5-fluorouracil and leucovorin predictive pharmacokinetics after administration of standard treatment or Deflexifol™

Tahlia R Meola[1], Madhu B Garg[2], Stephen P Ackland[2,3], Natalie Strange[4], Christian Toouli[4], David Ranson[4], Stephanie E Reuter[1]

[1]UniSA Clinical and Health Sciences, University of South Australia, Adelaide, SA, Australia
[2]Calvary Mater Newcastle, Waratah, NSW, Australia
[3]University of Newcastle, Callaghan, NSW, Australia
[4]FivepHusion, Austinmer, NSW, Australia

Email: Tahlia.Meola@unisa.edu.au | Website: www.fivephusion.com

BACKGROUND

5-fluorouracil (5-FU), in combination with its biomodulator leucovorin, remains a fundamental component of many efficacious chemotherapy regimens for patients with solid tumours.

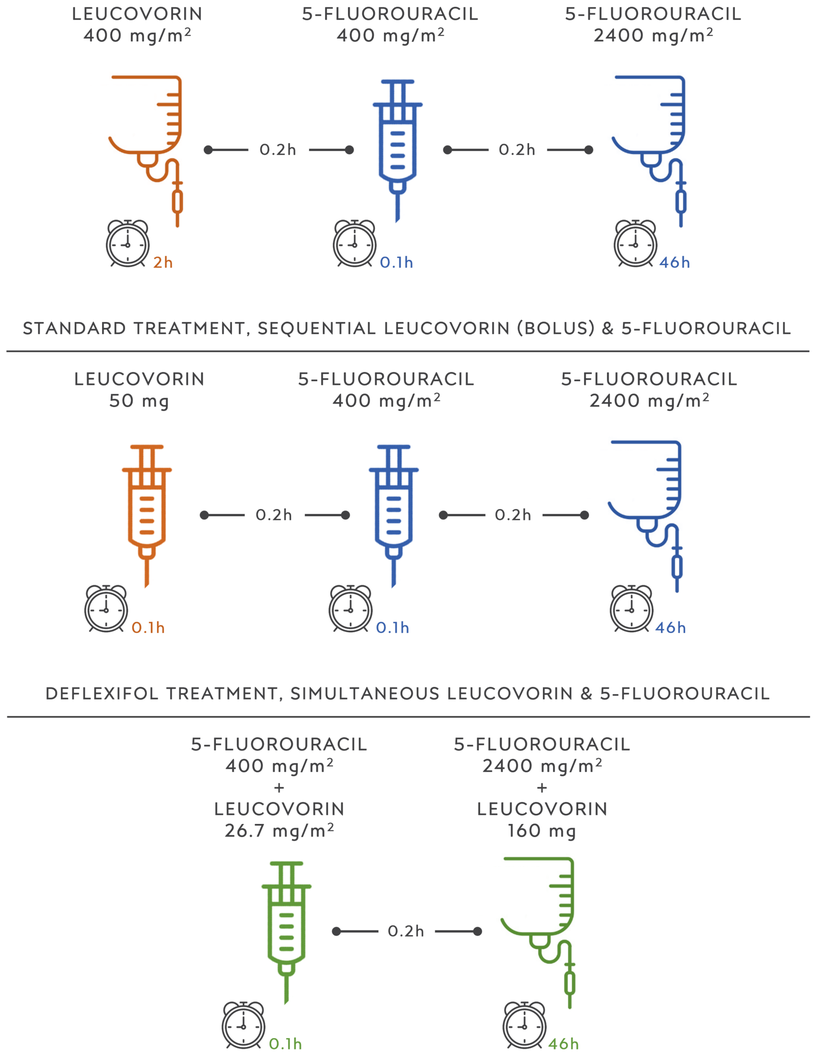
Due to physical incompatibility issues, standard administration schedules involve sequential administration of leucovorin, followed by 5-FU.

Simultaneous administration of 5-FU and leucovorin is expected to enhance anti-tumour effect.

Deflexifol™ has been developed as an all-in-one injectable reformulation of 5-FU and leucovorin at physiological pH, using HPβCD to maximise the clinical activity and safety profile of 5-FU [1].

Deflexifol™ is currently in clinical development.

Objective: To examine the comparative pharmacokinetics of 5-FU, racemic leucovorin and L-leucovorin (active enantiomer) after administration of US/EU and AU standard treatment regimens, and Deflexifol™.



