Supplementary Information

Supplementary Table 1. Scoring for assessment of preclinical candidate medicines for pre-eclampsia.

a) Quality of evidence for preclinical candidate medicines for pre-eclampsia. Calculation of candidate quality of evidence is first calculated per study. For each variable, the study is assigned a coding value. These coding values are then added together to obtain the overall quality of evidence for that study (max total coding value of 48 per study). For candidates with multiple studies, the average score among all associated studies will then be calculated. Once this score has been determined, the final coding value (regarding number of studies per candidate) can be added to this average score. This creates the final quality of evidence score given to the preclinical drug candidates' (max total coding value of 53 per candidate).

Variable	Answer options	Answer criteria	Coding value
Clearly stated aims/objectives	Adequately scored	Well defined and specific aims and objectives to the study.	4
	Inadequately scored	Hypothesis stated but no set aim mentioned beyond testing the drug (vague aims).	2
	Not specified	No aims, hypothesis and/or objectives mentioned.	0
Detailed explanation of sample size calculation	Adequately scored	Well defined sample size calculation: all calculations and components reported; sample size stated.	4
	Inadequately scored	Sample size stated, but no calculation present.	2
	Not specified	No mention of sample size or calculation.	0
	Adequately scored	*For animal model:*	4

Detailed explanation of sampling technique		Pre-eclampsia animal model used. *For in vitro model:* Pre-eclampsia *in vitro* model used; cells taken from primary human tissue either from a patient with pre-eclampsia or cells are from a normal pregnancy and then placed under pre-eclampsia-like conditions (eg: hypoxia).	
	Inadequately scored	*For animal model:* Pregnant animal model used. *For in vitro model:* Cells taken from primary human tissue from a patient with normal pregnancy.	2
	Not specified	No information on population; non-pregnant model used.	0
Details of comparison group	Adequately scored	Vehicle control group mentioned, and details provided.	4
	Inadequately scored	Mention of comparison group with insufficient detail.	2
	Not specified	No mention of comparison group.	0
Detailed explanation of methodology	Adequately scored	Easy to comprehend procedure, explanation of novel terms and techniques.	4
	Inadequately scored	Somewhat vague procedure but can be followed appropriately or detailed but hard to follow, no missing information.	2
	Not specified	Confusing/vague procedures, novel terms/techniques not expanded upon, missing information/procedures.	0

Operator details	Adequately scored	Number of operators and training details identified.	4
	Inadequately scored	Number of operators or training details identified – one of the two.	2
	Not specified	Neither identified.	0
Randomisation	Adequately scored	Sequence generation and allocation concealment reported.	4
	Inadequately scored	Randomisation mentioned but not elaborated.	2
	Not specified	No mention of randomisation.	0
Method of outcome measurement	Adequately scored	Measurement of outcome/experiment performed has a clear rationale.	4
	Inadequately scored	Measurement of outcome/ experiment performed is mentioned but has a vague/no rationale.	2
	Not specified	Measurement of outcome is not mentioned.	0
Outcome assessor details	Adequately scored	Number of assessors and training details identified.	4
	Inadequately scored	Number of assessors or training details identified – one of the two.	2
	Not specified	Neither identified.	0
Blinding	Adequately scored	Blinding of operator, assessor and statistician maintained throughout study clearly specified and maintained throughout study.	4
	Inadequately scored	Blinding is mentioned but not elaborated.	2
	Not specified	No mention of blinding.	0
Statistical analysis	Adequately scored	Correct statistical analysis is performed and software package is mentioned.	4

	Inadequately scored	Correct statistical analysis is performed but no mention of software package.	2
	Not specified	No mention of statistical analysis or software package; wrong statistical analysis used.	0
Presentation of results	Adequately scored	Results/data from all experiments have been presented in a clear and concise manner either visually or in writing.	4
	Inadequately scored	Results/data from all experiments have been reported in a somewhat vague or overly complicated manner.	2
	Not specified	No mention of results or some results/data from experiments performed is missing.	0
Calculate average score from all associated studies for that drug candidate, then add coding value for next question.			
Number of studies per candidate	Five	Five studies performed on drug candidate.	5
	Four	Four studies performed on drug candidate.	4
	Three	Three studies performed on drug candidate.	3
	Two	Two studies performed on drug candidate.	2
	One	One study performed on drug candidate.	1

b) Product development for preclinical candidate medicines for pre-eclampsia.

