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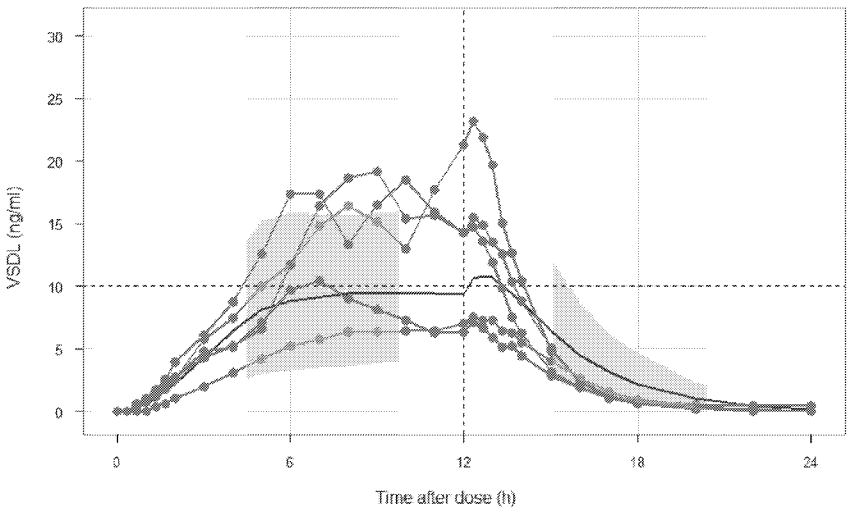

Figure 7

(57) Abstract: Disclosed herein is use of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in the manufacture of a medicament for treating a disease in a subject. The medicament is administered subcutaneously in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage. The initial dosage stage comprises infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof. The maintenance dosage stage(s) comprise(s) adjusting the dosage fate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

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DOSAGE REGIMEN FOR THERAPEUTIC METHOD

PRIORITY DOCUMENT

[0001] The present application claims priority from United States of America Provisional Patent Application No. 61/789557 titled "DOSAGE REGIMEN FOR THERAPEUTIC METHOD" and filed on 15 March 2013, the contents of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD

[0002] The present invention relates to methods and apparatus for treating subjects with peptides derived from atrial natriuretic peptide (ANP) prohormone or mimetics thereof.

BACKGROUND

[0003] Atrial natriuretic peptide (ANP) is a protein secreted by heart muscle cells which regulates blood pressure and maintains plasma volume in healthy individuals by mediating natriuretic, diuretic and haemodynamic effects. Vessel dilator (VSDL) is a naturally occurring 37 amino acid cardiac peptide consisting of amino acids 31-67 of the 126 amino acid ANP. The main biological activity of VSDL is to regulate blood pressure and maintain plasma volume in healthy individuals by mediating natriuretic, diuretic and haemodynamic effects (Vesely, 2003).

[0004] Investigations into the use of VSDL for the treatment of cardiac diseases such as congestive heart failure (CHF) have been conducted via both preclinical and human clinical studies. It has been shown that VSDL can significantly improve haemodynamic and renal parameters, such as cardiac index/output, pulmonary capillary wedge pressure, systemic and pulmonary vascular resistance, natriuresis, diuresis, and creatinine clearance without any symptomatic side effects (Vesely, 1994 and 1998). VSDL is considered to be a safe and potential effective treatment by mediating beneficial haemodynamic effects including, but not limited to, beneficial natriuretic, diuretic and renal effects, through mechanisms of regulating plasma volume and blood pressure (BP) within clinically acceptable ranges and without seriously adverse side effects. Accordingly, VSDL can be administered to subjects with acute decompensated congestive heart failure (ADCHF). Moreover, VSDL has also been found to have anticancer effects (Skelton *et al.* 2011), and is a promising candidate in the treatment of acute renal failure (Vesely, 2003). Accordingly, it will be appreciated that VSDL is a useful candidate for the treatment of various diseases.

[0005] The present applicant has surprisingly found that when a human subject is dosed with VSDL a steady state blood plasma concentration (Css) of the active agent is not necessarily achieved in accordance with classical pharmacokinetic dosage calculations.

SUMMARY

[0006] The present invention arises from clinical studies during which VSDL was infused subcutaneously into subjects at a dosage rate that was predicted, based on previous clinical data and standard pharmacokinetic calculations, to provide a steady state blood plasma concentration of VSDL within 6 hours. However, what was clinically observed was that the blood plasma concentration did not reach the calculated steady state concentration but rather, continued to increase beyond the steady state concentration that was calculated would be achieved based upon the dosage rate administered. As a result of these clinical studies, the present applicant has developed a novel dosage regime for administration of VSDL and related atrial natriuretic peptide (ANP) prohormone peptides. The dosage regime takes into account the non-classical pharmacokinetic behaviour of VSDL.

[0007] Accordingly, in a first aspect the present invention provides the use of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in the manufacture of a medicament for treating a disease in a subject, wherein said medicament is administered subcutaneously in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

[0008] In a second aspect, the present invention provides an apparatus for administering an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to a subject in need of treatment of a disease, the apparatus comprising: (i) an infusion device for delivery of the active agent to the subject subcutaneously; and (ii) a control unit operated by a series of commands, wherein the series of commands contains a set of instructions that causes the device to administer the active agent to the subject in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active ingredient at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to

substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

[0009] In embodiments of the second aspect of the invention the apparatus further comprises (iii) a monitoring unit capable of adjusting the control unit to achieve the target steady state blood plasma concentration.

[0010] In a third aspect, the present invention provides a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof for use in the treatment of a disease in a subject, wherein said peptide or mimetic thereof is administered subcutaneously in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the peptide or mimetic thereof at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the peptide or mimetic thereof or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the peptide or mimetic thereof or metabolite thereof.

[0011] In embodiments of the first, second and third aspects the disease is selected from the group consisting of cardio-renal syndromes and cancer. Cardio-renal syndromes to be treated include, but are not limited to, chronic congestive heart failure (CHF), acute decompensated congestive heart failure (ADCHF), pulmonary areterial hypertension (PAH), acute renal failure, chronic renal failure, and acute kidney injury (AKI).

[0012] In a fourth aspect, the present invention provides a method of treating a cardio-renal syndrome or cancer in a subject, said method comprising administering subcutaneously to the subject an effective amount of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

[0013] In embodiments of the first to fourth aspects, the multimodal dosage regime is a bimodal regime comprising the initial dosage stage and a maintenance dosage stage.

[0014] In a fifth aspect, the present invention provides a diagnostic test comprising obtaining a test sample of blood from a subject, determining the blood plasma concentration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof, and providing information on the blood plasma concentration.

[0015] In embodiments of the fifth aspect, the method further comprises using the results of the blood plasma concentration to adjust the dosage rate during administration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to the subject.

[0016] In a sixth aspect, the present invention provides a method of monitoring the blood plasma levels of a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in order to optimise dosing or scheduling, the method comprising:

(i) contacting a test blood sample obtained from a subject with a first capture binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic or fragment thereof to form a first capture binding agent-peptide complex;

(ii) contacting the first capture binding agent-peptide complex with a second detection binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic or fragment thereof and is conjugated to a detectable label to form a detection-capture binding agent-peptide complex;

(iii) determining the amount of the detection-capture binding agent-peptide complex formed by detecting the detectable label, wherein the amount of the detection-capture binding agent-peptide complex formed is the amount of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof contained in the test sample; and

(iv) comparing the amount of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in the test sample determined in step (iii) with a desired blood plasma level.

[0017] In a seventh aspect, the present invention provides a method of optimising dosing of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to a subject, the method comprising:

(i) administering subcutaneously to the subject an effective amount of the active agent in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma

concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof;

(ii) determining the concentration of at least one renal function biomarker in a body fluid of the subject at two or more time points;

(iii) comparing the concentrations of the at least one renal function biomarker at the two or more time points to ascertain whether renal function of the subject has improved over time;

(iv) using the data obtained from step (iii) to determine whether the dosage rate of the active agent should be adjusted; and

(v) if necessary, adjusting the dosage rate of the active agent during the initial dosage stage and/or the maintenance dosage stage(s) based on the determination made at step (iv).

[0018] In embodiments of the seventh aspect, the renal function biomarker is creatinine. In these embodiments, an increase in the concentration of creatinine in the body fluid of the subject over time indicates impairment of renal function whereas a decrease in the concentration of creatinine in the body fluid of the subject over time indicates an improvement of renal function. In embodiments, the rate of change in the concentration of creatinine in the body fluid of the subject over time can be used to adjust the dosage rate of the active agent.

BRIEF DESCRIPTION OF THE FIGURES

[0019] **Figure 1** shows a plot of time (h) after dose vs blood plasma VSDL concentration (ng/ml) for three subjects. The black line and ribbon is the mean and 90% CI predicted for 1000 patients and the symbols are the observed data.

[0020] **Figure 2** shows individual plots of time (h) after dose vs blood plasma VSDL concentration (ng/ml) observed for all subjects. The titles of each plot refer to the subject number.

[0021] **Figure 3** shows plots of time (h) after dose vs blood plasma VSDL concentration (ng/ml) observed at doses of 52.5 µg, 105 µg, 210 µg, 250 µg, 500 µg, 5400 µg, and 10800 µg. The symbols are the observed data and the lines are the population predicted data.

[0022] **Figure 4** shows plots of time (h) after dose vs blood plasma VSDL concentration (ng/ml) observed at doses of 52.5 μg, 105 μg, 210 μg, 250 μg, 500 μg, 5400 μg, and 10800 μg. The symbols are the observed data and the lines are the population predicted data.

[0023] **Figure 5** shows plots showing the results of Visual Predictive Checks of the model used in the study. The observed data is shown with symbols (median) and black lines (90% CI) whilst the simulated data is shown with red lines (median) and ribbon (90% CI). The green symbols show the data from the present study.

[0024] **Figure 6** shows plots showing the results of Visual Predictive Checks of the model used in the study. The observed data is shown with symbols (median) and black lines (90% CI) whilst the simulated data is shown with red lines (median) and ribbon (90% CI). The green symbols show the data from the present study.

[0025] **Figure 7** shows a plot of time (h) after dose vs blood plasma VSDL concentration (ng/ml) for the three subjects from Example 1 and two subjects from Example 2. The black line and ribbon is the mean and 90% CI predicted for 1000 patients and the symbols are the observed data.

[0026] **Figure 8** shows individual plots of time (h) after dose vs blood plasma VSDL concentration (ng/ml) observed for all subjects. The titles of each plot refer to the subject number.

[0027] **Figure 9** shows individual plots of time (h) after dose vs blood plasma VSDL concentration (ng/ml) observed for all subjects. The titles of each plot refer to the subject number.

[0028] **Figure 10** shows a plot of time (h) after dose vs blood plasma VSDL concentration (ng/ml) for patients eight subjects from Example 3. The black line and ribbon is the mean and 90% CI predicted for 1000 patients and the symbols are the observed data.

[0029] **Figure 11** shows plots of time (h) after dose vs blood plasma VSDL concentration (ng/ml) for subjects from Example 2 (top graph) and subjects from Example 3 (bottom graph).

[0030] **Figure 12** shows a plot of Mean Cardiac Output in ADCHF and Stable CHF patients over time.

[0031] **Figure 13** shows a plot of blood plasma VSDL concentration (ng/ml) vs estimated glomerular filtration rate (mL/min/1.73 m^2) for subjects from Example 3.

[0032] **Figure 14** shows a plot of blood plasma VSDL concentration (ng/ml) vs estimated glomerular filtration rate (mL/min/1.73 m^2) for subjects from Example 2.

[0033] **Figure 15** shows a plot of mean MAG3 clearances (percent baseline) for subjects from Examples 2 and 3 pre- and post-treatment with VSDL.

[0034] **Figure 16** shows a plot of urine output (L) vs percent of subjects from Examples 2 and 3.

[0035] **Figure 17** shows a plot of blood plasma VSDL concentration (ng/ml) vs urine sodium (mEq/L) for subjects from Examples 2 and 3.

[0036] **Figure 18** shows a plot mean FENa(%) for the 10ng/mL blood plasma VSDL concentration subjects from Example 2 and the 20ng/mL blood plasma VSDL concentration subjects from Example 3.

DETAILED DESCRIPTION

[0037] In a first aspect, the present invention provides the use of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in the manufacture of a medicament for treating a disease in a subject, wherein said medicament is administered subcutaneously in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

[0038] The multimodal dosage regime is not for a fixed time nor based on classical pharmacokinetic dosage calculations but rather the result of sophisticated modelling of hypothetical and observed behaviour of VSDL, or other peptides from the ANP prohormone in the human body.

[0039] A "steady state concentration" in a human subject receiving treatment is a concentration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic or metabolite thereof that is at a dynamic equilibrium, fluctuating periodically within a reasonably predictable and periodic range with the fluctuation determined by the dosing schedule.

[0040] In embodiments, the target steady state blood plasma concentration is greater than 10 ng/ml. In some embodiments, the target steady state blood plasma concentration is greater than 15 ng/ml. In some embodiments, the target steady state blood plasma concentration is from about 15 ng/ml to about 25 ng/ml. In embodiments, the target steady state blood plasma concentration is 15 ng/ml, 16 ng/ml, 17 ng/ml, 18 ng/ml, 19 ng/ml, 20 ng/ml, 21 ng/ml, 22 ng/ml, 23 ng/ml, 24 ng/ml or 25 ng/ml.

[0041] In some other embodiments, the dosage regime is a "low dose" regime and the target steady state blood plasma concentration is from about 3 ng/ml to about 15 ng/ml. In some specific embodiments of the low dose regime, the target steady state blood plasma concentration is from about 5 ng/ml to about 10 ng/ml. In embodiments, the target "low dose" steady state blood plasma concentration is 3 ng/ml, 4 ng/ml, 5 ng/ml, 6 ng/ml, 7 ng/ml, 8 ng/ml, 9 ng/ml, 10 ng/ml, 11 ng/ml, 12 ng/ml, 13 ng/ml or 14 ng/ml. In specific embodiments, the target "low dose" steady state blood plasma concentration is about 5 ng/ml. In other specific embodiments, the target "low dose" steady state blood plasma concentration is about 10 ng/ml. In still other specific embodiments, the target "low dose" steady state blood plasma concentration is about 15 ng/ml.

[0042] As used herein, the term "about" when used in reference to a steady state blood plasma concentration means the steady state blood plasma concentration is within ±10% of the stated value.

[0043] The gene encoding for the synthesis of the atrial natriuretic peptide (ANP) prohormone consists of three exons and two introns. Exon 1 encodes the signal peptide and the first 16 amino acids of the ANP prohormone. These 16 amino acids form the N-terminus of a peptide hormone named long-acting natriuretic hormone (LANH). Exon 2 of the proANP gene encodes for three peptide hormones, namely vessel dilator, kaliuretic hormone, and ANP. Therefore, as used herein, the term "peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof" includes within its scope long-acting natriuretic hormone (LANH), vessel dilator (VSDL), kaliuretic hormone (KP), and ANP.

