Studies with 13C- and 14C-Labeled Investigational Medicinal Products in Humans
Presented by ASCPT Partner: ICON
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Audience Questions

1. *What is the regulatory requirement (if any) for microtracer CMC manufacturing- can we use non GMP 14C material in a microtracer hAME study?*
    a. Within ICON you can use a non-GMP 14C-microtracer as long as the amount is equal or less than 100 µg. the lab for radiosynthesis needs to be audited by ICON (if not yet done)
2. *Can you comment on approaches for very long half-life drugs? I am thinking of things like dutasteride and other medicines with half-lives on the order of weeks and months. Is 5X T1/2 sufficient in these cases?*
    a. We have conducted human AME studies with continuous collection of excreta for up to 4 weeks, followed by discontinuous collection of excreta for up to 3 months after drug intake, and are currently in the process of completing a study with excreta collections until 4 months after intake. A maximum duration of discontinuous collections of up to 6 months may potentially be feasible. Such designs should cover the needs for most drugs; exceptional cases may require further discussions, also with regulators.
3. *What are the differences between ICRP 62, 100 and 103?*
    a. Weight factors for organ/tissue contributions to the whole body effective dose have changed to some extent over these ICRP publications, and the human alimentary tract model has been introduced. This latter change represents the current thinking that not all of the wall of the GI tract will be exposed to ionizing radiation (beta particles) originating from 14C-labeled drug material in the lumen, based on the relatively moderate energy and limited penetrating power of the particles.
4. *Will micro tracer approach compromise Met ID that is required in our hAME studies?*
    a. As a general rule, microtracer doses can be expected to allow metabolite profiling and identification just as well as regular doses of 14C. This is especially so since the overall amount of drug material (i.e., the mg dose) is the same no matter how much 14C is administered. Microtracer AME studies will probably require AMS as the bioanalytical technique used for radioanalysis.
5. *What if recovery is <90% but <1% excreted in 2 consecutive intervals- do you recruit another subject?*
    a. Not as a rule. Thus, we advise our clients to plan for 7 or 8 (healthy) subjects to be enrolled in the human AME study; in general, this will be feasible as one group, with dosing of all subjects on the same day. This will most probably lead to at least 6 evaluable subjects, as required per the FDA Guidance on human mass balance studies. In case one of the initial subjects shows less than 90% recovery and less than 1% of the dose excreted in 2 consecutive intervals, this is seen as a study result and we will aim to assess why this result was obtained.
6. *For cancer patients, would the discharge criteria with an "AND" in the middle be too strict and compliance could be a potential issue? What about " OR"?*

a. Very good point. We have worked with >90% recovery OR <1% excreted in 2 consecutive intervals as stopping criteria for more than 20 years and this generally yielded sufficient results, both in HV as well as in cancer patients. Now, with the FDA Guidance on human mass balance studies, we are indeed confronted with this type of situations. Under the FDA Guidance, we would not stop collections of excreta if recovery is >90% (which is generally seen as sufficient) but excretion per 24 h still above 1% of the administered dose. In my mind, continuation of excreta collection in such case (until ultimately the protocol-defined final interval) would be worthwhile, since mass balance and excretion of drug material will be better characterized than when we stop. Another, more interesting situation would arise when recovery is <90% but excretion has also dropped to below 1% of the dose, possibly to close to 0% per day. In such cases, there will be no use in continuing collection of excreta and it might be seen as unethical to keep bothering the patients. We have developed alternative languages that may be used in such cases.

7. *Are the EMA /PMDA guidelines similar to FDA on recovery requirements?*
    a. EMA and as far as we are aware PMDA do not have specific guidance documents on human mass balance studies. EMA has incorporated some guidance on human mass balance studies in their guidance on DDI studies of 21Jun2012; they suggest that the recovery should exceed 90% of the administered dose.
8. *The radioactivity that is recovered in feces could be from unabsorbed drug, doesn't that confound the estimate for fraction eliminated through the fecal route?*
    a. Correct, unabsorbed drug will appear in feces and cannot be distinguished from absorbed and excreted parent drug. This is always a confounder. Therefore, although not discussed during the webinar, having and oral and an iv mass balance assessment may be of value to get a complete picture of the ADME properties of your drug.
9. *What is your approach to recruiting cancer patients to these trials? What are typical I/E criteria for these patients (e.g., cancer type / stage / types of prior therapies)?*
    a. We typically recruit all solid tumor patients; I/E criteria are very much dependent on the drug to be investigated. Having an extension phase after the ADME study, allowing patients to participate in an ongoing therapeutic trial is a requirement.
10. *Can you use non GMP microtracer for oral hAME study e.g. 0.1uCi14C/250 mg Drug X?*
    a. 0.375 mg of the 250 mg can be accepted as non-GMP, so if the specific activity can be 0.267 Ci / mg. for the rest see answer 1.
11. *In what cases you would need a multiple dose Mass balance study?*
    a. In our minds, this is needed when metabolite formation and/or exposure is time-dependent.
12. *On slide #16, were there any sample collection for day 13 to day 21 interval when patients were not in the facility?*
    a. No, that is the crux of this type of design: we allow subjects to go home and not collect any excreta for a week (since not supervised) and request them to come back for a supervised 24-h interval of excreta collections. Excretion during the days when the subjects were at home is estimated using an interpolation approach.
13. *Why has the study shifted to being called an AME study (not ADME)? There is a distribution component of the study where you evaluate distribution to red blood cells.*

a. Some experts in the field are of the opinion that the D in ADME refers to actual tissue distribution, which is assessed as such in animals but not as a rule in humans; therefore they prefer to omit the D. Others are not so strict and may indeed argue that either the plasma concentration versus time (apparent CL, apparent volume of distribution) or the whole blood versus plasma ratio represent some type of "distribution", and they will keep the D.

