STARS
STRENGTHENING REGULATORY SCIENCE

University Medical Center Groningen

university of groningen

CBG MEB
COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

How Regulators Work & Think; the basics

Peter Mol

Principal clinical assessor,
CBG-MEB, Pharmacotherapy group II
Vice-chair EMA Scientific Advice Working Party
Professor, Department of Clinical Pharmacology, UMCG

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Today's program

09:00-09:40	Introduction to Day 3. How regulators work and think: the basics (Peter Mol)
09:40-09:45	Q&A
09:45-10:05	Novel regulatory tools & drug development support mechanisms (Peter Mol)
10:05-10:10	Q&A
10:10-10:25	Coffee break
10:25-10:50	Scientific advice (European & national) (Marjon Pasmooij)
10:50-10:55	Q&A
10:55-11:20	Case example – ATMP scientific advice (Viktoriia Starokozhko)
11:20-11:25	Q&A
11:25-11:40	Coffee break
11:40-12:10	Novel methodologies and Real World Evidence supporting drug regulatory decision-making
12:10-12:30	Final Q&A round (Moderator: Marjon Pasmooij)

Drug Approval – What you know!?

Comirnaty*

Drug Approval – What you know!?

Comirnaty*

Covid-19 vaccine Moderna*
Covid-19 vaccine AstraZeneca*

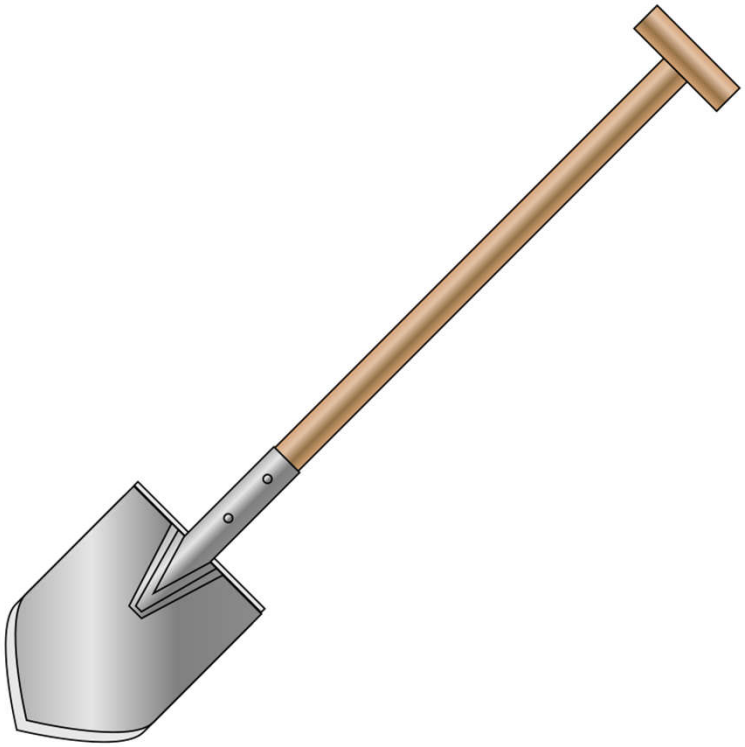
Dexamethasone (Article 5(3))
Remdesivir*

*Conditional Approval

How do drugs get approved?

How regulators work & think; the basic(tool)s

- when to approve
- the organisation
- the assessment
- SmPC
- pharmacovigilance



Comirnaty Key table

Table 2: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine** **N[a] = 18,198** **Cases** n1[b] Surveillance time[c] (n2[d])	**Placebo** **N[a] = 18,325** **Cases** n1[b] Surveillance time[c] (n2[d])	**Vaccine efficacy** % (95% CI)[f]
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL. 377 NO. 18

CBG MEB

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

ABSTRACT

BACKGROUND

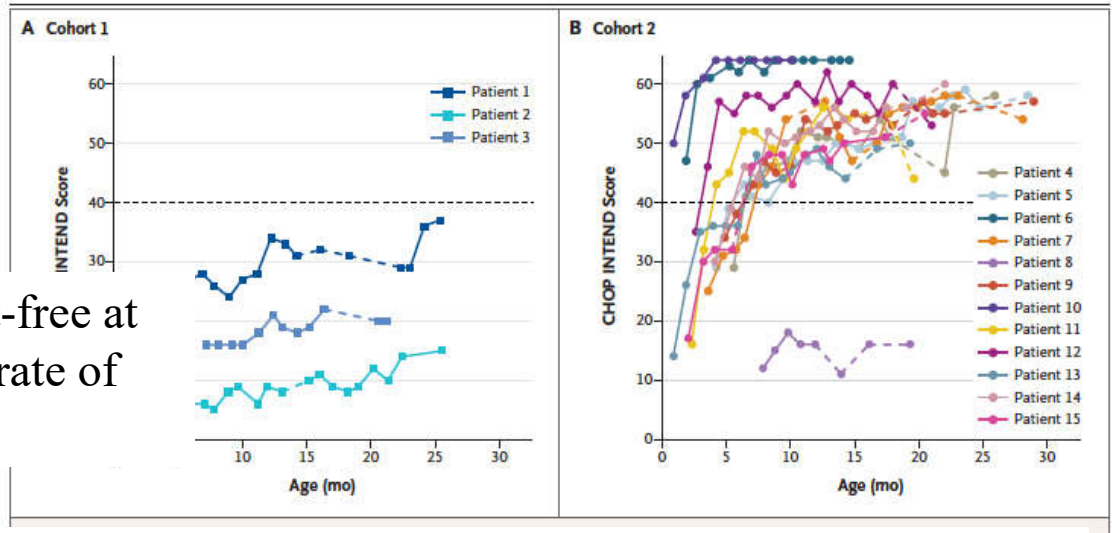
Spinal muscular atrophy type 1 (SMA1) is a progressive, monogenic motor neuron disease with an onset during infancy that results in failure to achieve motor milestones and in death or the need for mechanical ventilation by 2 years of age. We studied functional replacement of the mutated gene encoding survival motor neuron 1 (SMN1) in this disease.

METHODS

Fifteen patients with SMA1 received a single dose of intravenous adeno-associated virus serotype 9 carrying SMN complementary DNA encoding the missing SMN protein. Three of the patients received a low dose (6.7×10^{13} vg per kilogram of body weight), and 12 received a high dose (2.0×10^{14} vg per kilogram). The primary outcome was safety. The secondary outcome was the time until death or the need for permanent ventilatory assistance. In exploratory analyses, we compared scores on the CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale of motor function (ranging from 0 to 64, with higher scores indicating better function) in the two cohorts and motor milestones in the high-dose cohort with scores in studies of the natural history of the disease (historical cohorts).

RESULTS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mendell at the Research Institute at Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43205, or at jerry.mendell@nationwidechildrens.org.



"…all 15 patients were alive and event-free at 20 months of age, as compared with a rate of survival of 8% in a historical cohort."

CONCLUSIONS

In patients with SMA1, a single intravenous infusion of adeno-associated viral vector containing DNA coding for SMN resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts. Further studies are necessary to confirm the safety and efficacy of this gene therapy. (Funded by AveXis and others; ClinicalTrials.gov number, NCT02122952.)

CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale of motor function

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Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

Our Network | R... | Evaluation of Po... | About Us - HAR... | https://www.ah... | A Profile of Adv...

KLM

Jun 5, 2019, 10:32am

At Over $2 Million Zolgensma Is The World's Most Expensive Therapy, Yet Relatively Cost-Effective

Joshua Cohen Contributor
Healthcare
I write about drug value, market access, and healthcare systems

FILE - This Aug. 13, 2016, file photo shows a logo of Swiss pharmaceutical company Novartis in

Samenwerken | Kennis delen | Personeel | Telefoonlijst | Kalender

Home → Nieuws! → CBG in de media →

Duurste medicijn ter wereld goedgekeurd: $2,1 mln per dosis, Welke medicijnen gebruiken Nederlanders het meest? En waarvoor?, Minder bèta-amyloïd, maar niet beter functioneren

27 mei 2019

Contenteigenaar: COM - Communicatie

Overig nieuws

Duurste medicijn ter wereld goedgekeurd: $2,1 mln per dosis
Het Financiële Dagblad, AD, NU | *27 mei 2019*
Het Zwitserse farmaconcern Novartis mag Zolgensma, het duurste medicijn ter wereld, op de markt brengen. Vrijdag keurde de Food and Drug Administration (FDA), de Amerikaanse toezichthouder, het medicijn officieel goed voor kinderen onder de twee jaar. Zolgensma is een eenmalige gentherapie en zal ruim $2,1 mln kosten. Novartis wil het medicijn ook naar Europa brengen, maar heeft hier nog geen officiële goedkeuring voor gekregen.

Welke medicijnen gebruiken Nederlanders het meest? En waarvoor?
De Volkskrant | *25 mei 2019*
Nederlanders hebben veel vertrouwen in hun medicijnen, berichtte geneesmiddelenautoriteit CBG deze week. Wij vroegen ons af: welk type

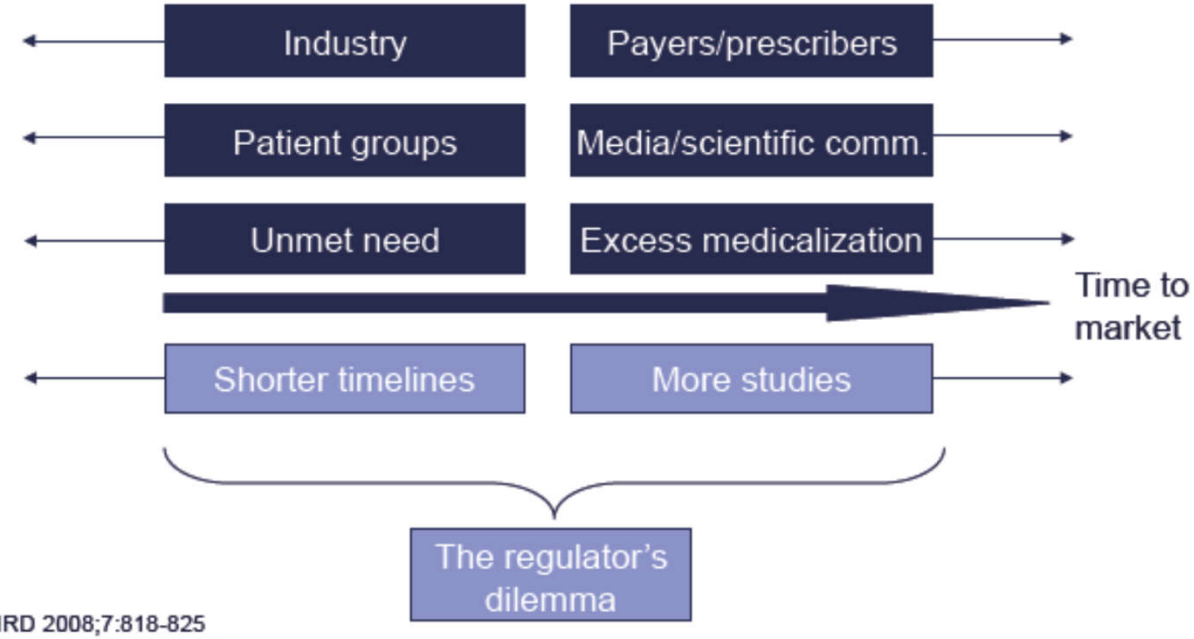
tion after Gene Therapy.

TEND (Children's Hospital of Philadelphia Infant euromuscular Disorders) scale of motor function

When to approve?

