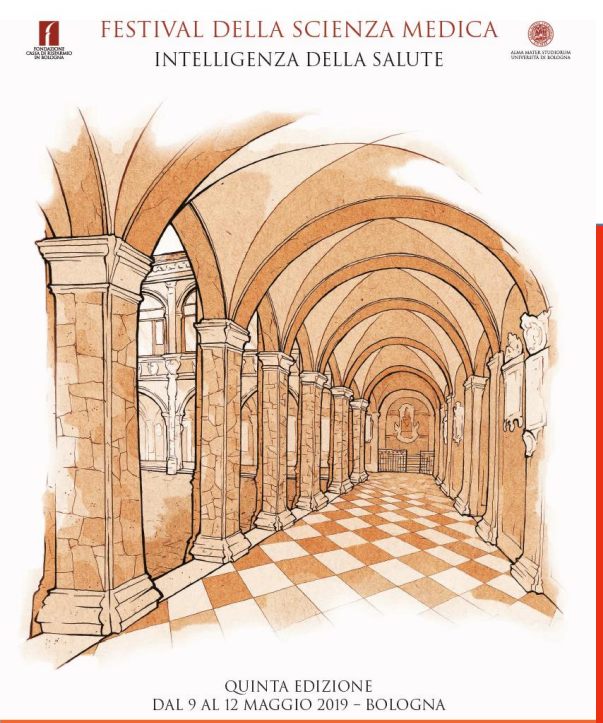

Correggere e riscrivere il genoma umano: applicazioni e regole

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UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

UNIVERSITY OF MIAMI

Medicina di Precisione
Ricerca, Sviluppo e Sostenibilità

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Disclaimer and Disclosure

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I do not bear any direct or indirect financial interest in products quoted in this talk.

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This presentation is updated to May 7th, 2019.

Current framework won't fit what is coming

Future treatments will be incompatible with the existing value frameworks:

- 932 cell and gene therapies in development; approx 39 expected approval by 2022
- Theoretical models for management entry agreements exist, but they are difficult to execute especially worldwide

Reimbursement challenging even for innovative and efficient treatments due to:

- Lack of suitable reimbursement models
- Payment terms unsustainable in the current environment

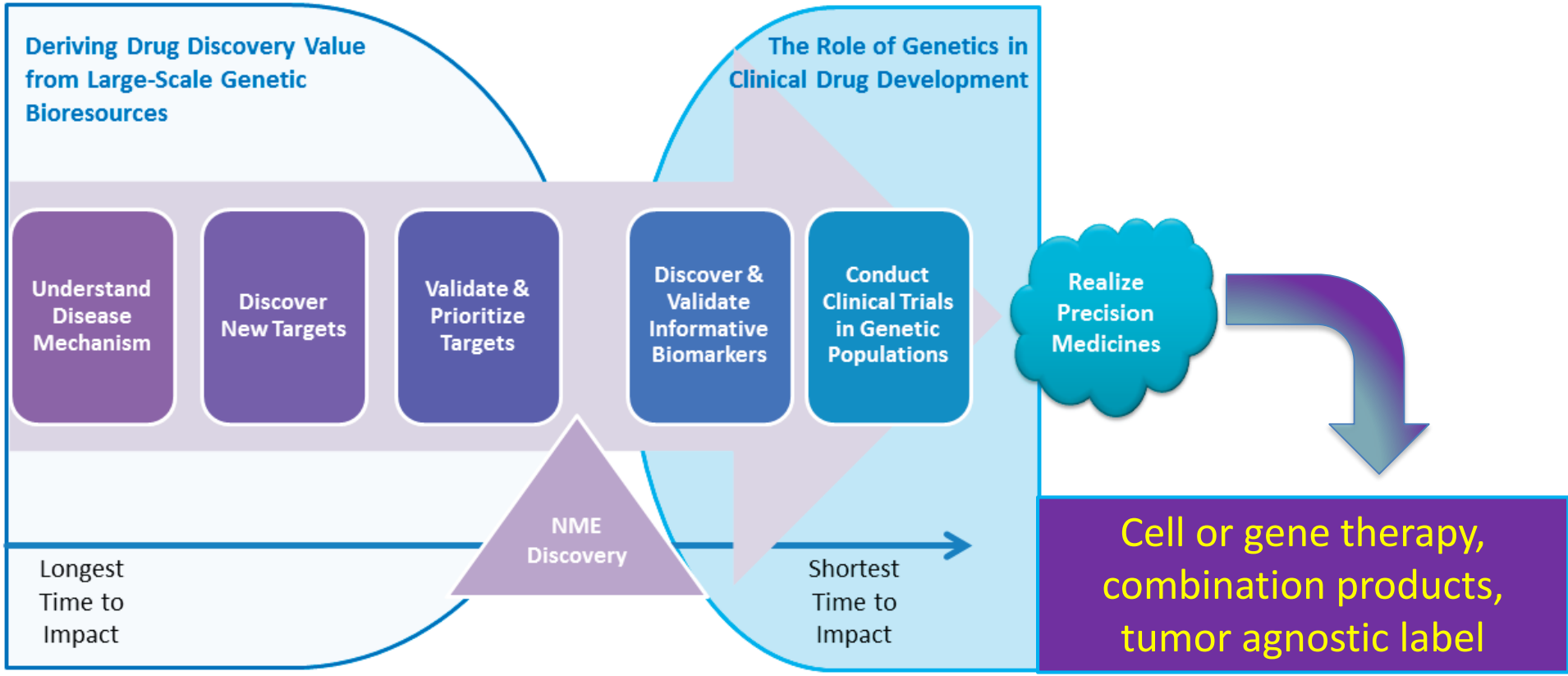
Pharma R&D Simple (sic!) Rules Lack Value Predictability

