AN INTEGRATED FIRST-IN-HUMAN STUDY DESIGN INVOLVING SEQUENTIAL SINGLE AND MULTIPLE ASCENDING DOSE COHORTS: AN EMERGING TREND IN PHASE I CLINICAL TRIALS

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Abstract:
BACKGROUND:
A first in human (FIH) clinical study design is aimed primarily to overcome the long delays challenge during early stage clinical development through integrated single ascending doses (SAD) and multiple ascending doses (MAD) phases.

METHODS:
In double blind trial, the SAD phase is conducted in prescheduled cohorts. To ensure safety, Sentinel approach is implemented. The MAD phase is initiated in parallel with SAD following favorable safety review of 3 SAD Cohorts. For subsequent MAD cohorts, the dose is confirmed based on safety data of (1) completed SAD cohorts and (2) previous MAD cohorts. Optional adaptive cohorts ran in parallel at intermediate doses, judged safe following review of available data and, did not exceed (1) ongoing cohort dose (2) MTD (3) preset cutoff dose.

RESULTS:
This approach is successfully implemented in multiple Phase I trials. In a clinical program for a new therapeutic peptide, 64 subjects were enrolled; 30 received single doses, 18 received multiple doses and 16 received placebo. The SAD was conducted over 10 weeks in 5 cohorts. MAD was initiated 4 weeks after SAD start and concluded 6 weeks thereafter over 3 cohorts. Each cohort is conducted over 10±4 days including safety review. The clinic portion lasted over 2.5 months. No subject was withdrawn for safety. In comparison, the clinic portion of same cohorts in traditional FIH trials, where MAD is initiated following completion of SAD, is conducted over 6±3 months. The interval from protocol to report is 6 months in integrated design versus 18±4 months in traditional design. This integrated design offers the advantage of conducting both phases in parallel with possibility of investigating new doses in adaptive cohorts. Although the design demands pretrial implementation of restrictive start and stop criteria to ensure safety, both SAD and MAD are completed simultaneously allowing expedited entry into PhaseII.

CONCLUSIONS:
This integrated design significantly decreases the overall period of the early stage clinical assessment of new entities.