TI PHARMA

Regulation - finding the right balance for drug development

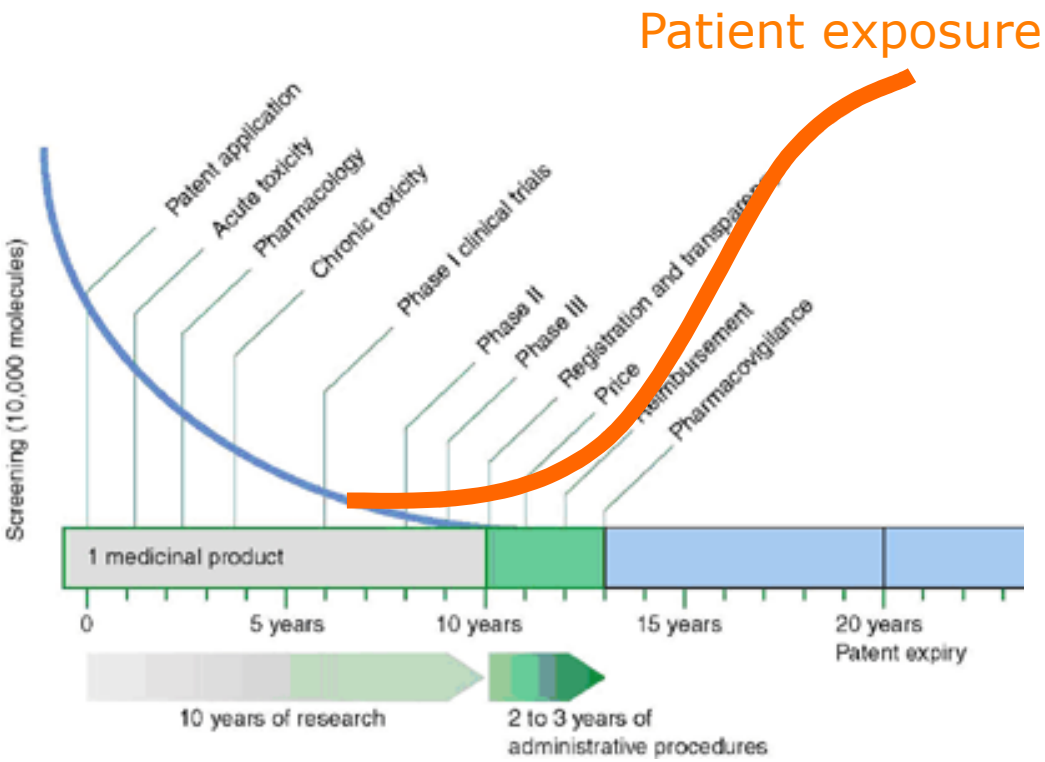


Source: NRD 2008;7:818-825

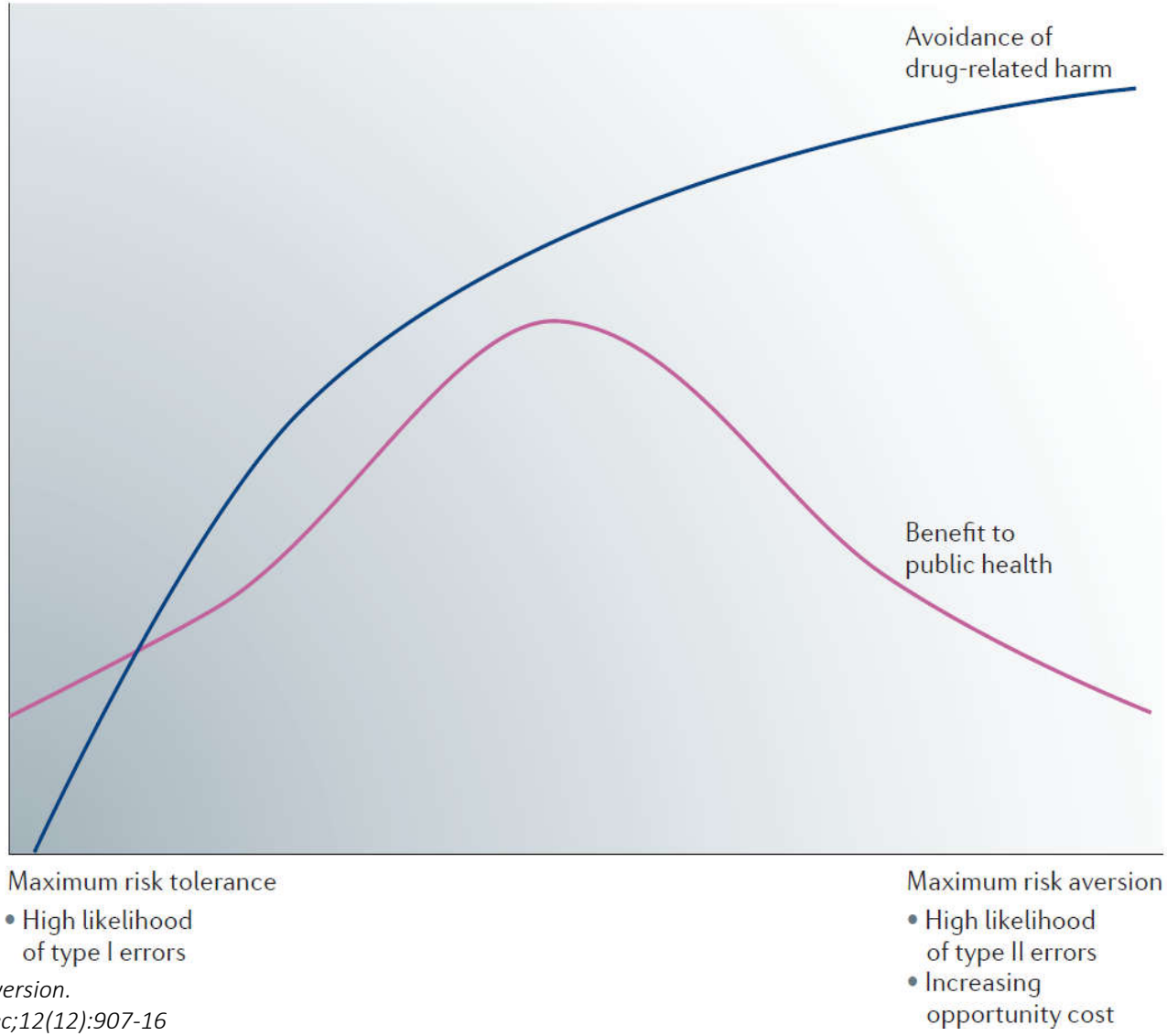
A drug's life cycle

At registration
[CBG, EMA, FDA]

- Limited patient exposure (strictly defined populations)
- Focus on efficacy
- Rare Adverse Events cannot be detected



The Regulatory Decision



Eichler et al. The risks of risk aversion.
Nature Rev Drug Disc 2013, Dec;12(12):907-16

Translated from *Rev Prescrire* February 2011; 31 (328): 134-141

New drugs and indications in 2010: inadequate assessment; patients at risk

- In 2010, we rated 97 new drugs or new indications in our French edition *la revue Prescrire*, only 4 of which provided a therapeutic advantage. However, 19 others (1 in 5) were approved despite having more harms than benefits.

BMJ

BMJ 2013;347:f4329 doi: 10.1136/bmj.f4329 (Published 16 July 2013)

LETTERS

INCRETINS AND PANCREATIC CANCER

Involving patients in drug licensing decisions

Nicky Britten *professor of applied health care research*, Sarah Denford *associate research fellow*, Ken Stein *director of peninsula technology assessment group (PenTAG)*

University of Exeter Medical School, Institute of Health Research, Exeter EX2 4SG, UK

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12566

Understanding drug preferences, different perspectives

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Keywords
benefit–risk assessment, drug preference, oral antidiabetes drug, survey

Received
18 August 2014
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Accepted Article Published Online
3 December 2014

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Oral antidiabetic drugs are approved without demonstrated long-term benefits, but some have been associated with important harms.
- Drugs are being approved with limited involvement of important stakeholders (patients and doctors).
- It is unknown whether regulators value benefits and risks of oral antidiabetic drugs in a similar manner to other stakeholders.

WHAT THIS STUDY ADDS

- Regulators, patients and doctors have mostly similar values concerning major drug effects but may differ in the value they attach to minor or short-term drug effects.

"…it has been said that the FDA has just two speeds of [drug] approval – too fast and too slow."

Hamburg MA & Sharfstein JM. NEJM 360;24: 2493-5; 2009

Based on what evidence?

The law: Medicinal products can be approved, if

- ***Balance*** efficacy & harm is positive
- Claimed ***efficacy*** is demonstrated
- Product has claimed ***quality and consistency***
- *Evidence is generated according to law*

Artikel 45 Geneesmiddelenwet
(https://wetten.overheid.nl/BWBR0021505/2020-04-01#Hoofdstuk4)

- Continued ***monitoring*** of benefit / risk balance ***post approval***

The organisation

CBG-MEB in Europe

27 National Competent Authorities (incl CBG-MEB) Responsible for expertise

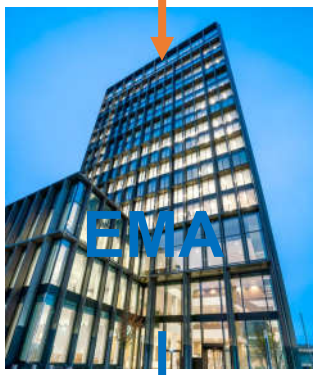
EU institutions: Commission – Parliament

Management Board

Committee on Herbal Medicinal Products
HMPC

Committee for Advanced Therapies
CAT

Pharmacovigilance Risk Assessment Comittee
PRAC



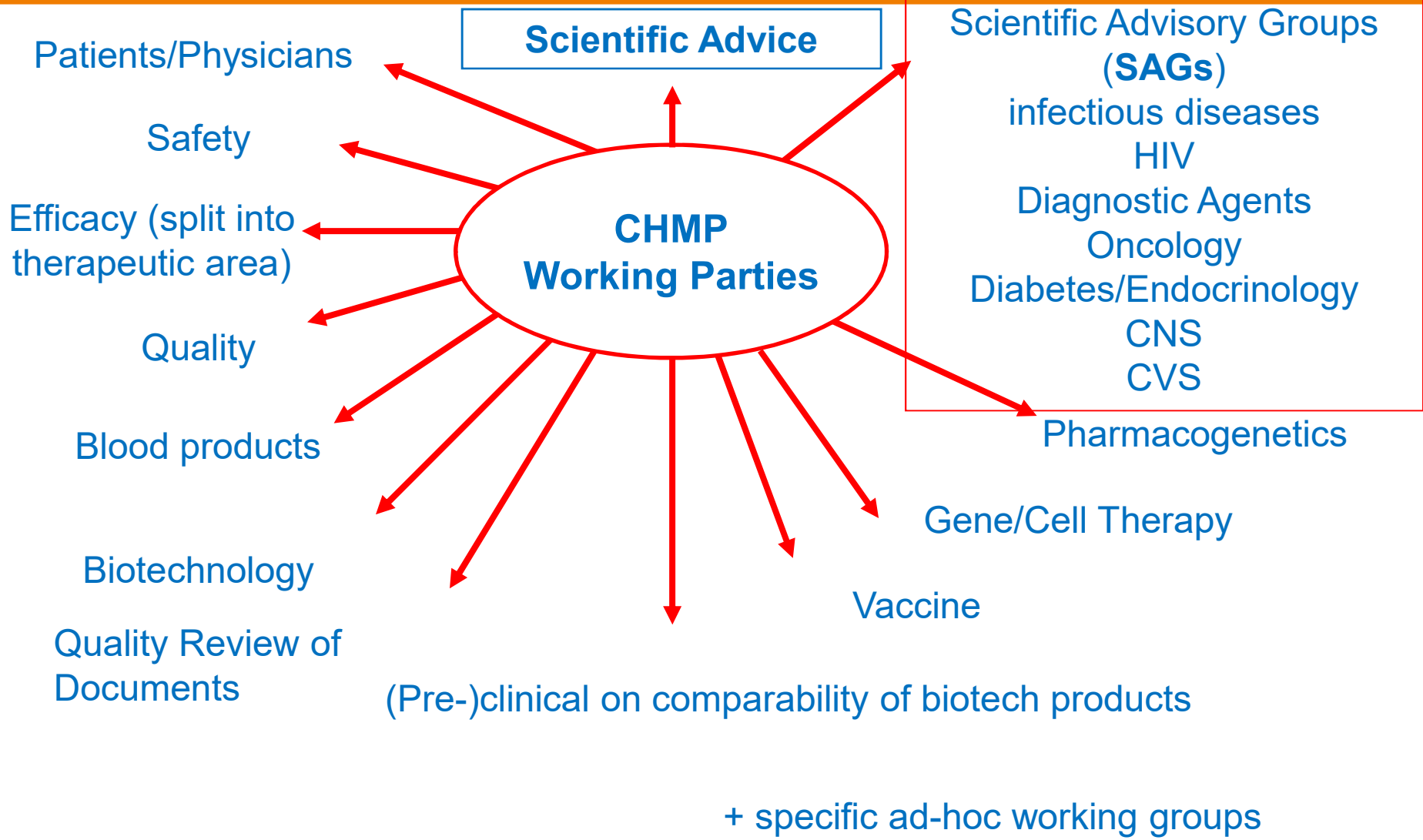
Committee for Human Medicinal Products
CHMP
and WPs