CONCLUSIONS

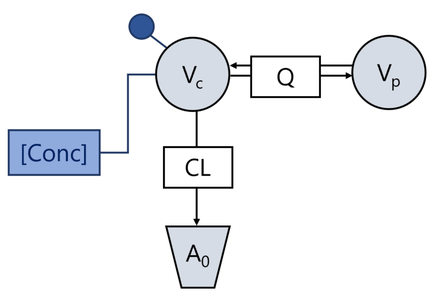
The pharmacokinetics of 5-FU, racemic leucovorin and L-leucovorin were well described by the pharmacokinetic models.

Simulations indicated that exposure of the active L-enantiomer is predicted to be approximately 2- and 10-fold greater for Deflexifol™ compared to the standard infusion and standard bolus regimens, respectively.

This work provides preliminary evidence to support the enhanced duration and extent of leucovorin exposure with Deflexifol™ treatment. Based on this, it is anticipated that Deflexifol™ treatment would maximise clinical activity and enhance anti-tumour effect when compared to current treatment regimens.

[1] Stutchbury T et al. Anticancer Drugs 2011 (1) 24-34. [2] Clingan P et al. Asia-Pac J Clin Oncol. 2018 (15)3 151-157. [3] Australian and New Zealand Clinical Trials Registry: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378626.

PHARMACOKINETIC MODEL DEVELOPMENT



Parameter	Estimate (95% CI)		
	5-Fluorouracil	Racemic Leucovorin	L-Leucovorin
CL (L/h)	83.3 (79.1 – 87.4)	1.36 (1.26 – 1.47)	16.4 (16.4 – 16.4)
V_c (L)	15.9 (14.1 – 17.7)	4.58 (2.74 – 6.42)	9.36 (9.34 – 9.38)
V_p (L)	4.70 (2.66 – 6.73)	8.11 (6.84 – 9.37)	1.49 (1.49 – 1.50)
Q (L/h)	72.2 (3.86 – 141)	7.55 (5.65 – 9.44)	1.73 (1.71 – 1.75)

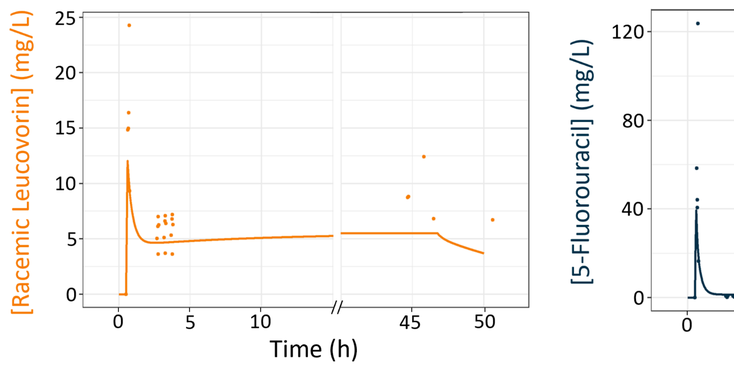
Abbreviations: CL, clearance; V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment; Q, intercompartmental clearance; A_0, elimination compartment;

Data describing 5-FU and leucovorin pharmacokinetics were extracted from the literature and characterised using pharmacokinetic modelling.

Pharmacokinetics of 5-FU, racemic leucovorin and L-leucovorin were best described by two-compartment models, with first-order elimination from the central component.

