a_concerned_amyloidosis💜🐭

Follow @a_nineties 1,278 followers

Dec 14 · 27 tweets · 12 min read

holy fucking SHIT. mRNA-1647 is the "bioequivalent" GTMP all of the Moderna regulatory paperwork was done with, and it's been around since 2017. Moderna had mRNA tech ready to go five years ago. @CharlesRixey @joshg99 @TheJikky

Judicial Watch ⚖️
@JudicialWatch · **Follow**

BREAKING: Judicial Watch received records from HHS regarding data Moderna submitted to FDA on mRNA COVID-19 vaccine, which indicate a "significant" number of rats were born w/skeletal deformations after their mothers were injected w/the vaccine (1/3).

judicialwatch.org
Judicial Watch: FDA Records Show Significant Number of mRNA ...
(Washington, DC) – Judicial Watch announced today that it received 699 pages of records from the Department of Health a...

1:13 PM · Dec 13, 2022

Read the full conversation on Twitter

1.1K **See the latest COVID-19 information on Twitter**

Read 68 replies

3. INTRODUCTION

The objective of this study was to determine the tissue distribution of mRNA-1647, when given once by intramuscular injection to rats. In addition, the toxicokinetic characteristics of mRNA-1647 were determined.

The design of this study was based on the study objective and the overall product development strategy for the Test Item.

The Study Director signed the study plan on 28 Jun 2017, and dosing was initiated on 10 Jul 2017. The study plan, the last amended study plan, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test Item and Vehicle

4.1.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) No.:	MTDP17048
Concentration:	1.9 mg/mL
Retest Date:	20 Apr 2018
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

the first pages are different versions of the 2017-18 study, here's a neat little freudian slip on page 75.

Appendix 1

SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 28-Jun-2017

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 07-Jul-2017**
6. RESPONSIBLE PERSONNEL	To include the pathologist's contact information.
7.1. TEST ITEM AND VEHICLE	To complete the Test Item information (Botch/lot number, concentration and retest date).
14.1.2. Bioanalytical Tissue Sample Collection	To clarify the samples of tissues that should be collected, the target weight and the processing.
15. TERMINAL PROCEDURES	To clarify the samples of tissues that should be collected.
15.4. Sample Tissue Weights	To clarify the samples of tissues that should be weight.
Amendment 2	
6. RESPONSIBLE PERSONNEL	To clarify that no pathology report is required.

p97... no comment LOL

Appendix 2

moderna
messenger therapeutics

200 Tech Square • Cambridge, MA 02139
phone 617-714-6500 • fax 617-583-1998

Summary of Analysis

(b) (4)

the summary of analysis was done 6 july 2017? when dosing started 10 july?

(b) (6)

Date: 06Jul2017

spicy! the material for the sprague dawley study was made february 2017, page 103

Appendix 3

4.1.2. Reference Material

Identification:	mRNA-1647
Physical Description:	0.5 mL per vial, white to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17015
Concentration:	2.4 mg/mL (used for calculations)
Date of Manufacture:	24 Feb 2017
Retest Date:	24 Feb 2018
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

analytical procedure is 7 pages of [redacted], but at the end is another set of signatures from 6 july 2017.

Appendix 3

Analytical Procedure (AP.5002121.SP.01) Page 1 of 7

(b) (4)

AP Version Control

Initial version.

Verified by (b) (6) Date 06 Jul 2017

Approved by (b) (6) Date 06 Jul 2017

Authorized by (b) (6) Date 06 Jul 2017

Scientific Director

Next up "certificates of analysis" p116, two pages of redactions from 12.4., a single page from 31.5., and another two from 22.6.

Appendix 3

Document Number: DSAD-SOA-0025 Version: 3.0 Final Date: 13 Apr 2017
CX-005128 MTDS16027 SoA

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SUMMARY OF ANALYSIS
(b) (4), (b) (6)

Principal Scientist, DP Analytical Development (b) (6) Date: 31 May 2017

Senior Director, DP Analytical Development (b) (6) Date: 31-MAY-17

ed in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Page 1 of 2

Signatures:

(b) (6)
Generated by: (b) (6) Date: 12 Apr 17

(b) (6)
Reviewed by: (b) (6) Date: 12 APR 2017

(b) (6) Date: 22 Jun 2017

ok i'll have to stop noting the redacted bits because lots of it is. p190 is the first unscarred page in quite a while.

Appendix 8

Toxicokinetic Report

Clarification

The average value of terminal half-life for the muscle (i.e. injection site) in Sections 4.2 and 5 of the toxicokinetic report should be read 14.9 instead of 8.39 based on the results of the toxicokinetic evaluation.

Changes indicated below had no impact on the study conclusion.

Note: Additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in sections indicated below. Values were not updated directly in the toxicokinetic report.

Section 4.2. Pharmacokinetic Evaluation

The half-life ($t_{1/2}$) of mRNA-1647 was reliably estimated in muscle (site of injection), proximal popliteal and axillary distal lymph nodes and spleen with average values for all construct $t_{1/2}$ of **14.9** ~~**8.39**~~, 34.8, 31.1 and 63.0 hours, respectively.

