TECHNICAL SUMMARY OF RESULTS
2012-003495-39 [Debio-0932-102]

Name of Sponsor/Company: Debiopharm International SA	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Study Treatment: Debio 0932		
Name of Active Ingredient: Debio 0932		

Title of Study: A Two-Part, Sequential Design Study to Determine Debio 0932 Absolute Oral Bioavailability, Mass Balance Recovery, Metabolite Profiling and Structural Identification in 3 Cohorts of Healthy Male Subjects (Debio-0932-102)

Principal Investigator: -

Study Centre: Quotient Clinical, Mere Way, Ruddington Fields, Ruddington, Nottingham, NG11 6JS, UK.

Publication (Reference): None

Studied Period: 24 Oct 2012 to 03 Dec 2012	**Phase of Development:** I

Objectives:

The primary objective of Part 1 of the study was:

- To determine the absolute oral bioavailability at 2 dose levels of Debio 0932 in healthy male subjects

The primary objectives of Part 2 of the study were:

- To assess the mass balance recovery of total radioactivity from excreta in healthy subjects after oral administration of carbon-14 labelled Debio 0932 ([^{14}C]-Debio 0932)
- To determine the metabolic profile of [^{14}C]-Debio 0932 in plasma, urine and faeces following oral administration

The secondary objectives of Part 1 of the study were:

- To determine the pharmacokinetic (PK) of total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1 following intravenous (IV) administration of [^{14}C]-Debio 0932 in healthy subjects
- To determine the PK of Debio 0932 and Debio 0932-MET1 following oral administration of Debio 0932 in healthy subjects
- To explore the routes and rates of elimination of total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1 following IV administration of [^{14}C]-Debio 0932 in healthy subjects
- To explore the elimination of Debio 0932 and Debio 0932-MET1 in urine following oral administration of Debio 0932 in healthy subjects
- To provide safety and tolerability information of Debio 0932 in healthy subjects
- To collect pharmacogenetic data to explore whether they may affect the PK of Debio 0932

The secondary objectives of Part 2 of the study were:

- To determine the PK of total radioactivity, [^{14}C]-Debio 0932, [^{14}C]-Debio 0932-MET1, Debio 0932 and Debio 0932-MET1 following oral administration of [^{14}C]-Debio 0932 in healthy subjects
- To determine the routes and rates of elimination of [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1 following oral administration in healthy subjects
- To determine the chemical structure of "major" metabolites of [^{14}C]-Debio 0932

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- To evaluate the blood to plasma ratio of total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1
- To determine the ex vivo protein binding for total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1
- To provide safety and tolerability information of Debio 0932 in healthy subjects
- To collect pharmacogenetic data to explore whether they may affect the PK of Debio 0932

Methodology:

This was a single centre, open-label, non-randomised, 2-part study in healthy male subjects.

Part 1

Part 1 of the study was conducted in 2 cohorts of subjects. Cohort 1 received the following regimens:

Regimen A: a single oral dose of 250 mg Debio 0932

Regimen B: an intravenous (IV) dose of [^{14}C]-Debio 0932 (100 µg) containing not more than (NMT) 10 kBq (270 nCi) ^{14}C, administered as a 15 minute (min) infusion to end at the estimated T_{max} of the oral dose [2 hours (h) post-dose]

As an additional safety measure, to limit subject exposure, a sentinel group of 2 subjects – each dosed 30 min apart – were selected to receive the planned dose 48 h in advance of the remaining 4 subjects. The remaining 4 subjects were dosed sequentially a few min apart, following a review of all available safety data by the principal investigator (PI) or delegate. The following safety data were reviewed: adverse events (AEs), vital signs and electrocardiograms (ECGs) up to 48 h post-dose, and clinical laboratory tests up to 24 h post-dose. If any subject from the sentinel group had experienced a severe or clinically significant AE that was considered possibly investigational medicinal product (IMP)-related, then dosing of the remaining 4 subjects would not have proceeded.

Cohort 2 was dosed a minimum of 1 week after completion of dosing Cohort 1 on the basis that an evaluation of all safety and tolerability data by the PI or delegate and the sponsor's medical monitor indicated that it was safe to proceed. The safety data included all AEs and clinically significant changes in vital signs, ECGs, physical examinations and in clinical laboratory tests up to 48 h post-dose. The data were summarised in an interim safety report and dose decision document, which were reviewed and signed by both the PI or delegate and the sponsor's medical monitor indicating that it was safe to escalate to the next planned dose level before dosing in Cohort 2 was commenced. If any of the stopping criteria had been met dosing of Cohort 2 would not have taken place.

Cohort 2 received the following regimens:

Regimen C: a single oral dose of 500 mg Debio 0932

Regimen B: an IV dose of [^{14}C]-Debio 0932 (100 µg) containing NMT 10 kBq (270 nCi) ^{14}C, administered as a 15 min infusion to end at the T_{max} of the oral dose (2 h post-dose).

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As for Cohort 1, a sentinel group of 2 subjects was dosed 48 h in advance of the remaining 4 subjects. The same conditions applied as described for Cohort 1.

Subjects were admitted to the clinic at approximately 21:00 on the evening prior to IMP administration (Day -1) and remained on site until discharge on the morning of Day 3 (48 h post-dose). Subjects received a single oral dose of Regimen A or C at approximately 09:00 following an overnight fast. Regimen B, the IV microtracer dose of [^{14}C]-Debio 0932 (100 µg), was administered as a 15 min infusion ending at 2 h after the oral dose (expected T_{max}). Subjects returned to the clinic for blood sampling at 72 h and 96 h post-dose, and for a follow-up visit (post-study safety assessments) within 5 to 10 days of dosing.

