[redacted]

Subject - **Carcinogenicity studies on Comirnaty (Pfizer)**

Paris 5/08/2021 – Letter

[redacted]

We thank you for your letter. It justifies the absence of carcinogenicity studies by administrative and legal elements to draw a conclusion without safety data to justify this decision. In this letter, we demonstrate that some of the elements you put forward, and others, support the urgent need for these carcinogenicity studies to ensure safety of young vaccinated to provide eventual screening and mitigation actions.

Our exchanges could be made public and could be used by us or others in a court of law.

In this letter we provide scientific and legal evidence in response to your arguments, as a matter of prudence and precaution, you should rapidly undertake safety studies on carcinogenicity. These are necessary because hundreds of millions of young people are being injected for the first time with an mRNA vaccine. The magnitude, the young target, the novelty of nanoparticles, the novelty of mRNA vaccines, the systemic biodistribution (liver, adrenal glands, spleen, blood, bone marrow and ovaries), the interference of spike with tumour suppressors P53 and BRCA proteins, the repetition of injections (3 to 7+) urgently require that these carcinogenicity studies be done. Extrapolations or opinions are not enough because you know that in science, extrapolations and opinions are not proof and are at the bottom of the evaluation pyramid. Modes of action, certain components, and the resulting reactions have never been tested for carcinogenicity. It is necessary to measure the risk in order to undertake possible screening, treatment or mitigation actions.

In this letter we respond to your arguments, we provide you with sourced elements and 2 requests, as you have authorised us to do...one concerns carcinogenicity and the other concerns more broadly the benefit/risk stratified by age and taking into account the latest data linked to variants and safety feedback.

Your arguments for not doing the carcinogenicity study:

a) "As carcinogenicity studies take a lot of time and human resources, they should only be carried out when human exposure justifies the need.."

b) "Imposing a disproportionate burden of testing may lead not to safer medicines, but to a lack of medicines, because this creates significant barriers to development "

c) " Carcinogenicity studies are not required for vaccine antigens. However, they may be required for specific vaccine components such as new adjuvants and additives "[1]

d) " As the The amount of excipient ALC-0159 in the finished product is low (50 ug/dose), that its clearance is high and **only two administrations** of the product are recommended for humans, the risk of genotoxicity would be expected to be very low."

e) "Unless safety concerns have been identified with the parent vaccine and/or safety concerns emerge from trials with the variant vaccine, the safety data collected in immunogenicity trials with the variant vaccine, as described above, should be sufficient for approval."[2]

f) "EMA considers that there is no biologically plausible mechanism of carcinogenicity/genotoxicity with any of the substances in currently approved vaccines "

g) "EMA continues its extensive safety monitoring of these medicines .... or take other necessary regulatory action if new evidence becomes available requiring such regulatory action."

In response to these arguments

1) Firstly, some of the texts of your documents that you do not quote ("**The Need for Carcinogenicity Studies of Pharmaceuticals**")[3]**:**

" Any cause for concern arising from laboratory investigations, animal toxicology studies and data in humans may necessitate carcinogenicity studies."

" Some classes of compounds cannot be used continuously for a minimum period of 6 months, but can be expected to be used **repeatedly or intermittently**."

" Other factors may also be taken into accountsuch as **the target patient population,** screening for carcinogenic potential, **the extent of systemic exposure,** (dis)similarity with endogenous substances, appropriate study design or timing of the study in relation to clinical development."

" For pharmaceutical products developed to treat certain serious diseases, it is not necessary to carry out carcinogenicity tests before marketing authorisation, **but these studies should be carried out after authorisation.** This speeds up the availability of pharmaceuticals for life-threatening or severely debilitating diseases, especially when there is no satisfactory alternative therapy."

2) We respond to your arguments justifying your intention not to carry out the carcinogenicity studies

[redacted]

