Preclinical activity of Debio 1347, an oral selective FGFR1, 2, 3 inhibitor, in models harboring FGFR alterations

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Abstract #547

Summary

- **Dysregulation of the fibroblast growth factor receptor (FGFR) signaling pathway due to receptor overexpression, gene amplification, point mutations or fusions/chromosomal translocations is associated with cancer development and progression.**
- **Debio 1347 (CH5183284), currently investigated in a Phase I trial in selected patients harboring FGFR genetic alterations (NCT01948297), selectively inhibits FGFR1, FGFR2, and FGFR3, but does not inhibit kinase insert domain receptor (KDR) or other kinases. Consistent with its high selectivity for FGFR enzymes, Debio 1347 displays preferential antitumor activity against cancer cells with various FGFR genetic alterations in a panel of 327 cancer cell lines and in xenograft models. Because of its unique binding mode, Debio 1347 can inhibit FGFR2 harboring one type of gatekeeper mutation which causes resistance to other FGFR inhibitors, and blocks FGFR2 V564F-driven tumor growth[1].**
- **This study evaluated Debio 1347 in 2 preclinical models harboring FGFR genetic alterations and explored PK/PD relationships.**

Background

Debio 1347 is a selective and orally available FGFR1, 2, and 3 ATP competitive inhibitor

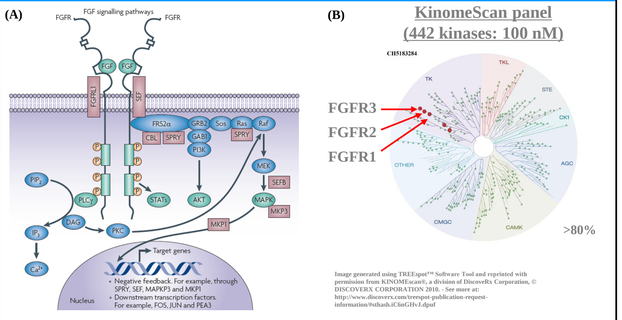


Figure 1. (A) FGFR signaling network. The signal transduction network downstream of FGFRs, along with negative regulators. Following ligand binding and receptor dimerization, the kinase domains transphosphorylate each other, leading to the docking of adaptor proteins and the activation of four key downstream pathways: RAS–RAF–MAPK, PI3K–AKT, STAT and PLCγ (green, adapted from Turner and Grose, 2010[2]). **(B) TREEspot™ Interaction Map** for Debio 1347 tested at 100 nM (Kinome Scan panel, DiscoveRx)[3].

Methods

These studies were conducted in accordance with institutional guidelines and NCRI Guidelines for the welfare and use of animals in cancer research[4]. D1 was set as the first day of treatment.

Mouse xenograft model (Charles River discovery research services, Morrisville, NC). Briefly, 5.10^6 RT112 tumor cells in 50% Matrigel were injected subcutaneously (sc) into the right flank of female NCr nu/nu mice. Tumor size was measured using a gauge twice per week and tumor volume (TV) was calculated using the following formula: $TV = ab^2/2$, where a is the length of the tumor, and b is the width. Debio 1347 was orally administered once or twice a day for 11 consecutive days (30 or 50 mg/kg BID, 60 or 100 mg/kg QD) in mice with established tumors (mean TV = 121 mm^3). Blood, organs and tumor were collected at different time points after last administration for subsequent analysis.

FGF23 determination. FGF23 was determined in mouse plasma (K_2EDTA) using quantitative ELISA (Millipore).

IHC analysis. FFPE tumors were stained with anti-phospho-FRS specific antibody (#ab78195, Abcam) using standard protocol IHC scoring: 1+ = weak, 2+ = moderate, 3+ = strong. Frequency modifiers were included to provide the approximate staining percentage of given cell types. The frequency was defined as follows: rare (1-5% of cells); rare to occasional (> 5-25% of cells); occasional (> 25-50% of cells); occasional to frequent (> 50-75% of cells); frequent (> 75-100% of cells).

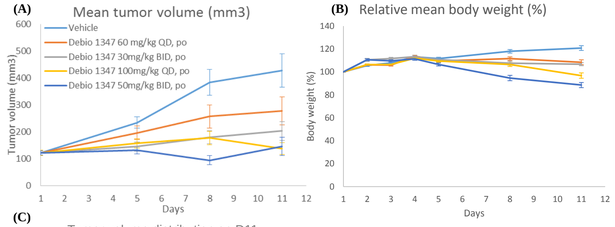
Pharmacokinetics. Debio 1347 plasma concentrations were determined using a validated LC/MS/MS method and PK parameters were derived by non-compartmental analysis using Phoenix™ WinNonlin® version 6.3 (Certara).

