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(54) Title: A METHOD OF TREATMENT

(57) Abstract: The present disclosure relates generally to methods and therapeutic protocols for managing a loss of pregnancy event in a female subject comprising administering to said subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and eliminate a conceptus. Also disclosed herein is a method for predicating whether a loss of pregnancy event in a subject will be successfully treated.

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A METHOD OF TREATMENT

FIELD

[0001] The present invention relates generally to a therapeutic protocol to manage a pregnancy loss event. The therapeutic protocol is applicable *inter alia* to the treatment of miscarriage including a missed miscarriage and to induce termination of pregnancy.

BACKGROUND

[0002] Bibliographic details of the publications referred to by author in this specification are collected alphabetically at the end of the description.

[0003] Reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgement or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavor to which this specification relates.

[0004] Gynecological disorders create an enormous burden on the health and wellbeing of pregnant mothers and families and communities as a whole. It also has the potential for significant commercial loss to the non-human animal husbandry industry. In either case, the potential economic and clinical care burden to the human and animal health systems is quite significant.

[0005] Pregnancy loss such as miscarriage and planned or unplanned terminations are an unfortunate reality of pregnancy. For example, around 10-15% of clinically recognized pregnancies end early in miscarriage, most during the first trimester of pregnancy, i.e. the first 13 weeks in humans.

[0006] When the fetus is no longer alive, i.e. fetus or part thereof such as a gestational sac is present (even without a fetus) but cardiac activity is not present, but still in the uterus, then it is classified as a "missed miscarriage".

[0007] The management of a missed miscarriage required for the patient is to empty the uterus safely. There are two main options.

1) ***Suction curettage (i.e. surgical management)***
This involves a light general anesthetic and the surgeon performs a procedure *via* the vaginal entrance and cervix to gently suck out the contents of the uterus. It is a safe procedure (has a small risk of making a hole in the uterus) but is still costly, needs a general anesthetic (which always carries a small risk) and some women would simply prefer not to have any operation.

2) ***Medical management by administering misoprostol***
This is a "watch and wait" approach where a prostaglandin analog such as misoprostol is given to try to induce the uterus to contract, and the cervix to open up to let the conceptus pass through (i.e. fetus, gestational sac).

Medical management has a success rate up to approximately 70% if given for 2-3 weeks. Thus, regrettably, many patients still end up needing surgery.

[0008] There is, therefore, considerable need to find a medical management option that is more effective than the current medical management options. It would:

1) allow more women to avoid surgery;

2) may clear the conceptus much more quickly than current medical management options; and

3) be a more cost effective way to manage missed miscarriage.

SUMMARY

[0009] The present invention provides a therapeutic protocol that targets placenta cells to manage a loss of pregnancy event. The protocol enables efficient induction of placenta cell death including activation of apoptosis whilst not being harmful to the Fallopian tube or subsequent fertility. Such a protocol is useful in the treatment of a miscarriage including a missed miscarriage and a planned or unplanned termination. The protocol comprises the administration of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof. The present therapeutic protocol enables an alternative to surgery.

[0010] The vinorelbine may be administered alone or in combination with another active agent such as a prostaglandin analog (e.g. misoprostol) and/or mifepristone (RU486), an epidermal growth factor receptor (EGFR) inhibitor (e.g. gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and/or pertuzumab/omnitarg) or a tyrosine kinase inhibitor (e.g. trastuzumab, lapatinib and/or suitnib). In an embodiment, a dose of vinorelbine is from a single dose to a regime of less than 5 doses. Whilst the drug may be administered by any route, oral administration provides a particularly convenient route of administration. It is proposed that a single to a dosage regime of 5 or less doses of vinorelbine or its pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof alone or in combination with another agent is effective in selectively inducing placental cell death in the management of a pregnancy loss event including a miscarriage (e.g. missed miscarriage) and a pregnancy termination.

[0011] It is proposed herein that the subject undergoing treatment includes a human female, in any trimester or any stage of pregnancy. In an embodiment, a pregnant female is in her first trimester although the subject invention is not limited to any one trimester or stage of condition.

[0012] Accordingly, enabled herein is a method of managing a pregnancy loss event in a subject, the method comprising administering to the subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug from thereof effective to induce placenta cell death and to induce clearance of the conceptus. The loss of pregnancy event may also be described herein as being "associated with the placenta". This means the target tissue for treating the event is the placenta. By "clearance" includes resorption of the conceptus. The term "conceptus" encompasses a fetus, embryo and/or gestational sac including the placenta/yolk sac.

[0013] A pharmaceutical preparation comprising vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof and one or more pharmaceutically acceptable carriers, diluents and/or excipients is also contemplated herein for use in the management of a loss of pregnancy event associated with the placenta. The pharmaceutical preparation includes an oral formulation. In an example, the condition is a missed miscarriage. In another embodiment, the event is a planned or unplanned pregnancy termination.

[0014] Further contemplated herein is the use of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof in the manufacture of a medicament to induce placenta cell death in the management of a loss of pregnancy event. In an example, the event is a missed miscarriage or a pregnancy termination. Again, the vinorelbine may be the sole active agent or it may be used in combination with one or more other active agents.

[0015] The present specification further teaches a method for predicting whether a miscarriage or termination of pregnancy can be successfully treated following administration of vinorelbine alone or in combination with another active agent (e.g. a prostaglandin analog, an EGFR inhibitor, a tyrosine kinase inhibitor). The predictor is the level of β-human choriogonadotropin (β-hCG). If β-hCG levels are reduced, treatment is likely to be successful.

BRIEF DESCRIPTION OF THE FIGURES

[0016] Some figures contain color representations or entities. Color photographs are available from the Patentee upon request or from an appropriate Patent Office. A fee may be imposed if obtained from a Patent Office.

[0017] **Figure 1** is a graphical representation showing the effects of vinorelbine (VB), gefitinib (GFT) and methotrexate (MTX) or a combination thereof on cell viability.

[0018] **Figures 2A through D** are graphical representations of the effect of vinorelbine on placenta cell viability and proliferation.

[0019] **Figures 3A through G** are graphical representations of mechanisms *via* which vinorelbine induces cell death of placenta cells.

[0020] **Figures 4A through C** are graphical representations of the effect of vinorelbine on human Fallopian tubes.

[0021] **Figures 5A through F** are graphical representations of the effect of vinorelbine on mouse fertility. Exposure to vinorelbine does not affect future fertility.

[0022] **Figure 6** is a graphical representation of the effect of vinorelbine, erlotinib and combinations thereof on HTR8/svneo placental cell viability. Cells were treated for 48 hours with 10nM vinorelbine, 4μM Erlotinib or 8μM Erlotinib, or combinations thereof. *$p<0.05$ vs 10nM vinorelbine.

[0023] **Figure 7** is a graphical representation of the effect of vinorelbine on murine fetal viability (left panel) and fetal resorption (right panel) during pregnancy.

DETAILED DESCRIPTION

[0024] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or method step or group of elements or integers or method steps but not the exclusion of any other element or integer or method steps or group of elements or integers or method steps.

[0025] As used in the subject specification, the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise. Thus, for example, reference to "a form" includes a single form, as well as two or more forms; reference to "an agent" includes a single agent, as well as two or more agents; reference to "the disclosure" includes single and multiple aspects taught by the disclosure; and so forth. Aspects taught and enabled herein are encompassed by the term "invention". All such aspects are enabled across the width of the invention. Any variants and derivatives contemplated herein are encompassed by "forms" of the invention.

[0026] The present invention is predicated in part on the determination of the high cytotoxic sensitivity placenta cells have in the presence of the vinca alkaloid, vinorelbine. This is significant since previous therapeutic treatment of a condition such as a miscarriage including a missed miscarriage or a planned or unplanned termination of pregnancy involved surgical intervention and other substantive medical intervention such as administration of misoprostol. This can have adverse side effects including damage to other cell types.

[0027] Taught therein is a method of managing a loss of pregnancy event in a subject, the method comprising administering to the subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and induce conceptus removal. A loss of pregnancy event includes a miscarriage such as a missed miscarriage and a termination of pregnancy. The latter may be planned or unplanned such as resulting from a medical or psychological need.

[0028] Reference to a "subject" means a female subject. The present protocol is effective in any trimester or stage of pregnancy. In an embodiment, the trimester is the first trimester.

[0029] Taught herein is a method of treating a loss of pregnancy event associated with the placenta in a pregnant human female subject, the method comprising administering to the pregnant human female subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and clearance of the conceptus.

[0030] Taught herein is a method of managing a subject with a missed miscarriage, the method comprising administering to the subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and eliminate the conceptus.

[0031] Further taught herein is a method of managing a subject requiring a termination of pregnancy, the method comprising administering to the subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and eliminate the conceptus.

[0032] In an embodiment, the subject is a human female subject. Accordingly, enabled herein is a method of treating a loss of pregnancy event in human female subject, the method comprising administering to the subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and eliminate the conceptus. The term "conceptus" encompasses a fetus, embryo and/or gestational sac including the placenta/yolk sac. Further enabled is a method of treating a human female subject with a missed miscarriage or requiring a termination of pregnancy of the placenta, the method comprising administering to the subject an amount of vinorelbine or a

pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and eliminate the conceptus.

[0033] Reference to "vinorelbine" encompasses pharmacologically active and pharmaceutically acceptable salts, solvates, tautomers, stereoisomers, derivatives, biosimilars and prodrug forms thereof. The vinorelbine may be used alone or in combination with another active agent such as but not limited to a prostaglandin analog (e.g. misoprostol) an epidermal growth factor receptor (EGFR) inhibitor and a tyrosine kinase inhibitor. An EGFR inhibitor includes gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and pertuzumab/omnitarg. In an embodiment, the EGFR inhibitor is gefitinib. A tyrosine inhibitor includes trastuzumab, lapatinib and suitnib.