Part 2

Part 2 of the study was conducted in a single cohort of subjects. Cohort 3 received the following regimen:

Regimen D: oral administration of 500 mg [^{14}C]-Debio 0932 containing NMT 0.70 MBq (19 µCi) ^{14}C.

Following appropriate safety data from Part 1 all subjects in Cohort 3 were dosed as a single group with individual subjects dosed sequentially a few min apart.

Subjects were admitted to the clinic at approximately 21:00 on the evening prior to IMP administration (Day -1) and received the oral dose of Regimen D at approximately 09:00 on Day 1 following an overnight fast. Subjects remained on site until 168 h post-dose and were discharged on the morning of Day 8, but subjects may have been discharged sooner if a mass balance recovery of >90% was achieved or if 2 consecutive days showed <1% recovery, whichever was the sooner. If neither discharge criterion were achieved, subjects may have been required to continue collection of urine and faeces on an out-patient basis.

Number of Subjects (Planned and Analysed):

Part 1: Planned: 12 subjects (2 cohorts of 6); Enrolled: 12; Completed: 12; Analysed: 12

Part 2: Planned: 8 subjects; Enrolled: 8; Completed: 8; Analysed: 8

Diagnosis and Main Criteria for Inclusion:

Healthy male subjects between 18 and 65 years of age for Part 1, and between 30 and 65 years of age for Part 2, with a body mass index between 18 to 32 kg/m^2.

Test Product, Dose and Mode of Administration, Batch Number:

Regimen A:

- Cohort 1 Sentinel; 250 mg Debio 0932 immediate release (IR) oral tablets
- Cohort 1 Main; 250 mg Debio 0932 IR oral tablets

Regimen B:

- Cohort 1 Sentinel; 100 µg [^{14}C]-Debio 0932 IV infusion (the actual dose of radioactivity administered to the 2 subjects was 8.722 and 8.791 kBq)
- Cohort 1 Main; 100 µg [^{14}C]-Debio 0932 IV infusion (the actual dose of radioactivity ranged from 8.663 to 8.843 kBq)

- Cohort 2 Sentinel; 100 µg [^{14}C]-Debio 0932 IV infusion (the actual dose of radioactivity administered to the 2 subjects was 8.530 and 8.735 kBq)
- Cohort 2 Main; 100 µg [^{14}C]-Debio 0932 IV infusion (the actual dose of radioactivity ranged from 8.682 to 8.907 kBq)

Regimen C:

- Cohort 2 Sentinel; 250 mg Debio 0932 IR oral tablets
- Cohort 2 Main; 250 mg Debio 0932 IR oral tablets

Regimen D:

- Cohort 3; 100 mg Debio 0932 active pharmaceutical ingredient (API) powder in capsules spiked with [^{14}C]-Debio 0932 ethanol (the actual dose of radioactivity administered for all subjects was 0.6 MBq)

Duration of Treatment:

Part 1

Regimen A: A single oral dose of 250 mg Debio 0932 IR tablet administered on Day 1.

Regimen B: A single IV dose of 100 µg [^{14}C]-Debio 0932 solution administered on Day 1.

Regimen C: A single oral dose of 2 × 250 mg Debio 0932 IR tablet administered on Day 1.

Subjects had a follow-up assessment 5 to 10 days after dosing.

Part 2

Regimen D: A single oral dose of 5 × 100 mg [^{14}C]-Debio 0932, consisting of Debio 0932 API powder in capsules, each spiked with [^{14}C]-Debio 0932 ethanol administered on Day 1.

Subjects remained on site until approximately 168 h post-dose.

Criteria for Evaluation:

Mass Balance and Pharmacokinetics (PK)

The following PK parameters were estimated where possible for each subject and regimen unless otherwise specified:

Part 1: Debio 0932, total radioactivity, [^{14}C]-Debio 0932, Debio 0932-MET1 and [^{14}C]-Debio 0932-MET1, where appropriate

In plasma:

- **T_{lag}:** the elapsed time from dosing to the first quantifiable concentration in a concentration vs time profile (oral dose only)
- **T_{max}:** the time at which C_{max} was apparent
- **C_{max}:** the maximum observed concentration
- **C_{24}:** the concentration at 24 h post-dose
- **$AUC_{(0\text{-}last)}$:** the area under the concentration vs time curve from time zero to the last quantifiable time point
- **AUC_{∞}:** the area under the concentration vs time curve from time zero extrapolated to infinity

- **$AUC_{\%extrap}$:** the percentage of AUC accounted for by extrapolation
- **F:** absolute bioavailability (Debio 0932 only)
- **λ_z:** the slope of the apparent elimination phase
- **$T_{1/2}$:** the apparent elimination half-life
- **CL:** clearance (IV dose only)
- **CL/F:** clearance after oral dose
- **V_d:** volume of distribution (IV dose only)
- **V_d/F:** volume of distribution after oral dose
- **MRT:** mean residence time

In urine and faeces:

