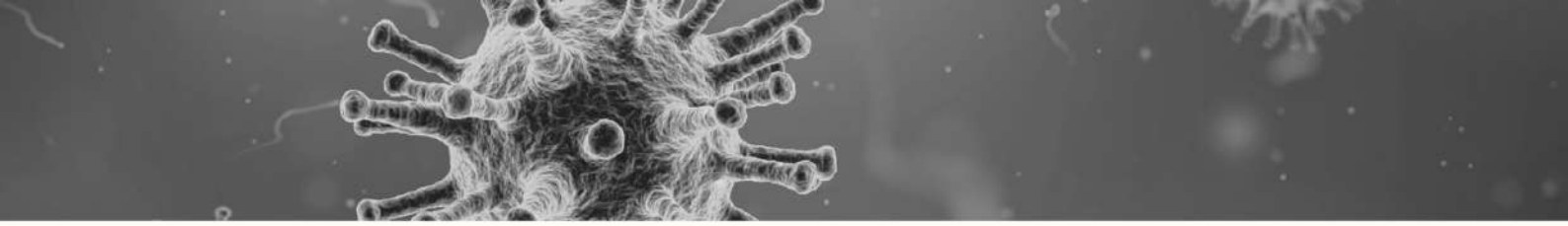

The following images are from private and classified emails exchanged between senior European officials and the Pfizer laboratory.

They relate to COVID-19 and more specifically to Pfizer's vaccine.

We have shared and compiled this information for purely journalistic purposes, as we consider it to be information of public utility.

We disclaim all liability for any misuse of this information.

Subject:	H0005735: Transfer Plan
From:	gudenus@granzer.biz
To:	claudio.facchini@ema.europa.eu
Cc:	vanessa.seguin@ema.europa.eu, covid-19.mrna.vaccine.biontech-5735@ema.europa.eu, gudenus@granzer.biz
Sent:	Wed, 11 Nov 2020 14:50:00 +0100
Expiration:	Sat, 21 Nov 2020 14:50:00 +0100

Secure Reply Sender (Eudralink) | Secure Reply All (Eudralink) | **Email Reply All (non-secure)**

Dear Claudio, please find enclosed the Transfer Plan. We're hapy to discuss it at tomorrow's GMP meeting.
Best wishes,
Rosmarie

Dr. Rosmarie Gudenus | Principal Consultant
Granzer Regulatory Consulting & Services
Kistlerhofstrasse 172 C
D-81379 München
Germany
Phone: +49 89 7806898 14

Attachments (1/1 downloaded)

Filename	Type	Size	Downloaded
INX100434736_AnalyticalMethodTransferBNT162b2-DPMethods.pdf	Portable Document Format File	1388 kb	2020-11-16 15:04

To save the file, click on the file name.

Please click on the button on the right to download all files attached to this package.
If more than one file, a zip file will be returned.

Download All

Black = New file
Green = Downloaded file
Grey = Expired file

From: Jekerle Veronika <Veronika.Jekerle@ema.europa.eu>
Sent: 24 November 2020 12:02
To: Korakianiti Evdokia <Evdokia.Korakianiti@ema.europa.eu>
Cc: Facchini Claudio <claudio.facchini@ema.europa.eu>; Moseley Jane <Jane.Moseley@ema.europa.eu>; van der Stappen Ton <ton.vanderstappen@ema.europa.eu>; Dooley Brian <Brian.Dooley@ema.europa.eu>; Rager Irene <Irene.Rager@ema.europa.eu>; Seguin Vanessa <Vanessa.Seguin@ema.europa.eu>
Subject: update from BWP meeting on BioNTech

Dear Evdokia,

The BWP has just discussed the BioNTech BWP and below you will find the main conclusions:

The Dossier is generally of good quality considering the speed in development and compilation.

- 3 major objections are agreed:

- **MO1**: GMP distant assessments for US manufacturing sites (Note: Distance assessment on the Wyeth, Andover site (DS, QC DS, QC DP) and on the Pfizer, Chesterfield site (QC DS, QC DP) are ongoing → interim reports expected 11 Dec 2020, MO reworded to allow statement of GMP)
- **MO2**: Differences in the level of mRNA integrity; comparability between clinical and commercial material, DS and DP is questioned (Note: root cause analysis ongoing an 2 additional PPQ batches manufactured with a slightly adjusted process – waiting for results, if RNA integrity is improved back to initial levels this could be accepted / characterisation data requested to understand protein variability from mRNA fragments → potential impact on safety).
- **MO3**: Pending PPQ-batches for DP: comparability, process validation and stability (Note: as above: 2 PPQ batches manufactured and currently undergoing testing).
- Note that full information on two novel excipients (lipid in the nanoparticles) is not yet provided. This data is expected in the next CMC wave.

Conclusions: a number of major concerns remain that impact the benefit/risk of the vaccine (efficacy/safety) most notably the comparability issue around % mRNA integrity. These concerns are shared by most member states. **An approval by the end of the year could potentially be possible, if these concerns + GMP will be resolved**. Any remaining Quality issues will need to be considered in the context of overall B/R (& could potentially be addressed via specific obligations/Annex II conditions/recommendations).

The BWP report reflecting these conclusions is undergoing written adoption today.

With thanks to Ton, Brian and Claudio,

Kind regards,

Veronika

Veronika Jekerle, PhD

Head of Pharmaceutical Quality Office

Quality and Safety of Medicines

Office: 09-N-02

Extension: 8438

secure document transfer
Eudralink

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Subject:	COVID-19 mRNA Vaccine BioNTech, (EMEA/H/C/005735/0000) Rapporteur's Assessment Report(s)
From:	Agnese.Auzina-Vundere@ema.europa.eu
To:	gudenus@granzer.biz
CC:	covid-19.mrna.vaccine.biontech-5735@ema.europa.eu vanessa.seguin@ema.europa.eu agnese.auzina-vundere@ema.europa.eu
Sent:	Fri, 20 Nov 2020 09:19:44 +0100
Expiration:	Fri, 18 Dec 2020 09:19:44 +0100

Message:

Dear Dr Gudenus,

Please find enclosed the Rapporteur's assessment reports (ARs) for the above-mentioned procedure. These reports outline the preliminary conclusions of the Rapporteur's Assessment. They do not bind the Committee and are sent to you at this point for information only.

