Safety, tolerability and pharmacokinetic characterisation of DACRA KBP-042 in healthy male subjects

Short running title: DACRA KBP-042 in healthy males

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Abstract

There is a need for anti-diabetic agents successfully targeting insulin sensitivity and treating obesity control at the same time. The aim of this first-in-human study was 1) to evaluate safety and tolerability; 2) to evaluate pharmacokinetics and 3) to assess indications of receptor engagement of single ascending doses of KBP-042, a Dual Amylin and Calcitonin Receptor Agonists (DACRA) that has shown promising preclinical data, with superior activity in terms of typical amylin-induced responses including reduction of food intake, weight loss and gluco-regulatory capacities. A randomised double-blind placebo-controlled single ascending dose study was performed with six dose levels of KBP-042 (5, 7.5, 10, 20, 20 evening and 40µg) in healthy male adults. KBP-042 or placebo was administered as a single dose after an overnight fast, followed by a standardized lunch after four hours. KBP-042 was associated with dose-dependent complaints of nausea and vomiting, with a lack of tolerability at doses of 20µg and above. Doses of 5 to 40 µg KBP-042 were behaved according to a linear pharmacokinetic profile. Indications of target receptor engagement were observed at the level of glucose control and lowering of bone resorption, compared to placebo.

The results of this study showed that doses up to 40 µg were safe, although tolerability was not present at the highest doses. The study confirmed target receptor engagement at the studied doses.

Introduction

Obesity and insulin resistance, resulting in hyperglycemia, are the hallmarks of type 2 diabetes mellitus (T2DM).[1] Treatment agents reaching both glycaemic *and* weight control have proven mostly effective.[2–5] Despite the large availability of anti-diabetic agents, it remains a substantial challenge to maintain both glycaemic and weight control, as this has the potential to further improve co-morbidities of T2DM, such as hypertension, cardiovascular disease and kidney failures.[6,7] Studies of weight loss therapy, either through intensive dietary and lifestyle modifications or bariatric surgery have underscored the potential of substantial weight loss for improving insulin resistance and complications thereof.[8] As gradual loss of insulin sensitivity is a driving factor in disease progression in T2DM, especially agents capable of improving insulin sensitivity while facilitating weight loss would be highly beneficial.

The pancreatic hormone amylin, co-synthesized and co-released with insulin from pancreatic beta-cells[9–11], has a well-investigated role as satiation signal, as it controls nutrient fluxes by reducing energy intake, modulating nutrient utilization and increasing energy expenditure.[12,13] Studies of chronic amylin administration presented reduced body weight and food intake in diet-induced obese rodents[14,15], effects which were also observed in clinical trials. Here, the stabilized amylin analogue pramlintide showed reductions of body weight and food intake[16,17] ,as well as prandial glucose control. Accordingly, pramlintide was approved as adjunct to insulin therapy for treatment of type 1 and type 2 diabetes, albeit only in the US.[16–20]

Dual Amylin and Calcitonin Receptor Agonists (DACRAs) are a novel group of peptides, which differ from amylin in terms of potency, dual action and prolonged receptor activation.[21–23] DACRAs have shown promising preclinical data, with superior activity in terms of reduction of food intake, weight loss and importantly improved insulin sensitivity independent of weight loss, when dosed as once daily injections[22,24,25], and therefore are of interest as novel therapeutics for T2DM.

Here we report the results of the first-in-human study of single doses of KBP-042 in healthy male volunteers. The study aims were: 1) to evaluate safety and tolerability; 2) to evaluate

pharmacokinetics and 3) to explore indications of target receptor engagement of single ascending doses of KBP-042.

Research design and methods

The study protocol was reviewed and approved by the independent Medical Review and Ethic Committee BEBO (Assen, the Netherlands) prior to initiation of the study in March, 2015. The study was conducted according to the Dutch Act on Medical Research Involving Human Subjects (WMO) and in compliance with Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. The trial was registered in the European Union Clinical Trials Register (EudraCT 2014-005464-15).