Paediatric Committee
PDCO

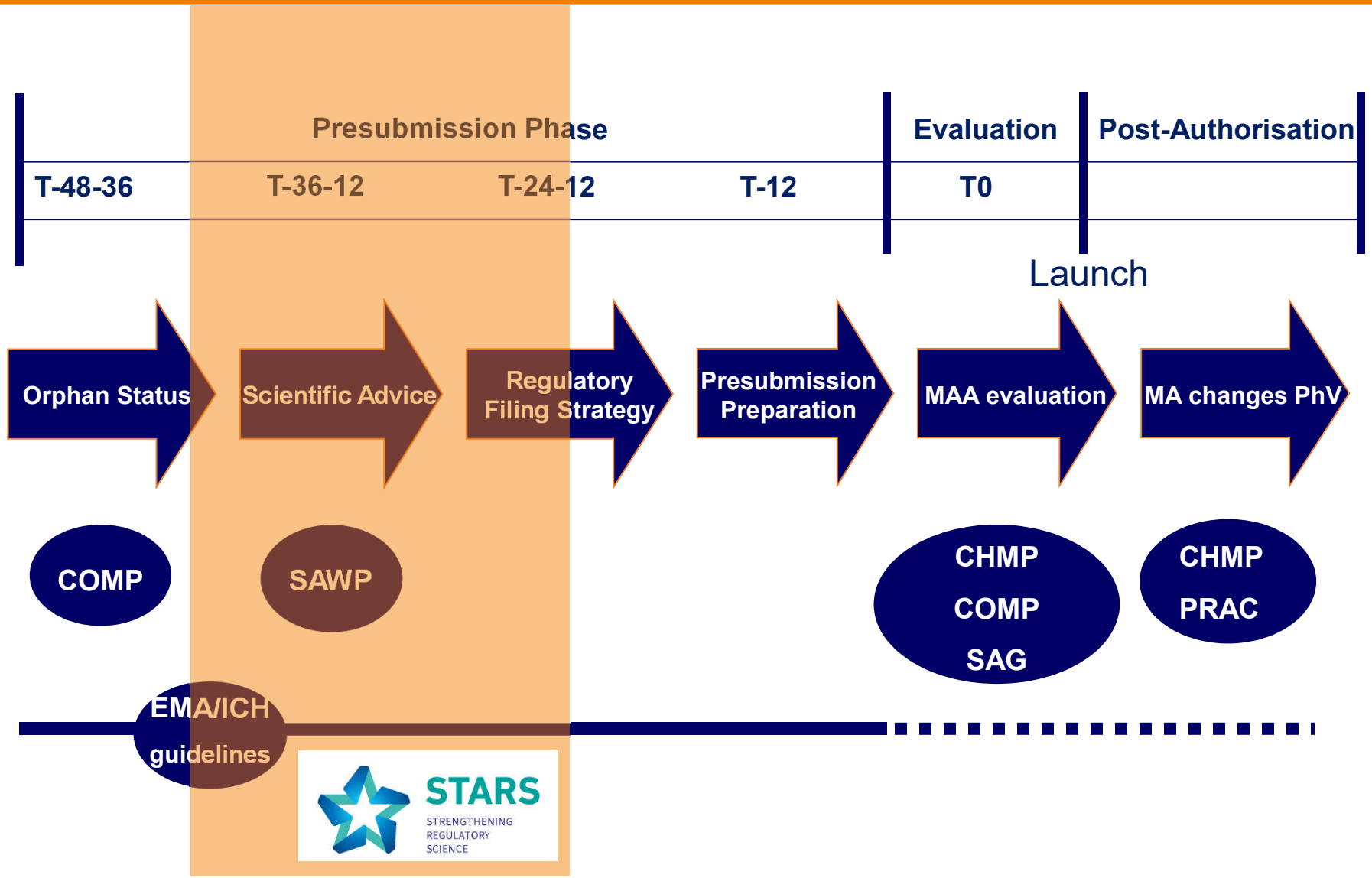
Committee for Veterinary Medicinal Products
CVMP

Committee for Orphan Medicinal Products
COMP

Inputs


Scientific Advice
CHMP
Working Parties
Patients/Physicians
Safety
Efficacy (split into therapeutic area)
Quality
Blood products
Biotechnology
Quality Review of Documents
(Pre-)clinical on comparability of biotech products
Vaccine
Gene/Cell Therapy
Pharmacogenetics
Scientific Advisory Groups (SAGs)
infectious diseases
HIV
Diagnostic Agents
Oncology
Diabetes/Endocrinology
CNS
CVS
+ specific ad-hoc working groups

Regulatory review in the drug's lifecycle



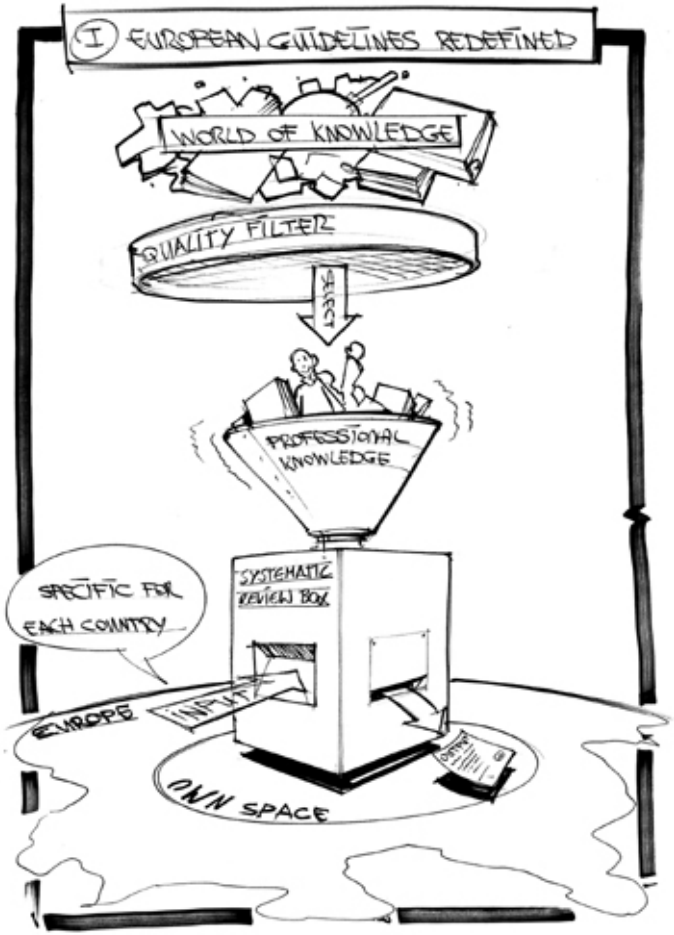
For each step in the procedure: guidelines!

http://www.ich.org/products/guidelines.html

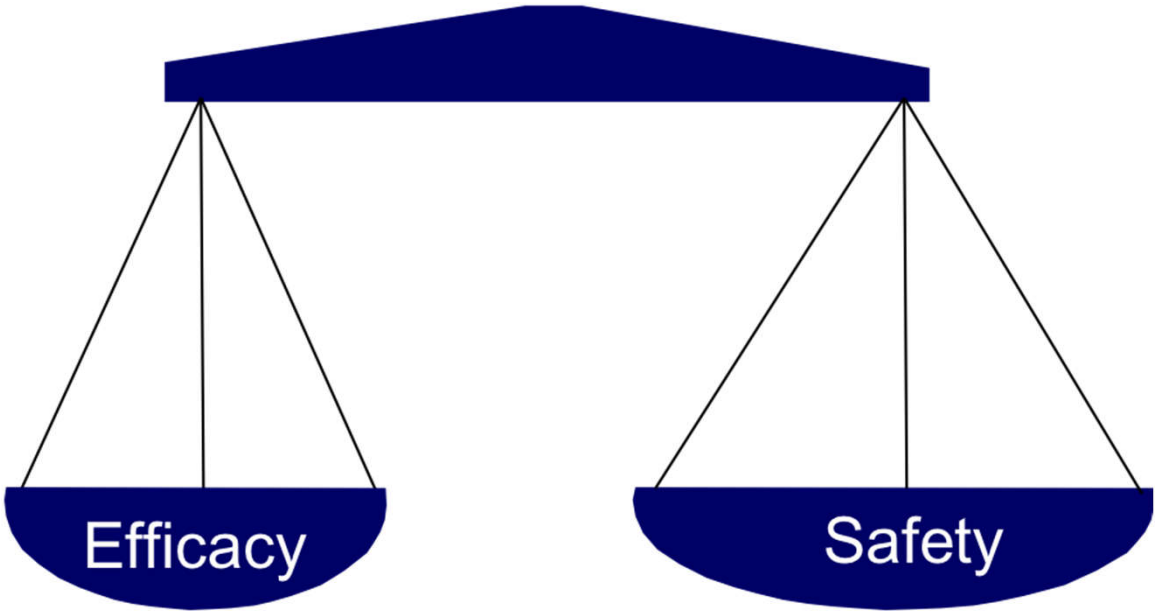
The Purpose of Guidelines?

- To ensure quality of the product
- To get high quality data (GCP, GLP)
- To get sufficient non-clinical and clinical data

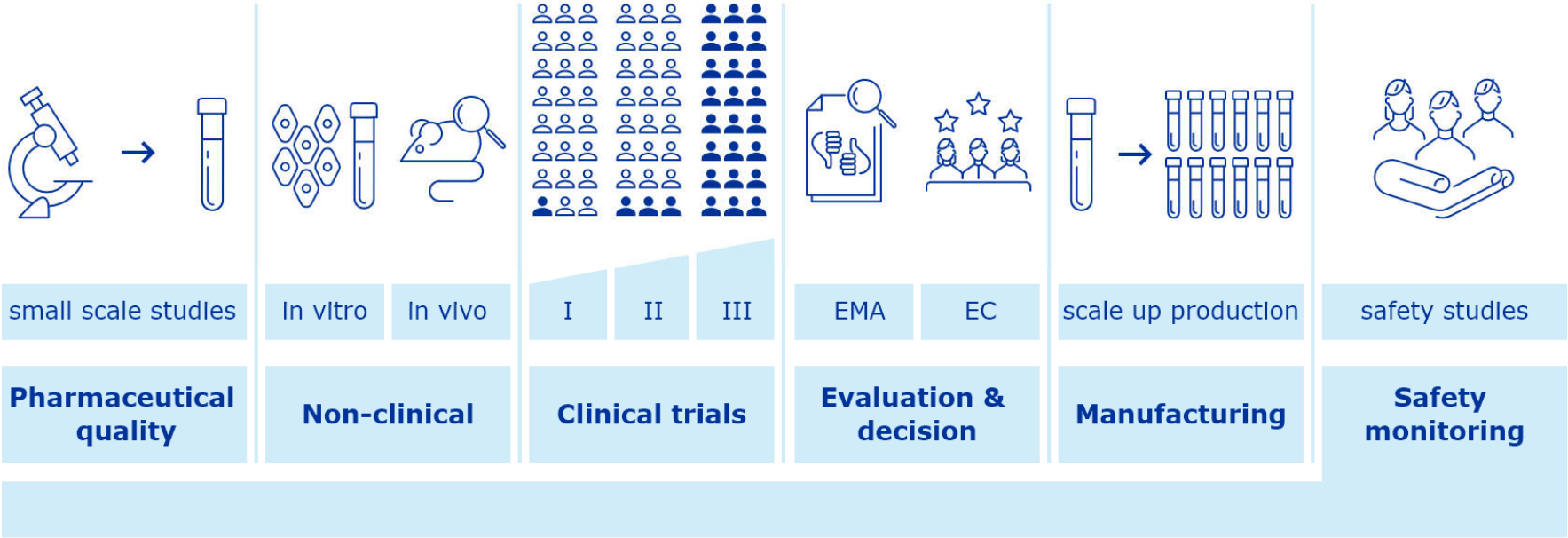
To enable an adequate Benefit/risk assessment