- **A_e (urine)**, **A_f (faeces)** and **A_t (urine and faeces combined):** the amount of recovery in urine, faeces and overall (ie urine and faeces combined) was calculated for total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1, and for urine only, Debio 0932 and Debio 0932-MET1
- **F_e (urine)**, **F_f (faeces)** and **F_t (urine and faeces combined):** the fraction of dose recovered in urine, faeces, and overall (ie urine and faeces combined) was calculated for total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1, and for urine only, Debio 0932 and Debio 0932-MET1
- **CL_r:** renal clearance

In addition, the following AUC and C_{max} ratios were calculated:

- Debio 0932-MET1: Debio 0932 (oral dose only)
- [^{14}C]-Debio 0932-MET1: [^{14}C]-Debio 0932 (IV dose only)

Part 2: Total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1

- **A_e (urine)**, **A_f (faeces)**, **A_a (expired air)** and **A_t (ie urine, faeces and expired air combined):** cumulative recovery in urine, faeces, expired air and overall (ie urine, faeces and expired air combined) was calculated for total radioactivity, Debio 0932, Debio 0932-MET1
- **F_e (urine)**, **F_f (faeces)**, **F_a (expired air)** and **F_t (ie urine, faeces and expired air combined):** cumulative fraction of dose recovered in urine, faeces, expired air and overall (ie urine, faeces and expired air combined) was calculated for total radioactivity, Debio 0932, Debio 0932-MET1
- **CL_r** for Debio 0932 and Debio 0932-MET1

For total radioactivity, Debio 0932 and Debio 0932-MET1 in plasma:

- T_{lag}, T_{max}, C_{max}, $AUC_{(0\text{-last})}$, AUC_{∞}, $AUC_{\%extrap}$, F (for total radioactivity and Debio 0932 only using mean IV data from Part 1), λ_z, $T_{1/2}$, MRT (for total radioactivity and Debio 0932)

In addition, the following ratios were calculated:

- AUC and C_{max} Debio 0932-MET1: Debio 0932
- Whole blood: plasma concentrations for total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1

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Safety

The evaluation of safety parameters comprised analysis of AEs, laboratory variables, vital signs, ECG and physical examination findings.

Statistical Methods:

No formal statistical analysis was performed.

Summary – Conclusions:

Mass Balance, Pharmacokinetic and Metabolite Profiling and Identification Results

Part 1

The geometric mean values (geometric mean coefficient of variation [CV%]) of the key PK parameters for the parent drug Debio 0932 and [^{14}C]-Debio 0932 are presented below.

	Cohort 1		Cohort 2	
Regimen **Dose** **Route** **Analyte** **Parameter**	**Regimen A** **250 mg** **oral** **Debio 0932** **(N = 6)**	**Regimen B** **100 µg** **IV** **[^{14}C] Debio 0932** **(N = 6)**	**Regimen C** **500 mg** **oral** **Debio 0932** **(N = 6)**	**Regimen B** **100 µg** **IV** **[^{14}C] Debio 0932** **(N = 6)**
T_{lag} [a] (h)	0.00 (0.00–0.50)	NC	0.00 (0.00–0.25)	NC
T_{max} [a] (h)	0.500 (0.50–2.03)	0.17 (0.08–0.25)	0.75 (0.5–1.50)	0.25 (0.17–0.33)
C_{max} (ng/mL) [b]	21.3 (24.7%)	973 (23.1%)	16.3 (14.7%)	501 (32.2%)
C_{24} (ng/mL) [b]	1.21 (21.8%)	NC	1.82 (47.5%)	NC
$AUC_{(0\text{-last})}$ (ng.h/mL) [b]	47.2 (42.3%)	1130 (17.0%)	99.5 (39.3%)	925 (31.6%)
AUC_{∞} (ng.h/mL) [b]	61.3 (32.3%) [n=5]	1700 (33.5%) [n=4]	150 (31.1%) [n=5]	1100 (18.5%) [n=4]
$T_{1/2}$ (h)	10.412 (66.2%) [n=5]	19.238 (132.0%) [n=4]	23.657 (58.6%) [n=5]	13.623 (48.1%) [n=4]
CL or CL/F[c] (mL/min)	67900 (32.3%) [n=5]	955 (35.1%) [n=4]	55500 (31.1%) [n=5]	1540 (19.2%) [n=4]
CLr (mL/min)	5.18 (74.9%) [n=2]	NC	10.9 (53.3%)	NC
V_d or V_d/F[d] (L)	61200 (50.3%) [n=5]	1590 (78.5%) [n=4]	114000 (48.2%) [n=5]	1820 (27.8%) [n=4]
$MRT_{(0\text{-last})}$ (h)	4.430 (68.1%)	6.709 (27.7%)	12.481 (53.6%)	7.723 (62.1%)
MRT_{∞} (h)	11.350 (65.5%) [n=5]	21.709 (27.7%) [n=4]	32.236 (37.7%) [n=5]	16.415 (44.6%) [n=4]
$F_{(0\text{-last})}$ (%)	1.65 (41.7%)	NC	2.20 (48.8%)	NC

Cohort 1: Regimen A (250 mg Debio 0932 oral IR tablet) followed by Regimen B (100 µg [^{14}C]-Debio 0932 IV solution)
Cohort 2: Regimen C (2 × 250 mg Debio 0932 oral IR tablets) followed by Regimen B (100 µg [^{14}C]-Debio 0932 IV solution)
NC: not calculated
[a] median (range)
[b] for ^{14}C doses (Regimen B) units are pg instead of ng
[c] CL for Regimen B and CL/F for Regimens A and C
[d] V_d for Regimen B and V_d/F for Regimens A and C

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Following IV administration of 100 µg of [^{14}C]-Debio 0932 solution (Regimen B) 1.75 h after the oral dose, plasma concentration vs time profiles of [^{14}C]-Debio 0932 were consistent with an IV infusion in both Cohorts 1 and 2. Maximum concentrations of [^{14}C]-Debio 0932 occurred no later than the end of infusion (0.25 h) in the majority of subjects and at 0.33 h in 1 subject. Concentrations subsequently declined and were quantifiable until 70.25 h post-dose. The T_{max} occurred by the end of the infusion, followed by a rapid decline in concentrations. This is typical of a short period of rapid distribution following the end of an IV infusion.

