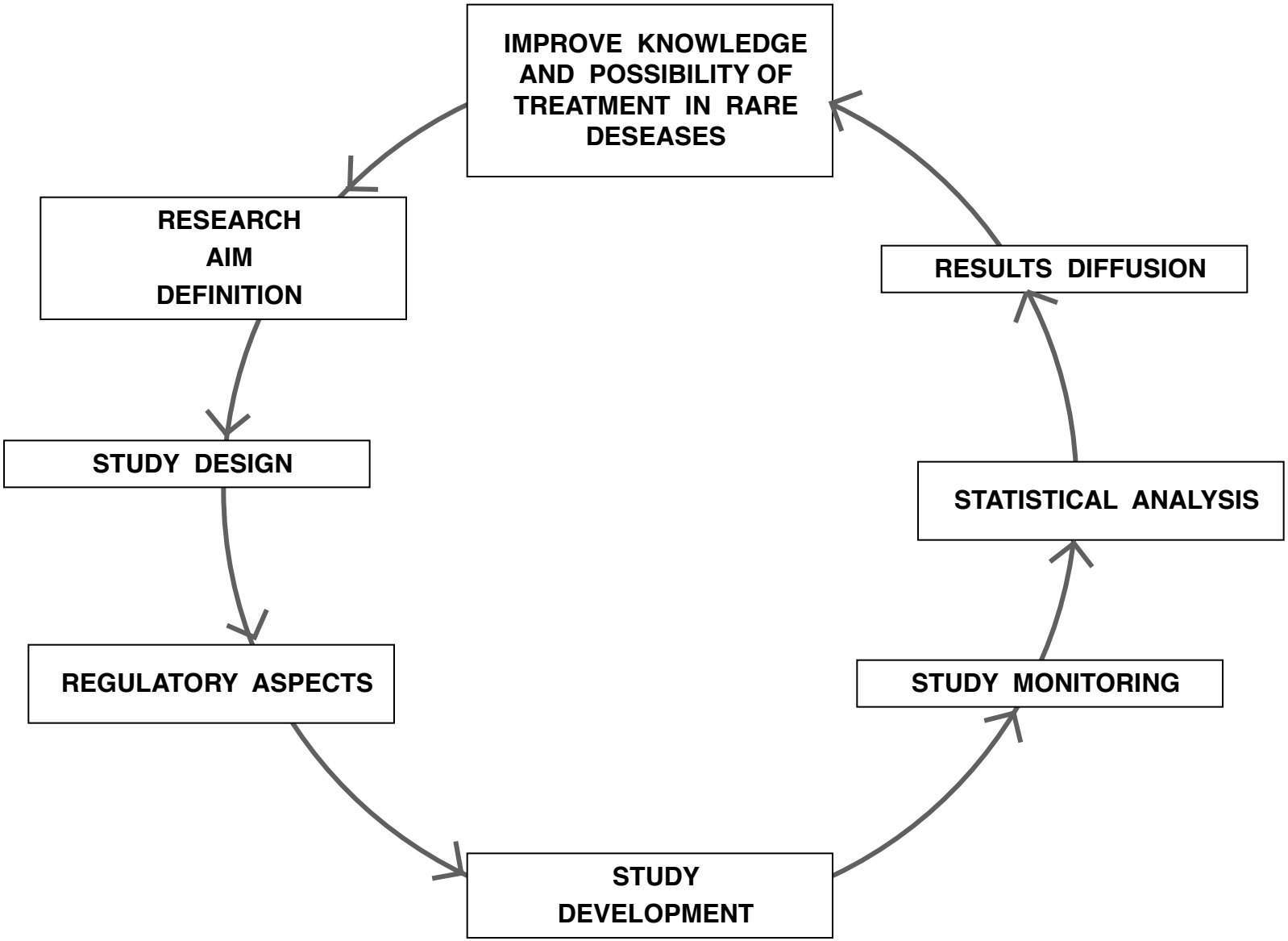
RESEARCH



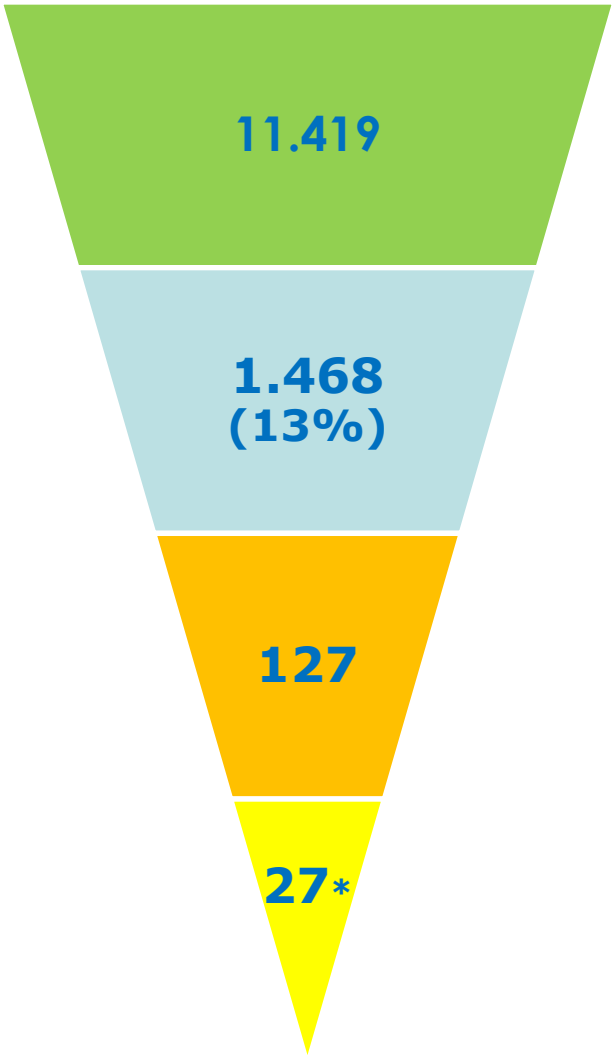
Since 2001

COORDINATING CENTRE OF THE LOMBARDY NETWORK FOR RARE DISEASES

EXPERTISE AND ORGANIZATIONAL SUPPORT IMPLEMENTED AT THE CENTER



THE DATABASE OF THE DOCUMENTATION CENTRE FOR RARE DISEASES (1993-2017)



RARE DISEASE CASES SUBMITTED TO MULTIDISCIPLINARY TEAM EVALUATION
- 34% LOMBARDY
- 66% OTHER ITALIAN REGIONS

UNDIAGNOSED CASES ADDRESSED TO REVALUATION AT REFERENCE CENTRES

MONITORED CASES
(UNDIAGNOSED FOLLOWING CAREFUL PERIODIC REVALUATIONS)