Calculation of candidate product development is calculated per candidate. For each variable, the candidate is assigned a coding value. These coding values are then added together to obtain the overall candidate product development (max total coding value of 26).

Variable	Answer options	Answer criteria	Coding value
TRL1 – basic scientific research			
Have basic principles about the drug candidate been observed and reported?	Yes	Basic principles observed, published competitive landscape and market analysis report.	2
	Probably yes	Basic principles observed, drug being developed by pharma company.	1
	Probably no	Basic principles observed but no competitive landscape and market analysis report.	0
	No	No basic principles observed.	-1
	Unsure	Unknown or basic principles observed, and drug is being developed by an academic institute.	0
TRL2 – concept formulation			
Has a drug concept been formulated (development of hypothesis and experimental designs) and has a clear product profile been defined?	Yes	Drug concept formulated and product profile defined for a prevention or treatment of pre-eclampsia.	2
	To an extent	Drug concept formulated and product profile defined for a symptom management of pre-eclampsia.	1
	No	No drug concept formulated, and no product profile defined.	-1
	Unsure	Unknown.	0
TRL3 – mechanism of action			
Has efficacy been demonstrated in an	Yes	Strong evidence provided by the *in vitro* studies performed, demonstrate that the drug can be	2

in vitro model for pre-eclampsia?		used to prevent/treat pre-eclampsia.	
	To an extent	*In vitro* studies have provided some evidence that the drug works to prevent/treat pre-eclampsia, but they mention that future studies are needed to confirm this evidence.	1
	No	No evidence of efficacy in an *in vitro* model.	0
	Unsure	Unknown.	0
Has efficacy been demonstrated in an animal model for pre-eclampsia?	Yes	Strong evidence provided by the animal studies performed, demonstrate that the drug can be used to prevent/treat pre-eclampsia.	2
	To an extent	Animal studies have provided some evidence that the drug works to prevent/treat pre-eclampsia, but they mention that future studies are needed to confirm this evidence.	1
	No	No evidence of efficacy in an animal model.	0
	Unsure	Unknown.	0
Is the mechanism of action for the drug candidate known?	Yes	Repurposed drug. All of the following is known: target, pathway, or end-result/indication.	3
	Probably yes	Two of the following is known: target, pathway, or end-result/indication.	2
	Probably no	One of the following is known: target, pathway, or end-result/indication.	1
	No	Mechanism of action has not yet been discovered.	-1
	Unsure	Unknown.	0
Is there a proposed mechanism of action for how the drug	Yes	Drug is suspected to work via “this mechanism of action” against pre-eclampsia.	2

candidate acts against pre-eclampsia?	No	Drug seems to work against pre-eclampsia however it is unknown how it does so.	0
	Unsure	Unknown	0
Is the mechanism of action for how the drug candidate acts against pre-eclampsia evidenced in a pre-eclampsia model?	Yes	Drug works via “this mechanism of action” as evidenced in a pre-eclampsia model.	2
	No	Suspected mechanism of action has not been evidenced in a pre-eclampsia model.	0
	Unsure	Unknown.	0
Does the drug candidate improve pre-eclampsia outcomes?	Yes	Drug candidate has been shown to improve pre-eclampsia outcomes in an animal pre-eclampsia model.	2
	To an extent	Drug candidate has been shown to improve pre-eclampsia outcomes in an *in vitro* pre-eclampsia model OR it only improves pre-eclampsia outcomes as symptom management OR drug has not been tested for fetal outcomes only maternal outcomes.	1
	No	Either: 1- drug candidate has not shown improvements to pre-eclampsia outcomes in pre-eclampsia models OR 2. pre-eclampsia outcomes were not assessed in a pre-eclampsia model.	-1
	Unsure	Unknown.	0
TRL4 – toxicology and safety			
Has the drug demonstrated any safety concerns in pregnant and lactating women?	Yes	Safety concerns have been raised in a clinical safety trial or in a large retrospective cohort study in pregnant or lactating women.	-2
	To an extent	Safety concerns have been raised in one or two small retrospective cohort studies in pregnant or lactating women OR safety	-1