[0044] In specific embodiments, the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof is vessel dilator (VSDL). VSDL is a naturally occurring 37 amino acid (aa) peptide, which is produced *in vivo* following processing of the 126 amino acid atrial natriuretic peptide (ANP, also known as atrial natriuretic factor (ANF)) prohormone (proANP; Vesely, 2003). VSDL consists of amino acids 31-67 of the ANP prohormone. The VSDL for use herein may comprise the native amino acid sequence of human VSDL, namely

> Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Ser-Glu-Pro-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Thr-Gly-Glu-Val-Ser-Pro-Ala-Gln-Arg
> (SEQ ID NO: 1).

[0045] Other suitable native VSDL peptides include:

Pongo pygmaeus (common orang-utan)

Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Ser-Glu-Gln-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Thr-Gly-Glu-Val-Ser-Pro-Ala-Gln-Arg (SEQ ID NO: 2);

Macaca mulatta (rhesus monkey)

Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Arg-Glu-Gln-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Thr-Gly-Asp-Val-Ser-Pro-Ala-Gln-Arg (SEQ ID NO: 3);

and

Felis catus

Glu-Val-Val-Pro-Pro-Gln-Val-Leu-Ser-Glu-Gln-Asn-Glu-Glu-Ala-Gly-Ala-Ala-Leu-Ser-Pro-Leu-Pro-Glu-Val-Pro-Pro-Trp-Ala-Gly-Glu-Val-Asn-Pro-Ala-Gln-Arg (SEQ ID NO: 4).

[0046] The peptide may also be a variant of VSDL. As used herein, variants of the VSDL peptide include derivatives or mimetics of a native VSDL peptide, which include minor variations in the amino acid sequence, may be a suitable VSDL peptide for the method of the present invention providing that such derivatives, variants or mimetics of said native peptide do not result in any substantial decrease or variation in biological activity. These variations may include conservative amino acid substitutions as known to the person skilled in the art. Some specific examples of suitable amino acid substitutions within the VSDL peptide may include Pro→Gln (especially at position 41 of proANP; ie position 10 of the VSDL peptide), Thr→Ala (especially at position 59 of proANP; ie position 28 of the VSDL peptide), Glu→Asp (especially at position 61 of proANP, ie position 30 of the VSDL peptide), and Ser→Asn (especially at position 63 of proANP, ie position 32 of the VSDL peptide).

[0047] Peptides derived from ANP prohormone may be produced by any of the standard protein synthesis methods known to the person skilled in the art or by recombinant techniques involving, for example, the introduction of a polynucleotide molecule encoding the particular peptide into a suitable host cell (eg a host cell selected from bacterial cells such as *E. coli*, Streptomyces and *S. typhimurium*; fungal cells such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as Chinese hamster ovary (CHO), monkey kidney (COS) cells and human embryonic kidney 293 (HEK 293) cells; and plant cells) and culturing the cell under conditions suitable for the expression of the particular peptide.

[0048] Typically, the peptide derived from ANP prohormone or a mimetic thereof will be administered as a composition consisting of a solution or suspension of the peptide or mimetic in a pharmaceutically-acceptable carrier. However, it will be readily appreciated by the person skilled in the art, that the peptide or mimetic may be bound or associated with a carrier molecule (eg a carrier protein or fusion partner such as human serum albumin (HSA) or a polysaccharide (eg Dextran) or polyether (eg polyethylene glycol)) in order to modulate the biological activity and/or serum half-life time of the peptide or mimetic.

[0049] The pharmaceutically-acceptable carrier may be any pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the peptide derived from ANP prohormone or mimetic thereof to the subject. The carrier may include one or more pharmaceutical additives of a type appropriate for subcutaneous administration, such as excipients, preservatives, stabilisers, and the like. Suitable carriers, excipients, preservatives, stabilisers and the like can be found in "Remington's Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991).

[0050] The pH of the composition may be between about pH 3 and pH 11. For example, the composition may be pH 3, pH 4, pH 5, pH 6, pH 7, pH 8, pH 9, pH 10 or pH 11.

[0051] The peptide derived from ANP prohormone or a mimetic thereof may be administered to the subject in a combination therapy.

[0052] In an earlier study, a steady state blood plasma concentration of VSDL of 10 ng/ml was achieved; it was found that the subcutaneous dose required to be infused was consistent with the known relationship

$$Dose = \frac{Css \times Cl}{F}$$

where Css is the steady state concentration, Cl is the clearance and F is the bioavailability.

[0053] Steady state occurs when the amount of drug administered (in a given time period) is equal to the amount of drug eliminated in that same period. At steady state, the plasma concentration of the drug (*Css*) at any time during any dosing interval, as well as the peak and trough, are similar.

[0054] For the same active, doubling the dose would be expected to double the Css in the same time. However, when the dose was doubled in the clinical studies, it was found that the Css reached 20 ng/ml (ie double the earlier study), but then did not plateau but continued to increase such that it reached 30 ng/ml in some subjects.

[0055] Taking into account the non-classical pharmacokinetics of VSDL, the present applicant has developed a multimodal dosage regime comprising at least an initial dosage stage and a maintenance dosage stage. This is a bimodal dosage regime. However, it will be appreciated that the dosage regime may also comprise other dosage stages comprising administration of the active agent at a dosage rate and/or dosage period that is different to the dosage rate and/or period of the initial and maintenance dosage stages. The other dosage stages may be intermediate stages between the initial and maintenance dosage stages and/or they may follow the maintenance dosage stage.

[0056] In embodiments, the initial dosage rate is from about 20 µg/hour to about 2000 µg/hour. In embodiments having a target steady state blood plasma concentration of about 10 ng/ml, the initial dosage rate is about 900 µg/hour. In other embodiments having a target steady state blood plasma concentration of about 20 ng/ml, the initial dosage rate is about 1800 µg/hour. In embodiments having a target steady state blood plasma concentration of about 5 ng/ml, the initial dosage rate is about 450 µg/hour.

[0057] In embodiments, the initial period is from about 4 to about 6 times the half-life of the active agent. In the case of VSDL, the initial period may be from about 4 hours to about 6 hours. In specific embodiments, the initial period is about 5 hours.

[0058] In embodiments, the maintenance dosage rate is from about 450 µg/hour to about 1200 µg/hour. In embodiments having a target steady state blood plasma concentration of about 10 ng/ml, the maintenance dosage rate is about 550 µg/hour. In other embodiments having a target steady state blood plasma concentration of about 20 ng/ml, the maintenance dosage rate is about 1080 µg/hour. In embodiments having a target steady state blood plasma concentration of about 5 ng/ml, the maintenance dosage rate is about 270 µg/hour.

[0059] In our clinical studies, lead patients were dosed at 900 µg/h for 6 hours based on the standard calculation shown earlier to reach a target steady state blood plasma concentration of 10 ng/ml and plasma levels of VSDL measured. Six hours is more than five half-lives for VSDL and, as such, should result in a steady state blood plasma concentration. Having verified the target steady state blood plasma concentration from lead patients, then Cohort 1 "Part 1" received 900 µg/h for 12 hours so as to achieve target steady state blood plasma concentration. However, the target steady state blood plasma concentration was not observed and as such the dosing regime required modification. After significant postulation and modelling of the hypothetical behaviour of VSDL the multimodal dosage regime was developed. Cohort 1 "Part 2" was introduced using the bimodal dosing regime in an effort to reach a steady state blood plasma concentration of 10 ng/ml. Cohort 1 "Part 2" patients received VSDL at 900 µg/h (ie initial dosage rate) for 5 hours (ie initial period), followed by 550 µg/h for 7 hours (ie maintenance dosage rate).

[0060] The dosing model was then used to calculate the dosages required for a 20 ng/ml target steady state blood plasma concentration and Cohort 2 "Part 2" will receive a dosing regime of 1800 µg/h for 5 hours (initial dose), followed by 1080 µg/h for 7 hours (maintenance dose) which is not simply "twice" that of the 10 ng/ml "low dose" as the model predicted the maintenance dose to be 1080 ug/hr and not 1100 ug/hr.

[0061] In a second aspect, the invention provides an apparatus for administering an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to a subject in need of treatment of a disease, the apparatus comprising: (i) an infusion device for delivery of the active agent to the subject subcutaneously; and (ii) a control unit operated by a series of commands, where the series of commands contains a set of instructions that causes the device to administer the active agent to the subject in a multimodal dosage regime comprising at least an initial dosage stage and a maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

[0062] In embodiments, the infusion device comprises an infusion pump and the set of instructions provides for administering the active agent to the subject via subcutaneous infusion in a substantially continuous or continuous manner by the infusion pump.

[0063] Optionally, the infusion pump is an implantable infusion pump. An implantable infusion pump can be implanted at any suitable subcutaneous implantation site using methods and devices known in the art.

[0064] In embodiments, the set of instructions causes the infusion pump to (i) administer the active agent to the subject subcutaneously at an initial dosage rate of from about 700 µg/hour to about 2000 µg/hour for an initial period of from about 4 hours to about 6 hours, and then (ii) administer the active agent to the subject subcutaneously at a maintenance dosage rate of from about 450 µg/hour to about 1200 µg/hour.

[0065] Typically, the infusion pump will be in fluid connection with a fluid reservoir containing the active agent. The infusion pump may be provided within the reservoir or may otherwise be operably connected thereto.

[0066] The infusion pump may be a mechanical or an electromechanical pump, examples of which are described in United States patent Nos. 4,692,147; 4,360,019; 4,487,603; 4,360,019; 4,725,852;

5,820,589; 5,643,207; 6,198,966; and the like. Osmotic pumps may be particularly suitable due to their consistent controlled release and relatively small size. Suitable implantable drug infusion pumps include an Alzet® osmotic pump (Durect Corporation, Cupertino CA, United States of America), a Duros® device (Intarcia Therapeutics, Inc., Hayward CA, United States of America), and a Paradigm™ device (Medtronic Australasia Pty Ltd, Gladesville NSW, Australia).

[0067] The infusion device also comprises catheters, injection devices, and the like, as is known in the art. For example, the infusion device may comprise a standard catheter or implantable drug port (eg a Port-a-Cath®; Smiths Medical MD, Inc., St. Paul MN, United States of America).

[0068] In embodiments, the control unit is not designed to accept user input. In these embodiments, the apparatus is manufactured with the control unit pre-set to administer the multimodal dosage regime. In other embodiments, the control unit is designed to allow the user to select a desired multimodal dosage regime from two or more pre-programmed multimodal dosage regimes. In other embodiments, the control unit is designed to allow the user to (i) select a desired initial dosage rate, (ii) select a desired initial period, and/or (iii) select a desired maintenance dosage rate. The desired initial dosage rate, initial period, and/or maintenance dosage rates may each be selected from a set of values programmed into the control unit.

[0069] In embodiments, the apparatus may be designed to allow the user to select a desired steady state concentration from a fixed set of values specified by the set of instructions. In these embodiments, the set of instructions can be designed to calculate and cause the device to utilise appropriate dosage amounts, dosage rates and dosage times to achieve the desired steady state concentration. For example, the apparatus may be designed to allow the user to select a steady state concentration of 10 ng/ml and the set of instructions can then calculate and cause the device to administer the active agent at an initial dosage rate of 900 µg/hour for an initial period of 5 hours and then lower the dosage rate to a maintenance dosage rate of 550 µg/hour. Alternatively, the apparatus may be designed to allow the user to select a steady state concentration of 20 ng/ml and the set of instructions can then calculate and cause the device to administer the active agent at an initial dosage rate of 1800 µg/hour for an initial period of 5 hours and then lower the dosage rate to a maintenance dosage rate of 1080 µg/hour for 7 hours.

[0070] In the embodiments of the invention that allow user input, the apparatus comprises a user interface for user input that permits the user to set the apparatus as desired. The user interface may be an interactive, computer-controlled interface that prompts the user for input. Alternatively, the user interface may be a manual, switch-operated interface.

[0071] In embodiments, the apparatus further comprises a monitoring unit capable of adjusting the control unit to achieve the target steady state blood plasma concentration.

[0072] In a third aspect, the present invention provides a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof for use in the treatment of a disease in a subject, wherein said peptide or mimetic thereof is administered subcutaneously in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the peptide or mimetic thereof at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the peptide or mimetic thereof or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the peptide or mimetic thereof or metabolite thereof.

[0073] In a fourth aspect, the present invention provides a method of treating a cardio-renal syndrome or cancer in a human subject, said method comprising administering subcutaneously to the subject an effective amount of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active ingredient at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

[0074] The methods and uses described herein may be used in conjunction with a diagnostic test for determining the blood plasma concentration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof. The results of the test can then be used to alter the dosage rate during the course of treatment to assist in maintaining the target steady state blood plasma concentration. The diagnostic test may be a companion diagnostic which is a privately used device that has one or more disposable components for point-of-care and/or in-home use.

[0075] Thus, in a fifth aspect the present invention provides a diagnostic test comprising obtaining a test sample of blood from a subject, determining the blood plasma concentration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof, and providing information on the blood plasma concentration. Preferably, the method further comprises using the results of the blood plasma concentration to adjust the dosage rate during administration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to the subject.

[0076] The test sample is preferably a blood sample taken from a subject using methods known in the art.

[0077] The step of determining the blood plasma concentration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof can be performed by protein assay methods. Suitable protein assay methods are known in the art and comprise, for example, immunoassays involving binding of a labelled binding agent to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof, proteomic based or "protein chip" assays, fibre optic *in-situ* assays, and the like.

[0078] The labelled binding agent may be, for example, an antibody, antibody fragment, protein, aptamer or small-molecule binding agent.

[0079] Immunoassays can be conducted using any format known in the art, such as, but not limited to, a sandwich format, a competitive inhibition format (including both forward or reverse competitive inhibition assays) or in a fluorescence polarization format.

[0080] Thus, the present invention also provides a method of monitoring the blood plasma levels of a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in order to optimise dosing or scheduling, the method comprising:

(i) contacting a test blood sample obtained from a subject with a first capture binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic or fragment thereof to form a first capture binding agent-peptide complex;

(ii) contacting the first capture binding agent-peptide complex with a second detection binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic or fragment thereof and is conjugated to a detectable label to form a detection-capture binding agent-peptide complex;

(iii) determining the amount of the detection-capture binding agent-peptide complex formed by detecting the detectable label, wherein the amount of the detection-capture binding agent-peptide complex formed is the amount of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof contained in the test sample; and

(iv) comparing the amount of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in the test sample determined in step (iii) with a desired blood plasma level.

[0081] In some embodiments the method comprises: i) providing a substrate comprising the first capture binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof; ii) contacting the substrate with the test sample, iii) exposing the substrate to the second detection binding agent under conditions in which the binding agent-peptide complex is bound by the detection binding agent, and iv) detecting the binding of the detection binding agent to the binding agent-peptide complex.

[0082] The binding agent may be a suitable antibody, antibody fragment, protein, aptamer or small-molecule binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof can be used. Monoclonal antibodies are preferred.