[0034] Taught herein is a method of managing a subject with a loss of pregnancy event, the method comprising administering to the subject an amount of vinorelbine and an agent selected from the group consisting of a prostaglandin analog, and an EGFR inhibitor and a tyrosine kinase inhibitor or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or the other agent effective to induce placenta cell death and eliminate the conceptus.

[0035] Further taught herein is a method of treating a subject with a missed miscarriage or requiring a termination of pregnancy, the method comprising administering to the subject an amount of vinorelbine and an agent selected from the group consisting of a prostaglandin analog, an EGFR inhibitor and a tyrosine kinase inhibitor, a cytotoxic agent and an antimetabolite or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or the other agent effective to induce placenta cell death and eliminate the conceptus.

[0036] In an embodiment, the subject is a human female subject. Accordingly, enabled herein is a method of managing a human female subject with a loss of pregnancy event, the

method comprising administering to the subject an amount of vinorelbine and an agent selected from the group consisting of a prostaglandin analog, an EGFR inhibitor and a tyrosine kinase inhibitor or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or the other agent effective to induce placenta cell death and eliminate the conceptus. Further enabled is a method of treating a human female subject with a missed miscarriage or requiring a termination of pregnancy, the method comprising administering to the subject an amount of vinorelbine and an agent selected from the group consisting of a prostaglandin analog, an EGFR inhibitor and a tyrosine kinase inhibitor or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or the other agent effective to induce placenta cell death and eliminate the conceptus.

[0037] In an embodiment, taught herein is a method of managing a subject with a loss of pregnancy event an, the method comprising administering to the subject an amount of vinorelbine and a prostaglandin analog, wherein the prostaglandin analog is misoprostol, an EGFR inhibitor selected from the group consisting of gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and pertuzumab/omnitarg and a tyrosine inhibitor selected from the group consisting of trastuzumab, lapatinib and sunitinib or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of any or all thereof effective to induce placenta cell death and eliminate the conceptus. Further contemplated herein is use of a combination of vinorelbine and mifepristone (also known as RU486).

[0038] Further taught herein is a method of treating a subject with a missed miscarriage or requiring a termination of pregnancy, the method comprising administering to the subject an amount of vinorelbine and a prostaglandin analog wherein the prostaglandin analog is misoprostol, an EGFR inhibitor selected from the group consisting of gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-

R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and pertuzumab/omnitarg and a tyrosine inhibitor selected from the group consisting of trastuzumab, lapatinib and sunitinib or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of any or all thereof effective to induce placenta cell death and eliminate the conceptus. The aspects above further extend to other end of pregnancy events.

[0039] In an embodiment, the subject is a human female subject. Accordingly, enabled herein is a method of managing a human female subject with a loss of pregnancy event, the method comprising administering to the subject an amount of vinorelbine and a prostaglandin analog wherein the prostaglandin analog is misoprostol, mifepristone (RU486), an EGFR inhibitor selected from the group consisting of gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and pertuzumab/omnitarg and a tyrosine inhibitor selected from the group consisting of trastuzumab, lapatinib and sunitinib or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of any or all thereof effective to induce placenta cell death and eliminate the conceptus. Further enabled is a method of treating a human female subject with a missed miscarriage or needing a termination of pregnancy, the method comprising administering to the subject an amount of vinorelbine and a prostaglandin analog wherein the prostaglandin analog is misoprostol, an EGFR inhibitor selected from the group consisting of gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and pertuzumab/omnitar and a tyrosine inhibitor selected from the group consisting of trastuzumab, lapatinib and sunitinib or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of any or all thereof effective to induce placenta cell death and eliminate the conceptus.

[0040] In the above embodiments, further contemplates herein is the use of vinorelbine and

mifepristone, vinorelbine and misoprostol and vinorelbine, mifepristone and misoprostol.

[0041] In an embodiment, vinorelbine is used in combination with misoprostol, or mifepristone (RU486) or both mifepristone and misoprostol. In an embodiment, taught herein is a method of managing a subject with a loss of pregnancy event, the method comprising administering to the subject an amount of vinorelbine and misoprostol and/or mifepristone or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or misoprostol effective to induce placenta cell death and eliminate the conceptus.

[0042] Further taught herein is a method of treating a subject with a missed miscarriage or needing a termination of pregnancy, the method comprising administering to the subject an amount of vinorelbine and misoprostol and/or mifepristone or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or misoprostol effective to induce placenta cell death and eliminate the conceptus.

[0043] In an embodiment, the subject is a human female subject. Accordingly, enabled herein is a method of managing a human female subject with a loss of pregnancy event, the method comprising administering to the subject an amount of vinorelbine and misoprostol and/or mifepristone or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or misoprostol effective to induce placenta cell death and eliminate the conceptus. Further enabled is a method of treating a human female subject with a missed miscarriage or needing a termination of pregnancy, the method comprising administering to the subject an amount of vinorelbine and misoprostol and/or mifepristone or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form of vinorelbine and/or misoprostol effective to induce placenta cell death and eliminate the conceptus.

[0044] It is proposed herein that vinorelbine is effective at a low dose. In an embodiment,

according to the present invention, only from 1 to 5 doses of vinorelbine are administered in an amount of from 1mg to 200mg per subject. In an embodiment, a single dose is administered of from 1mg to 200mg vinorelbine. In another embodiment, a single dose is administered in an amount of from about 30mg to about 60mg vinorelbine. In another embodiment, a single dose is administered in an amount of about 30mg vinorelbine. In another embodiment, a single dose is administered in an amount of about 60mg vinorelbine.

[0045] Reference to from "1 to 5 doses" means 1, 2, 3, 4 or 5 doses. From "1mg to 200mg" means 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199 or 200mg" per dose or a fraction of a dose inbetween. Put in other terms, the dose of vinorelbine may be from 0.001μM to 1000μM including 0.01μM, 0.05μM, 0.1μM, 1μM, 5μM, 10μM and 100μM. These dose amounts may be significantly reduced if vinorelbine is administered in combination with another active agent.

[0046] Taught herein is vinorelbine or its pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form or a pharmaceutical composition comprising same for use in managing a subject having a loss of pregnancy event associated with the placenta. In this regard, enabled herein is the use of vinorelbine or its pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form in the manufacture of a medicament for treating a subject with a loss of pregnancy event.

[0047] In an embodiment, enabled herein is vinorelbine or its pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form or a pharmaceutical composition comprising same for use in treating a subject with a missed miscarriage or needing a termination of pregnancy. In this regard, enabled herein is the use of vinorelbine or its pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form in the manufacture of a medicament for treating a subject with a missed miscarriage or needing a termination of pregnancy.

[0048] Taught herein is vinorelbine or its pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form or a pharmaceutical composition comprising same for use in treating a human female subject with a missed miscarriage or needing a termination of pregnancy. In this regard, enabled herein is the use of vinorelbine or its pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form in the manufacture of a medicament for treating a human female subject with a missed miscarriage or needing a termination of pregnancy.

[0049] As indicated above, vinorelbine may be used alone or in combination with another agent such as a prostaglandin analog (e.g. misoprostol), mifepristone (or both misoprostol and mifepristone), an EGFR inhibitor or a tyrosine inhibitor.

[0050] Pharmaceutical formulations comprising an active agent such as vinorelbine are described in Remington's Pharmaceutical Sciences (1990) 18th Ed., Mack Publishing, Company. The term "pharmaceutically acceptable salt" (or solvate) refers to physiologically and pharmaceutically acceptable salts of vinorelbine and, if relevant, agents used in combination with vinorelbine.

[0051] The vinorelbine compound of the present invention or pharmaceutically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative or biosimilar thereof may be administered as such or in the form of a suitable prodrug.

[0052] The term "prodrug" refers to a compound, which is a drug precursor and which, following administration and absorption, release the drug *in vivo* via some metabolic process.

[0053] Prodrugs include those that increase the bioavailability of the active agent (e.g. by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the active agent to a specific biological organ (e.g. the placenta). Thus, examples of suitable prodrugs of the substances according to the present invention include compounds modified at one or more reactive or derivatizable groups of the active agent (e.g. vinorelbine).

[0054] The agents according to the present invention including vinorelbine may be in the form of salts. The salts of the compounds of the present invention are pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts.

[0055] The pharmaceutically acceptable salts include acid addition salts, base addition salts, salts of pharmaceutically acceptable esters and the salts of quaternary amines and pyridiniums. The acid addition salts are formed from a compound of the invention and a pharmaceutically acceptable inorganic or organic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, toluenesulphonic, benzenesulphonic, acetic, propionic, ascorbic, citric, malonic, fumaric, maleic, lactic, salicyclic, sulfamic or tartaric acids. The counter ion of quaternary amines and pyridiniums include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, sulfamate and tartrate. The base addition salts include but are not limited to salts such as sodium, potassium, calcium, lithium, magnesium, ammonium and alkylammonium. The salts may be made in a known manner, for example by treating the compound with an appropriate acid or base in the presence of a suitable solvent.

[0056] The compounds useful according to the present invention may be in crystalline form and/or in the form of solvates (e.g. hydrates) and it is intended that all of these forms be within the scope of the present invention. The term "solvate" is a complex of variable stoichiometry formed by a solute (in this case, a thyroid hormone agonist compound of the present invention) and a solvent. Such solvents should not interfere with the biological activity of the solute. Methods of solvation are generally known within the art.

[0057] In an aspect, the vinorelbine alone or in combination with another active agent is/are provided as a composition with a pharmaceutically acceptable carrier or diluent or excipient. Pharmaceutically acceptable vehicles and/or diluents and/or excipients include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active agent, use thereof in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0058] The compounds or pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or *via* an implanted reservoir. The administration as used herein includes intravenous, intraperitoneal, intrauterine, percutaneous, intranasal, subcutaneous, intramuscular, intra-articular or by infusion techniques. In an embodiment, the route of administration is *via* oral administration.

[0059] Hence, in one aspect, the vinorelbine or pharmaceutical compositions comprising same or together with another agent are administered in any orally acceptable dosage form. Examples of suitable dosage forms include, but are not limited to, capsules, tablets, syrups, aqueous suspensions and solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include, for example, lactose. When aqueous suspensions are required for oral use, the active ingredient

is combined with emulsifying and suspending agents.