As the IV microtracers were administered on top of 250 mg and 500 mg dose levels, 2 sets of IV pharmacokinetics are described.

Exposures to [^{14}C]-Debio 0932 were similar, as would be expected of 2 equivalent 100 µg IV administrations. However, the C_{max} observed following IV administration on top of the 500 mg oral dose was lower than that observed for the 250 mg oral dose and is likely to be a result of the rapid decline in systemic concentrations following the end of an IV administration making the true C_{max} difficult to capture.

The estimated half-lives demonstrated high variability due to fluctuating plasma concentrations in the samples taken at later time points. These were often associated with food intake and could be indicative of entero-hepatic re-circulation. Plasma clearance estimates following IV administration of Debio 0932 at these 2 dose levels approximately equated to liver blood flow. When administered as IV microtracers on top of different oral doses, these clearance values should be considered in terms of the total dose administered and it appears an increased clearance was observed at the higher total dose level of 500 mg Debio 0932 (by approximately 60%).

The volume of distribution observed following the 250 and 500 mg oral dose of Debio 0932 with 100 µg IV tracer was high. This indicates distribution beyond the central compartment suggesting extensive distribution of Debio 0932 into the tissues.

Following administration of a single oral dose of 250 mg Debio 0932 IR tablet (Regimen A) and a single oral dose of 500 mg Debio 0932 IR tablet (Regimen C) plasma concentration vs time profiles for Debio 0932 were consistent with extra-vascular dosing. Debio 0932 was rapidly absorbed with no apparent lag phase.

A 2-fold increase in dose resulted in a reduction in C_{max}, which would suggest initial solubility and in vivo dissolution may be limited at the higher dose level; however, $AUC_{(0\text{-last})}$ demonstrated a dose proportional increase suggesting the proportion of dose absorbed was equivalent for both dose levels.

The half-life determined was highly variable due to concentrations fluctuating around the lower limits of quantification for the samples taken at the later time points. Again this could also be indicative of entero-hepatic re-circulation. Longer absorption may be contributing to a longer half-life for the higher dose level of 500 mg.

Following oral dosing of Debio 0932 at 250 mg, the renal clearance of Debio 0932 was considered equivalent to the glomerular filtration rate (125 mL/min) when correcting flow rate for fraction unbound (4.5%). Following oral dosing of Debio 0932 at 500 mg, an apparent 2-fold increase in renal clearance was observed. Mean residence time after oral dosing increased with increasing dose level.

The geometric mean values (geometric mean CV%) of the key PK parameters for the metabolite Debio 0932-MET1 and [^{14}C]-Debio 0932-MET1 are presented below.

	Cohort 1		**Cohort 2**	
Regimen **Dose** **Route** **Analyte** **Parameter**	**Regimen A** **250 mg** **oral** **Debio 0932-MET1** **(N = 6)**	**Regimen B** **100 µg** **IV** **[^{14}C] Debio 0932-MET1** **(N = 6)**	**Regimen C** **500 mg** **oral** **Debio 0932-MET1** **(N = 6)**	**Regimen B** **100 µg** **IV** **[^{14}C] Debio 0932-MET1** **(N = 6)**
T_{lag} [a] (h)	0.250 (0.25–0.75)	NC	0.250 (0.00–0.50)	NC
T_{max} [a] (h)	1.250 (1.00–3.00)	0.210 (0.08–4.22)	2.250 (0.75–2.50)	0.33 (0.17–4.25) [n = 5]
C_{max} (ng/mL)[b]	38.9 (33%)	14 (50.2%)	38.6 (43.2%)	10.2 (35.7%) [n = 5]
C_{24} (ng/mL)[b]	4.48 (29.2%)	NC	8 (36.6%)	NC
$AUC_{(0\text{-last})}$ (ng.h/mL)[b]	336 (36.8%)	147 (49.3%)	540 (42.8%)	135 (51.1%) [n = 5]
AUC_{∞} (ng.h/mL)[b]	449 (37.7%) [n=4]	NC	647 (38.2%)	262 (24.2%) [n=3]
$T_{1/2}$ (h)	14.384 (9.4%) [n=4]	NC	16.334 (24.3%)	50.716 (45.5%) [n = 3]
CLr (mL/min)	38.1 (27.4%)	NC	48.7 (50.8%)	NC
$MRT_{(0\text{-last})}$ (h)	9.654 (12.3%)	25.517 (21.8%)	13.755 (22%)	18.889 (58.4%) [n = 5]
MRT_{∞} (h)	16.410 (6.9%) [n=4]	NC	21.976 (28.5%)	62.465 (55.8%) [n=3]
M:P C_{max}	1.828 (42.2%)	0.014 (45.2%)	2.363 (43.6%)	0.021 (50.2%) [n = 5]
M:P $AUC_{(0\text{-last})}$	7.124 (42.8%)	0.130 (42.1%)	5.430 (46.3%)	0.138 (67.5%) [n = 5]