[0083] The binding agent-peptide complexes formed in the assay can be detected using any suitable technique. Any suitable label can be used. The label must be capable of producing a detectable signal either by itself or in conjunction with one or more additional substances. Useful detectable labels, their attachment to binding agents and detection techniques therefore are known in the art. For example, the detectable label can be a radioactive label, such as ^{3}H, ^{125}I, ^{35}S, ^{14}C, ^{32}P, ^{33}P, an enzymatic label, such as horseradish peroxidase, alkaline peroxidase, glucose 6-phosphate dehydrogenase, etc., a chemiluminescent label, such as, acridinium derivatives, luminol, isoluminol, thioesters, sulfonamides, phenanthridinium esters, etc. a fluorescence label, such as, fluorescein (5-fluorescein, 6-carboxyfluorescein, 3'6-carboxyfluorescein, 5(6)-carboxyfluorescein, 6-hexachloro-fluorescein, 6-tetrachlorofluorescein, fluorescein isothiocyanate, etc.), rhodamine, phycobiliproteins, R-phycoerythrin, quantum dots (zinc sulfide-capped cadmium selenide), a thermometric label or an immuno-polymerase chain reaction label.

[0084] The detectable label can be bound to the binding agent either directly or through a coupling agent. An example of a coupling agent that can be used is EDAC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, hydrochloride) that is commercially available from Sigma-Aldrich (St. Louis, Mo.). Other coupling agents that can be used are known in the art. Methods for binding a detectable label to binding agents such as antibodies are known in the art.

[0085] After formation of the detection-capture binding agent-peptide complex, the amount of label in the complex is quantified using techniques known in the art. For example, if an enzymatic label is used, the labelled complex is reacted with a substrate for the label that gives a quantifiable reaction such as the development of colour. If the label is a fluorescent label, the label is quantified by stimulating the label with a light of one colour (which is known as the "excitation wavelength") and detecting another colour (which is known as the "emission wavelength") that is emitted by the label in response to the stimulation. If the label is a chemiluminescent label, the label is quantified detecting the light emitted either visually or by using luminometers, x-ray film, high speed photographic film, a

CCD camera, etc. For solution phase immunoassays, once the amount of the label in the complex has been quantified, the concentration of peptide in the test sample is determined by use of a standard curve that has been generated using serial dilutions of the peptide of known concentration. Other than using serial dilutions of the peptide, the standard curve can be generated gravimetrically, by mass spectroscopy and by other techniques known in the art.

[0086] Preferably, the assays are carried out in a lab-on-a-chip device and system.

[0087] The companion diagnostic test can be used with any of the methods and uses described herein. The test may be particularly useful in conjunction with the apparatus whereby the information on the blood plasma concentration that is provided by the diagnostic test is fed back to the apparatus. This could be manual or electronic feedback. A processor in the apparatus can be programmed to adjust the flow rate depending on the blood plasma concentration identified by the test. For example, if the amount of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof detected in the test sample is less than the desired level the information may be fed back to the apparatus and the processor may increase the dosage rate accordingly.

[0088] Data we have obtained from subjects adminstered the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof shows that urine output and urinary sodium excretion increases after administration of the peptide. Without intending to be bound by a specific theory, we propose that the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof increases Na^+ secretion and water elimination in subjects treated with the peptide and, resulting in a concomitant improvement in renal function and also in cardiac function. As is known in the art, renal function can be monitored by determining the concentration of at least one renal function biomarker in a body fluid, such as blood or urine. Thus, a change in the concentration over time of at least one renal function biomarker in a body fluid of subjects treated with the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof may be used as an indicator of the efficacy of the treatment. Accordingly, in a seventh aspect, the present invention provides a method of optimising dosing of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to a subject, the method comprising:

(i) administering subcutaneously to the subject an effective amount of the active agent in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period

to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof;

(ii) determining the concentration of at least one renal function biomarker in a body fluid of the subject at two or more time points;

(iii) comparing the concentrations of the at least one renal function biomarker at the two or more time points to ascertain whether renal function of the subject has improved over time;

(iv) using the data obtained from step (iii) to determine whether the dosage rate of the active agent should be adjusted; and

(v) if necessary, adjusting the dosage rate of the active agent during the initial dosage stage and/or the maintenance dosage stage(s) based on the determination made at step (iv).

[0089] Any of the renal function biomarkers known in the art can be used, including creatinine, urea, and electrolytes as an indicator of renal function. Alternatively, or in addition, markers such as inulin or sinistrin may be injected into the plasma of a subject and the glomerular filtration rate (GFR) can be measured over time and the measurement used as an indicator of renal function (Israni *et al.*, 2011).

[0090] In specific embodiments, the concentration of creatinine in a body fluid of the subject is measured over time. In these embodiments, the body fluid may be blood or urine. An increase in the concentration of creatinine in the body fluid of the subject over time indicates impairment of renal function whereas a decrease in the concentration of creatinine in the body fluid of the subject over time indicates an improvement of renal function. In embodiments, the rate of change in the concentration of creatinine in the body fluid of the subject over time can be used to adjust the dosage rate of the active agent. For example, the dosage rate of the active agent may be increased if the creatinine clearance rate has not decreased at a desired rate over a predetermined period of time.

[0091] The present invention also provides an infusion device when used in accordance with the method of the fourth aspect of the invention.

EXAMPLES

[0092] The invention is hereinafter described by reference to the following non-limiting examples and accompanying figures.

[0093] **Example 1**

[0094] *Formulation*

[0095] VSDL in the form of a white lyophilised powder (synthesised using standard protein synthesis method by Auspep Pty Ltd, Parkville, VIC, Australia), stored in an ultra low freezer (-80°C), was reconstituted in a vial with 10 ml of 0.9% saline (preservative free) and aseptically transferred into a 20 ml syringe (that connects to a patient cannula) before use.

[0096] *Study Population*

[0097] Test adult subjects, both male and female, showing either acute exacerbations of chronic CHF or ADCHF (ie in individuals who had not previously shown heart failure), were recruited for the study. All subjects used in these studies also underwent existing standard of care treatments for the condition for which they presented. These treatments were typically diuretic therapy (eg loop diuretic especially furosemide) and an antihypertensive drug (eg an Angiotensin Converting Enzyme (ACE) inhibitor).

[0098] A cohort of 10 subjects with stable CHF and undergoing standard of care treatment was treated with the formulation as follows:

i) 2 sentinel subjects were treated with a one stage 6 hour sc infusion of VSDL at 900 µg/h (Subjects 1 and 3)

ii) 5 subjects were treated with a one stage 12 hour sc infusion of VSDL at 900 µg/h (Subjects 102, 103, 104, 105 and 106); and

iii) 3 subjects were treated with a bimodal sc infusion of VSDL at 900 µg/h for 5 hours and then 550 µg/h for 7 hours (Subjects 111, 112 and 114).

[0099] *Dose regimen*

[00100] The dose regimen for this trial was designed using a pharmacokinetic model for VSDL based on prior data.

[00101] The final model was used to simulate the median and 90% prediction intervals for 1000 patients given VSDL at 900 µg/h for 5 h then 550 µg/h for 7 h. This dose regimen targeted a population value of 10 ng/ml for the period 6-12h after the start of the infusion.

[00102] The predictions of the model were compared to observed VSDL concentration data from the three subjects referred to at iii) above.

[00103] *Results*

[00104] The parameters of the final pharmacokinetic model are shown in Table 1.

[00105] **Table 1**

Parameter	Description	Pop value	Unit	se (%)	BSV	Unit	se (%)
CL	Clearance	15.8	L/h	fixed	39.66	%	32.86
V	Central volume	8.93	L	8.00	46.49	%	35.28
LGT1	Logit F value	-1.05		11.80	0.77	additive	43.47
F	Bioavailability	0.259	.	.	.	.	.
KA	Absorption rate constant	0.265	1/h	19.80	49.92	%	27.07
V2	Multiplier of V for sc bolus	1.596	.	37.8			
V3	Multiplier of V for sc infusion	3.142	.	27.1			
KARATE	Effect of infusion rate of KA	-0.135	.	20.2			
KAVOL	Effect of infusion volume on KA	0.222	.	58.9			
RUVCV	Residual Error (Proportional)	0.234	Ratio	13.36	.	.	.
RUVADD	Residual Error (Additive)	0.071	ng/ml	26.05	.	.	.

[00106] The actual and predicted VSDL plasma concentrations are shown in Figure 1 and the observed data is shown in Figure 2.

[00107] Patients 111 and 114 had concentrations in the 6-12 h window at the upper level of predictions (Figure 1; grey ribbon).

[00108] Patient 112 had concentrations in the 6-12 h window at the lower level of predictions (Figure 1; grey ribbon).

[00109] Only Patient 111 appeared to be at steady-state in the 6-12h window.

[00110] The post-infusion concentrations declined quicker than model predictions, as the new patients appeared to have a shorter period of sustained concentrations once the infusion was stopped.

[00111] The observed and individual predicted VSDL concentrations are shown in Figures 3 and 4 in which the data labeled MADE03 is from the present study.

[00112] A model where infusion rate (ml/h) and delivered volume (ml) affected KA was an acceptable empirical description of the data. This model reproduced the observed increase in VSDL concentrations at the end of a subcutaneous infusion. The net effect was generally that KA increased with time during subcutaneous infusions.

[00113] The results of Visual Predictive Checks of the final model are shown in Figures 5 and 6.

[00114] A final model where infusion rate (ml/h) and delivered volume (ml) affected KA was an acceptable empirical description of the data. The final model had acceptable predictive performance based on the Visual Predictive Checks (allowing for low number of subjects).

[00115] The final model can be used to design a dose regimen targeting a constant VSDL concentration.

[00116] **Example 2** – *Dosing subjects to achieve a target Css of 10 ng/mL*

[00117] The materials and dosage protocols used in Example 1 were used to treat two patients, 201 and 202. Each subject received sc VSDL at 900 µg/h for 5 h then 550 ug/h for 7 h.

[00118] *Method*

[00119] The dose regimen was designed using the pharmacokinetic model discussed in Example 1. The final model was used to simulate the median and 90% prediction intervals for 1000 patients given VSDL at 900 µg/h for 5 h then 550 µg/h for 7 h.

[00120] This dose regimen targeted a population value of 10 ng/ml for the period 6-12h after the start of the infusion.

[00121] The predictions of the model were compared to observed VSDL concentration data from the two patients and the data are shown in Figures 7 to 9.

[00122] **Example 3** - *Dosing subjects to achieve a target Css of 20 ng/mL*

[00123] The materials used in Example 1 were used to treat six subjects. Each subject received sc VSDL at 1800 µg/h for 5 h then 1080 µg/h for 7 h.

[00124] *Results - Css*

[00125] The observed VSDL concentration data for subjects treated according to Example 3 are shown in Figure 10. The concentrations of VSDL achieved in subjects treated according to Example 2 (top graph) and Example 3 (bottom graph) are also shown in Figure 11.

[00126] *Results - Cardiac Parameters*

[00127] Regression of cardiac output on time accommodating repeated measures demonstrated that patients treated with VSDL had a significant increase in cardiac output which equates to an increase on average of 0.000472L/min above baseline ($t=3.16$; $p\leq0.05$) (Figure 12). Additionally, there were no severe adverse events reported and all reported adverse events were self-limiting, recovering without need for intervention.

[00128] *Results - Renal Parameters*

[00129] There was a significant increase in eGFR in the Stable CHF patient group (Baseline = 37 ± 11 mL/min/1.73m^2; 10ng/kg = 42 ± 15 mL/min/1.73m^2; 20ng/kg = 45 ± 9 mL/min/1.73m^2, $p\leq0.05$) (Figure 13). However, since the patient cohort in the ADCHF included patients with relatively well preserved renal function and since the patient numbers were small the increases in eGFR were not significant but the same trend was also evident in this group (untreated=59 ± 3 mL/min/1.73m^2; treated: 60 ± 2 mL/min/1.73m^2) (Figure 14). The improvement in renal function was also demonstrated by a 17% increase in 99Tc-MAG3 clearances in the VSDL treated group (Figure 15). Similarly, there was an increase in 24-hour urine output in the Stable CHF groups (10ng/kg = 2898 ± 335mls; 20ng/kg = 3028 ± 302mls) (Figure 16). This increased urine output was accompanied by an increase of fractional extraction of sodium from $2.2 \pm 0.3\%$ at baseline to $3.3 \pm 0.8\%$ in the 10ng/ml group and from $1.6 \pm 0.3\%$ to $2.4 \pm 0.9\%$ in the 20ng/ml group at 6-12hrs post treatments (Figures 17 and 18). This concomitant increase in sodium and water excretion demonstrates that the water loss was not due to aberrant water reabsorption. These results indicate a strong renal protective role for VSDL in the setting of congestive heart failure.

[00130] *Results - Vasodilation*

[00131] There was a significant drop in systolic and diastolic blood pressures in the stable CHF group (Table 2). However, none of these resulted in symptomatic hypotension.

[00132] **Table 2** - Blood Pressures in patients treated with MP3167 in Stable Congestive Heart Failure ($p<0.05$)

	Baseline	**10ng/kg**	**20ng/kg**
Systolic Blood Pressure (mmHg)	119 ± 15	122 ± 10	115 ± 19

Diastolic Blood Pressure (mmHg)	65 ± 10	64 ± 7	65 ± 6

[00133] **Example 4** – *Monitoring plasma VSDL levels*

[00134] Monoclonal antibodies (Mabs) to VSDL can be produced using techniques known in the art such as, for example, the procedure exemplified in US Patent No. 4,196,265, incorporated herein by reference.

[00135] To produce detection substrates, the antibodie(s) of interest can be bound to a solid support such as for example glass, polycarbonate, polytetrafluoroethylene, polystyrene, silicon oxide, metal or silicon nitride. This immobilization can either be direct (e.g. by covalent linkage, such as, for example, Schiff's base formation, disulfide linkage, or amide or urea bond formation) or indirect. Methods of generating protein chips are known in the art and are described in for example U.S. Patent Application No. 20020136821, 20020192654, 20020102617 and U.S. Patent No. 6,391,625.

[00136] Specifically, a NUNC plate can be coated with a serial dilution of the selected anti-VSDL capture antibody and incubated overnight at 4°C. After blocking, the plate can be incubated with various dilutions of the test peptide followed by HRP-conjugated secondary detection antibody. The plate can be washed between each addition. The immune reaction can be stopped by the addition of H_2SO_4 after an appropriate time based on visual examination of colour, and the OD read in a microplate reader at wavelengths of 450nm and 620nm.

[00137] The resulting data can be recorded for data analysis. A standard curve can be plotted using an X-Y graph with the mean OD +SD ($OD = OD_{450\ nm} - OD_{620\ nm}$) on the Y axis and the peptide concentration (eg. ng/mL) on the X axis (logarithmic scale).

[00138] **Example 5** – *Monitoring renal function*

[00139] Blood or urine samples can be collected at set time points from subjects undergoing treatment according to Examples 2 or Example 3. The creatinine levels in the blood or urine at each time point can be determined using methods described in Israni *et al.* (2011).

[00140] The dosage rate of the VSDL may be increased if the rate of decrease in creatinine levels in the blood or urine over time is not as high as required.

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[00146] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[00147] All publications mentioned in this specification are herein incorporated by reference. Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia or elsewhere before the priority date of each claim of this application.

[00148] It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS

1. Use of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in the manufacture of a medicament for treating a disease in a subject, wherein said medicament is administered subcutaneously in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

2. The use according to claim 1, wherein the disease is selected from the group consisting of cardio-renal syndromes and cancer.