- Safety
- Efficacy
- Quality
- Population
- Endpoints
- Comparator
- Duration of Response
- **Outcome Values and Costs**

- Make sure you understand the pathophysiology
- Rely on informative animal models
- Translate effects from health to disease
- Paradoxically diagnostic entities in precision medicines such as gene therapies could be more heterogeneous and have different underlying biology than previously thought
- Real life data and drug usage could be different (sometimes radically different) from those collected in registration clinical trials
- **Approval by benefit risk evaluation carries an intrinsic quote of uncertainty**

Corbellini G. and Pani L., Prescrivere Valore. Storia e Scienza dei Farmaci che fanno vivere più a lungo e meglio. EDRA, Milano 2017

Extract and enable precision medicine from human genetics



Laura Nisenbaum, National Academies of Sciences, Engineering, and Medicine workshop presentation, 3/8/17

Approved by FDA in uncertainty (and reimbursed by who?)

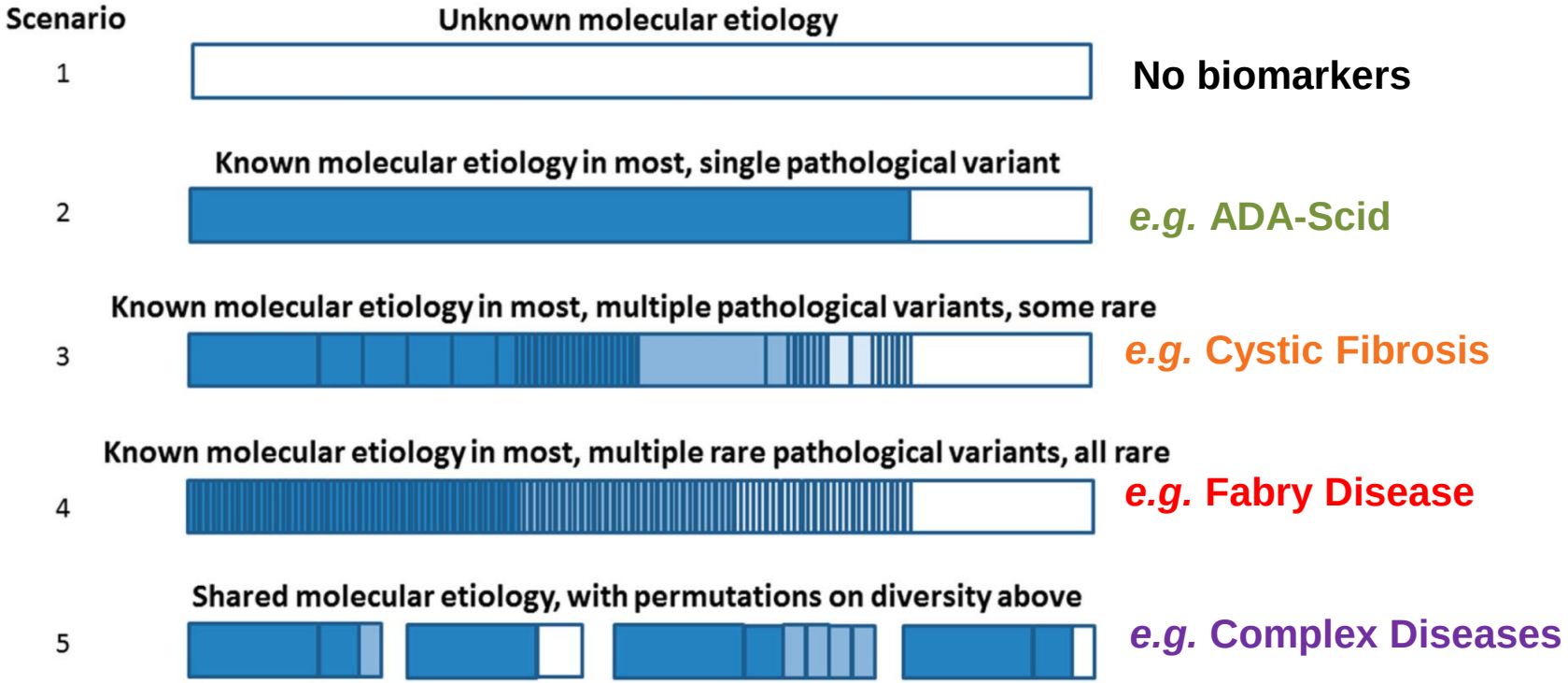
Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting

Remarks by Scott Gottlieb, M.D.
Commissioner of Food and Drugs
Alliance for Regenerative Medicine's Annual Board Meeting
May 22, 2018
Washington, DC

"There is also the question of durability of response, which often can't be fully answered in any reasonably sized pre-market trial. For some of these products, there's going to be some **uncertainty, even at the time of approval. "**

https://www.fda.gov/NewsEvents/Speeches/ucm608445.htm

The added molecular complex diversity of genetic diseases



https://precision.fda.gov/ (accessed April 8, 2019).

Michael Pacanowski, NASEM workshop presentation, 3/8/17

Keeping in mind Regulators and Payers objectives

- Expedite the research and development of new medicines
- Increase the rate of success of new products
- Develop more efficient and safer targeted therapies
- Envision strategies towards diseases (progression) modifiers
- Provide new tools for screening, monitoring progression or relapse of disease, patients treatment selection and monitoring response to drugs

Various barriers needs addressing

- Decision makers not aligned on **evidentiary standards** for precision medicine
- Consider **insuring the risk** of developing a product through third party insurers
- Current economic evaluation methods not suitable for curative therapies (**limitations of the QALY model**)
- **Timing and facilitation of information sharing** and engagement with stakeholders necessary to enable system-level changes
- **Risk reduction** through preliminarily agreed price adjustment as evidence becomes available – becomes a commitment for industry and payers

