# Final Results from the Phase I Study Expansion Cohort of Debio 0932, an Oral HSP90 Inhibitor, in Patients with Solid Tumors

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## Background

### HSP90

- HSP90 is a molecular chaperone that functions as a buffer against stress endured by tumors and controls the folding and processing of certain client proteins.
- HSP90 clients include multiple oncogenic proteins, such as EGFR, HER2, c-MET, AKT, KIT, FLT3, and VEGFR, which are particularly sensitive to HSP90 inhibition.
- Thus, inhibition of HSP90 leads to degradation of client proteins targeting multiple oncogenic signaling pathways

### Debio 0932

- Debio 0932 is an oral second-generation HSP90 inhibitor. Debio 0932-MET1, the N-mono de-methylated metabolite retains 5-25% of Debio0932's pharmacological activity of Debio 0932 *in vitro*.
- Debio 0932 has shown extended tumor retention, blood-brain-barrier penetration, and promising anti-tumor activity both as monotherapy and in combination with other drugs against a broad range of tumors in pre-clinical models.

## Methods

Expansion Part of the Phase I open-label study was designed to collect additional safety, PK and antitumor activity data of Debio0932 at the Recommended Dose established during the dose escalation phase

### Key inclusion criteria:

- Diagnosis of advanced solid tumours or lymphoma*, refractory to standard curative or palliative therapy
- Measurable disease per RECIST 1.1 criteria
- ECOG performance ≤1
- No significant cardiovascular disease

### Dosing & Schedule:

- Debio0932 1000mg once-a-day (QD ) oral dosing

### Cardiac safety monitoring

- Triplicate ECGs, 24 h Holter monitoring, LVEF, BNP, and troponin

### ClinicalTrials.gov identifier NCT01168752

*No patient with lymphoma entered the study

### Pharmacokinetics:

- Debio 0932 and Debio 0932-MET1 were assessed through serial PK measurements on days 1-2 and days 29-30.
- Steady-state PK disposition in fasting (at day 29) compared to fed (at day 30) state was explored in a subset of patients to evaluate the food effect on PK.
- Unique blood sampling for exploration of genetic polymorphism of metabolic enzymes and drug transporters was performed on day 1 using Affymetrix DMET™ Plus chip assay.

### Tumor assessment:

- Tumor metabolic assessment was performed at baseline and on days 21 and 57 by an 18F-FDG-PET scan in NSCLC patients determined on the SUV percentage change from baseline according to EORTC 1999 criteria
- Tumor assessments were performed after every 8 weeks of treatment, and tumor responses were determined by the investigator according to RECIST 1.1 criteria

## Results

### Patient Characteristics & Safety

| | ALL Debio 0932 1000 mg QD N = 39 | NSCLC Debio 0932 1000 mg QD N = 15 |
|---|---|---|
| Mean Age (range) (years) | 56 (22-74) | 57 (35-70) |
| Gender M / F [N(%)] | 23 (59%) / 16 (41%) | 8 (53%) / 7 (47%) |
| Predominant cancer types (%) | Lung-NSCLC 38.5% Colorectal 15.4% Kidney 12.8% | - |
| ≥ 3 previous treatment regimes (%) | 79% | 80% |
| Days of treatment (range) | 63 (10-264) | 66 (20-264) |
| Most frequent AEs (%) | | |
| Diarrhea | 72% | 80% |
| Nausea | 64% | 53% |
| Decreased appetite | 62% | 60% |
| Vomiting | 59% | 67% |
| Astenia | 54% | 47% |
| Best overall tumor response (%) | | |
| SD% | 25% | 14% |
| PD% | 75% | 86% |

**Table 1.** Demographics and Baseline Status

- Patients remained on treatment for an average of 63 days (10-264).
- The main reason for withdrawal was disease progression (89.7%).
- AEs were mostly CTCAE Grade 1 or 2.
- Most common AEs were diarrhea, nausea, decreased appetite, vomiting and asthenia.
- No clinically relevant ocular or cardiac toxicity was observed.
- No substantial changes in laboratory parameters (biochemistry and hematology) or vital signs from pre-treatment to study end were observed.