[0060] Sterile injectable forms of the compositions of the present invention may be aqueous or an oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid or other dosage forms may also be used for the purposes of formulation.

[0061] Alternatively, vinorelbine or pharmaceutical compositions comprising same or together with another agent are administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0062] In another aspect, vinorelbine or pharmaceutical compositions comprising same alone or together with another active agent of this invention are administered topically. For topical applications, the compositions may be formulated in a suitable ointment containing

the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0063] In another aspect, the compounds or pharmaceutical compositions are administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons and/or other conventional solubilizing or dispersing agents.

[0064] As will be readily appreciated by those skilled in the art, the route of administration and the nature of the pharmaceutically acceptable carrier will depend on the nature of the condition and the subject (e.g. human or non-human animal) to be treated. The choice of a particular carrier or delivery system, and route of administration could be readily determined by a person skilled in the art. In the preparation of any formulation containing the active agent (e.g. vinorelbine), care should be taken to ensure that the activity of the agent is not destroyed in the process and that the agent is able to reach its site of action without being destroyed. Similarly the route of administration chosen should be such that the compound reaches its site of action.

[0065] It is especially advantageous to formulate the compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutically acceptable vehicle. The specification for the novel dosage unit forms of the present invention are dictated by and

directly dependent on (a) the unique characteristics of the active agent (e.g. vinorelbine) and the particular therapeutic effect to be achieved (cytotoxicity of placenta cells); and (b) the limitations inherent in the art of compounding the active agent for the treatment of an adverse gynecological condition associated with the placenta.

[0066] Therapeutic kits or pharmaceutical packs are further contemplated herein. In an embodiment, the vinorelbine may be administered as the sole active agent or in combination with one or more active agents such as vinorelbine in combination with a prostaglandin analog (e.g. misoprostol), mifepristone (or both misoprostol and mifepristone), an EGFR inhibitor or a tyrosine kinase inhibitor. In this regard, vinorelbine may be co-formulated with the other active agent or a pharmaceutical kit is provided whereby vinorelbine and one or more other active agents are co-mixed prior to administration or co-administered separately. Administration of vinorelbine and another agent may be simultaneous or sequential. By "sequential" means within seconds, minutes or hours, in either order. "Simultaneous" means in the same or different formulation.

[0067] Further taught herein is a method for predicating whether a loss of pregnancy event in a subject will be successfully managed comprising:

(i) administering to the subject one or more doses of vinorelbine alone or in combination with another active agent; and

(ii) measuring the concentration of β-hCG in body fluid from the subject;

wherein a reduction in the concentration of β-hCG is predictive of successful treatment of the loss of pregnancy event.

[0068] In addition, enabled herein is a method for predicating whether a missed miscarriage or termination of pregnancy in a subject will be successfully treated comprising:

(i) administering to the subject one or more doses of vinorelbine alone or in combination with another active agent; and

(ii) measuring the concentration of β-hCG in body fluid from the subject;

wherein a reduction in the concentration of β-hCG is predictive of successful elimination of the conceptus.

EXAMPLES

[0069] Aspects disclosed herein are further described by the following non-limiting Examples.

EXAMPLE 1

Placenta cell viability of the treatment with vinorelbine

[0070] Vinorelbine is a vinca alkaloid which disrupts the cytoskeleton of cells. It binds β-tubulin of microtubules and disrupts microtubule dynamics. Cells cannot progress from metaphase to anaphase and this causes mitotic arrest and cell death (Jassem *et al.* (2001) *Ann Oncol 12(10)*:1375-1381).

EXAMPLE 2

Minimalization of side effects

[0071] To minimalize side effects of vinorelbine (*e.g.* Jassem *et al.* (2001) *supra*), a low dose oral formulation is provided. A single dose is also trialed. Side effects are assessed by monitoring hemoglobins and neutrophil counts. If nausea, vomiting or diarrhoea is observed then these are symptomatically treated (e.g. ondansetron for nausea and loperamide for diarrhoea). Fertility is also monitored. It is proposed herein that low dose vinorelbine successfully treats an ectopic pregnancy or choriocarcinoma without adversely affecting fertility, especially at a low dose.

EXAMPLE 3

Effects of vinorelbine

[0072] It is proposed herein that vinorelbine is highly effective in inducing placental cell death and reducing hCG secretion from primary first trimester placenta tissue. Vinorelbine is tested on whether it activates potent apoptosis in placenta cells but not in human Fallopian tube explants. The efficacy of vinorelbine is tested in reducing human placenta tumor xenograft volume on SCID mice and mice exposed to vinorelbine are tested for fertility.

[0073] For *in vitro* experiments, methotrexate and vinorelbine are administered at different doses (from 10nM to 100,000nM). When used, gefitinib is combined with methotrexate at 8μM. Cells/tissues are treated for 24 hours and 48 hours. Methodology for the following standard techniques are: Tissue culture (Nilsson *et al.* (2013) *Obstet Gynecol 122(4)*:737-44) , RNA, qPCR, immunohistochemistry (Nilsson *et al.* (2013) *supra*; Onda *et al.* (2015) *Hypertension*:10.1161/hyptertensionaha.114.04781; Kaitu'u-Lino *et al. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 2014* placenta explants (Brownfoot *et al.* (2015) *Hypertension*), FACs sorting (Nilsson *et al.* (2013) *supra*), trophoblast purification ((Nilsson *et al.* (2013) *supra*; Onda *et al.* (2015) *supra*; Kaitu'u Lino *et al.* (2014) *supra*) and western blots (Onda *et al.* (2015) *supra*).

[0074] Normally distributed data are compared using parametric tests and non-normally distributed data are compared with non-parametric tests. For *in vitro* studies experiments are repeated at least three times and each experiment performed at least in triplicate. Statistics are done on the median (or means) obtained from the replicate experiments, depending on data distribution.

[0075] Placental cell lines (HTR8 and JEG3 cells) were treated with different doses of vinorelbine. Placenta cells are purified as previously described (Nilsson *et al.* (2013) *supra*). They are treated with different doses (10-100,000nM) of vinorelbine, methotrexate, methotrexate + gefitinib, gefitinib alone (and vehicle control). Cell viability is measured by MTS assay (see Figure 2).

[0076] To compare the relative potencies, the EC50 is calculated for the drugs (dose that induces 50% cell death).

[0077] Vinorelbine is proposed to be significantly more effective than either methotrexate alone, or combination methotrexate + gefitinib in inducing death of placenta cells.

EXAMPLE 4

Studies of programmed cell death (apoptosis)

[0078] It is useful to confirm that vinorelbine induces cell death mainly by apoptosis rather than necrosis. Apoptosis incites less of an inflammatory response that may otherwise injure local tissues. In this Example, the number of apoptotic cells after treatment with vinorelbine is assessed.

[0079] Vinorelbine is expected to induce placenta cell death mainly by apoptosis rather than necrosis. Vinorelbine is expected to induce late apoptosis.

EXAMPLE 5

Studies of fertility

[0080] It is important to show that vinorelbine does not affect fertility. Women treated with methotrexate, for example, are asked to wait 3 months before conceiving to allow progression of 3 menstrual cycles. A shorter period of 1 month is tested in mice given their shorter estrous cycle (approximately 1 week) for the effect on fertility in mice exposed to vinorelbine.

[0081] Vinorelbine is administered by tail vein injection to wild type swiss mice. The drug (or vehicle controls) is administered by tail vein twice weekly (i.e. approximately mirroring the frequency of dosing for the xenograft studies). The middle dose that was effective in

regressing tumor size (2.5mg/kg) is to be used. After one month the mice are paired for breeding. It is proposed to sacrifice mice at about day 19 of pregnancy.

[0082] Parameters measured include 1) Number of fetuses' and implantations sites; 2) fetal crown rump length; 3) fetal weight; 4) placenta weights.

[0083] Mice exposed to vinorelbine are fertile. There was no difference in pups per litter, placental weight, pup weight or crown to rump length. AMH was measured in the blood of the mothers, which is a marker of ovarian reserve, which was not different between the groups.

[0084] These preclinical studies are expected to show vinorelbine is far more potent than methotrexate in inducing placenta cell death by apoptosis and regressing placental xenografts *in vivo*. They will also show vinorelbine does not affect fertility, nor causes apoptosis in human Fallopian tube. A set of preclinical studies are completed to justify translating vinorelbine to clinical use.

EXAMPLE 6

Combination of vinorelbine and gefitinib

[0085] Figure 1 shows the effects of a combination of gefitinib (GFT) and vinorelbine (VB) compared to GFT and methotrexate (MTX). VB doses were 10,000 times lower than MXT. Data show that VB + GFT is more potent at inducing cell death at a dose that is 10,000 times lower than MTX.

EXAMPLE 7

Pregnancy conceptus

[0086] *First trimester miscarriage or early pregnancy loss*. This occurs in 15% of all clinically recognized pregnancies. The complication includes missed miscarriage, whereby a failed pregnancy, diagnosed on ultrasound is retained spontaneous signs of evacuation.

The current medical management of early pregnancy loss is *via* prostaglandin analogs, such as misoprostol, which allows for the planned expulsion of non-viable pregnancy tissue (by inducing uterine contractility) and aims to be an alternative to traditional management of uterine aspiration (vacuum or suction aspiration). However, the standard dose of vaginal misoprostol has limited efficacy, with 15-40% of treated women requiring a second dose or ultimately requiring uterine evacuation, which results in prolonged treatment periods.

[0087] *Termination of pregnancy*. Currently the most effective treatment regime for medical termination of pregnancy is the combination of misoprostol which induces uterine contractility, and mifepristone (RU 486), an antiprogesterone and anti-glucocorticoid agent, which induces bleeding and shedding of the uterine lining and detaches the embryo from the uterine lining. Under current TGA guidelines in Australia combination misoprostol and mifepristone is only registered for use for termination of pregnancy up to 63 days (approximately 8 weeks of pregnancy), after which efficacy is reduced. After this time period surgical removal via uterine aspiration or dilation and evacuation, dependent on gestational age, are more commonly performed.