Study design and subjects

A randomised double-blind placebo-controlled single ascending dose study was performed with six dose levels of KBP-042 in healthy male adults (18-45 years) recruited at the Centre for Human Drug Research (CHDR) in Leiden, The Netherlands. Main exclusion criteria were clinically significant disorders, clinically relevant 12-lead electrocardiogram (ECG) abnormalities and use of interfering concomitant medication. Main inclusion criteria were fasting plasma glucose (FPG), HBA1c and body mass index (BMI) within normal limits.

Investigational drug

The study was originally planned to evaluate the safety, tolerability, and pharmacokinetic properties of KBP-042 at single ascending doses of up to 320µg in six cohorts. This dosing scheme was based on the Food and Drug Administration (FDA)'s guidance for industry "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (2005).[26] Preclinical toxicology, pharmacology and toxicokinetic data from the pivotal studies were used for these calculations, following the FDA guidance. Due to events of significant vomiting at 40 µg of KBP-042 (described in the Results section), adjustments were made to the dosing scheme. Figure 1 shows the anticipated six cohorts, as well as the actual six dosing cohorts for KBP-042 at doses of 5 µg, 7.5 µg, 10 µg, 20 µg, 20 µg at night, and 40 µg.

Randomization

Subjects were randomised to either placebo or active drug. In the first dose group, due to a sentinel approach 2 subjects were randomised on placebo and 5 on active and in the other five dose groups, the subjects were randomly assigned in a 5:1 active-to-placebo ratio. The randomization code was generated by a statistician. Sealed individual randomization codes, per subject and per treatment, were placed in a sealed envelope labelled 'emergency decoding envelopes' and were kept in a safe cabinet at the study centre (CHDR).

Procedures

Subjects were admitted to the study centre (CHDR) in the afternoon (day -1). After eligibility check, KBP-042 or placebo was administered as a single subcutaneous dose in the morning of day 1 after an overnight fast of at least 10 hours. Dietary restrictions included to abstain from alcohol, caffeine and grapefruit-containing products for 48 hours prior to drug administration until discharge from the unit. Four hours post-dose a standardized lunch was provided (nutritional contents: 625 kCal, 71.6 g Carbohydrates, 27.3 g Proteins, 22.7 g Fat). Subjects remained at the study centre until approximately 24 hours post-dose (day 2) and returned for a visit on day 3 and a follow-up visit on day 8. All subjects gave written informed consent for participation in the study.

Safety and tolerability assessments

Throughout the study, safety was assessed using monitoring of vital signs, inspection of the injection site, continuous 3-lead cardiac monitoring and 12-lead ECG, and safety chemistry and haematology blood sampling. During day 1, until 24 hours post-dose, blood sampling was performed for electrolytes (sodium, potassium, calcium, inorganic phosphate and bicarbonate), Adrenocorticotropic Hormone (ACTH), aldosterone, cortisol, renin and creatinine monitoring. Urine was collected to monitor sodium, potassium, calcium, inorganic phosphate and creatinine for 24 hours after drug administration. Unsolicited adverse events (AEs) were collected by open-ended questioning and/or were self-reported by subjects.

Pharmacokinetic assessment

Venous blood samples for pharmacokinetic (PK) analysis were taken in non-additive tubes at baseline and at 1, 5, 10, 15, 20, 25, 30, 45, 60 minutes, and at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose. Samples were centrifuged at 2000*g* for 10 minutes within 60 minutes at 4°C. Serum concentrations for KBP-042 were measured at Medpace Bioanalytical Laboratories, Cincinnati, USA using a LC-MS/MS based bioanalytical method (BLOQ = 0.025 ng/mL). Non-compartmental data analysis was performed to derive maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the curve from zero to time infinity ($AUC_{0\text{-}inf}$), area under the curve to the last measured sampling time ($AUC_{0\text{-}last}$), percentage of the $AUC_{0\text{-}inf}$ obtained by extrapolation (PercAUCextrap), extrapolation of the terminal disposition rate constant (λz) and respective half-life ($t_{½}$). Apparent distribution of volume (Vz/F) and apparent clearance (CL/F) were also determined.

