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Sustainability: Budgetary Impact and Cost Drivers

for

Rare and Ultra-Rare Diseases

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Workshop "**Health Systems Resilience for Rare Diseases**" – Paris / France, June 27, 2018

Background: Michael Schlander

- Head of Division of Health Economics, **DKFZ Heidelberg** (since 2017)

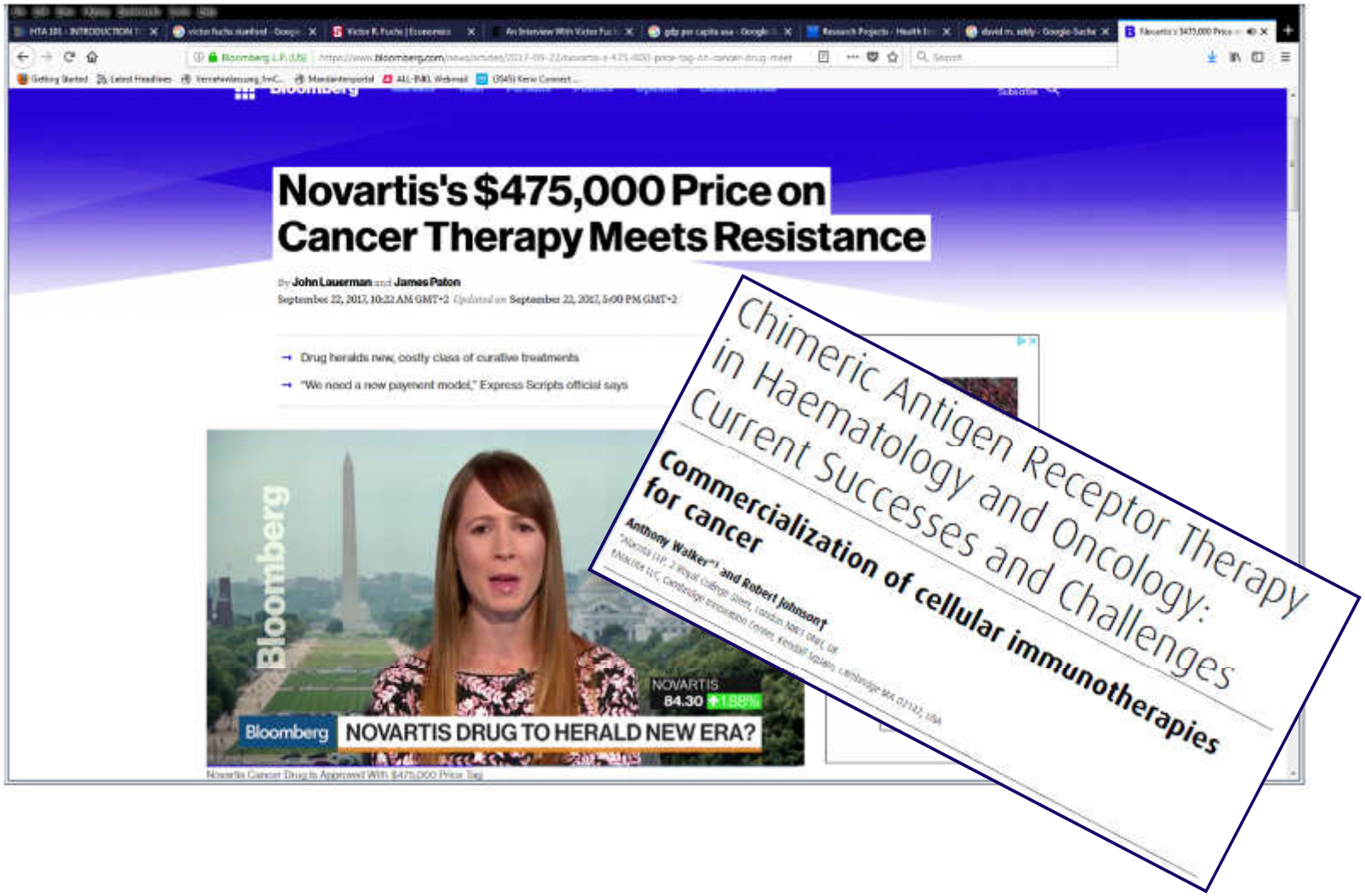
[Academic]
- Professor of Health Economics – U of Heidelberg (since 2017)
- Professor of Health Care & Innovation Management (2002-2016)
- Chairman & Scientific Director – InnoVal^{HC} / Wiesbaden (since 2005)

[Professional]
- CEO – industry [turn-around management] (in D; 1999-2002)
- Director of Strategic Business Unit – industry [including pantoprazole] (Byk Gulden; Johnson & Johnson; in D, B, USA; 1993-1999)
- European Clinical Development – industry (Sandoz; in D, CH; 1987-1993)

[Academic]
- Exp. Brain Research & Clinical Neurology – U of Frankfurt (1982-1987)

[Education]
- PhD Equivalent (*Habilitation*) – Health Economics, U of Heidelberg (2007)
- Diploma – Health Economics, Stockholm School of Economics (2002)
- MBA (*valedictorian*) – Management, City U of Seattle, Washington (1994)
- MD (*summa cum laude*) – Exp. Brain Research, U of Frankfurt (1985/87)

Hand Clapping for Science…



"Hand clapping for science is now inextricably linked to hand wringing over affordability."[1]

[1] **Peter B. Bach**
New England Journal of Medicine 2015 (November 05); 373 (19): 1797-1799.

The 5 Most Expensive Drugs in the World[1]

1. **Soliris (Alexion)**
   paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS); average annual cost: US-$ 409,500
2. **Elaprase (Shire)**
   Hunter syndrome (ERT); US-$ 375,000 p.a.
3. **Naglazyme (BioMarin)**
   mucopolysaccharidosis (MPS) VI (ERT); US-$ 365,000 p.a.
4. **Cinryze (ViroPharma)**
   hereditary angioedema (HAE); US-$ 350,000 p.a.
5. **Myozyme (Sanofi / Genzyme)**
   Pompe disease (ERT); US-$ 300,000 p.a.

[1]S. Williams, The Motley Fool, June 29, 2013. http://www.fool.com/investing/general... [last accessed Jan. 22, 2016]

Cost Effectiveness ("Efficiency")

Orphan drugs and the NHS: should we value rarity?

Christopher McCabe, Karl Claxton, Aki Tsuchiya

The growing number and costs of drugs for rare diseases are straining healthcare budgets. Decisions on funding these treatments need to be made on a sound basis…

[…]

The justification for special status for rare diseases must rest on the question: **should we value the health gain to two individuals differently because one individual has a common disorder and the other has a rare disorder?**

[…]

While orphan drugs were rare, healthcare systems were able to deal with them in an ad hoc manner. But there are now over 6000 orphan diseases with over 200 treatments approved by the US Food and Drugs Administration and 64 trials currently sponsored by the US Office of Orphan Products Development. […] Genomics is expected to disaggregate currently prevalent diseases into many genetically defined distinct conditions. Orphan status is thus likely to become increasingly common.

[…]

Special status for orphan drugs in resource allocation will avoid difficult and unpopular decisions, but it may impose substantial and increasing costs on the healthcare system. The costs will be borne by other, unknown patients, with more common diseases who will be unable to access effective and cost effective treatment as a result.

British Medical Journal 2005, 331: 1016-1019

Cost Effectiveness ("Efficiency")

Orphan drugs policies: a suitable case for treatment

Michael Drummond, Adrian Towse

A starting point for designing any health policy is to clarify society's views and objectives in relation to the issues concerned.

Although there is scant evidence on what the general public in different countries expect from their health care system, **the utilitarian perspective of maximising the total benefits to the population as a whole is a reasonable starting point**, particularly in jurisdictions where public financing of health care predominates.

This notion also underpins most of the assessments of value for money conducted in those jurisdictions where these are explicitly required. Namely, the implicit or explicit objective is to maximise the total health gain from the use of health care resources, although the methods for measuring health gain v ary from jurisdiction to jurisdiction.

However, since orphan drugs are never as cost-effective as drugs for more prevalent diseases, **departures from a strict utilitarian perspective would have to be justified** if they were to be funded. That is, society would have to be willing to give up some of the health gain to the population as a whole.

