Buchtele *et al.: Intrinsic Activity*, 2018; **6**(Suppl.1):A1.4
doi:10.25006/IA.6.S1-A1.4
published online: 20 September 2018

INTRINSIC ACTIVITY

24th Scientific Symposium of the Austrian Pharmacological Society

Graz, 27–28 September 2018

MEETING ABSTRACT

A1.4

Safety, tolerability, pharmacokinetics and pharmacodynamics of parenterally administered dutogliptin: a prospective dose-escalating trial

Nina BUCHTELE[1], Michael SCHWAMEIS[2], Christian SCHÖRGENHOFER[1], Ulla DERHASCHNIG[1,2], Christa FIRBAS[1], Darrell NIX[3], Roman SCHENK[3] and Bernd JILMA[1,*]

[1]Department of Clinical Pharmacology, Medical University of Vienna, Austria; [2]Department of Emergency Medicine, Medical University of Vienna, Austria; [3]Recardio Inc., San Francisco, CA, USA

Background: Animal studies suggest that inhibition of dipeptidyl peptidase 4 (DPP-4) may improve heart function and survival after myocardial infarction by increasing cardiac myocytes' regenerative capacity. Parenterally administered dutogliptin may provide continuous strong DPP-4 inhibition to translate these results into humans. This trial investigated the safety and tolerability as well as pharmacokinetics and pharmacodynamics (PK/PD) of parenterally administered dutogliptin after single and repeated doses.

Methods: In an open-label trial, volunteers received dutogliptin at increasing doses of 30–120 mg subcutaneously or 30 mg intravenously in the single-dose cohorts. Subjects in the multiple-dose cohort received 60 mg, 90 mg or 120 mg dutogliptin subcutaneously once daily on 7 consecutive days.

Results: Forty healthy males were included in the trial. No related serious adverse events occurred. Out of the 153 related adverse events, 147 (96%) were mild local injection-site reactions, which did not require any medication. Subcutaneous bioavailability was approximately 100%. Multiple dose injection did not lead to accumulation of the study drug. All subjects receiving ≥ 60 mg dutogliptin yielded a maximum DPP-4 inhibition > 90%. The duration of DPP-4 inhibition over time increased in a dose-dependent manner and was highest in the 120 mg multiple-dose cohort, translating into 86% DPP-4 inhibition 24 hours after dosing.

Discussion: Parenteral dutogliptin had a good safety profile overall. Subcutaneous injection of dutogliptin resulted in approximately 100% bioavailability with peak plasma concentrations of 5,000 ng/ml after subcutaneous injection of 120 mg. Compared to 500 mg orally administered dutogliptin, this translates into a > 6-fold increase in maximal plasma levels [1]. The half-life of oral dutogliptin was 3-fold longer [1] than that after i.v. or s.c. dosing in the current trial. The apparently longer half-life after oral intake may probably be due to prolonged (but incomplete) resorption after oral intake. Subcutaneous injection of 120 mg dutogliptin reduced DPP-4 activity to below 6%, translating into > 85% DPP-4 inhibition over 24 hours. In comparison, currently available oral doses and formulations of gliptins are capable of reducing DPP-4 activity by 60–80% over 24 h [2]. However, besides its well-known function of improving glycemic control, DPP-4 activity influences several other pathways providing potential cardio- and renoprotective effects [3]. Notably, while low administration of the DPP-4 inhibitor vildagliptin could not yield benefits in cardiac function after infarction [4], 6 times higher doses, applied twice daily, indeed improved cardiac remodeling and renal function in a rat model of heart failure [5]. Yet, it is unclear, if and which degree of DPP-4 inhibition will reduce maladaptive cardiac remodeling in humans which may putatively translate into improved survival and quality of life. Clinical data to determine the required levels to facilitate beneficial cardiac remodeling post-infarction in humans are lacking. Large-scale clinical phase II/III trials involving patients after myocardial infarction are warranted to determine whether DPP-4 inhibition achieved by parenterally administered dutogliptin can prevent maladaptive remodeling.

Acknowledgements: This study was funded by Recardio GmbH.

References

1. O'Farrell AM, van Vliet A, Abou Farha K, Cherrington JM, Campbell DA, Li X, Hanway D, Li J, Guler HP: **Pharmacokinetic and pharmacodynamic assessments of the dipeptidyl peptidase-4 inhibitor PHX1149: double-blind, placebo-controlled, single- and multiple-dose studies in healthy subjects.** *Clin Ther,* 2007; 29(8): 1692–1705. doi:10.1016/j.clinthera.2007.08.005
2. Scheen AJ: **A review of gliptins in 2011.** *Expert Opin Pharmacother,* 2012; 13(1):81–99. doi:10.1517/14656566.2012.642866
3. Salles TA, dos Santos L, Barauna VG, Girardi AC: **Potential role of dipeptidyl peptidase IV in the pathophysiology of heart failure.** *Int J Mol Sci,* 2015; 16(2):4226–4249. doi:10.3390/ijms16024226
4. Yin M, Silljé HH, Meissner M, van Gilst WH, de Boer RA: **Early and late effects of the DPP-4 inhibitor vildagliptin in a rat model of post-myocardial infarction heart failure.** *Cardiovasc Diabetol,* 2011; 10:85. doi:10.1186/1475-2840-10-85
5. Arruda-Junior DF, Martins FL, Dariolli R, Jensen L, Antonio EL, dos Santos L, Tucci PJ, Girardi AC: **Dipeptidyl Peptidase IV Inhibition Exerts Renoprotective Effects in Rats with Established Heart Failure.** *Front Physiol,* 2016; 7:293. doi:10.3389/fphys.2016.00293

*Corresponding author e-mail: *bernd.jilma@meduniwien.ac.at*