The first world gene-therapy was developed and approved / reimbursed in Italy

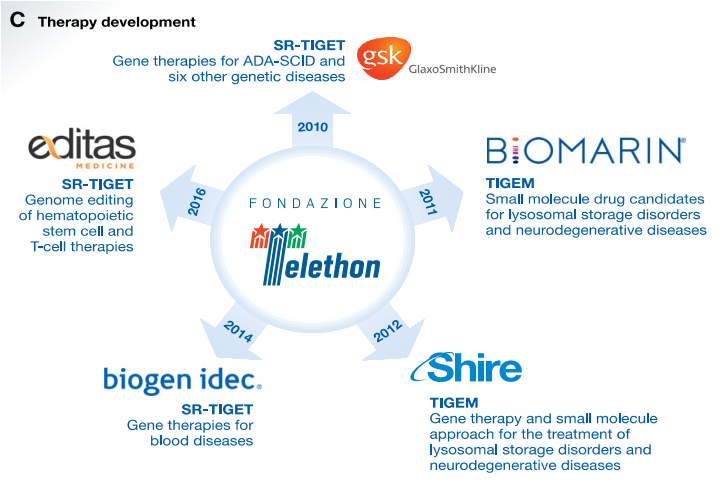
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells.

Used to treat Severe Combined Immunodeficiency due to adenosine deaminase deficiency (ADA-SCID).

ADA-SCID is a rare inherited condition in which there is a change (mutation) in the gene needed to make an enzyme called adenosine deaminase (ADA). As a result, patients lack the ADA enzyme. Because ADA is essential for maintaining healthy lymphocytes, the immune system of patients with ADA-SCID does not work properly and without effective treatment they rarely survive more than 2 years.

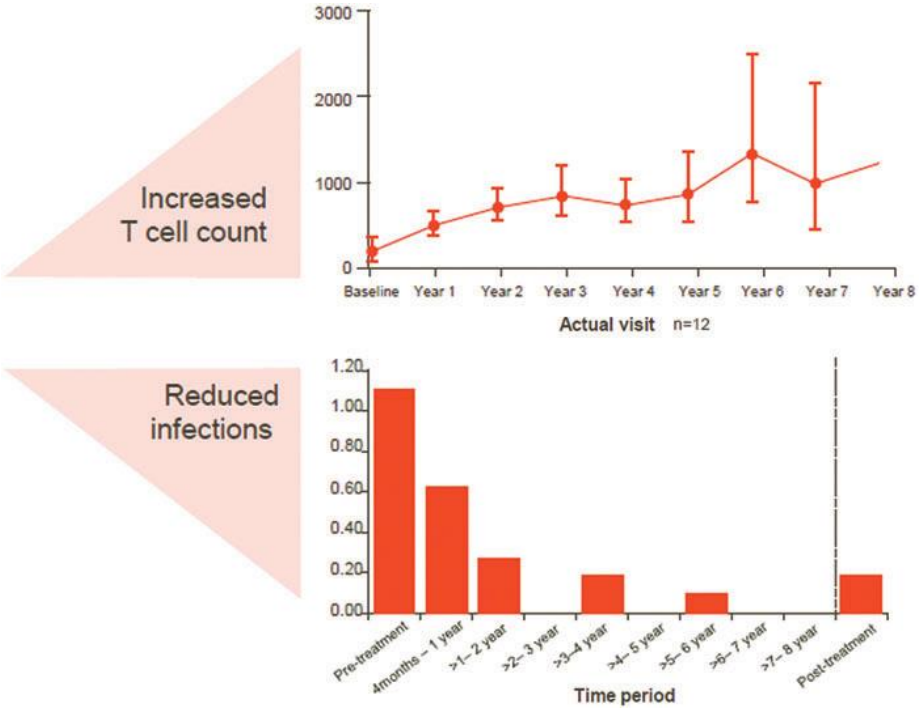
Orphan Designation EU/3/05/313: 1st 26/08/2005 confirmed 08/04/2016

GlaxoSmithKline's (GSK) and partner San Raffaele Telethon Institute for Gene Therapy's recent EU approval for Strimvelis represents the second EU-approved gene therapy and the first c-retrovirus and first ex vivo gene therapy.