The assessment



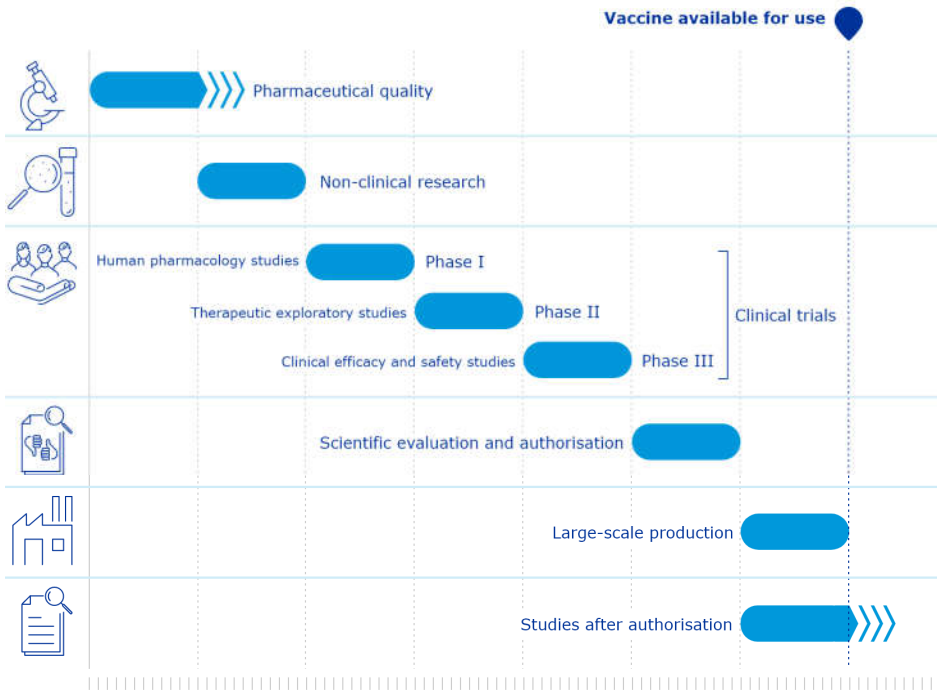
Overview of vaccine development and approval stages



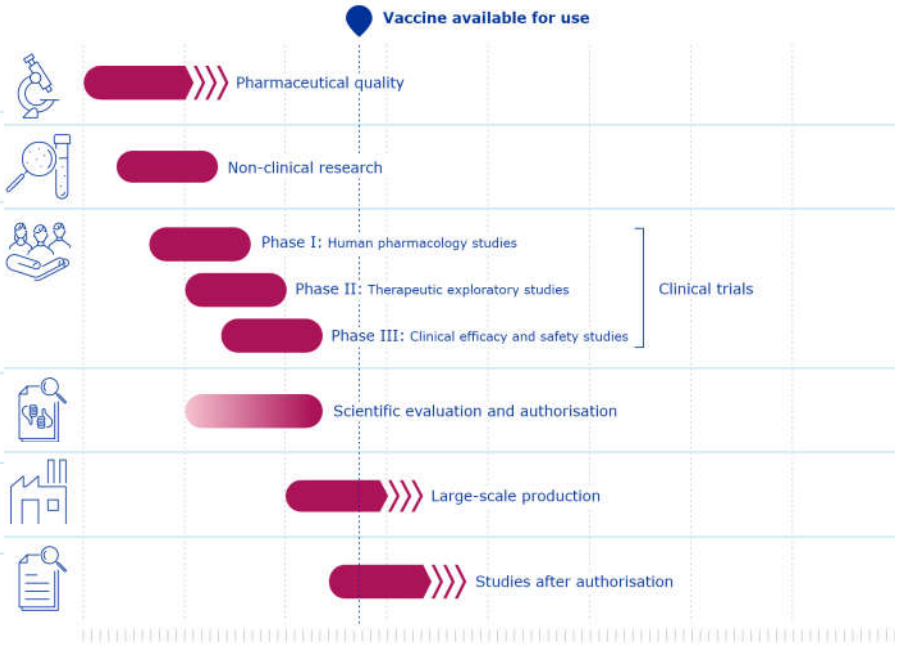
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring

Vaccine development

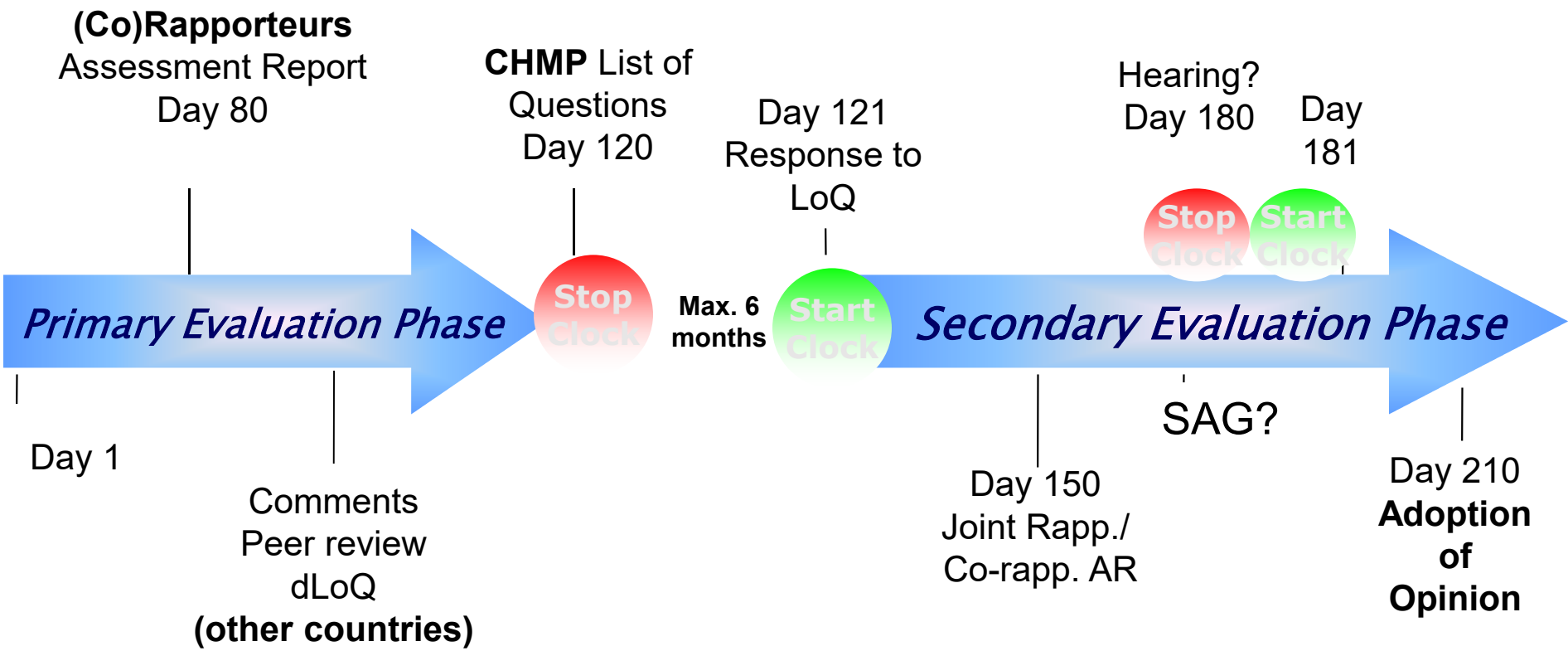
Standard



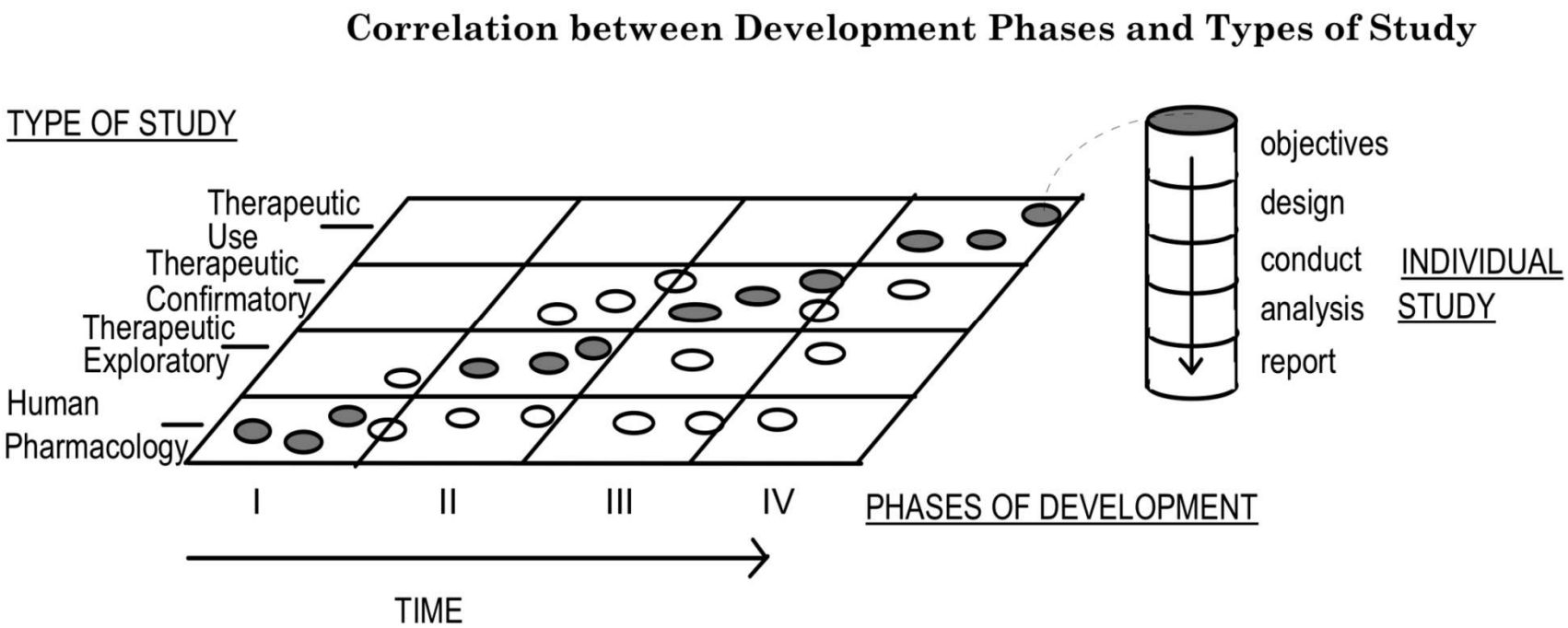
Covid-19



Centralised Procedure Strict protocol



Correlation between Development Phases and Types of Study

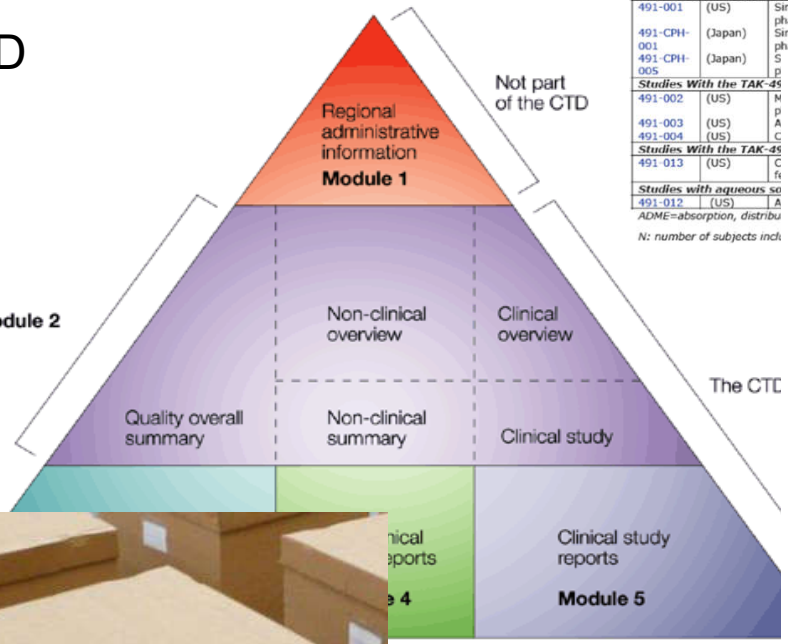


ICH E8

Phase I studies

A dossier

CTD



Nature Reviews | Drug Discov

Table PK2 Phase 1 Clinical Studies With TAK-491 Tablet or Capsule

Study No.	(Region)	Description	N	P	S
Studies With the Proposed Commercial TAK-491 Tablet					
491-007	(US)	QTc (single dose)	60	x	
491-015	(US) (a)	Relative bioavailability of TAK-536 derived from the TAK-491 capsule and the TAK-491 tablet, and food effect on the TAK-491 tablet	24	x	
491-017	(US)	Multiple ascending dose: pharmacokinetics and relative bioavailability	50	x	
491-101	(US)	Multiple ascending dose: pharmacokinetics	24	x	
491-102	(US)	Hepatic impairment (mild/moderate): pharmacokinetics	32	x	
491-103	(US)	Renal impairment (mild/moderate/severe or ESRD): pharmacokinetics	48	x	
491-104	(US)	Digoxin multiple dose, drug interaction	24	x	
491-107	(US)	Aluminum-magnesium hydroxide: drug interaction (b)	24	x	
491-110	(EU)	Amlodipine: drug interaction		x	
Studies With the TAK-491 Capsule in Both Fasted and Fed States					
491-001	(US)	Single ascending dose(5-160mg): pharmacokinetics with pharmacodynamics and food effect	60	x	
491-CPH-001	(Japan)	Single ascending dose: pharmacokinetics with pharmacodynamics and food effect	124		x
491-CPH-005	(Japan)	S p			
Studies With the TAK-49					
491-002	(US)	N p			
491-003	(US)	A			
491-004	(US)	C			
Studies With the TAK-49					
491-013	(US)	C fi			
Studies with aqueous so					
491-012	(US)	A			

