2 SUMMARY

The growth of global outbreaks of Severe Acute Respiratory Syndrome (SARS)-CoV-2 infection is a threat. The infection causes Coronavirus Disease 2019 (COVID-19). Therefore, we must create a new prophylactic vaccine. ~~There is an urgent need for the development of a new prophylactic vaccine given the threat posed by the increasing number of globally distributed outbreaks of Severe Acute Respiratory Syndrome (SARS) CoV 2 infection and thus its associated disease Coronavirus Disease 2019 (COVID 19).~~

A ribonucleic acid (RNA)-based vaccine can encode a viral antigen. ~~The development of a ribonucleic acid (RNA) based vaccine encoding a viral antigen~~ Once vaccinated, the organism translates the antigen to a protein that induces a protective immune response. ~~that is translated by the vaccinated organism to protein to induce a protective immune response~~ This response has advantages over standard vaccines. ~~provides significant advantages over more conventional vaccine approaches.~~

BioNTech developed three RNA platforms:

- Non-modified uridine containing mRNA (uRNA)
- Nucleoside modified mRNA (modRNA)
- Self-amplifying mRNA (saRNA)

Non-clinical data - ~~At BioNTech, there are three different RNA platforms under development, namely non-modified uridine containing mRNA (uRNA), nucleoside modified mRNA (modRNA), and self-amplifying mRNA (saRNA).~~

A GLP-compliant, repeat-dose toxicity study assessed the non-clinical safety and toxicity of the BNT162 family. These are lipid nanoparticle (LNP) enveloped RNA vaccines that encode SARS-CoV-2 antigens. We gave ~~The non-clinical safety and toxicity of the BNT162 family of lipid nanoparticle (LNP) enveloped uRNA, modRNA, and saRNA vaccine platforms encoding SARS-CoV-2 antigens was tested in a GLP-compliant repeat-dose toxicity study.~~ Wistar Han rats the following vaccine candidates:

- BNT162a1
- BNT162b1
- BNT162b2
- BNT162c1

Intramuscular (IM) injections of 2 or 3 doses occurred weekly. The rats tolerated these doses with no evidence of systemic toxicity. ~~In this study in Wistar Han rats, administration of the vaccine candidates BNT162a1, BNT162b1, BNT162b2, or BNT162c1 using intramuscular (IM) injections weekly for 2 (BNT162c1) or 3 administrations was tolerated without evidence of systemic toxicity. Non-adverse~~

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Commented [SR2]: Page 32 of "Targeted Regulatory Writing Techniques" shows the use of the pronoun "we." Page 191 of the AMA style guide, 9th edition, also shows the use of "we" in section 5.8.2 Mood.

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~~inflammatory changes at the injection sites and the draining lymph nodes, increased hematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites were observed. Transient vacuolation of portal hepatocytes unassociated with evidence of hepatocellular damage was observed in dosed animals.~~ The findings in this study ~~are~~ were consistent with those that ~~typically~~ often occur when subjects receive ~~associated with the~~ IM ~~administration of~~ LNP encapsulated RNA-based vaccines. To learn more, see section 5, NON-CLINICAL STUDIES.

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Clinical data -

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~~BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in three clinical trials with healthy adults (men and women) aged between 18 and 85 yrs. In these trials, the subjects are either younger adults (aged 18 to 55 yrs), older adults (aged 55 to 85 yrs), or elderly adults (aged 65 to 85 yrs).~~

~~As summarized~~The table below ~~below~~has a summary (as of August 6, 2020) of three clinical trials that had healthy adults (men and women). ~~, as of August 6th, 2020, a total of 1,506 subjects (men and women)~~Each received at least one ~~were dosed at least once w~~dose of ~~ith~~the BNT162 vaccine candidates. ~~In these trials, the subjects are either younger adults (aged 18 to 55 yrs), older adults (aged 55 to 85 yrs), or elderly adults (aged 65 to 85 yrs).~~
~~in the ongoing clinical trials (i.e., BNT162-01, BNT162-02/C4591001, and BNT162-03).~~

BNT162 vaccine candidate	[REDACTED]	[REDACTED]	BNT162b2	[REDACTED]	
Dosing regimen (age group)					
Phase I					
SD (younger adults)	30	93	199	71	
P/B (younger adults)	24	61	121	1	
SD (elderly adults)	0	36	36	0	
P/B (elderly adults)	0	36	36	0	
Phase II/III					
SD (younger and older adults)			1,041*		
Total all adults dosed at least once in Phase I & II/III	**30**	**129**	**1,276**	**71**	**Sum=1,506**

*Estimated / includes estimated number based on 1.1 verum: placebo assignment
Years = yrs; Younger adults = adults aged 18 to 55 yrs; Elderly adults = adults aged 65 to 85 yrs.