Cohort 1: Regimen A (250 mg Debio 0932 oral IR tablet) followed by Regimen B (100 µg [^{14}C]-Debio 0932 IV solution)

Cohort 2: Regimen C (2 × 250 mg Debio 0932 oral IR tablets) followed by Regimen B (100 µg [^{14}C]-Debio 0932 IV solution)

NC: not calculated

[a] median (range)

[b] for ^{14}C doses (Regimen B) units are pg instead of ng

Following IV administration of 100 µg of [^{14}C]-Debio 0932 solution (Regimen B) 1.75 h after the oral dose, plasma concentration vs time profiles of [^{14}C]-Debio 0932-MET1 were consistent with the appearance of metabolite following IV infusion following both treatments. After reaching C_{max}, concentrations declined and remained quantifiable until 94.25 h post-dose. [^{14}C]-Debio 0932-MET1 formation was rapid. [^{14}C]-Debio 0932-MET1 also showed a reduced C_{max} following the administration of the 500 mg total dose, whilst the $AUC_{(0\text{-last})}$ remained equivalent. Again, it is thought to represent the difficulty in capturing the true C_{max} at the end of an IV infusion where rapid distribution takes place. Apparent terminal half-life estimates for [^{14}C]-Debio MET1 following IV administration of [^{14}C]-Debio 0932 at these 250 and 500 mg dose levels were longer than observed following oral dosing and may indicate the higher sensitivity

(lower limit of quantification) of the accelerator mass spectrometry (AMS) analytical methodology may have revealed a further phase of elimination.

Overall exposure to [^{14}C]-Debio 0932-MET1 was 7.7-fold and 7.2-fold lower for Cohort 1 and 2, respectively, compared to that for [^{14}C]-Debio 0932. This suggests very limited breakdown of [^{14}C]-Debio 0932 into [^{14}C]-Debio 0932-MET1 following IV administration. However, following oral administration of Debio 0932 exposure to Debio 0932-MET1 was 7.1-fold and 5.4-fold higher, respectively, compared to that observed for Debio 0932. This suggests extensive breakdown of Debio 0932 into Debio 0932-MET1 following oral administration and is indicative of pre-systemic metabolism/high first pass loss of Debio 0932 prior to introduction into systemic circulation.

Debio 0932-MET1 plasma concentrations were quantifiable by 1.00 h post-dose in all subjects. There was evidence of multiple concentration peaks within the plasma concentration vs time profiles, and many were co-incident with meal times. Debio 0932-MET1 was quantifiable for a maximum of 48 h in individual subjects.

Following administration of 250 mg Debio 0932, the appearance of the metabolite, Debio 0932-MET1, exhibited a short lag phase in subjects; however, following the lag formation of the metabolite was rapid. Following an increase in dose to 500 mg Debio 0932, formation of Debio 0932-MET1 remained rapid. The 2-fold increase in dose resulted in a 1.4-fold increase in AUC_{∞}, slightly less than was observed for Debio 0932. C_{max} remained unchanged.

The half-lives of Debio 0932-MET1 were similar to those observed for Debio 0932 and may suggest that elimination of this metabolite is formation rate limited. Renal clearance following correction for fraction unbound (5.9%) of Debio 0932-MET1 was greater than the glomerular filtration rate suggesting active secretion in the renal tubules.

The geometric mean values (geometric mean CV%) of the key PK parameters for total radioactivity in plasma are presented below.

	Cohort 1	**Cohort 2**
Regimen	**Regimen B**	**Regimen B**
Dose	**100 µg**	**100 µg**
Route	**IV**	**IV**
Analyte	**Total Radioactivity**	**Total Radioactivity**
Parameter	**(N = 6)**	**(N = 6)**
T_{max} [a] (h)	0.21 (0.08–0.25)	0.25 (0.25–0.25)
C_{max} (pg equiv/mL)	1070 (21.0%)	677 (25.1%)
$AUC_{(0\text{-last})}$ (pg equiv.h/mL)	6950 (14.0%)	6750 (16.8%)
AUC_{∞} (pg equiv.h/mL)	9640 (21.3%)	8940 (17.1%)
$T_{1/2}$ (h)	52.284 (27.6%)	45.610 (29.6%)
CL (mL/min)	171 (17.3%)	191 (17.3%)
CLr (mL/min)	61.6 (5.7%)	62.6 (30.6%)
Vz (L)	774 (16.2%)	753 (24.8%)
$MRT_{(0\text{-last})}$ (h)	33.07 (4.8%)	34.28 (6.4%)
MRT_{∞} (h)	70.712 (26.6%)	64.456 (27.2%)

Cohort 1: Regimen A (250 mg Debio 0932 oral IR tablet) followed by Regimen B (100 µg [^{14}C]-Debio 0932 IV solution); Cohort 2: Regimen C (2 × 250 mg Debio 0932 oral IR tablets) followed by Regimen B (100 µg [^{14}C]-Debio 0932 IV solution); [a] Median (range)

Following IV administration of [^{14}C]-Debio 0932, the concentration vs time profiles for total radioactivity were consistent with an IV infusion. The median T_{max} occurred by the end of the infusion in all subjects, followed by a rapid decline in concentrations which is typical of a short period of rapid distribution. There was a divergence of total radioactivity and [^{14}C]-Debio 0932 concentrations after approximately 0.08 h, with AUC_{∞} for total radioactivity being approximately 5.7-fold and 8.1-fold greater than that for [^{14}C]-Debio 0932 for Cohort 1 and 2, respectively. [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1 together only represented around 17% of the circulating total radioactivity with Debio 0932 contributing approximately 15% and Debio 0932-MET1 contributing approximately 2%. This indicates extensive formation of other radiolabeled metabolites.