Section 5. Conclusion

Concentrations of mRNA-1647 were quantifiable in the majority of tissues examined at the first time point collected (2 hours post dose) and peak concentrations were reached between 2 and 24 hours post dose in tissues with exposures above that of plasma. The $t_{1/2}$ of mRNA-1647 was reliably estimated in muscle (site of injection), proximal popliteal and axillary distal lymph nodes and spleen with average values for all construct $t_{1/2}$ of **14.9** ~~**8.39**~~, 34.8, 31.1 and 63.0 hours, respectively.

p217 and following comes some actual data. this might be good to compare to the data there is on the euro version

Table 1.1: Mean Male Sprague-Dawley Rat Plasma mRNA-1647 Concentrations Following Intramuscular Administration of 100 µg mRNA-1647 on Day 1

Time (hr)	mRNA (ng/mL)											
	gB		gH		gL		UL128		UL130		UL131A	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.0	BQL	NA	0.00400[a]	0.00548	BQL	NA	BQL	NA	BQL	NA	BQL	NA
2.0	2.02	0.406	1.91	0.417	1.74	0.395	1.66	0.338	2.30	1.39	1.60	0.341
8.0	0.480	0.249	0.470	0.297	0.492	0.323	0.520	0.342	0.494	0.281	0.538	0.351
24.0	0.468	0.391	0.586	0.468	0.552	0.412	0.588	0.455	0.542	0.411	0.624	0.471
48.0	BQL	NA	0.00600[a]	0.00548	BQL	NA	BQL	NA	BQL	NA	BQL	NA
72.0	BQL	NA	0.00200[a]	0.00447	BQL	NA	BQL	NA	BQL	NA	BQL	NA
120.0	BQL	NA	0.00400[a]	0.00548	BQL	NA	BQL	NA	BQL	NA	BQL	NA

BQL = Below Quantifiable Limit (at 0.05, 0.01, 0.01, 0.05, 0.01, and 0.01 ng/mL for gB, gH, gL, UL130, UL131A, and UL128)
NA = not applicable; all values are BQL
a mean value was calculated with several BQL data points, hence the resulting value appears to be below the LLOQ.

p246 "gross pathological findings" for each rat euthanized. lots of lymph node and thymus findings

Appendix 9

Individual Gross Pathological Findings
5002121

Animal:	1018	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100 ug	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 2 (1)	

Gross Pathology Animal Details:

Animal Complete gross examination was performed.
Animal Notes: EUTHANASIA VIA ANESTHESIA AND PERFUSION

Gross Pathology Observations:

LYMPH NODE, AXILLARY : Focus; dark : 1 to >10, bilateral
SITE, INJECTION : Swelling : Right
SITE, INJECTION : Abnormal consistency; firm : Right
THYMUS : Focus; dark : >10

Gross Pathology - The following Tissues were Not Examined:

None

p289 pharmacokinetics. finally a description of what mRNA-1647 actually is: mRNA-1647 contains 6 mRNAs that encode the full-length CMV gB and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex. is that hexavalent? sounds a lot like comirnaty LNP-wise

2.6.5.1 PHARMACOKINETICS: OVERVIEW

Type of Study	Test Article	Test System	Method of Administration	Testing Facility	Report Number	Location in eCTD
Distribution						
Single Dose IM tissue distribution study in male Sprague Dawley rats	mRNA-1647[a]	Rat, Sprague Dawley	Single IM Dose	Charles River Laboratories, Sherbrooke, QC, Canada	5002121 Amendment 1	4.2.2.3

Abbreviations: CMV = cytomegalovirus; gB = glycoprotein B; gH = glycoprotein; gL = glycoprotein L; eCTD = electronic common technical document; IM = intramuscular; mRNA = messenger RNA.

[a] mRNA-1647 contains 6 mRNAs that encode the full-length CMV gB and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex. The 6 mRNAs are combined at a target mass ratio of 1:1:1:1:1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.

so this "worked" in instantly euthanized rats five years ago, at least we know that protein was expressed at certain parts of the body, so that's what we've got. wonder what else is coming, this can't be all

2.6.4.3 ABSORPTION

No absorption studies with mRNA-1273 have been performed.

2.6.4.4 DISTRIBUTION

2.6.4.4.1 Tissue Distribution Studies

The objective of this non-GLP study was to determine the tissue distribution of mRNA-1647 when given once by IM injection to rats. The PK characteristics of mRNA-1647 were determined in plasma and tissue. A group of 35 male Sprague Dawley rats was given a single IM injection of 100 µg of mRNA-1647 in a dose volume of 200 µL (dose concentration of 0.5 mg/mL) on Day 1. Subgroups of 5 rats each were sacrificed pre-dose and 2, 8, 24, 48, 72, and 120 hours after IM dosing. Blood and tissues were collected and processed for quantitation of the 6 mRNA constructs (gB, gH, gL, UL128, UL130, and UL131A) present in mRNA-1647 using a qualified bDNA multiplex method (Section 2.6.4.2). The overall design of this study is presented in Table 2.

oh the mRNA did not persist longer than three days when you killed all the rats by then? although i haven't gotten to the breeding study yet.

As observed with other IM delivered vaccines, the highest mRNA concentrations were observed at the injection site followed by the proximal (popliteal) and distal (axillary) lymph nodes, consistent with distribution via the lymphatic system. These tissues, as well as spleen and eye, had tissue-to-plasma AUC ratios > 1.0.

Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than muscle (injection site), proximal popliteal and distal axillary lymph nodes, and spleen, in which the average $T_{1/2}$ values for all constructs ranged from 14.9 to 63.0 hours.. The completed nonclinical PK and biodistribution study is presented in Table 1.

absolutely incredible. they had this stuff written up since 2017, just waiting on the right pandemic. mrna-1647 could be the placeholder for mrna-1273, covid 2p-S, or maybe mrna-1192, ebola glycoprotein, etc? these screenshots are both p302

2.6.4.5 METABOLISM

No metabolism studies with mRNA-1273 have been performed.

2.6.4.6 EXCRETION

No excretion studies with mRNA-1273 have been performed.

2.6.4.7 PHARMACOKINETIC DRUG INTERACTIONS

No PK drug interaction studies with mRNA-1273 have been performed.

2.6.4.8 OTHER PHARMACOKINETIC STUDIES

No other PK studies with mRNA-1273 have been performed.

2.6.4.9 DISCUSSION AND CONCLUSION

A non-GLP biodistribution study was completed with mRNA-1647, an mRNA-based vaccine combined in SM-102–containing LNPs, in male Sprague Dawley rats and is provided to support the development of mRNA-1273 using the Sponsor's mRNA technology platform. The biodistribution of mRNA-based vaccines in LNPs is predicted to be driven by the LNP characteristics. Therefore, mRNAs that are within an LNP of the same composition (eg, mRNA-1273 and mRNA-1647) are expected to distribute similarly.

so i've already been reading this for two hours now, gonna take a break.

let me just make this clear, Moderna had more than 2 years do do all kinds of safety studies. the documentation they submitted to the FDA is from a 2017 study.

p306 the moderna FDA submission for mrna-1273 begins. lots of weasely language about using mrna-1647 data

vaccines to prevent the spread of this disease.

ModernaTX, Inc. (Sponsor) has used its messenger RNA (mRNA)-based, rapid-response proprietary vaccine platform to develop mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA that encodes the full-length SARS-CoV-2 spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the S protein into the prefusion conformation. The mRNA is combined in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG. The mRNA-1273 Drug Product is provided as a sterile liquid for injection at a concentration of 0.20 mg/mL in 20 mM Tris buffer containing 87 g/L sucrose and 4.3 mM acetate, at pH 7.5.

The clinical development of mRNA-1273 to support its use in the adult population consists of 3 ongoing clinical trials being conducted in the US: a Phase 1, open-label, dose-ranging study

2.6.1.1 Nonclinical Development Program for mRNA-1273

The nonclinical pharmacology, pharmacokinetics and tissue distribution, and toxicology studies conducted with mRNA-1273 or other mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs support the intended clinical use of mRNA-1273. The program was designed in accordance with guidelines applicable at the time the studies were conducted, including relevant International Council for Harmonisation (ICH) and other global regulatory guidelines, and Good Laboratory Practice (GLP) regulations. The pivotal nonclinical safety studies were conducted according to the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (ENV/MC/CHEM[98]17) or GLP regulations in other countries that are signatories to the OECD Mutual Acceptance of Data agreement (eg, US Food and Drug Administration Code of Federal Regulations Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies).

The nonclinical studies were conducted in mice, rats, hamsters, and rhesus macaques (nonhuman primates [NHPs]), species determined to be relevant for the assessment of the immunogenicity, efficacy, and safety of mRNA-1273.

p308. so they mention lots and lots of studies they did on all these different animals, but then the nonclinical summary looks like this. insane.

oh yeah and there's 5 other moderna vaccines referenced.

2.6.1.1.2 Nonclinical Pharmacokinetic Program

mRNA is degraded within minutes in biological fluids and is unlikely to persist in tissues; therefore, the biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics and mRNAs that are within LNPs of the same composition (ie, SM-102-containing LNPs) are expected to distribute similarly to the LNPs. Thus, the distribution of mRNA-1647, an mRNA-based cytomegalovirus (CMV) vaccine that contains 6 mRNA sequences combined in SM-102-containing LNPs, assessed in a non-GLP, single intramuscular (IM) dose biodistribution study supports the development of mRNA-1273.

2.6.1.1.3 Nonclinical Toxicology Program

The toxicological profile associated with mRNA-based vaccines formulated in SM-102-containing LNPs, including mRNA-1273, is driven primarily by the LNP composition and, to a lesser extent, by the biologic activity of the antigen(s) encoded by the mRNA. The safety and tolerability of 5 mRNA-based vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs (2 Zika virus vaccines: mRNA-1706 and mRNA-1893; 1 human metapneumovirus and parainfluenza virus type 3 vaccine: mRNA-1653; and 2 CMV vaccines: mRNA-1647 and mRNA-1443) have been evaluated in 6 GLP-compliant repeat-dose toxicity studies in Sprague Dawley rats. Additionally,

p316 the genotoxicity of mRNA vaccines is mainly associated with the LNP formulation and to a lesser extent, the encoded antigen.

well at least they apparently did a genotox study or two. biontech didn't.

concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 g/L sucrose and 10.7 mM acetate, at pH 7.5.