Monaco L & Faccio L. Patient-driven search for rare disease therapies: the Fondazione Telethon success story and the strategy leading to Strimvelis *EMBO Molecular Medicine* Vol 9, No 3, 2017

Italian Medicines Agency (AIFA) Strimvelis Negotiation Strategy:
Innovativeness' recognition based on pure scientific results



Safety: summary of subject disposition and duration of follow-up
(All studies and CUP safety population)

	Gene therapy (N=18)
Completion Status, n (%)	
Ongoing	16 (89)
Died	0
Prematurely withdrawn	2 (11)
Primary reason for withdrawal, n (%)	
Investigator discretion	1 (6)[a]
Lack of efficacy	1 (6)[a]
Duration of follow-up	
n	18
Median (min, max), years	6.94 (2.3-13.4)

a. The reason for withdrawal of Subject 8 was recorded as 'investigator discretion' in the CRF and source tables. Subjects 8 and 17 had unsuccessful responses to gene therapy

AIFA-GSK Contractual Agreement

1. GSK filed the request for reimbursement on April 11th, 2016
2. AIFA and GSK agreed to reimburse the treatment at a price of €594,000 significantly less than the cost of long-term enzyme replacement therapy.
3. The agreement was backed up by a confidential limited risk-share scheme as it is customary with specialty medicines in Italy with payback in case of treatment failure (so called Payment by Result scheme)
4. The negotiation was closed on May 30th, 2016 (less than 50 days later).

National Registry: mandatory data collection 1028/2016 AIFA Deliberation

http://www.aifa.gov.it/content/pubblicazione-schede-di-monitoraggio-registro-strimvelis-02082016

AIFA Strimvelis Payment by Result

Treatment failure was defined by:

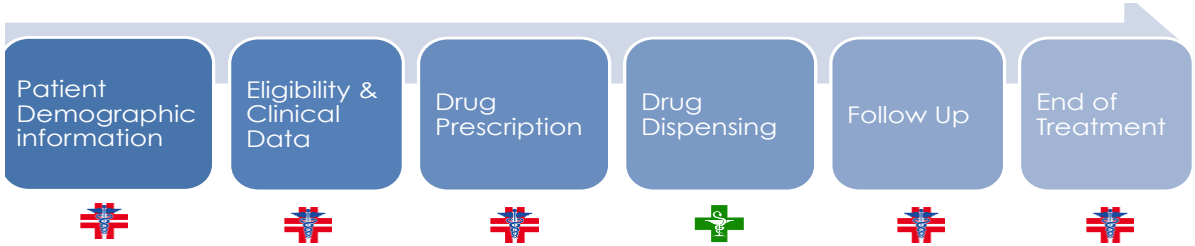
1.Use of PEG-ADA for a continuous period of three months

OR:

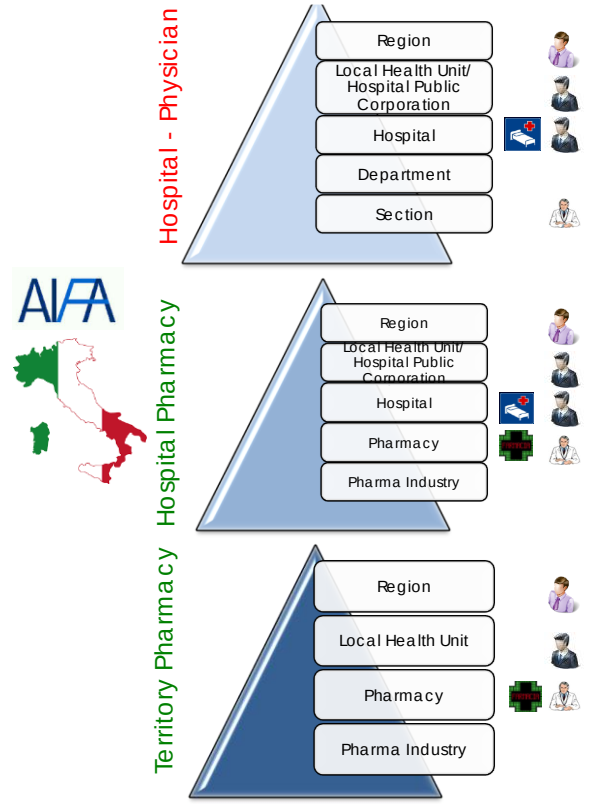
2. Hematopoietic stem cell transplantation

OR:

3. Death



(*) LD 2015
(**) ITS, 135/2012 Italian Law



It took 17 additional months for NICE to concur with the price given by AIFA…

NICE Approves Novel GSK Gene Therapy

Share this article

23 OCT 17

Source: Immune Deficiency Foundation

ANIMAL HEALTH DRUG DELIVERY

FiercePharma

PHARMA MANUFACTURING MARKETING PHARM

Pharma

GlaxoSmithKline picks up NICE recommendation for Strimvelis, a €594,000 gene therapy

by Eric Sagonowsky | Oct 23, 2017 11:57am

HEALTH NEWS OCTOBER 22, 2017 / 7:24 PM / 9 DAYS AGO

Britain backs GSK's gene therapy for 'bubble boy' syndrome

Reuters Staff 2 MIN READ

(Reuters) - GlaxoSmithKline's gene therapy for the so-called "bubble boy" disease was approved by Britain's healthcare cost watchdog NICE, despite a price tag of almost 600,000 euros ($700,000).

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23 October 2017

NICE approves gene therapy for rare 'bubble baby syndrome'

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Strimvelis, a treatment for an ultra-rare inherited immune deficiency condition that has been dubbed 'bubble baby syndrome' has been approved by NICE in draft guidance.

Children with ADA-SCID, severe combined immunodeficiency due to adenosine deaminase deficiency, are extremely vulnerable to infection and usually live in isolation to minimise the risk, hence the nickname 'baby in a bubble'.

Up until now the only treatment has been a stem cell transplant but these are risky and it is not always possible to find a good match.

Now NICE has approved a new treatment for those children who cannot find a good match. It could mean children with ADA-SCID have the chance of going to school and socialising without the constant fear of catching a simple infection that could prove life threatening.

Around 3 babies a year in England are born with ADA-SCID and if left untreated infants die before school age. Their quality of life is affected by developmental delay, chronic diarrhoea, failure to thrive and recurrent infections.

The draft guidance, which is the first time NICE has applied its new, higher cost effectiveness limits for treatments for very rare conditions, recommends Strimvelis when no suitable matched related stem cell donor is available.

Strimvelis is only the second gene therapy for an inherited disease to be licensed anywhere in the world. The treatment involves removing bone marrow cells and modifying them outside the body to produce working ADA enzyme. The modified cells are then returned to the patient via an infusion drip into a vein.

Costing €594,000, the treatment is usually given once only and the effects are thought to be life-long. Strimvelis has to be given at a hospital in Milan, so people will travel to Italy to have the treatment..

Professor Carole Longson, director of the centre for health technology assessment at NICE, said: "Strimvelis represents an important development in the treatment of ADA-SCID, offering the potential to cure the immune aspects of the condition and avoid some of the disadvantages of current treatments. This means that children born with ADA-SCID will now have a better chance of being able to lead as near normal a life as possible, going to school, mixing with friends, free from the constant threat of getting a potentially life-threatening infection."

The draft guidance is available for public consultation until 13 November.

> Strimvelis represents an important development in the treatment of ADA-SCID, offering the potential to cure the immune aspects of the condition and avoid some of the disadvantages of current treatment
>
> Professor Carole Longson, director of the centre for health technology assessment at NICE

Related Resources

Draft guidance found here.

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From Regulatory Science Leadership to System Value

Scientific Advices, CHMP Rapporteurships, Joint HTAs, International Recognition

YEAR	Number of Advanced Therapies Approved in Europe and Developed / Owned in Italy	Total number of Advanced Therapies Approved in Europe	% of Italian Advanced Therapies in Europe
2016	3	3	100%
2017	3	6	50%
2018	3	9	33%
2019	3	?	<33%

Regulators / Payers issues to consider in such negotiations

1. The strength of the evidence provided to support biomarker which directed precision drug development should also direct reimbursement criteria;

2. The identification and management of micro-heterogeneity which leads to combine therapies (*e.g.* ipilinumab + nivolumab in metastatic melanoma) should be backed up by a consistent adaptive reimbursement scheme (*e.g.* see IATA tariff products)

3. Evidence concerning the effectiveness and clinical need for a linked biomarker(s) should be provided

To address these issues, trials should be designed such that they gather evidence for both the drug and the biomarker(s) test and that product sponsors plan ahead for the development of the biomarker(s) value not only for the regulators but also for the payers.