Assessment for biological activity

Because of the expected dual action of KBP-042, targeted at the amylin and calcitonin receptor, endpoints related to glucose and calcium homeostasis were collected by blood sampling. Effects on the glucose homeostasis were assessed by measuring (fasting) glucose, insulin, glucagon and C-peptide at baseline and at 0.5, 1, 1.5, 2, 3 (glucose only), 4, 4.5, 5, 5.5, 6 and 7 hours post-dose. Blood samples for glucose, insulin and C-peptide were taken in non-additive tubes and centrifuged within 60 minutes at 2000*g* for 10 minutes at 4°C and were measured at Atal Medial, The Netherlands (glucose by Architect C16000, Abbott and insulin and C-peptide by Immulite 2000 Xpi, Siemens). Glucagon was measured at the central chemistry and hematology laboratory of the Leiden University Medical Center (Radio immune assay, Millipore GL-32K); blood samples were collected in DTA tubes and were centrifuged immediately at 2000*g* for 10 minutes at 4°C.

In order to quantify the effects on calcium homeostasis blood samples were taken for serum C-telopeptide of cross-linked collagen type I (CTX-I), osteocalcin and calcium at baseline and at

15, 30 minutes and 1, 2, 3, 4, 8 and 24 hours after drug administration. In addition, blood samples for parathyroid hormone (PTH) were taken at baseline and at 4, 8, 12 and 24 hours after drug administration. CTX-I and osteocalcin were measured by a high-sensitivity (5th generation) assay on a Roche Cobas e411 platform (Roche Diagnostics, Basel, Switzerland) at Nordic Bioscience, Herlev, Denmark. Calcium and PTH were measured by Architect C16000 and Architect i2000, Abbott, respectively at Atal Medial, The Netherlands. Data of the cohort dosed with 20 µg in the evening was not included in the biological activity analysis, as the timing of the sampling was different.

Statistical analysis

The sample size of 37 subjects (30 allocated to KBP-042 and 7 to placebo) was considered adequate for first-in-human studies. No formal power calculations were performed to assess sample size, as the primary aim of this study was to evaluate the safety and tolerability and pharmacokinetics of KBP-042. Interim safety evaluations were performed before dose escalation, based on reviews of available blinded safety and PK and/or data on pharmacological activity. Plasma drug concentration versus time curves were plotted per treatment cohort, whereon PK parameters were determined. The PK analysis was performed from all subjects who received KBP-042 and administered at least one measurable drug concentration in the samples collected. Pharmacokinetic analysis was performed using R (version 2.12.0).

To detect treatment effects on the parameters for pharmacological activity, each parameter was analysed with a mixed model analysis of covariance (ANCOVA) with treatment, time and treatment by time as fixed factors and subject as random factor and the (average) baseline measurement as covariate. The general treatment effect and specific contrasts are reported with the estimated difference and the 95% confidence interval, the Least Square Mean (LSM) estimates and the p-value. Graphs of the LSM estimates over time by treatment are presented with 95% confidence intervals as error bars, as well as change from baseline LSM estimates. Statistical summaries, descriptive statistics and frequency tables were generated using SAS software (version 9.1.3).

Results

Study design and subjects

Sixty-three (63) subjects signed the informed consent form and underwent a medical screening. Twelve (12) subjects were excluded based on the in- and exclusion criteria. Fourteen (14) eligible subjects were not enrolled, mainly because the dosing group for which they assigned to be available was already complete. A total number of 37 subjects were randomized in the study, all completing the total follow-up period. In total, 37 healthy males received a single dose of KBP-042 (n=30, 5 subjects equally divided over 6 cohorts) or placebo (n=7). See Table 1 for baseline characteristics and Figure 2 for a CONSORT diagram with the participant flow.

Safety and tolerability

On examination of the vital signs and ECG parameters there were no significant changes. However, a prolongation of the QTc intervals was observed in the high dose groups, although no clear dose-response relationship was observed (data not shown). No clinically significant changes were found in haematology urinalysis and serum chemistry, including liver enzymes.