CASES SELECTED FOR GENOMIC AND FUNCTIONAL ANALYSES

*** 1 patient enrolled in NIH Undiagnosed diseases program**

RETE REGIONALE MALATTIE RARE

46 Hospital
642 Rare disease
60000 Patients

center
center
center
center
Registry

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS
Coordinating center

Data Set

ISS

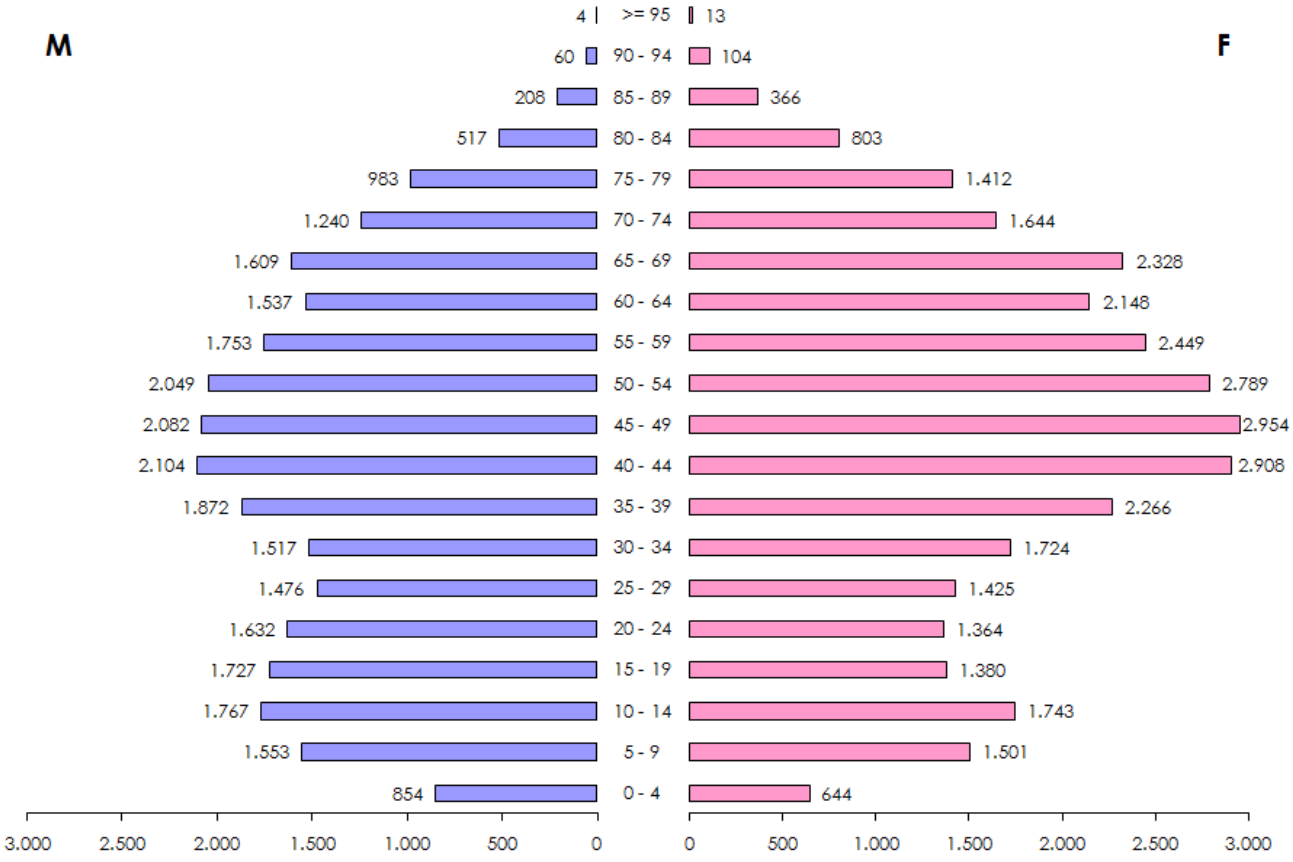
Istituto Superiore di Sanità

National registry

Analisi dei dati

Reports periodical

Registro Lombardo Malattie Rare
Distribuzione dei pazienti in Lombardia al 31/12/2015 (Età e Genere)



Population	**10.008.349***
Prevalence	**58.509**
Rare Deseases / Coded graphs	**294**
Prevalence	**5,8/1000 People**

**ISTAT Censimento popolazione italiana – 01/01/2016*

EXPERIMENTAL AND CLINICAL STUDIES AT THE MARIO NEGRI INSTITUTE

- HUS
- MEMBRANOUS GLOMERULONEPHRYTIS
- SYSTEMIC AMYLOIDOSIS
- FABRY DISEASE
- CEREBRAL CAVERNOUS MALFORMATIONS
- PRIONS DISEASES
- ALS
- RETT SYNDROME
- SMA
- EFI
- LIPOFUSCINOSI
- MOLIBDO DEFICIENCY
- APL
- MYXOID LIPOSARCOMAS
- MESOTHELIOMAS
- THYMOMAS
- B-LYMPHOMAS
- UTERINE LEIOMYOSARCOMAS
- OVARIAN CANCER