ADME=absorption, distribu

N: number of subjects incl

Table PK3 Clinical Studies With TAK-536

Study No.	(Region)	Description (a)	N	P	S
536-316	(US)	Single ascending dose: pharmacokinetics with pharmacodynamics	84		x
536-GHBA-328	(EU)	Single ascending dose: pharmacokinetics with pharmacodynamics	8	x	
536-CPH-001	(Japan)	Single ascending dose: pharmacokinetics with pharmacodynamics and food effect	64	x	
536-317	(US)	Multiple ascending dose: pharmacokinetics with pharmacodynamics	36		x
536-EC101	(EU)		37		
536-014	(U				
536-016	(U				
536-CPH-009	(Ja				
536-008	(U				
536-CPH-005	(J				
536-661	(U				
536-007	(U				
536-005	(U				
536					
536					
536					
536-006	(US				
536-011	(US				

ADME=absorpti

of subjects incl

(a) Subjects in

otherwise state

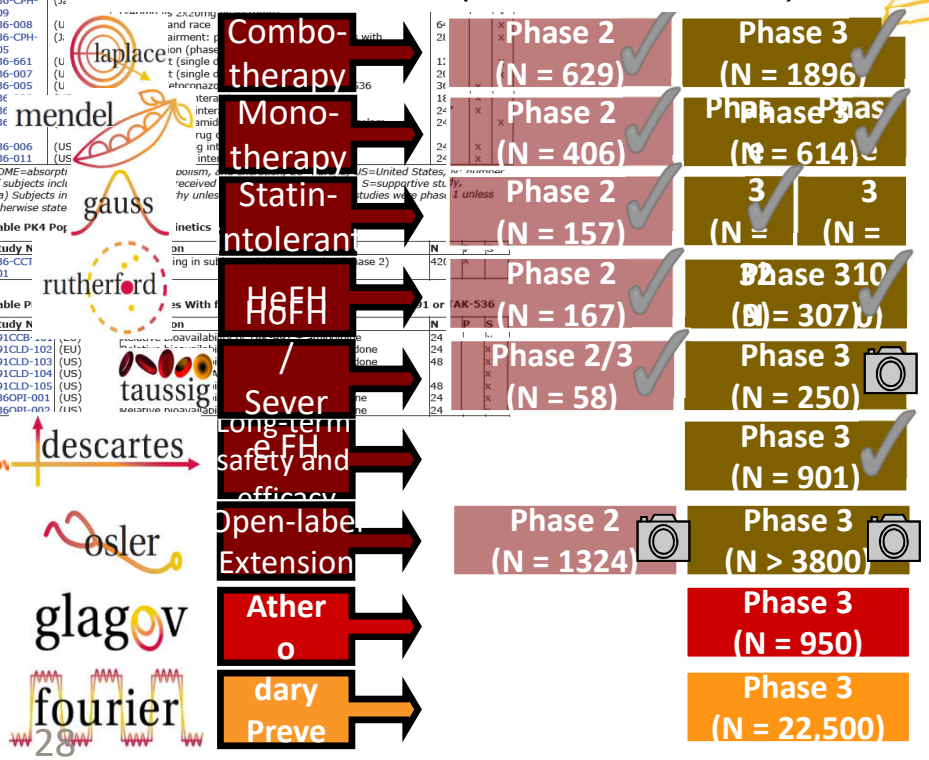
Table PK4 Po

Study N
536-CCT 001

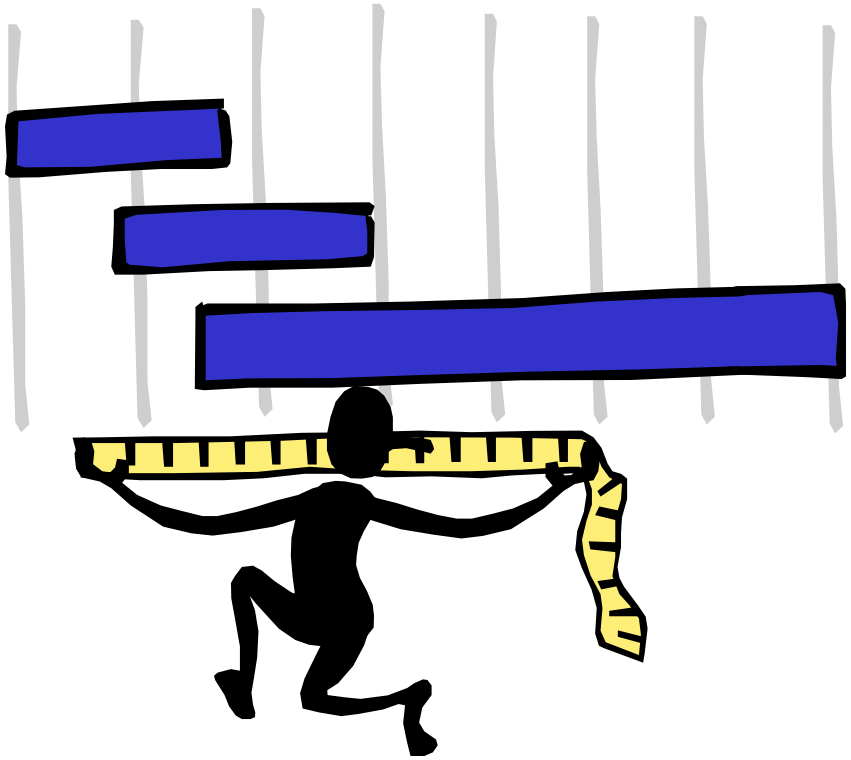
Table P

Study N
491CCB-
491CLD-102
491CLD-103
491CLD-104
491CLD-105
536OPI-001
536OPI-002

Phase III studies (PCSK9-inibitor)



The critical evaluation of the individual study



Methodology: internal validity

Aim of the study / indication determine:

- Patient selection
- Comparator = placebo or other similar drug (active control)
- Chosen endpoints
- Statistical analysis (incl. power analysis)
- Follow-up

Internal validity – KEY CONCEPT

A comparative trial has *internal validity* if, based on the methodology, it can be expected that the observed therapeutic effect is not biased by other differences in the group caused by

- differences in the natural history
- observational errors
- non-specific external facors

How solved?

- Randomisation
- Blinding
- Introduce control groups
- Parallel (preferred)
- Cross-over

  (disadvantage carry over & unstable disease)

So, what is REALLY important!

The NEW ENGLAND JOURNAL of MEDICINE

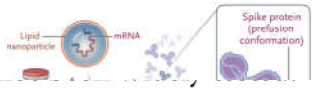
RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577

CLINICAL PROBLEM

Safe and effective vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 are urgently needed. No vaccines that protect



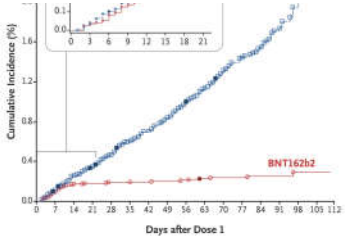
CLINICAL TRIAL

A randomized, double-blind study of an mRNA vaccine encoding the SARS-CoV-2 spike protein.

RESULTS

Safety:
Vaccine recipients had local reactions (pain, erythema, swelling) and systemic reactions (e.g., fever, headache, myalgias) at higher rates than placebo recipients, with more reactions following the second dose. Most were mild to moderate and resolved rapidly.

Efficacy:
The vaccine showed protection 7 days after the second dose; 95% efficacy was observed.



Vaccine efficacy of 95% (95% credible interval, 90.3 –97.6%)

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- Safety and efficacy beyond 2 months and in groups not included in this trial (e.g., children, pregnant women, and immunocompromised persons).
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to deal with those who miss the second vaccine dose.

CONCLUSIONS

Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older.