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Immune response - Immunogenicity data (as of July 24, 2020) are available from younger and elderly adults who received BNT162b2 (modRNA). ~~Preliminary immunogenicity data (status July 24th, 2020) are available from younger and~~

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These data suggested that, by day 21, this vaccine induced a robust IgG-binding response to RBD/S1 and a neutralizing response specific to SARS-CoV-2. ~~elderly adults dosed with BNT162b1 or BNT162b2. The available immunogenicity data suggest that, by day 21, the BNT162b (i.e., modRNA-based) vaccine candidates induce a robust IgG-binding response to RBD/S1 and neutralizing response specific to SARS-CoV-2. Immunogenicity~~ This immune response appears to ~~be substantially~~ increase~~d following~~ after the second dose of vaccine.

~~For BNT162b1, P/B doses of 1, 10, 30, and 50 µg administered 21 d apart elicited antibodies and robust CD4+ and CD8+ T cell responses. All subjects exhibited antibody responses superior to those observed in a COVID-19 convalescent human serum (HCS) panel. The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs, at least 14 d after PCR-confirmed diagnosis, and at a time when the individuals were asymptomatic. The serum donors predominantly had symptomatic infections (35/38), and one had been hospitalized.~~

~~For BNT162b2, P/B doses of 10 µg of BNT162b2 administered 21 d apart elicited substantial Th1-type CD4+ and CD8+ T cell responses.~~

The ~~BNT162b1 and~~ BNT162b2 vaccine~~s~~ elicited~~,~~ antigen specific CD8+ and CD4+ T cell responses were ~~comparable~~ similar to or higher than the memory responses in the same subjects against:

- ~~,~~C~~c~~ytomegalovirus (CMV)
- ~~,~~Epstein-Barr virus (EBV)
- ~~I,~~ influenza virus
- ~~, and t~~Tetanus toxoid~~.~~

Toxicity -

~~In the trial BNT162-02/C4591001 (status July 24th, 2020) in younger adults administered BNT162b1 P/B at 10 µg or 30 µg, RBD-binding IgG levels had increased at day 7 to approximately 8- and 46-fold that seen in a COVID-19 HCS panel. After 10 µg or 30 µg BNT162b1 doses, preliminary data show modest increases in SARS-CoV-2 neutralizing titers (geometric mean titers, GMTs) at 21 d after the prime dose. Higher titers were observed at 7 d after the boost dose, reaching 1.8 to 2.8-fold neutralization GMT, compared to that seen in the COVID-19 HCS panel. Similar results were seen for BNT162b2.~~

~~Similar results were seen for BNT162b1 and BNT162b2 after administration to younger adults in the trial BNT162-01.~~

~~Preliminary safety data are available from the ongoing trials BNT162-01 and BNT162-02/C4591001.~~

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~~Generally~~In general, we observed good tolerability ~~was observed~~. Overall, many of the reported adverse events (AEs) appeared to be like the reactions one could anticipate for IM-administered vaccines. Onset occurs within the first 24 h after immunization. ~~Overall, many of the reported adverse events (AEs) appear to be similar to reactogenicity events anticipated for intramuscularly (IM) administered vaccines, typically with an onset within first 24 h post immunization.~~ All AEs or reaction symptoms resolved on their own, mostly within 24 h of onset. Use of simple measures (e.g., paracetamol) managed the reactions. ~~All AEs / reactogenicity symptoms resolved spontaneously, mostly within 24 h of onset, and were managed with simple measures (e.g., paracetamol).~~ There were no serious adverse events (SAEs) and no unexpected toxicities. Creation of a safe COVID-19 vaccine is the Sponsor's highest priority. Thus, the favorable tolerability profile was the major driver for choosing BNT162b2.

Dosage -

~~In the trial BNT162-01, BNT162a1 P/B has been tested at doses of 0.1, 0.3, and 3 µg in younger adults. In the first 6 subjects treated with the 3 µg prime dose, the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) led to a decision not to administer the 3 µg boost dose and to defer further dosing with this vaccine candidate.~~

~~In the trials BNT162-01 and BNT162-02/C4591001, BNT162b1 P/B dosing has been tested at dose levels between 1 µg and 100 µg in younger adults. Acceptable tolerability was shown after both doses up to 50 µg BNT162b1.~~

In the trials, we tested ~~BNT162-01 and BNT162-02/C4591001,~~ BNT162b2 P/B ~~has been tested~~ at dose levels between 1 µg and 30 µg in younger adults. ~~Acceptable tolerability was shown after b~~Both doses at all dose levels showed acceptable tolerability.