| Treatment Emergent Adverse Events | N | % | M |
|---|---|---|---|
| Total number of patients | 39 | | |
| Patients with AEs | 39 | 100.0 | 487 |
| ≥ Grade 3 AEs | 20 | 51.3 | 53 |
| Related AEs | 37 | 94.87 | 256 |
| Serious Adverse Events | 21 | 53.85 | 43 |
| • SAEs not related | 18 | 46.2 | 28 |
| • SAEs related | 9 | 23.1 | 15 |
| Death | 15 | 38.46 | |
| Death occurring within 30 days of last drug administration* | 3 | 7.69 | |

| Most Common Grade ≥ 3 Aes (>10% incidence) | N | % | M |
|---|---|---|---|
| Anemia | 4 | 10.3 | 4 |
| Asthenia | 4 | 10.3 | 4 |
| Hyponatreamia | 4 | 10.3 | 8 |
| Dyspnoea | 5 | 12.8 | 5 |

**Tables 2 & 3. Overview of AEs.** N = number of patients; M = number of mentions; * = 3 patients died within 30 days of last drug administration due to disease progression (days 17, 28 and 30).

### Pharmacokinetics & Antitumor Activity

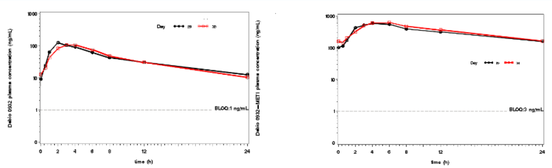

**Fig. 1.** Debio 0932 (left) and Debio 0932-MET1 (right) plasma concentration vs time profiles at day 29 (black line – fasted state) and day 30 (red line – fed state)

- Debio 0932 was rapidly absorbed (median $t_{max}$ 2 hours) with rapid conversion to the de-methylated metabolite. The plasma levels for Debio 0932-MET1 were 5-8 fold higher than for Debio 0932.
- High inter-individual variability in PK disposition
- The half life was approx. 10-20 h for both Debio 0932 and 0932-MET1
- Steady-state conditions were reached within the first week of dosing
- No food effect was observed on PK disposition of Debio0932.
- A particular CYP450 polymorphism may have had an impact on mean exposure, but the number of patients per polymorphism class was too small for a formal conclusion.

### Pet Scan:

1 (8.3%) Partial Metabolic Response
5 (41.7%) Stable Metabolic Responses
6 (50%) Progressive Metabolic Disease
were observed among the 12 evaluable NSCLC patients in the efficacy population.

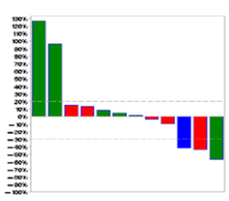

**Fig. 2.** Best $^{18}$F-FDG-PET Scan lesion response–NSCLC patients.

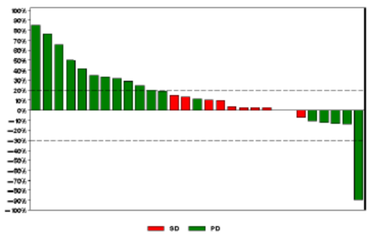

**Fig. 3.** Best target lesion response in patients with ≥1 on-treatment assessment.

### Antitumor activity:

36 out of 39 patients were assessed for antitumor activity. Although no objective tumor responses were seen, 9 (25%) out of 36 patients achieved lengthy episodes of disease stabilization (mean 77.2 days).
Individual PFS range was 16-281 days with a mean of 60.4 days.

## Conclusions

- Debio 0932 monotherapy was generally well tolerated at 1000 mg daily doses.
- Food had limited impact on Debio 0932 PK disposition. Consequently, the drug can be administered regardless of food intake.
- Debio 0923 showed promising signs of antitumor activity in patients with advanced solid tumors, especially in lung cancer.
- A Phase I/II study of Debio 0932 in combination with standard of care for first- and second-line treatment of NSCLC is in progress.

## References

[1]. Van Ingen et al. 2021. *J. Thor. Oncol.* 7(6;S1):S72 (abstract 196P)

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