FOI 23/070

20th February 2023

Dear

Thank you for your message of 26 January 2023.

In response, it may be useful to clarify that for applications to the MHRA, it is the responsibility of the company making the application, and not the MHRA, to provide the data that support their application. Data submitted by the company are evaluated by regulatory authorities such as the MHRA.

For ALC-0315, this was a novel excipient and the company were expected to provide data to regulatory authorities on testing of the compound, although these data need not be published. In relation to the half-life in plasma of ALC-0315, the company reported an initial value 1.62 hours and a further value of 139 hours after its intravenous injection. This was judged to reflect a period where the material first distribute into tissues (primarily the liver) after its intravenous injection and a further period where it is eliminated from tissues.

With reference to page 46 of the published EPAR, and regarding the statement 'that ALC-0159 posted the highest liver concentrations 30 mins post IV injection', the company reports identified that after intravenous injection, the highest concentration at the timepoint of 30 minutes was the liver. When used in humans, the vaccine was given by intramuscular injection: this information following its intravenous injection therefore describes a different situation to its human use by intramuscular injection. The MHRA considers that the difference you identify is explained by the difference in route of administration. This result with ALC-0159 and is in line with published data indicating that the liver is recognised as the likely target organ for mRNA in lipid nanoparticles, if given intravenously (e.g. Kim et al 2020).

Regarding the absence of genotoxicity studies, the purpose of the lipid nanoparticle is to deliver the mRNA into the inside of the cell. The components in the nanoparticle are included to improve fusion with cellular membranes to so aid intracellular mRNA delivery, as well as to impart particle stability and to protect mRNA from degradation prior to its entry into cells. It is not essential that such data are published on the ALC excipients: this has been shown with other cationic liposomes including some present in other approved medicinal products (Akinc et al 2019; Liu, et al 2021; Hou et al 2021).

References

Akinc 2019

https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1038%2Fs41565-019-0591-y&data=05%7C01%7CMHRACustomerServices%40mhra.gov.uk%7Ce0668e68beea4b7da14408db135fe325%7Ce527ea5c62584cd2a27f8bd237ec4c26%7C0%7C0%7C638125074772958047%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMD

AiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=YucIMgPUEpOFS3EFqxaaL19KjG%2B6rDhbVrVjCp3U6Kc%3D&reserved=0

Hou 2021

https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1038%2F&data=05%7C01%7CMHRACustomerServices%40mhra.gov.uk%7Ce0668e68beea4b7da14408db135fe325%7Ce527ea5c62584cd2a27f8bd237ec4c26%7C0%7C0%7C638125074772958047%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=Jk2kjmd2fwlA57fq5GSRIvtMVhOkDAP86HmY8S%2BIqdM%3D&reserved=0 s41578-021-00358-0

Kim 2020

https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1007%2Fs12195-020-00619-y&data=05%7C01%7CMHRACustomerServices%40mhra.gov.uk%7Ce0668e68beea4b7da14408db135fe325%7Ce527ea5c62584cd2a27f8bd237ec4c26%7C0%7C0%7C638125074772958047%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=HhyQz8niVpn3bcVGSYoRbyfUONPx1m%2B1pM4Hx8kJ5KQ%3D&reserved=0

Liu 2021

https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1038%2Fs41563-020-00886-0&data=05%7C01%7CMHRACustomerServices%40mhra.gov.uk%7Ce0668e68beea4b7da14408db135fe325%7Ce527ea5c62584cd2a27f8bd237ec4c26%7C0%7C0%7C638125074772958047%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=b3ro64fWSuG3UP3Jcq9lRqR5BZ8twNmq5u4HoKWxFqw%3D&reserved=0.

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Yours sincerely

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