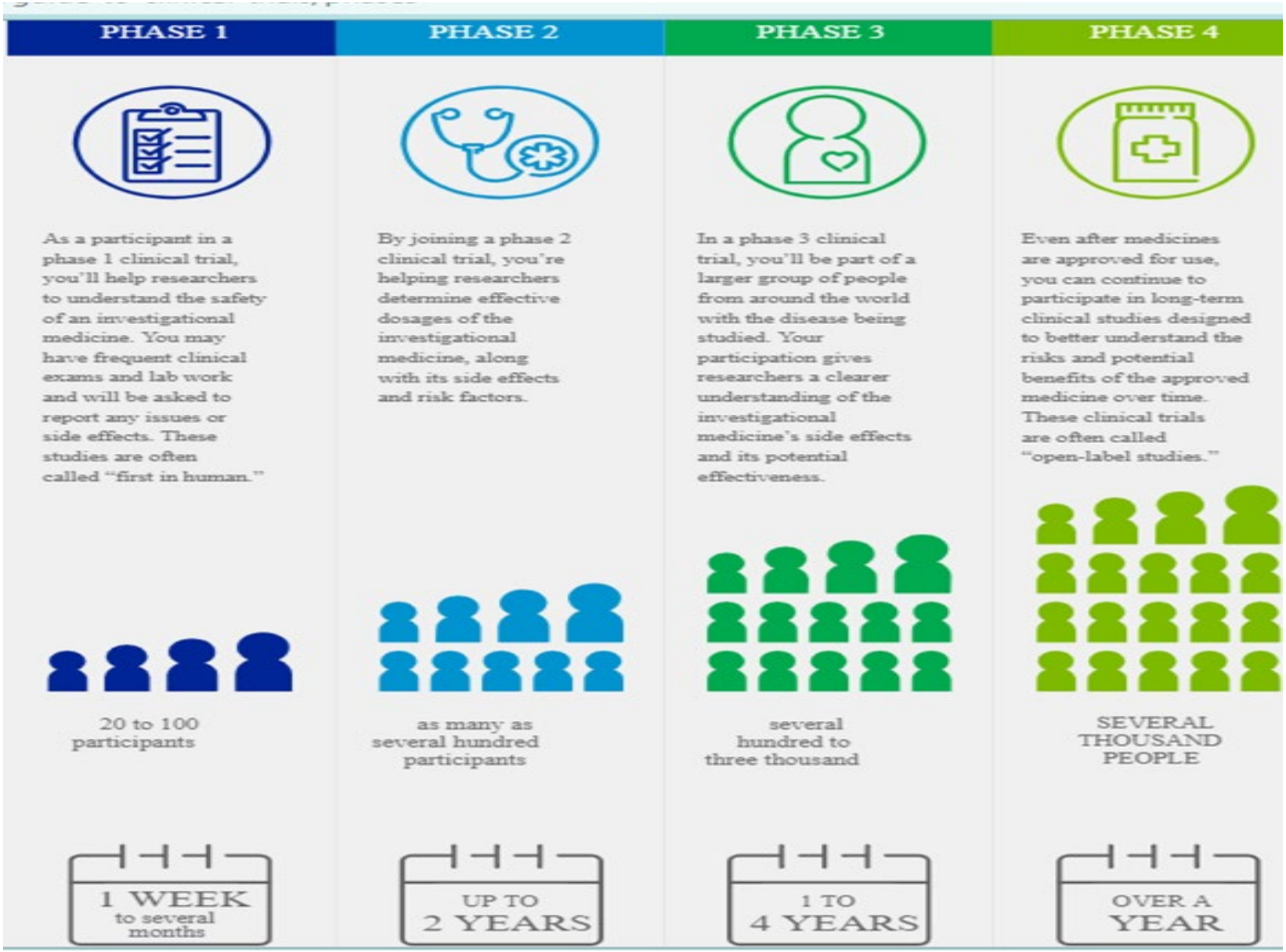
Clinical trials



Criteria and conditions

EMA's CHMP may grant a conditional marketing authorisation for a medicine if it finds that all of the following **criteria** are met:

- the benefit-risk balance of the medicine is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the medicine fulfils an unmet medical need;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Conditional marketing authorisations are **valid for one year** and can be renewed annually.

Once a conditional marketing authorisation has been granted, the marketing authorisation holder must fulfil **specific obligations** within defined timelines.

These obligations could include completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive.

EMA publishes the conditions of the marketing authorisation in the medicine's European public assessment report.

The marketing authorisation can be converted into a **standard marketing authorisation** (no longer subject to specific obligations) once the marketing authorisation holder fulfils the obligations imposed

Unmet Medical Need according to EC

Article 4 paragraph 2 of Commission Regulation (EC) No. 507/2006 (about conditional marketing authorization):

"Unmet medical needs means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected"

Very general, not enough guidance.

emergency situations to speed up the procedure for approval, whilst fully ensuring that all requirements in terms of efficacy, quality and safety of the vaccine are fully assessed.

In view of the urgency due to the COVID-19 pandemic, **EMA** has put i place rapid review procedures to assess applications in the shortest possible timeframes while ensuring robust scientific opinions. Key to speeding up the process are '**rolling reviews'**, allowing EMA in public health emergencies to **assess data** for promising medicines or vaccin **as they become available** instead of waiting until all trials have concluded to start its work.

Through these rolling reviews, EMA can start evaluating data while the development is still ongoing, and before the vaccine developer has submitted a request for marketing authorisation. The rolling review assesses data on the vaccine's quality as well as results from laborato studies. EMA also looks at results on the vaccine's efficacy and initial safety data emerging from large-scale clinical trial as they become available. This **significantly shortens the normal assessment time while maintaining the principles of quality, safety and efficacy.**

Clinical trials

enrolled who are COVID-19 vaccine-naïve (ie, **BNT162b2**-naïve) and have not experienced COVID-19. They will receive **BNT162b2**SA
2-dose series, separated by 21 days.

Condition or disease	Intervention/treatment	Phase
SARS-CoV-2 Infection	Biological: BNT162b1	Phase 2
COVID-19	Biological: **BNT162b2**	Phase 3
	Other: Placebo	
	Biological: **BNT162b2**SA	

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	43998 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Prevention
Official Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDIN TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS- RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS
Actual Study Start Date :	April 29, 2020
Estimated Primary Completion Date :	May 2, 2023
Estimated Study Completion Date :	May 2, 2023

Investigational = experimental

(The situation is similar in Europe, where four covid-19 vaccines have been granted "conditional marketing authorisations," a fast track mechanism that can be used in emergencies. These can be converted into standard "marketing authorisations" pending positive data after authorisation, but this has not yet happened for any covid-19 vaccine being administered.)

As hundreds of millions of people around the world get vaccinated, it may seem like wordsmithing to highlight the fact that none of the covid-19 vaccines in use are actually "approved." Through an emergency access mechanism known as Emergency Use Authorisation (EUA), the products being rolled out still technically remain "investigational."[3] Factsheets distributed to vaccinees are clear: "There is no FDA approved vaccine to prevent covid-19."[4]

The approval-authorisation distinction is often misunderstood by the media,[5] even in the scientific press. But it was the focus of much discussion back in September 2020. With large phase III trials by Pfizer and Moderna well under way, and the November US presidential election looming, many worried about political pressure resulting in the rollout of an unsafe or ineffective vaccine.[6]

https://www.bmj.com/content/373/bmj.n1244

MEDICINAL PRODUCTS INTENDED FOR RESEARCH AND CLINICAL TRIALS AND INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

The Community Code relating to medicinal products for human use excludes, in Article 3(3) of Directive 2001/83/EC, "*medicinal products intended for research and development trials*" from its scope of application.

Regulation (EU) No 536/2014 Article 2 (5) defines an IMP as "*a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial*". Further information on IMPs can be found in "The rules governing medicinal products in the European Union" Volume 10 – Guidance documents applying to clinical trials, Clinical Trials Regulation (EU) No 536/2014 Questions and Answers (currently being updated).

It follows that medicinal products with a marketing authorisation are IMPs too when they are to be used as the test product, reference product or placebo in a clinical trial.

https://ec.europa.eu/health/sites/default/files/files/clinicaltrials/2016_06_pc_guidelines/gl_2

Understanding Investigational Drugs

Have you ever thought about joining a clinical trial that is trying to find out if an investigational drug works in treating your disease or medical condition? Or maybe your healthcare provider has talked to you about treating you with an investigational drug through expanded access.

An investigational drug can also be called an experimental drug and is being studied to see if your disease or medical condition improves while taking it. Scientists are trying to prove in clinical trials:

- If the drug is safe and effective.
- How the drug might be used in that disease.
- How much of the drug is needed.
- Information about the potential benefits and risks of taking the drug.

Experimental Unapproved Treatments for COVID-19

All categories

Name	Experimental Unapproved Treatments for COVID-19
Accession Number	DBCAT005151
Description	Drugs that are being investigated as potential treatment options for coronavirus disease 2019 (COVID-19). Towards the end of 2019, a large number of patients in Wuhan, China presented with atypical pneumonia. The cause of this disease was identified as 2019 novel coronavirus (2019-nCoV), which was renamed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 11, 2020 by the World Health Organization (WHO).