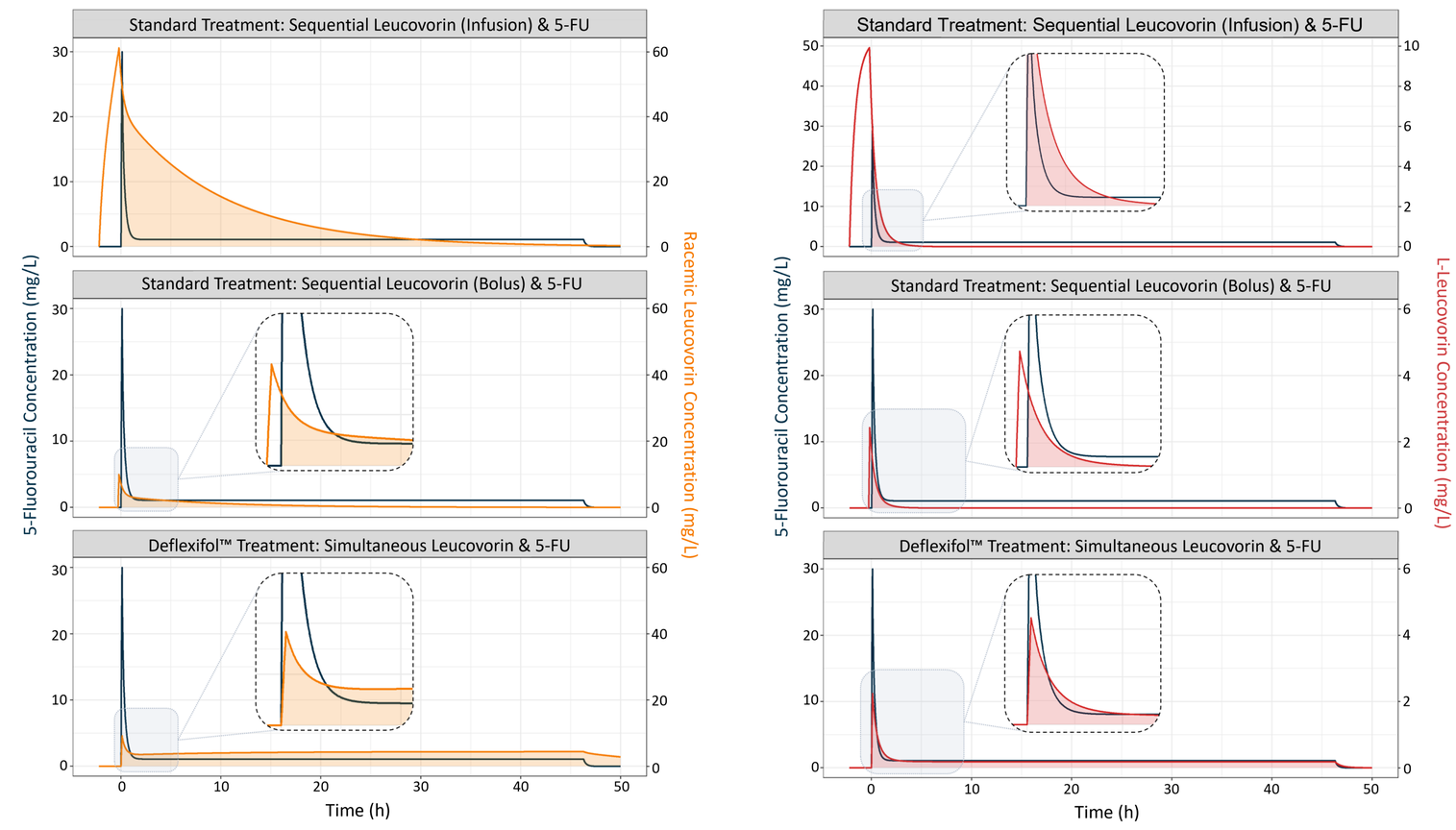
Standard diagnostic plots indicated uniform distribution and a lack of bias.

PHARMACOKINETIC MODEL VALIDATION



Pharmacokinetic models of 5-FU and racemic leucovorin indicated good agreement between observed concentrations obtained in Deflexifol™ clinical trial FP101A and predicted concentrations [2,3].

PREDICTION OF 5-FU AND LEUCOVORIN EXPOSURE



Parameter	Standard Treatment (Infusion)	Standard Treatment (Bolus)	Deflexifol™ Treatment
Racemic Leucovorin			
AUC_{total} (mg.h/L)	506	36.5	209
$AUC_{partial}$ (mg.h/L)	420	34.3	209
T_{syn} (h)	46.9	28.2	46.9
L-Leucovorin			
AUC_{total} (mg.h/L)	21.1	1.52	9.84
$AUC_{partial}$ (mg.h/L)	4.70	0.995	9.84
T_{syn} (h)	3.42	1.76	46.7

Abbreviations: AUC_{total}, total leucovorin exposure; $AUC_{partial}$, leucovorin exposure after 5-FU administration; T_{syn}, duration of leucovorin and 5-FU co-exposure.

For racemic leucovorin, Deflexifol™ is expected to have an equivalent or longer period of concurrent 5-FU and leucovorn exposure, compared to standard treatment.

For L-leucovorin, synergistic action of 5-FU and leucovorin is predicted to occur over 46.7 h for Deflexifol™, compared with 3.42 h and 1.76 h for standard infusional and bolus regimens, respectively.