Results of the trial "EP4 receptor antagonism and PGE2 in a human headache model" (2008-008713-20)

Eight healthy volunteers completed the study. 11 subjects were enrolled with 3 participants being withdrawn after the first day of dosing. One was withdrawn due to severe chills and shivering during PGE_2 infusion, another due to an unspecific T-wave inversion in the pre-cordial leads on ECG and the third due to a drop in diastolic blood pressure below 40 mmHg, which was a safety limit according to the study protocol.

Baseline values

There were no differences in baseline recordings for any variables between placebo and active days. There were no differences in baseline velocity in the middle cerebral artery (V_{MCA}) between the left and the right side on all three study days (data not shown).

Effect of BGC20-1531 on PGE_2-induced headache

The incidence of immediate and delayed headache is shown in Table 1. There was a large variation in the severity of headache between the subjects on placebo day and we found no difference in area under the curve (AUC) for headache between both pretreatment days and placebo day (BGC20-1531 200 mg: $P = 0.14$; BGC20-1531 400 mg: $P = 0.173$) (Fig. 1).

Effect of BGC20-1531 on velocity of middle cerebral artery

We found no difference in the AUC_{VMCA} between placebo and BGC20-1531 200 mg ($P = 0.849$) and 400 mg ($P = 0.529$) (Fig. 2). There was no difference in the AUC for end-tidal partial pressure of pCO_2 ($PetCO_2$) between both pretreatment days and placebo day (BGC20-1531 200 mg: $P = 0.700$; BGC20-1531 400 mg: $P = 0.712$). Explorative ANOVA analysis revealed significant changes over time in V_{MCA} after placebo ($P < 0.05$) but not after BGC20-1531 200 and 400 mg ($P > 0.05$). As expected, post hoc Dunnetts test showed a significant drop in V_{MCA} at T_{20} after PGE_2 infusion on placebo day compared to baseline ($P < 0.05$).

Table 1 Incidence of Prostaglandin E_2 (PGE_2)-induced immediate and delayed headache in eight healthy subjects

	Placebo plus PGE_2	BGC20-1531 200 mg plus PGE_2	BGC20-1531 400 mg plus PGE_2
Incidence of immediate headache	6	6	7
Incidence of delayed headache	1	1	1

McNemar test showed no difference in incidence of immediate and delayed headache between placebo and BGC20-1531 200 and 400 mg ($P > 0.05$)

Effect of BGC20-1531 on diameter of superficial temporal and radial arteries

The superficial temporal artery AUC (AUC_{STA}) on BGC20-1531 200 mg day was significantly larger than on placebo day ($P = 0.033$). We found no difference in the AUC_{STA} between placebo and BGC20-1531 400 mg day ($P = 0.451$) (Fig. 3). There was no difference in the radial artery AUC (AUC_{RA}) between each pretreatment day compared with placebo day ($P = 0.678$ and $P = 0.575$ on BGC20-1531 200 mg and BGC20-1531 400 mg pretreatment day respectively).

Peripheral hemodynamics

We found no difference in the AUC for mean arterial blood pressure (AUC_{MAP}) between placebo and BGC20-1531 200 mg day ($P = 0.267$) and placebo and BGC20-1531 400 mg day ($P = 0.450$). There was also no difference in the AUC_{HR} on placebo day compared with the AUC_{HR} on BGC20-1531 200 mg ($P = 0.799$) day and 400 mg day ($P = 0.074$).

Pharmacokinetic profile of BGC20-1531

The highest plasma concentration of BGC20-1531 in our study was detected 75 min after oral administration of BGC20-1531 200 and 400 mg at T_0 (Fig. 4). No plasma BGC20-1531 was detected in samples taken on placebo day. The AUC plasma concentration on pretreatment with BGC20-1531 400 mg was significantly larger compared to the AUC plasma concentration on BGC20-1531 200 mg ($P = 0.036$) (Fig. 4). Putative therapeutic concentrations of ≥10,000 ng.hr/ml were only reached in 5 out of 8 subjects.

Effect of BGC20-1531 on PGE_2 related AEs

We found no difference in incidence of the AEs between the trial days (Table 2). No adverse events were reported during the pre-infusion period T_{-75}–T_0 except one participant who had an asymptomatic T-way inversion on ECG during pre-infusion period. The finding was defined by cardiologist as non-specific, but a decision was taken to exclude the participant from further experiments.