Should you require any clarification on the above, please do not hesitate to contact your PM: Vanessa Seguin, email: Vanessa.Seguin@ema.europa.eu.

Kind regards,

Agnese Auzina-Vundere
Procedure Assistant

This message and any attachment contain information which may be confidential or otherwise protected from disclosure. It is intended for the addressee(s) only and should not be relied upon as legal advice unless it is

-----Original Message-----
From: Wathion Noel <Noel.Wathion@ema.europa.eu>
Sent: Thursday, 19 November 2020 19:12
To: Cooke Emer <Emer.Cooke@ema.europa.eu>; Sweeney Fergus <Fergus.Sweeney@ema.europa.eu>; Nolte Alexis <Alexis.Nolte@ema.europa.eu>; Boone Hilde <Hilde.Boone@ema.europa.eu>; Dias Monica <Monica.Dias@ema.europa.eu>; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>
Subject: Some reflections after today's TC with the Commissioner

Dear all,

Since Alexis and Monica were no longer connected when we had our short discussion after today's TC with the Commissioner, a brief summary of what I already said together with some additional reflections.

As a minimum we can say that the TC was interesting, the atmosphere was rather tense, at times even a bit unpleasant, and provides a hint on what EMA may expect if the expectations are not being met, irrespective if such expectations are realistic or not.

The real added value of today's TC in my view is that we have more clarity now on what may not be easily acceptable for the EC, ie a delay of several weeks between an authorisation granted by the FDA/ MHRA (under whatever form) and a CMA opinion issued by EMA. The political fall-out seems to be too high, even if the "technical" level at the MSs (as it was referred to by the Commissioner) could defend such a delay in order to make the outcome of the scientific review as robust as possible.

Although we know that whatever we do (speeding up the process to align as much as possible with the "approval" timing by FDA/MHRA versus taking the time needed to have robust assurance in particular as regards CMC and safety) EMA will have a very big challenge addressing questions and criticism from various parties (EC, MSs at political level, EP, media, the general public) in case of a delay of several weeks.

Even if it can not be excluded now that at the end we are aligned with the FDA/MHRA (both in the outcome of the scientific review and the timing), the opposite certainly can not be excluded at this moment so we need to prepare for the worst case scenario. So how do we go from here? Are the current measures enough? In my view, probably not. We will be overwhelmed from all fronts and be in the middle of the storm. And on who's support will we be able to count? I hope it will not be a rethorical question...

What can we do on top, without creating the perception that we are interfering outside our "technical" mandate?
A non-exhaustive list:
1. Explaining the EMA process and what it will deliver:
- A public event is organised on 11/12: I think we need to critically review if we will achieve what is needed, taking into account the already brought forward date and the content related aspects.
- Making better use of social media tools as referred to by Emer today: we urgently need a dedicated strategy. However the resources in Comms are so stretched already that they have at this moment enormous difficulties to cope with the high influx of (media) queries. Reaching out to a specialist company to help out?
2. Explaining the differences between US/U.K. EUA and CMA: although the general public and the media will not (necessarily) understand the nuances between the 2 concepts we have to finalise this exercise which is currently ongoing ASAP, and then, more importantly, decide how to make best use of it. CMC, responsibility and accountability are certainly elements to be considered in my view.
3. Making the CMA process adapted as much as possible to the current pandemic situation: this exercise is ongoing but (1) the time gained may be limited and (2) any changes may be too late for the Pfizer/BioNTech vaccine. Nevertheless I think we should finalise ASAP if only to demonstrate that we did our utmost.

I hope these reflections can contribute to coming to a decision how to best address the important challenges ahead.

KR,

Noel

Few highly confidential news after talking with FDA:

Pfizer:
- they need to sort out CMC aspects which will require a bit of time.
-They are in negotiation with Pfizer to postpone submission for EUA until end of NOV (planned NOV 21).
-Mature efficacy data will be ready likely beg of DEC (earlier than expected)
-FDA may target an AC 18 DEC for issuing EUA before end of the year
- we agreed to keep channels open and share views so to avoid misleading messages going through (Pfizer CEO lobbied Peter Marks telling him EMA wants the data earlier!!)
-we may discuss together with FDA (and HC) the CMC package once ready
- we concurred that a conclusion roughly at the same time, if at all possible, would be fantastic

Moderna:
-they plan to submit EUA application end of NOV and could follow a similar pattern or even faster as CMC seems to more straight forward
-for us this may take a bit longer but colleagues are pushing hard to compress review timeframe

Can tell you more at tomorrow's SG

Marco

Wathion Noel

Mon 11/16/2020 12:42 PM

Inbox

Time for decision-making at EU; tomorrow phone call with Olga et al to prepare for EU Exe SG on Wednesday.

Wednesday EU Exe SG with HoAs.

Thursday TC with Commissioner.

The feasibility to "adapt" the CMA to these extraordinary circumstances will be key for determining the approach.

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Saint Raymond Agnes

Mon 11/16/2020 12:37 PM

Inbox

Azar is pro-Trump and still under his influence. Trump is still pulling strings ont his

Dr Agnès Saint-Raymond

Head of Division International Affairs

+31 (0)88781 7017

Office 17-S-27

Cavaleri Marco

Mon 11/16/2020 12:36 PM

Inbox

US Health secretary

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Wathion Noel

Mon 11/16/2020 12:35 PM

Inbox

AZAR is what?

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Cavaleri Marco

Mon 11/16/2020 12:34 PM

Inbox

FDA has a call with MHRA in 3 hours to discuss Biontech CMC aspects. They are going to rush into EUA.