Drugs

Show 100 entries Search

DRUG	DRUG DESCRIPTION
Ritonavir	An HIV protease inhibitor used in combination with other antivirals in the treatment of HIV infection.
Chloroquine	An antimalarial drug used to treat susceptible infections with P. vivax, P. malariae, P. ovale, and P. falciparum. It is also used for second line treatment for rheumatoid arthritis.
Darunavir	A HIV protease inhibitor used in the treatment of human immunodeficiency virus (HIV) infection in patients with history of prior antiretroviral therapies.

Unapproved/Other Products

Show 10 entries

NAME	INGREDIENTS	DOSAGE	ROUTE	LABELLER	MARKETING START
Astrazeneca Covid-19 Vaccine	AstraZeneca COVID-19 Vaccine (50000000000 {VP}/0.5mL)	Injection, suspension	Intramuscular	AstraZeneca Pharmaceuticals LP	2020-12-22

Showing 1 to 1 of 1 entries

CATEGORIES

Drug Categories	Experimental Unapproved Treatments for COVID-19
Classification	Not classified
Affected organisms	Humans and other mammals

THE COVID-19 VACCINE MATERNAL STUDY

For expectant mothers 18 years old and over. **Now enrolling.**

Learn More

THE COVID-19 VACCINE PEDIATRIC STUDY

For children 6 months to 11 years old. **Now enrolling.**

Learn More

THE COVID-19 VACCINE STUDY FOR IMMUNOCOMPROMISED PATIENTS

For adults and children 2-17 **Now enrolling.**

Learn More

THE COVID-19 VACCINE LANDMARK STUDY

For individuals 12 years old and over. **This study is ongoing but no longer enrolling new participants.**

Learn More

Datum:

Handtekening:

Ik geef ook toestemming aan de behandelend arts voor het doorgeven van mijn vaccinatiegegevens aan het RIVM ten behoeve van de veiligheidsbewaking, de bestrijding van de epidemie en voor het onderzoek naar de werkzaamheid van het vaccin.
Zie voor meer informatie de bijlage 'informatie over de registratie' bij de uitnodigingsbrief. Hierin leest u welke gegevens worden doorgegeven. Alleen wanneer u kiest voor een vaccinatie, worden gegevens aan het RIVM doorgegeven. Gegevens zullen zodanig worden verwerkt, dat zij bij publicatie nooit herleidbaar zijn tot individuele personen.

0 Ja

0 Nee

Datum:

Handtekening:

2. Waarom gebruikt het RIVM persoonsgegevens in een centraal registratiesysteem?

Het RIVM heeft de persoonsgegevens nodig om het effect van het vaccinatieprogramma voortdurend te meten. Op deze manier kan het RIVM

- tijdig maatregelen nemen bij ernstige bijwerkingen of bij andere problemen;
- bijhouden hoeveel mensen in Nederland gevaccineerd zijn;
- de werking en veiligheid van de vaccins controleren;
- uitnodigingen en herinneringen voor vaccinatie versturen.

Als een infectieziekte uitbreekt, is het heel belangrijk om te weten hoeveel mensen door vaccinatie al beschermd zijn. Aan de hand daarvan kun je bepalen hoe groot de kans is dat niet gevaccineerde mensen ziek worden en of speciale overheidsmaatregelen nodig zijn.

3. Wat staat er in de wet over het gebruik van uw gegevens

iemand een bijwerking meldt, kan Lareb, met toestemming van de melder, vaccinatiegegevens opvragen bij het RIVM. Dit zijn de volgende gegevens:

- Vaccinatiegegevens eerste en tweede prik;
- BSN
- Naam, adres, woonplaats
- Geboortedatum
- Geslacht

Op grond van wet- en regelgeving of als gevolg van een rechtszaak is het mogelijk dat uw gegevens uit het CIMS vrijgegeven moeten worden.

De Inspectie voor de Gezondheidszorg en Jeugd kan op basis van haar wettelijke taken gegevens opvragen.

De gegevens kunnen op termijn gebruikt worden voor wetenschappelijk onderzoek. De onderzoekers krijgen dan uitsluitend *gepseudonimiseerde* informatie, dus zonder Burgerservicenummer, naam, adres of geboortedatum. Onderzoekers hoeven hiervoor geen toestemming aan u te vragen, omdat deze gegevens niet meer naar u te herleiden zijn. Als zij wel persoonlijke informatie nodig hebben voor het onderzoek, wordt daar altijd toestemming voor gevraagd.

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign

Wat wil het RIVM van u weten?

- Uw geboortedatum
- Uw burgerservicenummer
- Uw voornaam en achternaam
- Uw adres
- De datum en plaats van uw vaccinatie
- De naam van het vaccin en het nummer

Wat moet u doen?
Als u via de computer een afspraak maakt, krijgt u een vraag of u het goed vindt dat we uw gegevens bewaren. U kunt ja of nee invullen.
Als u belt, vragen wij dit.
Als u niet wilt dat het RIVM uw gegevens bewaart, krijgt u wel gewoon de vaccinatie.

Bewaren van uw gegevens
Het RIVM bewaart uw gegevens 20 jaar. Dit staat zo in de wet. Alleen mensen die het vaccinatieprogramma uitvoeren, kunnen uw gegevens bekijken. Ook onderzoekers kunnen gegevens bekijken, maar dan alleen anoniem. Zij zien dus geen privé-gegevens van u.

U kunt ook later nog zeggen dat u niet meer wilt dat het RIVM uw gegevens bewaart. Ga dan naar **mijn.rivm.nl/vaccinaties**. U heeft uw DigiD nodig.

Boosters 15 jan 2021

Experimental: Booster vaccination of Phase 1 participants with BNT162b2 at a dose of 30 µg	Biological: BNT162b2 Intramuscular injection
Experimental: Booster vaccination of Phase 3 participants with BNT162b2 at a dose of 30 µg	Biological: BNT162b2 Intramuscular injection
Experimental: Booster vaccination of Phase 3 participants with BNT162b2SA at a dose of 30 µg	Biological: BNT162b2SA Intramuscular injection
Experimental: Vaccination of BNT162b2-naive participants with BNT162b2SA at a dose of 30 µg	Biological: BNT162b2SA Intramuscular injection
Experimental: Booster and further vaccination of Phase 3 participants with BNT162b2SA at a dose of 30 µg	Biological: BNT162b2SA Intramuscular injection
Experimental: Booster vaccination of Phase 3 participants with BNT162b2 at a dose of 5 µg	Biological: BNT162b2 Intramuscular injection
Experimental: Booster vaccination of Phase 3 participants with BNT162b2 at a dose of 10 µg	Biological: BNT162b2 Intramuscular injection

Pfizer studies Covid-19 booster dose with pneumococcal shot

25 May 2021 (Last Updated October 21st, 2021 10:17)

Pfizer starts a study of co-administration of third dose Covid-19 vaccine followed by pneumococcal vaccine candidate in elderly.

The first batch of the mRNA required for the clinical trial has been produced at BioNTech's facility in Mainz, Germany. Subject to regulatory approvals, Pfizer and BioNTech will initiate clinical studies next month.

According to real-world data reported by the Israeli Ministry of Health, vaccine efficacy to prevent infection and symptomatic disease was observed to decline six months after a two-dose vaccination. The vaccine preserved efficacy in preventing serious illness.

This data is in line with an ongoing analysis in the Phase III study conducted by the companies.

In a statement, BioNTech said: "That is why we have said, and we continue to believe that it is likely, based on the totality of the data we have to date, that a third dose may be needed within six to 12 months after full vaccination."

This May, Pfizer commenced a new study analysing the co-administration of a booster dose of its Covid-19 vaccine followed by its 20-valent pneumococcal conjugate vaccine (20vPnC) candidate in adults aged 65 years and above.

https://www.clinicaltrialsarena.com/news/pfizer-biontech-booster-vaccine/

Fda 'approval' 23 aug 2021

Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 11, 2021

Progress Report Submission: September 30, 2021

Interim Report 1 Submission: March 31, 2022

Interim Report 2 Submission: September 30, 2022

Interim Report 3 Submission: March 31, 2023

Interim Report 4 Submission: September 30, 2023

Interim Report 5 Submission: March 31, 2024

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

6. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Study	Purpose of the study
C4591001	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.

II.C.2. Other Studies in Post-Authorisation Development Plan

Study	Purpose of the study
C4591007	Dose selection. Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 18-25 years of age. Efficacy if sufficient cases accrue. (Study in healthy children and adolescents 5 to <12 years of age).
C4591011	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.
C4591012	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.
C4591010	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.
C4591015	Clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine. Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women.
C4591014	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified.
BNT162-01 Cohort 13	To assess potentially protective immune responses in immunocompromised adults.
C4591018	Safety, immunogenicity over 12 months; description of COVID-19 cases; rheumatoid arthritis activity by Clinical Disease Activity Index; N-antigen antibodies for detection of asymptomatic infection.
C4591024	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals; description of COVID-19 cases; N-antigen antibodies for detection of asymptomatic infection.
ACCESS/ VAC4EU	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.
Co-administration study with seasonal influenza vaccine	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.
C4591023	Dose selection. Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age. Efficacy if sufficient cases accrue. [Study in healthy toddlers, infants and children (0 to <5 years of age)].