[0088] *Fetal resorption experiments to support missed miscarriage and termination of pregnancy*. Time-mated pregnant mice are treated at embryonic day 8 and again on day 11 aqnd culled on embryonic day 14 with 5mg/kg of vinorelbine or vehicle control. The inventors have shown in an animal model that this dose resolves placental mass without affecting future fertility. Mice are culled on embryonic day 15, with uterine horns removed and implantation sites examined for viable or resorbed fetuses (*i.e.* fetal loss).

[0089] The presence of fetal resorption provides evidence to support that: 1) vinorelbine has potential to clear missed miscarriage which would otherwise be removed via uterine aspiration; and 2) vinorelbine has potential as a medical alternative for termination of pregnancy.

[0090] A mouse gestation is 20 days. However, relative to stage of development, embryonic day 8 to 12 is around late first trimester of pregnancy in humans.

EXAMPLE 8

Effect of vinorelbine on placenta cell viability and proliferation

[0091] The ability for vinorelbine to reduce placenta cell viability was assessed in two placenta cell lines (A;HTR8, B; JEG3) using a MTS cell viability assay. Results are shown in Figures 2A through D. Treatment with vinorelbine induced a significant dose dependent reduction in cell viability in both cell types, which was more significant than either methotrexate alone (MTX) or methotrexate plus gefitinib (MTX + GFT).

[0092] The effect of vinorelbine on placenta cell (HTR8) proliferation was assessed using xCELLigence (C). Vinorelbine reduced HTR8 proliferation in a dose-dependent manner and appeared to do so earlier than methotrexate or methotrexate plus gefitinib. When data are analyzed at 48h post plating (D) it was found that proliferation was reduced at 1, 10 and 100μM of vinorelbine, but no significant effect of methotrexate for methotrexate + gefitinib compared to control. Data expressed as mean±SEM. *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$ *vs.* control. Together these data show that vinorelbine is more potent at reducing placenta cell viability and inhibiting proliferation than methotrexate alone or combination methotrexate plus gefitinib.

EXAMPLE 9

Mechanisms via which vinorelbine induces cell death of placenta cells

[0093] The effect of Vinorelbine on cell cycle progression in HTR8 cells was assessed using FACs analysis (Figures 3A through G). Vinorelbine at 1μM (B) and 10μM (C) inhibits cell cycle progression, with cells arrested in the G2 phase of mitosis. The proportion of cells in G1, S and G2 is graphically represented in n=3 replicates (D). Compared to control (0 vinorelbine), there are significantly more cells halted at G2 in the 1μM and 10μM vinorelbine treated groups.

[0094] To further assess the effects of vinorelbine in HTR8s, flow cytometry was undertaken to determine whether vinorelbine enhances cells death and apoptosis. Treating with combination methotrexate + gefitinib and vinorelbine alone significantly reduced the percentage of live HTR8 cells (E). Vinorelbine alone significantly increased the percentage of apoptotic HTR8 cells (F) assessed *via* Annexin V expression. No significant changes was found in the percentage of dead cells (G). Data expressed as mean±SEM. *$p<0.05$, **$p<0.01$. Together these data demonstrate that vinorelbine's mechanism for reducing cell viability and cellular proliferation in placenta cells occurs as a result of impairment of the cell cycle at G2 and *via* increased apoptosis.

EXAMPLE 10

Effect of vinorelbine on human Fallopian tubes

[0095] For preservation of future fertility, it is important that vinorelbine does not cause and damage to the human Fallopian tube. Human Fallopian tubes were obtained at hysterectomy (from women of child-bearing age). Human Fallopian tubes were treated *ex vivo* with vinorelbine and the effect on apoptotic markers BCL 2 and BAX protein expression determined *via* western blot (Figure 4A). Densitometric analysis of western blots performed on n=3 tubes (From 3 separate patients) confirmed no effect (Figures 4B, C). It is proposed to collect n=8 Fallopian tubes in total in order to assess other apoptotic markers, including caspase-3 and PARP. A cell death stain is also be performed.

[0096] Preliminary data suggest that vinorelbine does not upregulate markers of apoptosis in human Fallopian tubes.

EXAMPLE 11

Effect of vinorelbine on mouse fertility

[0097] To determine whether vinorelbine would affect future fertility, breeding experiments in mice were undertaken (Figure 5). Intravenous administration of the highest dose of 5mg/kg of vinorelbine to female mice (n=7 per a group) 4 weeks prior to breeding

did not alter litter size (A), fetal weight (B), placental weight (C), crown to rump length (D), fetal/placenta ratio (E) or serum anti-Mullerian hormone (F).

[0098] In the clinic, females are advised to wait a minimum of three months post methotrexate treatment for ectopic pregnancy before attempting to conceive again. For future studies it is planned to repeat this experiment with 3 doses of 2.5mg/kg vinorelbine (as performed in xenograft experiments) treatment before breeding (n=7 mice/group). Exposure to vinorelbine does not affect future fertility.

[0099] This experiment shows that mice given a large dose of vinorelbine while not pregnant still retain the ability to fall pregnant.

EXAMPLE 12

Combination of vinorelbine and erlotinib

[0100] Placenta cells (HTR8/SVneo) were utilised as previously described (Nilsson *et al.* (2013) *supra*) and treated with 10nM vinorelbine alone or in the presence of the EGFR inhibitor erlotinib at 4μM or 8μM. Cell viability was measured by MTS assays. As shown in Figure 6, the combination of vinorelbine with the EGFR inhibitor erlotinib enhanced placental cell death, evidenced by a greater reduction in placental cell viability when compared to placental cells that were exposed to either erlotinib alone or to vinorelbine alone. These data are consistent with the data shown in Figure 1 herein, demonstrating that EGFR inhibitors act synergistically with vinorelbine to induce placental cell death.

EXAMPLE 13

Effect of vinorelbine on pregnancy loss

[0101] Vinorelbine (n=9; 5mg/kg i.v.) or vehicle control (n=8) was administered to mice at day 8.5 and day 11.5 of pregnancy. At day 14.5, mice were culled and the uteri inspected for pup viability. Vinorelbine administration significantly reduced offspring viability when

administered during pregnancy (see Figure 7; left panel; ****$p<0.05$ vs Control). Vinorelbine administration also resulted in fetal resorption (see Figure 7; right panel).

[0102] Those skilled in the art will appreciate that the disclosure described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the disclosure contemplates all such variations and modifications. The disclosure also enables all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of the steps or features or compositions or compounds.

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CLAIMS:

1. A method of managing a loss of pregnancy event in a female subject, said method comprising administering to said subject an amount of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof effective to induce placenta cell death and eliminate a conceptus.

2. The method of Claim 1 wherein the female subject is a human female subject.

3. The method of Claim 2 wherein the human female subject has a missed miscarriage.

4. The method of Claim 2 wherein the human subject needs a termination of pregnancy.

5. The method of any one of Claims 1 to 4 further comprising administering vinorelbine, simultaneously or sequentially, with another active agent.

6. The method of Claim 5 wherein the other active agent is selected from the group consisting of a prostaglandin analog, an epidermal growth factor receptor (EGFR) inhibitor and a tyrosine kinase inhibitor.

7. The method of Claim 6 wherein the prostaglandin analog is misoprostol and/or mifepristone.

8. The method of Claim 6 wherein the EGFR is selected from the group consisting of gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and pertuzumab/omnitarg.

9. The method of Claim 7 wherein the tyrosine kinase inhibitor is selected from the group consisting of trastuzumab, lapatinib and suitnib.

10. The method of any one of Claims 1 to 9 wherein the vinorelbine is given in an oral dosage form.

11. The method of Claim 10 wherein from 1 to 5 oral doses of vinorelbine is administered.

12. The method of Claim 10 or 11 wherein from 1 to 200mg of vinorelbine is administered orally.

13. The method of Claim 12 wherein from 10 to 100mg of vinorelbine is administered orally.

14. The method of any one of Claims 5 to 13 wherein vinorelbine is administered with a separate or combined oral dosage form of another active agent.

15. Use of vinorelbine or a pharmacologically active and pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, derivative, biosimilar or prodrug form thereof in the manufacture of a medicament for the treatment of a loss of pregnancy event in a human subject.

16. The use of Claim 15 wherein the human female subject has a missed miscarriage or is in need of a termination of pregnancy.

17. The use of Claim 15 or 16 further comprising use of another active agent to be administered simultaneously or sequentially.

18. The use of Claim 17 wherein the other active agent is selected from the group consisting of a prostaglandin analog, an epidermal growth factor receptor (EGFR) inhibitor and a tyrosine kinase inhibitor.

19. The use of Claim 18 wherein the EGFR is selected from the group consisting of gefitinib, erlotinib/tarceva, certuximab, lapatinib/tykerb, panitumumab/vectibix, theraCIMh-R3/nimotuzumab, matuzumab, MDX447, PKI166, Cl-1033, EKB-569, GW2016, zalutumumab and pertuzumab/omnitarg.

20. The use of Claim 18 wherein the tyrosine kinase inhibitor is selected from the group consisting of trastuzumab, lapatinib and suitnib.

21. The use of any one of Claims 15 to 20 wherein the medicament comprising vinorelbine is given in an oral dosage form.

22. The use of Claim 21 wherein from 1 to 5 oral doses of vinorelbine is to be administered.

23. The use of any one of Claims 15 to 22 wherein the medicament comprising vinorelbine and other active agents is given in the same or separate oral dosage forms.

24. A therapeutic protocol to managing a female human subject with a loss of pregnancy event, said protocol comprises the administration of from 1 to 5 doses of vinorelbine at from 1mg to 200mg per dose.

25. A therapeutic protocol to treat a human female subject with a missed miscarriage or in need of a termination of pregnancy, said protocol comprises the administration of from 1 to 5 doses of vinorelbine at from 1mg to 200mg per dose.