a) **The cost of these studies is negligible given the scale** and extent of this campaign. As it takes time, it is **essential and urgent** to conduct these carcinogenicity studies to **secure** this large population **vaccinated** and, where appropriate, screen and **mitigate possible** side effects.
b1) Given the novelty of the mRNA Vaccines being applied for the first time, the scale, young healthy individuals, it is **is appropriate or even minimal to carry out** carcinogenicity's studies, its cost is negligible in relation to the risk, the sums involved, and **lives** of people who **trusted you** and who deserve well **better than a risky extrapolation.** This is needed even if it **imposes some constraints on the manufacturer**.
b2) The proportionality differs when medicine is intended for to a small population that is ill from when it is intended for a large healthy population with a long life expectancy....The study is necessary!
b3) Such study does not block availability of the medicine for those at risk "it is not necessary to carry out carcinogenicity tests before marketing authorisation, **but these studies should be carried out after authorisation.** This helps to speed up the availability of pharmaceuticals for life-threatening diseases"
c) The WHO recommendation was intended for a another vaccine technology that has been tested multiple times over decades and has a known profile. In this case, **for mRNA vaccines it is a different mechanism** in its biodistribution, and which **causes the body to produce the dangerous spike protein**. These mRNA vaccines are different and result in systemic exposure (liver, adrenal glands, spleen, blood, bone marrow and ovaries) [4]. The derogation does not apply.
d) You acknowledge the risk of ALC-0159 and justify the lack of studies with a simple opinion based on a small quantity and the **limitation to 2 doses for humans**. However, a 3rd dose, has and will take place for many, EU has placed orders that suggest possibly up to **7 doses** by 2023 and beyond ? ALC-0315 has never been evaluated for carcinogenicity. The lipid nanoparticles and mRNA are new, we know little and without studies we will remain in the dark. The health of citizens deserves better than an "opinion" expressed as a "conjecture".
e) European Union orders and your own documents concerning vaccines for the variants **suggest repeated, recurrent exposure**, to mRNA vaccines and different spike protein variants in a large majority of the population, including children, without intent to perform carcinogenicity studies.[5] Orders suggest 7 foreseeable injections if newborns and children are included and more if they are not by 2023. Yet you do not plan to do further safety studies following repeated injections.
f) The spike protein, whose production is induced by the mRNA vaccine, is thought to interact with the BRCA and P53 proteins [6] and could increase the risk of cancer since, as you know, these two proteins are major tumour suppressors.[7] [8] This mechanism is plausible, even likely, and would be in addition to other indirect mechanisms related to altered immunity [9], or a retro-transcription [10].

Only independent studies, not expert opinions or manufacturers' or extrapolations, may **conclude to security and enlighten us** on benefit/risk stratified by category. Humility of science has taught us that **unforeseen mechanisms or reactions may be activated** in the complexity of the human being. Far from the beliefs and interests, mRNA vaccines may offer hope, can offer a benefit/risk for some and be harmfull for others. It is **your responsibility** to obtain the knowledge to better understand, better target and act with awareness and wisdom to keep the positive and remove the dangers.

The absence of these studies delays knowledge and could **destroy lives**. Reducing safety on new processes as you propose in order to have more drugs is **dangerous** when applied to healthy populations at very low risk....Do you really think that the safety of new processes in healthy populations should not be explored in order to reduce constraints on manufacturers and have more drugs ?

Humility, caution, the magnitude of this mRNA vaccination, the novelty of the process, the young and healthy target, the knowledge suggesting risks, all call for caution and the carrying out of these studies in order to prepare possible mitigation actions. To this end we ask you to :

i) Initiate without delay cancerogenicity studies for Comirnaty (Pfizer) and failing that, your deliberations document and data, definitively and certainly excluding any increased risk of cancer in the medium or long term in humans after repeated administration of this mRNA vaccine.
ii) Your updated detailed benefit/risk analysis document and data, stratified by age group, immunity status (covid and non-covid), taking into account knowledge of the new dominant variants - delta, gamma, lambda - but also pharmacovigilance signals, all-cause mortality signals by age group, all-cause hospitalisation data by age group, autopsy data available to you and interim safety data from the current phase 3 clinical trial.

Signature

1 WHO guidelines on nonclinical evaluation of vaccines Annex 1
WHO Technical Report Series, No. 927, 2005
https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1
2 https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-vaccines-intended-provide-protection-against-variant_en.pdf
3 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s-1-need-carcinogenicity-studies-pharmaceuticals-step-5_en.pdf
Eurpoean Medicines Agency EMA July 1996
4 https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf
5 https://ec.europa.eu/commission/presscorner/detail/en/ip_21_2548
6 Nishant Singh et al.
S2 subunit of SARS-nCoV-2 interacts with tumor suppressor protein p53 and BRCA: an in silico study
Translational Oncology Elsevier October 2020
https://doi.org/10.1016/j.tranon.2020.100814
7 Liz J. Hernández Borrero, Wafik S. El-Deiry,
Tumor suppressor p53: Biology, signaling pathways, and therapeutic targeting,
Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 2021
https://doi.org/10.1016/j.bbcan.2021.188556
8 Ogata AF et al.
Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients
Clinical Infectious Diseases May 2021
https://doi.org/10.1093/cid/ciab465
9 Konstantin Fohse F et al.
The BNT162b2 mRNA vaccine against SARS-CoV-2 reprograms both adaptive and innate immune responses
medRxiv May 2021
doi: https://doi.org/10.1101/2021.05.03.21256520
10 Chandramouly G et al.
Polθ reverse transcribes RNA andpromotes RNA-templated DNA repair
Science Advances Jun 2021:
DOI: 10.1126/sciadv.abf1771