QR code →

→

→

QR code →

III.2 - Additional pharmacovigilance activities

Continuation of safety surveillance from **ongoing clinical trials** should be a priority and included as additional pharmacovigilance activities. Protocol review of long-term follow-up should be performed early in the RMP assessment, before the Opinion, acknowledging that changes at that stage might be limited in scope. The final safety results from pivotal trials are expected to be submitted for assessment.

Traceability using the provision of vaccination cards (one for each vaccinee) and of stickers 2D-barcoded and human readable with brand name and batch numbers to the vaccinators (two for each dose) are considered useful for pharmacovigilance needs, acknowledging that the circumstances in each Member State for vaccination might not allow their optimal use in all cases. The use of such tools for traceability should be described in this section of the RMP.

The vaccination card would typically contain:

- Placeholder space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Placeholder space for due date and actual date of first and subsequent doses, and associated batch/lot number (if vaccine requires two or more doses);
- Reminder to retain the card and bring to the appointment for the second and subsequent doses of the vaccine (if vaccine requires two or more doses);
- Optional QR code that links to the MAH website with additional information on product use;
- Adverse event reporting information. The importance of including brand name and batch numbers with every ADR report is even higher if formulations including additional strains are approved for use; this information should be highlighted if applicable.

Recording of brand name and batch numbers information using electronic tools should be facilitated by the inclusion of a 2D bar code on the traceability stickers containing both printed and a 2D-code encoding brand name, expiry date, and batch number[11].

Updated traceability tools are considered paramount for the post-approval monitoring and should be in place at the launch of a new formulation including changed/additional strains, to ensure that ADRs received can be traced to the original formulation vs the updated ones.

Heterologe vaccinatie

In enkele studies is heterologe boostervaccinatie onderzocht, dat wil zeggen, een booster met een vaccin van een andere producent of een ander type vaccin dan de primaire vaccinatieserie. De immuunrespons na booster toont een sterke toename van bindende en neutraliserende antistoffen voor verschillende combinaties van de Pfizer-, Moderna- en Janssenvaccins, waarbij alleen de homologe combinatie van een primair Janssenvaccin gevolgd door een Janssenvaccin als booster tot lagere niveaus van antistoffen leidde dan de andere combinaties.[27,29] Een studie uit het VK rapporteert eveneens de meeste toename van antistoffen na een Pfizer- of Modernabooster, ongeacht primaire vaccinatie met het Pfizer-, Moderna- of AstraZenecavaccin.[30] Hoewel heterologe toepassing van de vaccins van Moderna en Pfizer niet is geregistreerd, lijkt een booster met deze mRNA-vaccins het meest effectief, ongeacht welk vaccin er in de primaire vaccinatiereeks is gegeven.

Bijwerkingen

In de tot nu toe gepubliceerde studies verschillen de reactogeniciteit en veiligheid van een homologe boosterdosis van het Pfizervaccin niet wezenlijk van die na de tweede dosis.[23,31] Hetzelfde geldt voor de studies naar een homologe booster met het Modernavaccin.[22,31] In vergelijking met homologe boostervaccinatie werden ook na heterologe boostervaccinatie in twee trials[27,29] en een praktijkstudie[31] voor de verschillende combinaties van Pfizer-, Moderna- en Janssenvaccins geen belangrijke verschillen in bijwerkingen gerapporteerd. Ook na primaire AstraZenecavaccinatie werden met een heterologe booster geen belangrijke verschillen in bijwerkingen gerapporteerd.[30]

Huidige epidemiologische situatie

Het aantal SARS-CoV-2-infecties en COVID-19-gerelateerde ziekenhuisopnames in Nederland neemt toe sinds het meer loslaten van de maatregelen, eind september, en mogelijk ook door het seizoenseffect. Ook in verpleeghuizen wordt een sterke stijging gezien van het aantal infecties. De verwachting is dat de infectiedruk nog verder zal toenemen in de komende maanden. Een boosteraanbod zal geen direct effect hebben op de COVID-19-gerelateerde ziekenhuisopnames onder niet-gevaccineerden. Volledige vaccinatie beschermt momenteel voor meer dan 90% tegen ziekenhuisopnames in de meeste groepen, maar niet 100%.[11] Bij toenemende viruscirculatie zal daarom onvermijdelijk het absolute aantal ziekenhuisopnames onder gevaccineerden stijgen, ook bij gelijkblijvende bescherming. Voor oudere gevaccineerden, bij wie de bescherming wat minder is dan bij mensen onder 60 jaar, is de verwachting dat boostervaccinatie de bescherming tegen ernstige ziekte verder verhoogt.

korea

older who are scheduled for the vaccination. COMIRNATY will be administered according to the "Dosage and Administration" of the approved labeling. There is no visit or activity mandated by this study. The investigator will collect data from the subject's medical records and patient (subject) report outcome (PRO), and record the information on each subject's case report form (CRF).

About 3000 subjects will be enrolled in several centers in this study. Pfizer Pharmaceuticals Korea will conclude a post-marketing surveillance agreement with an investigator site before performing the study. Investigators at the institution that sign the agreement should consecutively prepare the CRFs from the subjects who this vaccine was administered to first after the start date of the study.

Each investigator will sequentially enroll all subjects to whom COMIRNATY is prescribed for the first time according to the local product document and who agree to participate in this study by signing the data privacy statement used in place of the informed consent form until the total requested cases per center are collected for this study.

An electronic diary will be used in this study to collect adverse events that occur after injection. Follow-up exams will be carried out from after the first injection to before the second injection, and from after the second injection to 28 days after the second injection. For the follow-up adverse event CRF, either an application using the mobile phones of subjects or entry on a paper questionnaire may be selected. The CRF will be filled out every day after the first and second injections. If an application is used, it is automatically sent as an eCRF. If a paper questionnaire is used, the questionnaire filled out after the first injection is collected at the time of the visit for the second injection and 28 days after the second injection by mail.

To promote the collection of adverse events after injection, a reminder may be given by phone about entering the information and the collection of the CRF to subjects who gave consent beforehand.

Safety is the primary interest of this study, which will be assessed based on adverse events (AEs) that occur during 28days from the first and the last dose of COMIRNATY.

Study Design

Go to

Study Type :	Observational
Estimated Enrollment :	3000 participants
Observational Model:	Case-Only
Time Perspective:	Prospective
Official Title:	A Prospective, Single-arm, Open-label, Non-interventional, Multicenter to Assess the Safety of COMIRNATY in Domestic Post-marketing Surveillance
Estimated Study Start Date :	September 30, 2021
Estimated Primary Completion Date :	March 4, 2027
Estimated Study Completion Date :	March 4, 2027

Groups and Cohorts

Go to

Group/Cohort	Intervention/treatment
Comirnaty	Biological: Comirnaty

Pfizer – FDA

Jackson told *The BMJ* it was the first time she had been fired in her 20 year career in research.

Concerns raised

In her 25 September email to the FDA Jackson wrote that Ventavia had enrolled more than 1000 participants at three sites. The full trial (registered under NCT04368728) enrolled around 44 000 participants across 153 sites that included numerous commercial companies and academic centres. She then listed a dozen concerns she had witnessed, including:

- Participants placed in a hallway after injection and not being monitored by clinical staff
- Lack of timely follow-up of patients who experienced adverse events
- Protocol deviations not being reported
- Vaccines not being stored at proper temperatures
- Mislabelled laboratory specimens, and
- Targeting of Ventavia staff for reporting these types of problems.

Within hours Jackson received an email from the FDA thanking her for her concerns and notifying her that the FDA could not comment on any investigation that might result. A few days later Jackson received a call from an FDA inspector to discuss her report but was told that no further information could be provided. She heard nothing further in relation to her report.

5.5 Purchaser Acknowledgement.

Purchaser acknowledges that the Vaccine and materials related to the Vaccine, and their components and constituent materials are being rapidly developed due to the emergency circumstances of the COVID-19 pandemic and will continue to be studied after provision of the Vaccine to Purchaser under this Agreement. Purchaser further acknowledges that the long-term effects and efficacy of the Vaccine are not currently known and that there may be adverse effects of the Vaccine that are not currently known. Further, to the extent applicable, Purchaser acknowledges that the Product shall not be serialized.

