Speaker Abstracts

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Containment of respiratory viruses: a case study of unexpected HPIV infection during an A/Belgium/4217/2015 [H3N2] influenza challenge study

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BACKGROUND—An unexpected diagnosis of hPIV was made in a subject prior to discharge (day 10) from a commercial isolation unit during a phase IIb influenza challenge study to assess the safety and efficacy of an inhaled, antiviral drug in healthy volunteers (primary endpoint was a statistically significant reduction in the viral AUC). All subjects had previously been pre-screened (d-2) against a panel of upper-respiratory tract pathogens including hPIV and found to be negative by multiplex PCR (BioFireTM). Root cause analysis offered three possible scenarios for undiagnosed infection. Following discussion, the subject's data was subsequently removed from the efficacy dataset but was included in follow-up and SDTM database for the general and safety analyses.

METHODS— 80 subjects were enrolled in the study. Subject suitability was primarily based upon a pre-screening MNT value of <10, as part of the protocol's IC/EC criteria. Subjects were admitted to a human challenge (containment) unit in cohorts of 20 at d-2 for randomisation. The challenge unit incorporated negative pressure HVAC systems appropriate for CL3 and HCU staff employed reverse barrier-nursing techniques, including appropriate PPE, to minimise the possibility of cross-infection between staff and subjects. Subjects were required to wear an FP3 mask at all times when in communal areas. Subject screening at d-2 included a multiplex PCR for common URT pathogens inclusive of hPIV. Subjects were subsequently inoculated on d1 with an influenza challenge agent (A/Belgium/4217/2015, H3N2) before being dosed with drug or placebo daily over a 5-day period. Subjects were monitored for shedding (qRT-PCR and TCID50 x2 daily) and symptoms (Symptom Scorecard x2 daily) from d1 to d10. Subjects were released at d10 pending a satisfactory physical examination and a negative BioFireTM test.

RESULTS— A mild to moderate ARI or ILI was noted in a proportion of subjects from d3 to d6 with an uneventful recovery by d8. NP testing for virus showed H3N2 shedding consistent with previous studies using A/Belgium. Upon testing for URT pathogens prior to discharge at d10 it was discovered that one subject was positive for hPIV. This was confirmed by PCR testing at Erasmus MC who further identified the pathogen as hPIV-1. The subject confirmed to be shedding hPIV-1 was positive from d1 until d11 with only minor variations in viral load (normal variation: 1log10 = 3.3 Ct).

CONCLUSIONS— It is possible that the hPIV-1 positive subject became infected in one of three scenarios: 1. d-2 sample was already positive for HPIV-1 but it was not detected; 2. The subject became infected between d-2 and d1 or 3. The subject was in the incubation period on d-2 and commenced shedding on day 1. Given the sensitivity of the BioFireTM assay, the short incubation period of hPIV-1 (2-7 days) and the duration of shedding (11 days), scenarios 2. and 3. are most probable. Since this incident additional BioFireTM testing at d-1 has been introduced.