PDX mouse model (Precos, UK). Briefly, in a sterile, chilled, petri-dish, tissue from donor animals was pooled, finely minced, and mixed with a volume of Cultrex/MSC. Equal volumes of tumor/Cultrex/MSC mixture (~100 mm^3) were implanted subcutaneously into the left flank of female MF1 nude mice under anesthesia. Mice were randomly allocated to treatment groups when the tumors reached a mean TV~160 mm^3 (day 16). Debio 1347 was administered orally daily for 15 consecutive days, after which all mice were terminated 4 hours post-final dose.

Results

Debio 1347 inhibits tumor growth of a FGFR3-TACC3 translocated bladder cancer model

Significant antitumor activity was observed at 100 mg/kg QD and 50 mg/kg BID (TGI ≥ 60%, Table 1). Debio 1347 administration frequency affected efficacy at the low dose level (30 mg/kg BID displayed a higher activity as compared to 60 mg/kg QD) and toxicity at the high dose level (50 mg/kg BID induced higher body weight loss (BWL) and deaths as compared to 100 mg/kg QD).



Regimen	Day	optimal TGI (%)
60 mg/kg QD	11	47.8
30 mg/kg BID	11	57.0
100 mg/kg QD	11	68.4
50 mg/kg BID	8	76.6

Table 1. Optimal TGI (%).

Figure 2. (A) Debio 1347 showed potent antitumor efficacy in vivo in FGFR3 translocated RT112 bladder model. **(B)** Relative mean body weights during treatment. (50 mg/kg BID: 3 deaths/ BWL=12.3%; 100 mg/kg QD: 1 death/ BWL = 2.4%). **(C)** Tumor volumes on the last day of treatment.

Debio 1347 modulates pharmacodynamic markers in plasma and tumor

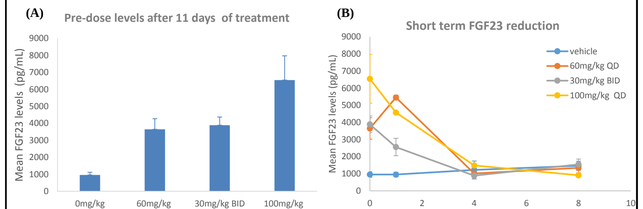


Figure 5. Debio 1347 induced dose-dependent long term FGF23 induction **(A)** and short term inhibition after each administration **(B)**. The FGF23 inhibition plateau was reached 4 hours after dosing with a maximal effect obtained at 60 mg/kg daily while maximal FGF23 induction and antitumor effect were observed at higher doses (n=3 /time point).

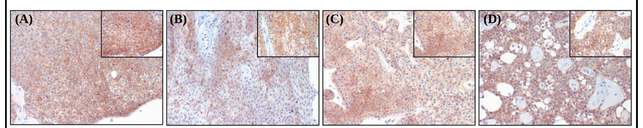


Figure 6. Phospho-FRS2 staining of RT112 tumors treated with vehicle **(A)**, Debio 1347 60 mg/kg QD **(B)**, Debio 1347 30 mg/kg BID **(C)**, Debio 1347 100 mg/kg QD **(D)** (20X). Tumors were collected 4 hours post-last administration and paraffin-embedded. IHC score was performed on 3 animals per group (not shown). Phospho-FRS2 membrane staining was reduced in Debio 1347-treated groups as compared to the vehicle-treated group.

PK/PD relationships between Debio 1347 plasma levels, FGF23 plasma levels, and tumor growth inhibition in a FGFR translocated bladder cancer model

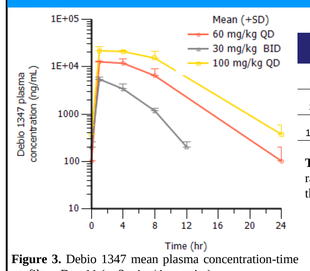


Figure 3. Debio 1347 mean plasma concentration-time profile at Day 11 (n=3 mice/time point).

Regimen	Daily dose (mg/kg)	T_{max} (hr)	C_{min} (ng/mL)	C_{max} (ng/mL)	AUCt (hr·ng/mL)	daily AUC (hr·ng/mL)	$t_{1/2}$ (hr)
60 mg/kg QD	60	1	102	12664	102854	102854	2.8
30 mg/kg BID	60	1	204	5431	26339	52678	2.0
100 mg/kg QD	100	1	373	21792	209883	209883	3.3

Table 2. Debio 1347 plasma PK parameters indicate that Debio 1347 was rapidly absorbed after oral administration, with exposure increasing more than dose-proportionally.