3. The use according to claim 2, wherein the cardio-renal syndrome is chronic congestive heart failure (CHF), acute decompensated congestive heart failure (ADCHF), pulmonary hypertension, acute and chronic renal failure or acute kidney injury.

4. The use according to any one of the preceding claims, wherein the multimodal dosage regime is a bimodal regime consisting of the initial dosage stage and a maintenance dosage stage.

5. The use according to any one of the preceding claims, wherein the active agent comprises vessel dilator (VSDL).

6. The use according to claim 5, wherein the VSDL comprises the amino acid sequence shown as SEQ ID NO: 1.

7. The use according to any one of the preceding claims, wherein the initial dosage rate is from about 700 µg/hour to about 2000 µg/hour.

8. The use according to any one of the preceding claims, wherein the maintenance dosage rate is from about 450 µg/hour to about 1200 µg/hour.

9. The use according to any one of the preceding claims, wherein the target steady state blood plasma concentration is from about 3 ng/ml to about 15 ng/ml.

10. The use according to any one of the preceding claims, wherein the target steady state blood plasma concentration is about 10 ng/ml.

11. The use according to claim 10, wherein the initial dosage rate is about 900 µg/hour.

12. The use according to either claim 10 or claim 11, wherein the maintenance dosage rate is about 550 µg/hour.

13. The use according to any one of claims 1 to 8, wherein the target steady state blood plasma concentration is about 20 ng/ml.

14. The use according to claim 13, wherein the initial dosage rate is about 1800 µg/hour.

15. The use according to either claim 13 or claim 14, wherein the maintenance dosage rate is about 1080 µg/hour.

16. The use according to any one of claims 1 to 9, wherein the target steady state blood plasma concentration is about 15 ng/ml.

17. The use according to any one of the preceding claims, wherein the initial period is about 4 to about 6 times the half-life of the active agent.

18. The use according to any one of the preceding claims, wherein the initial period is from about 4 hours to about 6 hours.

19. The use according to claim 17, wherein the initial period is about 5 hours.

20. The use according to any one of the preceding claims, wherein the maintenance period is from about 6 hours to about 8 hours.

21. The use according to claim 19, wherein the maintenance period is about 7 hours.

22. An apparatus for administering an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to a subject in need of treatment of a disease, the apparatus comprising: (i) an infusion device for delivery of the active agent to the subject subcutaneously; and (ii) a control unit operated by a series of commands, where the series of commands contains a set of instructions that causes the device to administer the active agent to the subject in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the

active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

23. The apparatus according to claim 22, wherein the apparatus further comprises a monitoring unit capable of adjusting the control unit to achieve the target steady state blood plasma concentration.

24. The apparatus according to any one of claims 22 to 23, wherein the active agent is contained within a reservoir provided within the device or which is otherwise operably connected thereto.

25. The apparatus according to claim 24, wherein the infusion device comprises an infusion pump in fluid connection with the reservoir.

26. The apparatus according to any one of claims 22 to 25, wherein the medicament comprises vessel dilator (VSDL).

27. The apparatus according to any one of claims 22 to 26, wherein the control unit is programmed to operate the infusion device at an initial dosage rate of from about 700 µg/hour to about 2000 µg/hour.

28. The apparatus according to any one of claims 22 to 27, wherein the control unit is programmed to operate the infusion device at a maintenance dosage rate of from about 450 µg/hour to about 1200 µg/hour.

29. The apparatus according to any one of claims 22 to 28, wherein the control unit is programmed to operate the infusion device to achieve a target steady state blood plasma concentration of from about 3 ng/ml to about 15 ng/ml.

30. The apparatus according to claim 29, wherein the target steady state blood plasma concentration is about 10 ng/ml.

31. The apparatus according to claim 30, wherein the control unit is programmed to operate the infusion device at an initial dosage rate of about 900 µg/hour.

32. The apparatus according to either claim 30 or claim 31, wherein the control unit is programmed to operate the infusion device at a maintenance dosage rate of about 550 µg/hour.

33. The apparatus according to claim 29, wherein the target steady state blood plasma concentration is about 20 ng/ml.

34. The apparatus according to claim 33, wherein the control unit is programmed to operate the infusion device at an initial dosage rate of about 1800 µg/hour.

35. The apparatus according to either claim 33 or claim 34, wherein the control unit is programmed to operate the infusion device at a maintenance dosage rate of about 1080 µg/hour.

36. The apparatus according to claim 29, wherein the target steady state blood plasma concentration is about 15 ng/ml.

37. The apparatus according to any one of claims 22 to 36, wherein control unit is programmed to operate the infusion device for an initial period of from about 4 hours to about 6 hours.

38. The apparatus according to claim 37, wherein control unit is programmed to operate the infusion device for an initial period of about 5 hours.

39. The apparatus according to any one of claims 22 to 36, wherein control unit is programmed to operate the infusion device for a maintenance period of from about 6 hours to about 8 hours.

40. The apparatus according to claim 39, wherein control unit is programmed to operate the infusion device for a maintenance period of about 7 hours.

41. A peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof for use in the treatment of a disease in a subject, wherein said peptide or mimetic thereof is administered subcutaneously in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the peptide or mimetic thereof at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the peptide or mimetic thereof or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the peptide or mimetic thereof or metabolite thereof.

42. The peptide according to claim 41, wherein the disease is selected from the group consisting of cardio-renal syndromes and cancer.

43. The peptide according to claim 42, wherein the cardio-renal syndrome is chronic congestive heart failure (CHF), acute decompensated congestive heart failure (ADCHF), pulmonary hypertension, acute and chronic renal failure or acute kidney injury.

44. The peptide according to any one of claims 41 to 43, comprising vessel dilator (VSDL).

45. The peptide according to claim 44, wherein the VSDL comprises the amino acid sequence shown as SEQ ID NO: 1.

46. The peptide according to any one of claims 41 to 45, wherein the initial dosage rate is from about 700 µg/hour to about 2000 µg/hour.

47. The peptide according to any one of claims 41 to 46, wherein the maintenance dosage rate is from about 450 µg/hour to about 1200 µg/hour.

48. The peptide according to any one of claims 41 to 47, wherein the target steady state blood plasma concentration is from about 3 ng/ml to about 15 ng/ml.

49. The peptide according to any one of claims 41 to 48, wherein the target steady state blood plasma concentration is about 10 ng/ml.

50. The peptide according to claim 49, wherein the initial dosage rate is about 900 µg/hour.

51. The peptide according to either claim 49 or claim 50, wherein the maintenance dosage rate is about 550 µg/hour.

52. The peptide according to any one of claims 41 to 47, wherein the target steady state blood plasma concentration is about 20 ng/ml.

53. The peptide according to claim 52, wherein the initial dosage rate is about 1800 µg/hour.

54. The peptide according to either claim 52 or claim 53, wherein the maintenance dosage rate is about 1080 µg/hour.

55. The peptide according to any one of claims 41 to 48, wherein the target steady state blood plasma concentration is about 15 ng/ml.

56. The peptide according to any one of claims 41 to 55, wherein the initial period is about 4 to about 6 times the half-life of the active agent.

57. The peptide according to any one of claims 41 to 56, wherein the initial period is from about 4 hours to about 6 hours.

58. The peptide according to claim 57, wherein the initial period is about 5 hours.

59. The peptide according to any one of claims 41 to 58, wherein the maintenance period is from about 6 hours to about 8 hours.

60. The peptide according to claim 59, wherein the maintenance period is about 7 hours.

61. A method of treating a cardio-renal syndrome or cancer in a subject, said method comprising administering subcutaneously to the subject an effective amount of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof.

62. The method according to claim 61, wherein the active agent comprises vessel dilator (VSDL).

63. The method according to claim 62, wherein the VSDL comprises the amino acid sequence shown as SEQ ID NO: 1.

64. The method according to any one of claims 61 to 63, wherein the initial dosage rate is from about 700 µg/hour to about 2000 µg/hour.

65. The method according to any one of claims 61 to 64, wherein the maintenance dosage rate is from about 450 µg/hour to about 1200 µg/hour.

66. The method according to any one of claims 61 to 65, wherein the target steady state blood plasma concentration is from about 3 ng/ml to about 15 ng/ml.

67. The method according to any one of claims 61 to 66, wherein the target steady state blood plasma concentration is about 10 ng/ml.

68. The method according to claim 67, wherein the initial dosage rate is about 900 µg/hour.

69. The method according to either claim 67 or claim 68, wherein the maintenance dosage rate is about 550 µg/hour.

70. The method according to any one of claims 61 to 65, wherein the target steady state blood plasma concentration is about 20 ng/ml.

71. The method according to claim 70, wherein the initial dosage rate is about 1800 μg/hour.

72. The method according to either claim 70 or claim 71, wherein the maintenance dosage rate is about 1080 μg/hour.

73. The method according to any one of claims 61 to 66, wherein the target steady state blood plasma concentration is about 15 ng/ml.

74. The method according to any one of claims 61 to 73, wherein the initial period is about 4 to about 6 times the half-life of the active agent.

75. The method according to any one of claims 61 to 74, wherein the initial period is from about 4 hours to about 6 hours.

76. The method according to claim 75, wherein the initial period is about 5 hours.

77. The method according to any one of claims 61 to 76, wherein the maintenance period is from about 6 hours to about 8 hours.

78. The method according to claim 77, wherein the maintenance period is about 7 hours.

79. A diagnostic test comprising obtaining a test sample of blood from a subject, determining the blood plasma concentration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof, and providing information on the blood plasma concentration.

80. The diagnostic test according to claim 79, further comprising using the results of the blood plasma concentration to adjust the dosage rate during administration of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to the subject.

81. A method of monitoring the blood plasma levels of a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in order to optimise dosing or scheduling, the method comprising:

(i) contacting a test blood sample obtained from a subject with a first capture binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic or fragment thereof to form a first capture binding agent-peptide complex;

(ii) contacting the first capture binding agent-peptide complex with a second detection binding agent that binds to the peptide derived from atrial natriuretic peptide (ANP) prohormone or

a mimetic or fragment thereof and is conjugated to a detectable label to form a detection-capture binding agent-peptide complex;

(iii) determining the amount of the detection-capture binding agent-peptide complex formed by detecting the detectable label, wherein the amount of the detection-capture binding agent-peptide complex formed is the amount of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof contained in the test sample; and

(iv) comparing the amount of the peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof in the test sample determined in step (iii) with a desired blood plasma level.

82. A method of optimising dosing of an active agent comprising a peptide derived from atrial natriuretic peptide (ANP) prohormone or a mimetic thereof to a subject, the method comprising:

(i) administering subcutaneously to the subject an effective amount of the active agent in a multimodal dosage regime comprising at least an initial dosage stage and at least one maintenance dosage stage, the initial dosage stage comprising infusing the active agent at an initial dosage rate for an initial period to achieve a target steady state blood plasma concentration of the active agent or metabolite thereof, and the maintenance dosage stage(s) comprising adjusting the dosage rate to a maintenance dosage rate for a maintenance period to substantially maintain said target steady state blood plasma concentration of the active agent or metabolite thereof;

(ii) determining the concentration of at least one renal function biomarker in a body fluid of the subject at two or more time points;

(iii) comparing the concentrations of the at least one renal function biomarker at the two or more time points to ascertain whether renal function of the subject has improved over time;

(iv) using the data obtained from step (iii) to determine whether the dosage rate of the active agent should be adjusted; and

(v) if necessary, adjusting the dosage rate of the active agent during the initial dosage stage and/or the maintenance dosage stage(s) based on the determination made at step (iv).

83. The method according to claim 82, wherein the renal function biomarker is creatinine.

84. The method according to claim 83, wherein body fluid is blood or urine.

85. The method according to claim 84, wherein the rate of change in the concentration of creatinine in the body fluid of the subject over time is used to adjust the dosage rate of the active agent.