FDA still unclear and not so easy for them to be faster than Xmas, but pushed hard by Azar and US GOV

Marco

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Saint Raymond Agnes

Mon 11/16/2020 12:20 PM

Inbox

This means MHRA is definitely going to issue an EUA or equivalent very soon…

Dr Agnès Saint-Raymond

Head of Division International Affairs

secure document transfer
Eudralink

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Subject:	COVID-19.mRNA.Vaccine.BioNTech - CHMP Interim Opinion and CHMP Overview
From:	Agnese.Auzina-Vundere@ema.europa.eu
To:	gudenus@granzer.biz
CC:	vanessa.seguin@ema.europa.eu covid-19.mrna.vaccine.biontech-5735@ema.europa.eu agnese.auzina-vundere@ema.europa.eu
Sent:	Mon, 30 Nov 2020 17:39:20 +0100
Expiration:	Mon, 28 Dec 2020 17:39:20 +0100

Message:

Dear Rosmarie,
Please find attached CHMP Interim Opinion together with the CHMP Overview and LoQ as adopted today, 30th of November 2020 for COVID-19.mRNA.Vaccine.BioNTech-5735 focusing on the assessment of quality data.

Should you require any clarification on the above, please do not hesitate to contact your PL:vanessa.seguin@ema.europa.eu
Kind regards,
Agnese
Procedure Assistant

	Filename	Type	Size
Delete	COVID-19 mRNA Vaccine BioNTech - CHMP Overview and LoQ.docx	MS Word Document	836kb
Delete	COVID-19 mRNA Vaccine BioNTech - CHMP Opinion.docx	MS Word Document	113kb

Package retrieved by

From: Boone Hilde <Hilde.Boone@ema.europa.eu>
Sent: Thursday, November 12, 2020 3:57 PM
To: SOLOMON Olga (SANTE) <Olga.Solomon@ec.europa.eu>; SCHMIDT Florian (SANTE) <Florian.SCHMIDT@ec.europa.eu>
Cc: GIRARD Thomas (EMA) <Thomas.Girard@ema.europa.eu>; CAVALERI Marco (EMA) <Marco.Cavaleri@ema.europa.eu>; WATHION Noel (EMA) <Noel.Wathion@ema.europa.eu>
Subject: Art 5(2) vs CMA

Dear Olga & Florian

Just a heads-up: we just finished the TC between the Commissioner and ECDC/EMA in which the Commissioner asked questions about the expected approval of the Pfizer vaccine, and timing of FDA vs EU approval. So, automatically the issue of national Art 5(2) vs CMA came up, which Noel explained in detail and also how we plan to further discuss it with the NCAs next week and in HMA. Guido also suggested to consider raising it with the Health Ministers at EPSCO.

Sandra and Giorgios said that they would further discuss also within SANTE, so, hence my email to you.

(Andrzej was also present)

Also of note:
The Commissioner said that, since EC made a commitment to the MSs and EP that the vaccines will be available to all MSs at the same time – and that therefore it will be important that MSs will not be 'forced' to use that national route due to "delays" in the formal approval procedure.

She also said that she will be prepared to call relevant health ministers personally to avoid the use of Art 5(2).

Best regards,

Hilde

Cavaleri Marco

ma 23/11/2020 15:31

Hilde

I think we may want to say that we need first to understand if this can be actually done as it is really compressed and there are still a number of uncertainties not last when the CY can submit and how the CMC gaps are evaluated

Marco

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Boone Hilde

ma 23/11/2020 15:00

Dear Irene, this is the Eudralink with the Excel timetable that Florian sent to us, and which already sets the CHMP opinion on 21 December – hence my questions below.

They need our feedback by 18h today.

Kind regards, Hilde

Classified as internal/staff & contractors by the European Medicines Agency

Rager Irene

ma 23/11/2020 14:57

Dear Hilde

To bring it even forward to 21 Dec will be very difficult, so I would be better to not yet promise this – even though we are going to do our best, of course!

I would suggest that we will wait for the updated submission proposal from BNT/Pfizer this late afternoon, as this will make fine tuned planning much easier.

Thanks and Kind Regards,

Irene.

Classified as internal/staff & contractors by the European Medicines Agency

Boone Hilde

ma 23/11/2020 14:26

Dear Marco & Irene,

In the EC table, CHMP opinion is presented for 21 December, whereas this morning 23rd was mentioned as per current timetable, I understand.

But, indeed we agreed trying to bring Opinion forward by a few days eg to 21 or even 18 Dec.

So, what response should we give back to EC now:

Current EMA planning is 23 Dec for Opinion, but we are looking into bringing adoption forward?

Or

Do we already say that 21 Dec for Opinion, as listed in the EC table, is correct, but that we are looking into bringing adoption forward even more?

I take it that the Eudralink TT request that we just received, replaces Olga's question below (as it is in essence the same).

Best, Hilde

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Garcia Juan

Mon 23/11/2020 17:26

Deleted Items

Thanks – quite a relief they wont go for EUA on 11th but a week later!

Juan

Juan García Burgos

Head of Public and Stakeholders Engagement Department

Stakeholders and Communication Division

Cavaleri Marco

Mon 23/11/2020 16:14

Deleted Items

An update from FDA:

Pfizer/Biontech:

Advisory committee on 10 December and opinion for EUA likely one week later.

CMC issues would affect authorisation but not EUA. In any case, the issue on the mRNA content not perceived as major. Gaps are around comparability and process validation for drug substance.

For EUA, commercial lots will be used but maybe also clinical lots (to be confirmed)

Unclear if GCP inspections ever done (TBC), but no major interest from FDA

Moderna:

Advisory committee on 17 December for an EUA opinion by end of the year.