26. The therapeutic protocol of Claim 24 or 25 wherein said protocol comprises a single dose of vinorelbine at from 1mg to 200mg per dose.

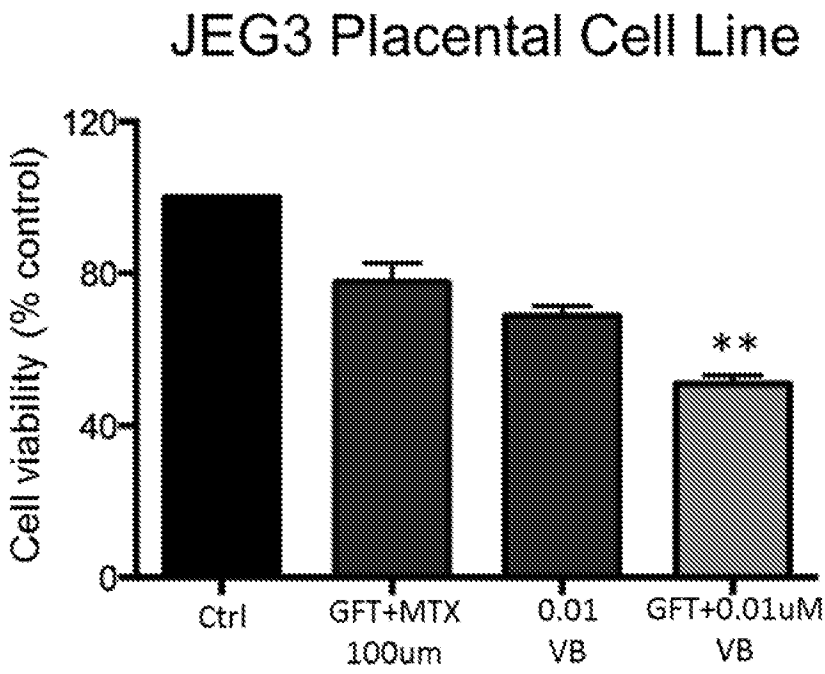
27. A method for predicating whether a loss of pregnancy event in a subject will be successfully treated comprising:

(i) administering to the subject one or more doses of vinorelbine alone or in

combination with another active agent; and

(ii) measuring the concentration of β-hCG in body fluid from the subject;

wherein a reduction in the concentration of β-hCG is predictive of successful treatment of the loss of pregnancy event.


JEG3 Placental Cell Line
Cell viability (% control)
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Ctrl
GFT+MTX 100um
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Figure 1

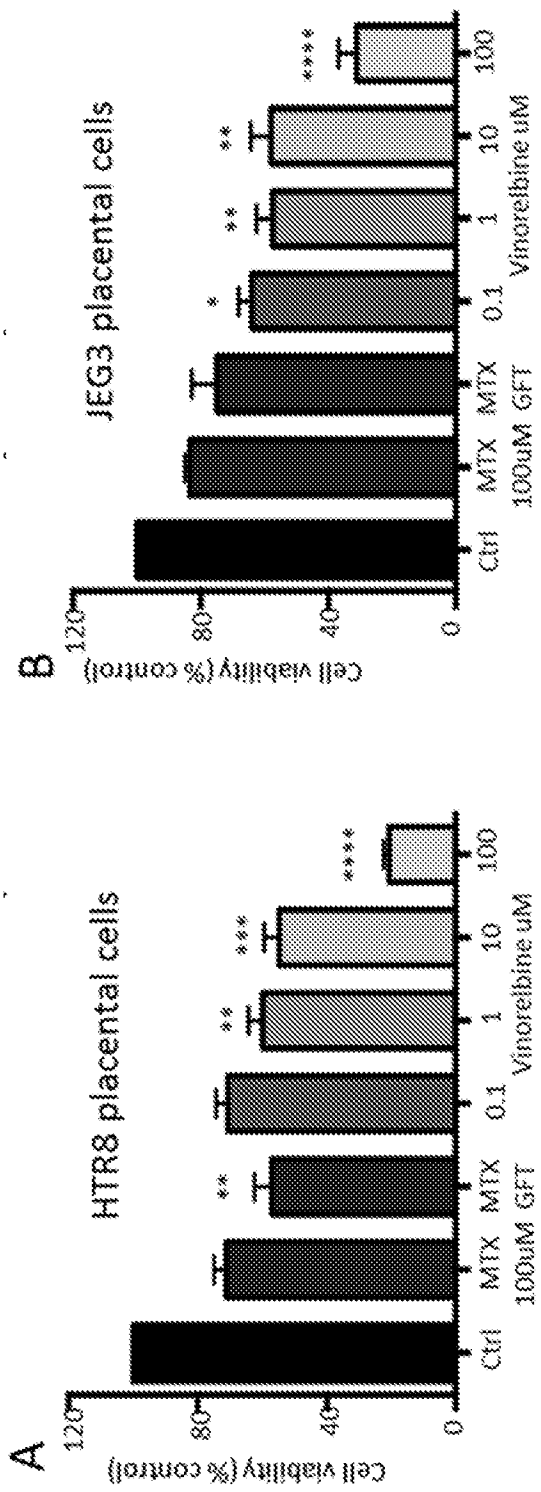


Figure 2A and B

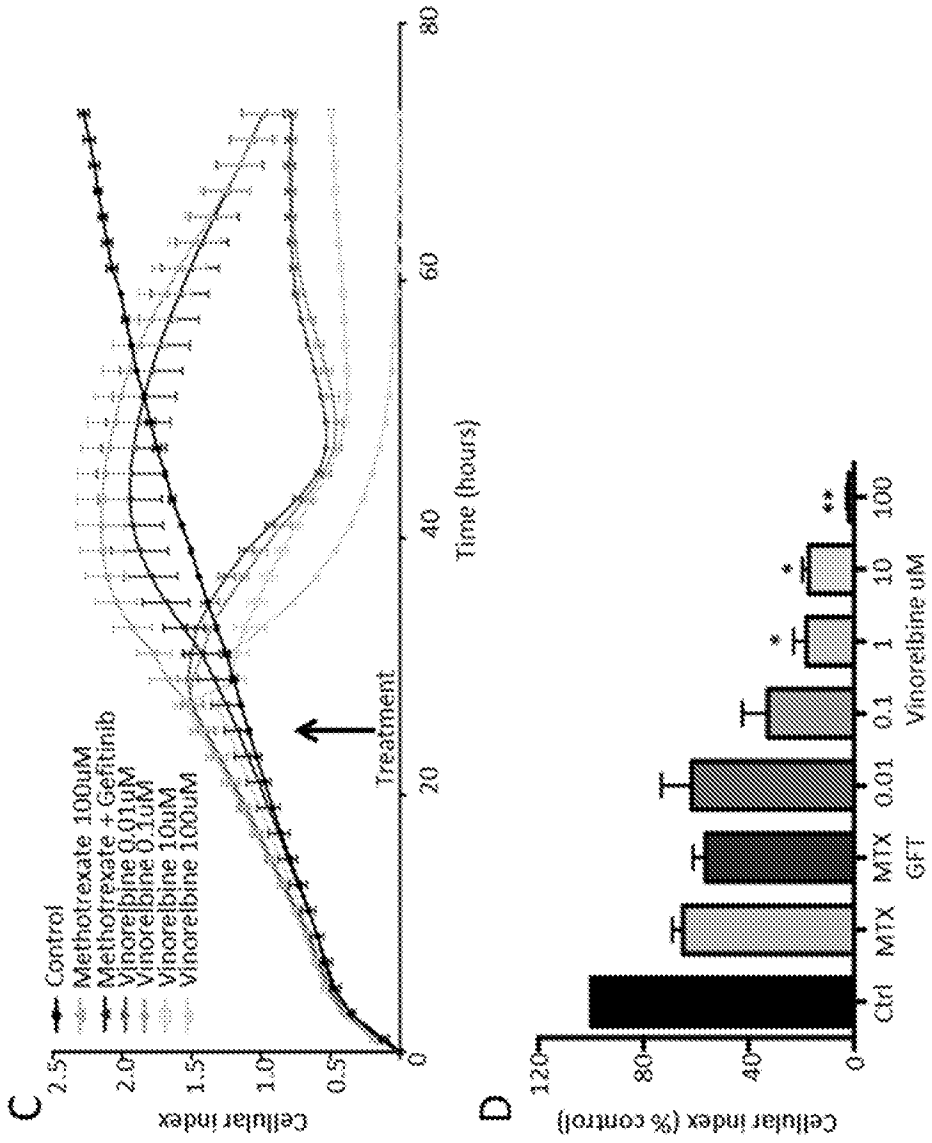
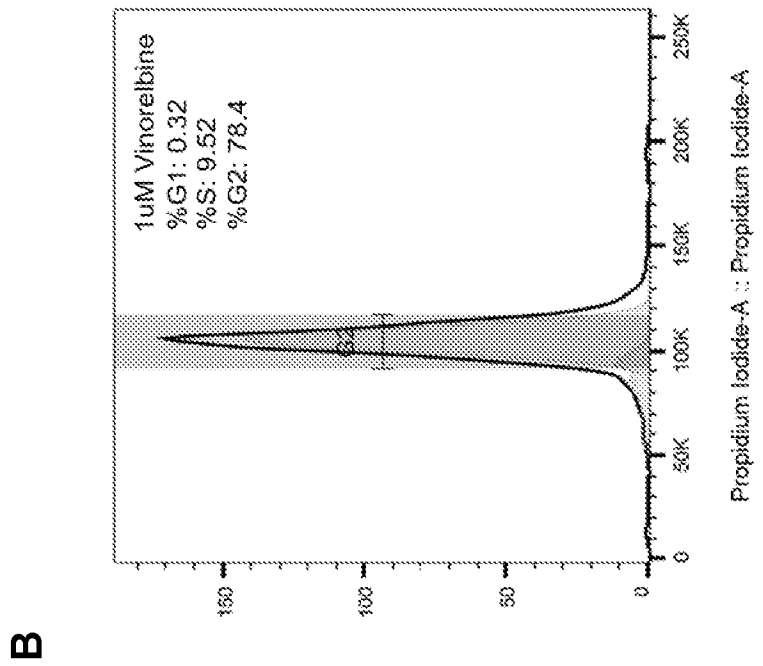