Overall, 105 treatment emergent adverse events (TEAEs) were reported by 25 (67.6%) participants. Most TEAEs (73) were mild in nature, 30 TEAEs were of moderate severity and 2 were considered severe. A dose-proportional tolerability profile was observed, showing increasing complaints of acute nausea (with or without vomiting) in the 10, 20 and 40 µg cohorts, as shown in Table 2. To explore whether the time of daily dosing would influence the incidence and intensity of nausea and vomiting, it was decided to include an additional cohort in which 20 µg KBP-042 or placebo was delivered during the evening instead of the morning. Dose administration in the evening did not appear to reduce nauseous symptoms, and the two severe AEs (nausea and vomiting) were both observed in this group. Therefore, dose administrations in following cohorts continued with morning dosing at lower doses (5 and 7.5 µg KBP-042 or placebo). All TEAEs were reported as being recovered at the end of the trial.

Pharmacokinetic endpoints

KBP-042 plasma levels returned below the limit of quantification (BLOQ, 0.025 ng/mL) already at approximately 1 hour post-dose in the 5 and 7.5 µg dose group. Observed levels were dose-proportional within the range of the detection method (figure 3). Measurable KBP-042 plasma concentrations were observed up to 4 hours post-dose in the highest dose group with a maximum mean concentration (C_{max}) of 0.24 ng/mL reached at approximately 1 hour post-dose (T_{max}) (see Table 3). The half-life ($T_{1/2}$) of KBP-042 ranged between 0.64 (20 µg, evening dose group) and 2.66 (7.5 µg dose group) hours in the different dose groups, albeit the value from the 5 and 7.5 mg groups should be interpreted with caution as many of the values were outside the detection range of the assay.

Indication of pharmacodynamic activity

Glucose homeostasis

Following the administration of KBP-042 (30-240 minutes), yet before the meal, we observed small and dose-responsive increases of fasting glucose concentrations of 2-15% in all treatment groups, compared to placebo (Figure 4). After the standardized meal, glucose levels continued to increase, compared to placebo, particularly in the 10 µg group. Figure 4 also shows that after the standardized meal, insulin and C-peptide concentrations increased in all treatment groups, except in the KBP-042 40 µg group. In the 40 µg group, postprandial glucose elevations were accompanied by decreased insulin and C-peptide levels, compared to placebo, but without a general, clear dose-response relationship (Figure 4). There were trends towards lowering insulin levels in some of the dose groups; however, these data are confounded by the nausea/vomiting which interfered with the meal intake. No large changes in glucagon levels were observed.

Calcium homeostasis

The calcium time course, albeit highly variable between treatment groups and within normal range, suggested a minor decline in calcium levels for all KBP-042 dose groups, changes which were most prominent in the two highest dose-groups (Figure 5). After KBP-042 administration PTH increased dose-dependently, peaking at 4 hours post-dose with persistent increases in the

two highest dose groups (20 and 40µg KBP-042) compared to placebo. PTH levels returned to baseline between 8 and 24 hours (see Figure 5).

Serum CTX-I concentrations were largly reduced by KBP-042 with a maximum mean change from baseline values of approximately 80% reached 3 to 4 hours post-dose, with no clear dose-response relationship. A trend towards faster normalisation of CTX-I concentrations at the low doses (<10 µg) was seen after the initial four hours. Osteocalcin showed a dose-dependent decrease over time with a maximum decrease compared to baseline of 38% in the highest dose group, compared to a decrease of approximately 17% in both the placebo and 5 µg KBP-042 dose group, and the effect particularly in the high dose group appeared to be maintained over 24 hours.

Discussion

Results of this first-in-human trial show that KBP-042 was well tolerated at doses below 20µg, while transient nausea and vomiting were observed in higher doses. KBP-042 had a serum half-life of <1hour and a linear pharmacokinetic profile. Indications of target receptor engagement were observed based on the observed nausea and indications of post-prandial insulin regulation (amylin receptor) and lowering of bone resorption (calcitonin receptor), compared to placebo.