536/2014

Klinische proeven op minderjarigen

1. Een klinische proef op minderjarigen mag alleen worden uitgevoerd als behalve aan de voorwaarden in artikel 28 ook aan alle volgende voorwaarden wordt voldaan:

a) de wettelijke vertegenwoordiger heeft zijn of haar geïnformeerde toestemming gegeven;

b) de minderjarigen hebben de in artikel 29, lid 2, bedoelde informatie op een op hun leeftijd en geestelijke rijpheid afgestemde wijze gekregen van de onderzoekers of de leden van het onderzoeksteam die opgeleid zijn voor of ervaring hebben met het werken met kinderen;

c) de onderzoeker respecteert de uitdrukkelijke wens van een minderjarige die zich een mening kan vormen en de in artikel 29, lid 2, bedoelde informatie kan beoordelen, om op enig moment niet of niet langer aan de klinische proef deel te nemen;

d) er worden geen aansporingen of financiële prikkels gegeven aan de proefpersoon of aan zijn of haar wettelijke vertegenwoordiger, afgezien van een vergoeding voor onkosten en gederfde inkomsten die rechtstreeks verband houden met de deelname aan de klinische proef;

e) de klinische proef is bedoeld om onderzoek te doen naar behandelingen van een medische aandoening die alleen voorkomt bij minderjarigen of de klinische proef is essentieel met betrekking tot minderjarigen voor de validering van gegevens die in klinische proeven bij personen die in staat zijn geïnformeerde toestemming te geven of met andere onderzoeksmethoden zijn verkregen;

f) de klinische proef houdt direct verband met een medische aandoening waaraan de minderjarige lijdt of is van zodanige aard dat zij uitsluitend op minderjarigen kan worden uitgevoerd;

g) er zijn wetenschappelijke redenen om te verwachten dat de deelname aan de klinische proef:

   i) een voordeel voor de betrokken minderjarige zal opleveren dat groter is dan de risico's en lasten, of

   ii) enig voordeel zal opleveren voor de populatie waarvoor de betrokken minderjarige representatief is en slechts een minimaal risico en een minimale belasting inhoudt in vergelijking met de standaardbehandeling van de aandoening van de minderjarige.

2. De minderjarige neemt op een op zijn leeftijd en geestelijke rijpheid afgestemde wijze deel aan de geïnformeerde toestemmingsprocedure.

3. Wanneer de minderjarige in de loop van de klinische proef volgens het recht van de betrokken lidstaat de leeftijd bereikt waarop hij juridisch gezien zijn geïnformeerde toestemming kan geven, moet diens geïnformeerde toestemming worden verkregen vooraleer die proefpersoon zijn deelname aan de klinische proef kan verderzetten.

NL wet

Regeling van de Minister van Infrastructuur en Waterstaat van 28 maart 2020, nr. IENW/BSK-2020/57427, houdende spoedmaatregelen met betrekking tot gentherapie ter bestrijding van COVID-19 (Tijdelijke regeling afwijkende behandeling vergunningaanvragen gentherapie in verband met bestrijding COVID-19)

De Minister van Infrastructuur en Waterstaat,

Handelende in overeenstemming met de Minister van Volksgezondheid, Welzijn en Sport;

Gelet op artikel 9.2.2.6 in samenhang met de artikelen 9.2.2.1 en 9.2.2.3 van de Wet milieubeheer;

BESLUIT:

Artikel 1

In deze regeling wordt verstaan onder:

– *Besluit:* Besluit genetisch gemodificeerde organismen milieubeheer 2013;

– *COVID-19:* Coronavirus SARS-CoV-2;

– *genetisch gemodificeerd organisme:* genetisch gemodificeerd organisme als bedoeld in artikel 1.1, eerste lid, van het Besluit;

– *Minister:* Minister van Infrastructuur en Waterstaat.

Artikel 2

1. Afdeling 3.4 van de Algemene wet bestuursrecht, afdeling 13.2 van de Wet milieubeheer en artikel 3.10 van het Besluit zijn niet van toepassing op de voorbereiding van een aanvraag voor een vergunning, als bedoeld in artikel 3.2, eerste lid, van het Besluit, voor de toepassing van medicinale

regels ggo gelden niet voor klinisch onderzoek COVID-19

Op 17 juli 2020 heeft de Europese Commissie een Verordening gepubliceerd welke een dag later, op 18 juli 2020, van kracht is geworden. Door deze Verordening 2020/1043 zijn delen van de ggo-regelgeving buiten werking gesteld indien sprake is van klinisch onderzoek voor COVID-19. Zo is er geen ggo-vergunning nodig voor klinisch onderzoek naar curatieve of preventieve behandeling van COVID-19. Als gevolg van de Verordening 2020/1043 is de Nederlandse “Tijdelijke regeling afwijkende behandeling vergunningaanvragen gentherapie in verband met bestrijding COVID-19” buiten werking gesteld.

Staatscourant van het Koninkrijk der Nederlanden

Datum publicatie	Organisatie	Jaargang en nummer	Rubriek	Datum ondertekening
14-12-2020 09:00	Ministerie van Infrastructuur en Waterstaat	Staatscourant 2020, 63350	Besluiten van algemene strekking	11-12-2020

Regeling van de Minister van Infrastructuur en Waterstaat van 11 december 2020, nr. IENW/BSK-2020/231778 tot wijziging van de Regeling genetisch gemodificeerde organismen milieubeheer 2013 (vervallen onderscheid II-k en II-v en wijziging procedure gentherapie)

De Minister van Infrastructuur en Waterstaat,

Gelet op de artikelen 2.2, eerste lid, 3.4 eerste lid, 3.24 eerste lid, en 3.25, derde lid, van het Besluit genetisch gemodificeerde organismen milieubeheer 2013;

BESLUIT:

ARTIKEL I

De Regeling genetisch gemodificeerde organismen milieubeheer 2013 wordt als volgt gewijzigd:

A

Artikel 17 wordt als volgt gewijzigd:

(hierna: MRB) van de aangevraagde activiteiten met ggo's en publieke consultatie van de ontwerpbeschikking. De procedure wordt toegepast voor gemodificeerde gewassen en bij gentherapie. Het Besluit ggo houdt rekening met de maximale termijnen die ten behoeve van een Europese consultatieronde i richtlijn 2001/18 zijn opgenomen.

2.3 Ontwikkelingen in de praktijk

a. Onderscheid II-k en II-v

De verduidelijking van de criteria die tot een inschaling op II-v moeten leiden door aanpassing van de Regeling ggo heeft weliswaar een verbetering voor de gebruikers gebracht – met een reductie van het aantal inschalingen op II-v – maar zij bleven in de praktijk moeite houden met het onderscheid tussen II-k en II- en het maken van de juiste keuze; II-k of II-v.

b. Verminderen procedurelast gentherapie

De afgelopen jaren is met toepassing van gentherapie veel ervaring en kennis opgedaan, met name als het gaat om de veiligheid van bepaalde, al vaak toegepaste 'platforms' waarmee de feitelijke therapeutica worden gemaakt. Deze platforms bestaan uit ongevaarlijk gemaakte Adeno-associated dependoparvovirus A of B (hierna: AAV) virussen en buiten het lichaam gemodificeerde menselijke cellen.

2.4 Advisering COGEM

De COGEM-adviezen die voor het wijzigingsbesluit zijn gebruikt, werken ook door in deze wijzigingsregeling. Zie daarom verder paragraaf 2.4 van de nota van toelichting bij het wijzigingsbesluit.

Mede op grond van de hiervoor genoemde COGEM-adviezen zal het gebruik van zowel AAV-vectoren als *ex-vivo* getransduceerde humane cellen in klinische studies toegestaan worden via een vergunning onder vaste voorwaarden zoals bedoeld in paragraaf 3.3.2 van het Besluit ggo.

2.5 Wijziging van de Regeling ggo

a. Onderscheid II-k en II-v

Van Nieuwenhuizen versnelt vergunningprocedure gentherapie

Nieuwsbericht | 23-12-2020 | 13:52

Bedrijven en wetenschappelijke instellingen kunnen vanaf nu sneller starten met klinisch onderzoek met medicijnen en vaccins met genetisch gemodificeerde organismen (ggo's). Minister Van Nieuwenhuizen (Infrastructuur en Waterstaat) heeft de doorlooptijd van de verplichte vergunningprocedure voor veel van dit type onderzoek verkort van 120 dagen tot maximaal 56 dagen. Dat is belangrijk omdat op deze manier sneller nieuwe behandelmethoden kunnen worden ontwikkeld om verschillende ziektes en aandoeningen bij mensen te bestrijden.

> "
>
> Minister Van Nieuwenhuizen: "Mooi dat we er samen met alle betrokken partijen voor hebben kunnen zorgen dat onderzoek naar de inzet van nieuwe behandelingen sneller kan starten. Met 56 dagen behoort Nederland tot de top, zonder in te boeten op de

COGEM

Dank voor de toelichting. De COGEM is echter niet de juiste instantie om je vragen te beantwoorden. Je vragen lijken meer op het terrein van VWS te liggen:

Ja, dit vaccin valt onder gentherapie. En gentherapie is altijd vergunningplichtig, waarbij de risico beoordeeld worden. Hierbij moet een onderscheid gemaakt worden tussen: 1) klinische studies waarbij de veiligheid en effectiviteit van de gentherapie worden onderzocht op beperkte groepen patiënten of proefpersonen, en 2) zogenaamde markttoelating waarbij het als regulier geneesmiddel, therapie of vaccin aan alle patiënten of personen kan worden toegediend.

COGEM takes a positive view of the emergency procedure introduced in the Netherlands for speeding up the authorisation of COVID-19 clinical trials to within 28 days.[6] According to COGEM this is sufficient to prevent any significant hold-ups to the development of a GM vaccine or medicine. COGEM therefore sees no reason to take drastic measures such as those proposed by the European Commission. COGEM is of the opinion that from the viewpoint of human and environmental safety a generic setting aside of the GMO legislation and the authorisation of GMOs without a prior environmental risk assessment is irresponsible and disproportional.