CMC seems more streamlined. Interim clinical report awaited

AZ:

FDA very sceptical on data from the ongoing studies outside US and data are indeed quite puzzling as released today. They are not encouraging any submission for EUA at this stage

We may go first on this one, but it would still take a bit longer even in the best case scenario

Marco

Classified as internal/recipients only by the European Medicines Agency

Mark as unread

From: Jekerle Veronika <Veronika.Jekerle@ema.europa.eu>
Sent: 25 November 2020 16:28
To: Korakianiti Evdokia <Evdokia.Korakianiti@ema.europa.eu>; Prilla Stefanie< Stefanie.Prilla@ema.europa.eu>; Nolte Alexis <Alexis.Nolte@ema.europa.eu>
Subject: RE: Ad-hoc MLT minutes for comment by 16:30 today

Dear Evdokia,

Please see the additional points resulting from the TC with FDA we just had:

FDA shared with us the following information:

- FDA have received 7 commercial DS and 6 additional DP lots (2 additional GMP lots which EU hasn't received yet). The latest lots indicate that %intact RNA are back at around 70 – 75%, which leaves us cautiously optimistic that additional data could address the issue

- FDA and Health Canada indicated that the safety concerns associated with variable species of mRNA/protein are more of a theoretical concern as 5' caped intact species appear to stay comparable (which equates to fully functional mRNA)

- FDA/HC/EMA agreed that alignment on specifications % mRNA integrity are key in order to avoid that one regions gets all the suboptimal material (in particular a concern by Health Canada), specifications should be clinically qualified

- FDA mentioned an amendment of the CT protocol to compare immunogenicity of process 1 and 2 material; however unclear whether patients have received these doses yet; this info would be valuable to bring clinical bridge in the range of the specs for % of mRNA integrity; very likely to not be available though before end of the year

- FDA indicated that for a full BLA they would require 3 PPQ lots each for DP and DS

- Applicant has shared with FDA and us/MHRA only today an issue with visible particles in the DP (appears to be lipid nanoparticle components). FDA has posed questions to applicant, we will also FU on this issue.

Kind regards,

Veronika

Cavaleri Marco

Tue 10/11/2020 14:00

Deleted Items

Thanks Irene

I just learned from FDA that there are some issues on CMC to be sorted out so I guess that if we can try to catch up would be good. I fear CMC will end up being the difficult bit

FDA may conclude on EUA by Xmas (not earlier); any chances we can issue CMA at the same time?

Marco

Classified as internal/staff & contractors by the European Medicines Agency

Rager Irene

Tue 10/11/2020 13:32

Deleted Items

Marco

See BNT timelines below.

ETF recommendation for CMA submission hence earliest Thu next week (**19/11**)

Currently, second CMC submission is timed for 18 Dec – should we accept this as a potential CMA submission date and plan accordingly or should we try to start CMC even earlier (beginning of Dec) and get the 2nd CMC wave in during the MAA procedure?

This would be important to further push the CMC assessors, who obviously came back challenging a more strict TT for the 1st CMC round.

Your view?

Thanks and Kind Regards,

Irene.

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	Filename	Type	Size
Delete	Rapporteur's Rolling Review Report Quality - COVID-19 mRNA Vaccine BioNTec.doc	MS Word Document	14487kb
Delete	Rapporteur's Rolling Review Report New Active Substance Status - COVID-19 mRNA Vaccine BioNTec.doc	MS Word Document	184kb
Delete	Rapporteur Rolling Review Report Overview LoQ - COVID-19 mRNA Vaccine BioNTech.docx	MS Word Document	684kb

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[Reduce expiry date] [Extend expiry date] [Remove package] [Resend package]

[Logged on as: auzinavunderea]

The Ad26.COV2.S drug substance is manufactured by Janssen Vaccines & Prevention B.V. in Leiden, the Netherlands. The drug product is manufactured by Grand River Aseptic Manufacturing, Inc. in Grand Rapids, USA. Batch release is performed by Janssen Biologics B.V. in Leiden, the Netherlands.

Summary of the data available

Quality

Most of the module 3 data are currently already available for both DS and DP. These include description of the process and process controls, process development, control of starting materials, specifications analytical methods, method validations,... Stability data will be provided later. Also some other data may not be available for the initial submission (RR1), but these will be provided in the next submissions (AtoQ,RR3).

Non-Clinical:

J&J Ad26.COV has been shown to be immunogenic in mice, rabbits, hamsters and NHP models, inducing neutralizing antibody response, as well as CD4 and CD8 T cell responses. Further, in hamster and NHP SARS-CoV-2 challenge models, a single administration of J&J Ad26.COV significantly reduced symptoms in hamsters and viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated animals as compared to controls in both species. Data on durability of the immune response (6 and 8 months after vaccination), immunogenicity and efficacy in aged monkeys and vaccine titration in hamsters could be submitted in the third RR package or at cMAA depending on the time of efficacy signal.

A biodistribution study has not been performed, following consideration of the results of other biodistribution studies of replication-deficient adenoviruses. This platform data are considered sufficient to support development.

Studies evaluating any toxicity due to Ad26COV have not been conducted to date. In a toxicology study on related Ad26-based vaccines, no toxicologically relevant effects were noted. The Applicant however started a specific Ad26COV - GLP Repeat-dose toxicity/local tolerance study.

Finally, the applicant conducted a combined embryo-foetal and pre- and postnatal development study in female rabbits with another Ad26-based vaccine, there was no maternal or developmental toxicity observed following maternal exposure during the premating and gestation period. A specific Ad26COV DART study will be conducted.

The results of both safety studies will be submitted during rolling review.

Clinical:

Platform data available

Replication-incompetent Ad26 is being used as a vector in the development of vaccine candidates against diseases such as malaria, RSV, HIV, Ebola virus, Zika virus, and filovirus. The Applicant's clinical AdVac® safety database includes safety data from 26 completed clinical studies using Ad26-based vaccines in which 4,224 adult participants were vaccinated with an Ad26-based vaccine. One vaccine based on Ad26 platform has been granted a MA in the EU is Zabdeno, Ad26.ZEBOV, (5x10exp10 virus particles) for the prevention of Ebola (MA under exceptional circumstances).