Links: Full article | Quick Take | Editorial

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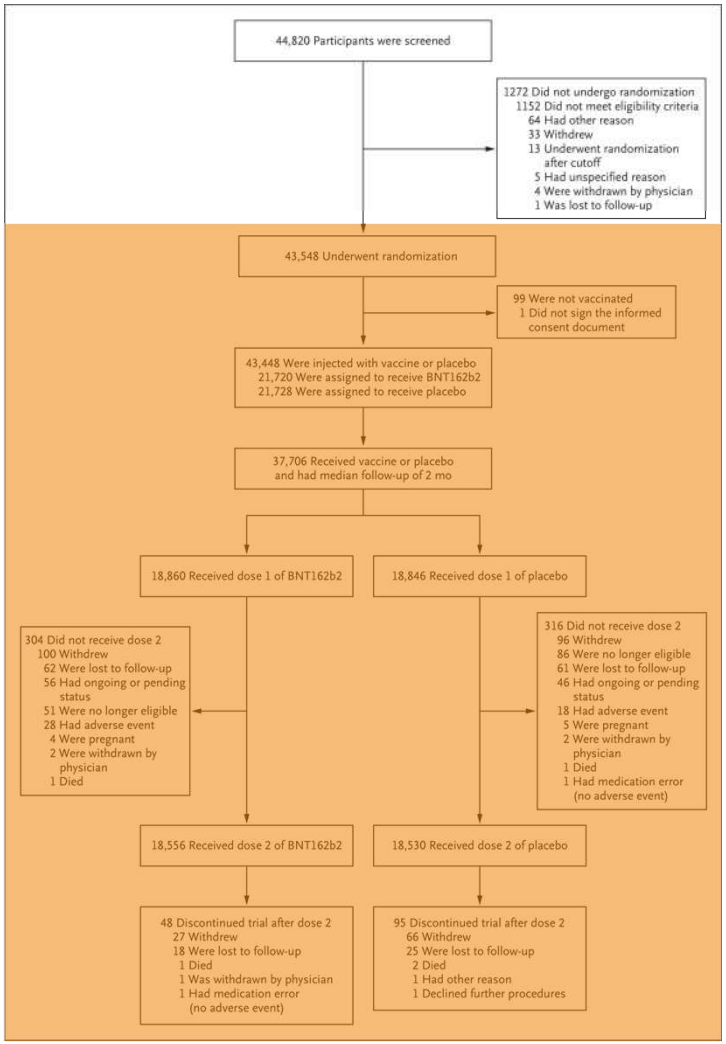
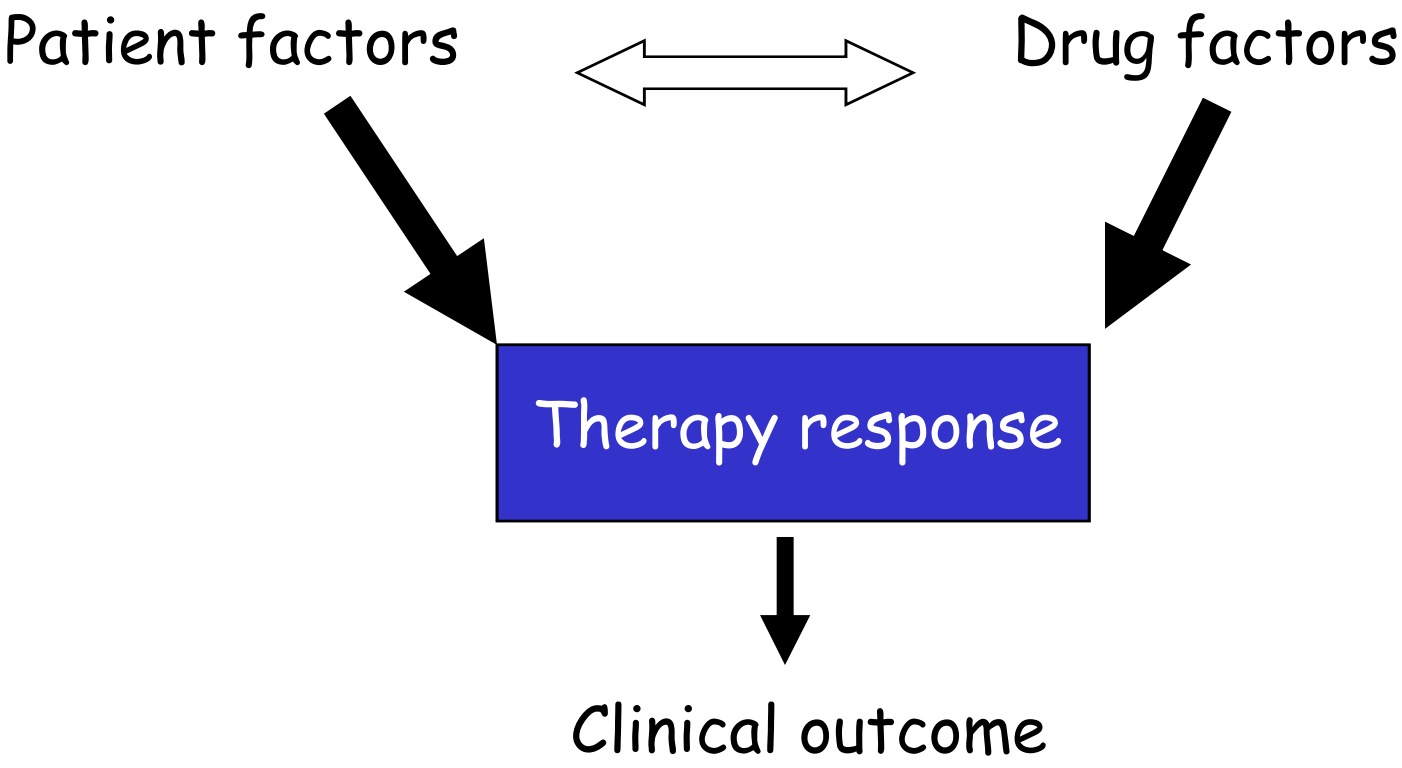
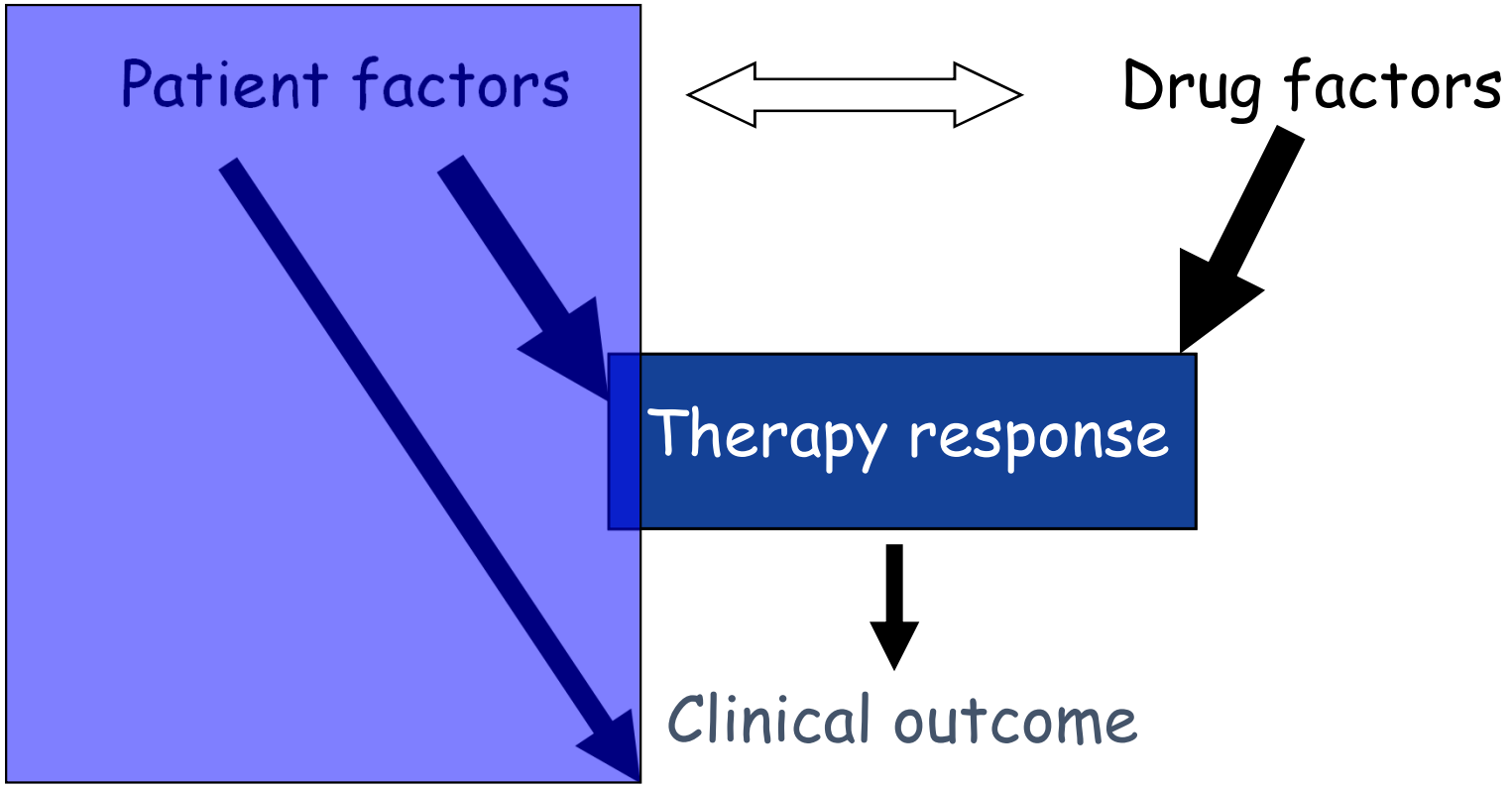


https://www.nejm.org/doi/full/10.1056/NEJMoa2034577

Determinants of drug response: a balanced view

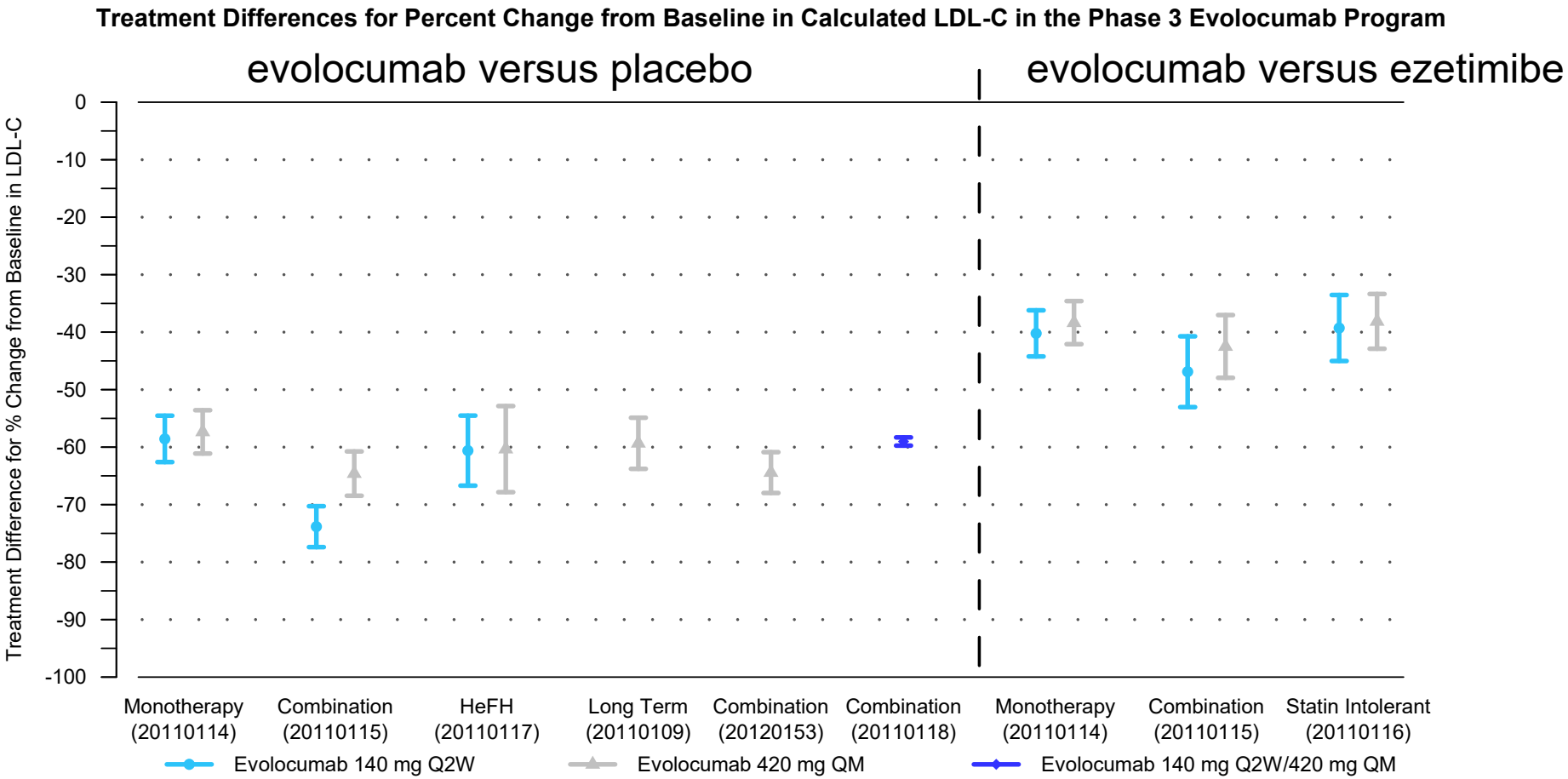


Determinants of drug response: a balanced view



Comparative clinical trial: Randomization to ELIMINATE patient factors

Repatha Substantially and Consistently Lowers LDL-C Across All Clinical Settings



Least squares means from repeated measures model and associated 95% confidence intervals
Week 12 for all studies except 20110109 at week 52, 20120153 at week 52 and 20110118 at week 48
Program: /userdata/stat/amg145/lipid/20110118/analysis/final/stats/output/ldl-across-study/w48/cds_p3_cal_ldl_w12.R

Comirnaty PD – neutralizing antibodies

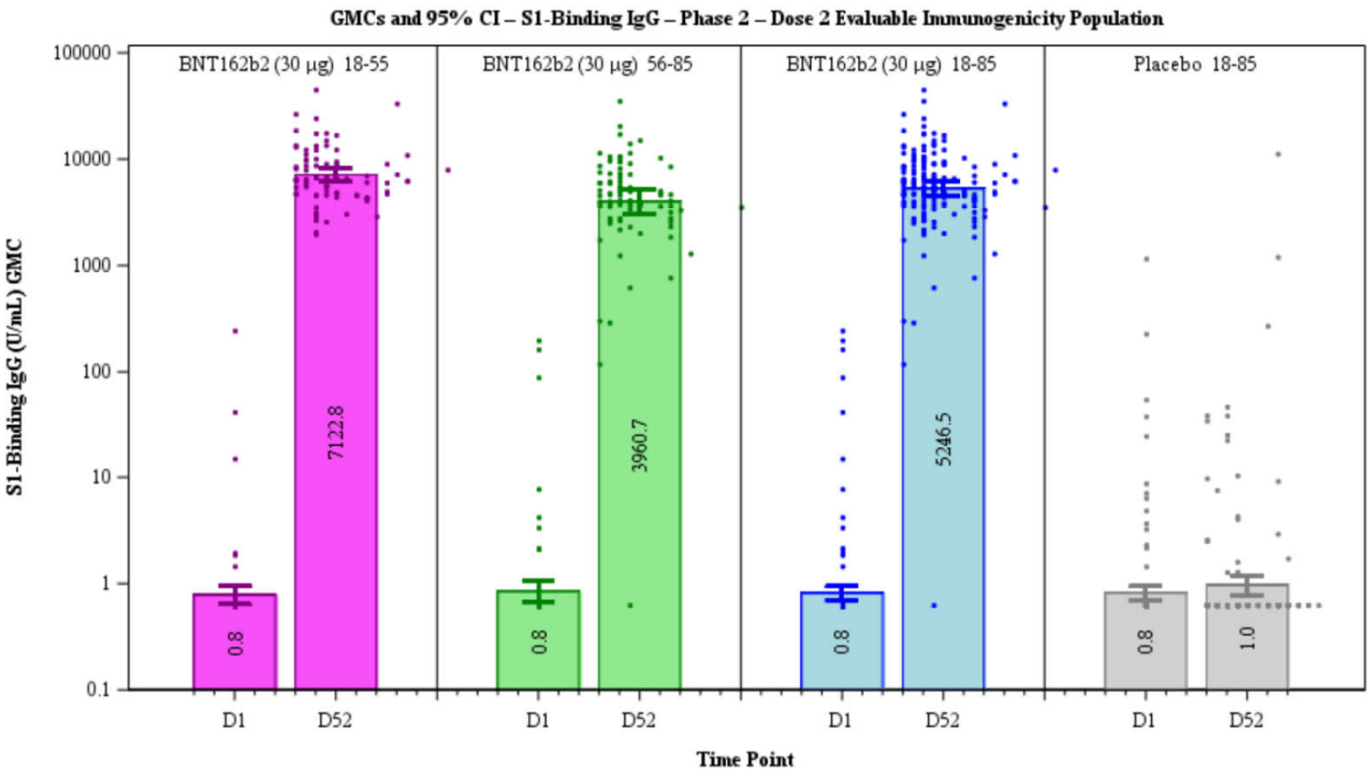
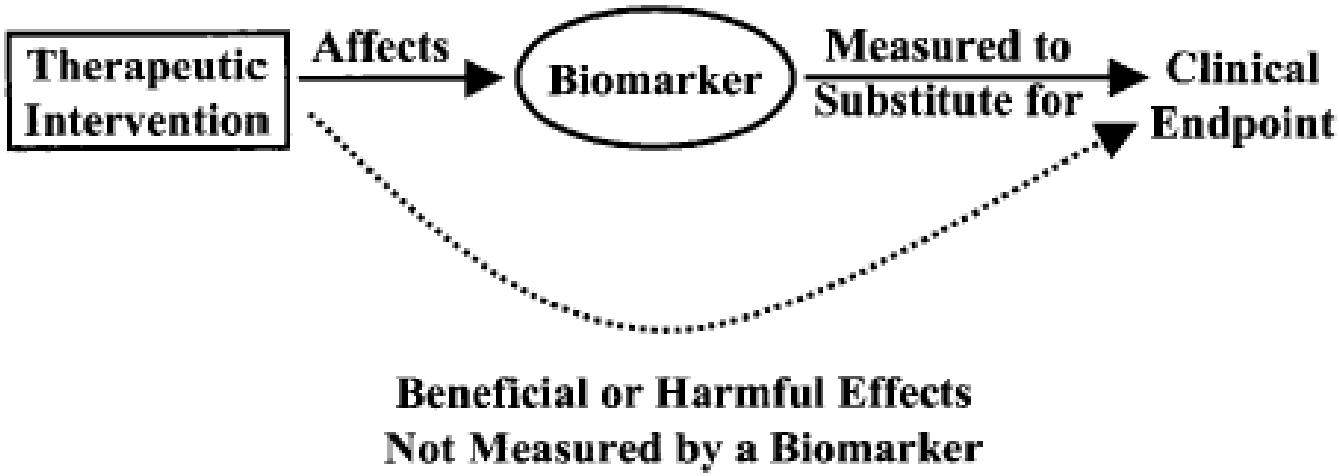