		concerns have been raised in preclinical studies.	
	No	No safety concerns in pregnant or lactating women.	1
	Unsure	Unknown.	0
Has a safe allowable human dose been established for the drug candidate?	Yes	Repurposed drug: safe dosage for humans has been approved for drug by FDA.	2
	To an extent	A safe dose for humans has been approved for novel candidates.	1
	No	No safe human dose had been established for this candidate.	0
	Unsure	Unknown.	0
Was an equivalent safe human dosage used in the study?	Yes	An acceptable safe human dosage was used in the studies.	1
	No	A safe human dosage was not used in the studies; dosage was higher than safe allowable dose used to demonstrate efficacy.	-2
	Unsure	Either unknown or safe allowable human dose has not been established.	0
TRL5 – Chemistry, Manufacturing and Control (CMC) & Absorption, Distribution, Metabolism and Excretion (ADME)			
Have formulation studies been performed for the drug candidate?	Yes	Repurposed drug. Novel candidates have mentioned that formulation studies have been published.	1
	No	Explicit mention that no formulation studies have been performed.	0
	Unsure	Unknown if formulation studies have been performed/no mention of formulation studies.	0
Is controlled production of the drug candidate performed under cGMP (current Good	Yes	Repurposed drug. Evidence needed for novel candidates to ensure that the candidate is manufactured under cGMP.	1
	No	Not manufactured under cGMP.	0
	Unsure	Unknown.	0

Manufacturing Practices)?			
Has a half-life been established for the drug candidate?	Yes	Half-life established.	1
	No	Half-life not established.	0
	Unsure	Unknown.	0
Is the metabolic pathway of the drug candidate known?	Yes	Metabolic pathway known.	1
	No	No research into metabolic pathway of the drug.	0
	Unsure	Unknown.	0
Are any potential drug-drug interactions known?	Yes	Proven interaction interactions with other drugs.	-2
	To an extent	Potential/unproven interaction with another drug.	-1
	No	No interactions with other drugs.	1
	Unsure	Unknown.	0

c) Implementability for preclinical candidate medicines for pre-eclampsia. Calculation of candidate implementability is calculated per candidate. For each variable, the candidate is assigned a coding value. These coding values are then added together to obtain the overall implementability (max total coding value of 11).

Variable	Answer options	Answer criteria	Coding value
Therapeutic indication	Prevent underlying aetiology	N/A	4
	Treat underlying aetiology	N/A	3
	Prevent and treat	N/A	4
	Symptom management	N/A	1
	Unsure	Unknown.	0
Route of administration	Intraarterial	N/A	1
	Intravenous	N/A	1
	Subcutaneous	N/A	2
	Oral	N/A	4
	Intraperitoneal	N/A	1
	Intramuscular	N/A	2
	Unspecified	Unknown.	0
Storage conditions – is cold chain required?	Yes	Storage/transport of drug within the range of +2°C to +8°C (cold chain).	-2
	No	Cold chain not required.	2
	Unsure	Unknown.	0
Place of development	Academic institute	N/A	1
	Private company	N/A	1
	Both	N/A	1
	Unsure	Unknown.	0

d) Threshold for ranking of potential for preclinical candidate medicines for pre-eclampsia. The summation of all coding values from the three domains are used to determine the final ranking of potential for each candidate. Quality of evidence accounts for 58.89% (max total coding value of 53), product development accounts for 28.89% (max total coding value of 26), and implementability accounts for 12.22% (max total coding value of 11) of the final score given to the preclinical candidates assessed. The maximum score a candidate can achieve is 90. The cut-off points as shown below were sense checked with experts in the field. The cut-off points and associated rankings allow candidates that are considered high potential by the systematic assessment to be scored as high.