European Journal of Health Economics 2014, 15: 335-340

Health Economic Evaluation Principles

The Logic of Cost-Effectiveness – Questions Asked:

1. Safety

- **Does it harm?**
  (controlled conditions)

↓

2. Efficacy

- ***Can* it work?**[1]
  (controlled conditions)

↓

3. Effectiveness

- ***Does* it work and is it safe?**[1]
  (normal practice)

↓

4. Efficiency

- **Do its benefits outweigh its costs?**
  (*frequently*: "Is it cost-effective"?)

EBM[2]: How sure can we be?

[1]cf. D. Schwartz and J. Lellouch (1967); [2]EBM: "evidence-based medicine"

Health Technology Assessment (HTA)

NICE (England and Wales):

The Logic of Cost-Effectiveness in Action

- Ultra-Orphan Medicines (prevalence <1/50,000)
  - "Highly Specialised Technologies (HST)" program
  - introduction of modified cost effectiveness analyses as of April 01, 2017
- Base Benchmark of 100,000 GBP / QALY gained
  - applying a weighting system for QALYs produced by HSTs:
  - if, over the time horizon of the disease, 11-29 incremental QALYs will be produced, these will be weighted between 1 and 3,
  - if >30 incremental QALYs will be produced, these will be weighted 3 times

HTA: Early Benefit Assessments

Germany: The Logic of Comparative Effectiveness

1. **Safety**
   - ¬ **Does it harm?**
     (controlled conditions)

2. **Efficacy**
   - ¬ ***Can* it work?**[1]
     (controlled conditions)

3. **Effectiveness**
   - ¬ ***Does* it work and is it safe?**[1]
     (normal practice)

4. **Comparative Effectiveness**
   - ¬ **Does it outperform current standard therapy?**
     (*Germany*: "Is it more effective"?)

[1]cf. D. Schwartz and J. Lellouch (1967); [2]EBM: "evidence-based medicine"

HTA: Early Benefit Assessments and OMPs

Germany: Orphan Medicinal Product Reimbursement

- OMP Designation by EMA
- Immediate Market Access
  - reimbursement at price asked for by manufacturer
- Additional Benefit Assumed under present AMNOG regulation
- Early Appraisal by GBA: Size of Additional Benefit
  - mostly “unquantifiable”
- Revenue Threshold: max. €50m p.a.
  - once exceeded,
    OMP will be subject to standard Early Benefit Assessment

HTA: Early Benefit Assessments and OMPs

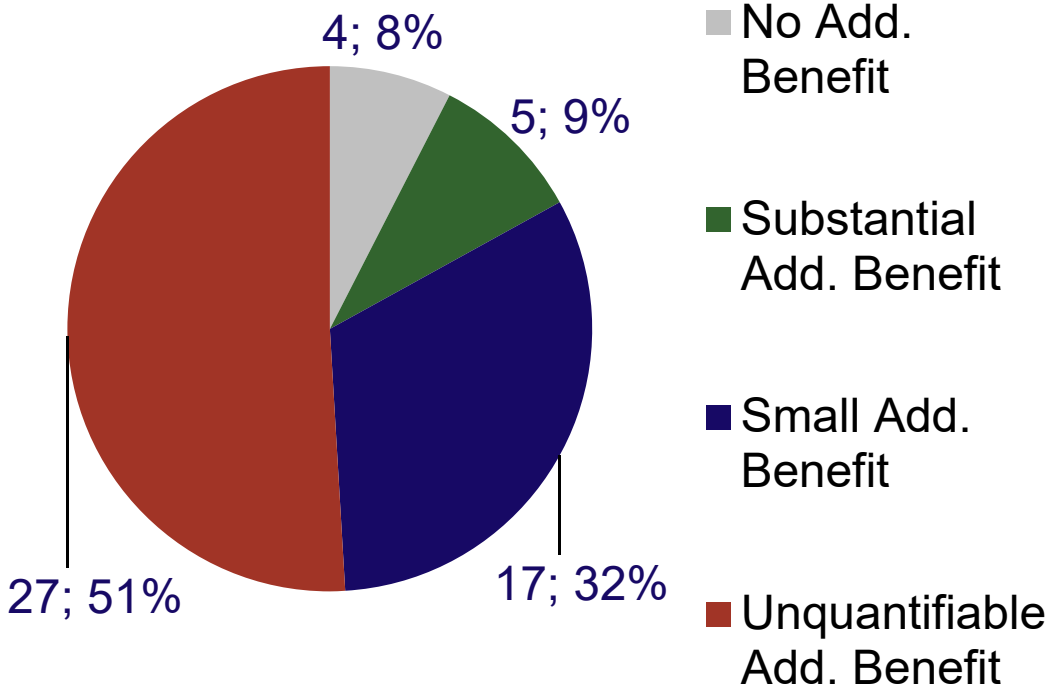
AMNOG: Orphan Medicinal Product Reimbursement

- Sustainable?
  - 26% of all newly launched drugs had OMP status in 2010
  - 32% of all newly launched drugs had OMP status in 2015
  - Additional Benefit mostly “unquantifiable” (10/12 in 2015)
  - Health Care and Drug Spending growing faster than GDP
- Controversial:
  - Marginal Benefit, at (sometimes) extreme acquisition costs?
  - Immediate Market Access (at manufacturer’s price)?
  - Revenue Threshold (too high?)
  - Adaptive Pathways?

HTA: Early Benefit Assessments and OMPs

AMNOG: Orphan Medicinal Product Reimbursement

Orphan Drugs



OMP Early Benefit Appraisals:

Size of additional benefit; reference: patient (sub)groups.

Status as at Aug. 01, 2016

Data source:
U. Schwabe, D. Paffrath (2016), p. 161

Clinical Effectiveness

Clinical evidence for orphan medicinal products a cause for concern?

Eline Picavet, David Cassiman, Carla E Hollak, Johan A Maertens, Steven Simoens

[…]

We quantitatively assessed the characteristics and quality of clinical evidence of the pivotal studies of 64 OMPs as described in the European Public Assessment Report and/or the Scientific Discussion document prepared by the Committee for Human Medicinal Products of the EMA.

[…]

The 64 OMPs were altogether authorized for 78 orphan indications, for which 117 studies were identified as 'pivotal' or 'main' studies. In approximately two thirds of the studies, the allocation was randomized (64.8%) and a control arm was used (68.5%). Half of the studies applied some type of blinding. Only a minority (26.9%) of the studies included a Quality-of-Life (QoL) related endpoint, of which a third claim an improvement in QoL.

[…]

In conclusion, the pivotal studies that are the basis for marketing authorization of OMPs are a cause for concern, as they exhibit methodological flaws […]

Orphanet Journal of Rare Diseases 2013, 8: 164

Clinical Effectiveness

Systematic review of available evidence on 11 high-priced inpatient orphan drugs

Tim A Kanters, Caroline de Sonneville-Koedoot, W Ken Redekop, Leona Hakkaart

[…]

A systematic review was performed […] for 11 inpatient orphan drugs listed on the Dutch policy rule on orphan drugs. For included studies, we determined the type of study and various study characteristics.

[…]

A total of 338 studies met all inclusion criteria. Almost all studies (96%) focused on clinical effectiveness of the drug. Of these studies, most studies were case studies (41%) or observational studies (39%). […] a randomized clinical trial was available for 60% of the orphan drugs. Eight studies described the cost-effectiveness of an orphan drug; an equal number described an orphan drug's budget impact.

[…]

Despite the often heard claim that RCTs are not feasible for orphan drugs, we found that an RCT was available in 60% of orphan drugs investigated. Cost-effectiveness and budget impact analyses for orphan drugs are seldom published.

Orphanet Journal of Rare Diseases 2013, 8: 124

Clinical Effectiveness

Generating health technology assessment evidence for rare diseases

Karen Facey et al.

[…]

Discussion with an expert panel was augmented with references and case studies to explore robust approaches for HTA evidence generation for rare disease treatments.