The distribution, toxicity, and genotoxicity associated with mRNA vaccines formulated in LNPs are driven primarily by the composition of the LNPs and, to a lesser extent, by the biologic activity of the antigen(s) encoded by the mRNA. Therefore, the distribution study, Good Laboratory Practice (GLP)-compliant toxicology studies, and in vivo GLP-compliant genotoxicity study conducted with mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs are considered supportive and BLA-enabling for mRNA-1273. SM-102, the novel lipid used in mRNA-1273, was evaluated as an individual agent in GLP-compliant in vitro genotoxicity studies. Additionally, the immunogenicity and toxicity profiles of mRNA-1273 were assessed in a non-GLP repeat-dose study.

they had ralph baric build a mouse-cov-2 !! p317 @TheJikky out to get you from the start @BillyBostickson

Nonclinical primary pharmacology evaluations were conducted in young and aged mice (BALB/c, BALB/cJ, C57/BL6J, and B6C3F1/J strains), golden Syrian hamsters, and rhesus macaques (nonhuman primates [NHPs]) animal models to characterize the immunogenicity of mRNA-1273, as well as its effects on viral replication and disease progression after SARS-CoV-2 challenge, and to evaluate its safety profile and its potential to promote vaccine-associated enhanced respiratory disease (ERD) after viral challenge, which has previously been observed with vaccines against respiratory syncytial virus (Kim et al 1969), measles (Polack 2007), and in animal models of SARS-CoV vaccination (Czub et al 2005; Deming et al 2007; Bolles et al 2011; Corbett et al 2020a). Additionally, the immunogenicity of mRNA-1273 was assessed in a non-GLP repeat-dose pharmacology study in Sprague Dawley rats.

As SARS-CoV-2 is a newly emerged CoV, there were no established animal models for the evaluation of prophylactic vaccines and therapeutics. Therefore, nonclinical studies were initiated in multiple animal species in order to gain a comprehensive understanding of the effects of mRNA-1273 immunization. Wild-type (WT) mice are a convenient and easy-to-use model to assess vaccine immunogenicity; however, the ACE-2 receptor, the primary route for SARS-CoV-2 binding and entry, differs significantly between mice and humans and, as result, WT SARS-CoV-2 does not infect mice. Therefore, a mouse-adapted SARS-CoV-2 strain, which was developed by the laboratory of Dr. Ralph Baric at the University of North Carolina at Chapel Hill, was used to assess protection of immunized mice from SARS-CoV-2 challenge. Although this mouse-adapted strain infects young mice and induces mild disease symptoms, more severe

p327 has an overview of all the studies, and 328 a comprehensive cliffnote of the moderna vaccine nonclinical work

Table 3: Summary of Toxicology Program for mRNA-1273

Study Type	Test Article	Species, Strain	Method of Administration; Dose	GLP	Report Number
Repeat-Dose Toxicity					
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1706[a]	Rat, Sprague Dawley	IM; 0, 13, 65, 129 µg/dose[b] (Days 1, 15, 29)	Yes	5002045
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1706[a]	Rat, Sprague Dawley	IM; 0, 10, 50, 100 µg/dose (Days 1, 15, 29)	Yes	5002231
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1653[c]	Rat, Sprague Dawley	IM; 0, 10, 50, 150 µg/dose (Days 1, 15, 29)	Yes	5002033
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1893[d]	Rat, Sprague Dawley	IM; 0, 10, 30, 96 µg/dose (Days 1, 15, 29)	Yes	5002400
6-week (4 doses) repeat-dose study with 2-week recovery	mRNA-1647[e]	Rat, Sprague Dawley	IM; 0, 8.9, 27, 89 µg/dose[f] (Days 1, 15, 29, 43)	Yes	5002034
6-week (4 doses) repeat-dose study with 2-week recovery	mRNA-1443[g]	Rat, Sprague Dawley	IM; 0, 9.6, 29, 96 µg/dose[h] (Days 1, 15, 29, 43)	Yes	5002158
In Vitro Genotoxicity					
Bacterial reverse mutation test	SM-102	*Salmonella typhimurium, Escherichia coli*	Incubation for 67 hours 29 minutes with 0, 1.58, 5.0, 15.8, 50, 158, 500, 1581, 5000 µg/plate SM-102 with or without supplemented rat liver fraction	Yes	9601567
Mammalian cell micronucleus test	SM-102	Human peripheral blood lymphocytes	Incubation for 4 and 24 hours with 0, 163, 286, 500 µg/mL SM-102 with or without supplemented rat liver fraction	Yes	9601568
		lymphocytes	liver fraction		
In Vivo Genotoxicity					
In vivo mammalian erythrocyte micronucleus test	mRNA-1706[a]	Rat, Sprague Dawley	Single IV; 0, 0.6/6.2 (F), 1.3/13.5, 2.6/27.0, 5.2/54.1 (M) mg/kg mRNA-1706/SM-102[i,j]	Yes	9800399
In vivo mammalian erythrocyte micronucleus test	NPI luciferase mRNA[k]	Rat, Sprague Dawley	Single IV; 0, 0.32/6.0, 1.07/20, 3.21/60 mg/kg NPI luciferase mRNA/SM-102	No	AF87FU.125012 NGLPICH.BTL
Other Toxicology					
5-week (2 doses) repeat-dose immunogenicity and toxicity study	mRNA-1273[l]	Rat, Sprague Dawley	IM; 0, 30, 60, 100 µg/dose (Days 1 and 22)	No	2308-123

Abbreviations: CMV = cytomegalovirus; CoV = coronavirus; F = female; gB = glycoprotein B; gH = glycoprotein H; gL = glycoprotein L; GLP = Good Laboratory Practice; h = hour; IM = intramuscular; IV = intravenous; M = male; min = minute; mRNA = messenger RNA; NPI = nascent peptide imaging; pp65 = phosphoprotein 65; prME = pre-membrane and envelope; S-2P = spike protein modified with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = 2019 novel coronavirus; SoA = summary of analysis.