Figure 2C and D



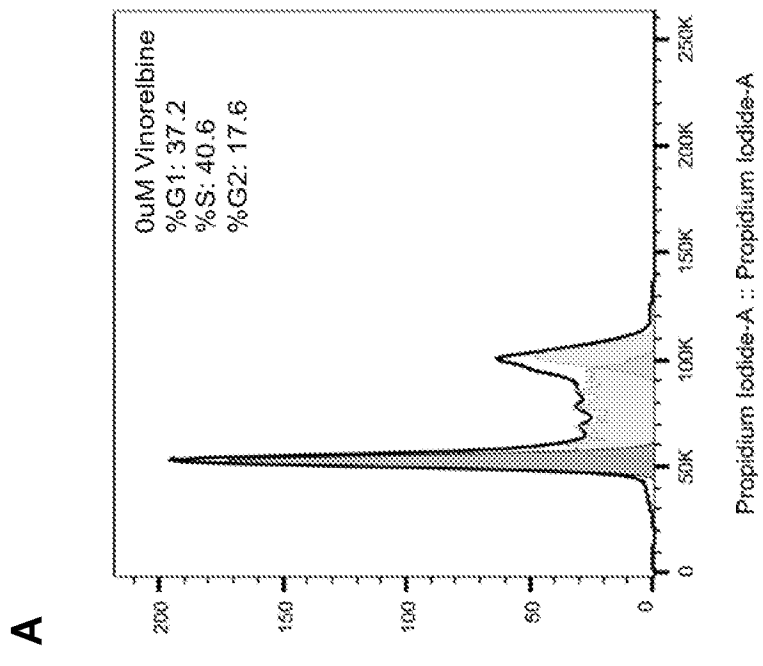


Figure 3A and B

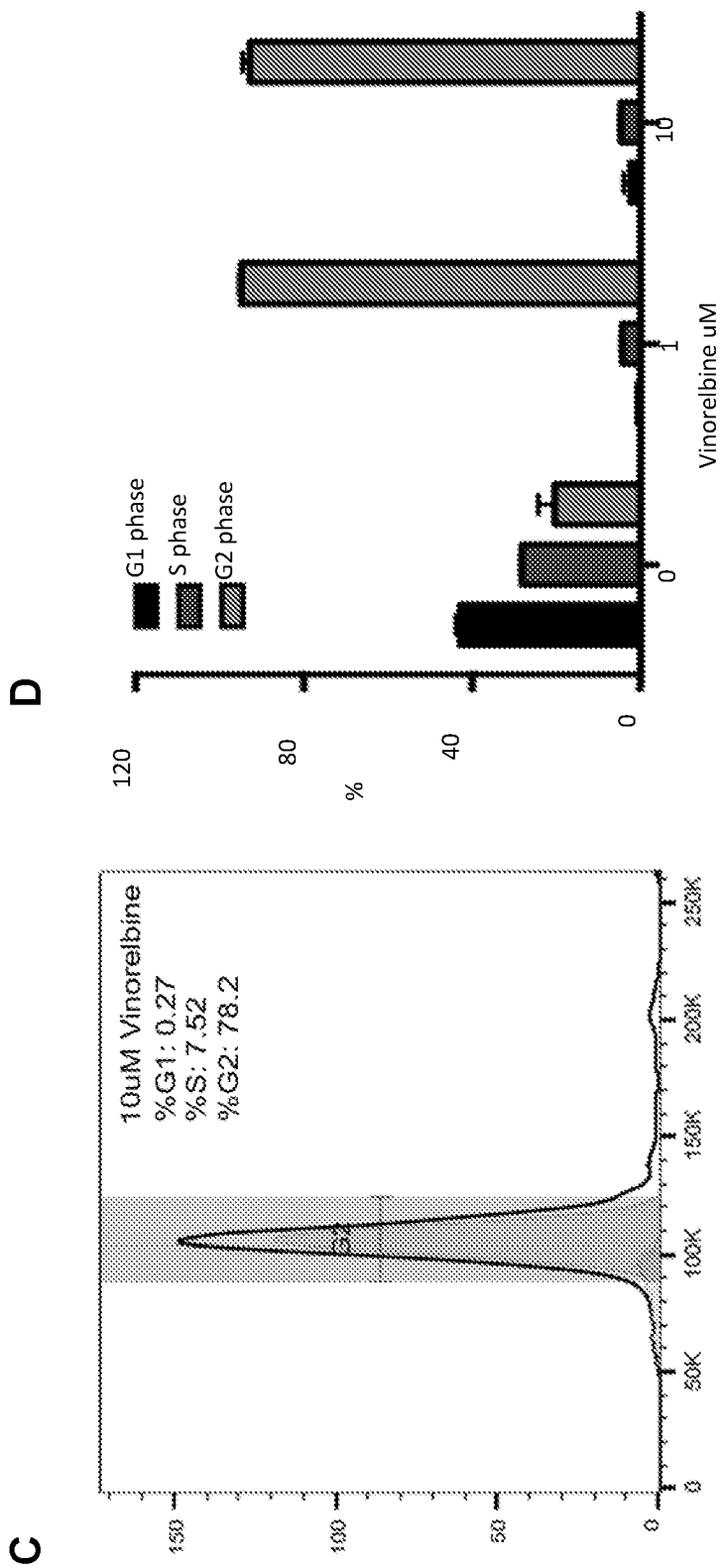


Figure 3C and D

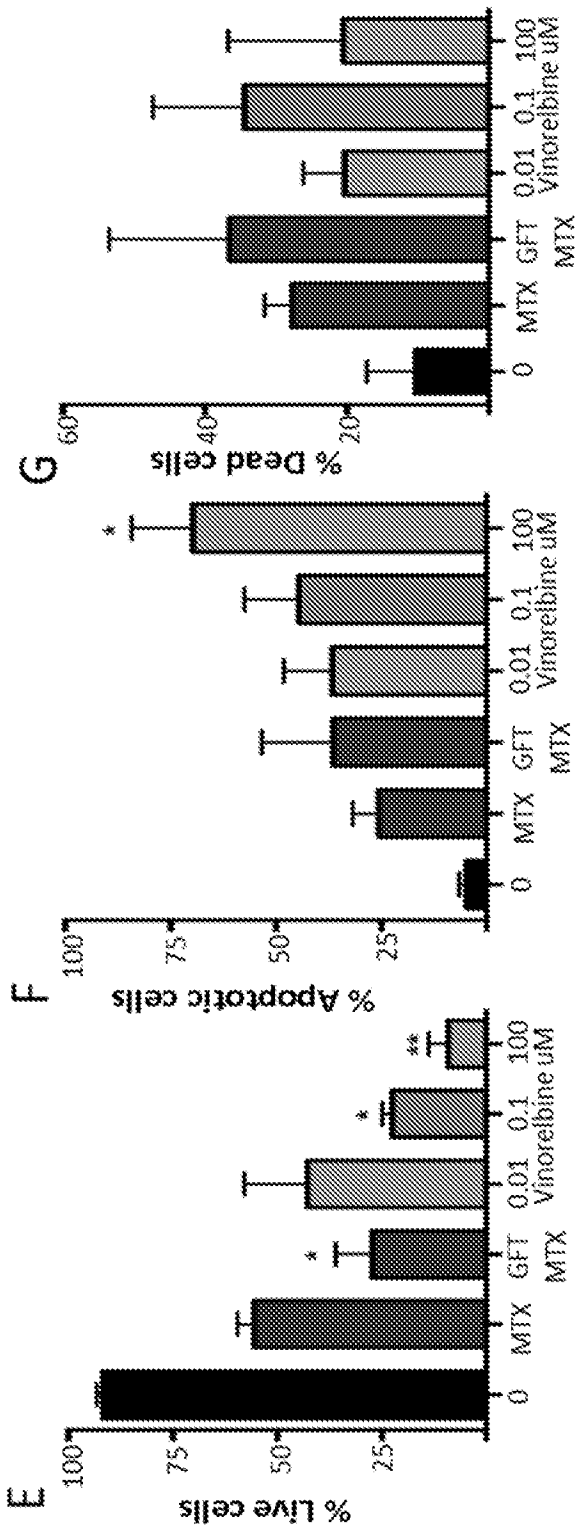
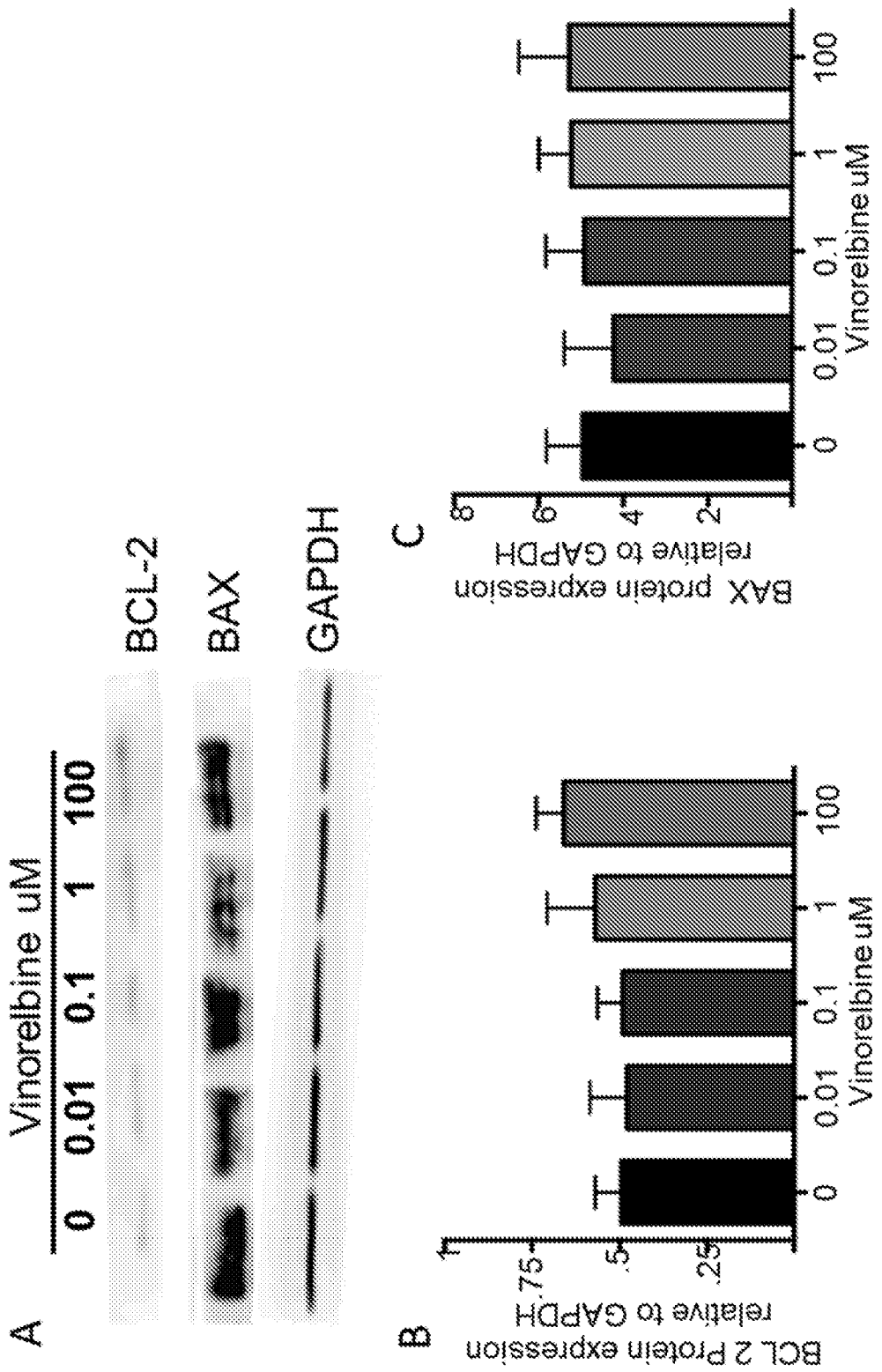