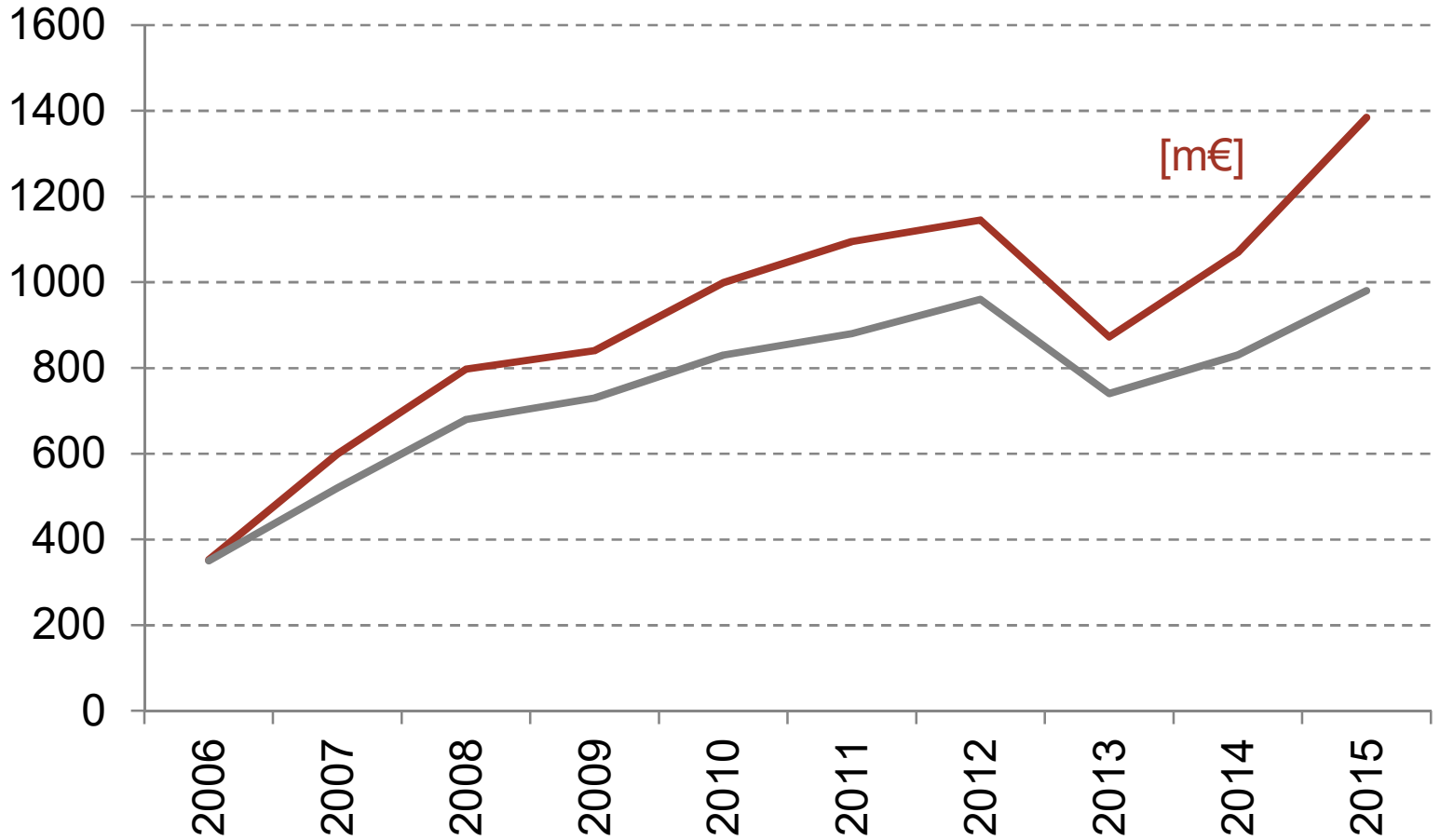
Results: Traditional RCTs can be modified using sequential, three-stage or adaptive designs to gain more power from a small patient population or to focus trial design. However, such designs need to maintain important design aspects such as randomization and blinding and be analyzed to take account of the multiple analyses per formed. N-of-1 trials […] could be particularly valuable for rare diseases and when prospectively planned across several patients and analyzed using Bayesian techniques, a population effect can be estimated that might be of value to HTA. When the optimal outcome is unclear in a rare disease, disease specific patient reported outcomes can elucidate impacts on patients' functioning and wellbeing. Likewise, qualitative research can be used to elicit patients' perspectives, with just a small number of patients.

Conclusions: International consensus is needed on ways to improve evidence collection and assessment of technologies for rare diseases […].

International Journal of Technology Assessment in Health Care 2014, 30 (4)

Early Benefit Assessments and OMPs

Outpatient Orphan Drug Revenues, 2006-2015



OMP Outpatient Revenues Germany:

2006-2015, data source: U. Schwabe, D. Paffrath (2016), p. 17

Red: annual revenues [m€]
Grey: annual DDDs [10,000s]

Early Benefit Assessments and OMPs

Sustainability? – The Orphan Drug Pipeline in Europe[1]

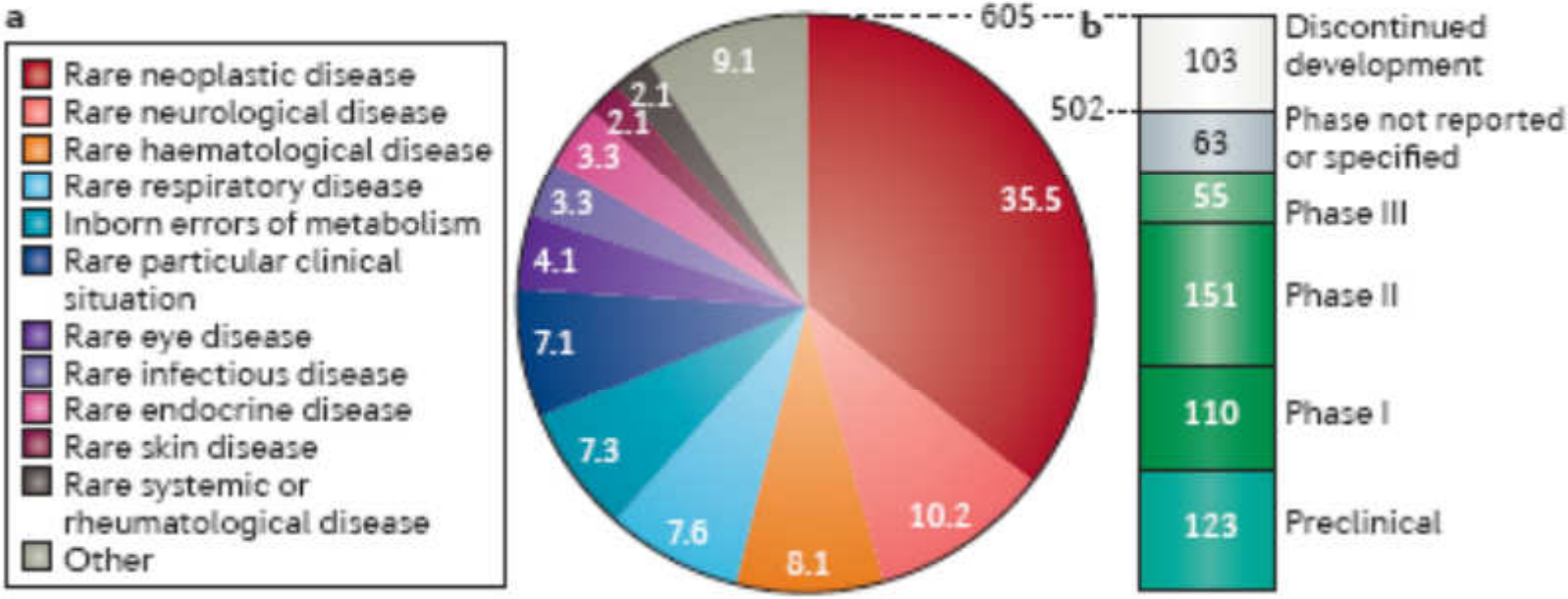
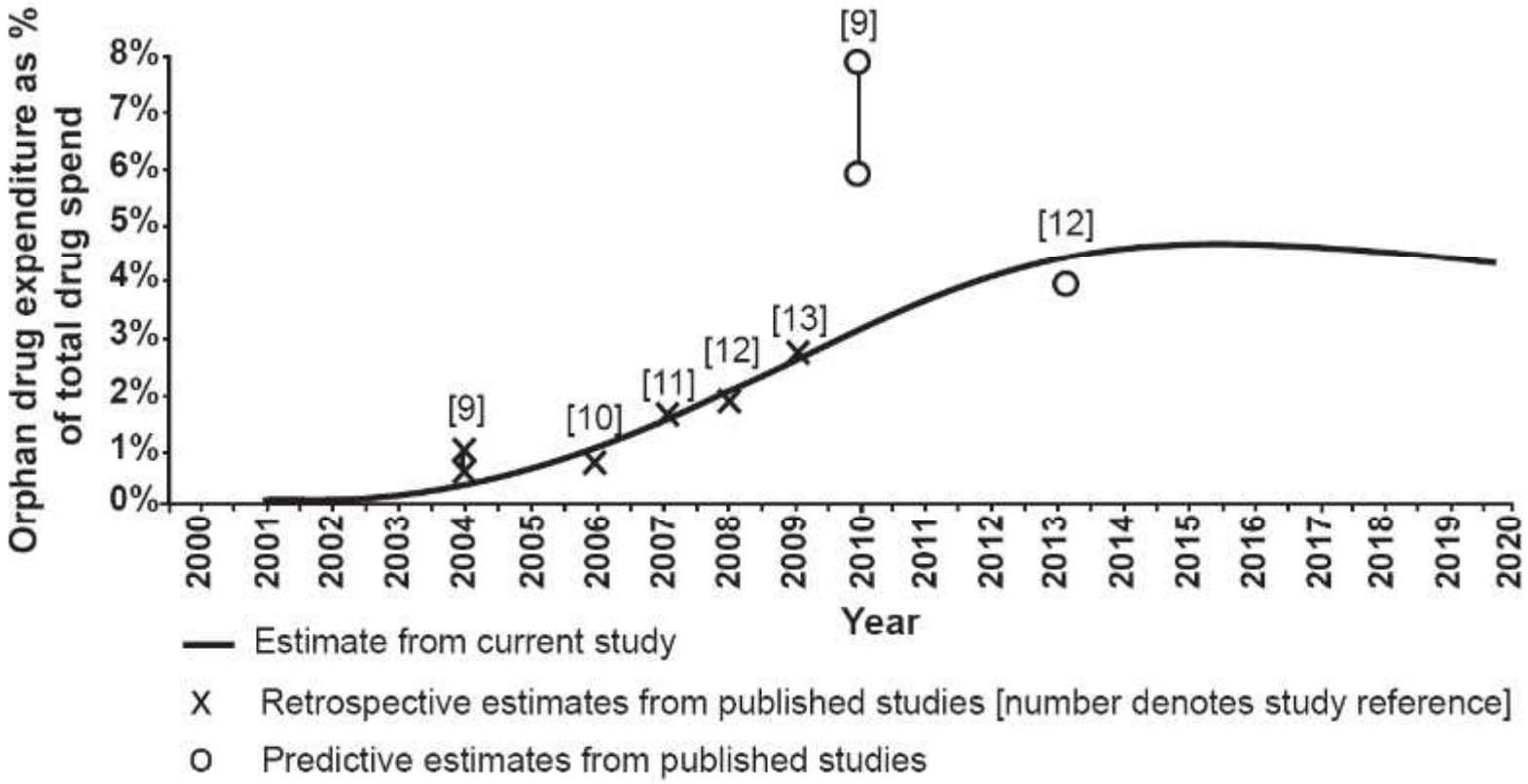