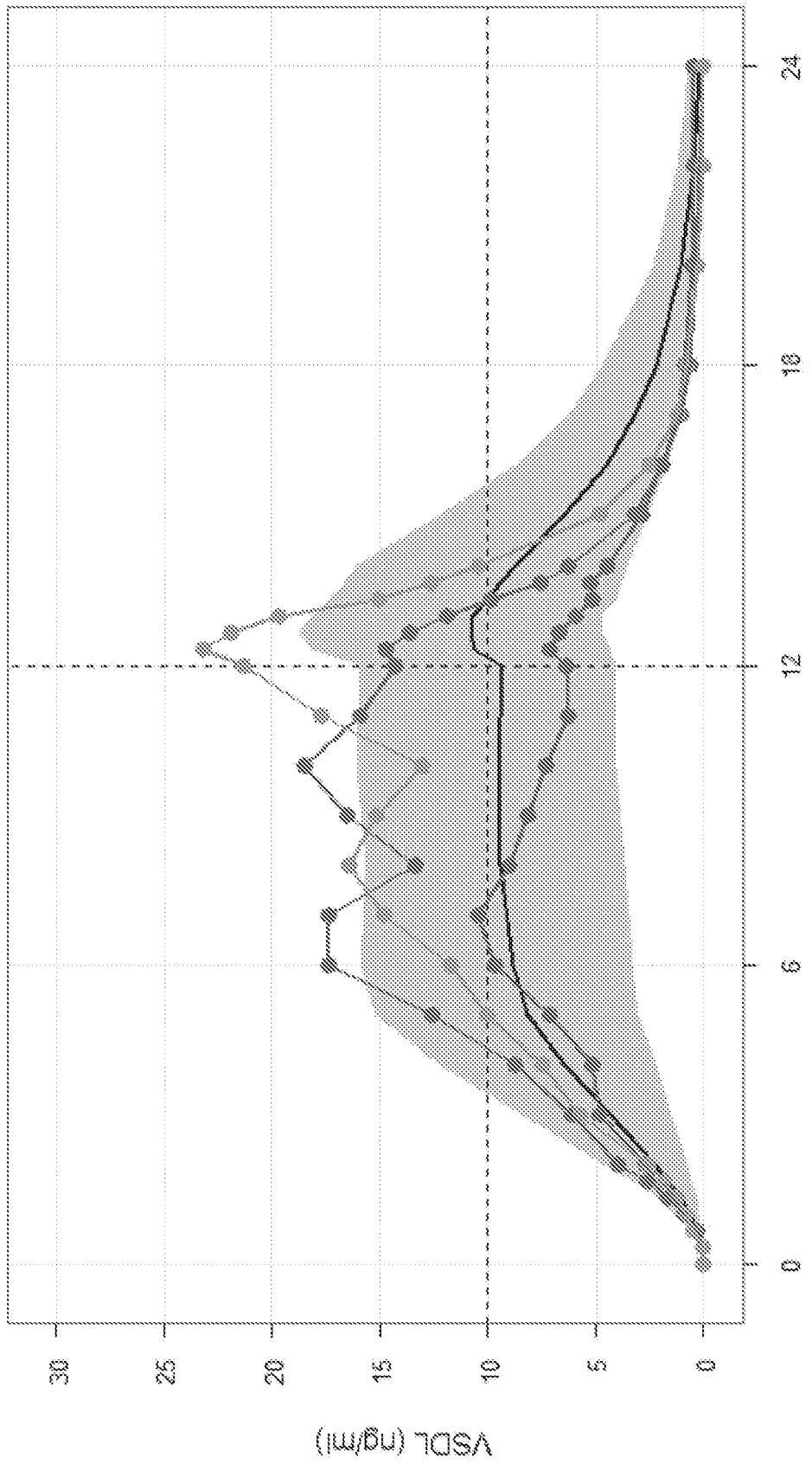

Figure 1

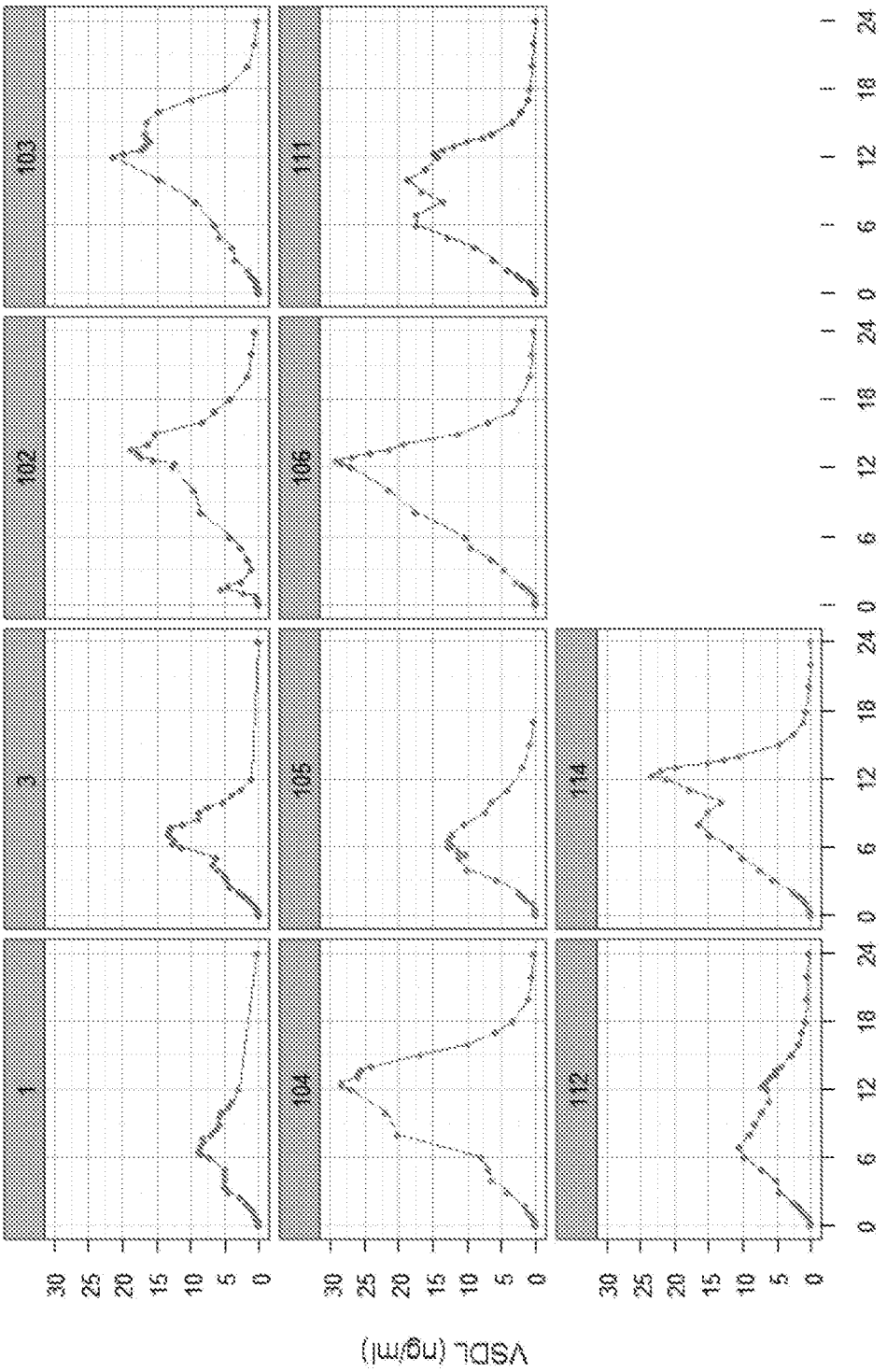

Figure 2

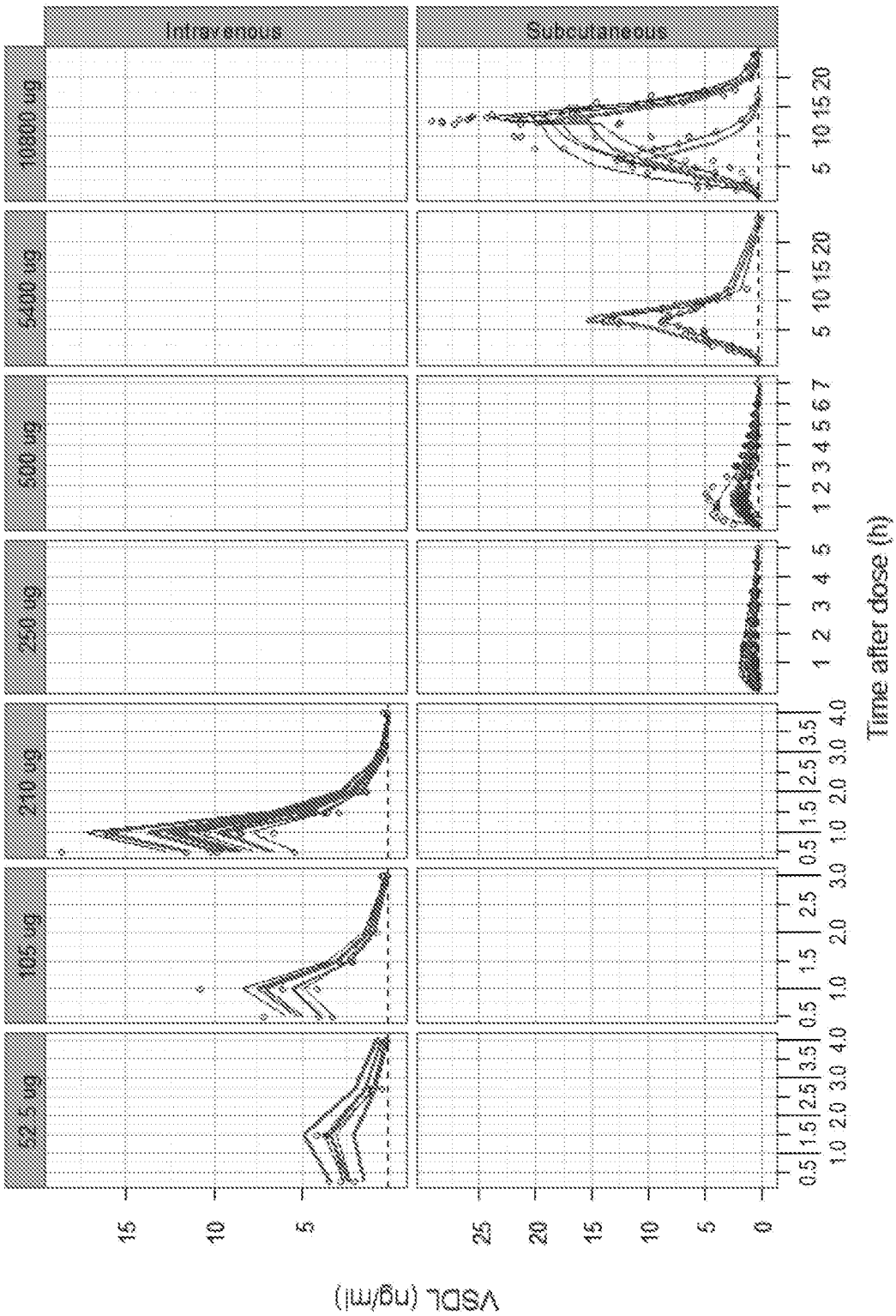
Intravenous
Subcutaneous
22.5 ug
105 ug
210 ug
230 ug
300 ug
3400 ug
10000 ug
VSDL (ng/ml)
Time after dose (h)

Figure 3

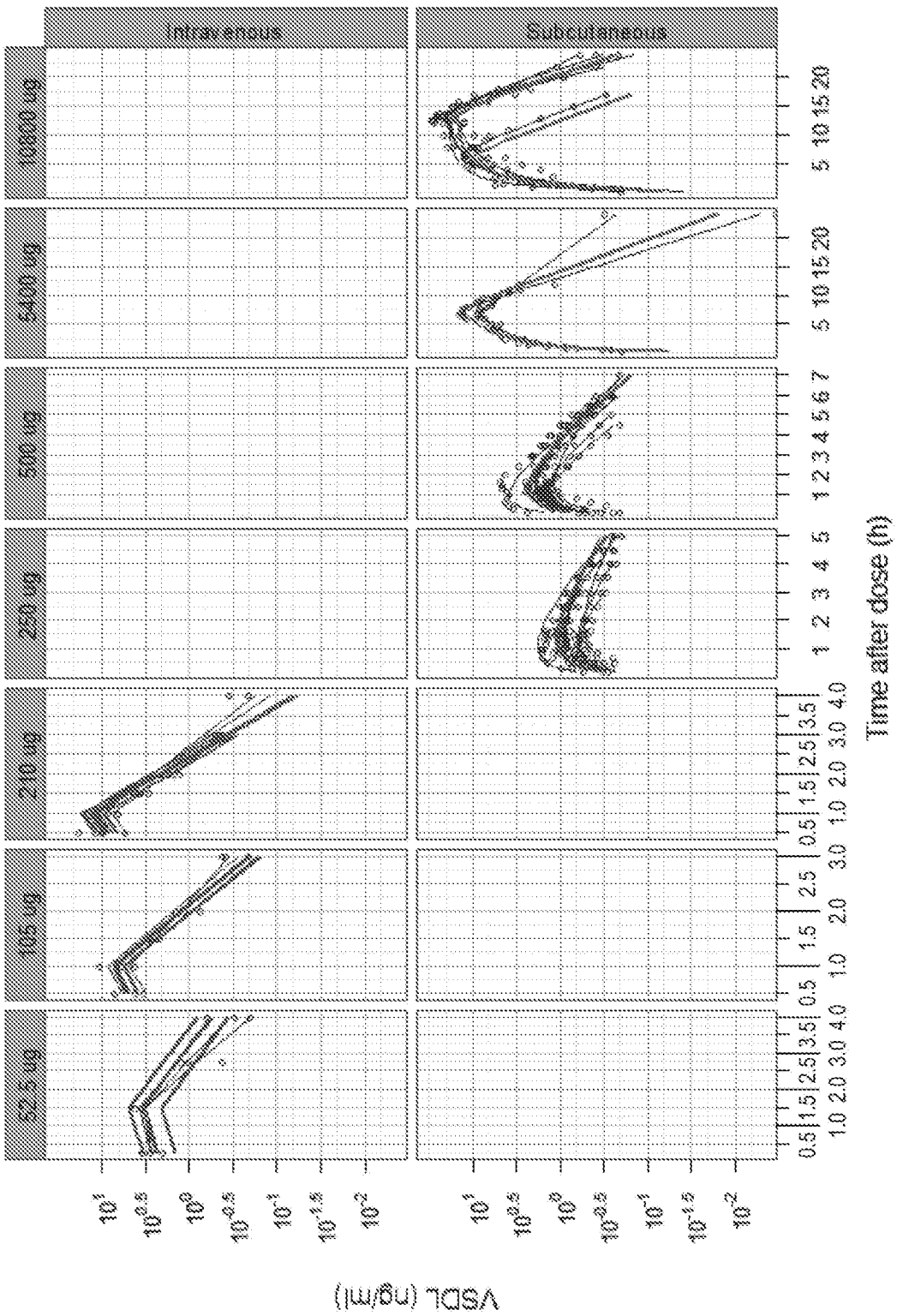
Intravenous
Subcutaneous
52.5 ug
105 ug
210 ug
420 ug
560 ug
5400 ug
10800 ug
VSDL (ng/ml)
Time after dose (h)

Figure 4

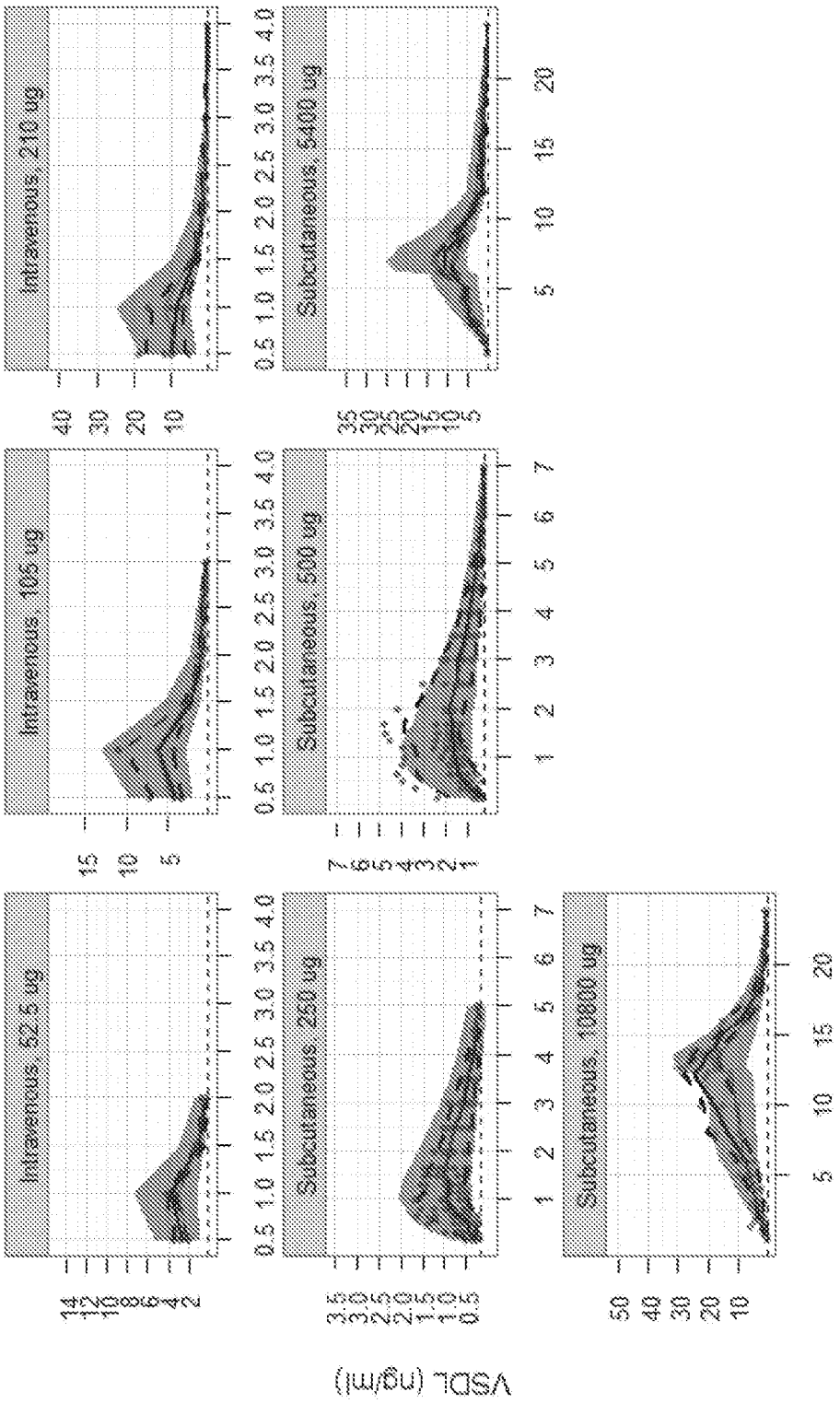
Intravenous, 52.5 ug
Intravenous, 105 ug
Intravenous, 210 ug
Subcutaneous, 250 ug
Subcutaneous, 600 ug
Subcutaneous, 1600 ug
Subcutaneous, 6400 ug
VSDL (ng/ml)
Time after dose (h)