Amylin is a naturally occurring satiety hormone, and accordingly pharmacological studies of the stabilized amylin analogue pramlintide have shown beneficial effects on weight and post-prandial glucose regulation.[27] However, pramlintide was developed as adjunctive therapy for use with mealtime insulin. Studies exploring its use to promote weight loss in obese subjects demonstrated that multiple daily doses were required due to its short half-life. This ultimately resulted in cessation of the development of pramlintide as a therapy for weight loss.[17] KBP-042 is a DACRA with superior efficacy on the amylin receptor and rat preclinical data indicating weight loss, insulin sensitivity and glucose control beyond that of amylin when dosed as a once daily injection.[25,28,29]

With respect to safety of KBP-042, there was a higher number of TEAEs in the KBP-042 treated subjects, with nausea and vomiting occurring in a dose-dependent manner. Importantly, only

two AEs were classified as severe, and all were fully resolved within 24 hours after dosing. These events were expected as a function of the amylin receptor agonism[27], and as seen from a comparison of the planned cohorts to the actualized cohorts, KBP-042 is a potent amylin receptor agonist. Conduct of a cohort receiving 20 µg or placebo delivered as an evening dosing did not indicate any differences in tolerability based on the time of dosing. As has been reported for both amylin and salmon calcitonin, as well as for other peptides with appetite and gastric emptying, such as GLP-1 analogues, nausea and vomiting are anticipated AEs.[2730] However, on the other hand, it is also well known that tolerability towards these phenomena is obtained through the determination of a dose-escalation regimen for chronic dosing.[30]
On examination of the vital signs which included heart rate, blood pressure and electrocardiographic parameters there were no findings of clinical concern. Further calculations of the QTc intervals according to the Bazett and Frederica formula showed some variability in QTcB/F which was considered to be non-clinically significant. In addition, QTc intervals are known to be affected by vagal responses, such as dizziness, which is commonly observed with nausea and vomiting, as was observed in this study. Furthermore, both salmon calcitonin and pramlintide report vagal responses[31], such as dizziness as AEs, and these are considered related to nausea and vomiting. Finally, safety pharmacology studies on hERg channel activation and using telemetry in dogs (KeyBioscience data on file), were negative at doses exceeding the clinically relevant doses by a 100-fold.

Pharmacokinetic analyses demonstrated linear exposure as a function of the increased dose, a T_{max} of approximately 0.4-0.9 hours, and a $T_{½}$ of 0.6-0.9 hours, findings which are consistent with the preclinical data.[32] The two low doses, 5 and 7.5 µg did not produce consistent data in the PK analyses, due to the detection limit of the PK assay.
From a pharmacodynamic point-of-view, we observed potent reductions in bone resorption as indicated by CTX-I, as well as concordant changes in PTH and serum calcium levels. These findings are consistent with data on the well-known DACRA salmon calcitonin[33], and which clearly underscores the calcitonin receptor activation.[34] Importantly, the transient lowering of serum calcium was within the normal range and no hypocalcemia was observed. Similarly, the

increase in PTH mirrored the lowering of serum calcium and reflects the classical feedback mechanism. However, hypocalcemia has been reported with salmon calcitonin treatment, albeit in an elderly postmenopausal population with a recommendation for calcium and vitamin D supplements.[31] In the phase 2 study of KBP-042 on type 2 diabetic subjects, no incidences of hypocalcemia were reported among the AEs[35], and thus there does not appear to be a major risk for chronic hypocalcemia.

Interestingly, glucose levels appeared elevated following dosing, but before the standardized meal. These data are consistent with data from Starke *et al*., showing that acute dosing with salmon calcitonin leads to elevated plasma glucose in healthy adults.[36] However, this was not observed during chronic dosing and not in insulin-resistant subjects indicating that it is an acute phenomenon in healthy subjects.[37] Importantly, salmon calcitonin has been dosed in thousands of post-menopausal women, and hyperglycemia is not reported.[31]

In contrast, following the standardized meal blood glucose levels increased as expected, although in the 40 µg group virtually no increase was observed. This is most likely a result of no meal ingestion due to significant nausea. Interestingly, after the standardized meal there were indications of lowering of insulin and C-peptide in the doses above 10 µg. These findings are consistent with preclinical data showing reductions of insulin secretion during oral glucose tolerance tests[24,25], and indicating activation of the amylin receptor.[29] Furthermore, clinical data on the amylin receptor agonist Pramlintide also show post-prandial insulin regulation.[38]

Overall, data of this study indicate that the DACRA KBP-042 elicits activation of the respective receptor targets at the tested doses in humans. A main limitation to keep in mind is that the interpretation of the glucose and insulin levels following the meal is confounded by the lack of monitoring of food intake after the standardized meal, in combination with nausea and vomiting of subjects during the study.