[a] mRNA-1706 contains a single mRNA sequence that encodes the prME structural proteins of Zika virus combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 20 mM Tris, 8% sucrose, pH 7.4.

[b] The original dose levels selected were 0, 10, 50, and 100 µg/dose, respectively (SoA issued on 11 October 2016). The calculated dose levels were revised based on the updated concentration reported for mRNA-1706 Lot No. MTDP16064 (SoA issued on 03 May 2017). The change in the reported mRNA content for mRNA-1706 was 29%.

[c] mRNA-1653 contains 2 distinct mRNA sequences that encode the full-length membrane-bound fusion proteins of human metapneumovirus and parainfluenza virus type 3. The 2 mRNAs are combined at a target mass ratio of 1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 7% PG, 1 mM DTPA, pH 7.4.

[d] mRNA-1893 contains a single mRNA sequence that encodes the prME structural proteins of Zika virus in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 100 mM Tris, 7% PG, 1 mM DTPA, pH 7.5.

[e] mRNA-1647 contains 6 mRNAs that encode the full-length CMV gB and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex. The 6 mRNAs are combined at a target mass ratio of 1:1:1:1:1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.

[f] The original dose levels selected were 0, 10, 30, and 100 µg/dose, respectively (SoA issued on 16 Mar 2017). The calculated dose levels were revised based on the updated concentration reported for mRNA-1647 Lot No. MTDP17015 (SoA issued on 31 May 2017). The change in the reported mRNA content for mRNA-1647 was –11%.

[g] mRNA-1443 contains a single mRNA sequence that encodes a phosphorylation mutant of the CMV phosphoprotein 65 protein (ie, deletion of amino acids 435-438) combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.

[h] The original dose levels selected were 0, 10, 30, and 100 µg/dose, respectively (SoA issued on 16 Mar 2017). The calculated dose levels were revised based on the updated concentration reported for mRNA-1443 Lot No. MTDP17017 (SoA issued on 30 May 2017). The change in the reported mRNA content for mRNA-1443 was 4%.

[i] A dose-range finding test was performed prior to the main phase of the study, wherein male and female rats (3 animals/sex) were given a single IV injection (doses 2.6/27.0, 3.9/40.6, and 5.2/54.1 mg/kg mRNA-1706/SM-102 for females, and 2.6/27.0, 5.2/54.1, and 10.3/107.1 mg/kg mRNA-1706/SM-102 for males).

[j] The original dose levels selected were 0, 1.0, 2.0, 4.0, 0.5, 1.0, and 2.0 mg/kg mRNA-1706, respectively (SoA issued on 11 October 2016). The calculated dose levels were revised based on the updated concentration reported for mRNA-1706 Lot No. MTDP16064 (SoA issued on 03 May 2017). The change in the reported mRNA content for mRNA-1706 was 29%.

[k] The NPI luciferase mRNA is combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 25 mM Tris, 123 g/L sucrose, 1 mM DTPA, pH 7.5.

[l] mRNA-1273 contains a single mRNA sequence that encodes the full-length SARS-CoV-2 S-2P combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 20 mM Tris, 87 mg/mL sucrose, 10.7 mM sodium acetate, pH 7.5.

page 330.

"well we found some genotoxicity and some minimal bone marrow damage but because it stays in your arm we think the risk is... low."

the EMA/FDA got this document and decided not to ask for any genotox from pfizer 😬

2.4.4.2 Genotoxicity

SM-102, the novel lipid used in mRNA-1273, was evaluated in genotoxicity studies as an individual agent using a standard ICH S2 (R1) approach (ICH 2011), including a GLP-compliant in vitro bacterial reverse mutation (Ames) test in *S. typhimurium* and *E. coli* (Table 2.6.7.8A [Module 2.6.7] and Report 9601567) and a GLP-compliant in vitro micronucleus test in human peripheral blood lymphocytes (Table 2.6.7.8B [Module 2.6.7] and Report 9601568).

In addition, SM-102 was evaluated for in vivo genotoxicity risk in a GLP-compliant in vivo rat micronucleus test using a similar mRNA-based vaccine formulated in SM-102 LNPs (Table 2.6.7.9A [Module 2.6.7] and Report 9800399) and in a non-GLP-compliant in vivo rat micronucleus test using a reporter mRNA (NPI luciferase mRNA) formulated in SM-102 LNPs (Table 2.6.7.9B [Module 2.6.7] and Report AF87FU.125012NGLPICH.BTL).