Yours sincerely,

EU 2001/18

Artikel 2

Definities

In deze richtlijn wordt verstaan onder:

1. „organisme": een biologische entiteit met het vermogen tot replicatie of tot overdracht van genetisch materiaal;

2. „genetisch gemodificeerd organisme (GGO)": een organisme, met uitzondering van menselijke wezens, waarvan het genetische materiaal veranderd is op een wijze welke van nature door voortplanting en/of natuurlijke recombinatie niet mogelijk is.

Volgens deze definitie:

a) vindt in elk geval genetische modificatie plaats indien een van de in bijlage I A, deel 1, genoemde technieken wordt toegepast;

b) worden de in de bijlage I A, deel 2, genoemde technieken niet beschouwd als technieken die tot genetische modificatie leiden;

IN ARTIKEL 2, LID 2, BEDOELDE TECHNIEKEN

DEEL 1

De in artikel 2, lid 2, onder a), bedoelde genetische modificatietechnieken zijn onder andere:

1. recombinant-nucleïnezuurtechnieken waarbij nieuwe combinaties van genetisch materiaal worden gevormd door de invoeging van ongeacht op welke wijze buiten een organisme vervaardigde nucleïnezuurmoleculen in een virus, bacterieel plasmide of ander vectorsysteem en de opneming daarvan in een gastheerorganisme waarin ze van nature niet voorkomen maar waarin ze blijvend vermenigvuldigd kunnen worden;

2. technieken met rechtstreekse inbrenging in een organisme van erfelijk materiaal dat buiten het organisme vervaardigd is, waaronder micro-injectie, macro-injectie en micro-inkapseling;

3. celfusie (met inbegrip van protoplastfusie) of hybridisatietechnieken waarbij levende cellen met nieuwe combinaties van erfelijk genetisch materiaal worden gevormd door de fusie van twee of meer cellen met gebruikmaking van methoden die van nature niet voorkomen.

EU 2003/63

c) Toediening van tevoren bereide vectoren waarin (profylactisch, diagnostisch of therapeutisch) genetisch materiaal is ingebracht

De werkzame stof is een partij tevoren bereide vectoren.

Aanvullende stappen kunnen worden uitgevoerd om het eindproduct te verkrijgen. Dit type geneesmiddel is bestemd om aan diverse patiënten te worden toegediend.

De overdracht van genetisch materiaal kan plaatsvinden door rechtstreekse inbrenging van de tevoren bereide vector bij de ontvangers.

1.2. Specifieke eisen ten aanzien van module 3

Geneesmiddelen voor gentherapie omvatten:

- naakt nucleïnezuur;
- gecomplexeerd nucleïnezuur of niet-virale vectoren;
- virale vectoren;

2009/120

4.2. Specific requirements for gene therapy medicinal products

In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

4.2.1. *Pharmacology*

(a) *In vitro* and *in vivo* studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic "proof of concept" studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2. *Pharmacokinetics*

(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.

(b) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. *Toxicology*

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the *in vivo* effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.

(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant *in vivo/in vitro* models.

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

(g) *Additional toxicity studies*

— Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.

— Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

2009/120 (EUR)

Definities

Geneesmiddelen voor gentherapie

Een geneesmiddel voor gentherapie is een biologisch geneesmiddel met de volgende eigenschappen:

- bevat een actief bestanddeel dat een gerecombineerd nucleïnezuur bevat of vormt, en wordt toegediend aan personen met het oog op het regelen, herstellen, vervangen, toevoegen of verwijderen van een genetische sequentie;
- het therapeutische, profylactische of diagnostische effect ervan hangt rechtstreeks af van de gerecombineerde nucleïnezuursequentie die het bevat of van het genexpressieproduct van deze sequentie.

Vaccins tegen besmettelijke ziekten vallen niet onder de geneesmiddelen voor gentherapie.

https://www.fagg.be/nl/definities

Table 2

Inclusion/exclusion criteria in European Union.

Advanced Therapy medicinal products				
Product category	**Active substance**	**Purpose**	**Inclusions**	**Exclusions**
Gene therapy medicinal products (GTMPs)	Recombinant nucleic acid of biological origin	Administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence Therapeutic, prophylactic, or diagnostic effects that relate directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence	• Plasmids DNA • Viral vectors • Genetically engineered microorganisms • Human gene–editing technology • Patient-derived cellular gene therapy products	• Non-biological products (e.g., chemical synthetized nucleic acids) • Vaccines against infectious diseases
Somatic cell therapy medicinal products (SCTMPs)	Cells or tissues that have been subject to substantial manipulation or not intended to be used for the same essential function(s)	Treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic actions of its cells or tissues	• Products containing or consisting of animal cells or tissues • Cancer immunotherapies • Other autologous and allogeneic cells	• Products containing or consisting exclusively of non-viable cells or tissues and which do not act principally by pharmacological.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6728416/

Table 3

Inclusion/exclusion criteria in United States.

Cell and gene therapy products				
Product category	**Definition**	**Purpose**	**Examples**	**Exclusions**
Human gene therapy	Administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use	Prevention, treatment, or cure of a disease or condition of human beings	• Plasmid DNA • Viral vectors • Genetically engineered microorganisms • Human gene–editing technology • Patient-derived cellular gene therapy products	• Non-biological products (e.g., chemical synthetized nucleic acids) • Products that are destined for the treatment or prophylaxis of infectious diseases
Somatic cell therapy	Autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo*	Therapeutic, diagnostic, or preventive purposes	• Cancer vaccines • Cellular immunotherapies • Other types of both autologous and allogeneic cells • Xenogeneic living cells • Stem cells and stem cell–derived products • Gene therapy–modified cells	HCT/Ps under section 361 of the PHSA

CAT 15-17 july 2020

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission's initiative on GMO requirements for medicines used for treatment/prevention of COVID-19

Scope: oral feedback from the European Commission's representative

Action: for information

The European Commission representative presented to CAT at its June 2020 meeting the draft Regulation on the application of certain aspect of the GMO legislation to medicinal product against COVID-19. The explanatory memorandum of the Commission Proposal also includes the Commission's interpretation on the interplay between the GMO and medicinal product legislation in case of medicines used under compassionate use authorisation.

7.4.2. Regulatory status of RNA products in the context of vaccines against COVID-19

Scope: European Commission's feedback and possible implications for ATMPs

Action: for information

7.4.3. Inspection of manufacturers of viral vectors used as starting materials for genetically modified cells

Scope: updates on the inspection of manufacturers of viral vectors used as starting materials for genetically modified cells

Action: for discussion

7.4.4. Viral vectors used in the production of genetically modified cells - principles of GMP

CAT: Martina Schüssler-Lenz

Scope: call for a drafting group to define *'Principles of GMP'*

CAT 2-4 dec 2020

Note: information on the multistakeholder webinar can be found here: https://www.ema.europa.eu/en/events/multi-stakeholder-webinar-support-implementation-medical-devices-regulation-drug-device-combinations

7.4.5. Regulatory status of RNA products

CAT: Marcos Timón, Violaine Closson-Carella, Egbert Flory, Hans Ovelgönne

Scope: reflection on the consequences for ATMPs of the Commission's feedback on the regulatory status of RNA products in the context of vaccines against COVID-19

Action: for discussion

Note: further to a discussion in July 2020 (see CAT minutes of the July CAT meeting, point 7.4.2), a brainstorming meeting took place (between CAT secretariat and CAT members) to reflect upon the consequence for the ATMP field of the Commission's feedback on a question from EMA on the status of RNA vaccines that are prepared fully synthetically. Feedback from the brainstorming meeting will be provided.

7.5. Cooperation with international regulators

7.5.1. ATMP cluster teleconference with FDA-USA, Health Canada and PMDA-Japan

CAT: Martina Schüssler-Lenz

Scope: feedback on the teleconference to took place on 12 November 2020

Action: for information

CAT 17-18 march 2021

CAT drafting group members: Heli Suila, Ivana Haunerova, Marcos Timón, Violaine Closson Carella

Scope: draft Q&A on principles for GMP

Action: for discussion

Note: CAT members are requested to send comments by 17 March 2021

7.4.2. Product information for medicinal products that contain or consist of modified viruses

Scope: wording agreed regarding GMO aspects (in the context of Covid-19 vaccines): consequences for the SmPC of the gene therapy products that contain or consist of viral vectors

Action: for discussion

7.4.3. Questions and Answers related to the assessment of similarity for ATMPs in the context of the orphan legislation

CAT members and experts: Claire Beuneu, Barbara Bonamassa, Violaine Closson-Carella, Niamh Curran, Rune Kjeken, Ilona Reischl, Heli Suila, Marja van der Bovenkamp

