Clinical trials for intiviral in general

General Information on the Clinical Trials for Antiviral Drugs Clinical trials are biomedical research studies performed in human beings following a pre-defined protocol (1). The goal of clinical trials is to produce data that shows the safety and efficacy of a drug, leading to the approval for marketing by a regulatory body. The clinical trial also involves data acquisition, validation, and integration. This is known as clinical data management, which is an integral component of the drug development process. The conclusions derived from data analysis are the basis of for regulatory approval and subsequent marketing (2).

After the promising drug has been identified based on its mode of action on the target , it undergoes a thorough pre-clinical testing involving biological test-tube and animal studies. The primary goal is to determine the safety of the product for initial use in humans, and if the drug shows pharmacological activity that justifies commercial development. These studies will show if the test drug works against its viral target. In the case of HIV, after it was reported that diketo acids can inhibit strand transfer step (3), studies were used to exhibit the disease progression and test treatments in macaque monkeys (4). Animal studies have utilized the simian immunodeficiency virus (SIV) to study acquired immunodeficiency in primates, however, SIV shares only 50% homology to HIV. Recently, a genetically altered HIV can infect rhesus monkeys in such a way that the resulting infection mimics the early stages of HIV human infection (5).

Successful pre-clinical trials pave the way for a drug company to file an Investigational New Drug application. The application will include data on animal pharmacology and toxicological studies, manufacturing information, the protocols for the clinical trials, and the information about the

investigators. The investigators and sponsors are responsible for the protection of the clinical trial subjects (6).

Drugs have to be subjected to several phase of clinical trials for them to be approved for marketing. Phase I trials are meant to determine the metabolic and pharmacological actions, and the maximum tolerable dose of the drug in 20 to 80 volunteers. The trial normally lasts for a minimum of one month to a year. Measured outcomes are vital signs, virus plasma and serum levels and adverse events or reactions to the drug. Trials are unblinded and do not employ controls (7), although blinding and controls can be used to improve the validity.

Phase I trials usually do not have therapeutic objectives, and may be conducted in healthy volunteer subjects. If the drug has potential toxicity, then the studies are conducted on patients. Phase I also estimates the initial safety and tolerability of the drug, therefore, single and multiple dose administration are part of the treatment. The drug’s preliminary characterization of the drug’s absorption, distribution, metabolism, and excretion is an important goal of Phase I. Assessment of pharmacokinetics are also included to assess drug clearance, accumulation and drug interactions. An appropriate measure of pharmacodynamic data can estimate activity and potential efficacy of the drug (6).

Phase II studies will assess the effectiveness, side effects and risks of the use of drugs. During this phase, dose response, dose tolerance, adverse events, and efficacy are measured from 100-300 patients. Additional objectives may include evaluation of therapeutic regimens, and target populations (e. g. mild versus severe disease) by exploratory analyses and examining subsets of data (6). The trials will have placebo control, and active control

comparisons. Participants have with well-defined entry criteria leading to a relatively homogeneous population that is closely monitored (7). Dose escalation designs are used to estimate the dose response and regimen, which are to be used in Phase III. Doses in Phase III are usually, but not always, less than the highest doses in Phase II (6).

Phase III trials aim to demonstrate or confirm therapeutic benefit by obtaining additional information about the effectiveness of the clinical outcomes and the overall risks and benefits in a diverse population. The trial can have 100-1000 patients, and could last for many years. The design is randomized and controlled with 2-3 treatment combinations; however, the inclusion criterion is broader than Phase II (7).

Phase III studies are intended to provide data and conclusions that will lead to the approval for the marketing of the drug. Dose response relationships and the drug’s use in larger populations, different disease stages or in combination with another drug are studied in Phase III. At this phase, the results should be adequate to complete the information required for use of the drug (official product information) (6).

Phase IV studies are usually conducted after the drug has been approved for marketing and release. Phase IV studies go on for many years and could have thousands of participants. Safety in large populations is monitored, so with identification of additional uses for the drug. The trials are uncontrolled and observational (7). Commonly studied are additional drug-drug interaction, dose-response, epidemiology, and indications (6).

References

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