Characterization of hADME and pharmacokinetics of inhaled Velsecorat: alternative use of IV dosing and AMS

Marta Pelay-Gimeno[a], Ann Aurell Holmberg[b], Lars Weidolf[b], Sofia Necander[b], Peter Bold[b], Sharan Sidhu[c], Rianne A.F. de Ligt[a], Elwin R. Verheij[a], Alexandra Jauhiainen[b], Ioannis Psallidas[b] and Susanne Prothon[b]

[a]TNO, Leiden, The Netherlands; [b]AstraZeneca, Gothenburg, Sweden; [c]Quotient Sciences, Nottingham, United Kingdom

TNO innovation for life

INTRODUCTION

Velsecorat is a potent non-steroidal glucocorticoid receptor modulator investigated as a potential treatment for asthma. In general, inhaled drugs suffer from additional complications during characterization of human absorption, distribution, metabolism and excretion (hADME), as well as pharmacokinetics (PK). Main challenges are: preparation of the right particle size for the ^{14}C-compound, quantification of actual inhaled dose, and unknown long-term toxicity of inhaled ^{14}C accumulated in the lungs. Thus, intravenous (IV) dosing is used as a surrogate route for inhaled administration.

Techniques like accelerator mass spectrometry (AMS) have changed one of the main paradigms of the hADME strategy and are shaping a more flexible and sustainable drug development process. AMS' high sensitivity for ^{14}C analysis has enabled the implementation of ^{14}C-microtracer studies by reducing the radioactive dose, thereby enabling the conduct of hADME studies earlier in development. In addition, this completely eliminates the need for ^{14}C-radiolabelled studies in animals.

STUDY DESIGN AND MASS BALANCE RESULTS

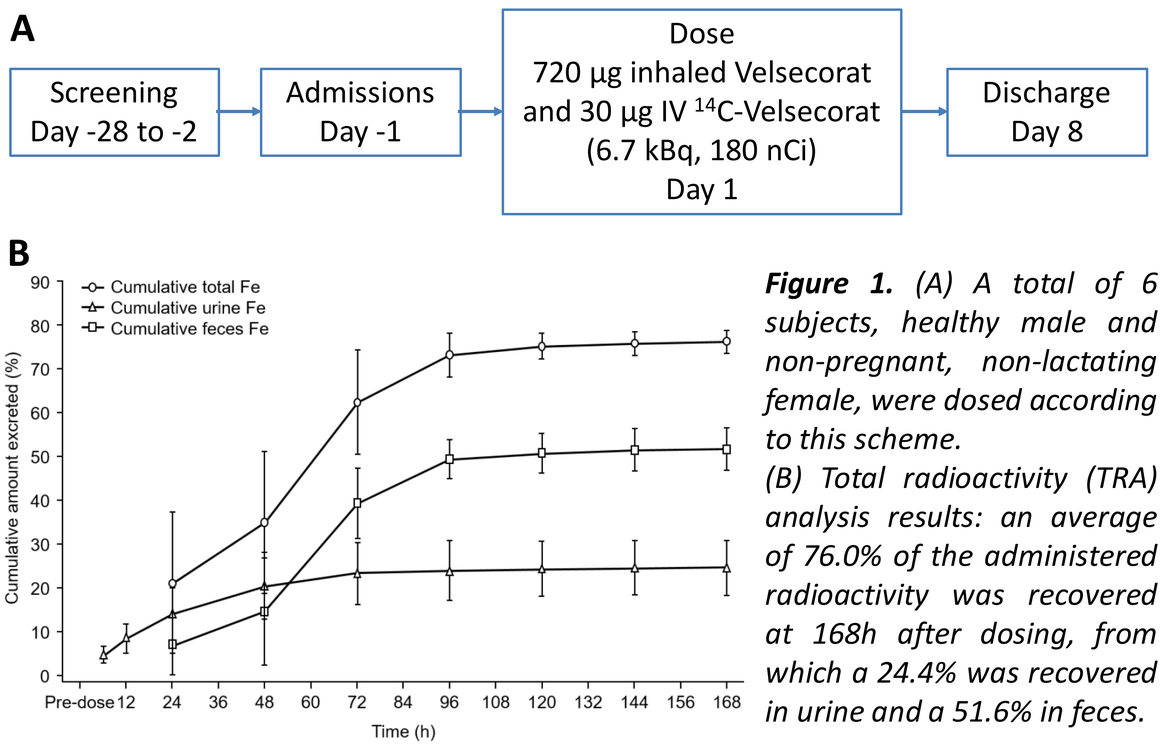


Figure 1. *(A) A total of 6 subjects, healthy male and non-pregnant, non-lactating female, were dosed according to this scheme. (B) Total radioactivity (TRA) analysis results: an average of 76.0% of the administered radioactivity was recovered at 168h after dosing, from which a 24.4% was recovered in urine and a 51.6% in feces.*