Conclusion and future perspective

This study set out to determine safety and tolerability, pharmacokinetics and biological activity of the DACRA KBP-042 in healthy male subjects and indicated target receptor engagement at the studied doses.

It is noteworthy that clinical data from a phase 2 study on the efficacy and safety of KBP-042 in patients with type 2 diabetes failed to show significant improvements in HbA1c.[35] On the other hand, a phase 2 trial of a long acting amylin analogue both alone and in combination with a GLP-1R agonist in people with obesity or overweight showed promising effects on weight loss.[39] As such, the mechanism of action, especially weight independent insulin sensitivity, is still of interest, albeit a different molecule than KBP-042 is needed.

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Article information

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Duality of Interest

This study was funded by KeyBioscience. KH and RKU report being employees of KeyBioscience, represented by Nordic Bioscience. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

K.H., K.B., W.M.I.B, M.A.K., M.R.D., C.C., M.K., R.K, K.B., A.B., and I.M.C.K. contributed to the study design and writing of the manuscript. W.M.I.B, M.D. and I.M.C.K. contributed to the study investigation and data collection.

Data Availability

The data sets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Tables and figures

Figure 1: Planned and actual study doses and cohorts

Figure 2: CONSORT diagram

Figure 3: Pharmacokinetic parameters of KBP-042 per treatment cohort

A) Serum concentration of KBP-042 as a function of dose and time. The dashed line indicates the lower detection limit of the assay (0.025ng/mL). B) Individual C_{max} values as a function of dose, with the orange dots indicating the mean. C) Individual area under the curve from zero to time infinity ($AUC_{0\text{-}inf}$) with the orange dots indicating the mean of KBP-042 per treatment dose.

Figure 4: Glucose homeostasis related parameters over time.

A) %-change from baseline in blood glucose levels. B) %-change from baseline in insulin levels, C) %-change from baseline in C-Peptide levels, D) Change from baseline in glucagon levels. At t=0, the study drug was administered; at t=240 minutes the standardized meal was served (indicated by the arrow). All data are plotted as LSM changes for the individual dose arms (+/-SEM).

Figure 5: Bone turnover markers and calcium homeostasis over time. A) Change from baseline in serum calcium levels, B) Change from baseline in PTH levels, C) Change from baseline in CTX-I levels, D) %-change from baseline in N-MID osteocalcin levels. At t=0, the study drug was administered; at t=240 minutes the standardized meal was served. All data are plotted as LSM changes for the individual dose arms (+/-SEM).

Table 1. Demographic and other baseline characteristics

	All	Placebo	KBP-042 5 µg	KBP-042 7.5 µg	KBP-042 10 µg	KBP-042 20 µg	KBP-042 40 µg	KBP-042 20 µg(E)†
N	37	7	5	5	5	5	5	5
Age in years (min-max)	24 (18, 45)	22 (18, 25)	22 (20, 23)	24 (20, 32)	31 (22, 45)	26 (18, 43)	24 (19, 35)	24 (18, 42)
BMI in kg/m² (Mean (SD))	22.4 (2.3)	22.3 (2.6)	22.9 (3.2)	22.7 (2.3)	23.0 (1.9)	22.5 (2.9)	22.4 (1.8)	20.9 (1.4)
Race (N (%))								
Black or African American	2 (5)	1 (14)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mixed	4 (11)	1 (14)	0 (0)	0 (0)	0 (0)	1 (20)	1 (20)	1 (20)
White	30 (81)	4 (57)	4 (80)	5 (100)	5 (100)	4 (80)	4 (80)	4 (80)
Other	1 (3)	1 (14	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 2: Treatment emergent adverse events per cohort