Figure 1 | **Analysis of orphan designations in the European Union.** The data are for orphan designations granted between 2002 and 2012 with annual reports filed to the European Medicines Agency in 2013 or 2014 ($n = 605$). a | Orphan designations granted, subdivided by therapeutic area. b | Orphan designations granted, subdivided by development stage.

Th. Morel, E. Picavet, et al.: The orphan drug pipeline in Europe. *Nature* 2016; 15: 376

Early Benefit Assessments and OMPs

Sustainability? – OMP Budget Impact Projection (2011)



Source of graph: Schey et al. (2011), p. 6.

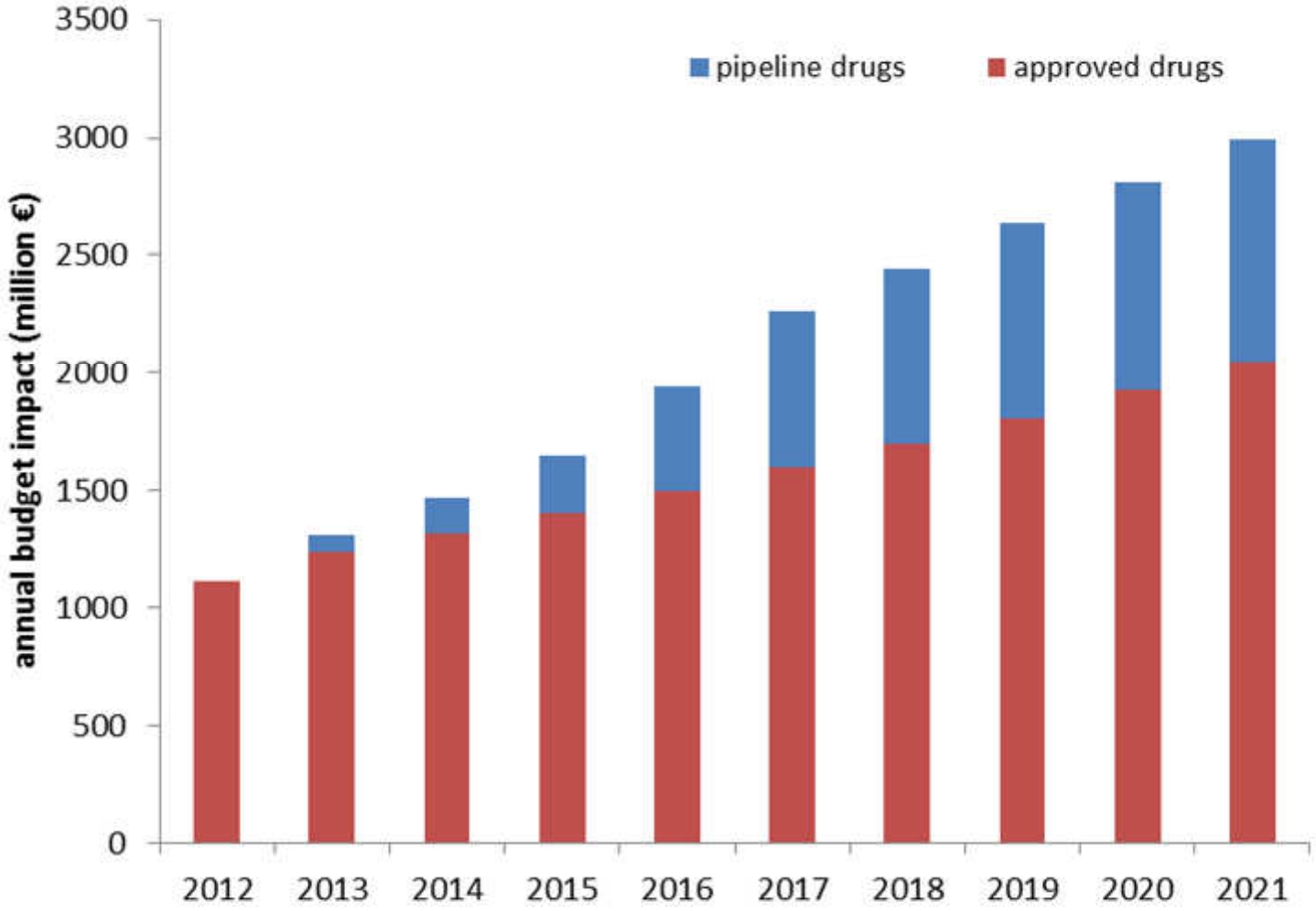
C. Schey et al.: Estimating the budget impact of orphan medicines in Europe: 2010 – 2020. *Orphanet Journal of Rare Diseases* 2011; 6: 62

Projecting URD Budget Impact (2014 onward)

Study (year)	Variable	Base case (range)
Schey *et al.* (2011)	Market penetration rate	22% (10–30%)
EvaluatePharma (2013)	Annual growth rate in sales volume	10% (5–15%)
EU competition commission	Savings 1 year after the first generic entry	0% (0–20%)
EU competition commission	Savings 2 years after the first generic entry	0% (0–25%)
Tufts Center for the Study of Drug Development (REF)	Clinical phase durations	
	Phase I trials	2 years (1.5–2.5)
	Phase II trials	1.5 years (1–2)
	Phase III trials	1.5 years (0–2)
	Approval	1.5 years (1–2)
Tufts Center for the Study of Drug Development	Transition probabilities	
	Phase I → Phase II	70.6% (60%)
	Phase II → Phase III	45.4% (40%)
	Phase III → New Drug Application	63.6% (50–100%))
	New Drug Application → approval	93.2% (80%)
Average of the discount rates recommended in England, Germany and The Netherlands	Discount rate	3.5% (0–5%)

Annual budget impact of approved and pipeline drugs for ultra-rare diseases over 10 years (2012 to 2021) in Europe from a payer's perspective . Source: M. Schlander et al.: Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe. *Expert Review of Pharmacoeconomics & Outcomes Research*, 14 (1), 2014: 123-129.