~~In the trial BNT162-02/C4591001, o~~Overall, P/B dosing with ~~BNT162b1 and~~ BNT162b2 doses of 10 µg to 30 µg showed acceptable tolerability in elderly adults. This seems better than the tolerability in younger adults at the same doses. ~~This tolerability appears to be better than seen in younger adults at the same doses.~~

The Sponsor put more weight on the SARS - CoV-2 neutralizing antibody response level in elderly adults. This response was higher at the 30 µg dose level for this age group, which is at the highest risk of severe disease.

~~[REDACTED]~~

The BNT162 vaccine candidates have neither been approved for use nor ~~been~~ marketed in any country.

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3.4 Clinical development

We investigated the BNT162b2 vaccine candidate as part of a program to create a prophylactic vaccine to stop infection with SARS-CoV-2. The infection causes COVID-19.

~~BNT162 vaccine candidates based on the uRNA, mod RNA, and saRNA formats are currently under investigation i~~In three clinical trials, we evaluated the safety and immunogenicity of BNT162b2. The trials included ~~with~~ healthy subjects (men and women), aged ~~aged between~~ 18 ~~and~~ to 85 years. ~~One further clinical trial is planned.~~

For an overview of the ~~different~~ BNT162b2 vaccine candidate~~s under~~ investigated in the clinical ~~investigation~~trials, see Table 1.

Table 1: Characteristics of ~~the different~~the BNT162b2 vaccine candidate~~s~~ in clinical investigation

~~RNA platform~~	~~BNT162 vaccine candidate (Product code)~~	~~Encoded antigen~~	~~Evaluation in clinical trial~~
~~uRNA~~			
~~modRNA~~	~~BNT162b2~~	~~Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites~~	~~BNT162-01 (GER) and BNT-162-02/C4591001 (USA, BRA, ARG, TUR, GER)~~
~~saRNA~~	~~BNT162c2~~	~~[REDACTED]~~	~~BNT162-01 (GER)~~

RNA platform	BNT162 vaccine candidate (Product code)	Encoded antigen	Evaluation in clinical trial
modRNA	BNT162b2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites	BNT162-01 (GER) and BNT-162-02/C4591001 (USA, BRA, ARG, TUR, GER)

ARG = Argentina; BRA = Brazil; CHN = China; GER = Germany; modRNA = modified RNA; RBD = receptor binding domain; ~~saRNA = self-amplifying RNA; uRNA = uridine RNA;~~ TUR = Turkey; USA = United States (of America).

~~The safety and immunogenicity of five BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162b3, BNT162c2) are being investigated clinically, as part of a program to develop a prophylactic vaccine to prevent infection with SARS-CoV-2 and thus its associated disease COVID-19.~~

The participants tolerated i~~The clinical program started with the immunization of healthy adults, both men and women, aged between 18 and 55 yrs, and has since then been expanded to include older healthy adults aged between 56 and 85 yrs. If the i~~mmunization ~~was~~ well ~~tolerated. ,~~In the future, we will ~~immunization will also b~~study

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other ~~e investigated in other likely target populations, which will include~~ at risk ~~populations~~groups, such as immunocompromised populations.

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At the time of this update, ~~further~~ dosing with ~~the [REDACTED]~~30 µg of ~~the~~ BNT162b2 has entered a Phase II/III evaluation of its efficacy. The goal is to ~~, with the intent to~~ support an application for marketing authorization for this candidate~~, and development of BNT162b1, BNT162b3, and BNT162c2 is ongoing~~.

Candidates for streamlining in Section 6 (Effects in Humans)

- 6.1 Ongoing and planned clinical trials: Table 13
- 6.1.1 BNT162-01 - Preliminary results
- 6.1.1.1 Summary of immunogenicity in trial BNT162-01
- 6.1.1.1.1 Summary of immunogenicity (status July 1st, 2020)
- 6.1.1.1.2 T cell responses (status July 24th, 2020)
- 6.1.1.1.3 IFNγ ELIS pot analysis - BNT162b1
- 6.1.1.2 Summary of safety in trial BNT162-01 (status July 1st, 2020)
- 6.1.1.2.4 BNT162c2 - Summary of safety
- 6.1.2 BNT162-02 / C4591001 - Preliminary results
- 6.1.2.1 Summary of immunogenicity in BNT162-02 (status July 24th , 2020)
- 6.1.2.1.1 BNT162b1 - Summary of immunogenicity
- 6.1.2.2 Summary of safety in BNT162-02 (status July 24th
- 6.1.2.2.1 BNT162b1 - Summary of safety
- 6.1.2.3 Conclusions from Phase I data (BNT162-02)
- 6.1.3 BNT162-03 in Chinese adults
- 6.1.4 BNT162-04 for BNT162b3

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