PHARMACOKINETIC RESULTS

	Cmax [pmol/L]	T_{max} [h]	$T_{1/2}$ [h]	AUC_{0-t} [ng.h/mL]	CL/F or CL [L/h]	V_{ss} [L]
Velsecorat (inhaled)	509	0.88	26.9	10600	107	-
^{14}C-Velsecorat (IV)	543	1.00	1.99	671	70.7	113
TRA	565	1.00	18.4	3380	13.6	276

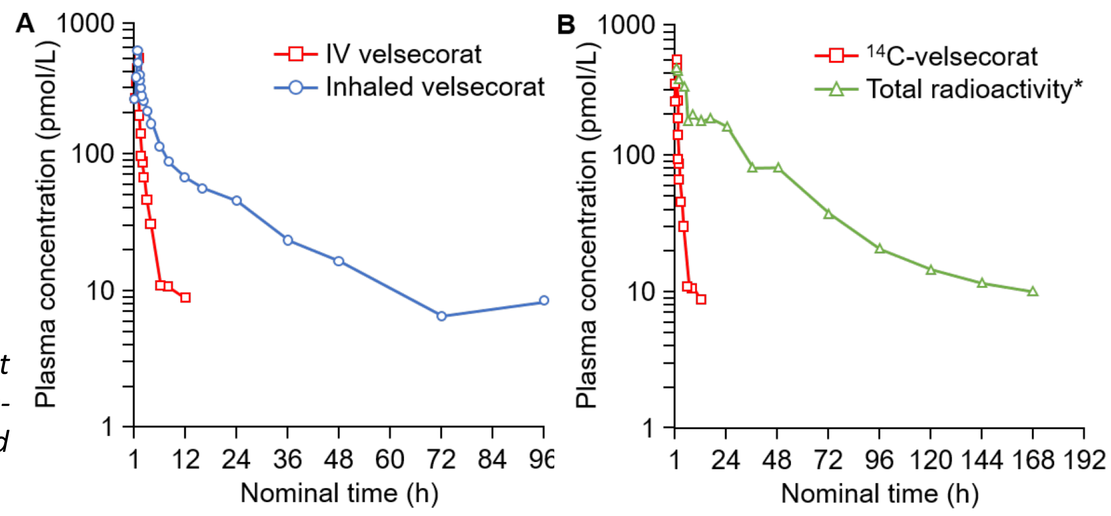
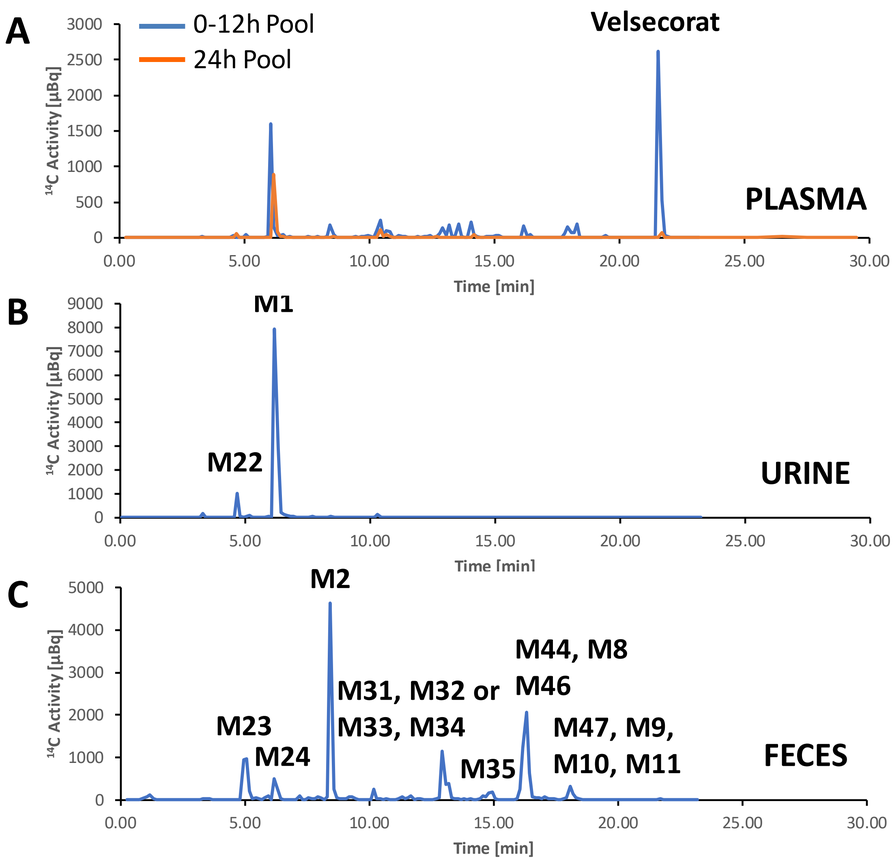


Figure 2. *The difference between the $t_{1/2}$ in plasma estimated for inhaled Velsecorat (27h) and for intravenous ^{14}C-Velsecorat (2h) confirmed its elimination is absorption-rate-limited from the lungs. Thus, a long pulmonary residence time is ensured supporting a once-daily administration.*