The geometric mean $T_{1/2}$ for total radioactivity for Cohorts 1 and 2 suggested the presence of metabolites with slower elimination than seen for the parent drug.

Mass Balance Recovery

The mass balance of total radioactivity for the IV dose co-incident with the 250 mg oral dose was determined and an average of 23.92% of the total radioactive dose was recovered during the 48 h sampling period. As 18.27% of the total administered radiolabeled dose was recovered in the urine this suggests that renal excretion is the main route of excretion for drug-related product. Recovery of radioactivity observed in the faeces was low, amounting to 5.23% of the total administered dose.

Following administration of the IV dose co-incident to the 500 mg oral dose, an average of 32.67% of the total radioactive dose was recovered during the 48 h sampling period. A recovery of 17.46% of radioactivity was recovered in the urine with a recovery of 15.43% of the total administered dose in faeces. Recovery in the faeces increased following the 500 mg dose level (in comparison to the 250 mg dose level) and may be related to the similar increase observed for plasma clearance.

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Part 2

The geometric mean (geometric CV%) of the key PK parameters for Debio 0932, Debio 0932-MET1 and total radioactivity following a single oral dose of 500 mg [^{14}C]-Debio 0932 in plasma are presented below.

Parameter	Debio 0932 (N = 8)	Debio 0932-MET1 (N = 8)	Total Radioactivity (N = 8)
T_{max} [a] (h)	0.750 (0.50–1.50)	2.250 (0.75–6.00)	2.00 (1.50–4.00)
C_{max} (ng/mL)[b]	25.7 (54.9%)	57.9 (47.9%)	1860 (33.2%)
$AUC_{(0\text{-}last)}$ (ng.h/mL)[b]	121 (32.6%)	668 (33.9%)	30700 (28.9%)
AUC_{∞} (ng.h/mL)[b]	159 (36.9%) [n = 7]	783 (28.8%)	52200 (35.7%) [n = 5]
$T_{1/2}$ (h)	18.737 (47.7%) [n = 7]	17.665 (30.8%)	37.096 (84.2%) [n = 5]
CL/F (mL/min)	52400 (36.9%) [n = 7]	10600 (28.8%)	9570 (35.7%) [n = 5]
CLr (mL/min)	8.22 (40.4%)	46.7 (40.6%)	NC
V_d/F (L)	85000 (26.1%) [n = 7]	16300 (43.7%)	512 (44.4%) [n = 5]
$MRT_{(0\text{-}last)}$ (h)	11.897 (52.1%)	13.991 (36.5%)	19.488 (43%)
MRT_{∞} (h)	24.083 (50.1) [n = 7]	22.443 (32.4%)	49.978 (85%) [n = 5]
$F_{(0\text{-}last)}$ (%)[c]	2.36	NC	NC
M:P C_{max}	NA	2.251 (63.2%)	NA
M:P $AUC_{(0\text{-}last)}$	NA	5.530 (42.1%)	NA

NA: not applicable; NC: not calculated
[a] median (range)
[b] for total radioactivity units are pg instead of ng
[c] calculated using mean data from Part 1

Following oral administration of 500 mg [^{14}C]-Debio 0932, plasma concentrations of Debio 0932 were quantifiable from between 0.25 h and 0.75 h post-dose. Following C_{max}, concentrations declined remaining quantifiable for a maximum of 72 h post-dose. Debio 0932 was rapidly absorbed, with a short lag phase of 0.25 h. The geometric mean C_{max} and AUC_{∞} were similar to the exposure seen following the same oral dose in Part 1 (Regimen C).

Plasma concentrations of Debio 0932-MET1 were quantifiable between 0.25 h and 0.75 h post-dose. Concentrations tended to decrease in a triphasic manner and Debio 0932-MET1 was quantifiable for a maximum of 72 h post-dose in individual subjects. Debio 0932-MET1 exhibited a short lag phase of 0.30 h, following which formation of the metabolite was rapid. The observed geometric mean C_{max} and AUC_{∞} values were similar to the exposure seen in Part 1 following Regimen C and 2.3-fold and 5.1-fold higher, respectively, compared to the parent, Debio 0932. The geometric mean value for $T_{1/2}$ was similar to the parent, suggesting elimination of Debio 9032-MET1 is formation rate limited.

Total radioactivity plasma concentrations were quantifiable by 0.75 h post-dose in all subjects. Total radioactivity was detectable for a maximum of 72 h post-dose in individual subjects. There was an immediate divergence of total radioactivity and Debio 0932 concentrations, with AUC_{∞} for total radioactivity being approximately 328-fold greater than that for Debio 0932 indicating extensive breakdown of the parent drug. Debio 0932 and Debio 0932-MET1 together only represented around 2.5% of the circulating total radioactivity, with Debio 0932 contributing 0.39% and

Debio 0932-MET1 contributing 2.18%. The geometric mean $T_{1/2}$ for total radioactivity suggested the presence of metabolites with slower elimination than the parent drug.