Transgenic SOD1 mutant mouse, the first animal model of fALS

Tg SOD1G93A mouse

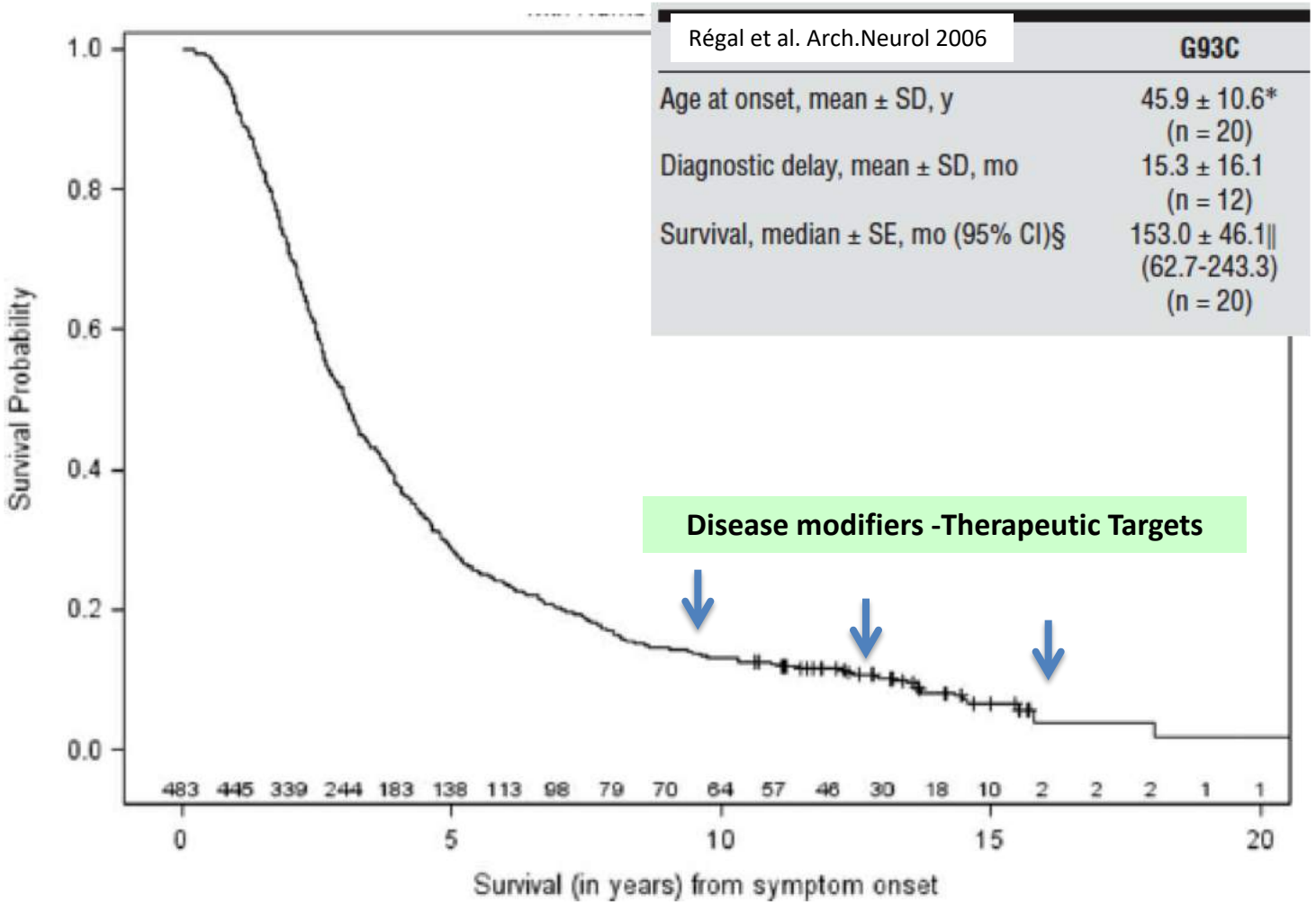
Adapted from Bendotti and Carrì, TRENDS Mol. Med. 2004

Similarities and differences with human fALS

- Loss of lower MN
- Reactive gliosis
- Ubiquitinated inclusions
- Loss of glutamate transporter
- Oxidative damage
- Neuroinflammation

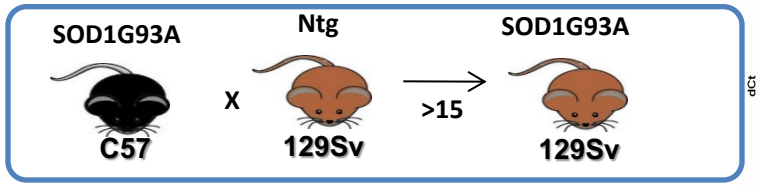
- Lack of upper MN loss
- Hyper-vacuolization
- Overexpression of mutant SOD1

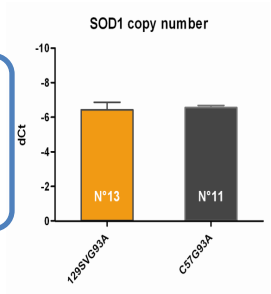
Variable disease course in ALS patients



modified Pupillo et al. Ann Neurol 2014

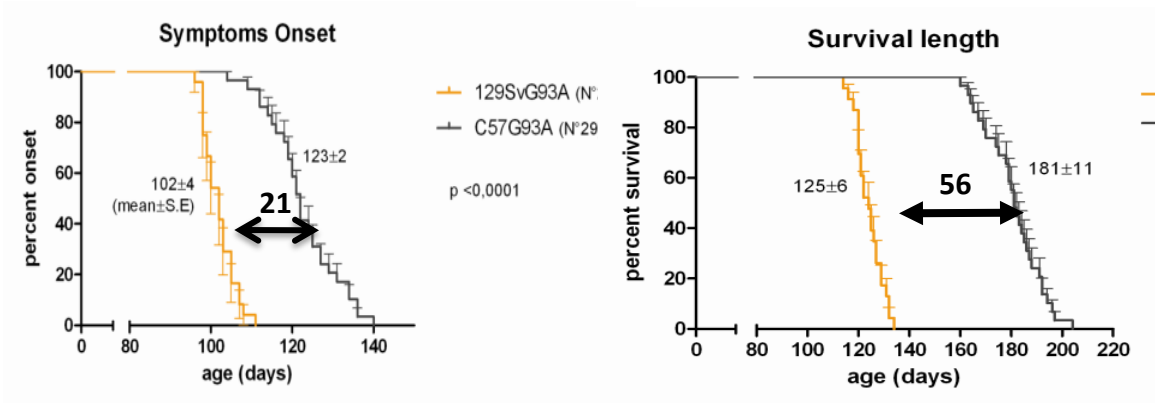
Variable disease course in two mouse models of ALS: a udseful paradigm to identify potential disease modifiers





Fast progressor at onset

- ✓ Reduced protein catabolism
- ✓ Massive mitochondrial dysfunction
- ✓ Impaired nerve regeneration
- ✓ Massive NMJs denervation



