AMS-ENABLED HUMAN ADME STUDY OF THE FGFR INHIBITOR DERAZANTINIB

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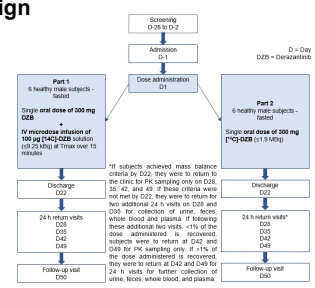
Background: Derazantinib (DZB) is an oral FGFR inhibitor under clinical development for patients with intrahepatic cholangiocarcinoma (iCCA), urothelial, and gastric cancer. As part of the development program of derazantinib, an innovative open-label, parallel group clinical study design was conducted to assess the absorption and disposition of derazantinib after intravenous (IV) and oral administrations. Accelerator mass spectrometry (AMS)-enabled and LC-MS/MS analysis were performed for mass balance, routes of excretion and elimination, absolute oral bioavailability, and metabolism of derazantinib in healthy male subjects.

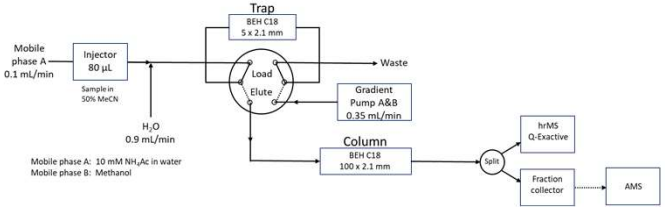
Study design

- Part 1, microtracer study: 6 healthy subjects, single oral dose of 300 mg DZB, followed 8 hours later by an IV microdose of 100 µg [^{14}C]-DZB (250 nCi, 9.25 kBq).
- Part 2: 6 healthy subjects, single oral dose of 300 mg [^{14}C]-DZB (53 µCi, 1.9 MBq).



Material and Methods

- Blood, urine, and feces samples were collected throughout the study for assessment of total radioactivity, DZB, its acid metabolite M-13, and metabolite profiling.
- AMS was used to determine total radioactivity in plasma, urine and feces and [^{14}C]-DZB concentrations in plasma. For the quantification and characterization of metabolites in acidified plasma and feces, samples were fractionated using an ultra-performance liquid chromatography (UPLC) system that was coupled to a high-resolution mass spectrometer (hrMS).
- Due to the low [^{14}C] levels in the Part 1 plasma pools, a large volume of injection (80 µL) was required to load an adequate amount of [^{14}C] on the column and a 2D UPLC setup was developed to profile plasma pool sample at approximately 1 mBq total radioactivity on column.

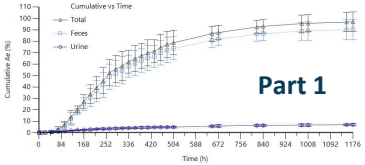


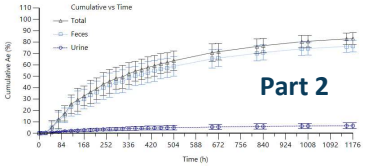
Total radioactivity recovery in urine and feces

Subject #	Part 1 (IV-microtracer) Percentage of administered dose (%) 101	102	103	104	105	106	Mean (%) ± SD
Urine 0-1176h	6.15	7.74	7.81	5.73	6.28	7.41	**6.85 ± 0.905**
Feces 0-1176h	90.5	96	82.8	97.5	97.9	76	**90.1 ± 8.96**
Total	**96.7**	**104**	**90.6**	**103**	**104**	**83.4**	**97.0 ± 8.49**

Subject #	Part 2 (Oral) Percentage of administered dose (%) 201	202	203	204	205	206	Mean (%) ± SD
Urine 0-1176h	7.05	5.38	11.6	5.88	4.13	5.64	**6.62 ± 2.63**
Feces 0-1176h	85.5	72.8	72.0	74.1	79.9	74.8	**76.5 ± 5.20**
Total	**92.5**	**78.1**	**83.6**	**79.9**	**84.0**	**80.4**	**83.1 ± 5.14**

- The majority of total radioactivity following oral and IV administration of [^{14}C]-DZB was recovered in feces indicating that hepatic excretion was the main route of elimination.



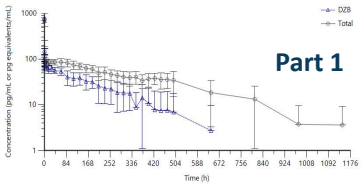


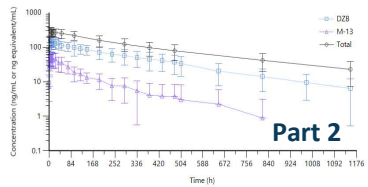
Total radioactivity, DZB, and acid metabolite (M-13) Plasma PK

		T1/2 (h)	Cmax (ng/mL)	Tmax (h)	AUC0-72h (ng.h/mL)	AUCinf (ng.h/mL)	CL (mL/min)	Vss (L)
Part 1	[^{14}C]-DZB	172	0.85	0.325	4.53	17.0	96.8	1480
	Total Radioactivity	290	0.83	0.283	6.38	38.4	NC	NC
Part 2	[^{14}C]-DZB	243	154	7.99	8070	40200	116	2440
	Total Radioactivity	346	297	7.00	17100	97600	NC	NC
	Acid metabolite (M-13)	292	53.3	10.0	2490	5990	NC	NC

NC: Not calculated

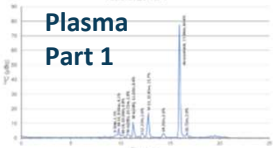
- The minimum fraction absorbed was above 60% and the oral bioavailability of DZB was 56% based on AUCinf.

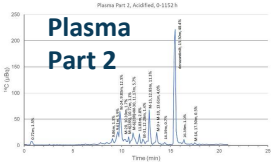


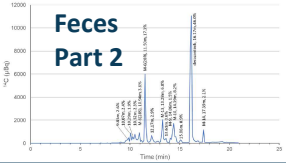


Metabolite profiling and identification

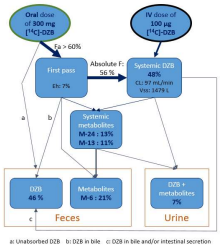
- Unchanged DZB was the major circulating component in plasma after oral and IV dosing, representing 48 and 62% of the [^{14}C]-radiochromatogram respectively. M-13 and M-24 (glucuronide conjugate of M-6) were the only other circulating components contributing to more than 10% of total radioactivity (11% and 13%, respectively) after oral dosing. M-13 was the most abundant component in plasma after IV dosing (16%).
- Unchanged DZB and M-6 (hydroxylated metabolite of DZB) were the main components in feces after oral and IV dosing: respectively, 46% and 21% (oral) / 15% and 36% (IV) of the radiochromatogram with no other metabolites contributing to >10% of radioactivity.

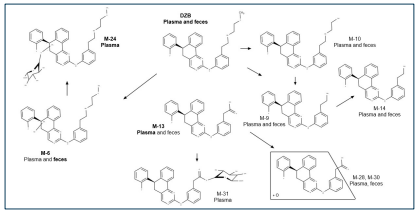






Distribution and elimination





Conclusion: A new and innovative approach combining 2D UPLC and AMS analysis was used successfully to profile low level of [^{14}C] in plasma pool samples. Following a 300 mg oral dose administration, derazantinib was well absorbed with an absolute bioavailability of 56%. Hepatic excretion was the main route of elimination following IV and oral dosing of [^{14}C]-derazantinib. DZB was well tolerated in healthy male subjects.