Clinical development plan

Nolte Alexis

Mon 23/11/2020 10:48

Sent Items

To:

Korakianiti Evdokia;

Evdokia,

One way to understand how the lower mRNA level in the finished product translates to efficacy would be to measure whether it affects significantly levels of protein expression. It could be that the level of antigenic protein expressed is not significantly affected. However, I don't know whether there is a test that would allow to predict impact on efficacy without clinical trial for comparability.

Alexis

Classified as internal/staff & contractors by the European Medicines Agency

Korakianiti Evdokia

Mon 23/11/2020 10:38

Inbox

Dear Colleagues,

This email is for awareness and to flag an important comparability issue with the BioNTech vaccine that needs to be addressed prior to approval.

Issue: A significant difference in %RNA integrity / truncated species has been observed between the clinical batches (~ 78% mRNA integrity) based on which the Interim analysis was performed and the proposed commercial batches (~ 55%).

The company claims that the efficacy of the drug product is dependent on the expression of the delivered RNA, which requires a **sufficiently intact RNA molecule.** The root cause for for the lower %RNA integrity at commercial batches has not yet been identified

Impact: The potential implications of this RNA integrity loss in commercial batches compared to clinical ones in terms of both safety and efficacy are yet to be defined. Whether or not the observed comparability issues could be a blocking point will depend on the relevance of these observations to safety and efficacy and the company will be requested to fully justify the lower %RNA integrity (and other differences noted).

Point for discussion will be whether the comparability issues can be solved only by Quality data (additional functional/ in vitro biological data + available non-clinical) or that further clinical data (bridging studies are/will be performed) will be needed. It is difficult to make any projections on this.

Way forward: This issue and other MO (but in our view not blocking to a potential approval) have been raised at ETF and are being discussed at BWP this week and in a TC with FDA on Wednesday

With many thanks to Ton who's is the Quality specialist for this vaccine together with Brian looking after the chemical elements

Best regards

Evdokia

Ext. 7150

Phase 1/2a (COV1001), Phase 1 (COV1002) and Phase 2 (COV2001) clinical studies to assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S are ongoing. Two Phase 3 studies (COV3001, COV3009) are ongoing as well.

The FIH study COV1001 is a randomized, double-blind, placebo-controlled, Phase 1/2a multicenter study in adults aged ≥18 to ≤55 years and aged ≥65 years (US and Belgium). The safety, reactogenicity, and immunogenicity of Ad26.COV2.S is evaluated at 2 dose levels (5×10^{10} vp and 1×10^{11} vp), administered IM as a single-dose or 2-dose schedule with a 56-days interval. Overall, a target of 1,045 adult participants will be randomly assigned in this study.

COV1002 is a Phase 1 trial ongoing in Japan (n=250).

COV2001 is a Phase 2a ongoing in The Netherlands, Germany, and Spain (n=550) in healthy adults to assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S. The vaccine candidate is evaluated across a range of dose levels ($1x10^{11}$, $5x10^{10}$, $2.5x10^{10}$, $1.25x10^{10}$ vp) and schedules (2 dose vs 1 dose primary regimen, with different compressed or expanded intervals for the 2-dose regimen [1m, 2m, 3m]). Anamnestic responses will be compared by using a later, low-dose vaccination ($1.25x10^{10}$ vp) as a surrogate of antigen exposure upon SARS-CoV-2 infection.

Based on the interim immunogenicity and safety data (28 days post-Dose 1 data from participants aged ≥18 to ≤55 years and available data from participants aged ≥65 years) from study COV1001 (described below), the Applicant decided to proceed with Ad26.COV2.S at a dose level of 5×10^{10} vp in its Phase 3 studies.

Study COV3001 is a randomized, double-blind, placebo-controlled Phase 3, pivotal efficacy and safety study in adults aged ≥18 to <60 years of age and ≥60 years of age, with and without relevant comorbidities. The primary objective of study COV3001 is to demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe/critical COVID-19 when given as a single-dose vaccination regimen, in SARS-CoV-2 seronegative adults. A total of 60,000 subjects are planned to be enrolled in this trial.

Study COV3009 has a similar design but assesses efficacy of Ad26.COV2.S when given as a two-dose vaccination regimen (same dose level as in COV3001; doses given 8 weeks apart), and plans to enrol 30,000 subjects. Even though a single-dose regimen in study COV1001 showed robust immunogenicity, data from other vaccines using the Ad26 platform suggest that a second vaccination may potentially result in a higher and more durable immune response, providing justification for the evaluation of a 2-dose regimen in this study.

Preliminary data

Preliminary safety and immunogenicity data from the first interim analysis are available for 402 participants aged ≥18 to ≤55 years and 403 participants aged ≥65 years who received at least one dose of study vaccine. The results from the safety analyses showed that both dose levels had acceptable reactogenicity in participants aged ≥18 to ≤55 and ≥65 years with no significant safety issues during the 28-day observation period. One participant aged ≥18 to ≤55 years experienced a SAE (pyrexia) which was considered to be related to blinded study vaccine.
In both age groups, a single vaccination (both dose levels) with Ad26.COV2.S was shown to induce neutralizing and binding antibody responses, a Th1-skewed phenotype, and specific CD4+ and CD8+ T cell responses.

Temporary pause phase 3 study

The Company halted the COV3001 trial following detection on the 11th of October of a case with initial diagnosis of transverse sinus thrombosis resulting in cerebral haemorrhage detected in a 25-year-old

male that started with symptoms 19 days after receiving the first dose of the vaccine (after experiencing flu-like illness starting Day 9). The sponsor assessed this event to be not causally related to the study vaccine/placebo (no clear cause identified). Based on a cumulative ad hoc safety review the sponsor considers that, from the data available to date, there is insufficient evidence for a causal role of Ad26.COV2.S or any other Ad26 vaccines, in the development of thrombotic, thromboembolic, or neurovascular events.