Projected URD Budget Impact (2014 onward)



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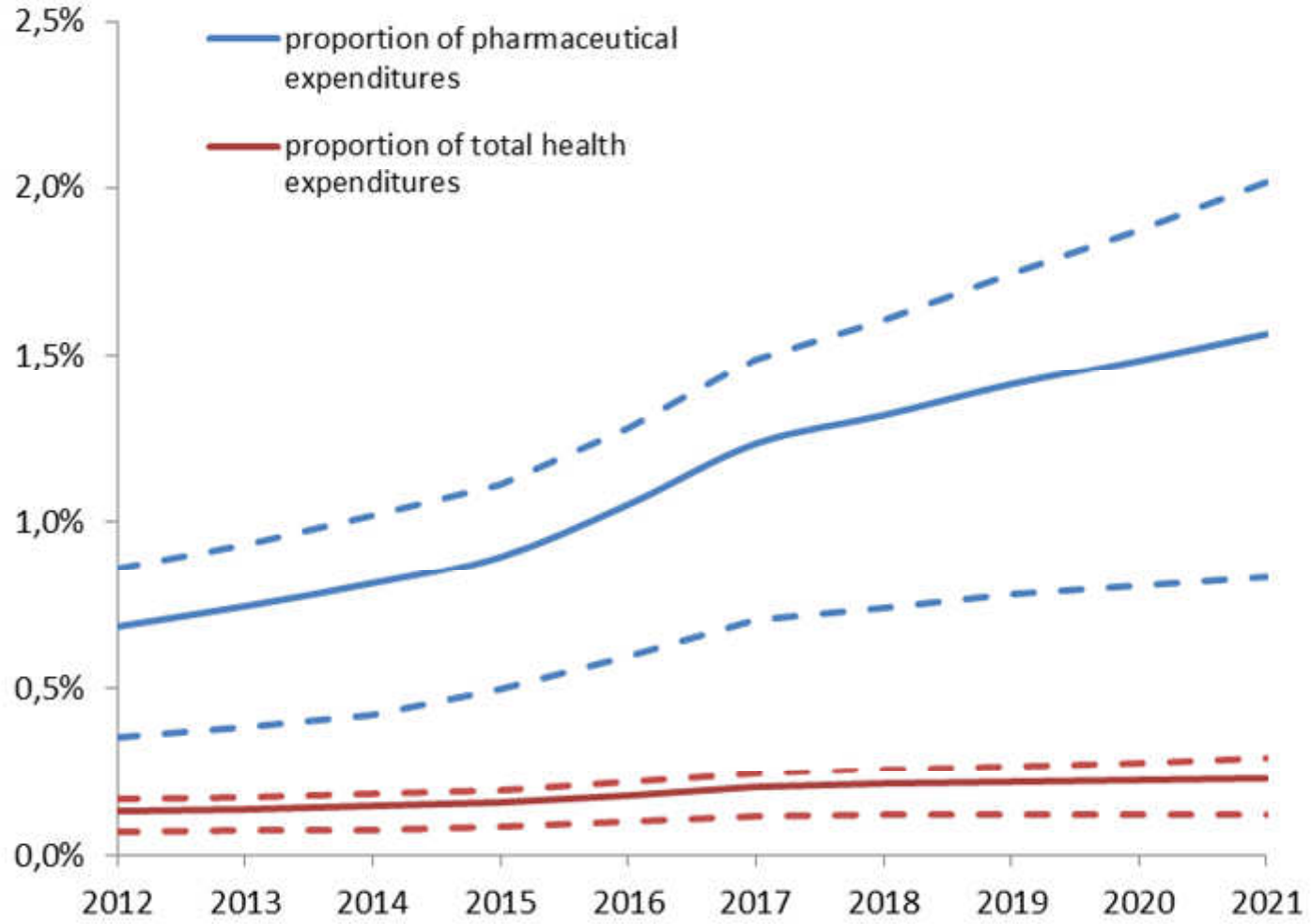
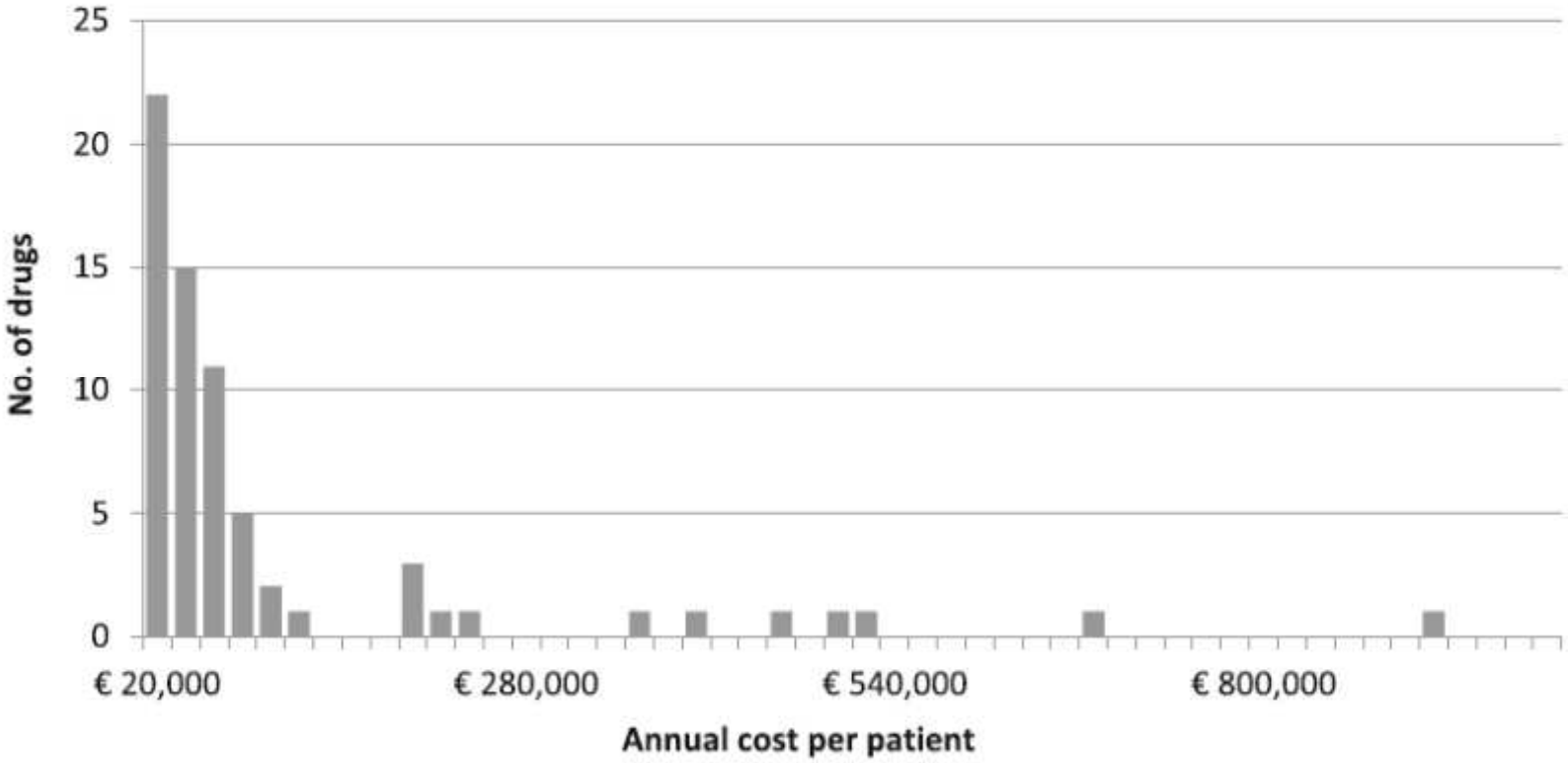
Projected URD Budget Impact (2014 onward)



