Introduction to Phase 0 Imaging Studies with Radiopharmaceuticals

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Drug development undergoes three primary phases. Initially, there's the research and development phase, focusing on molecule development and selection. Following this, preclinical studies are conducted to evaluate the drug's potential. Upon obtaining promising results in preclinical trials, the subsequent phase involves initiating clinical trials with human participants. These trials are traditionally categorized into Phase I, II, and III studies.

In 2006 the FDA added Phase 0, as a translational clinical trial between preclinical and Phase I. A Phase 0 clinical trial, also known as Exploratory Investigational New Drug applications eIND or Exploratory Clinical Trials, is an early stage clinical trial conducted to assess the Pharmacokinetics and Pharmacodynamics of a drug candidate in a small number of human subjects. Preferably patients that express the drug's target.

Unlike later-phase trials that focus on efficacy and safety, Phase 0 trials involve administering a very low non-therapeutic dose of the drug (microdose) to a small number of participants (usually less than 15). This approach enables drug developers to obtain preliminary insights into the behavior of the drug within the human body. The main objective is to provide data for an early go/no-go decision before moving the drug candidate to the next clinical trial phases which are more costly and time-consuming. Additionally, conducting a Phase 0 study allows drug developers to skip large animal models and move to first-in-human studies faster.

Imaging in clinical trials can provide indisputable proof that the investigational drug reaches and binds to the target, and if applicable, shows uptake in diseased tissue and no or little uptake in healthy tissue. Imaging in clinical trials is not limited to radiopharmaceuticals. Non-radioactive compounds can be labeled with radionuclides to make them suitable for imaging in the drug development process.

Phase 0 using labeled drugs provides data that drug developers can use for further development.

- In-human data regarding Pharmacokinetics and Biodistribution are useful in later phases of development
- The on- and off-target effect (background-to-target ratio) can be determined. This data is especially important for radiopharmaceuticals intended to be used in radioligand therapy (RLT)
- Precision (radioligand) therapy and the corresponding indication(s) can be determined with the right study design. For example, selecting tumor types
- The possibility of studying multiple indications in Phase II and III can be explored
- The path of excretion and potential risk of accumulation can be made visible.

It is important to highlight that Phase 0 does not aim to study toxicity and safety, nor to establish the treatment dose. However, in some cases initial dosimetry can be performed.

One important aspect of Phase 0 is that it can replace large animal studies and instead provide early in-human data. Regarding resources, this means that all or at least a large amount of time and cost normally spent on extensive preclinical experiments can be reallocated. For this reason, in most cases, conducting a Phase 0 study requires minimal additional resources. Further, with early go-/no-go decisions drug developers avoid spending resources on taking non-targeting drugs to the next development stages.

Considerations for clinical trials with radiopharmaceuticals

- The use of materials meeting Good Laboratory Practice (GLP) standards is adequate for Phase 0 clinical trials. Namely, the process of labeling the drug takes place in a controlled environment adhering to Good Manufacturing Practice (GMP) standards, making it fit for in-human use
- For imaging and therapy, the effective dose is often already a microdose or lower
- It is a current prerogative in the radiopharmaceutical area that the tracer should not have pharmacological activity when it binds to the receptor, instead, it should work only as a vector.

Conclusion

In conclusion, the introduction of Phase 0 imaging studies with radiopharmaceuticals marks a significant advancement in translational clinical research, bridging the gap between preclinical evaluations and traditional Phase I trials. These exploratory investigational studies offer a unique opportunity to assess the Pharmacokinetics and Pharmacodynamics of potential drug candidates in a small cohort of patients. This enables early go/no-go decisions in drug development while minimizing costs and time.

However, it's imperative to recognize that Phase 0 studies primarily focus on early human data acquisition and do not replace the necessity of subsequent phases for toxicity assessment and dose establishment. Still, the early data can accelerate Phase I and II trials and help drug developers to have much smarter study designs (e.g., less participants).

As the field of radiopharmaceuticals continues to evolve, Phase 0 imaging studies can contribute to the success of radiopharmaceutical development. The chances of getting new drugs to the right patients can be increased simply by careful consideration of study design, and of course, adherence to regulatory standards.

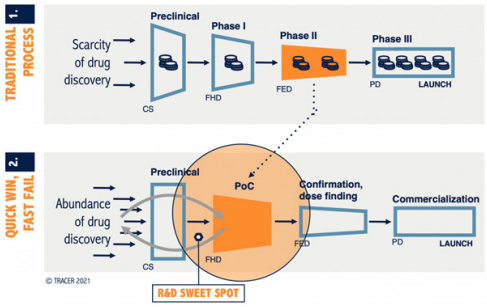

Figure 1 – A comparison of drug development processes adapted from Paul et al., 2010