The DSMB has recommended resuming trial recruitment, and regulators have approved it in US and in various countries in Europe (Belgium, Germany, Nederland, France and Spain, to our knowledge).

Conclusion

Demonstration of the proof of principle (non-clinical) including challenge models and proof of concept (clinical immunogenicity, neutralising antibodies) justify the start of the rolling review.

coRapporteur comments

The Rapporteur's conclusion is fully supported.

COVID-ETF recommendation:

<The available information on the product is <not> considered sufficient to establish proof of concept and warrant start of a rolling review of this application.>

Annex 1

Briefing document or other documents from the Applicant on proof of concept data to support the start of the Rolling Review

Briefing Materials for CMC Meeting on 26th November

The purpose of the meeting is to provide an update on quality aspects of the COVID19 mRNA vaccine program including revised drug product manufacturing plans, changes to specification criteria, description and data in support of an increase in batch size , and a summary of the process validation strategy. This updated and new information is being provided in the upcoming CMC submission. We are prepared to discuss any other quality topics in this meeting to support the MAA, potential approval and roll out of of vaccine doses for administration in 2020/21.

Update of Drug Product (DP) specifications

The 2nd CMC Roll will include updated DP specifications for the appearance of visible particulates and RNA integrity.

Appearance of visible particulates

Product-related visible particles have been observed in drug product lots. Therefore, the DP specification for appearance of visible particulates has changed from "Essentially free from visible particulates" to "May contain white to off-white opaque, amorphous particles".

Characterization by FTIR indicates that these particles contain lipids and are thus intrinsic to the product. Complete justification and characterization are described in Section 3.2.P.2.2 Drug Product, subsection 3.2.P.2.2.3.5 Appearance and Characterization of Intrinsic Particles. In brief, The toxicity has been characterized in nonclinical repeat-dose toxicity studies (Study Numbers 38166 and 20GR142), and their presence as visible particulates (versus sub-visible LNPs) would not be associated with any unique chemical toxicological concern.

In the attachment, the current Draft Section 3.2.P.2.2 is provided to facilitate early review of the information that will be provided in the 2nd CMC Roll. Further discussion of visible particulates will be included within the reply to FDA questions, which will be provided to EMA on 26th November to facilitate early review.

RNA integrity

Capillary gel electrophoresis is routinely used to evaluate the RNA integrity of the BNT162b2 drug product at release and during stability. The acceptance criterion lower limit for drug product RNA integrity had previously been set to align with the drug substance acceptance criterion of ≥ 50% intact RNA. In order to provide further assurance of 50% intact RNA at point of dosing, an acceptance criterion of ≥ 55% at release with an allowance of 5% decrease across stability is proposed. As additional supply nodes are introduced and manufacturing experience is gained, acceptance criteria will be evaluated and revised, as appropriate to assure consistent quality.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 November 2020
EMA/639119/2020EMA/639119/2020
Health Threats and Vaccines Strategy

COVID-ETF recommendation on the start of rolling review for Ad26.COV2.S Janssen-Cilag International NV (Ad26.COV2.S)

Rapporteur: Christophe Focke (BE)

CoRapporteur: Sol Ruiz (ES)

Background on the product

The Ad26.COV2.S vaccine contains the recombinant Ad26 vector Ad26.COV2.S as drug substance. The recombinant Ad26 vector Ad26.COV2.S is replication incompetent and contains a modified full-length SARS-CoV-2 spike (S) protein with stabilizing modifications.

Ad26 is being used as a vector in the development of vaccine candidates against diseases such as malaria, RSV, HIV, Ebola virus, Zika virus, and filovirus. One vaccine based on Ad26 platform has been granted a MA in the EU (Zabdeno, Ad26.ZEBOV).

The Ad26.COV2.S drug product (DP) is supplied as a sterile liquid suspension for injection with a target concentration of 1.0×10^{11} virus particles (vp)/mL. Each vial contains a fill volume of 3.1 mL to allow for an extractable volume of 2.5 mL as 5 extractions of 0.5 mL. The primary packaging consists of a 2R Type I glass vial with a chlorobutyl closure and an aluminium seal with a flip-off cap. The DP contains no preservative.

The initial shelf life of the Ad26.COV2.S drug product (DP) is 24 months when stored frozen at the recommended storage condition of -25 to -15°C, and within these 24 months, 3 months when stored at 2-8°C

The drug product is intended for administration by the intramuscular (IM) route. The indication under this application is active immunization against coronavirus disease-2019 (COVID-19) in adults aged 18 years or older.

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Cavaleri Marco

Wed 25/11/2020 17:09

Inbox

Dear Maria

Some answers below

Marco

Classified as restricted by the European Medicines Agency

From: Alves Maria <Maria.Alves@ema.europa.eu>
Sent: 25 November 2020 17:45
Subject: Questions for EMA - TC wiht Commissioner/ECDC/EMA - 26 November 2020
Importance: High

Dear colleagues

Please find attached and below the questions for tomorrow's TC with Commissioner Kyriakides and ECDC.

EMA

- General update on the state of play regarding therapeutics, vaccines, clinical trials or medicine shortages.

Baricitinib also received EUA from FDA. Lilly is pushing for baricitinb extension of indication after marginally successful ACTT-2 study in combination with remdesivir. We would like to see data from the ongoing Phase III study before coming to a conclusion, i.e. 1H 2021.

- Do you have any indication of when BioNTech/Pfizer will formally submit a request for conditional market approval, if they have not done so already?

30 November

- Do you have any update/feedback on contacts with partners about streamlining vaccine authorisation procedures and timing?

