ESGCT: Abstract 1

Employment of the CELLECTRA® in vivo gene delivery platform in a first in human (FIH) DNA encoding monoclonal antibody (DMAb) trial

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Monoclonal antibodies (mAbs) have proved an effective passive immunization strategy to provide protection against infectious disease. However, access to mAb biologics faces multiple challenges for broader population coverage including requirement for high doses (in milligrams/kilogram), shelf-stability, temperature stability and distribution barriers for low-/middle-income countries and resource-limited settings. Therefore, strategies which can further facilitate mAb uptake and global availability would be valuable for infection control. In vivo electroporation-mediated delivery of synthetic plasmid DNA encoding monoclonal antibodies to muscle cells has been demonstrated as a viable strategy against multiple disease targets in the preclinical setting. Specifically, synthetic DNA constructs are delivered to muscle tissues with in vivo electroporation to permit local tissue expression of the DNA-encoded monoclonal antibody (DMAb) and long-term production and secretion of mAbs into circulation. The technology allows for sustained antibody trough levels, flexibility for administration of multiple constructs, rapid production, and long-term drug product stability.

We applied DMAb technology as a COVID-19 countermeasure. We evaluated in vivo gene delivery of synthetic DNA constructs encoding AZD5396 and AZD8076, modified versions of the SARS-CoV-2 neutralizing mAbs in the cocktail Evusheld. Through a combination of CELLECTRA® EP parameters and synthetic pDNA drug formulations tailored for enhanced local muscle tissue transgene expression we demonstrated DMAb-mediated disease protection in nonhuman primates. An Investigational New Drug (IND) was opened to assess safety and pharmacokinetics in healthy individuals in a first-in-human trial (NCT05293249). In this FIH study, DMAb expression was measured in all 39 participants with serum concentrations above 1 μg/ml measured in some subjects. DMAb serum levels remained consistent in the participants who have now completed 72 weeks of follow-up. Functional assays confirmed SARS-CoV-2 receptor-binding domain (RBD) binding and neutralization activity in pseudovirus assays. Across all participants, no anti-drug antibody (ADA) responses were detected, suggesting durable expression without immune-mediated clearance, and thus, the potential for redosing or delivery of different DMAbs. Safety assessments revealed no serious adverse events, with mild injection site reactions being the most commonly reported.

Data presented here will focus on how a combination of drug formulation and in vivo gene delivery enhancements can be employed to achieve expression of biologically relevant gene-encoded biologics.