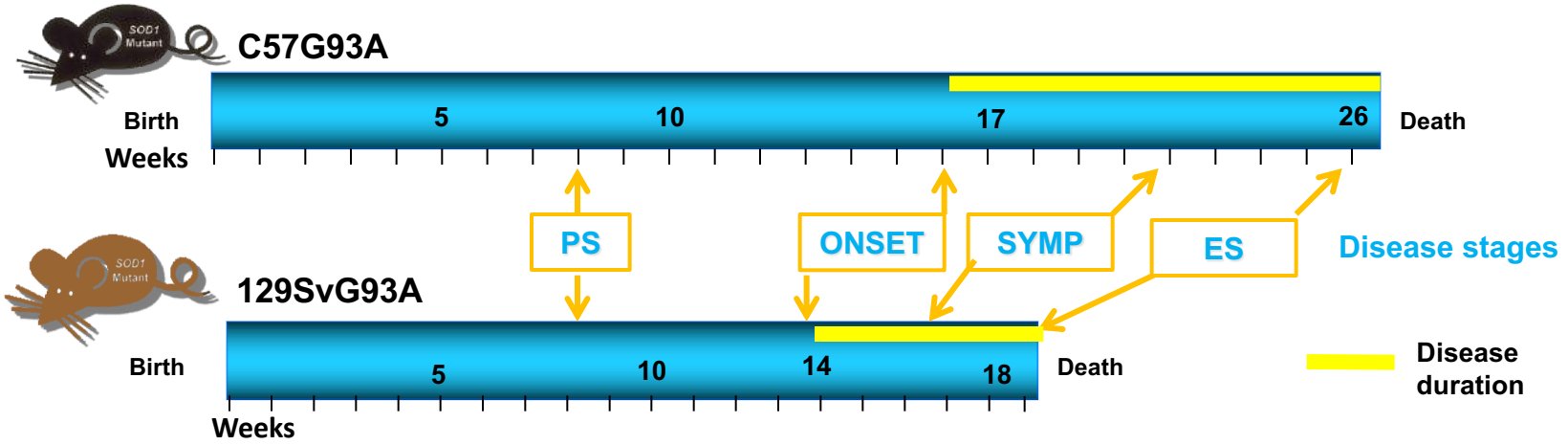
Slow progressor at onset

- ✓ prompt immune response in PNS
- ✓ Increase motor axons regeneration
- ✓ Early activation of neurotrofic factor

Nardo et al. Brain 2013
Marino et al. Neurobiol Aging 2015
Caron et al. PLoS One 2015
Nardo et al. Brain Pathol 2016
Nardo et al. J Neuroinflamm 2016

Variable disease course in two mouse models of ALS:

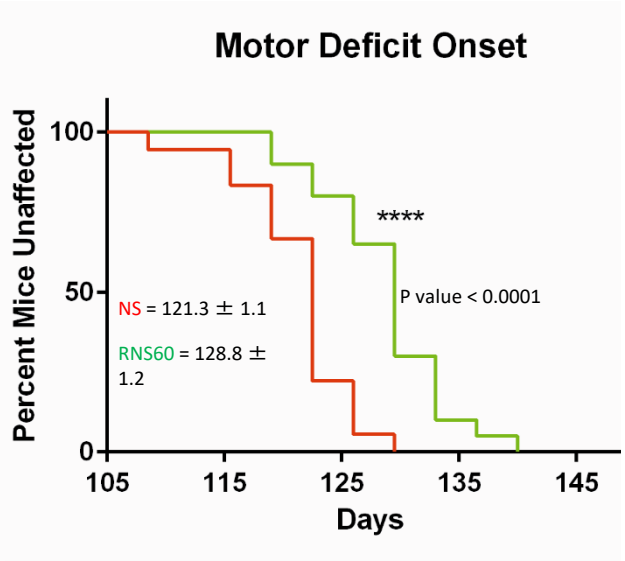
a usefulparadigm to identify potential disease modifiers, prognostic disease biomarkers, therapeutic targets

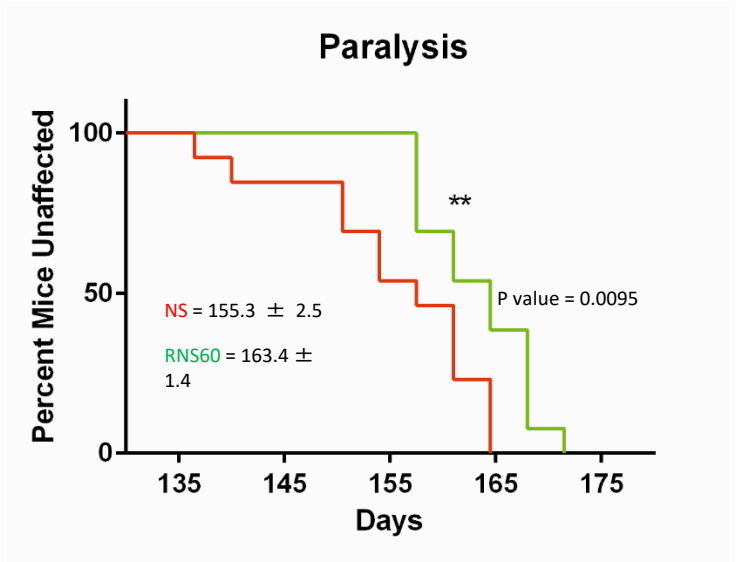


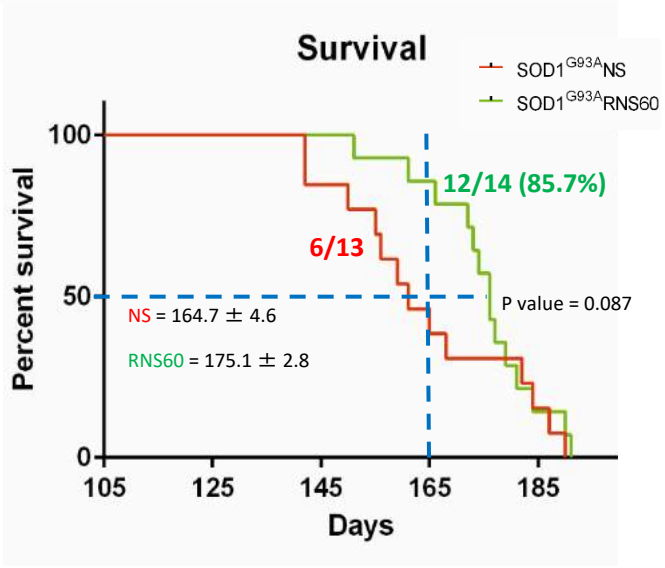
Potential mechanisms for slowing down the disease course

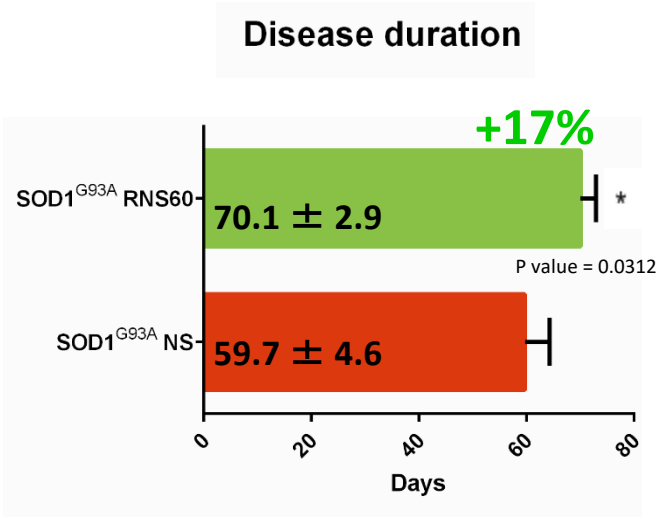
- Increase the protein quality
- Protection of mitochondria
- Activation of immune response in peripheral motor axons
- Increase of neurotrofic factor