Figure 11. Geometric Mean Concentrations and 95% CI: S1-Binding IgG Level Assay – Phase 2 Dose 2 Evaluable Immunogenicity Population

https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

Stop!

Disadvantages of surrogate endpoints / biomarkers



"There is no surrogate for safety"

JAMA. 1999;282(8):790-795.

Examples: CETP-inhibitor torcetrapib (ILLUMINATE), increases in HDL and decreases in LDL was mortality increased
Aliskiren (ALTITUDE), telmisartan (ONTARGET): BP & albuminuria decreases, but increase in CV endpoints

Evidence, licensing in cardiology
The use of surrogates

C B G
M E B

LDL-C & coronary events

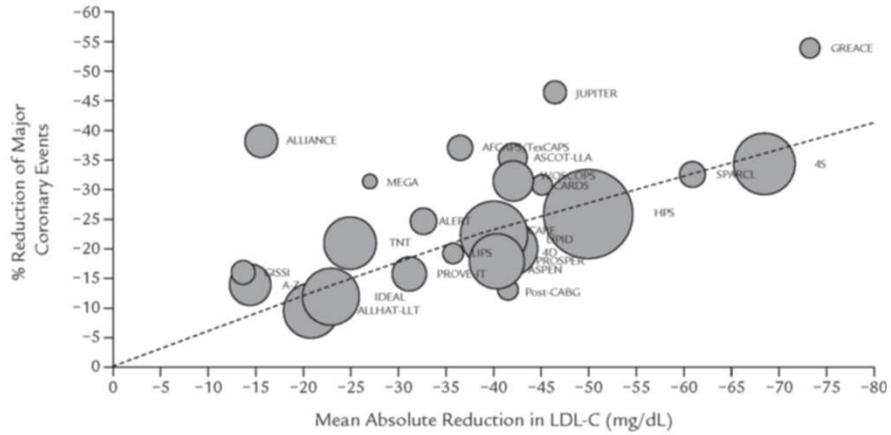


Figure 1. Relationship between reduction in low-density lipoprotein cholesterol (LDL-C) and reduction i relative risk for major coronary events. A *major coronary event* was defined as nonfatal myocardi

Delahoy PJ, Clinical Therapeutics 2009

Other lipids & clinical outcome

Results of Cardiovascular Outcome Trials of Drugs That Modulate Triglyceride and Cholesterol Levels.*

Trial	ar
ACCORD Li	.92; 9– 2
AIM-HIGH[1]	.02; 7– 0
HPS2-THRI	96; 0– 9
JELIS[3]	.81; 9– 1
ILLUMINAT	.25; 4– 06
Dal-OUTCC	.04; 3– 2

"But if a drug were put on the market and subsequently found to be ***ineffective*** or unsafe, patients would have been exposed to unnecessary and perhaps unforeseen risks. The FDA would then have to take action to remove the drug — a problem that is avoided if data showing ***convincing clinical*** benefit are required ***before*** approval."

Hiatt, WR & Smith, RJ. NEJM Jan 30, 2014

Back to evolocumab: Clinical Safety in n=7552 subjects

					OSLER-1/ OSLER-2 Year 1		OSLER-1/ OSLER-2 Year 2+
	Any Placebo (N = 1526) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)	Any EvoMab (N = 3946) n (%)	SoC (N = 655) n (%)	EvoMab + SoC (N = 1314) n (%)	Total (N = 933) n (%)
All adverse events	753 (49.3)	1031 (49.6)	1595 (49.8)	2012 (51.0)	374 (57.1)	856 (65.1)	569 (61.0)
Grade ≥ 2	364 (23.9)	484 (23.3)	705 (22.0)	870 (22.0)	215 (32.8)	463 (35.2)	304 (32.6)
Grade ≥ 3	53 (3.5)	65 (3.1)	123 (3.8)	145 (3.7)	37 (5.6)	82 (6.2)	54 (5.8)
Grade ≥ 4	6 (0.4)	6 (0.3)	20 (0.6)	24 (0.6)	6 (0.9)	10 (0.8)	8 (0.9)
Serious adverse events	36 (2.4)	43 (2.1)	95 (3.0)	110 (2.8)	40 (6.1)	78 (5.9)	43 (4.6)
Leading to discontinuation of investigational product	24 (1.6)	48 (2.3)	70 (2.2)	74 (1.9)	NA	34 (2.6)	7 (0.8)
Serious	4 (0.3)	4 (0.2)	16 (0.5)	16 (0.4)	NA	4 (0.3)	1 (0.1)
Non-serious	21 (1.4)	45 (2.2)	58 (1.8)	62 (1.6)	NA	30 (2.3)	6 (0.6)
Fatal adverse events	1 (0.1)	1 (0.0)	3 (0.1)	3 (0.1)	3 (0.5)	1 (0.1)	1 (0.1)

Consistent safety/tolerability profile regardless of baseline characteristics such as age, race, gender, body-mass index, glucose tolerance status, diabetes, PCSK9, statin dose, LDL-C, HDL-C and triglycerides.

Benefit-risk balance: writing the document

- Compare all the important favourable against all the important unfavourable effects.
- Explain if and how the combined favourable effects are judged to exceed the combined unfavourable effects.
- Indicate, if necessary what the minimum condition should be to obtain registration and how this compares to the results observed.

Discussion of B/R balance: writing the document

- Impact of the uncertainties on the B-R balance
- Perspectives of the stakeholders (physicians, patients etc.)
- Long-term effects beyond the duration of the trials
- Expert opinions (SAG, CHMP)
- Restrictions to product availability or usage or conditions or measures to improve B-R
- Need for further studies
- Acceptability of the indication and need for restriction to subgroups
- Regulatory options (conditional approval, exceptional circumstances) + motivation.

The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined.

4. CLINICAL PA

4.1 Therapeutic indication

Hypercholesterolaemia and mixed dysl

Repatha is indicated in adults with primary hyp (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunc

- in combination with a statin or statin with other l pies in patients unable to reach LDL-C goals with the maximum tolerated dose
- alone or in combination with other lipid-lowering therapi are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozyg hypercholesterolaemia in combination with other lipid-lowering therapies.

The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined.

PCSK-9 inhibitors & clinical outcomes

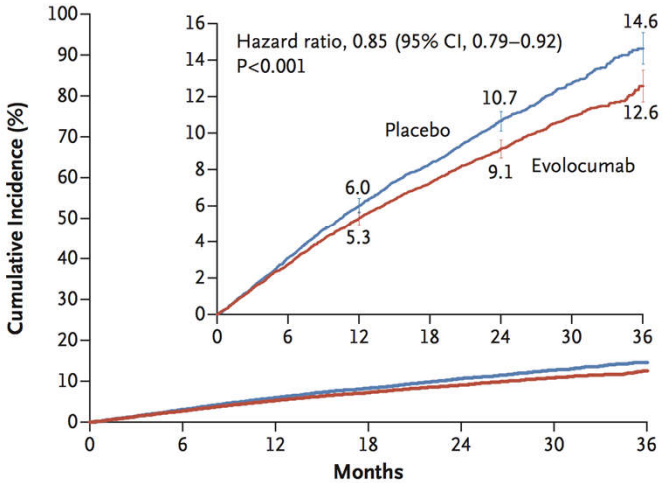
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D.,

A Primary Efficacy End Point



No. at Risk

Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

CONCLUSIONS

In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

The New England Journal of Medicine
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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 16, 2015 VOL. 372 NO. 16

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

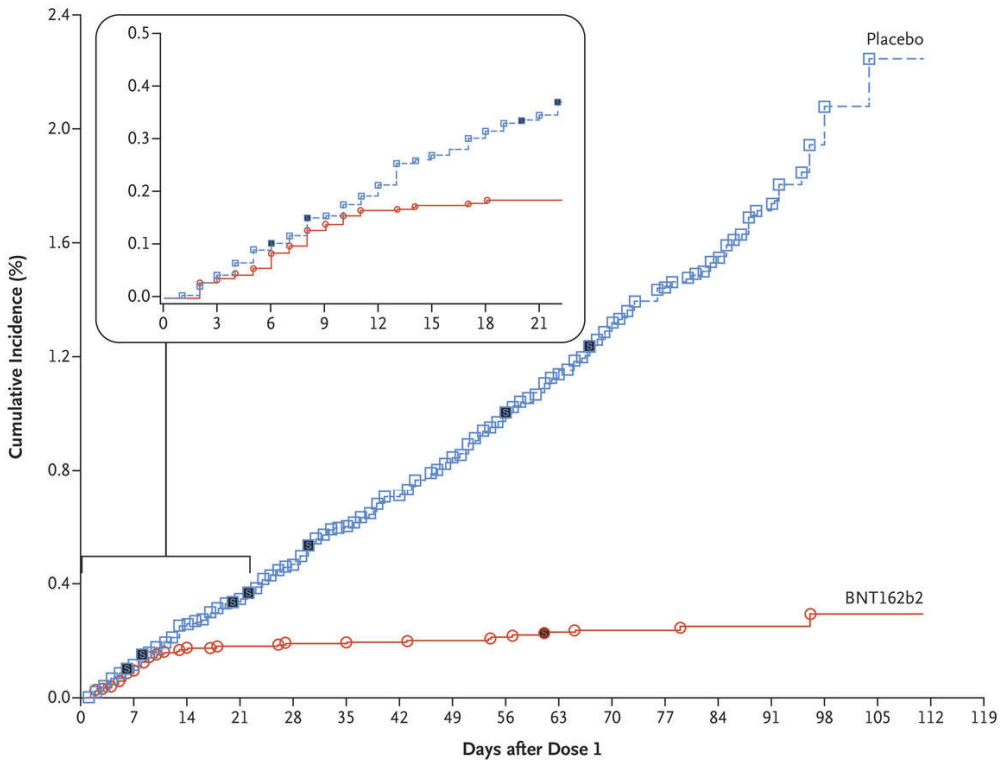
ORIGINAL ARTICLE

Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients

P.M. Ridker, J. Revkin, P. Amarenco, R. Brunell, M. Curto, F. Civeira, M. Flather, R.J. Glynn, J. Gregoire, H.W. Jukema, Y. Karpov, J.J.P. Kastelein, W. Koenig, A. Lorenzatti, P. Manga, U. Masiukiewicz, M. Miller, A. Mosterd, J. Murin, J.C. Nicolau, S. Nissen, P. Ponikowski, R.D. Santos, P.F. Schwartz, H. Soran, H. White, R.S. Wright, M. Vrablik, C. Yunis, C.L. Shear, and J.-C. Tardif, for the SPIRE Cardiovascular Outcome Investigators*

ABSTRACT

Efficacy of BNT162b2 against Covid-19 after the First Dose.