Proportion of pharmaceutical and total health expenditures in Europe spent on drugs for ultra-rare diseases (URDs). Dashed lines indicate ranges provided by the extreme-case scenario analyses. Source: M. Schlander et al.: Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe. *Expert Review of Pharmacoeconomics & Outcomes Research*, 14 (1), 2014: 123-129

Annual Cost per Patient

Analysis based on 68 orphan drugs in France



Median, €96,518 p.a.
Source: Daria Korchagina et al. *Orphanet Journal of Rare Diseases* (2017) 12:75

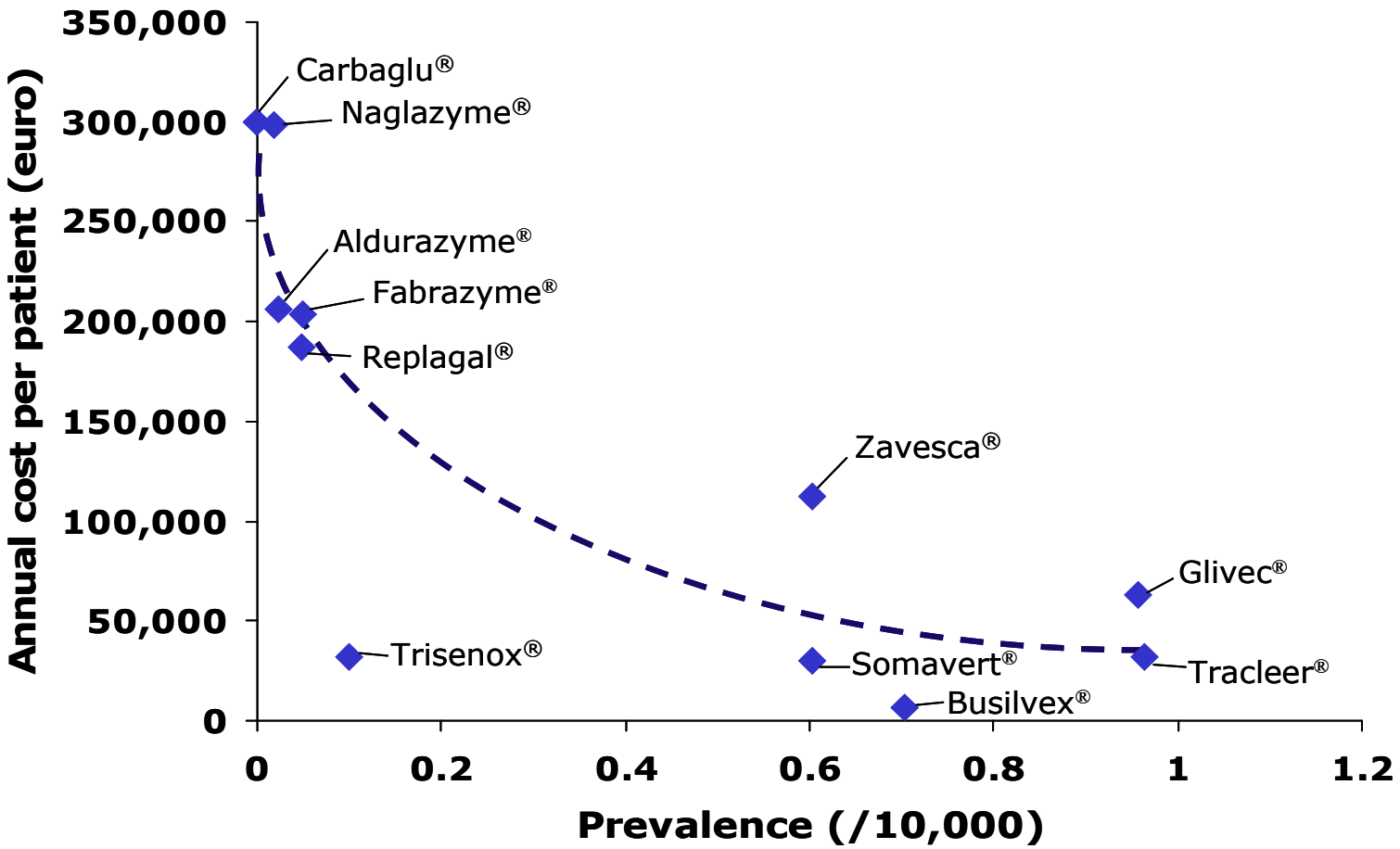
Annual Cost per Patient

Analysis based on 68 orphan drugs in France

- **Cost Drivers** *identified in French study*:
  - (Non-) Availability of alternative treatments
  - Therapeutic area
  - Prevalence (p=0.02)
- **Cost Drivers** *not confirmed in French study*:
  - Severity of condition
  - Age of targeted population
  - Marketing authorization date (time span, 2002-2015)
  - Clinical evidence (phase II or III data)
  - Clinical endpoint (surrogate or „hard“)

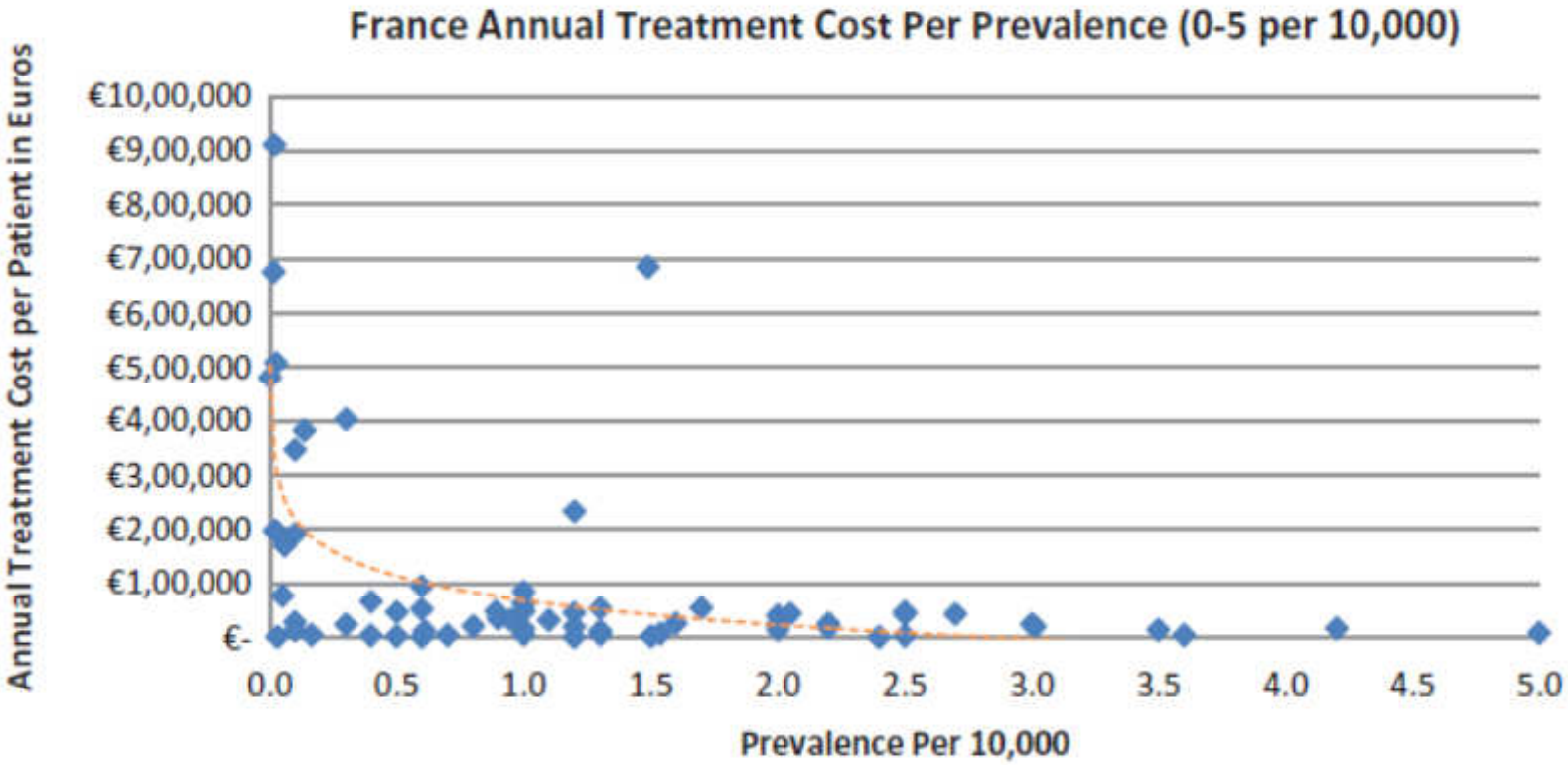
Source: Daria Korchagina et al. *Orphanet Journal of Rare Diseases* (2017) 12:75