METABOLISM RESULTS



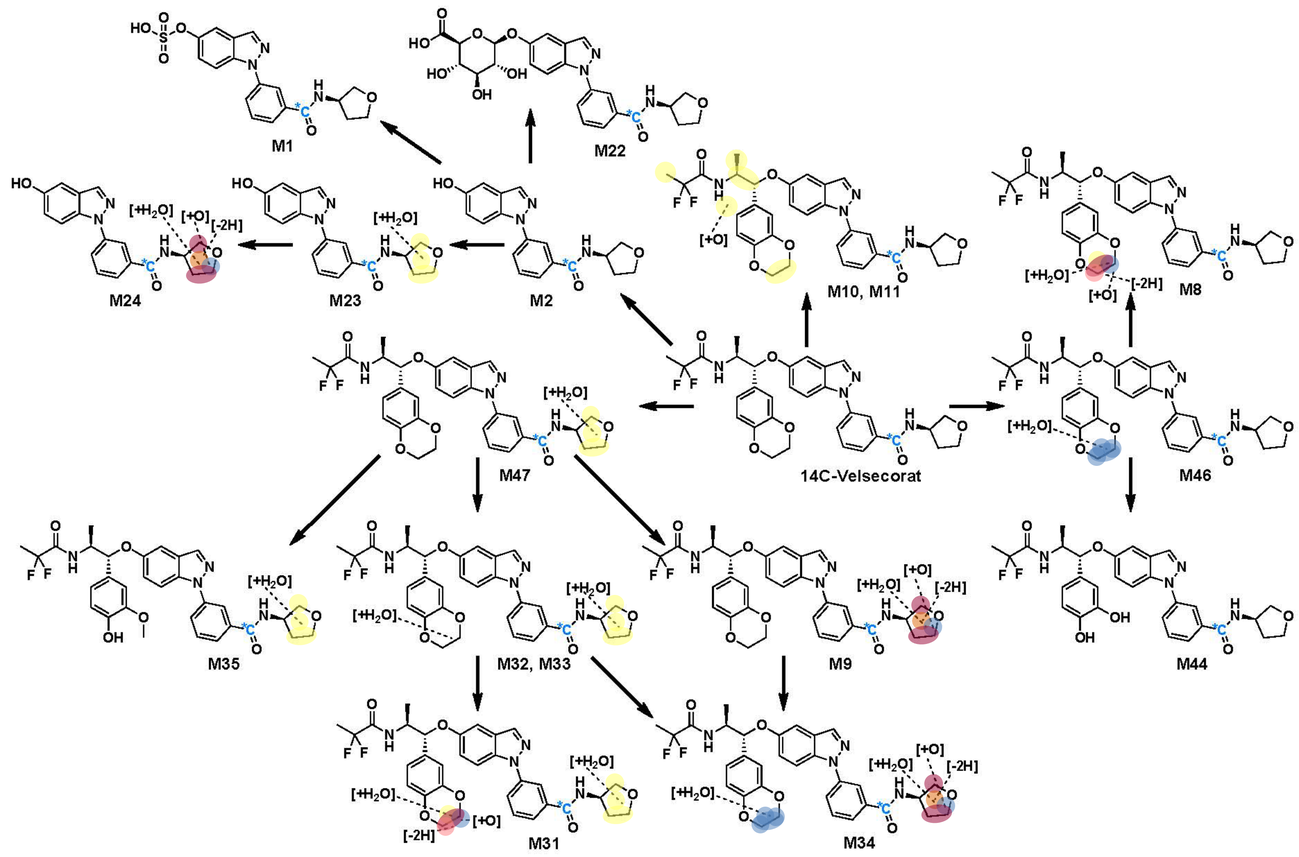


Figure 3. *AMS metabolic profiles in human (A) plasma (AUC_{0-12h} (blue) and 24h (orange) pools); B) urine (0-72h pool); (C) feces (0-96h pool); and (D) Proposed metabolic scheme for Velsecorat in humans. Urine and extracts of plasma and feces were fractionated using an ultra-performance liquid chromatography (UPLC) system coupled to a high-resolution mass spectrometer (HRMS, e.g. Q-Exactive). Post-column, the eluent was split between the Q-Exactive (for on-line generation of high-resolution MS and MS^2 data) and the fraction collector (for off-line ^{14}C determination in the fractions by AMS). Potential sites of metabolism are highlighted using the Markush coloring system.*

CONCLUSIONS

- Velsecorat showed a high clearance, volume of distribution and bioavailability, and a confirmed absorption-rate limited elimination following inhalation. It is substantially metabolized via three major routes: O-dealkylation of the indazole ether (M2); ring opening of the 1,4-dioxane ring (M46) and ring opening of the oxolane ring (M47).
- The use of an IV ^{14}C-microtracer enabled the determination of the mass balance, excretion routes and levels of circulating metabolites in humans with a radiation exposure similar to natural background levels. Additionally, high resolution metabolite profiles were obtained for all matrices, and metabolite identification was performed for all major metabolites and a number of minor metabolites.

REFERENCES

Aurell et al, *Drug Metabolism & Disposition* 50 (**2022**) 150-7; Young et al, *Clinical Pharmacology & Therapeutics* (**2022**).