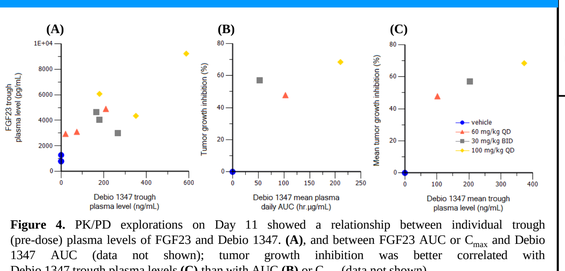
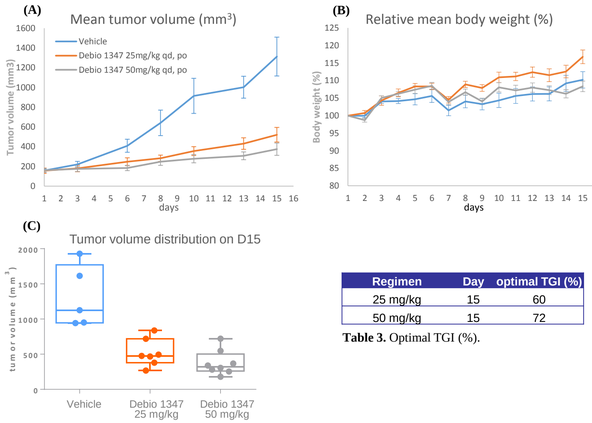


Figure 4. PK/PD explorations on Day 11 showed a relationship between individual trough (pre-dose) plasma levels of FGF23 and Debio 1347. **(A)**, and between FGF23 AUC or C_{max} and Debio 1347 AUC (data not shown); tumor growth inhibition was better correlated with Debio 1347 trough plasma levels **(C)** than with AUC **(B)** or C_{max} (data not shown).

Debio 1347 inhibits tumor growth of a FGFR amplified NSCLC PDX model (LION 137, Precos)

LION137 is a squamous cell carcinoma (SCC) PDX model derived from a male Caucasian ex-smoker; sequencing analysis by Ion Torrent Ampliseq™ Hotspot mutation analysis identified p53 homozygous mutations (R117P, R156P, R24P), PI3KCA (M1040I) and KDR (Q472H) heterozygous mutations (wild-type for FGFR1, FGFR2, KRAS, EGFR & LKB1). Expression of members of the FGFR gene family (FGFR1-3) was confirmed by Taqman copy number and expression analysis across multiple. Significant and reproducible in vivo sensitivity to clinically used FGFR inhibitors was documented at repeated passages.

A 15-day treatment with 2 doses of Debio 1347 resulted in a dose-dependent reduction in tumor growth as measured by both tumor volume (Table 3) and final tumor weight (not shown), however the difference between the 2 doses was not statistically significant (Fig. 7). No significant effect on body weight was observed.



Regimen	Day	optimal TGI (%)
25 mg/kg	15	60
50 mg/kg	15	72

Table 3. Optimal TGI (%).

Figure 7. (A) Debio 1347 showed potent antitumor efficacy in vivo in a FGFR amplified NSCLC PDX model in MF-1 nude mice. **(B)** Relative mean body weight during treatment. **(C)** Tumor volumes on the last day of treatment.

Conclusions

- **Debio 1347 administration resulted in a dose-dependent reduction in tumor growth in both animal models, displaying either a FGFR fusion or amplification. These results suggest that Debio 1347 will provide therapeutic opportunities for patients with FGFR genetic alterations.**
- **Debio 1347 was rapidly absorbed after oral administration and plasma exposure increased with dose in a more than a dose-proportional manner. The extent of changes in FGF23 plasma levels was correlated with Debio 1347 plasma exposure.**
- **Debio 1347 plasma trough levels rather than C_{max} or AUC appeared to be correlated with antitumoral activity in the RT112 xenograft model, as illustrated by the higher efficacy of the BID as compared to QD dosing regimens. This suggests sustained plasma levels above a threshold should be maintained to achieve optimal antitumoral efficacy.**

Clinical trial

Debio 1347 (CH5183284) is currently under phase I clinical investigation in selected patients harboring FGFR genetic alterations (NCT01948297).

Acknowledgements

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