Scope: revised Questions and Answers

Action: for discussion

Products/Research

- Liver disease: In 2019, Promethera Biosciences tested a new stem cell treatment for severe liver diseases in the first patient. The clinical trial will be conducted across eight European countries.
- Cancer vaccine: In 2019, researchers in Germany tested an RNA-based vaccine for patients with melanoma.
- Wiskott-Aldrich syndrome: In 2019, researchers from France and England successfully treated a rare genetic disease that causes bleeding, severe and recurrent infections, severe eczema and in some patients autoimmune reactions and the development of cancer.
- Blood disorder: Gene therapy to treat a blood disorder called beta thalassemia that reduces a patient's ability to produce hemoglobin, the protein in red blood cells that contains iron, leading to life-threatening anemia. Approved in 2019.
- Fatal muscle disease: Clinical trials ongoing for gene therapy for X-linked myotubular myopathy, a muscle disease in which patients typically survive only into early childhood.
- Rare form of blindness: Gene therapy for patients with a rare form of inherited blindness called biallelic RPE65 mutation-associated retinal dystrophy. Approved in 2018.
- Lymphoma: Gene therapy to treat a cancer called large B cell lymphoma. Approved in 2018.
- Crohn's disease symptoms: A cell therapy used to treat specific severe symptoms of Crohn's disease. Approved in 2018.
- Leukemia: Gene therapy for patients with B cell lymphoblastic leukemia. Approved in 2018.
- Vein disease: Gene therapy to treat severe cases of veno-occlusive disease, a disorder in which the small veins of the liver become obstructed, in patients who have received a bone marrow transplant. Approved in 2017.
- "Bubble boy" disease: Approved in 2016 to treat ADA Severe Combined Immune Deficiency (ADA-SCID), a disease in children that causes them to be extremely susceptible to infections.
- Eye damage: First stem cell therapy approved in Europe in 2015 to treat physical or chemical burns to the eye.
- Melanoma: A genetically engineered virus used to treat inoperable melanoma. Conditionally approved in Europe in 2015.
- Inability to digest fats: First gene therapy approved in Europe in 2012 to treat lipoprotein lipase deficiency, a rare disease that leaves individuals unable to digest fats and can cause life-threatening pancreatitis.

Regulatory Timeline

2018: European Court of Justice (ECJ) rules that organisms developed through gene editing are genetically modified organisms (GMOs) and are subject to the same regulations as transgenic organisms, rejecting a regulatory exemption or the issuance of a revised directive.

2012: First gene therapy in Europe is approved.

2007: EU Commission Regulation on advanced therapy medicinal products is finalized, which outlines the procedure for gene therapy approval.

2001: Directive on medicinal products for human use is finalized.

2000: EU Charter of Fundamental Rights

1997: Convention on Human Rights and Biomedicine (Oviedo Convention) of the Council of Europe.

https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/eu-therapeutic-stem-cell/

FDA

Gene therapy

From Wikipedia, the free encyclopedia

Gene therapy is a medical field which focuses on the genetic modification of cells to produce a therapeutic effect[1] or the treatment of disease by repairing or reconstructing defective genetic material.[2] The first attempt at modifying human DNA was performed in 1980 by Martin Cline, but the first successful nuclear gene transfer in humans, approved by the National Institutes of Health, was performed in May 1989.[3] The first therapeutic use of gene transfer as well as the first direct insertion of human DNA into the nuclear genome was performed by French Anderson in a trial starting in September 1990. It is thought to be able to cure many genetic disorders or treat them over time.

Between 1989 and December 2018, over 2,900 clinical trials were conducted, with more than half of them in phase I.[4] As of 2017, Spark Therapeutics' Luxturna (RPE65 mutation-induced blindness) and Novartis' Kymriah (Chimeric antigen receptor T cell therapy) are the FDA's first approved gene therapies to enter the market. Since that time, drugs such as Novartis' Zolgensma and Alnylam's Patisiran have also received FDA approval, in addition to other companies' gene therapy drugs. Most of these approaches utilize adeno-associated viruses (AAVs) and lentiviruses for performing gene insertions, *in vivo* and *ex vivo*, respectively. ASO / siRNA approaches such as those conducted by Alnylam and Ionis Pharmaceuticals require non-viral delivery systems, and utilize alternative mechanisms for trafficking to liver cells by way of GalNAc transporters.

The concept of gene therapy is to fix a genetic problem at its source. If, for instance, in an (usually recessively) inherited disease a mutation in a certain gene

ICH

Messenger RNA is considered by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to be gene therapy "even though RNA does not interact with the genome," said Meffen in giving a regulatory overview of the two types of RNA therapies. However, mRNA, which is regulated by the FDA's Center for Biologics Evaluation and Research (CBER) is not yet classified as a regenerative medicine advanced therapy (RMAT). EMA considers mRNA to be an advanced therapy medicinal product (ATMP).

Neither FDA nor EMA consider siRNAs to be gene therapy. "FDA regulates them as a drug, not a biologic, and they are not an ATMP," explained Meffen; siRNA therapies do not have RMAT status. For both types of RNA therapies, sponsors should be aware of the variety of regulatory programs available for rare genetic disorders, she noted.

https://www.raps.org/news-and-articles/news-articles/2020/11/euro-convergence-regulatory-and-c

SEC

authorities in any jurisdiction, and it is possible that none of our product candidates, or any product candidates we may seek to develop in the future, will ever obtain regulatory approval. We have limited experience in filing and supporting the applications necessary to gain marketing approvals and may need to rely on third-party contract research organizations, or CROs, regulatory consultants or collaborators to assist us in this process. To our knowledge, there is no current precedent for an mRNA-based immunotherapy such as the type we are developing being approved for sale by the FDA, European Commission or any other regulatory agency elsewhere in the world. Although we expect to submit BLAs for our mRNA-based product candidates in the United States, and in the European Union, mRNA therapies have been classified as gene therapy medicinal products, other jurisdictions may consider our mRNA-based product candidates to be new drugs, not biologics or gene therapy medicinal products, and require different marketing applications. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the

If we experience delays in obtaining, or if we fail to obtain, approval of any product candidates we may develop, the commercial prospects for those product candidates will be harmed, and our ability to generate revenues will be materially impaired. Additionally, even if we are successful in obtaining marketing approval for product candidates, because our preclinical studies and clinical trials have not been designed with specific commercialization considerations, the commercial prospects for those product candidates could be harmed, and our ability to generate revenues could be materially impaired.

No mRNA immunotherapy has been approved, and none may ever be approved. mRNA drug development has substantial clinical development and regulatory risks due to the novel and unprecedented nature of this new category of therapeutics.

As a potential new category of therapeutics, to our knowledge, no mRNA immunotherapies have been approved to date by the FDA, EMA or other regulatory agency. Successful discovery and development of mRNA-based (and other) immunotherapies by either us or our collaborators is highly uncertain and depends on numerous factors, many of which are beyond our or their control. To date, there has never been a Phase 3 trial for an mRNA-based product or a commercialized mRNA-based product. Our product candidates that appear promising in the early phases of development may fail to advance, experience delays in the clinic or clinical holds, or fail to reach the market for many reasons, including:

- discovery efforts aimed at identifying potential immunotherapies may not be successful;
- nonclinical or preclinical study results may show product candidates to be less effective than desired or have harmful or problematic side effects;
- clinical trial results may show the product candidates to be less effective than expected, including a failure to meet one or more endpoints or have unacceptable side effects or toxicities;
- manufacturing failures or insufficient supply of GMP materials for clinical trials, or higher than expected cost could delay or set back clinical trials, or make our product candidates commercially unattractive;

- the proprietary rights, products and technologies of our competitors may prevent our immunotherapies from being commercialized.

Currently, mRNA is considered a gene therapy product by the FDA. Unlike certain gene therapies that irreversibly alter cell DNA and may cause certain side effects, mRNA-based medicines are designed not to irreversibly change cell DNA. Side effects observed in other gene therapies, however, could negatively impact the perception of immunotherapies despite the differences in mechanism. In addition, because no mRNA-based product has been approved, the regulatory pathway in the United States and may other jurisdictions for approval is uncertain. The pathway for an individualized therapy, such as our iNeST mRNA-based immunotherapy where each patient receives a different combination of mRNAs, remains particularly unsettled. The number and design of the clinical and preclinical studies required for the approval of these types of medicines have not been established, may be different from those required for gene therapy products or therapies that are not individualized or may require safety testing like gene therapy products. Moreover, the length of time necessary to complete clinical trials and submit an application for marketing approval by a regulatory authority varies significantly from one pharmaceutical product to the next and may be difficult to predict.

Our product candidates may not work as intended, may cause undesirable side effects or may have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

As with most biological products, use of our product candidates could be associated with side effects or adverse events which can vary in severity from minor reactions to death and in frequency from infrequent to prevalent. The potential for adverse events is especially acute in the oncology setting, where patients may have advanced disease, have compromised immune and other systems and be receiving numerous other therapies. Undesirable side effects or unacceptable toxicities caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, the EMA or comparable regulatory authorities. Results of our trials could reveal a high and unacceptable severity and prevalence of side effects.