Figure 3E to G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BAX
GAPDH
B
BCL 2 Protein expression
relative to GAPDH
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.5
.25
0 0.01 0.1 1 100
Vinorelbine uM
C
BAX protein expression
relative to GAPDH
8
6
4
2
0 0.01 0.1 1 100
Vinorelbine uM

Figure 4

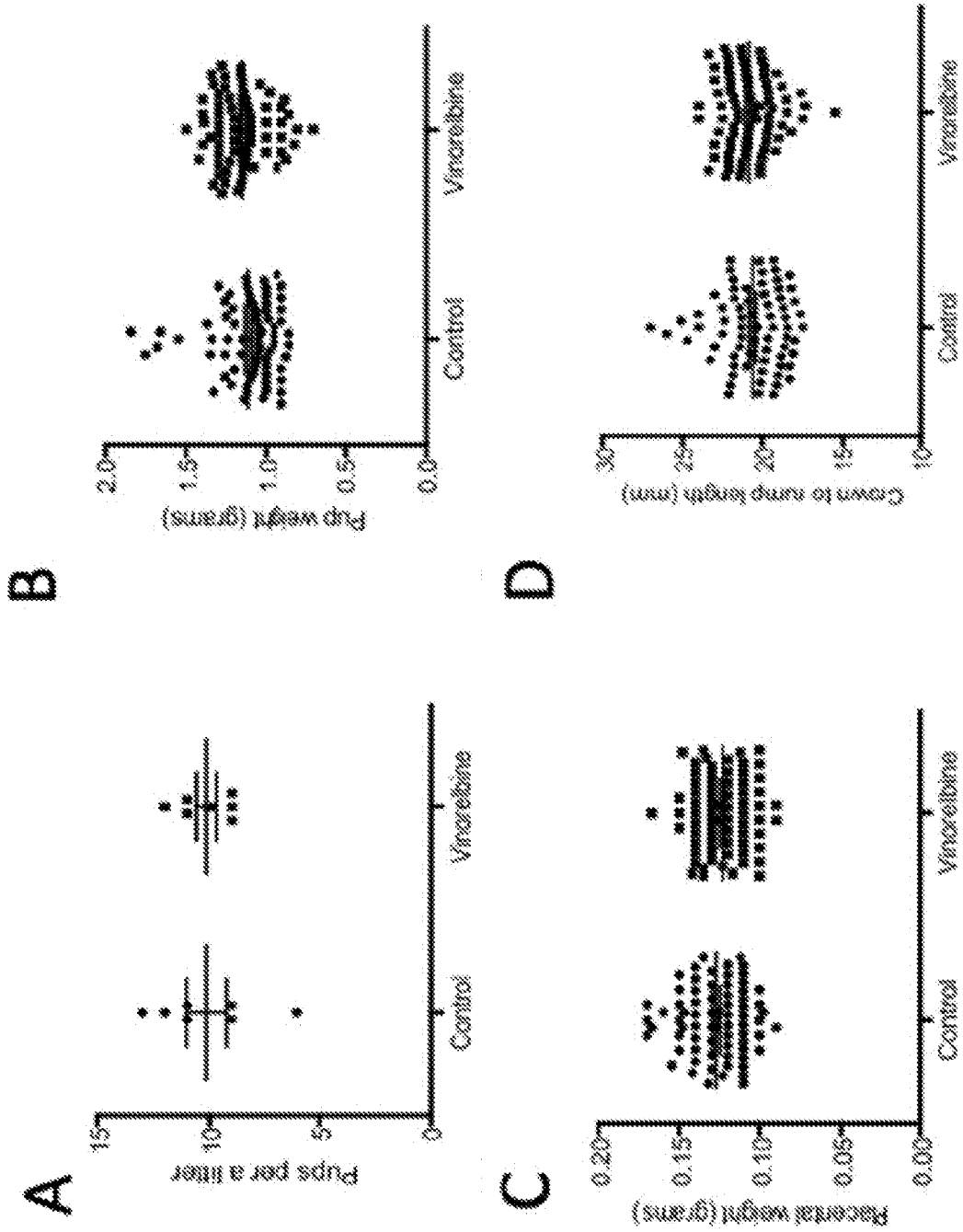

Figure 5A to 5D

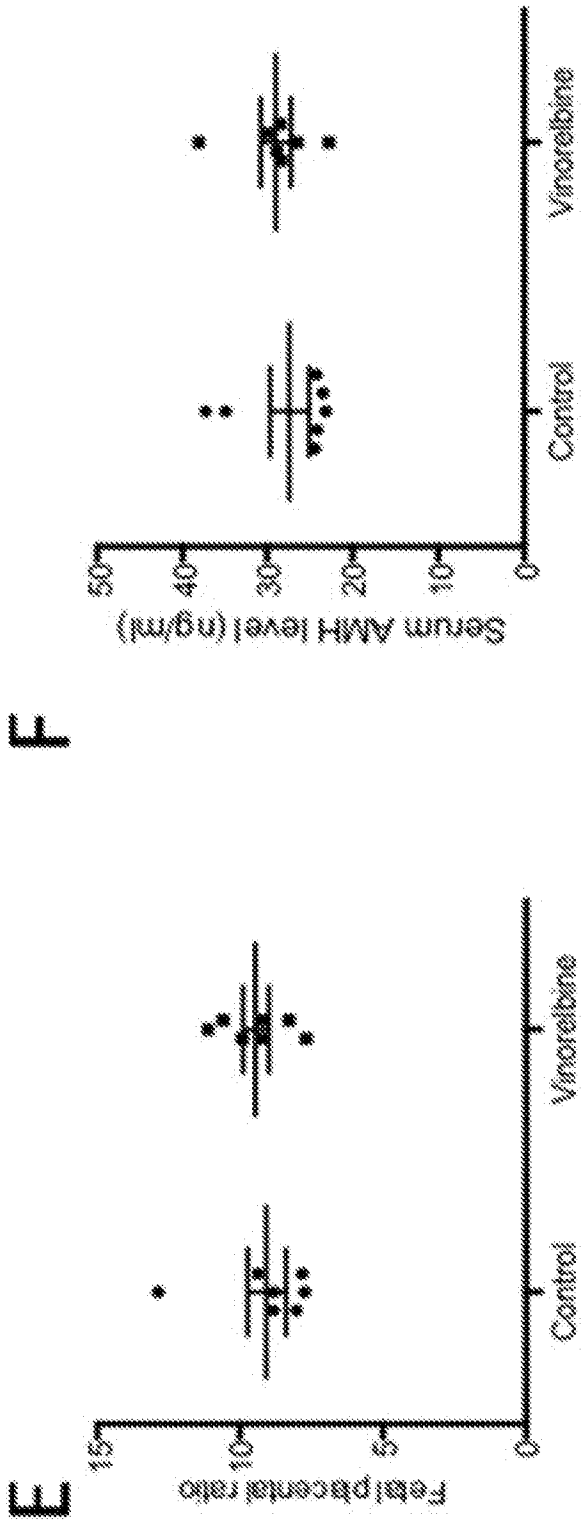

Figure 5E and 5F

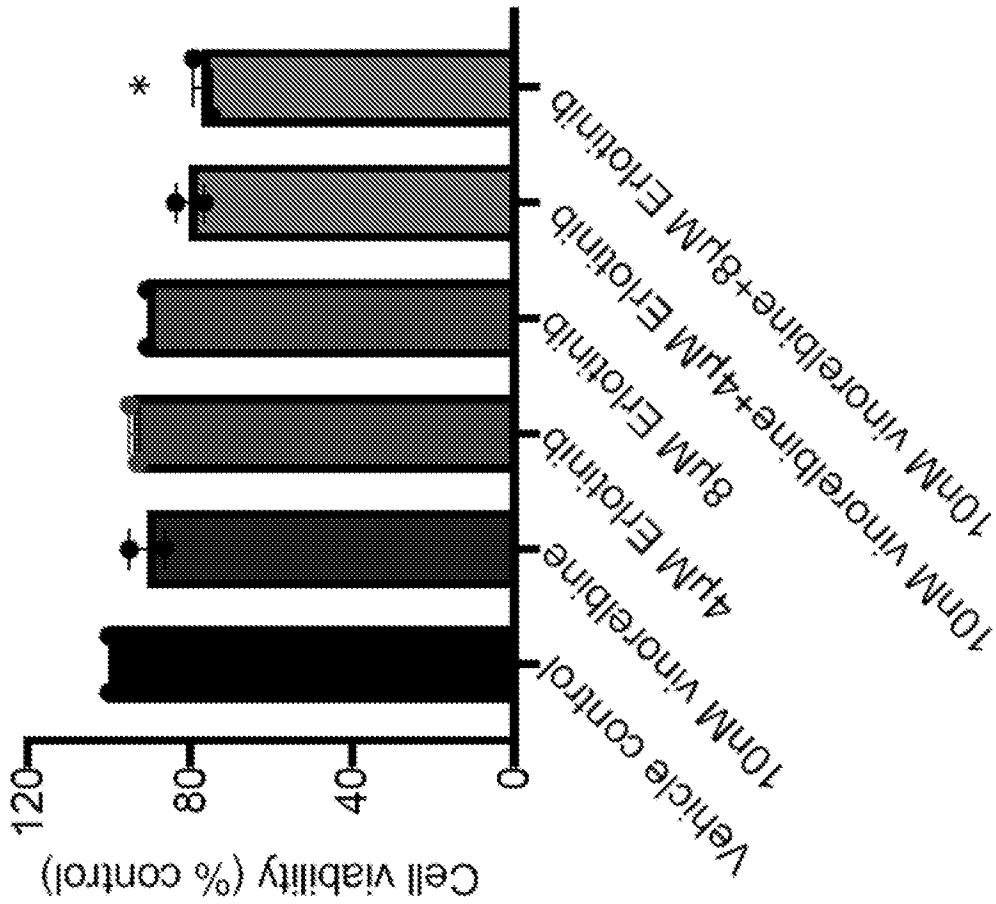
Cell viability (% control)
120
80
40
0
*
Vehicle control
10nM vinorelbine
4μM Erlotinib
8μM Erlotinib
10nM vinorelbine+4μM Erlotinib
10nM vinorelbine+8μM Erlotinib

Figure 6

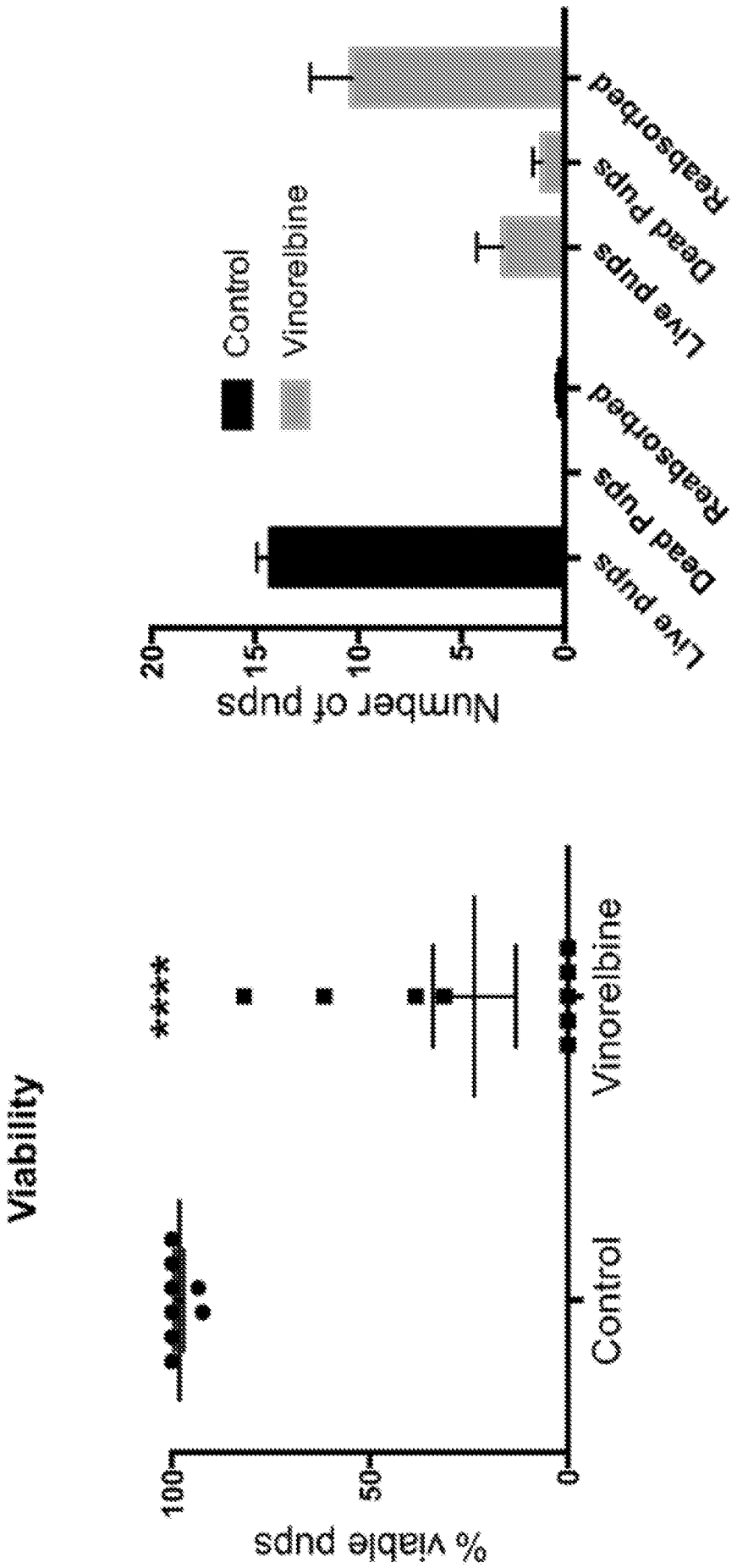
Viability
****
% viable pups
100
50
0
Control
Vinorelbine
Number of pups
20
15
10
5
0
Live pups
Dead Pups
Reabsorbed
Live pups
Dead Pups
Reabsorbed
Control
Vinorelbine

Figure 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2019/051212

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/475 (2006.01) A61P 15/04 (2006.01) A61K 31/5377 (2006.01) A61K 31/122 (2006.01)

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)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATENW, CAPLUS EMBASE, BIOSIS and MEDLINE keywords: VINORELBINE; NAVELBINE; PREGNANCY; GESTATION; ABORTION; MISCARRIAGE; PLACENTA; EMBRYO; FETUS; CONCEPTUS; TROPHOBLAST synonyms and associated terms. CAPLUS, REGISTRY: compound names: vinorelbine and navelbine synonyms and associated terms. PATENW IPC/CPC marks: A61K 31/475; A61P 15/04. GOOGLE keywords: VINORELBINE; NAVELBINE; PREGNANCY; MISCARRIAGE; PLACENTA CELL DEATH; applicant/inventor names; and synonyms and associated terms. Applicant/Inventors names were also searched in internal databases provided by IP Australia.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] 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

"D" document cited by the applicant in the international application

"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
13 December 2019	13 December 2019