RNS60 delays neuromuscular impairment and prolong survival in SOD1G93A mouse model









RNS60

A new agent with anti-inflammatory properties

Mechanism of action

- Activation of protective glial cells
- Immune system modulation

  increase of Tregs

  Reduction of Th17 cytokines
- Reduction of demyelination
- Mitochondrial protection and increased biogenesis
- Activation of antioxidant response

Clinical Trial with RNS60 Study Design

- Multicenter, randomized, double-blind, placebo-controlled, parallel group, add-on trial.
- Eligible patients (**total 142**) have definite or probable ALS (revised El Escorial criteria), disease duration 6 to 24 months, self sufficiency (measured by the ALS-FRS-R scale) and satisfactory bulbar function.
- Subjects will be randomly assigned to receive treatment with either RNS60 or placebo while concomitantly taking riluzole (50-mg tablet twice a day).
- Eligible patients currently treated with **edaravone** will not be included.

ONLY AFTER 17 YEARS

EUROPE FOLLOWS U.S.A.

OFF J.Eur.Communities

2000; L18:1

EC Regulation 141/2000

Orphan medicinal products

designation by the Comp at the Ema

Criteria for designation

• That it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects not more than 5 in 10,000 people in the Community when the application is made **('prevalence criterion')**

or

• That it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment **('insufficient return on investment criterion')**

and, in addition,

• That there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community **('no satisfactory method criterion')**

or

• If such a method exists, that the medicinal product will be of significant benefit to those affected by that condition **('significant benefit criterion')**

EC Regulation 141/2000

Incentives

Protocol assistance: access to free-of-charge protocol assistance at the EMA.

The centralized procedure is compulsory (as of 20 November 2005) for all orphan medicinal products to be authorized via a centralized procedure, which gives access to 29 countries in Europe (27 EU member states, including Norway and Iceland). Marketing authorization applications for orphan medicinal products in Europe currently also benefit from a reduction in the regular fee.

Market exclusivity (10-year) protects against a 'similar' drug being authorized in the EU for the same therapeutic indication. Three derogations from this rule exist: first, the sponsor's consent; second, a lack of supply; third, if a new product, although similar, could be demonstrated to be 'clinically superior'
- that is, "safer, more effective or otherwise clinically superior" to the product already on the market.

National incentives

Community research programmes support Europe-wide studies of the natural history of a rare disease and its pathophysiology, and the development of preventive, diagnostic and therapeutic interventions.

1/2.000	UE
1/1.250	US
1/2.500	JAPAN
1/15.000	Australia

ACCORDING TO THE EU LAW A RARE DISEASE IS REPRESENTED BY THE PREVALENCE OF

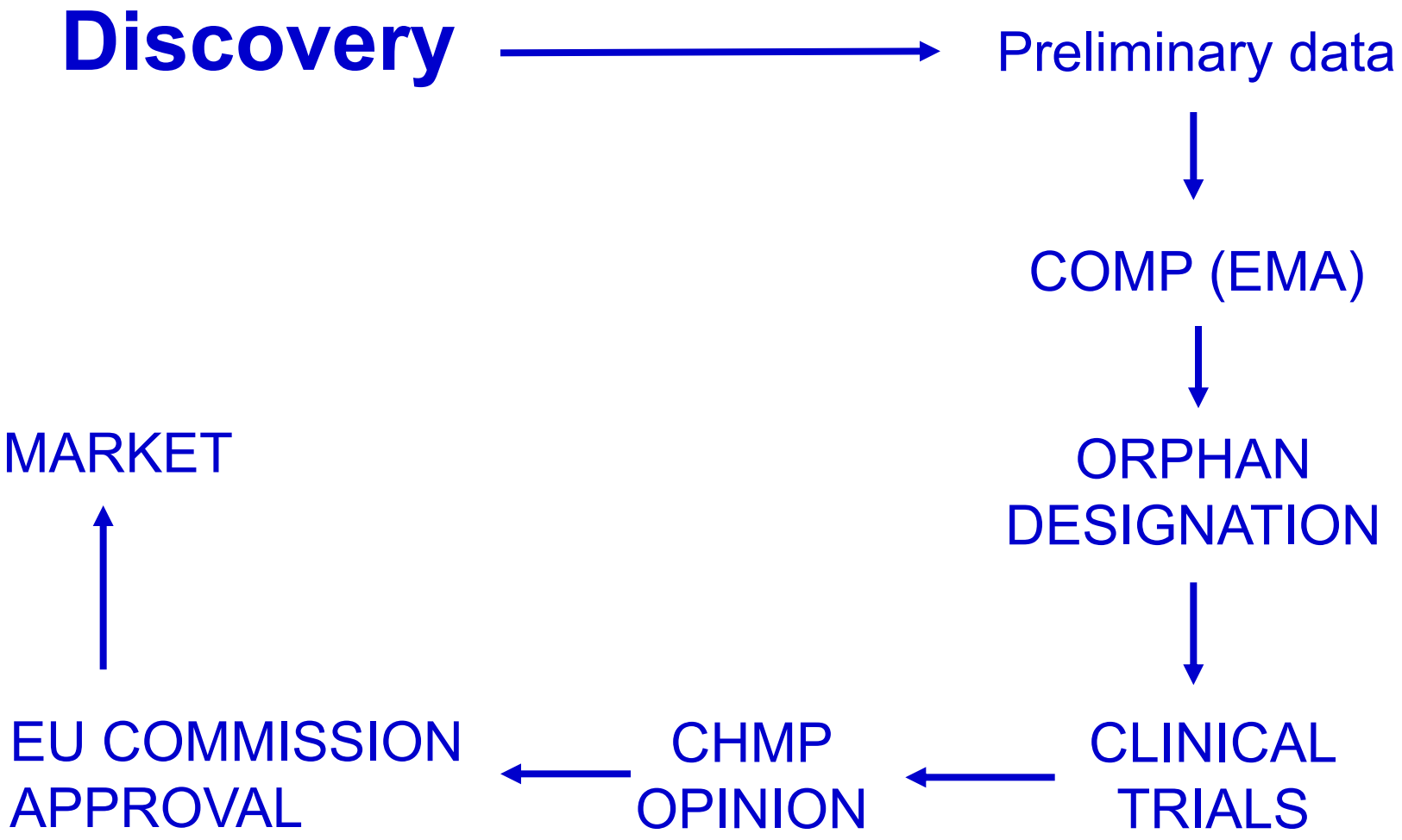
<5/10,000

(<250,000 PATIENTS)