Geometric mean values (geometric mean CV%) of key whole blood PK parameters following a single oral dose of 500 mg [^{14}C]-Debio 0932 are presented below.

Parameter	Debio 0932 (N = 8)	Debio 0932-MET1 (N = 8)
T_{max} [a] (h)	2.000 (2.00–2.00)	2.000 (2.00–6.00)
C_{max} (ng/mL)	15 (45.8%)	35.3 (51.8%)
$AUC_{(0\text{-last})}$ (ng.h/mL)	110 (29.2%)	467 (42.7%)
AUC_{∞} (ng.h/mL)	181 (37%) [n = 5]	606 (40.5%) [n = 7]
$T_{1/2}$ (h)	22.279 (90.4%) [n = 5]	12.523 (103.2%) [n = 7]
CL/F (mL/min)	46000 (37%) [n = 5]	NC
V_d/F (L)	88800 (50.9%) [n = 5]	NC
$MRT_{(0\text{-last})}$ (h)	8.467 (54.5%)	9.211 (43.1%)
MRT_{∞} (h)	25.409 (107%) [n = 5]	17.979 (98.5%) [n = 7]

[a] median (range)
NC = not calculated

Following oral administration of 500 mg [^{14}C]-Debio 0932, whole blood concentrations of Debio 0932 and Debio 0932-MET1 were quantifiable by the first sampling time point (2 h post-dose) in all subjects and concentrations remained quantifiable for up to 24 h post-dose in the majority of subjects.

Debio 0932 and Debio 0932-MET1 whole blood to plasma ratios, based on geometric mean AUC_{∞} values, were 1.14 and 0.77, respectively, suggesting limited distribution of Debio 0932 and Debio 0932-MET1 into the cellular components of whole blood. However, this conclusion should be considered with caution due to instability noted in whole blood.

The secondary objective to determine the ex vivo protein binding for total radioactivity, [^{14}C]-Debio 0932 and [^{14}C]-Debio 0932-MET1 was not achieved due to lower than expected concentrations, which were below the limits of detection of the scintillation method.

Mass Balance Recovery

Following oral administration of 500 mg [^{14}C]-Debio 0932, an average of 87.766% of the administered dose was recovered during the 312 h collection period, with over half of the dose being recovered by 72 h post-dose. Whilst the recovery may seem low, this would be considered typical of compounds with longer half-lives. The majority of radioactivity, 57.893%, was recovered in faeces, with a further 29.874% recovered in urine. No radioactivity was determined in expired air collections.

The recovery of Debio 0932 and Debio 0932-MET1 in the urine was considered to be low. The majority of the recovery was observed in the first 48 h post-dose with 0.014% and 0.386% recovered for Debio 0932 and Debio 0932-MET1, respectively. The total recovery observed over the 168 h collection period was 0.018% and 0.433% for Debio 0932 and Debio 0932 MET1, respectively.

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Comparison of Plasma Total Radioactivity Exposure Following Intravenous and Oral Dosing

After IV administration coincident with the 500 mg oral dose the total radioactivity recovered in the urine over 48 h was 17.45% of the administered dose. Whereas after oral administration at 500 mg, the recovery in the urine represented 24.34% of the administered dose collected over the corresponding 48 h post-dose period. The ratio of these values indicates that approximately 100% of the oral dose is absorbed giving a fraction absorbed value of approximately 1.0. This is further supported by comparison of the dose normalised geometric mean AUC for total radioactivity of both of the IV microtracer doses (Cohorts 1 and 2) with that for the oral therapeutic radiolabelled dose (Cohort 3). Comparison of the AUC_{∞} for Cohort 1 vs Cohort 3, and for Cohort 2 vs Cohort 3 gives estimates for fraction absorbed of 85.6% and 92.3%, respectively.

Metabolite Profiling and Identification

The metabolism of Debio 0932 was extensive with the compound undergoing phase I biotransformation including mono- and bis-N-demethylation to form Debio 0932-MET1 and Debio 0932 M2, N-de(neopentylation), mono-hydroxylation, oxidation of a terminal methyl group to an acid, N-de(neopentylation) followed by N-acetylation and N-formylation.

Metabolites resulting from ring-opening of the benzodioxolo ring to form O-methyl catechol related components and their subsequent phase II conjugation were also observed.

In addition, metabolites resulting from oxidation and loss of CH_2 as well as a loss of 2H from Debio 0932 were also observed in faeces.

Phase II metabolites observed included conjugation with sulphate, glucuronic acid (O and N conjugation) and formation of N-carbamoyl glucuronides.

Nine and 5 major components were observed in the 8 subject plasma and faecal extract pools, respectively, each of these major metabolites accounted for approximately 10% or greater of the total administered radioactivity in at least 1 subject. Despite up to 36 detected components, there were no major urinary metabolites observed in the 8 subject pools; no component represented more than 7.2% (the acid metabolite of Debio 0932-MET1) of the total administered radioactivity.