14. *Is a qualified manufacturer therefore operating under non GMP to support microtracer 14C study for an oral hAME?*
    a. See answer 1.
15. *If you, due to metabolic cleavage of the drug, plan to plan to perform the human AME study with 2 or more different 14C labels positions dosed to different subjects, would you consider that one study wrt sample size, that is ~8 subjects in total? or separate studies for each label position?*
    a. You can run such study under one protocol, but we expect that interpretable data will require 6 completers per label location; as a consequence, regulators will likely require 6 completers per label location as well. Thus, the total number of subjects enrolled will be in the order of 14 to 16 (7-8 per cohort/label position).
16. *Is there a rule of thumb for the amount of radioactivity to be dosed to allow ADME analysis with LSC and not AMS?*
    a. Not really, this largely depends on the PK properties of any given drug (fraction absorbed, distribution volume, metabolism, excretion).
17. *For multiple cold doses following a hot dose, if there are accumulation for certain metabolites, the %AUC by radioactivity could be inaccurate in assessing MIST, what are your thoughts about this approach for human AME?*
    a. We totally agree with you, and there are (at least) two options to cope with such situations: (i) derive your steady state metabolite exposures from multiple dose studies without 14C-labeling, which will require analytical standards for your metabolites; or (ii) run the 14C ADME study with multiple doses of labeled drug.
18. *For ABA, how good is it extrapolating from microdose PK to clinically relevant PK, any caveats?*
    a. Good point: we are using the intravenous microdose on top of an oral regular dose ('cold') to predict the exposure after an intravenous macrodose. Literature shows that this extrapolation (iv microdose to iv macrodose) generally shows good linearity.
19. *For ADME studies using microdose, how rich is the experience, eg, number of studies accepted by FDA/EMA?*
    a. I am not aware about any insight into these numbers, but have seen drug approvals based on microtracer AME studies; in my mind this shows that the approach in principle is acceptable (pending the actual data of course).
20. *What is the regulatory requirement for the quality of 14C tracer for macrotracer ADME study?*
    a. GMP.
21. *Would particularly like to know when use of 13C is better than 14C?*
    a. Using 13C is always better since no radioisotope involved. Whether it is feasible and financially attractive depends on the chemistry and bioanalytics.
22. *Is RBA required by all regulatory agencies worldwide for NDA submission; if not, when are we required to do so?*

    a. It is not required by all RA's but will always help you understand the PK and possible liabilities of your drug better.

23. *How can C-13 studies be conducted if C-13 is more naturally abundant such that it can lead to lower signal to noise ratio?*
    a. This can be because multiple C-atoms in the molecule will be replaced by 13C. Thus, radiolabeling with 14C generally aims at only one C-14 per molecule while 13C may need 6 replacements.
24. *I would appreciate if the speakers can provide example on how to calculate the human dose based on QWBA rat study?*
    a. An exact example was outside the scope of the webinar; we hope that our high level explanations were helpful. If not, we will be happy to follow up with you off-line.
25. *How to interpret the hAME data for a radio-label compound with two radio-label warheads?*
    a. To be honest, I do not immediately understand what you mean with "two warheads". Assuming you mean that you want to study the metabolism of a molecule that is split in two relatively equivalent halves: this can be done by making two different 14C-labeled molecules, with 14C in different positions; or, theoretically, by labeling one side of the molecule with 14C and the other side with 3H. We will be happy to follow up with you off-line.
26. *I am new to this area but would like to get educated.*
    a. We will be happy to follow up with you off-line anytime when helpful.
27. *How to determine the fraction metabolized to each individual metabolite?*
    a. This is generally done by comparing AUC's of individual metabolite versus AUC of total radioactivity and versus AUC of parent.
28. *Consideration for material (GMP OR NON GMP) in microtracer or traditional radiolabeled studies.*
    a. GMP for traditional (macro) and non-GMP is possible for microtracer, see A1
29. *What are the health risks for study participants that ingest 14C?*
    a. Ingestion of and exposure to beta radiation from 14C can theoretically lead to radiation damage to cells/tissues/organs, and to changes in genetic material. Hence, for regular dose 14C studies, we perform a dosimetry calculation to maximize the likelihood that with the intended 14C dose a predefined radioburden (mSv) is not exceeded.
30. *Are speakers aware of any human AME studies conducted with C-13-labeled material?*
    a. No, we are not aware of such studies.