Genotoxicity assessments of the SM-102 lipid concluded that the lipid is not genotoxic in the bacterial mutagenicity and human peripheral blood lymphocytes chromosome aberration assays. Two intravenous in vivo micronucleus assays were conducted with mRNA-based vaccines formulated in the SM-102-containing LNPs. Results from Report AF87FU.125012NGLPICH.BTL were negative up to 3.21/60 mg/kg NPI luciferase mRNA/SM-102, while results from Report 9800399 were positive at 2.6/27.0 mg/kg mRNA-1706/SM-102 in females and at 5.2/54.1 mg/kg mRNA-1706/SM-102 in males, indicating that there was minimal bone marrow toxicity. The equivocal results are likely driven by micronuclei formation secondary to elevated body temperature induced by LNP-driven systemic inflammation at high systemic (intravenous) doses. Overall, the genotoxic risk to humans is considered to be low due to minimal systemic exposure following IM administration, limited duration of exposure, and negative in vitro results.

p364 details the genotox studies a bit closer. the in vitros were negative, yet the in vivo was.. positive. they did this one intravenously, but because the human one is IM, its gonna be fine. what the fuck. no idea what micronucleated means and if i open another tab, its over

2.4.4.2.2 In Vivo

An in vivo micronucleus study was conducted with mRNA-1706, a representative SM-102-containing LNP investigational product (Study 9800399 in CBER MF# 19622). The study was conducted in rats using an intravenous route of administration. The intravenous route was selected to maximize exposure to SM-102 and the other lipids incorporated into the mRNA-based investigational product LNPs. SM-102 induced statistically significant increases in micronucleated immature erythrocytes in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak

and associated with minimal bone marrow toxicity. These observations indicate that the risk to humans after IM administration is low, due to minimal systemic exposure.

2.4.4.3 Other Toxicity Studies

A non-GLP study in Sprague Dawley rats was conducted by the Sponsor to characterize the immunogenic response and potential toxicity of mRNA-1273 at clinically relevant doses (Study 2308-123). mRNA-1273 was administered to male and female Sprague Dawley rats as an IM injection on Day 1 and Day 22 at dose levels of 30, 60, and 100 µg/dose. Safety endpoints

p377 mrna-1647 study again. charles river is the company, has several facilities apparently

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director	(b) (6)
Test Facility Management	(b) (6)

1.2. Individual Scientists (IS) at Test Facility

Analytical Chemistry	(b) (6) Charles River Laboratories Montreal ULC Senneville Site (CR MTL) Senneville, QC
Bioanalysis (mRNA Quantitation)	(b) (6) Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB) Sherbrooke, QC
Pathology (Necropsy Only)	(b) (6) Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB) Sherbrooke, QC

1.3. IS at Sponsor Test Site

Toxicokinetic Interpretation	(b) (6) Moderna Therapeutics Cambridge MA 02138, USA

few hundred pages of the same (its literally the study and all the redacted stuff as well) then this on page 687: new genotox studies! and repro/fertility. so the first ~x hundred pages were v1 of the submission, and this is an update?

mRNA-1273. Toxicology results are fully summarized in Module 2.6.6.

Table 3: Summary of Toxicology Program for mRNA-1273

Study Type	Test Article	Species, Strain	Method of Administration; Dose	GLP	Report Number
Repeat-Dose Toxicity					
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1706[a]	Rat, Sprague Dawley	IM; 0, 13, 65, 129 µg/dose[b] (Days 1, 15, 29)	Yes	5002045
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1706[a]	Rat, Sprague Dawley	IM; 0, 10, 50, 100 µg/dose (Days 1, 15, 29)	Yes	5002231
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1653[c]	Rat, Sprague Dawley	IM; 0, 10, 50, 150 µg/dose (Days 1, 15, 29)	Yes	5002033
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1893[d]	Rat, Sprague Dawley	IM; 0, 10, 30, 96 µg/dose (Days 1, 15, 29)	Yes	5002400
6-week (4 doses) repeat-dose study with 2-week recovery	mRNA-1647[e]	Rat, Sprague Dawley	IM; 0, 8.9, 27, 89 µg/dose[f] (Days 1, 15, 29, 43)	Yes	5002034
6-week (4 doses) repeat-dose study with 2-week recovery	mRNA-1443[g]	Rat, Sprague Dawley	IM; 0, 9.6, 29, 96 µg/dose[h] (Days 1, 15, 29, 43)	Yes	5002158
In Vitro Genotoxicity					
Bacterial reverse mutation test	SM-102	*Salmonella typhimurium, Escherichia coli*	Incubation for 67 hours 29 minutes with 0, 1.58, 5.0, 15.8, 50, 158, 500, 1581, 5000 µg/plate SM-102 with or without supplemented rat liver fraction	Yes	9601567
Bacterial reverse mutation test	PEG2000-DMG (b) (4)	*Salmonella typhimurium, Escherichia coli*	Incubation for 67 h and 57 min with 0, 1.58, 5.0, 15.8, 50, 158, 500, 1581, 5000 µg/plate PEG2000-DMG with or without supplemented rat liver fraction	Yes	9601035
Mammalian cell micronucleus test	SM-102	Human peripheral blood lymphocytes	Incubation for 4 and 24 hours with 0, 163, 286, 500 µg/mL SM-102 with or without supplemented rat liver fraction	Yes	9601568
Mammalian cell micronucleus test	PEG2000-DMG (b) (4)	Human peripheral blood lymphocytes	Incubation for 4 h and/or 24 hours with 0, 0, 53.3, 93.3, 163, 286, 500 µg/mL PEG2000-DMG with or without supplemented rat liver fraction	Yes	9601036
In Vivo Genotoxicity					