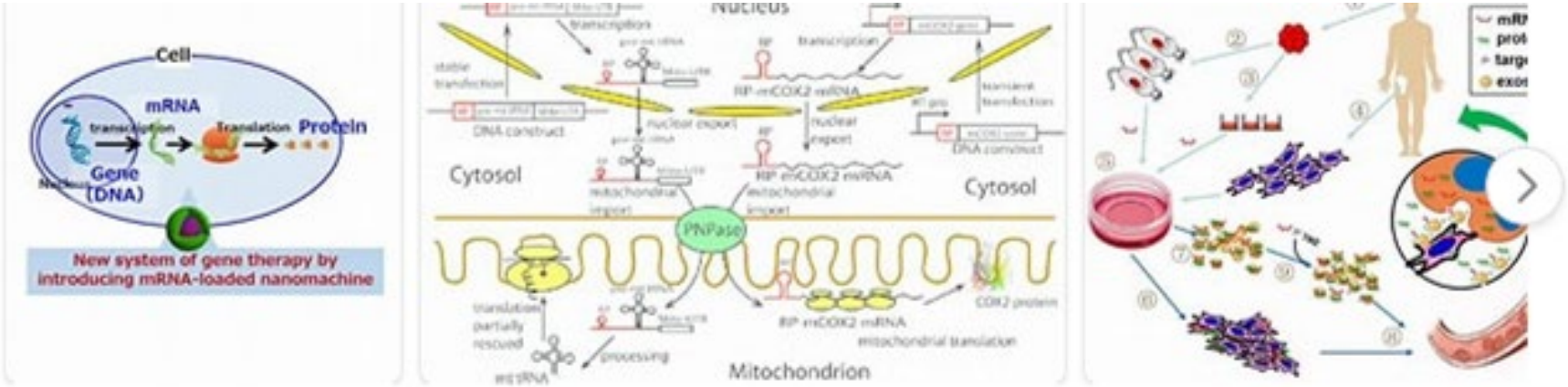
In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can initiate clinical trials or market and sell the product in those countries or jurisdictions.

Regulation and Procedures Governing Approval of Medicinal Products in the European Union

The process governing approval of medicinal products, including biological medicinal products and advanced therapy medicinal products, or ATMPs, which comprise gene therapy products, somatic cell therapy products and tissue-engineered products, in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of pharmaceutical development, nonclinical and clinical studies to establish the safety and efficacy of the medicinal product for each proposed indication. Moreover, an applicant must also demonstrate the ability to manufacture the product to a suitable quality.

The Committee for Advanced Therapies, or CAT, is responsible in conjunction with the CHMP for the evaluation of ATMPs. The CAT is primarily responsible for the scientific evaluation of ATMPs and prepares a draft opinion on the quality, safety and efficacy of each ATMP for which a MAA is submitted. The CAT's opinion is then taken into account by the CHMP when giving its final recommendation regarding the authorization of a product in view of the balance of benefits and risks identified. Although the CAT's draft opinion is submitted to the CHMP for final approval, the CHMP may depart from the draft opinion if it provides detailed scientific justification. The CHMP and CAT are also responsible for providing guidelines on ATMPs and have published numerous guidelines, including specific guidelines on gene therapies and cell therapies. These guidelines, which are not legally binding, provide additional guidance on the factors that the EMA will consider in relation to the development and evaluation of ATMPs and include, inter alia, the preclinical studies required to characterize ATMPs, the manufacturing and control information that should be submitted in a MAA; and post-approval measures required to monitor patients and evaluate the long term efficacy and potential adverse reactions of ATMPs.

Moderna



Moderna describes mRNA products as “gene therapy technology” in its SEC filing. BioNTech’s SEC filing also specifies that in the U.S. and Europe, mRNA therapies are classified as “**gene therapy medicinal products**”. mRNA technology has, since the start, been recognized as a form of gene therapy, but one that doesn’t permanently alter your DNA.

Gen therapie

Home › Life Sciences › Bioprocessing › Chromatography and Purification Solutions for Bioprocessing › Bioprocess Resins › Cell and Gene Therapy Purification Solutions

Cell and Gene Therapy Purification Solutions

‹ Bioprocess Resins

Affinity Chromatography Resins—Antibody Therapeutics

Affinity Resins—Biosimilars and Recombinant Proteins

Hydrophobic Interaction Chromatography

Protein A Chromatography Resins

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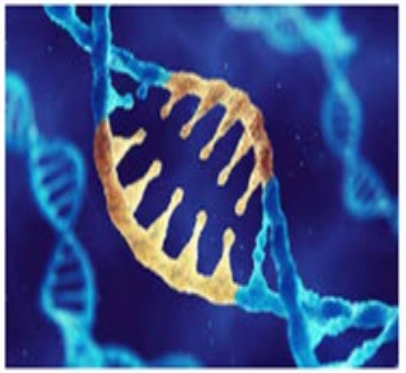
Anion Exchange Resins

Cation Exchange Resins



To support the manufacturing of Cell and Gene Therapies, we have developed innovative chromatography solutions, specifically designed to improve the downstream purification of mRNA and viral vectors such as the Adeno-Associated Virus (AAV), lentivirus, and Adv5.

Request information

Benefit from:

- High selectivity and capacity for the purification of viral vectors and mRNA
- An efficient and robust purification process, from crude material in one step, offering scalability and process consistency
- Significant improvement to the downstream process of viral vectors, by reducing the purification steps and maximizing productivity
- An efficient and scalable solution for the purification of *in vitro* transcribed mRNA

literatuur

Box 4 | mRNA-based passive immunotherapy

Recombinant monoclonal antibodies are rapidly transforming the pharmaceutical market and have become one of the most successful therapeutic classes to treat autoimmune disorders, infectious diseases, osteoporosis, hypercholesterolemia and cancer[188–192]. However, the high cost of protein production and the need for frequent systemic administration pose a major limitation to widespread accessibility. Antibody-gene transfer technologies could potentially overcome these difficulties, as they administer nucleotide sequences encoding monoclonal antibodies to patients, enabling *in vivo* production of properly folded and modified protein therapeutics[193]. Multiple gene therapy vectors have been investigated (for example, viral vectors and plasmid DNA) that bear limitations such as pre-existing host immunity, acquired

Adenovirus Vector

Adenovirus vectors (AdV) constitute very powerful vehicles for gene transfer with applications in vaccination, cancer treatment, and many monogenic and acquired diseases.

From: Adenoviral Vectors for Gene Therapy (Second Edition), 2016

Abstract

With rapid advances in understanding molecular pathogenesis of human diseases in the era of genome sciences and systems biology, it is anticipated that increasing numbers of therapeutic genes or targets will become available for targeted therapies. Despite numerous setbacks, efficacious gene and/or cell-based therapies still hold the great promise to revolutionize the clinical management of human diseases. It is wildly recognized that poor gene delivery is the limiting factor for most *in vivo* gene therapies. There has been a long-lasting interest in using viral vectors, especially adenoviral vectors, to deliver therapeutic genes for the past two decades. Among all currently available viral vectors, adenovirus is the most efficient gene delivery system in a broad range of cell and tissue types. The applications of adenoviral vectors in gene delivery have greatly increased in number and efficiency since their initial development. In fact, among over 2000 gene therapy clinical trials approved worldwide since 1989, a significant portion of the trials have utilized adenoviral vectors. This review aims to provide a comprehensive overview on the characteristics of adenoviral vectors, including adenoviral biology, approaches to engineering adenoviral vectors, and their applications in clinical and preclinical studies with an emphasis in the areas of cancer treatment, vaccination and regenerative medicine. Current challenges and future directions regarding the use

SECTION 2 –INFORMATION ABOUT THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1 Characterisation of the finished investigational medicinal product

a) General information

Description of the finished medicinal product	Cell-based products:	Autologous ☐ Allogeneic ☐ Xenogeneic ☐ If xenogeneic, specify species of origin: ..... Specify type of cells (e.g. hematopoietic stem cells…): .....
	Gene therapy:	In vivo gene therapy ☐ Ex vivo gene therapy[20] ☐
		Viral vector used: Retrovirus ☐ Lentivirus ☐ AAV ☐ Others. Please explain: .....
		Are the vectors used replication competent: Yes ☐ No ☐
	Bacterial-	Please describe species and strain:

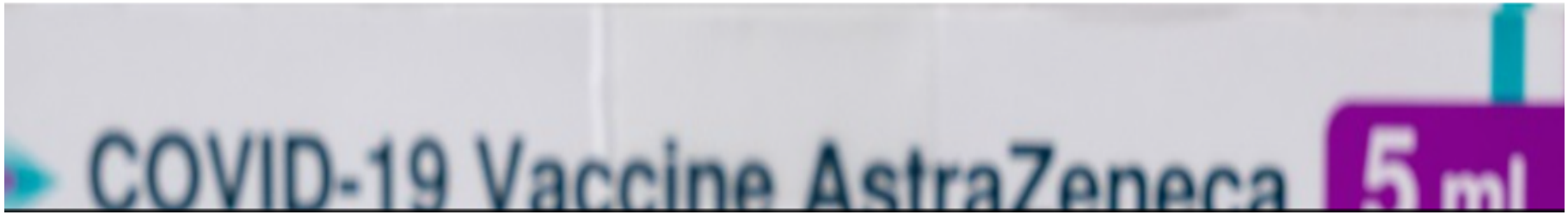
PHARMACEUTICAL TECHNOLOGY

COMMENT

Viral vector shortage is a problem for AZ's and J&J's Covid-19 vaccines, gene therapies

By GlobalData Healthcare | 19 Mar 2021 (Last Updated March 19th, 2021 15:58)

As the latest wave of Covid-19 vaccines—those from AstraZeneca (Oxford, UK) and Johnson and Johnson (New Brunswick, NJ, US)—are approved in the EU and poised for likely approval in the US, the news highlights the lack of manufacturing capacity for viral vectors, a vital step in making these vaccines.



› Hum Gene Ther. 2006 Oct;17(10):1027-35. doi: 10.1089/hum.2006.17.1027.

