Second International Phase-0/Microdosing Stakeholder Meeting

Enabling Human-Based Translation in Drug Development

Friday, April 23, 2021, 9:30 am - 5:30 pm, Japan Standard Time (ONLINE MEETING)

Organized by: Phase-0/Microdosing Network (phase-0microdosing.org) and **Japanese Association for Promoting Drug Development** (APDD; www.apdd-jp.org)

Chair: Tal Burt, MD - President, Phase-0/Microdosing Network and Burt Consultancy, LLC
Co-Chair: Hiroshi Yamazaki, PhD - President of APDD and Professor, Showa Pharmaceutical University

Organizing Committee:

Ichimaro Yamada, PhD., Vice President APDD and General Manager for R&D, TNAX Biopharma Corporation; Wooin Lee, PhD., Associate Professor, Laboratory of Molecular Pharmaceutics, College of Pharmacy, Seoul National University; Graeme Young, PhD., Director and GSK Fellow, DMPK, David Jack Centre for R&D, GSK; and Koji Chiba, PhD., Professor, Laboratory of Clinical Pharmacology Yokohama University of Pharmacy

Goals:

1. Formulate guidelines for the application of Phase-0/Microdosing approaches
2. Establish recommendations for further research and development

Objectives:

1. Provide update on validation, methodology, applications, and research
2. Obtain input from stakeholders (regulatory, academia, industry, CROs) on the value, prospects, and challenges of these approaches
3. Establish consensus statements on future directions in research and applications

9:30 - 12:45 pm: Plenary session:

State-of-the-art - Application Criteria - Adoption Challenges - Future Directions

Time	Chair	Speaker	Title
9:30-9:55	Hiroshi Yamazaki	Tal Burt	Meeting scope, Phase-0/Microdosing definitions, and application criteria
9:55—10:20	Tal Burt	Nader Sanai	Non-microdosing Phase-0 approaches: Applications in oncology and CNS drug development
10:20-10:45		Yuichi Sugiyama	Prediction of drug clearance and DDI/PGx at therapeutic doses from microdosing clinical studies using PBPK modeling with in-vitro data on metabolism and transport
10:45-11:10		Wooin Lee	Microdosing studies enabling a better look into target occupancy of small-molecule drugs: What are the key factors that make this possible?
11:10-11:20	Break		
11:20-11:45	Hiroshi Yamazaki	Yoshiyuki Yamaura	Japanese industry experience with microdosing studies
11:45-12:10		Yuuta Taniuchi	Micro tracer mass balance study in healthy subjects in drug development stage
12:10-12:15		Tal Burt	Connecting microtracer studies with Phase-0
12:15-12:40		Graeme Young	The impact of industry's drug development culture on Phase-0 approaches
12-40-12:45	Tal Burt		Review of morning presentations

12:45 - 13:45 pm: **Lunch time seminar** (talks by sponsors, Pharmaron, eurofins, etc.) and break

13:45 -15:30 pm: Breakout Sessions:

Science and Methodology – Feasibility – Culture – Future Directions

Time	Moderators	Discussion item
13:45-15:30	Wooin Lee, Yuichi Sugiyama	**Science and Methodology** Extrapolation from sub-therapeutic to therapeutic-level exposures, TMDD, PBPK modeling, simulations; Use in profiling drug PK, PD, and MOA
	Tal Burt, Koji Chiba	**Strategy and Feasibility** Applicability of Phase-0 approaches in drug development, identification of favorable scenarios, decision algorithms, timelines; ethical and economic considerations
	Graeme Young, Ichimaro Yamada	**Culture of Drug Development** Stakeholder perspectives: motivations and challenges facing Phase-O/microdosing approaches
	Hiroshi Yamazaki Tal Burt	**Future Directions** Recommendations for future research and development of the field, for drug development culture interventions, educational initiatives, management buy-in, and logistics

15:30 - 15:45 pm: Break

Closeout session:

15:45 - 17:30 pm: Summary of breakout sessions, consensus statements, and action items (Chairs: Tal Burt & Hiroshi Yamazaki)

Abstract

Drug development is associated with exponential increase in costs and only modest productivity. In addition, there are concerns about the risks of exposing humans and animals to novel chemical entities. These challenges have led to efforts to improve the drug development process. Such efforts include limited exposure clinical trials such as microdosing and other Phase-O approaches. These approaches are also called Exploratory Investigational New Drug (eIND) or exploratory clinical trials, are an alternative regulatory framework for First-in-Human (FIH) trials. Common to these approaches is the use and implied safety of limited exposure to the drug. For example, with microdosing the dose is less than 100 µg or 1/100th of the anticipated therapeutic dose. The primary applications of Phase-0 approaches include study of drug pharmacokinetic (PK) and pharmacodynamic (PD) properties. Specific applications include use in target localization, drug-drug interactions (DDIs), effects in vulnerable populations (e.g., pediatric), and Intra-Target Microdosing (ITM). The sub-therapeutic doses in Phase-O/Microdose studies require the use of sensitive analytic tools such as Accelerator Mass Spectrometer (AMS), Positron Emission Tomography (PET) and Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). These tools are used to study disposition, effects, and metabolites of the novel drug under study. Further, when these analytic techniques are used in combinations, they can increase the versatility of study design and the power of the data obtained. Validation studies over the past decade have demonstrated the reliability of extrapolation of data from sub-therapeutic exposures to therapeutic-level exposures in more than 80% of cases. This constitutes an improvement over traditional allometric approaches. Nevertheless, utilization of Phase-O/Microdosing by drug developers remains modest, although growing in number and scope. The purpose of the meeting is to understand and address this under-utilization and formulate recommendations for future research, development, and applications of these approaches.