Final ranking	**Preclinical cut-off points**
High potential	>55
Medium potential	41-54
Low potential	<40

Supplementary Data 1. Excel spreadsheet with analysis (raw data)

Supplementary Table 2. Explanation for excluded candidates

Candidate	Reason for Exclusion
CLR/RAMP agonists	Theoretical/hypothesised drug candidate.
Dasatinib	Studies report adverse effects of the drug candidate.
Kynurenine	Data not publicly available; private company researching under commercial intellectual property.
Menadione	Studies report adverse effects of the drug candidate.
MitoQ	Studies report adverse effects of the drug candidate.
Mycophenolate mofetil	Studies report adverse effects of the drug candidate.
Nicorandil	Data not publicly available; private company researching under commercial intellectual property.
GPCR-AAB binding aptamers	Theoretical/hypothesised drug candidate.
Gynaecological disorder therapeutics	Data not publicly available; private company researching under commercial intellectual property.
Simvastatin	Studies report adverse effects of the drug candidate.
Trehalose	Study was not a full, published preclinical study; abstract only.
VEGF-B	Studies report adverse effects of the drug candidate.

Supplementary Table 3. Extended summary of preclinical candidate medicines for pre-eclampsia/eclampsia.

	Drug Candidate	Drug subclass	Development status	Product type	Archetype	Target	Investigator	Stage of Pre-eclampsia	Therapeutic indication	Technology Readiness Level (TRL)
1	MZe786[1,2]	Hydrogen sulphide donors	Active	Drugs	Novel	HO1/Hmox1 promoter	Pharmaceutical	Undefined	Prevention	TRL 5
2	Gefitinib[3]	Small molecule	Active	Drugs	Repurposed	EGFR inhibitor	Academic	Early onset	Treatment	TRL 3.5
3	Cyclosporin A[4]	Small molecule	Active	Drugs	Repurposed	Calcineurin	Academic	Undefined	Treatment	TRL 3.5
4	SynB1-ELP-p50i[5]	Amino acid-peptide	Active	Biologics	Novel	NF-κB	Pharmaceutical/ Academic	Undefined	Treatment	TRL 3
5	Mangiferin[6,7]	Polyphenol	Active	Dietary supplements	Repurposed	Nrf-2	Academic	Undefined	Prevention/Treatment	TRL 5
6	Placental growth factor[8-10]	Amino acid-peptide	Active	Biologics	Novel	sFlt-1	Pharmaceutical/ Academic	Early and late onset	Treatment	TRL 3.5
7	L-ergothioneine[11]	Amino acid-peptide	Active	Dietary supplements	Repurposed	Multiple (i.e. OCTN1 transporter)	Academic	Undefined	Prevention/Treatment	TRL 3
8	Azathioprine[12]	Small molecule	Inactive	Drugs	Repurposed	Multiple (i.e. HPRT/TPMT enzymes)	Academic	Undefined	Treatment	TRL 3.5
9	Sodium hydrosulfide[13-15]	Hydrogen sulphide donors	Inactive	Drugs	Novel	Unknown	Academic	Undefined	Treatment	TRL 3.5
10	Etanercept[16,17]	Amino acid-peptide	Active	Biologics	Repurposed	TNF-a	Academic	Undefined	Treatment	TRL 5
11	Quercetin[18-20]	Polyphenol	Active	Dietary supplements	Repurposed	Multiple (i.e. MMP-1 and STK4)	Academic	Undefined	Prevention/Treatment	TRL 3.5
12	Ouabain[21]	Small molecule	Inactive	Drugs	Repurposed	HIF-1α	Academic	Undefined	Prevention	TRL 3.5
13	Ferulic acid[22,23]	Antioxidant	Active	Dietary supplements	Repurposed	sFlt-1	Academic	Undefined	Treatment	TRL 3.5
14	Celastrol[24]	Small molecule	Inactive	Drugs	Novel	MMP-9	Academic	Undefined	Treatment	TRL 3.5

