

Author's Reply to Srinivas: "A Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Orally Administered Des-Aspartate Angiotensin I in Healthy Subjects"

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We thank Dr. Srinivas for his comments [1]. Our explanation is as follows.

1 Blood Sampling

Section 2.6 of the article by Lee et al. [2] describes the rationale for the sampling time points, viz:

"Serial venous blood samplings (10 ml) for pharmacokinetic analyses were carried out on all subjects at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6 and 12 h post study drug administration. We anticipated that the range of sampling time points would cover the duration of early blood pressure response to intravenous administration of DAA-I observed in human subjects [19], and the detection of chromatographic [¹⁴C]-DAA-I-like peak at 4 h after [¹⁴C]-DAA-I was orally administered to rats during the preclinical toxicology studies."

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In the human study reported by Kono et al. [3], the increase in blood pressure to an intravenous infusion of des-aspartate-angiotensin I (DAA-I) was caused by angiotensin III, the immediate metabolite of DAA-I. The increase occurred within 2 min of the intravenous administration, indicating that DAA-I was rapidly degraded in the systemic circulation. When [¹⁴C-Val³]-DAA-I was incubated in a plasma sample, the degradation to angiotensin III, angiotensin IV and smaller fragments was a seamless process that lasted less than 3 min (unpublished data from a preclinical toxicology study). The oral bioavailability of DAA-I has been estimated to be 0.06 [4]. This low bioavailability together with its rapid degradation in the blood would indicate that orally administered DAA-I, like many endogenously produced compounds, does not have a canonical blood profile. Blood samplings at intervals of 2–3 min in the first 30 min post-DAA-I oral administration, as suggested by Dr. Srinivas, would approximate a continuous sampling, which is logistically difficult to execute and psychologically unfavourable to the volunteers. It also assumes that the peak plasma would be within the first 30 min post-DAA-I administration, which is not supported by preclinical data.

2 Incorporation of Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors

DAA-I (per se) has no effect on blood pressure [3]. We have also shown that orally administered DAA-I (up to a dose of 23.6 mg/kg) had no effect on the blood pressure in the rat (unpublished data from a preclinical toxicology study). Therefore, blood pressure, as suggested by Dr. Srinivas, would not be a suitable surrogate marker.

Angiotensin receptor blockers block the angiotensin AT₁ receptor and losartan has been shown to block the action of DAA-I [5, 6]. Hence, incorporation of an angiotensin receptor blocker or an angiotensin converting enzyme inhibitor in a proof-of-concept study, as suggested by Dr. Srinivas, would be incoherent. A definitive proof-of-concept study for DAA-I would be a phase IIa clinical trial on 24 patients with type 2 diabetes mellitus to establish its efficacy (effective glycaemic control). However, a phase IIa trial would have to be supported by safety data from a prior multi-dose phase I trial.

3 Surrogate Biomarker

The measurement of prostaglandin E₂ and or prostaglandin I₂ as surrogate biomarker/s of DAA-I is our preferred choice in tracking the biological action and bioavailability of DAA-I in a multi-dose phase I trial. Prostaglandin E₂ and prostaglandin I₂ have been associated with glycemic improvement of type 2 diabetes and its associated complications [7–9]. These two prostaglandins are therefore relevant surrogate biomarkers in our anticipated multi-dose phase I trial.

4 Angiotensin Peptide Drug

Angiotensin-(1–7) [10, 11] and TRV027 [12] are two other angiotensin peptides currently being developed as potential drugs. Like DAA-I, these two angiotensin peptides are biased agonists and exhibit specific therapeutic actions. However, unlike DAA-I they are not orally active and have to be given parenterally. The reason is because, unlike DAA-I, angiotensin-(1–7) and TRV027 are not effective at doses that are below the Km of peptidases. With this unique property, DAA-I is an investigator's dream drug. Doses above therapeutic levels that cause secondary biological actions or toxicities are rapidly brought down to physiological levels. Rapid internalisation of the bound DAA-I/angiotensin AT₁ receptor complex is reminiscent of drug-targeting therapy, especially when upregulation of the angiotensin AT₁ receptors is known to occur in DAA-I-responsive diseases [13, 14]. The lack of a canonical plasma profile is only a problem to naive institutional regulators, and DAA-I is pharmacologically a safe drug to develop.

Compliance with Ethical Standards

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Conflict of interest Meng-Kwoon Sim and Kok-Onn Lee have no conflicts of interest to declare.

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