Prevalence and Cost per Patient



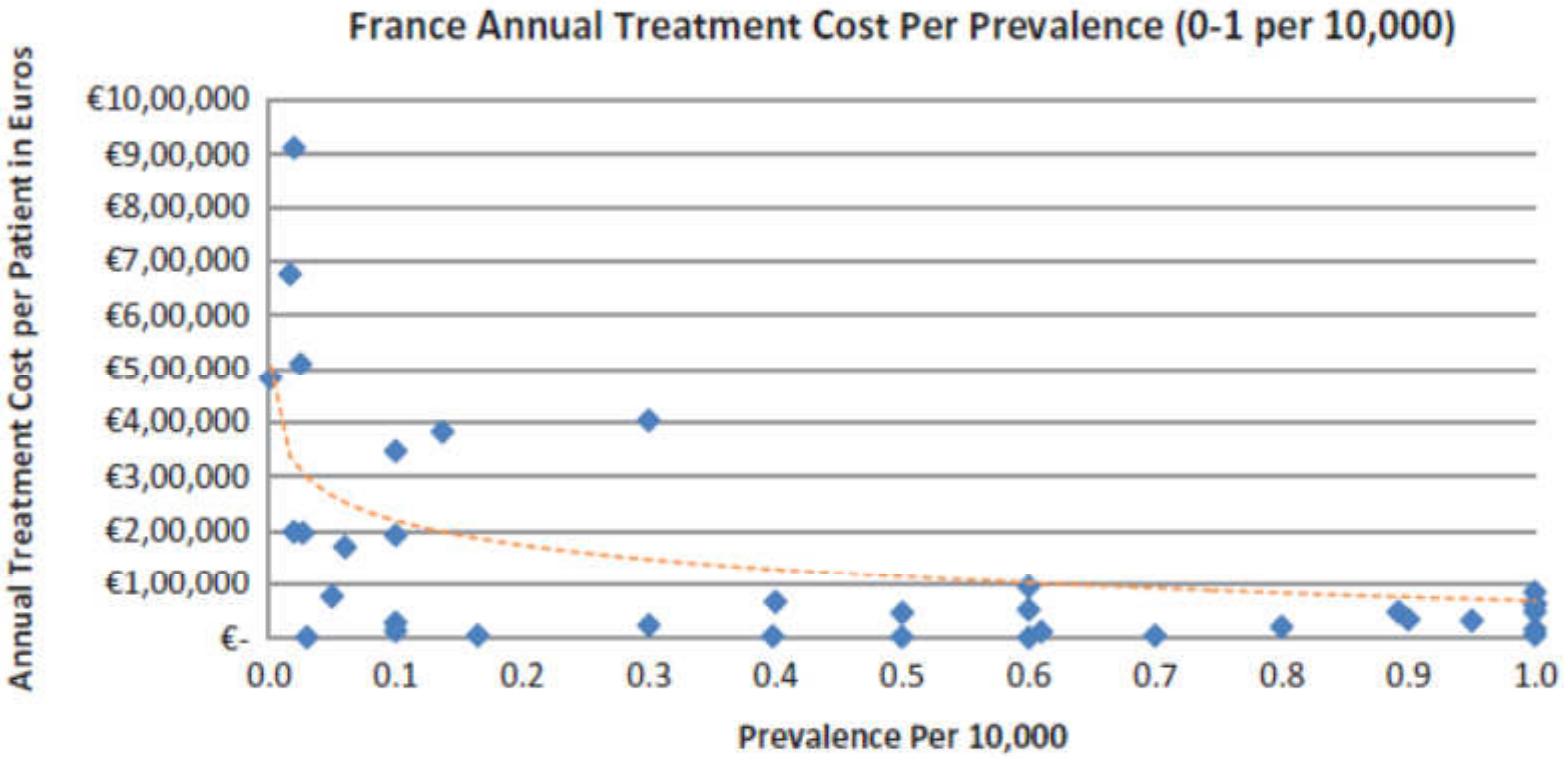
M. Schlander and M. Beck, *Current Medical Research & Opinion* 2009; 25 (5): 1285-1293

Prevalence and Cost per Patient



Goran Medic et al., *Journal of Market Access & Health Policy* (2017)

Prevalence and Cost per Patient



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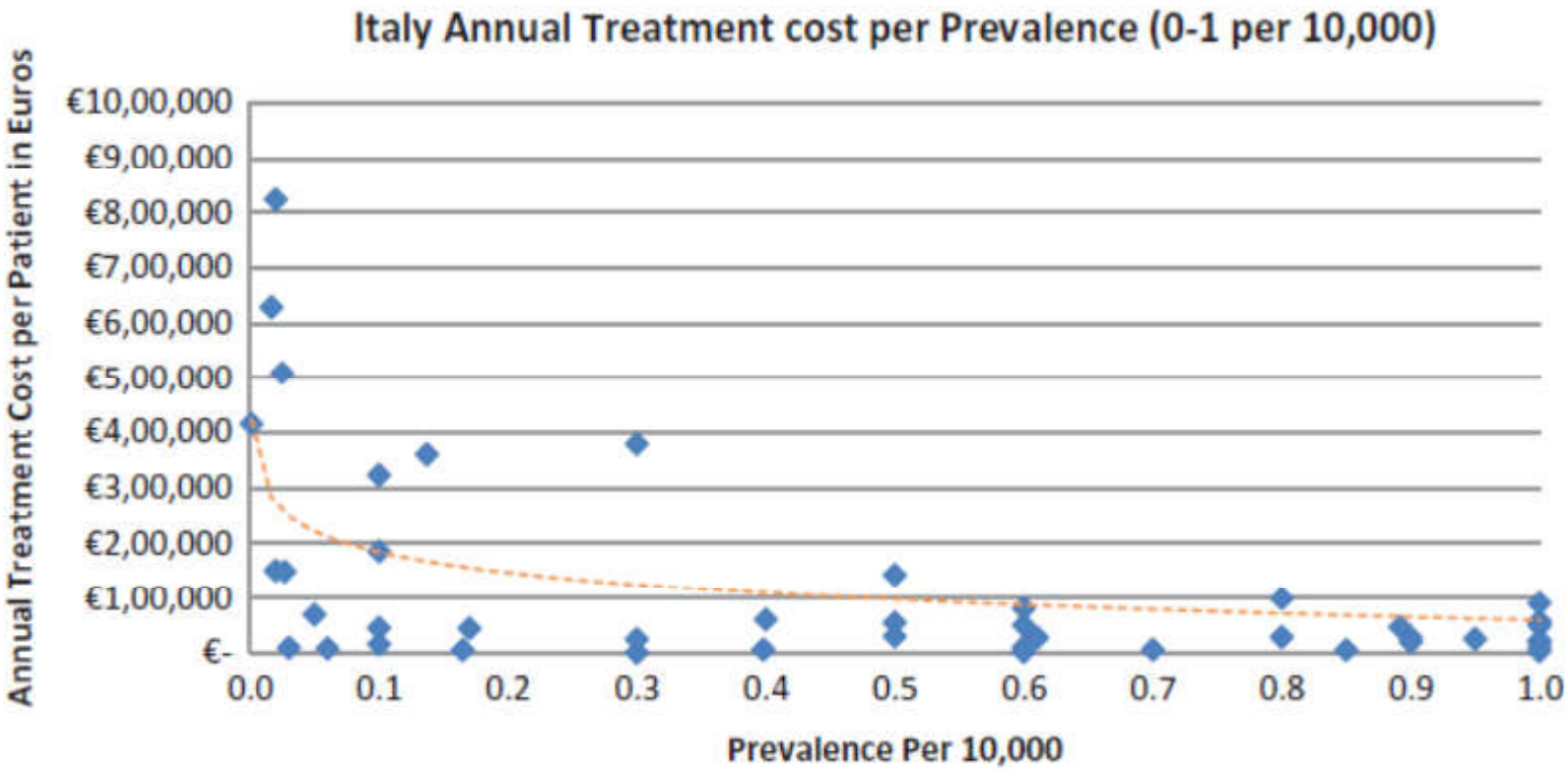