See https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf (accessed June 5, 2017).

Suggestions for Any R&D Teams

- Seek dialogue with regulators and payers **as early as possible** in the development of new medicines
- Whenever possible, seek ways to perform at least one RCT **comparing** the new therapy to beat any existing treatment. Consider the use of adaptive trial designs, weighted randomization, and cross-over to meet ethical requirements.
- Work with clinicians, patient groups, regulators and payers to establish robust patient (and/or drug) **Registries** to facilitate collection of **real world evidence** before and after regulatory approval
- Where appropriate, **collaborate** with payers and HTA groups on value assessment reports.

Suggestions for Any Market Access Teams and Payers

- Develop internal **deep knowledge** about your class of products, including understanding of the basic scientific techniques and of the usual approach taken by the FDA and EMA in assessing the safety and effectiveness of these agents. Think of a continuum risk/benefit/price.
- Engage in **early dialogue** with R&D of promising new medicines. The topics of mutual interest will include those listed above.
- Work with clinicians, patient groups, regulators and manufacturers to establish robust Patient **Registries** to facilitate collection of **real world evidence** following regulatory approval. Individual insurer in-house registries could be pooled with those of other insurers and/or with manufacturers.
- Use **digital medicine** to monitor effect and cost savings **in RWE** by three key area technologies:
    - Sensors for “activity” monitor
    - Pattern recognition
    - Human to machine interface

Examples of Real World Evidence Data Results/Studies

- In the real world of Italian diabetes centers incretins have been prescribed, in many cases, off-label the regulatory indications. Nevertheless, RWE showed that when appropriately utilized, incretins achieved results in line with trials.

- Insulin glargine and RWE (Sanofi planning World Evidence studies to show less risk of hypoglycemia in real life)

- Pablociclib in male breast cancer (RWE databases: here Department of Clinical Pharmacy, St. Antonius Hospital, NL or additional RWE from IQVIA insurance, Flatiron cancer; Pfizer safety)

Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 1346–1353

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

ELSEVIER

Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry

S. Montilla [a,*], G. Marchesini [b], A. Sammarco [a], M.P. Trotta [a], P.D. Siviero [a], C. Tomino [a], D. Melchiorri [c], L. Pani [a] for the AIFA Anti-diabetics Monitoring Group[1]

Original Article

Real-World Data Collection Regarding Titration Algorithms for Insulin Glargine in Patients With Type 2 Diabetes Mellitus

Journal of Diabetes Science and Technology
2016, Vol. 10(5) 1122–1129
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Andreas Pfützner, MD, PhD[1], Bernd Stratmann, PhD[2], Klaus Funke, MD[3], Harald Pohlmeier, MD[4], Ludger Rose, MD[4], Jochen Sieber, MD[5], Frank Flacke, PhD[5], and Diethelm Tschoepe, MD[2]

Real-World Effectiveness of Palbociclib Versus Clinical Trial Results in Patients With Advanced/ Metastatic Breast Cancer That Progressed on Previous Endocrine Therapy

Breast Cancer: Basic and Clinical Research
Volume 13: 1–6
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DOI: 10.1177/1178223418823238
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Tam Binh V Bui[1], Desirée MT Burgers[1], Mariette J Agterof[2] and Ewoudt MW van de Garde[1,3]

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Most importantly collect and certify these type of data

If a new pharma product breaks out of the marginal value mould of traditional pharmaceuticals with curative properties in indications with limited treatment options[1] we **need to have long term data**

Assuming that the effects are at least long term, if not curative, has two key implications:

I. Show that long lasting curative effects are likely to **reduce avoidable costs** of patient support and managing chronic (co)morbidities[2].

II. Show even more that early cures or **substantial benefits at younger ages** could help produce significant gains in work productivity for patients compared to treatments that bring marginal gains over many years.

Mod. from [1]Bubela et al., 2016; [2]Abou-El-Enein et al., 2016

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