IT IS SUGGESTED TO MODIFY THE PREVALENCE

<5/100,000

(<25,000 PATIENTS)

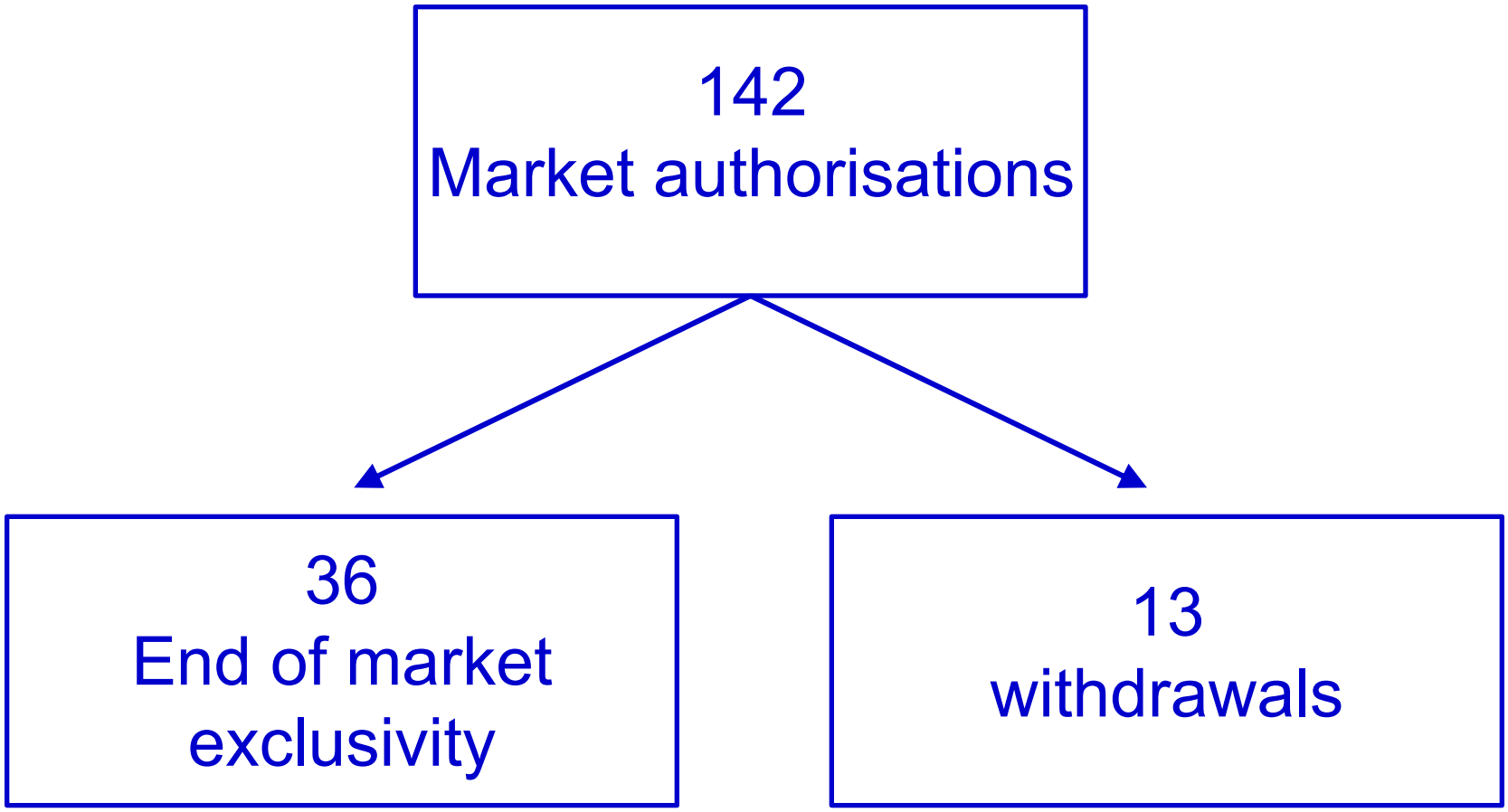

Discovery
Preliminary data
COMP (EMA)
ORPHAN DESIGNATION
CLINICAL TRIALS
CHMP OPINION
EU COMMISSION APPROVAL
MARKET