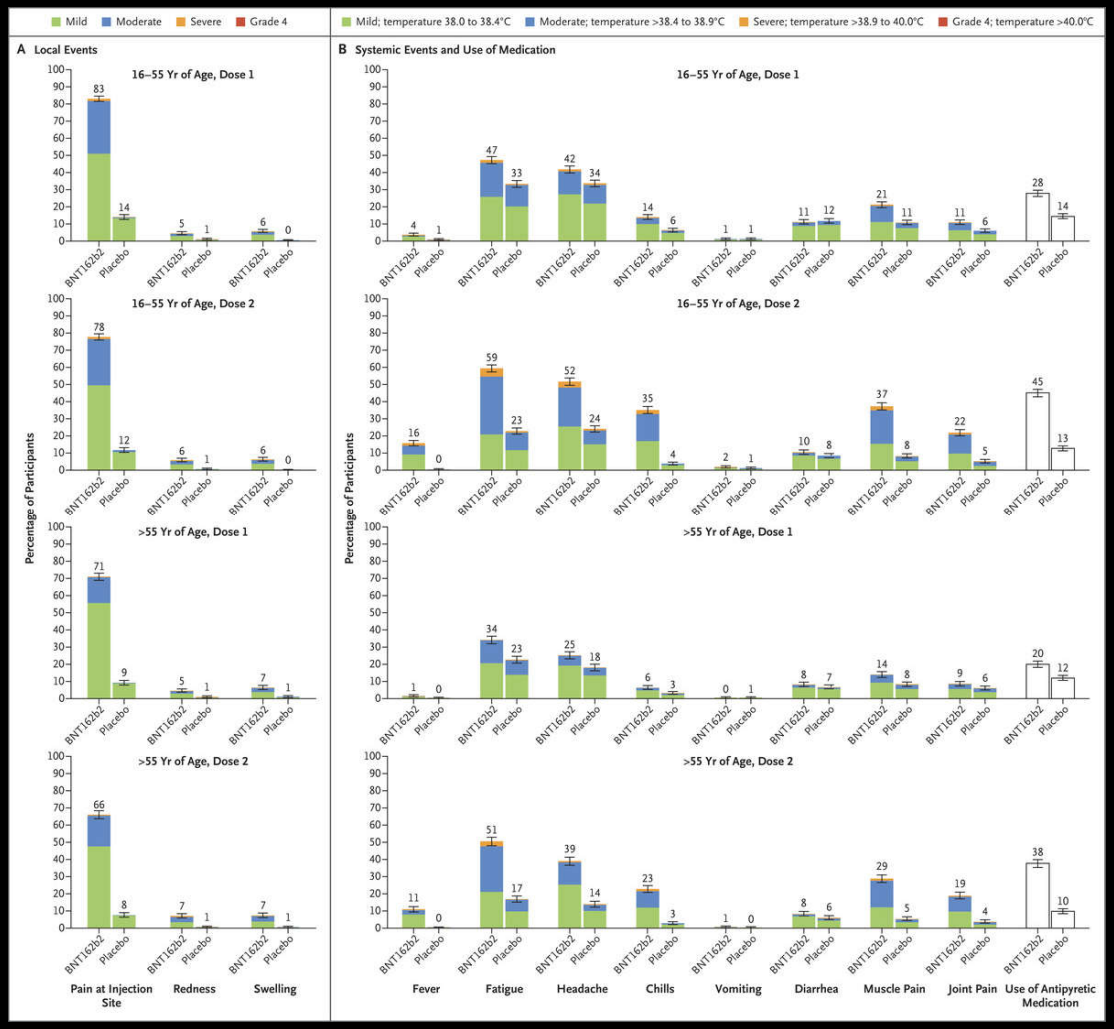


Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

FP Polack et al. N Engl J Med 2020;383:2603-2615.

The NEW ENGLAND JOURNAL of MEDICINE

Local and Systemic Reactions Reported within 7 Days after Injection of BNT162b2 or Placebo, According to Age Group.



FP Polack et al. N Engl J Med 2020;383:2603-2615.

The NEW ENGLAND JOURNAL of MEDICINE

College ter Beoordeling van Ge | Safety and Efficacy of the | Comirnaty, INN-COVID-19 | Comirnaty | European Med | Comirnaty, INN-COVID-19

https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

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Comirnaty

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COVID-19 mRNA vaccine (nucleoside-modified)

AUTHORISED
This medicine is authorised for use in the European Union.

Table of contents

- Overview
- Authorisation details
- Product information
- Assessment history
- Safety updates

Overview

Comirnaty is a vaccine for preventing coronavirus disease 2019 (COVID-19) in people aged 16 years and older.

Comirnaty contains a molecule called messenger RNA (mRNA) with instructions for producing a protein from SARS-CoV-2, the virus that causes COVID-19. Comirnaty does not contain the virus itself and cannot cause COVID-19.

How is Comirnaty used?

Comirnaty is given as two injections, usually into the muscle of the upper arm, 3 weeks apart.

Arrangements for the supply of the vaccine will be the responsibility of national authorities. For more information about using Comirnaty, see the package leaflet or consult a healthcare professional.

How does Comirnaty work?

What benefits of Comirnaty have been shown in studies?

Can people who have already had COVID-19 be vaccinated with Comirnaty?

Can Comirnaty reduce transmission of the virus from one person to another?

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial and must be diluted before use.

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see sections 4.2 and 6.6.

1 dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

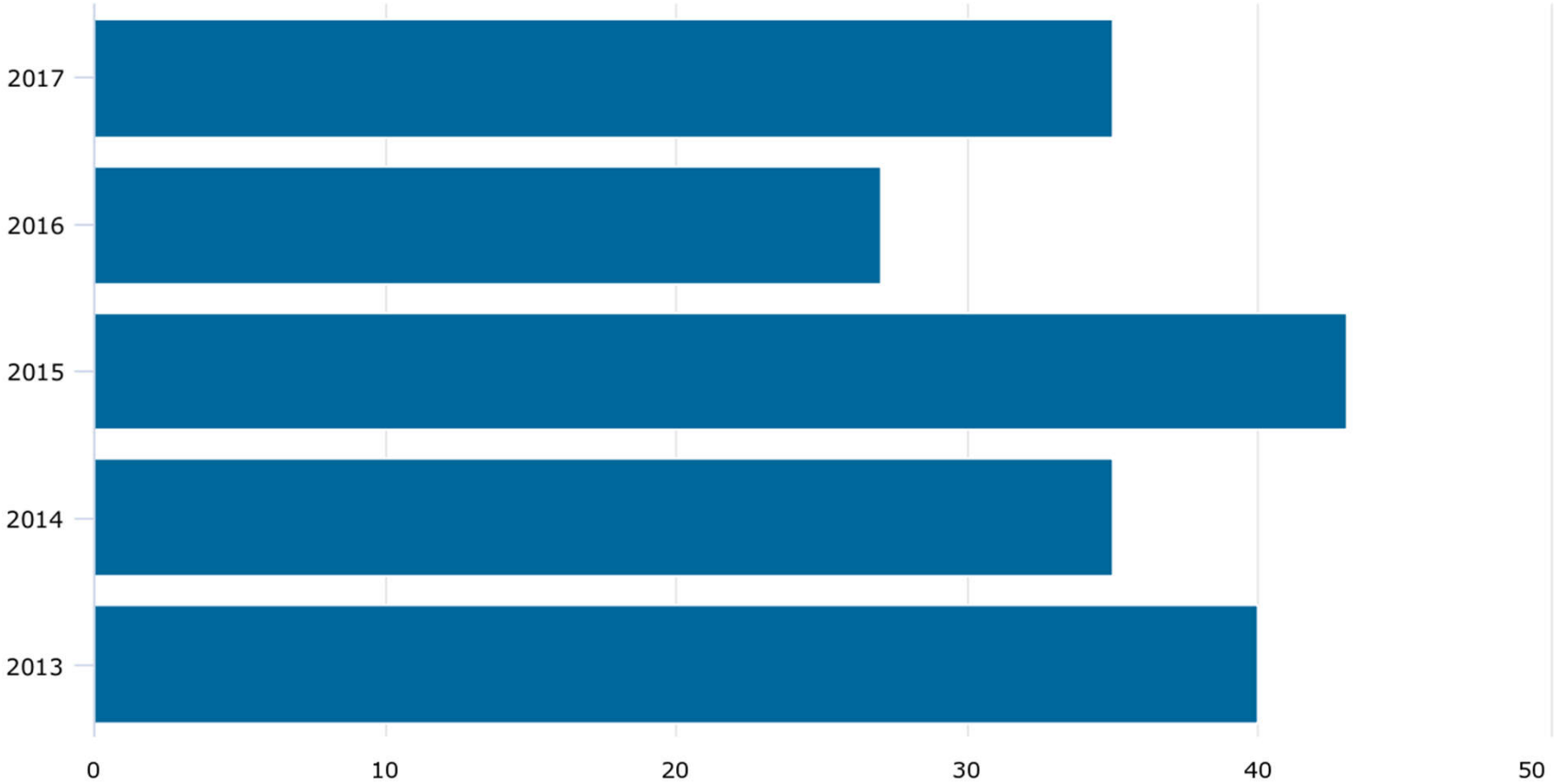
Individuals 16 years of age and older
Comirnaty is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each). It is recommended to administer the second dose 3 weeks after the first dose (see sections 4.4 and 5.1).

Where to find – The Official Drug Information

http://www.cbg-meb.nl/

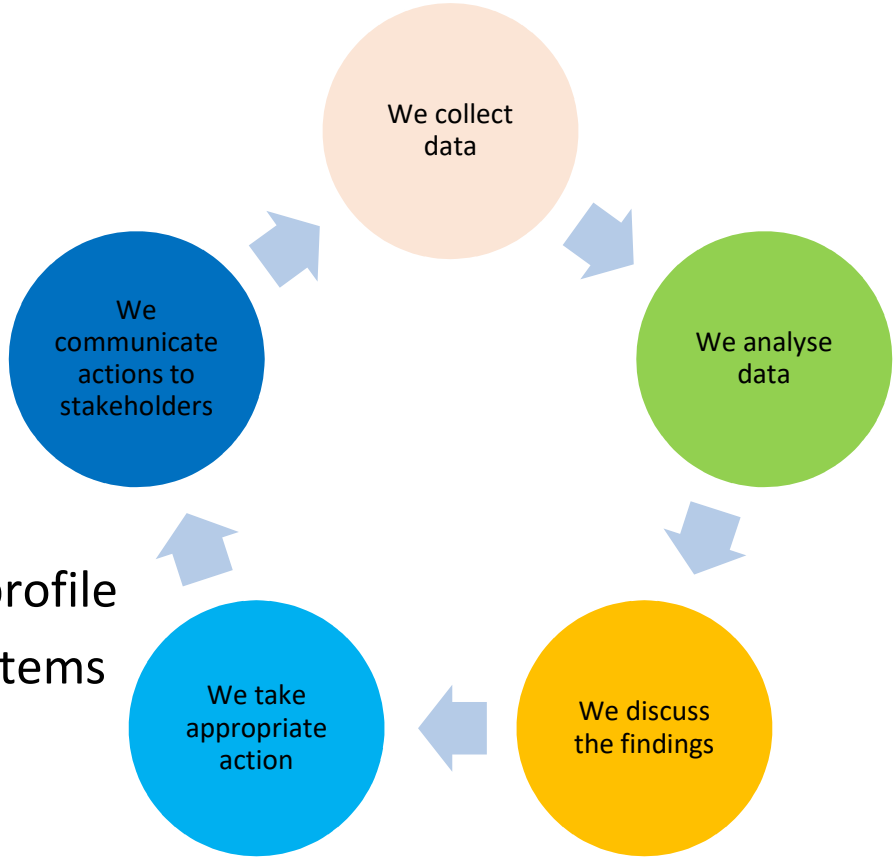
http://www.ema.europa.eu/

Centrally approved products with a new active substance



Pharmacovigilance

- Life cycle management
- Much larger exposure after approval
- Efficacy & safety in real life may shift
  - Different populations
  - Longer exposure
  - Comorbities, etceteras
- Risk Management Plan
  - Routine PhV
    - Continuous monitoring of B/R profile
    - Spontaneous ADR reporting systems
  - Additional activities
    - Risk minimisation measures
    - PASS/PAES studies



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Any questions?

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