Synthetic messenger RNA as a tool for gene therapy

Peter M Rabinovich [1], Marina E Komarovskaya, Zhi-Jia Ye, Chihaya Imai, Dario Campana, Erkut Bahceci, Sherman M Weissman

Affiliations + expand

PMID: 17007566 DOI: 10.1089/hum.2006.17.1027

Abstract

Transfection of human cells with DNA in biomedical applications carries the risk of insertional mutagenesis. Transfection with mRNA avoids this problem; however, in vitro production of mRNA, based on preliminary DNA template cloning in special vectors, is a laborious and time-consuming procedure. We report an efficient vectorfree method of mRNA production from polymerase chain reaction-generated DNA templates. For all cell types tested mRNA was transfected more readily than DNA, and its expression was highly uniform in cell populations. Even cell types relatively resistant to transfection with DNA could express transfected mRNA well. The level of mRNA expression could be controlled over a wide range by changing the amount of input RNA. Cells could be efficiently and simultaneously loaded with several different transcripts. To test a potential clinical application of this method, we transfected human T lymphocytes with mRNA encoding a chimeric immune receptor directed against CD19, a surface antigen widely expressed in leukemia and lymphoma. The transfected mRNA conferred powerful cytotoxicity to T cells against CD19+ targets from the same donor. These results demonstrate that this method can be applied to generate autologous T lymphocytes directed toward malignant cells.

Similar articles

Research article | Open Access | Published: 20 October 2010

Intranasal vaccination with messenger RNA as a new approach in gene therapy: Use against tuberculosis

Julio CC Lorenzi, Ana PF Trombone, Carolina D Rocha, Luciana P Almeida, Ricardo L Lousada, Thiago Malardo, Isabela C Fontoura, Renata AM Rossetti, Ana F Gembre, Aristóbolo M Silva, Celio L Silva & Arlete AM Coelho-Castelo

BMC Biotechnology **10**, Article number: 77 (2010) | Cite this article

Abstract

Background

mRNAs are highly versatile, non-toxic molecules that are easy to produce and store, which can allow transient protein expression in all cell types. The safety aspects of mRNA-based treatments in gene therapy make this molecule one of the most promising active components of therapeutic or prophylactic methods. The use of mRNA as strategy for the stimulation of the immune system has been used mainly in current strategies for the cancer treatment but until now no one tested this molecule as vaccine for infectious disease.

Nieuws

Gentherapie tegen de griep

En dan nu voor de allerlaatste keer...

Arjen Dijkgraaf | zondag 25 november 2012

Messenger-RNA kan de basis worden voor een vaccin dat mensen levenslang beschermt tegen alle bekende griepvarianten. En als een nog onbekende variant opduikt, kun je op deze manier in recordtijd ingrijpen. Bij muizen lukt het alvast, schrijven Duitse onderzoekers in Nature Biotechnology.

Het idee is dan om mRNA toe te dienen dat codeert voor virusspecifieke eiwitten. De ontvanger zou die eiwitten dan moeten gaan aanmaken. Als het goed is herkent het immuunsysteem die eiwitten als lichaamsvreemd en maakt er antilichamen tegen aan. En zoals gebruikelijk wordt het recept onthouden, klaar voor gebruik tegen identieke eiwitten die écht aan een virus vastzitten.

Gene Therapy (2020) 27:183–185
https://doi.org/10.1038/s41434-020-0132-1

COMMENT

Nanoparticle-based delivery of self-amplifying RNA

Kenneth Lundstrom[1]

Received: 18 October 2019 / Revised: 12 February 2020 / Accepted: 14 February 2020 / Published online: 28 February 2020

Several RNA viruses possess a genomic RNA replicon, providing a property of RNA self-amplification [1]. In this context, self-amplifying RNA (saRNA) viruses with a single-stranded RNA of positive polarity comprise of alphaviruses and flaviviruses, while measles viruses and rhabdoviruses carrying a negative-strand RNA genome have been engineered as expression vectors. Several studies in animal models have demonstrated that saRNA viral vectors expressing foreign antigens elicit strong immune responses and can further provide protection of immunized animals against challenges with lethal doses of infectious agents and tumor cells [2]. In addition, saRNA viral vectors have been subjected to several clinical trials targeting both infectious diseases and cancer. For example, a Phase III clinical trial in Guinea and Sierra Leone, provided substantial protection against Ebola virus (EBOV) after a single intramuscular injection with a vesicular stomatitis virus-

appropriate to only briefly mention that RNA stability can be improved by engineering of the RNA molecule itself [6]. For instance, engineering of anti-reverse 5′ 7-methylguanosine triphosphate (m7G) Cap analogs (ARCAs) provides more than double RNA transcription efficiency in comparison to conventional cap analogs [7]. Moreover, engineering of the poly(A) tail at the 3′ end of mRNAs has enhanced the stability of RNA [8]. Also, the 5′ and 3′ end untranslated regions have proven important for posttranscriptional regulation of gene expression and might be a target for improvement of mRNA optimization [9]. Finally, chemical modifications of nucleosides such as introducing pseudo-uridine into in vitro transcribed mRNA have been proven to enhance the therapeutic properties of RNA by improving stability and translation [10].

A major factor in achieving success of saRNA-based therapy relates to delivery. Numerous studies in animal

Eur 2001/83

Immunological medicinal product: Any medicinal product consisting of vaccines, toxins, serum

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, sm

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberc

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globu

(b) "allergen product" shall mean any medicinal product which is intended to identify or induce

Definitie vaccin EU 2003/63

For vaccines for human use and by derogation from the provisions of Module 3 on "Active substance(s)", the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.

The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

a) Principles

For the purposes of this Annex:

- Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

- A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

b) Content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on "Quality Data" as delineated in Part I of this Annex:

Active Substance

More Definitions of *Vaccine*

Vaccine means any antigenic preparation approved by the Australian Government and recommended by a government authority for prophylactic use in your occupation to produce immunity to the Human Immunodeficiency Virus.

Sample 1 | Sample 2 | Sample 3 | Based on 14 documents | ☆ Save | Copy

Vaccine means a preparation of killed or attenuated living microorganisms, or fraction thereof, that upon administration stimulates immunity that protects against disease and is approved by the federal food and drug administration as safe and effective and recommended by the advisory committee on immunization practices of the centers for disease control and prevention for administration to children under the age of nineteen years.

Sample 1 | Sample 2 | Sample 3 | Based on 11 documents | ☆ Save | Copy

Vaccine means a specially prepared antigen, which upon administration to a person may result

Sample 1 | Sample 2 | Sample 3 | Based on 10 documents | ☆ Save | Copy

Vaccine means a specially prepared antigen, which upon administration to a person, will result in immunity, or any other definition that is required by applicable law . "Vaccine Administration Fee" means a fee payable to the Participating Pharmacy for administering a Vaccine by the act of injection in accordance with applicable

Sample 1 | Sample 2 | Sample 3 | Based on 10 documents | ☆ Save | Copy

Covid: How long does vaccine based immunity last?

Sebastian Rushworth

Open Access Article

SARS–CoV–2 Spike Impairs DNA Damage Repair and Inhibits V(D)J Recombination In Vitro

by Hui Jiang [1,2,*] and Ya-Fang Mei [2,*]

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Received: 20 August 2021 / Revised: 8 September 2021 / Accepted: 8 October 2021 / Published: 13 October 2021

(This article belongs to the Special Issue SARS-CoV-2 Host Cell Interactions)

Rapid Communication

Spontaneous Abortions and Policies on COVID-19 mRNA Vaccine Use During Pregnancy

Aleisha R. Brock[1], Simon Thornley[2]

Abstract

The use of mRNA vaccines in pregnancy is now generally considered safe for protection against COVID-19 in countries such as New Zealand, USA, and Australia. However, the influential CDC-sponsored article by Shimabukuro et al. (2021) used to support this idea, on closer inspection, provides little assurance, particularly for those exposed in early pregnancy. The study presents falsely reassuring statistics related to the risk of spontaneous abortion in early pregnancy, since the majority of women in the calculation were exposed to the mRNA product after the outcome period was defined (20 weeks' gestation).

In this article, we draw attention to these errors and recalculate the risk of this outcome based on the cohort that was exposed to the vaccine before 20 weeks' gestation. Our re-analysis indicates a cumulative incidence of spontaneous abortion 7 to 8 times higher than the original authors' results ($p < 0.001$) and the typical average for pregnancy loss during this time period. In light of these findings, key policy decisions have been made using unreliable and questionable data. We conclude that the claims made using these data on the safety of exposure of women in early pregnancy to mRNA-based vaccines to prevent COVID-19 are unwarranted and recommend that those policy decisions be revisited.

Correspondence: s.thornley@auckland.ac.nz

Keywords
COVID-19; Pregnancy; Adverse Events; Spontaneous Abortion

Roland Pierik
@RolandPierik

Ik lees nu net bij @chrisklomp dat uit het jaarverslag van Viruswaanzin blijkt dat Willem Engel (@dancalegria) in 2020 via de doneerknop meer dan €300.000 heeft binnengeharkt.... Meer dan €300.000!!!

Translate Tweet

9:40 PM · Aug 25, 2021 · Twitter Web App

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