

SAGE Meeting, October 2019

Polio the last mile-Session 9

Presentation of clinical data from nOPV2 trials and plan for EUL

A. Bandyopadhyay

Bill & Melinda Gates Foundation

Synopsis

Background:

The epidemiology of type-2 vaccine-derived poliovirus (VDPV2) circulation in recent months was markedly different than anything seen since the switch, with continued circulation and spread of some outbreaks in Africa and numerous independent emergences of cVDPV2 in areas not included in an mOPV2 response area. The current strategy has not been successful in eliminating VDPV2 transmission and emergence. The uncontained emergence and on-going spread of VDPV2 viruses have led to an urgent need to accelerate development and maximize availability of novel OPV2 (nOPV2).

In the nOPV2 vaccine development program we are studying two live, attenuated poliovirus candidate vaccines derived from Sabin monovalent OPV2 (mOPV2). Both candidate vaccines are designed to stimulate the production of serum neutralizing antibodies and induce mucosal immunity to type 2 polioviruses. The goal of the project is product licensure and WHO prequalification of the final nOPV2 candidate in the context of control of outbreaks. The final candidate vaccine should be immunogenically non-inferior to mOPV2 and more genetically stable (less neurovirulent with fewer key mutations based upon deep sequencing), with an acceptable general safety profile. The clinical development plan provides data from adult populations with varying prior polio vaccine exposure and, based on the safety in adults, has now advanced to testing in young children and infants.

Given the cVDPV2 situation has been designated as a Public Health Emergency of International Concern, and the increasing risk of seeding new emergences with use of current mOPV2, enabling pre-licensure use of nOPV2 through early clinical data generation, at-risk manufacturing at scale, and submission for WHO Emergency Use Listing (EUL) is considered a high priority of the global eradication program.

Clinical Development and EUL pathway:

Prior to global cessation of Sabin OPV2 use in 2016 and prior to the availability of nOPV2 candidate vaccine for clinical trials, phase 4 clinical trials (Belgium, Panama) were conducted with mOPV2 to provide data for comparison with nOPV2 evaluated in later trials. To maximize comparability of safety, immunogenicity, and genetic stability data, the mOPV2 phase 4 trials were designed to parallel the expected design of the phase 1 and 2 nOPV2 studies with respect to overall design, endpoints, location and study populations and employed the same laboratory for the polio serologic and viral shedding assays. For studies aligning with the nOPV2 development plan (M1 and M2) serologic samples were reserved to be assayed alongside corresponding nOPV2 samples, in a blinded fashion.

A phase 1 study (M4a) in adults (15 adult participants each receiving either nOPV2 candidate 1 or nOPV2 candidate 2), conducted under biological containment in Belgium in 2017, provided an initial assessment of clinical safety, immunogenicity, and the genotypic and phenotypic stability of shed vaccine virus in exclusively IPV-vaccinated adults (*Van Damme, P., De Coster, I., Bandyopadhyay, A. S., et al. The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study. The Lancet. 2019*). Since the primary intent of

this study was to gather information on safety and the profile of shed virus, a relatively high dose (10^6 CCID₅₀ [50% cell culture infectious dose]) was used for this study. In general, the safety data were reassuring, and there were no serious adverse events reported. In M4a, immune responses to both candidates were observed despite the high baseline titers in the previously IPV-vaccinated subjects. Median rise in neutralizing antibody titer was 8.0-fold for candidate 1 and 12.7-fold for candidate 2. In addition, fecal shedding of the candidate vaccine viruses was observed in most participants for both candidates. The median time to shedding cessation, defined as the first instance of three consecutive PCR-negative stool samples, was 23 (95% CI: 13, 35) days for candidate 1 and 12 (95% CI: 1, 14) days for candidate 2. In this study, virus shed in participants' stools was assessed for genetic stability by two methods: a mouse neurovirulence test and deep sequencing. The modified transgenic mouse neurovirulence test (mTgmNVT), was used to assess the potential neurovirulence of shed virus and the administered candidate vaccine. No meaningful increases in neurovirulence were detected in any samples compared to the administered candidate. Deep sequencing was conducted on the shed virus to provide supportive information for genetic stability of the candidates, primarily by demonstrating retention of key genetic modifications. Deep sequencing analyses generally support the neurovirulence observations. For both candidates, no variants known to be consistent with increased virulence were detected in domain V of the 5' untranslated region, the site of the primary determinant of attenuation for Sabin OPV2 (nucleotide 481).

In addition to the completed dataset from M4a, preliminary, partial results are available from the subsequent, larger study (M4) in adults in Belgium that was implemented without containment, and an on-going study (M5) in toddlers (1 – 5 year) and infants (18 – 22 weeks) in Panama. Consistent with the first-in-human study, review of safety data by an independent data safety monitoring board supported progression into young children and then infants. For humoral immunogenicity, both the adults in M4 and toddlers in M5 generally showed high seroconversion rates when administered a 10^6 CCID₅₀ dose. Immunogenicity data from infant cohorts receiving 10^5 or 10^6 CCID₅₀ doses will be available later this year. Shedding post-vaccination with nOPV2 in adults was also consistent with prior observations with mOPV2. Results on genetic stability and neurovirulence of the shed vaccine virus from M4 and toddlers in M5, alongside comparative data from the historical control trials, are expected to be available over the next few months.

Conclusions:

Overall, the pre-clinical and clinical data generated so far are supportive of further clinical development for both candidates and prioritization of one candidate for initial EUL submission and stockpile production at-risk with an aim to have maximum possible volume of one of the nOPV2 candidates in the shortest possible time-frame, the target being by Q2-Q3 2020. We anticipate that data available in early 2020 should be sufficient to conduct a relative benefit-risk assessment for the selected candidate against mOPV2. Provided the data are sufficient to support an EUL approval, this assessment, the current epidemiological context, and information on supply of nOPV2 and mOPV2 should help inform a policy position on use of these vaccines.