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Tracey Huynh AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262832144

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2018/085877 A1 (THE UNIVERSITY OF MELBOURNE) 17 May 2018 see abstract, paragraph [0009], [0016], [0029], [0030], [0034], [0044], [0047], [0048], examples and claims see paragraph [0034], [0066] and claim 6	1-6 and 8-27 7
X	HASTIE, R. et al., 'Vinorelbine Potently Induces Placental Cell Death, Does Not Harm Fertility and is a Potential Treatment for Ectopic Pregnancy', EBioMedicine, 2018, Vol. 29, pages 166-176 see title and abstract, page 173 'Discussion', page 171 section 3.2	1-2, 4, 10-13, 15-16, 21-27
X	HASTIE, R. et al., 'New medical therapeutics for ectopic pregnancy', Reproductive Sciences, 64th Annual Scientific Meeting of the Society for Gynecologic Investigation, 2017, Vol. 24, No. 1, Supp. Supplement 1, pages 268A-269A. Abstract Number: S-109 see 'Methods and Results' and 'Conclusions'	1-2, 4, 15-16 and 27
Y	AU 2010212513 A1 (MONASH UNIVERSITY) 21 April 2011 see page 18 line 31-32	7
A	RU 1803119 C (RESPUB RODILNYJ DOM) 23 March 1993 & English translation retrieved from ESPACENET database see whole document	1-27
A	O. MIR, P. et al., 'Emerging therapeutic options for breast cancer chemotherapy during pregnancy', Annals of Oncology, 2008, Vol. 19, Issue 4, pages 607–613 see whole document	1-27
A	CUVIER C. et al., 'Vinorelbine in Pregnancy', European Journal of Cancer, 1997, Vol. 33, No. 1, pages 168-169 see whole document	1-27

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2019/051212**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2018/085877 A1	17 May 2018	WO 2018085877 A1	17 May 2018
		AU 2016429224 A1	20 Jun 2019
		US 2019282550 A1	19 Sep 2019
AU 2010212513 A1	21 April 2011	AU 2010212513 A1	21 Apr 2011
		AU 2010212513 B2	25 Aug 2016
		CA 2713610 A1	02 Apr 2011
		US 2011110933 A1	12 May 2011
		US 8858939 B2	14 Oct 2014
RU 1803119 C	23 March 1993		

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.