TC with FDA, HC and MHRA this week on Biontech. FDA could issue EUA around 17 december. We are still targeting 23 december. MHRA is considering EUA for this vaccine. At today TC it looked the issues on CMC could be solved based on new data that only FDA has seen so far. We will try to harmonize specs across regions if at all possible. For FDA no need of full qualification of process for EUA. For Moderna FDA could be issuing EUA by end of Dcecember, whiel for us it might take 2/3 weeks more pending decision on DS process validation.

- Is there an update on data and potential conditional market authorisation for monoclonal antibodies? (in particular Regeneron, which is attracting considerable interest at the moment).

It is considered premature to go for CMA. We need more clinical data form ongoing Phase III. CMA not possible until Q1 2021 at the very least. Compassionate use opinion could be considered if MSs interested.

May I kindly ask you to include the answers into the email.

With thanks and regards

Maria

NO RECIPIENTS HAVE COLLECTED THE PACKAGE YET

[Reduce expiry date] [Extend expiry date] [Remove package] [Resend package]

[Logged on as: auzinavunderea]

In addition, a so-called late migrating species (LMS) has been observed in capillary gel electrophoresis that migrates after the main mRNA peak. The LMS has been observed in drug product batches but is not present in the corresponding final RNA drug substance batches. Characterization results from an evaluation by multiple techniques demonstrate the LMS is intact RNA. The results of characterization evaluations has been included in Section 3.2.P.2.2 Pharmaceutical Development in the subsection titled Enhanced Analytical Characterization.

In the attachment, the current Draft Section 3.2.P.2.2 is provided to facilitate early review of the information that will be provided in the 2nd CMC Roll. Additional characterization data and justification will be included within the reply to FDA questions, which will be provided to EMA on 26th November to facilitate early review.

Updated DP process validation strategy and manufacturing plan

The Process Validation Plan for the 1st Phase of process validation is provided in the attachment. The first phase describes a holistic process validation approach that includes manufacture of one batch from each global supply node. In a later phase, the full validation of all supply nodes will be completed.

The phased approach ensures preliminary process validation data is available from each individual supply node as soon as possible to provide confirmatory manufacturing consistency for the conditional MA in the EU, the EUA in the US, and initial regulatory applications in other regions.

The first phase will provide data for a total of five PPQ lots manufactured in parallel in calender week 48. The timing of manufacturing campaigns is presented in detail in the attached Manufacturing Plan. One DP lot will be manufactured at Pfizer Manufacturing Belgium NV (FC2 filling line, 139 L scale, process as defined for the Puurs site in the 1st CMC Roll of the MAA), whereas four lots will be manufactured at other nodes of the global supply chain. Comparability assessment is planned for all PPQ lots.

A comparison of the process of each supply node is provided in the Supply Node Tables Document in the attachment. The process of supply nodes #4 and #5 (i.e., Pfizer Kalamazoo, USA, filling lines 8 and 18) are considered comparable to the EU supply node #1 (FC2 filling line, Pfizer Manufacturing Belgium NV) and thus representative of the DP process 139 L as defined in the MAA. The supply nodes #2 and #3 are considered supportive.

A preliminary timeline for full validation (i.e. 2nd phase of PPQ) of the DP process at Pfizer Manufacturing Belgium NV (Puurs) is presented in the attached Manufacturing Plan. Full validation is intended as matrix approach including a total of seven PPQ lots addressing different DS supply sites (Andover vs BioNTech/Rentschler), different fill lines (FC2 vs VC2) and different scales (139 L vs 278 L).

From: Wathion Noel
Sent: Sunday, 22 November 2020 17:19
To: SOLOMON Olga (SANTE) <Olga.Solomon@ec.europa.eu>; Boone Hilde <Hilde.Boone@ema.europa.eu>; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>
Cc: RYS Andrzej Jan (SANTE) <Andrzej.RYS@ec.europa.eu>; SCHMIDT Florian (SANTE) <Florian.SCHMIDT@ec.europa.eu>; Cooke Emer <Emer.Cooke@ema.europa.eu>
Subject: RE: Covid vaccines: information flow in the coming weeks

Dear Olga,

Of course we can discuss on Monday how to best provide updates to the EC on real time developments for these first vaccines. Let's see how to best achieve this.

Three comments I would like to make in addition:

- The likelihood that FDA (and also MHRA) will issue an EUA before a CMA is granted is extremely high. So we have to prepare for this. Certainly the lay public and the media will not understand the nuance…for them an "authorisation" is an authorisation. We have options to address this going from damage limitation to proactive expectation management. We have to choose which option is the best taking into account the exact circumstances.

- We are speeding up as much as possible but we also need to make sure that our scientific assessment is as robust as possible. Let's not forget the responsibility/ accountability attached to the recommendation to the EC to grant a CMA. And we need the (Co)-Rapps' and the CHMP's support for achieving this. Without them it will not happen.

- The fact that the company now suddenly wants to get a full MA instead of a CMA may even make things more challenging…

Kind regards,

Noel

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Additional filling line

At the DP manufacturing site in Puurs an additional filling line (VC2) is introduced for BNT162b2 drug product and is described in the respective sections in the MAA. The second filling line is added to BNT162b2 production as a measure to ensure supply from Puurs site.

Validation of the VC2 filling line is planned to be addressed in the 2nd phase of process validation, as described above.

Batch size increase for DP process

A batch size increase for DP process is intended to provide sufficient EU supplies for administration prior to the submission of variations for post-approval addition of further DP manufacturing sites.

Two tangential flow filtration (TFF) unit operations are run in parallel during the DP process (Step 5 in Section 3.2.P.3.3) to increase the batch size from 139 L to 278 L. The batch size in Section 3.2.P.3.2 are changed from 139 L to the 139-278 L range.

This change is supported by data from one completed engineering lot and a first GMP lot scheduled to be completed this week. Process validation of the 278 L range is planned to be addressed in the 2nd phase of process validation, as described above.