Figure 5

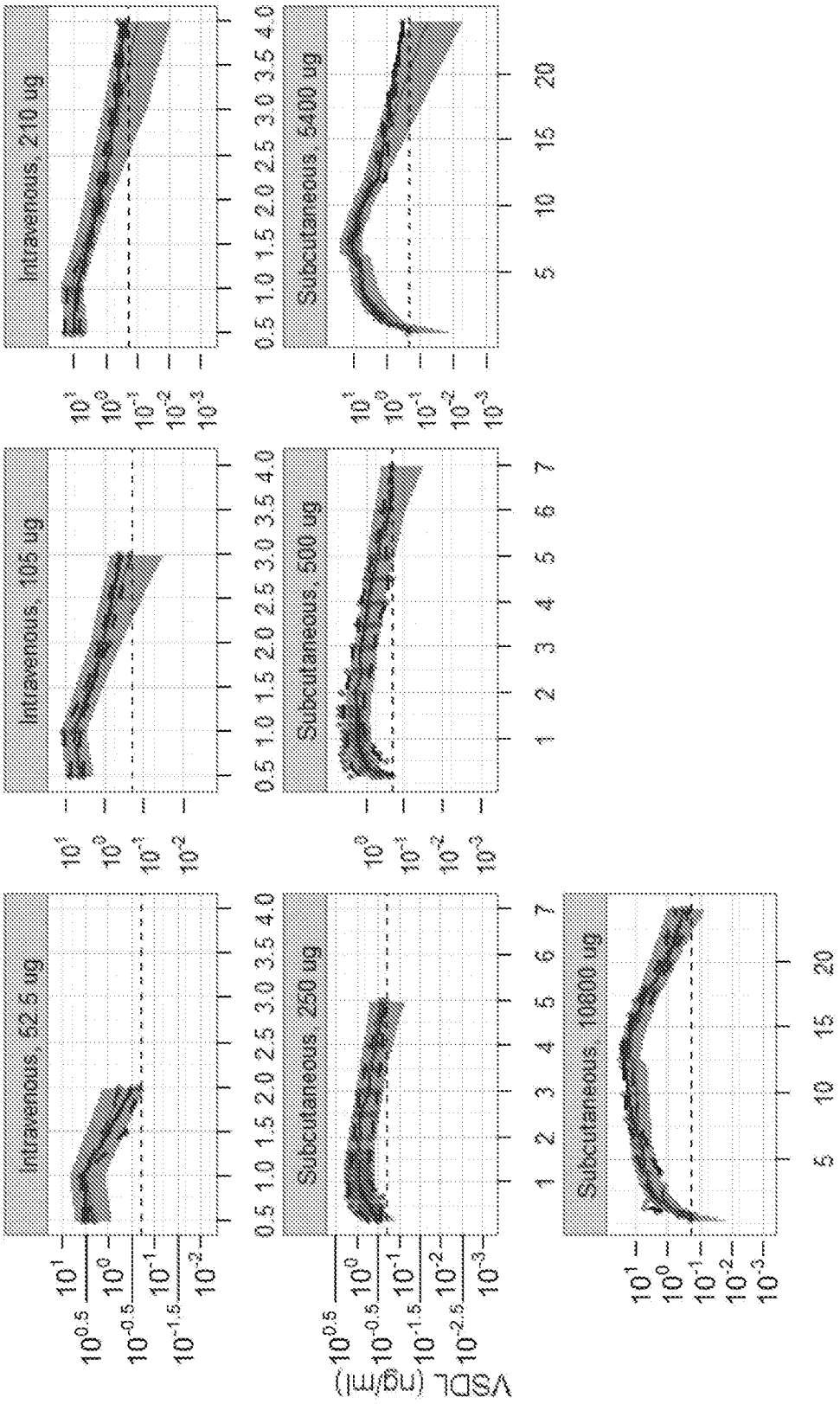
Intravenous 62.5 ug
Intravenous 105 ug
Intravenous 210 ug
Subcutaneous 250 ug
Subcutaneous 500 ug
Subcutaneous 5400 ug
Subcutaneous 10000 ug
VSDL (ng/ml)
Time after dose (h)

Figure 6

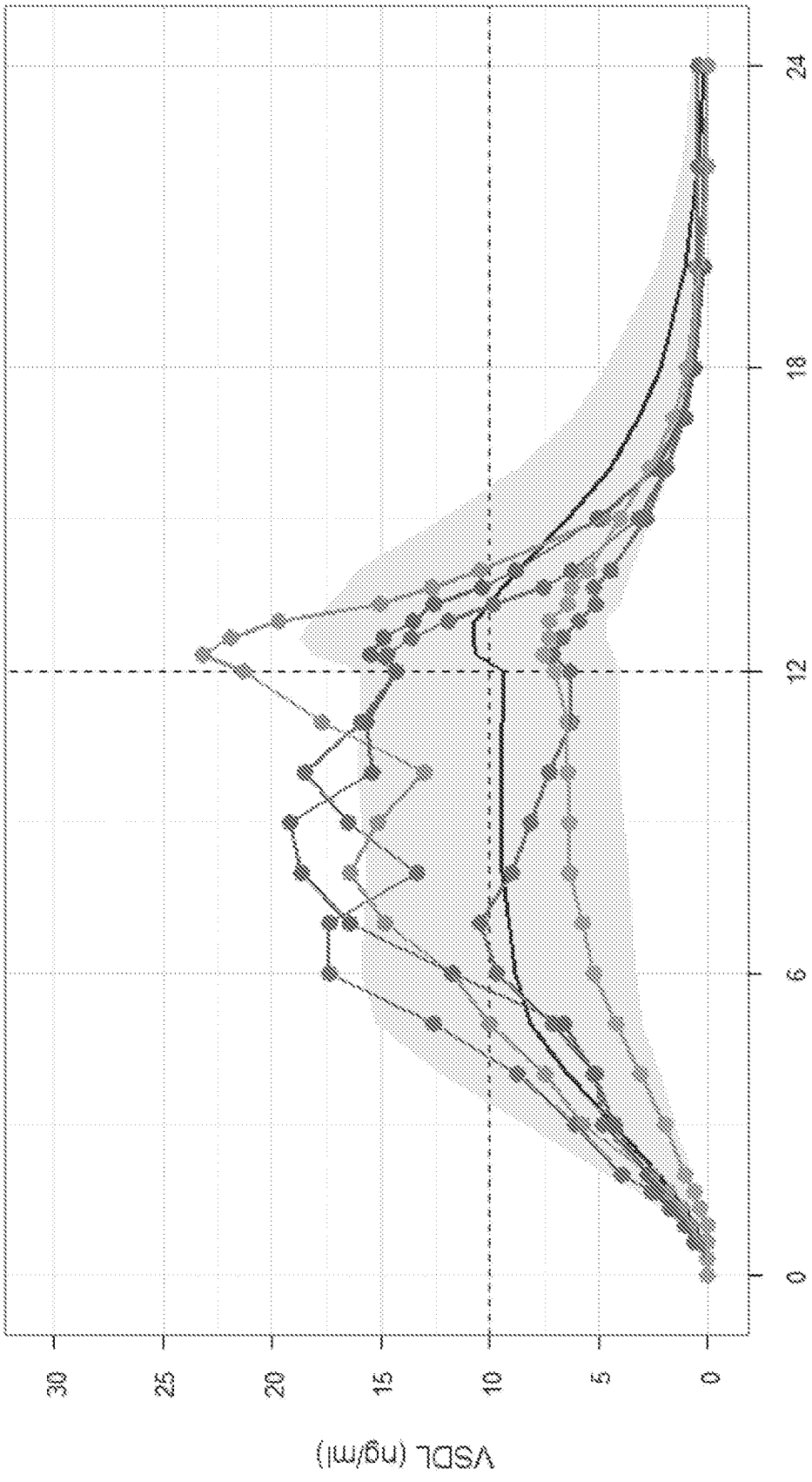

Figure 7

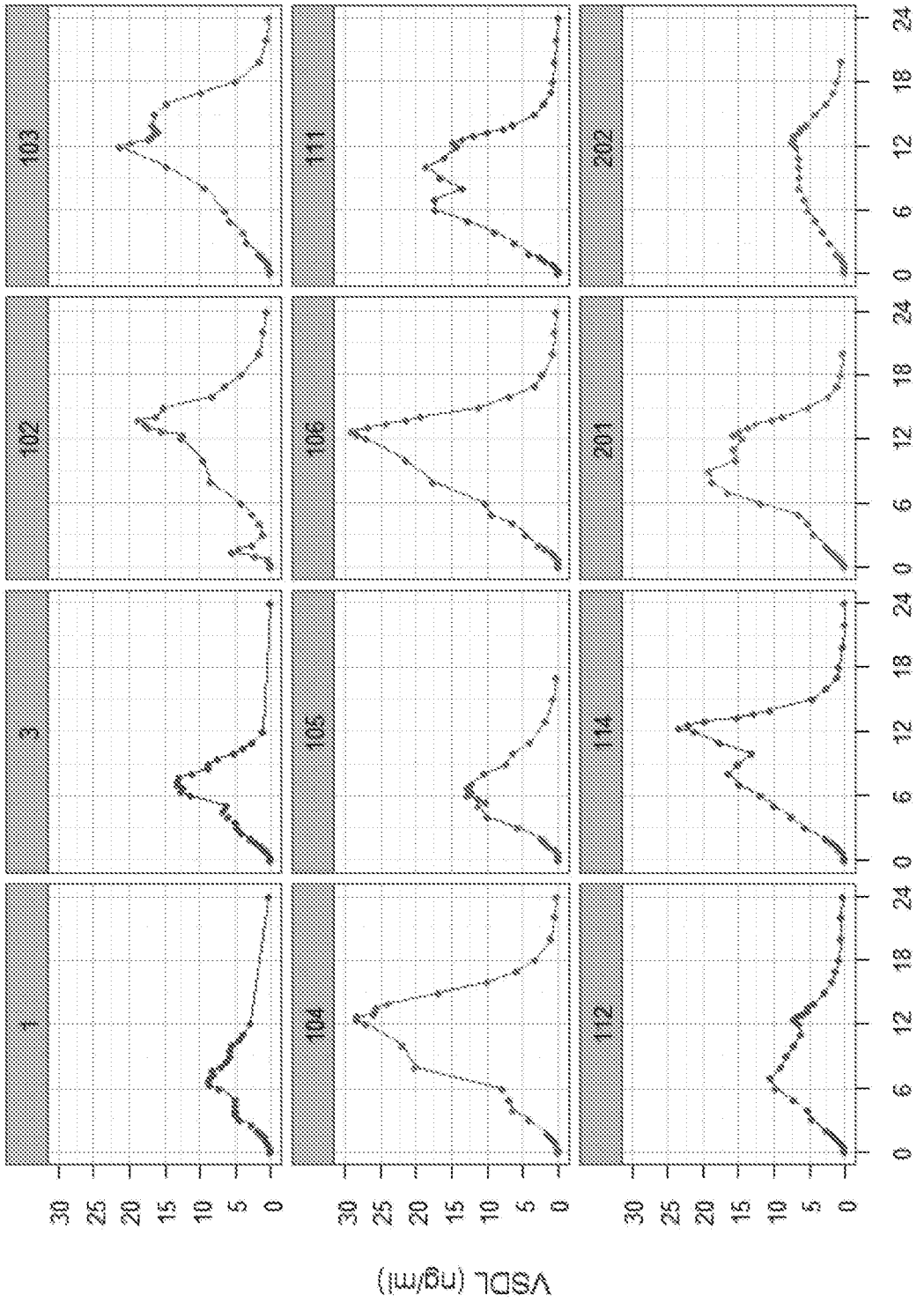
VSDL (ng/ml)
Time after dose (h)
1
3
102
103
104
105
106
111
112
114
201
202

Figure 8

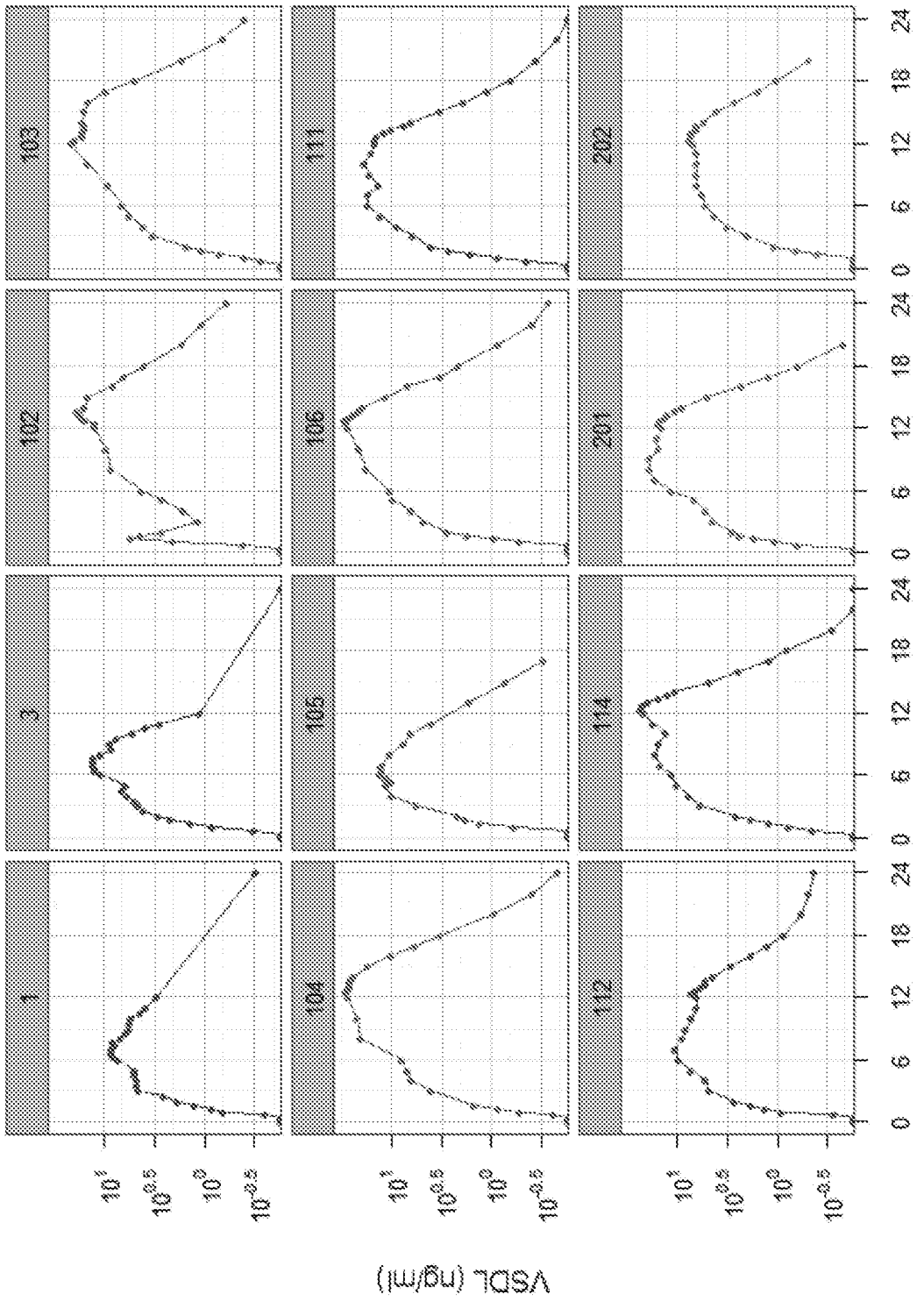
1
3
102
103
104
105
106
111
112
114
201
202
VSDL (ng/ml)
Time after dose (h)