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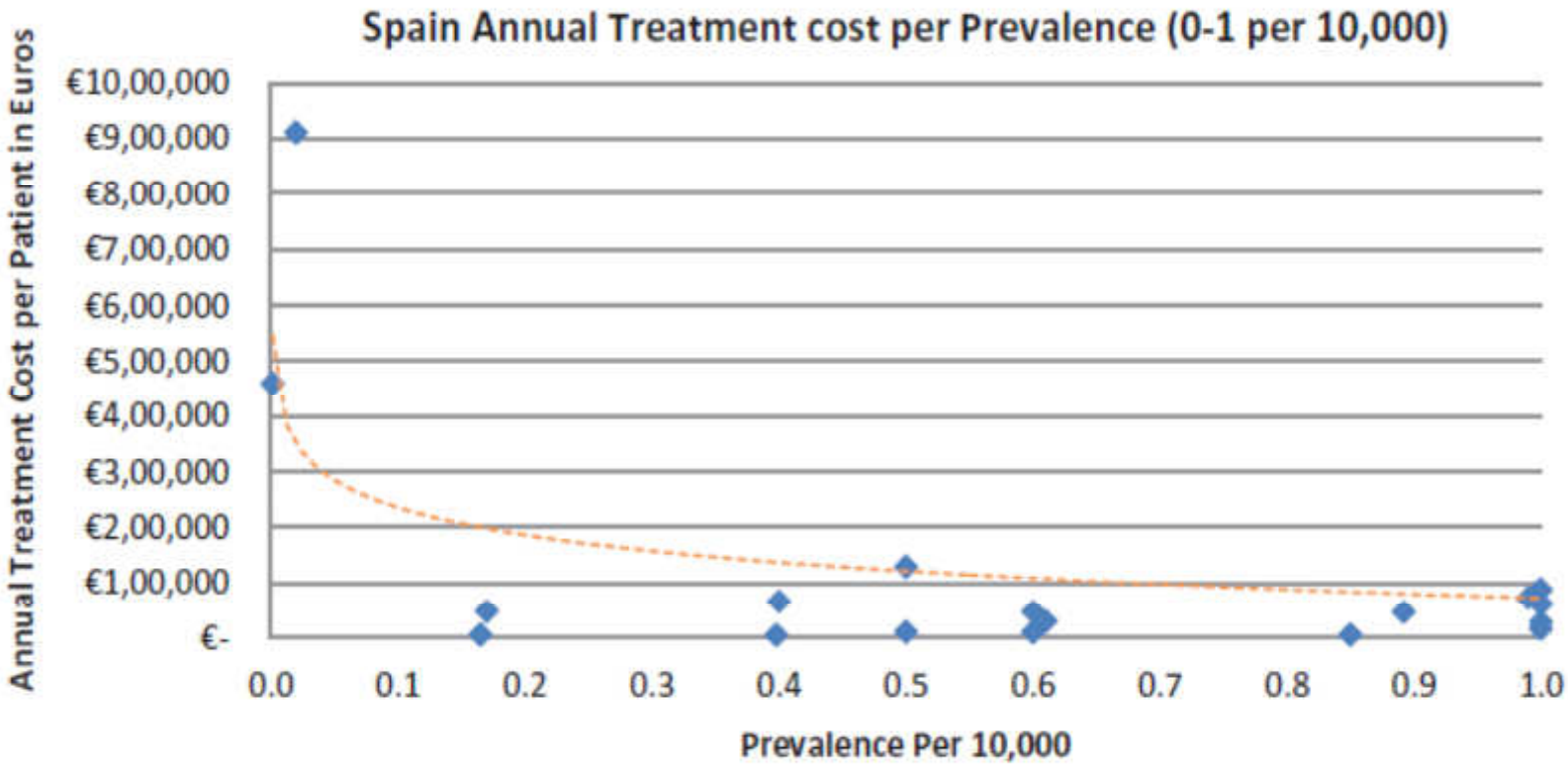

Goran Medic et al., *Journal of Market Access & Health Policy* (2017)

Specific Challenges for (Ultra-)Rare Disorders

- **Establishing Evidence of Clinical Effectiveness**
  - usually very small number only of physicians with specialized expertise, who tend to be based in few specialized centers;
  - often limited clinical understanding of disorder;
  - often limited understanding of natural history of disorder;
  - often limited availability of validated instruments to diagnose and measure disease severity / progression;
  - often resulting in difficulties to generate a large volume of clinical evidence based on RCTs, which may lead to
  - higher levels of uncertainty surrounding effect size estimators;
  - small numbers of patients are often geographically dispersed, resulting in the need to establish multiple clinical trial sites for only a small number of patients;
  - …

[1]M. Schlander, S. Garattini et al.: Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). A Consensus Statement. *Journal of Market Access & Health Policy* 2016; 4: 33039.

Specific Challenges for (Ultra-)Rare Disorders

- **Establishing "Value for Money" (Efficiency)**
  - international heterogeneity in institutional arrangements and established methodologies to determine "value for money";
  - the still prevailing "logic of cost-effectiveness", relying on cost per QALY benchmarks, in applied health economics;
  - the broadly held assumption that the social desirability of an intervention would be inversely related to its associated incremental cost per QALY gained;
  - the adoption of "efficiency-first" instead of "fairness-first" evaluation approaches in a number of jurisdictions;
  - the high fixed (i.e., largely volume-independent) cost of R&D and the need to recoup this investment from a small number of patients during limited periods of market exclusivity;
  - …

[1]M. Schlander, S. Garattini et al.: Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). A Consensus Statement. *Journal of Market Access & Health Policy* 2016; 4: 33039.

Ways Forward

Evidence of Clinical Effectiveness:

- Approval based on surrogate endpoints should be accepted as an interim solution only.
- Conditional reimbursement to ensure rapid patient access may be linked to "coverage with evidence development" agreements.
- Even at prevalence rates as low as 1/50,000 (the URD qualifier), there would be about 10,000 patients in Europe.
- Thus it should be possible to set up multinational RCTs designed to show relevant clinical endpoint benefit.
- If necessary, such trials might be supported by the not-for-profit *European Clinical Research Infrastructure Network* (ECRIN).

M. Schlander, S. Garattini et al.: Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). A Consensus Statement. *Journal of Market Access & Health Policy* 2016; 4: 33039.

Ways Forward

Perspectives on Cost:

- From a decision-makers' perspective, overall budgetary impact should be more relevant than incremental cost effectiveness ratios.
- If a social value perspective (instead of an almost exclusive focus on individual utility) was adopted, the social opportunity cost (or [social] value foregone) of adopting a program would be reflected by its net budgetary impact. This would move the focus from cost per patient to cost on the program level.
- Likewise, a pragmatic approach would reflect the commercial realities and the basic cost structure of the research-based biopharmaceutical industry, which incidentally is showing signs of a strategic shift from price maximization to life cycle revenue management (in order to "extract" maximum value).

M. Schlander, S. Garattini et al.: Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). A Consensus Statement. *Journal of Market Access & Health Policy* 2016; 4: 33039.

Ways Forward

Valuation Principles:

- **Alternative** economic (e)valuation principles – that promise to reflect normative concerns and capture social preferences better than the conventional logic of cost effectiveness – should be rigorously assessed for their potential to complement of replace the currently predominant standard.
- **Candidates** include (but are not limited to)
  - **social cost value analysis**, using the person-trade off or the [relative] social willingness-to-pay method;
  - **a multicriteria decision analysis framework**, which, in principle, might incorporate cost utility analysis with benchmarks adjusted to multiple contextual variables;
  - the use of **alternative methods to value benefit**.

M. Schlander, S. Garattini et al.: Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). A Consensus Statement. *Journal of Market Access & Health Policy* 2016; 4: 33039.

Thank You for Your Attention!

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