Study Type	Test Article	Species, Strain	Method of Administration; Dose	GLP	Report Number
In vivo mammalian erythrocyte micronucleus test	mRNA-1706[a]	Rat, Sprague Dawley	Single IV; 0, 0.6/6.2 (F), 1.3/13.5, 2.6/27.0, 5.2/54.1 (M) mg/kg mRNA-1706/SM-102[j, k]	Yes	9800399
In vivo mammalian erythrocyte micronucleus test	NPI luciferase mRNA[l]	Rat, Sprague Dawley	Single IV; 0, 0.32/6.0, 1.07/20, 3.21/60 mg/kg NPI luciferase mRNA/SM-102	No	AF87FU.125012 NGLPICH.BTL
Reproductive and Developmental Toxicity					
Combined developmental and perinatal/postnatal developmental and reproductive toxicity study	mRNA-1273[m]	Rat, Sprague Dawley	IM; 100 µg/dose (Study Days 1 and 15 [28 and 14 days prior to mating, respectively] and Gestation Days 1 and 13)	Yes	20248897
Other Toxicology					
5-week (2 doses) repeat-dose immunogenicity and toxicity study	mRNA-1273[n]	Rat, Sprague Dawley	IM; 0, 30, 60, 100 µg/dose (Days 1 and 22)	No	2308-123

PEG-2000 only gets a single sentence for two studies though :(

(intravenous) doses. Overall, the genotoxic risk to humans is considered to be low due to minimal systemic exposure following IM administration, limited duration of exposure, and negative in vitro results.

Genotoxicity assessments of the PEG2000-DMG lipid concluded that the lipid is not genotoxic in the bacterial mutagenicity and the human peripheral blood lymphocytes chromosome aberration assays.

p691 outlies the repro study. the pups had an immune response, woohey! 6 pups in 4 litters had skeletal aberrations, but they also had antibodies

2.4.4.3 Reproductive and Developmental Toxicity

A GLP-compliant combined developmental and perinatal/postnatal developmental and reproductive toxicity study was conducted to assess the potential effects of mRNA-1273 on fertility and pre- and postnatal development in pregnant and lactating female Sprague Dawley rats following IM administration of the human dose of 100 µg to dams on Study Days 1 and 15 (28 and 14 days prior to mating, respectively) and Gestation Days (GDs) 1 and 13 (Table 2.6.7.11 [Module 2.6.7], and Report 20248897).

Female rats assigned to Cohort 1 were euthanized on GD 21 for Caesarean-sectioning and fetal examinations. Female rats assigned to Cohort 2 were allowed to deliver their litters naturally and dams and pups were followed through Lactation Day (LD) 21.

Robust IgG response to S-2P antigen was observed in both the F_0 rats and F_1 generation rats following immunization of F_0 rats with mRNA-1273. In the F_0 rats, peak titer of 442,138 antibody units/mL was reached on GD 13. Titers subsequently plateaued at parturition (GD 21) and stayed relatively constant through LD 21. High IgG antibodies to SARS-CoV-2 S-2P were also observed in GD 21 F_1 fetuses and LD 21 F_1 pups, indicating strong transfer of antibodies from dam to fetus and from dam to pup.

In the F_1 generation, there were no mRNA-1273-related effects or changes in the following parameters: mortality, body weight, clinical observations, macroscopic observations, gross pathology, external or visceral malformations or variations, skeletal malformations, and mean number of ossification sites per fetus per litter. mRNA-1273-related variations in skeletal examination included statistically significant increases in the number of F_1 rats with 1 or more wavy ribs and 1 or more rib nodules. Wavy ribs appeared in 6 fetuses and 4 litters with a fetal prevalence of 4.03% and a litter prevalence of 18.2%. Rib nodules appeared in 5 of those 6 fetuses. Skeletal variations are structural changes that do not impact development or function of a developing embryo, are considered reversible, and often correlate with maternal toxicity and/or lack of other indicators of developmental toxicity (Carney and Kimmel 2007). Maternal toxicity in the form of clinical observations was observed for 5 days following the last dose (GD 13), correlating with the most sensitive period for rib development in rats (GDs 14 to 17). Furthermore, there were no other indicators of mRNA-1273-related developmental toxicity observed, including delayed ossification; therefore, these common skeletal variations were not considered adverse.

and p695 closes with the "integrated overview and conclusions". two pages further up mentions the end of the phase 3 being close to finished. and that's it. anyone knowledgeable about moderna? was the mRNA-1647 swap known?

A strong immunogenic response against SARS-CoV-2 S-2P was observed on Day 35, with measured IgG antibody titers above 10^6 at all dose levels. mRNA-1273 had no effect on body weights and limited, transient clinical signs starting at 30 µg/dose consisting of transient dose-dependent injection site edema with or without hindlimb impairment. Clinical pathology findings consisted, in part, of changes associated with inflammation starting at 30 µg/dose. In general, the changes observed are consistent with the results from the previous GLP rat toxicity studies conducted with other mRNA-based vaccines formulated with SM-102-containing LNPs.

2.4.4.5 Summary of Nonclinical Safety Margins

Pending the outcome of the Phase 3 clinical trial with mRNA-1273, a human dose of 100 µg/dose is anticipated to be safe and to provide protective immunization against SARS-CoV-2 infection.