Safety Results

There were no safety concerns associated with Debio 0932 when administered as an oral dose of 250 mg (Regimen A) or 500 mg (Regimen C) followed by an IV microtracer (Regimen B) in Cohorts 1 and 2 in Part 1, respectively, or when administered as an oral dose of 500 mg [^{14}C]-Debio 0932 (Regimen D) in Cohort 3 in Part 2. No deaths, serious AEs or severe AEs were reported, and no subject had IMP withdrawn as a result of an AE in either part of the study.

There was no notable cohort-related trend in the number of subjects reporting at least 1 AE (3, 2 and 3 subjects in Cohorts 1, 2 and 3, respectively); however, the number of subjects reporting IMP-related AEs was slightly higher for Cohorts 1 and 3 than Cohort 2 (3, 3 and 1 subjects, respectively). The most frequently reported AE across

both parts of the study was headache: 2 subjects in Cohort 1, 1 subject in Cohort 2 and 3 subjects in Cohort 3. No other AE was reported for more than 1 subject in either part of the study.

Only 1 subject in Part 2 experienced a moderate AE (iritis), which was considered by the investigator to have a reasonable causal relationship to IMP. All other AEs reported in Parts 1 and 2 were considered mild in severity.

There were no clinically significant findings in any laboratory assessments, vital signs, ECGs or physical examinations.

Conclusions

- The absolute oral bioavailability of a 250 and 500 mg dose of Debio 0932 has been determined at 1.65% and 2.20%, respectively. This low value resulted from a high first pass metabolism of Debio 0932, since fraction absorbed was estimated around 100%.
- Following IV administration of [^{14}C]-Debio 0932 plasma clearance was approximate to liver blood flow. There was evidence of dose dependent changes in plasma clearance following IV administration following an oral dose, with the higher oral 500 mg dose level demonstrating approximately 60% higher plasma clearance than the 250 mg oral dose level.
- Dose proportionality with respect to C_{max} between 250 and 500 mg oral doses has not been established; however, approximate dose proportionality was observed for AUC_{∞}.
- Evidence of entero-hepatic re-circulation was seen within the plasma concentration vs time profiles and was more marked for Debio 0932-MET1 than for Debio 0932.
- There was an immediate divergence of the plasma profiles for total radioactivity from Debio 0932 indicating extensive breakdown of the parent drug into radiolabelled metabolites/breakdown products.
- Metabolite to parent ratios were different following oral and IV administrations and was indicative of pre-systemic metabolism/high first pass loss of Debio 0932 prior to introduction into the systemic circulation.
- The renal clearance observed for Debio 0932 appeared higher following administration of the 500 mg dose level.
- The mass balance conducted following IV administrations showed recoveries of 23.9% and 32.7% in excreta in Cohorts 1 and 2, respectively within the first 48 h post-dose with similar proportions of urinary recovery at each dose level. At a dose of 250 mg, urinary excretion was the major route of elimination.
- The geometric mean $T_{1/2}$ value for Debio 0932-MET1 was similar to that observed for Debio 0932 suggesting elimination of Debio 0932-MET1 is formation rate limited.
- The geometric mean $T_{1/2}$ value for total radioactivity was longer than for Debio 0932 suggesting the presence of metabolites with slower re-distribution from the tissues (high volume of distribution) resulting in an associated slower elimination than seen for Debio 0932 or Debio 0932-MET1 single analytes.
- Debio 0932 and Debio 0932-MET1 whole blood to plasma ratios indicate limited distribution of Debio 0932 and Debio 0932-MET1 into the cellular component of

whole blood; however, this should be interpreted with caution due to sample instability.

- After oral administration of [^{14}C]-Debio 0932 an average of 87.766% of the total radioactive dose administered was recovered in excreta during the 312 h collection period.
- The majority of radioactivity, 57.893%, was recovered in faeces with a further 29.874% recovered in urine. No radioactivity was determined in expired air collections.
- The metabolism of Debio 0932 was extensive with Debio 0932 undergoing phase I biotransformation including mono- and bis-N-demethylation to form Debio 0932-MET1 and Debio 0932 M2, N-de(neopentylation), mono- hydroxylation, oxidation of a terminal methyl group to an acid, N-de(neopentylation) followed by N-acetylation and N-formylation.
- Metabolites resulting from ring-opening of the benzodioxolo ring to form O-methyl catechol related components and their subsequent phase II conjugation were also observed.
- Metabolites resulting from oxidation and loss of CH_2 as well as a loss of 2H from Debio 0932 were also observed in faeces.
- Phase II metabolites observed included conjugation with sulphate, glucuronic acid (O and N conjugation) and formation of N-carbamoyl glucuronides.
- Debio 0932 was well tolerated in all cohorts in both parts of the study.
- There were no serious or severe AEs during either part of the study and no subject was withdrawn as a result of an AE.
- There were no clinically significant findings in any laboratory assessments, vital signs, ECGs or physical examinations.

GCP Statement: This trial was conducted under ICH E6 Good Clinical Practices, which has its foundation in the Declaration of Helsinki, including the archiving of clinical documents.

Amendments: There was one substantial amendment made before the study was initiated, which was incorporated in Protocol Version 2.0 (Protocol Substantial Amendment 1.0, dated 02 Oct 2012, implemented at the request of the MHRA, to include the list of prohibited medication in the protocol rather than separately). Also 1 non-substantial amendment was made after the study was initiated: Protocol Non-Substantial Amendment 01 (dated 14 Dec 2012) was implemented as the sponsor decided to send the pharmacogenetic samples to an additional laboratory.

Date of Report: 16 Jul 2014