Figure 9

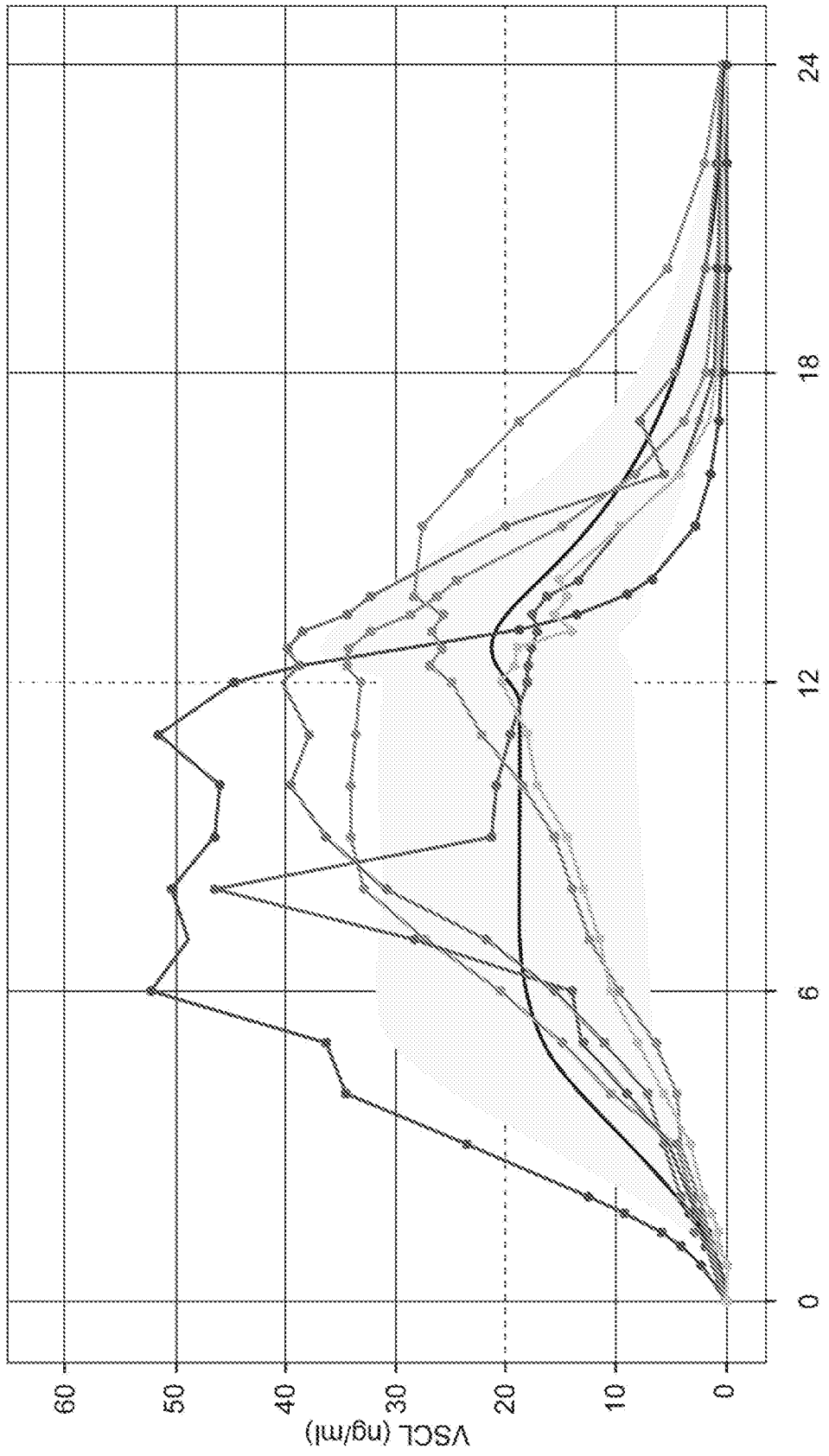

Figure 10

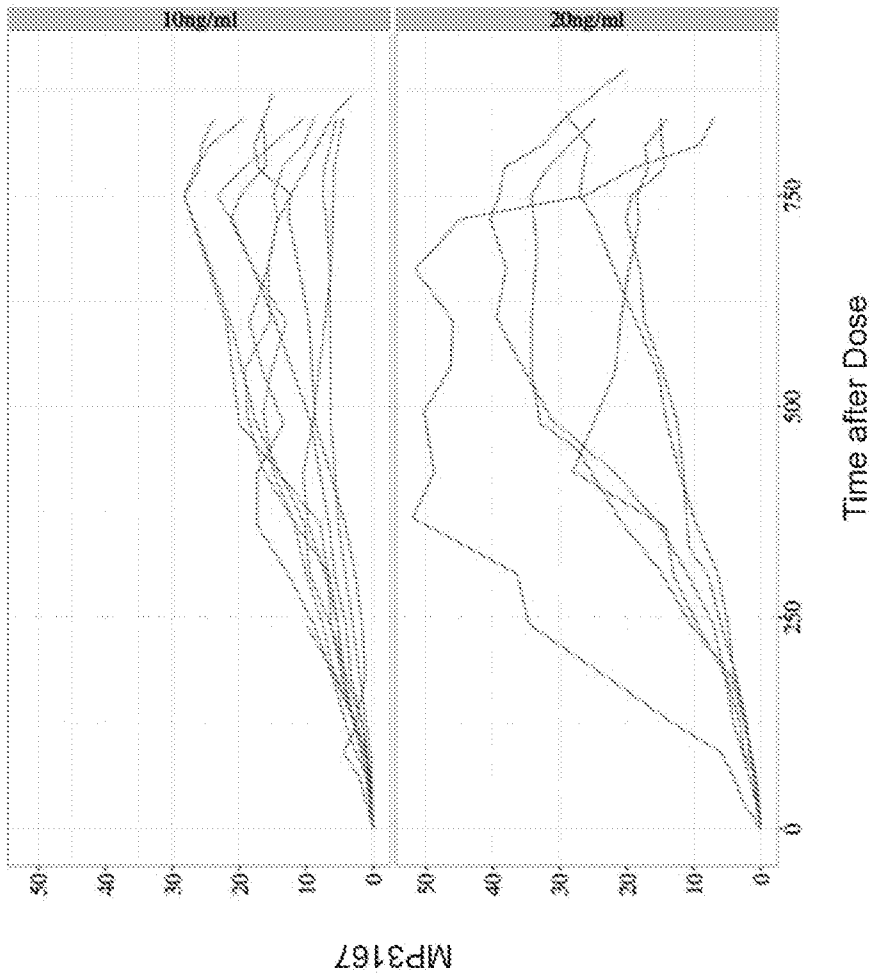
1ug/ml
2ug/ml
Time after Dose
0
250
500
750
0
10
20
30
40
50
MP3167

Figure 11

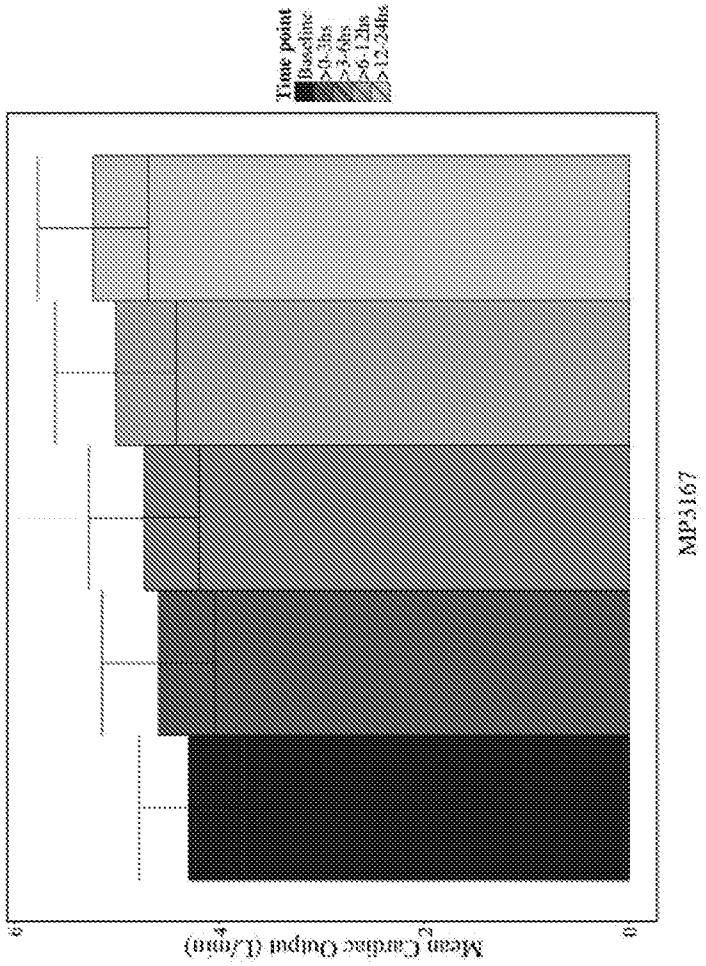
Time point
Baseline
>1-3hs
>3-6hs
>6-12hs
>12-24hs
Mean Cardiac Output (L/min)
0
2
4
MP3167

Figure 12

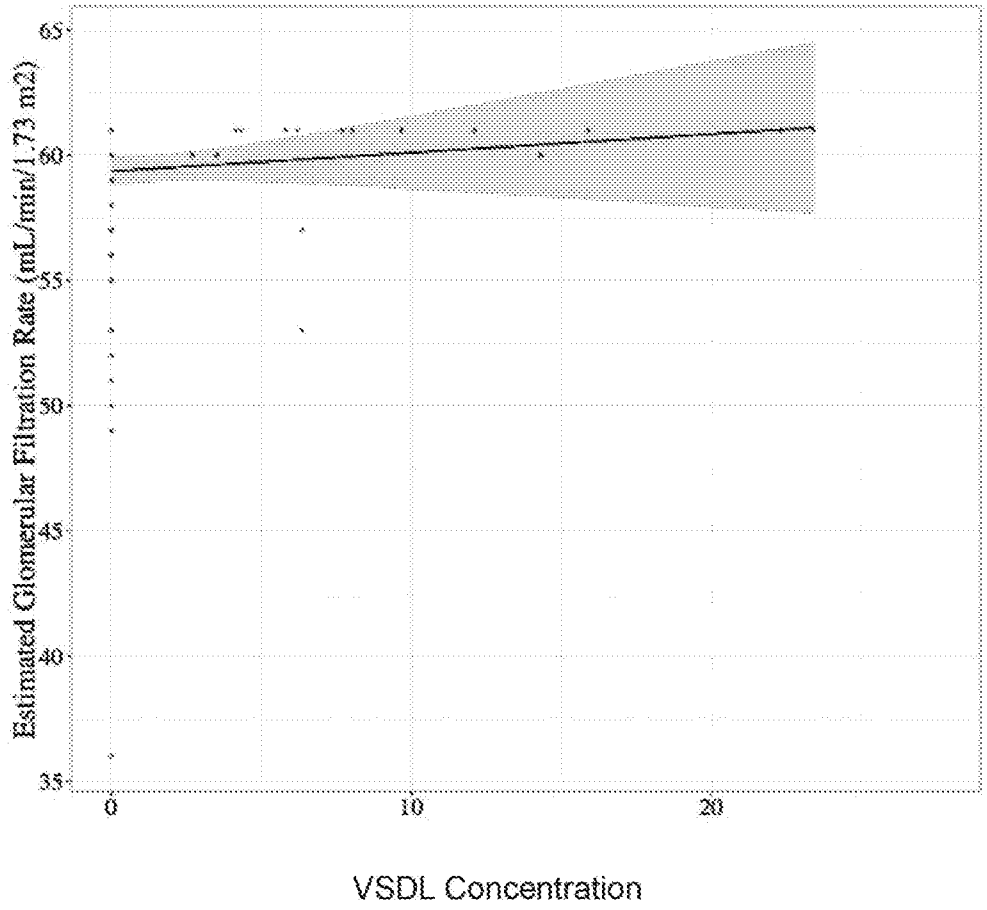
Estimated Glomerular Filtration Rate (mL/min/1.73 m2)
65
60
55
50
45
40
35
0
10
20
VSDL Concentration

Figure 13

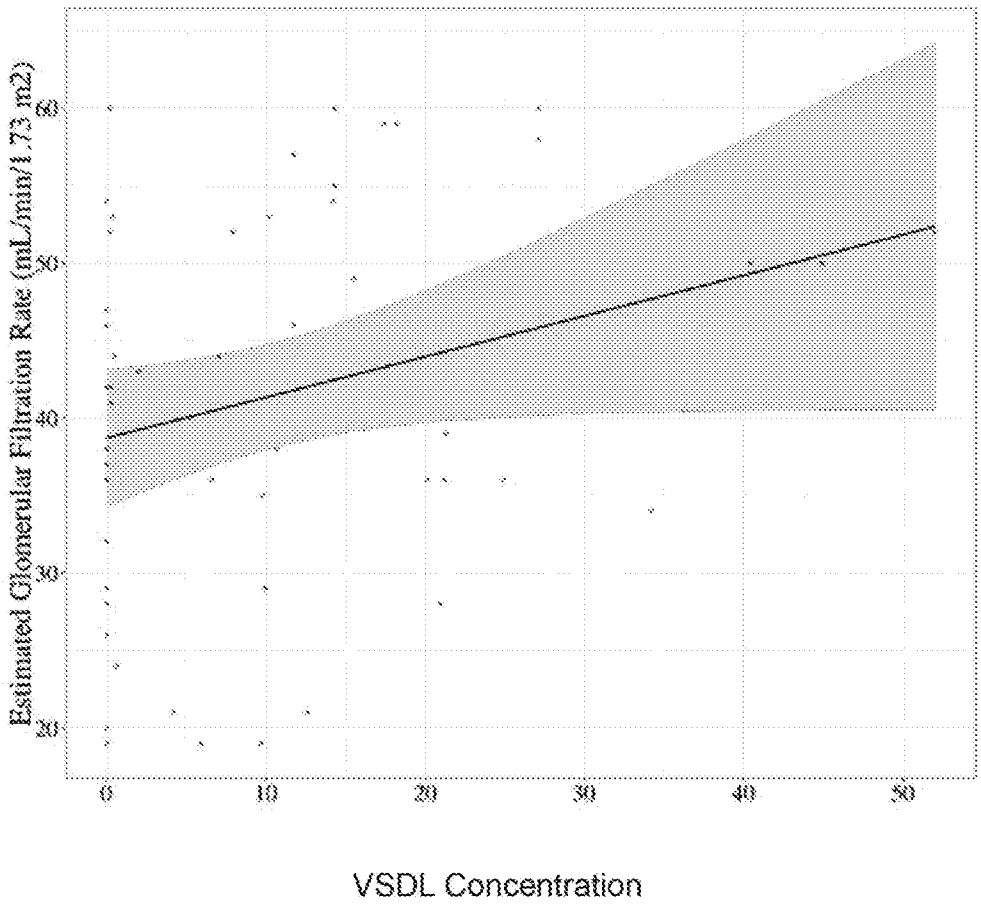
Estimated Glomerular Filtration Rate (mL/min/1.73 m2)
20
30
40
50
60
0
10
20
30
40
50
VSDL Concentration

