Responses to Hungary

1. It was mentioned in the presentation that the AZD1222 was designed to avoid pre-existing immunity to human AdV. Human AdV has several serogroups. How many was tested (cross reaction)?

AZD1222 utilizes a novel replication-deficient simian adenovirus vector (ChAdOx1) vaccine expressing the surface spike glycoprotein in order to induce protective T cell and antibody responses. Adenoviruses are attractive vectors for human vaccination. Human adenoviruses such as human adenovirus 5 (AdHu5) are under development as vectors for malaria, HIV and hepatitis C vaccines, amongst others. They have been used extensively in human trials with a good safety profile, mainly as vectors for HIV vaccines. However, the ubiquity of human adenovirus infections generates levels of host anti-vector immunity that may limit the utility of AdHu5 and other human adenoviruses as vectors. Depending on the geographical region, between 45 – 80 % of adults carry AdHu5-neutralising antibodies.

The prevalence of immunity to human adenoviruses prompted the consideration of simian adenoviruses as potential vaccine vectors. These adenoviruses have many structural similarities to human adenovirus vectors. Simian adenoviruses are not known to cause pathological illness in humans and the prevalence of antibodies to chimpanzee origin adenoviruses is less than 5% in humans residing in the US for example. In equatorial Africa (the natural habitat for chimpanzees), prevalence is higher but still below that to AdHu5. In a study in Kenya, 23% of children (aged 1-6 years) had high-titer neutralizing antibodies to AdHu5, whilst only 4% had high-titer neutralizing antibodies to ChAd63 another chimp adenovirus. Immunity to both vectors was age-dependent. Importantly, the prevalence of vector neutralizing antibodies against ChAdOx1 in British and Gambian human populations is markedly lower than for ChAd63. These data indicate that non-replicating vectors derived from species E simian adenoviruses have equal immunogenicity, but unequal seroprevalence. In a UK cohort of 100 individuals, not one individual possessed a neutralization titer of above 200 which is generally considered the threshold for a positive titer during routine pre-vaccination screening. In the Gambian cohort, only five individuals possessed a neutralization titer greater than 200 against ChAdOx1, as opposed to seventeen against ChAd63. The difference in serotype of the two vectors was confirmed by the finding that humans immunized with the ChAd63 vector developed extremely high ChAd63 neutralization titers but did not neutralize ChAdOx1. While we have not tested cross-reactivity between the AdHu5 and ChAdOx1 vectors directly, given the low seroprevalence of ChAdOx1 in humans, we don't anticipate cross-reactivity.

2. More and more paper say that the antibody level against SARS-CoV-2 (and coronaviruses) decrease quite fast and several months after the infection some people do not have measurable antibody level. Do you have any information regarding this issue about the AZD1222 (experience from animal studies, human studies)?

It is true that there is increasing literature to suggest that some people do not have measurable antibody levels several months after infection. In some cases, individuals have been shown to have more robust T cell responses. It is important to note that the correlate of protection for

SARS CoV2 and a vaccine against the virus is unknown. We do not have long term data on the durability of the AZD1222 vaccine in humans yet and this information will be collected during the course of ongoing studies to understand the magnitude and durability of immune responses over time. However, in the MERS paper from April 2020, Lancet ID using the ChAdOx1 vector with the MERS Spike antigen, a peak antibody response is observed at D28, followed by a decline to a plateau by D182 and maintenance of the response to D364. We would expect something similar for SARS-CoV-2.

3. Could you send the citation from the slide 7?
MERS Phase 1 paper , Lancet ID 2020 attached.