List of Attachments

Annex 1: Draft Section 3.2.P.2.2 Drug Product

Annex 2: Process Validation Plan for Covid-19 Vaccine Drug Product – Phase I

Annex 3: Draft Supply Node Tables Document

Annex 4: Updated manufacturing plan with tentative timelines

Fra: Wathion Noel <Noel.Wathion@ema.europa.eu>
Sendt: 20. november 2020 10:16
Til: Thomas Senderovitz <THS@dkma.dk>
Cc: Cooke Emer <Emer.Cooke@ema.europa.eu>
Emne: RE: von der Leyden statements

Dear Thomas,

I cc Emer in my response.
As such not that much has changed since she clearly states "if everything goes well". And yes, this is aligned with EMA and the statements we have made in several interviews since the moment the interim analysis results for the Pfizer/ BioNTech vaccine (confirmed this week by the final analysis results) and the interim analysis results for the 2nd mRNA vaccine for Moderna have been made public.
What is new in my view is that she clearly identifies the 2 vaccines that could be approved before the end of the year. There are still issues with both (CMC seems to be a concern for the Pfizer/ BioNTech, and the rolling review for Moderna just started giving less time to review) so its needs to be seen if all this can be sorted out on time, whilst not compromising the robustness of the review.
Acknowledging that the legal tools in the US versus the EU are different, and since the 1st option still is to aim for a CMA rather than an art 5(2) coupled or not with an Art 5(3), we are trying to make the CMA process as adapted as possible to the pandemic situation since so far it was primarily used for oncology medicines. The discussion at the EU Exe SG on Wednesday was very useful and we are speeding up this work.
This brings me to the next point, i.e. how to best ensure continuation of the alignment within the Network; we have now the following meetings scheduled over the next weeks to discuss COVID-19:

- HMA on Thursday: 10 minutes update by EMA and a specific topic on clinical trials if I am not mistaken, to be presented by PEI.
- EU Exe SG the week after next, where the point on making the CMA process as efficient as possible is again on the agenda.
- MB on 16-17/12.

As a point for reflection, since we are dealing with an extraordinary situation of utmost importance for the Network and its credibility, to be addressed over the next 6 weeks (we will be in the hotspot for the 1st vaccines, the pressure should be much less certainly with this level of efficacy and on condition that there are no major quality and safety issues), shouldn't we organize an urgent ad-hoc meeting HMA, EMA, EC (for some 3 hours) to have a more in-depth discussion on all bottlenecks for speeding-up the CMA process and also to align ourselves on the communication for the different scenarios (earlier approval by FDA/ MHRA, similar timelines, balance speed versus robustness)? Or alternatively to extend the HMA meeting next Thursday, or the EU Exe SG the week thereafter? But I wouldn't wait much longer than Wednesday next week.
Looking forward to your feedback.
KR,

Noel

Nolte Alexis

Thu 12/11/2020 14:04

Inbox; Sent Items

Colleagues,

See below Radhouane's briefing (thanks!) from the COVID SC yesterday. Lots of info that is relevant.

On the quality/inspections dashboard and the request to extend to clinical aspects: I had the same thought when seeing the dashboard: great job Evdokia and your team. I'm wondering is the PPO can be of help here and if capacity allows. Michael, could your team look into this with Irene and Marco?

Thanks,

Alexis

- OPEN initiative: meeting scheduled this Friday to finalise the document. Agnes mentioned that for the time being the pilot is on COVID only and involves participation of experts in ETF and CHMP.

- Redaction of PPD: Agnes mentioned that she is working on specific arrangement that would allow us not to redact documents shared with HC. She will f/u on this topic.

- Hilde provided an update on the EC legal proposal to extend EMA's mandate. Press release published today (EC press release with links to legal proposals): resource estimate to implement the proposal will have to be discussed with Emer. EC estimates: 40 FTEs by 2024 (never discussed with EMA). Timing of implantation: 2nd half of 2021 (should go through co-decision very fast) with immediate implementation. Will have an impact on the 2021 work program. Emer asked for an update on Monday next week. This will be followed by a discussion on November 17th with Christa and MB topic coordinators. EXB adoption: 24 November.

- Safety monitoring plan and guidance on risk management planning for COVID-19 vaccines: endorsed (no major comments)

Workstream 1 Therapeutic Response

- Biontech: FDA preparing for EUA by the end of December and is targeting an advisory committee on December 18th provided that the company submits data by November 26th (FDA has asked for all safety data available). It was mentioned that the EUA requirements that FDA will put in place are more stringent than what we would accept for the CMA. The Agency will try to align and get the CMA completed by the end of the year (currently planned in January).

- Moderna: They have more than 100 cases and could trigger an interim analysis anytime now. The CMC package looks more straightforward than the Biontech one. We could try to compress the timelines but not as much as for Biontech.

- AZ: FDA wants to wait for US data as they do not want to use data from Brazil and UK. This is the application r for which we will have most likely differences with FDA.

- Noel message (for discussion at EXB tomorrow): make sure that CMA concept is agile and that because of administrative requirements we do not finalise the application 6 weeks after the finalising the rolling-review for Biontech and Moderna.

- Lilly's mab: FDA might go for an EUA for the product. Another Mab from Regeneron could come as well (both for use in outpatient setting with mid disease).

- Reflection paper on COVID-19 vaccines: should be adopted by ETF this week. We will check with Harald if CHMP wants to endorse the document before publication.

- Sharing of information with CTFG: it was agreed that SA letters can be shared.

Workstream 2 Supply chain

- Dashboard - overview of Qual/Insp issues for COVID vaccines and Therapeutics: very positive feedback from the SG. Noel asked if a similar dashboard should be developed for clinical aspects. Marco will explore.

Communication:

- A GA is scheduled on Friday November 20th. Another one is scheduled in December. Noel will discussed with Emer what is her preferred date for an update from the COVID 19 SG to staff.

- Proposal for Public Stakeholder Meeting on COVID-19 vaccines on 15 December. Should be discussed at EXB tomorrow.