	Placebo	KBP-042 5 µg	KBP-042 7.5 µg	KBP-042 10 µg	KBP-042 20 µg	KBP-042 40 µg	KBP-042 20 µg (E)†
N (%)	7	5	5	5	5	5	5
Any events‡	5 (71)	2 (40)	3 (60)	4 (80)	3 (60)	5 (100)	3 (60)
GENERAL							
Chest discomfort	-	-	1 (20)	-	-	-	-
Fatigue	-	-	-	-	-	2 (40)	-
Feeling hot	-	-	-	1 (20)	-	1 (20)	-
Hot flush	-	-	-	-	-	1 (20)	-
Hyperhidrosis	-	-	-	3 (60)	-	-	-
Injection site haematoma	-	-	-	1 (20)	-	-	-
Abnormal taste	-	-	-	-	-	-	1 (20)
GASTROINTESTINAL							
Nausea	-	1 (20)	1 (20)	3 (60)	3 (60)	5 (100)	3 (60)
Vomiting	-	-	2 (40)	-	1 (20)	4 (80)	3 (60)
Abdominal pain (upper)	-	-	1 (20)	-	-	1 (20)	1 (20)
Abdominal pain (lower)	-	-	-	-	-	1 (20)	-
CARDIOVASCULAR							
Orthostatic hypotension	1 (14)	-	-	-	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL							
Epistaxis	-	-	-	-	-	1 (20)	1 (20)
Pharyngeal hypoaesthesia	-	-	-	-	-	1 (20)	-
IMMUNOLOGICAL							
Seasonal allergy	1 (14)	-	-	-	-	-	-
Nasopharyngitis	-	1 (20)	-	1 (20)	-	-	-
NERVOUS SYSTEM							
Dizziness	1 (14)	1 (20)	1 (20)	4 (80)	3 (60)	-	-

Headache	3 (43)	-	-	1 (20)	3 (60)	1 (20)	-
Paraesthesia	-	-	-	-	-	1 (20)	-
Presyncope	-	-	1 (20)	-	-	-	-
Syncope	-	-	-	-	1 (20)	-	-
METABOLISM AND NUTRITIONAL							
Decreased appetite	-	1 (20)	-	-	-	-	-
MUSCULOSKELETAL							
Neck pain	-	-	-	-	-	-	1 (20)
EYE DISORDERS							
Conjunctivitis	-	-	1 (20)	-	-	-	-
Vision blurred	-	-	-	1 (20)	-	-	-
PSYCHIATRIC DISORDERS							
Euphoric mood	-	-	-	-	-	-	1 (20)
Somnolence	-	-	-	-	1 (20)	-	-
EAR DISORDERS							
Tinnitus	-	-	-	-	-	1 (20)	-
DERMATOLOGIC DISORDERS							
Dermatitis contact	1 (14)	1 (20)	-	-	-	-	-
Rash	2 (29)	-	-	-	-	-	-

Table 3. Pharmacokinetic parameters of KBP-042 per cohort

	KBP-042 5 µg	**KBP-042 7.5 µg**	**KBP-042 10 µg**	**KBP-042 20 µg**	**KBP-042 40 µg**	**KBP-042 20 µg (E)†**
$AUC_{0\text{-}inf}$ (ng*h/ mL)	0.0844 (no SD)	0.161 (0.0592)	0.129 (0.0165)	0.196 (0.0318)	0.499 (0.125)	0.219 (0.0565)
$AUC_{0\text{-}last}$ (ng*h/ mL)	0.0106 (0.0132)	0.0226 (0.0183)	0.0826 (0.0217)	0.158 (0.0352)	0.439 (0.126)	0.182 (0.0554)
C_{max} (ng/mL)	0.0308 (0.00754)	0.0362 (0.00905)	0.0793 (0.0117)	0.137 (0.0297)	0.238 (0.0649)	0.164 (0.0482)
T_{max} (h)	0.438 (0.0417)	0.383 (0.0950)	0.350 (0.160)	0.450 (0.192)	0.976 (0.263)	0.383 (0.139)
$T_{1/2}$ (h)	1.24 (no SD)	2.66 (0.854)	0.937 (0.0721)	0.645 (0.155)	0.976 (0.263)	0.637 (0.128)

Means (SD) are reported; † KBP-042 20 µg (E) is dosed in the evening.