Figure 14

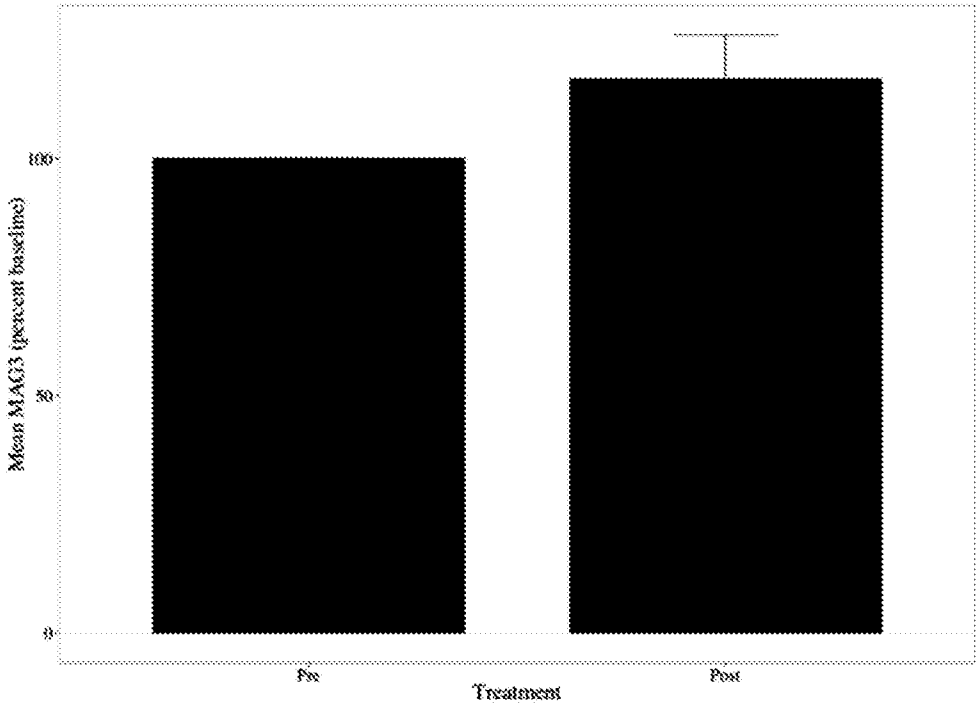

Figure 15

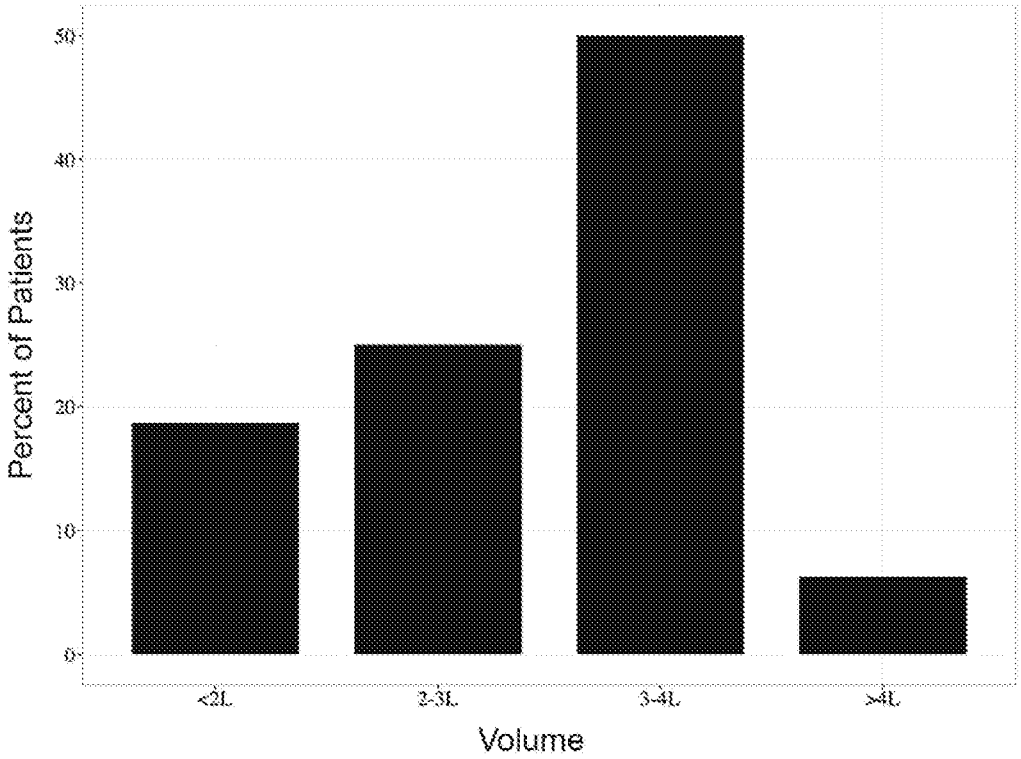

Figure 16

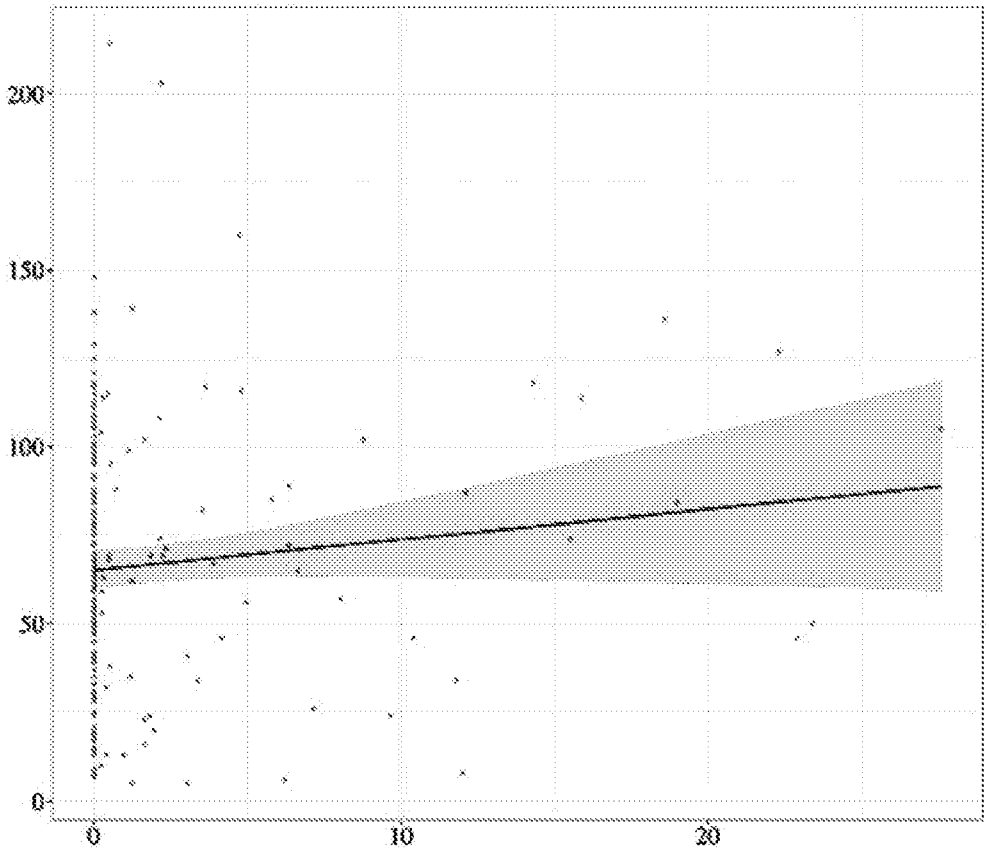

Figure 17

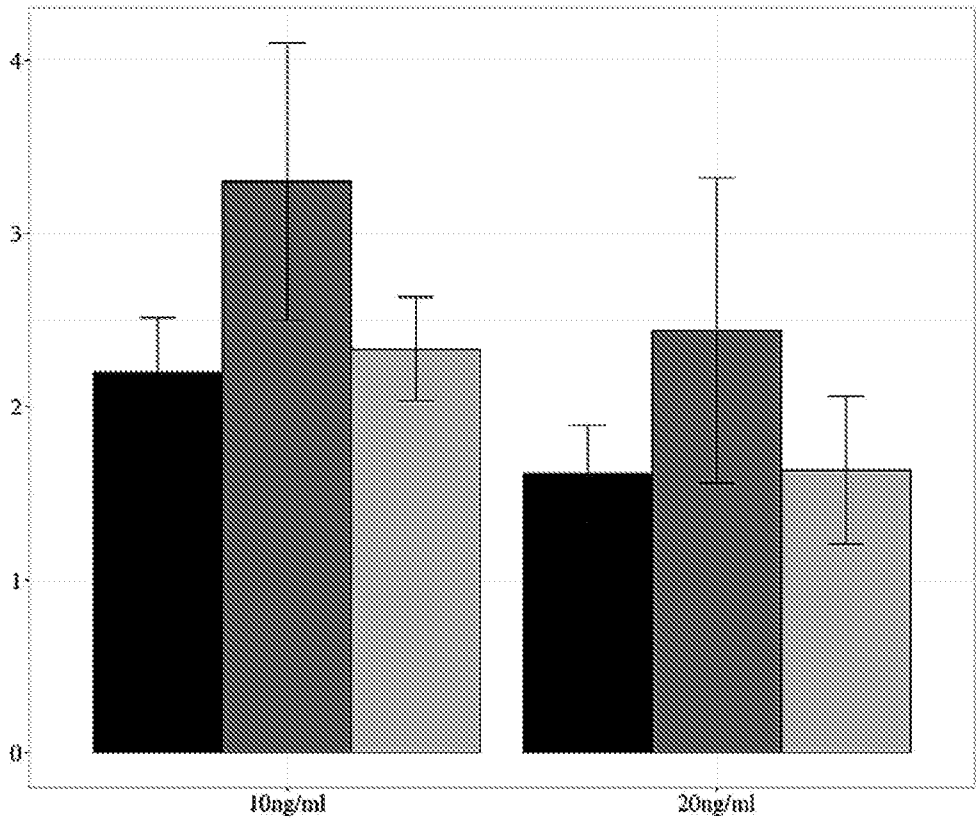

Figure 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2014/000256

A. CLASSIFICATION OF SUBJECT MATTER

A61K 38/17(2006.01)i, A61K 38/16(2006.01)i, A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 38/17; C07K 14/705; G01N 33/567; A61M 5/178; A61K 38/16; A61M 5/168; A61P 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & keywords: active agent, atrial natriuretic peptide(ANP), multimodal dosage, infusion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012-019237 A1 (MADELEINE PHARMACEUTICALS PTY LTD) 16 February 2012 See claims 1, 20, 24, 41.	1-4,22-25,41-44
Y		45
A		79-81
Y	GenBank accession XP_001141705.1 (25 October 2012) See the whole document.	45
X	US 2007-0141634 A1 (VUOLTEENAHO et al.) 21 June 2007 See paragraphs [0135], [0150]-[0155]; and claim 44.	79-81
A	US 2009-0062730 A1 (WOO) 05 March 2009 See claim 24.	1-4,22-25,41-45 ,79-81
A	SAITO et al., "Clinical application of atrial natriuretic polypeptide in patients with congestive heart failure: beneficial effects on left ventricular function" Circulation, Vol. 76. No. 1, pp. 115-124 (July 1987) See the abstract; and page 116, left column.	1-4,22-25,41-45 ,79-81

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2014 (11.06.2014)	**12 June 2014 (12.06.2014)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
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Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2014/000256

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VESELY et al., "Vessel dilator enhances sodium and water excretion and has beneficial hemodynamic effects in persons with congestive heart failure" Circulation, Vol. 98. No. 4, pp. 323-329 (July 1998) See the abstract; and page 328, left column.	1-4,22-25,41-45 ,79-81

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2014/000256

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012-019237 A1	16/02/2012	None	
US 2007-0141634 A1	21/06/2007	AT 538389 T	15/01/2012
		AU 2005-254028 A1	13/01/2005
		AU 254028 B2	14/10/2010
		CA 2530623 A1	13/01/2005
		DK 1664769 T3	19/03/2012
		EP 1664769 A2	07/06/2006
		EP 1664769 B1	21/12/2011
		ES 2377122 T3	22/03/2012
		GB 0315291 D0	06/08/2003
		GB 2403533 A	05/01/2005
		JP 04741485 B2	03/08/2011
		JP 2007-526988 A	20/09/2007
		NO 20060481 A	30/01/2006
		PT 1664769 E	09/03/2012
		SI 1664769 T1	30/04/2012
		US 8283123 B2	09/10/2012
		WO 2005-003764 A2	13/01/2005
		WO 2005-003764 A3	14/12/2006
US 2009-0062730 A1	05/03/2009	US 2009-0062727 A1	05/03/2009
		US 2009-0062728 A1	05/03/2009
		US 2009-0062729 A1	05/03/2009
		US 8070742 B2	06/12/2011
		WO 2009-029899 A1	05/03/2009

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2014/000256

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 61-78,82-85
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 61-78, 82-85 pertain to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and Rule 39.1(iv), to search.

2. ☒ Claims Nos.: 6,11,14,19,21,30-31,33-34,36,38,40,50,53,58,60,68,71,76,78
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 6, 11, 14, 19, 21, 30-31, 33-34, 36, 38, 40, 50, 53, 58, 60, 68, 71, 76, 78 are unclear since they refer to claims which are not searchable due to not being drafted in accordance with Rule 6.4(a).

3. ☒ Claims Nos.: See extra sheet.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

(Continuation of Box No. II)

3. Claim Nos. 5,7-10,12-13,15-18,20,26-29,32,35,37,39,46-49,51-52,54-57,59,65-67,69-70,72-75,77