5.000 - 8.000 RARE DISEASES

27 - 36 MILION PATIENTS

1900 ORPHAN DESIGNATIONS

141 ORPHAN DRUGS APPROVED AFTER 17 YEARS


142
Market authorisations
36
End of market exclusivity
13
withdrawals

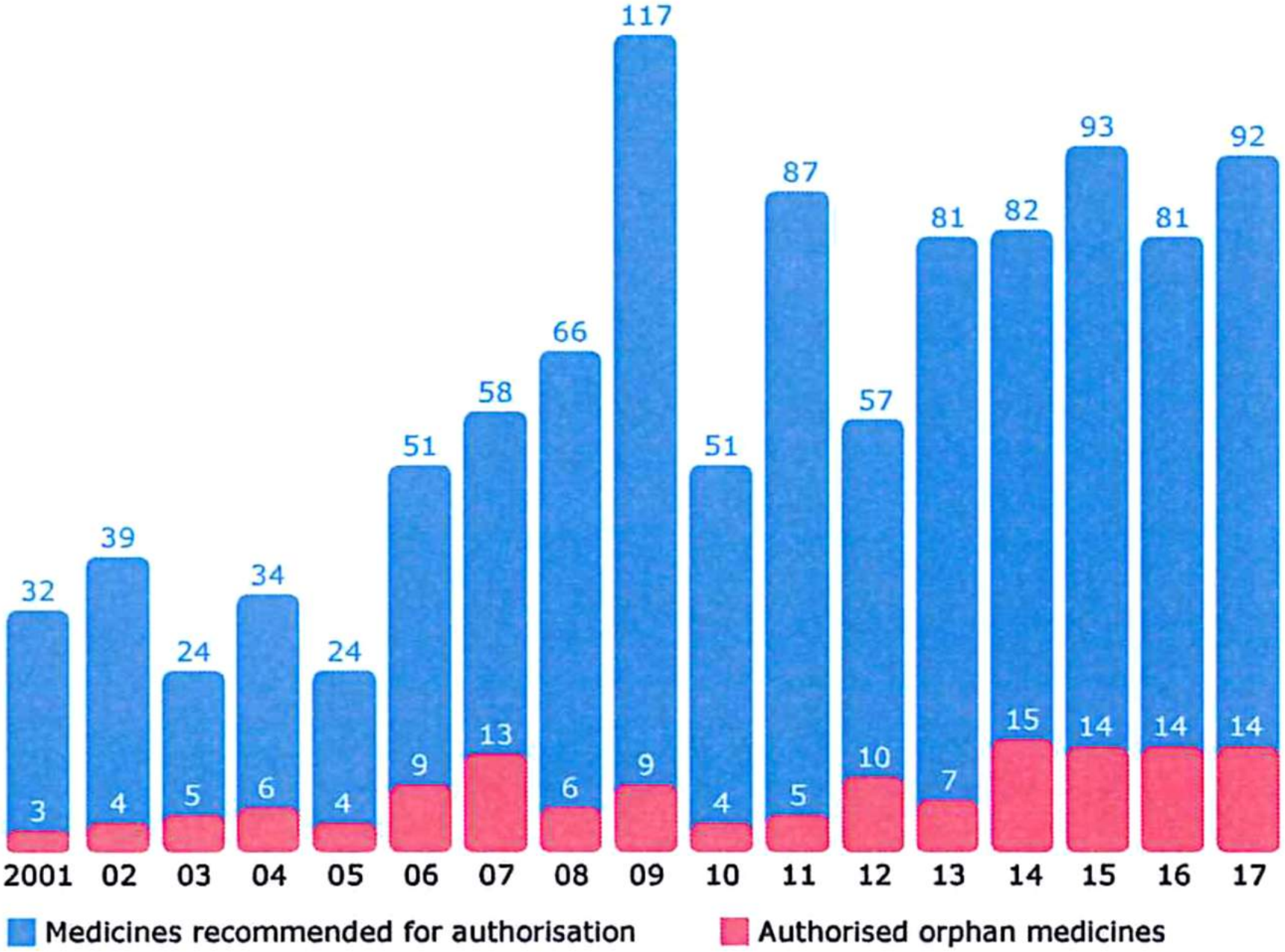
over 1900 medicines with orphan designation

EMA's Committee for Orphan Medicines

The Committee for Orphan Medicinal Products (COMP) is in charge of reviewing applications for orphan designation.

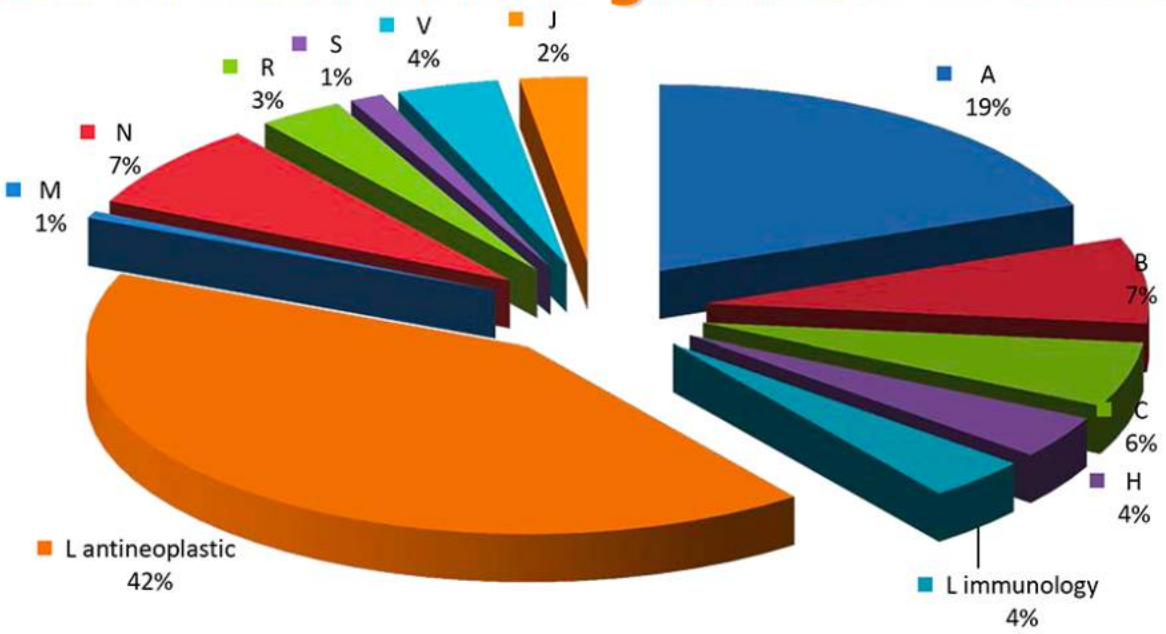
over 140 orphan medicines authorised in the EU

How orphan medicines reach patients


2001 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17
32 39 24 34 24 51 58 66 117 51 87 57 81 82 93 81 92
3 4 5 6 4 9 13 6 9 4 5 10 7 15 14 14 14
Medicines recommended for authorisation
Authorised orphan medicines

142 initial orphan marketing authorisations and 20 extension of indication granted to date

A Alimentary tract and metabolism
B Haematology
C Cardiovascular system
H Systemic hormonal
J Anti-infectives for systemic use
L Immunology
L Antineoplastic
M Musculo-skeletal system
N Nervous system
R Respiratory system
S Sensory organs
V Various



Number of conditions: 111
Active orphan MA: 94
Active extension of indication: 13

Chart includes:
13 authorised extensions of indication
13 withdrawals from the register of orphan medicinal products (including 6 ext. of indication)
5 withdrawals from register medicinal products human use
36 removals of initial MAA from register after expire of the market exclusivity period & 1 ext of indication

Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

Characteristics	No. (%)[a] Orphan Drug Pivotal Trials (n = 23)	No. (%)[a] Nonorphan Drug Pivotal Trials (n = 15)
Primary trial end point reported[b]		
Disease response[c]	17 (68)	4 (27)
Disease progression[d]	4 (16)	6 (40)
Overall survival	2 (8)	4 (27)
Other	2 (8)	1 (7)

Kesselheim et al., 2017

Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

Characteristics	No. (%)[a]	
	Orphan Drug Pivotal Trials (n = 23)	Nonorphan Drug Pivotal Trials (n = 15)
Blinding		
Double-blind	1 (4)	5 (33)
Single-blind	1 (4)	0
Open-label	21 (91)	10 (67)