In the rat repeat-dose toxicity studies in which up to 100 µg/dose of mRNA-1273 administered on Day 1 and Day 22, up to 150 µg/dose of mRNA-1706, mRNA-1653, or mRNA-1893 administered once every 2 weeks for 1 month (3 doses), or up to 96 µg/dose of mRNA-1647 and mRNA-1443 administered once every 2 weeks for 6 weeks (4 doses) were evaluated, the administered mRNA/LNP vaccines were well tolerated. In addition, results from the combined

2.4.5. INTEGRATED OVERVIEW AND CONCLUSIONS

In support of the development of mRNA-1273 against SARS-CoV-2, nonclinical pharmacology, biodistribution, and toxicology studies have been completed using mRNA-1273 or other mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs.

Data from the nonclinical testing program presented in this submission support the clinical efficacy and safety of mRNA-1273 at doses up to 100 µg administered twice IM 28 days apart.

- The expression of the mRNA-encoded SARS-CoV-2 S-2P antigen was confirmed in vitro and in vivo. HEK293T cells transfected with a dose range (0.003125 through 0.2 µg) of mRNA expressed the encoded SARS-CoV-2 S-2P antigen, as demonstrated by surface-protein staining with mAbs specific to the RBD (CR3022) or NTD (4A8) epitopes of the SARS-CoV-2 S protein. The expression of these epitopes was similarly confirmed in spleen and draining lymph node immune cells (cDCs and pDCs) in BALB/c mice administered a single IM dose (2 or 10 µg) of mRNA-1273.

- Nonclinical pharmacology studies of mRNA-1273 vaccination were performed in young and aged mice, golden Syrian hamsters, and rhesus macaques (NHPs). These studies demonstrate that mRNA-1273 is well tolerated, is immunogenic, and drives robust SARS-CoV-2-specific antibody and T-cell responses. Nonclinical viral challenge studies in animal models demonstrated that mRNA-1273 fully protects immunized animals from viral challenge when administered on a prime only or prime/boost schedule at dose levels ≥ 1 µg/dose in mice and hamsters and when administered on a prime/boost schedule at ≥ 30 µg/dose in nonhuman primates. In addition, these studies have shown that mRNA-1273 does not promote vaccine-associated ERD at any dose level evaluated, including those that only provided partial protection from challenge.

• • •

I spent my evening with potato soup and revisiting the Charles River biodistribution study 185350 FOIA'd by @JudicialWatch end of september.
judicialwatch.org/documents/jw-v...

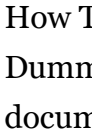
I haven't seen this one be discussed a lot, perhaps because it's so goddamn weird? 👇 First off, why did they start a radiocoded luciferase animal study EIGHTY-FIVE DAYS after BNT162-01 dosed it's first HUMAN? Literally ten days before Phase 2/3 started? @joshg99

Read 6 tweets

6/10 nicht-klinische Studien (sprich: tierversuchsreihen) der Pfizer-BioNTech Impfstoffentwicklung wurden in Shanghai durchgeführt. Ja, CCP-China, dass bis dato mRNA-Produkte nur in Hong Kong verwendet.

In diesem FOIA-release ist auch die Studie 185350 enthalten, die bislang nicht einsehbar war. Studiengegenstand: Bioverteilung eines modRNA-LNP-Gemisches mit den gleichen Lipiden, wie in den BNT162-produkten, und

Read 7 tweets



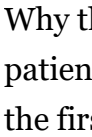
a_concerned_amyloidosis💜🐭
@a_nineties

Nov 23

Für meine vielen neuen Follower(u.a. @Tim_Roehn, merci!): Ein strang zu Ungereimtheiten in den zulassungsstudien BNT162-01 und C4591001 für den Pfizer-BioNTech Impfstoff, die mir in meiner fortlaufenden Beschäftigung mit den phmpt.org Daten aufgefallen sind.

Phase 1 C4591001 diente der Dosierungsfindung von insgesamt 6 Kandidaten () und hatte ursprünglich 840 Teilnehmer, die im Laufe der Studie (!) auf schliesslich 195 runtergekürzt wurden.

Read 19 tweets



a_concerned_amyloidosis💜🐭
@a_nineties

Nov 2

a brief outline of the Nov 1 PHMPT release.
mega.nz/file/yRgyQZzZ#... these are all the BNT162-01 related .xpt files as .csv, the C4591001 file is too big to open in excel 😅 and you don't need me for the .pdf (i hope)

first file is -suppex.csv. it seems to be a protocol checklist, with six rows per patient except if there was a protocol deviation. includes medication nr's. the screenshots show the only two deviations recorded in this file.

Read 11 tweets

a_concerned_amyloidosis💜🐭
@a_nineties

Oct 31

How To Read The #Pfizer .xpt Files For Dummies - By A Dummie in anticipation of tomorrow's fresh #PHMPT document dump, i'll be showing you how to open those pesky .xpt files, because it took me AGES to figure out. Be warned though, I REALLY dont know what i'm doing😂

so, first off you'll need to download R cloud.r-project.org pick your OS and download. Run it. You'll get an interface like this:

Read 10 tweets

a_concerned_amyloidosis💜🐭
@a_nineties

Oct 18

Why the full spike? a🧵 Study BNT162-01 dosed its first patient on April 23rd. On April 29th, BioNTech reported that the first cohort had been dosed, implying 12 pts per candidate. This is not factual. The first BNT162b2 patient in Cohort 1 was dosed on 15th June. >>

C4591001 dosed its first patient April 29th. The first two doses of BNT162b2 were administered on June 8th. So the

Read 16 tweets