Kesselheim et al., 2017

Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

Characteristics	No. (%)[a] Orphan Drug Pivotal Trials (n = 23)	No. (%)[a] Nonorphan Drug Pivotal Trials (n = 15)
Comparator		
Active	4 (17)	7 (47)
Supportive care	2 (9)	1 (7)
Placebo	1 (4)	4 (27)
None	16 (70)	3 (20)

Kesselheim et al., 2017

Active principle	Rare disease	Patients studied	Potential cases in EU
miglustat	Type 1 Gaucher disease and Niemann-Pick type C disease	28	10,000
velaglucerase	Gaucher disease	35	15,000
algasidase alpha	Fabry disease	41	10,000
algasidase beta	Fabry disease	56	10,000
clofarabine	Acute lymphoblastic leukaemia in paediatric patients	61	10,000
neralabine	T-cell acute lymphoblastic leukaemia or T-cell lymphoblastic lymphoma	100	50,000
eltrombopag	thrombocytopenic purpura	150	50,000
romiplostim	thrombocytopenic purpura	150	50,000
icatibant	hereditary angioedema	150	50,000
sapropterin	hyperphenylalaninemia	150	50,000

Drug	Repeated dosetoxicology	Exposure	Genotoxicity	Carcinogenicity	Reproduction toxicity
Agalsidase alpha	Rabbits, rats, monkeys	2–26 weeks	NA	NA	Yes (not conclusive)
Agalsidase beta	Rats	27 weeks	NA	NA	NA
Anagrelide	Rats, monkeys, dogs	12–52 weeks	Yes (negative)	NR	Yes (negative)
Arsenic trioxide	Mice, rats, dogs, monkeys	Not specified	Yes (positive)	NR	NR
Bosentan	Rats, dogs, marmosets	1–4 weeks	Yes (negative)	Yes (negative)	Yes (+ in rats, – in rabbits)
Busulfan	Dogs	4 days	NA	NR	Yes (positive)
Carglumic acid	Rats	2–18 weeks	Yes (positive)	Yes (negative)	Yes (not conclusive)
Celecoxib	Rats, dogs	24–52 weeks	Yes (negative)	Yes (not conclusive)	Yes (positive)
Cladribine	Mice	4 weeks	Yes (positive)	NR	Yes (positive)

Joppi et al, 2006

Drug	Repeated dosetoxicology	Exposure	Genotoxicity	Carcinogenicity	Reproduction toxicity
Ibuprofen	NR	NR	Yes (negative)	Yes (negative)	Yes (negative)
Iloprost	Rats, dogs	24–52 weeks	Yes (negative)	Yes (negative)	Yes (positive)
Imatinib	Monkeys	39 weeks	Yes (+ in vitro and –in vivo)	Ongoing	Yes (positive)
Laronidase	Dogs, monkeys	8–26 weeks	NA	NA	Yes (not conclusive)
Miglustat	Rats, monkeys	4–52 weeks	Yes (negative)	Yes (negative)	Yes (positive)
Mitotane	NA	NA	NA	NA	NA
Pegvisomant	Rats, monkeys	24 weeks	Yes (negative)	NA	Yes (negative)
Porfimer	Rats, dogs	13 weeks	Yes (positive)	NA	Yes (negative)
Zinc acetate	Rats	53 weeks	Yes (not conclusive)	Yes (not conclusive)	Yes (negative)

Joppi et al, 2006

European Reference Networks (ERNs)

ERN	HCP Italia	HCP Lombardia
ERN BOND - European Reference Network on bone disorders	7	1
ERN CRANIO - European Reference Network on craniofacial anomalies and ENT disorders	6	3
Endo-ERN - European Reference Network on endocrine conditions	9	2
ERN EpiCARE - European Reference Network on epilepsies	5	2
ERKNet - European Reference Network on kidney diseases	11	2
ERNICA - European Reference Network on inherited and congenital anomalies	1	
ERN EURACAN - European Reference Network on adult cancers (solid tumors)	17	4
ERN EuroBloodNet - European Reference Network on haematological diseases	21	5
ERN eUROGEN - European Reference Network on urogenital diseases and condition	4	1
ERN EYE - European Reference Network on eye diseases	6	
ERN GENTURIS - European Reference Network on genetic tumor risk syndromes		
ERN GUARD-HEART - European Reference Network on diseases of the heart	6	3

ERN	HCP Italia	HCP Lombardia
ERN ITHACA - European Reference Network on congenital malformations and rare intellectual disability	8	1
ERN RARE-LIVER - European Reference Network on hepatological diseases	3	2
ERN LUNG - European Reference Network on respiratory diseases	15	2
MetabERN - European Reference Network on hereditary metabolic disorders	11	2
ERN EURO-NMD - European Reference Network on neuromuscolar diseases	15	5
ERN PaedCan - European Reference Network on paediatric cancer (haemato-oncology)	9	2
ERN ReCONNET - European Reference Network on connective tissue and muscoloskeletal diseases	8	3
ERN RITA - European Reference Network on immunodeficiency, autoinflammatory and autoimmune diseases	5	3
ERN RND - Eurpean Reference Network on neurological diseases	4	2
ERN Skin - European Reference Network on skin disorders	6	1
ERN TRANSPLANT-CHILD - European Reference Network on transplantation in children	3	1
VASCERN - European Reference Network on multisystemic vascular diseases	6	3

The present system does not allow an efficient conduct of clinical trials

- **There is a need to carry out clinical trials**

  - timely
  - rapidly
  - with no deadlines (no restriction to 3-5 years)
  - with adequate financial support
  - addressing patients and public health needs
  - addressing comparative effectiveness
  - independent from pharma companies

A SPECIAL AREA SHOULD BE MADE AVAILABLE WITHIN FP9 OR OTHER KIND OF EU RESEARCH PROGRAMS ONLY FOR INDEPENDENT TRIALS

THE FUND SHOULD NOT HAVE DEADLINES.

PROPOSALS SHOULD BE EVALUATED BY AN INDEPENDENT COMMITTEE MADE UP BY CLINICIANS AND METHODOLOGISTS EXPERT IN RCTs.

NEED FOR INDEPENDENT CLINICAL RESEARCH

THE AMOUNT OF AT LEAST 1 BILLION EURO (<0,3% OF EU PHARMACEUTICAL MARKET) DEVOTED TO NON–PROFIT INDEPENDENT RESEARCH ON RANDOMIZED CONTROLLED CLINICAL TRIALS OF ORPHAN DRUGS

IMPRENDITORIAL NON-PROFIT COMPANIES MADE UP BY DIFFERENT INSTITUTIONS SUPPORTED BY PUBLIC AND CHARITY FUNDS TO PRODUCE NEW ORPHAN DRUGS AT LOW PRICES