15	Emiplacel[25]	Cell therapy	Active	Biologics	Novel	Unknown	Pharmaceutical	Undefined	Prevention/Treatment	TRL 3.5
16	Moringa oleifera[26]	Polyphenol	Active	Dietary supplements	Novel	IL-17	Academic	Undefined	Prevention	TRL 3
17	GYY4137[15,27]	Hydrogen sulphide donors	Active	Drugs	Novel	Heme oxygenase-1	Academic	Undefined	Treatment	TRL 4
18	Moxonidine[28]	Small molecule	Inactive	Drugs	Repurposed	Imidazoline I1 receptors	Academic	Undefined	Symptom management	TRL 3.5
19	Haemoglobin vesicles[29-31]	Cell therapy	Inactive	Biologics	Novel	sFlt-1	Academic	Undefined	Treatment	TRL 3.5
20	Apolipoprotein A-I[32,33]	Amino acid-peptide	Inactive	Biologics	Novel	ATP binding cassette transporter A1	Pharmaceutical/ Academic	Undefined	Symptom management	TRL 3.5
21	Tetramethylpyrazine[34,35]	Vascular agents	Active	Drugs	Repurposed	CHOP and GRP78	Academic	Undefined	Treatment	TRL 4
22	VEGF-121[36]	DNA, siRNA, mRNA	Inactive	Biologics	Novel	sFlt-1	Academic	Undefined	Prevention/Treatment	TRL 3.5
23	AGT-targeting siRNA[37]	DNA, siRNA, mRNA	Active	Biologics	Novel	Angiotensinogen	Pharmaceutical	Early and late onset	Treatment	TRL 3.5
24	Liraglutide[38]	Amino-acid peptide	Active	Drugs	Repurposed	GLP-1 receptor	Academic	Undefined	Treatment	TRL 3.5
25	Lovastatin[39,40]	Enzyme inhibitors (statins)	Inactive	Drugs	Repurposed	HMG-CoA reductase	Academic	Undefined	Treatment	TRL 3.5
26	Scutellaria baicalensis root extract (Baicalin)[41,42]	Polyphenol	Active	Dietary supplements	Repurposed	Multiple (i.e. Annexin A2)	Academic	Undefined	Symptom management	TRL 3
27	sFlt-1-targeting siRNA[43,44]	DNA, siRNA, mRNA	Active	Biologics	Novel	sFlt-1	Academic	Undefined	Prevention/Treatment	TRL 4
28	TRV027[45,46]	Small molecule	Active	Drugs	Novel	Vascular AT1-B2 heterodimer receptor	Academic	Late onset	Prevention	TRL 3.5
29	Uncaria rhynchophylla extract[47-49]	Polyphenol	Active	Dietary supplements	Repurposed	COX2	Academic	Undefined	Treatment	TRL 3
30	Hydrogen rich saline[50,51]	Antioxidant	Inactive	Drugs	Repurposed	sFlt-1	Academic	Undefined	Prevention/Treatment	TRL 3
31	YC 1[52,53]	Small molecule	Inactive	Drugs	Novel	Hypoxia-inducible factor 1α (HIF-1α)	Pharmaceutical	Early onset	Treatment	TRL 3.5
32	HTHQ[54]	Antioxidant	Active	Drugs	Novel	Nrf-2	Academic	Undefined	Prevention/Treatment	TRL 3.5

33	AP39[55]	Hydrogen sulphide donors	Active	Drugs	Novel	Multiple (i.e. ERK1/2 and caspase-1)	Pharmaceutical/Academic	Undefined	Prevention/Treatment	TRL 3
34	Cibinetide[56]	Amino acid-peptide	Active	Drugs	Novel	Erythropoietin receptors	Academic	Undefined	Treatment	TRL 3.5
35	Vitexin[57]	Polyphenol	Active	Dietary supplements	Novel	TFPI-2 and HIF-1α/VEGF expressions	Academic	Undefined	Symptom management	TRL 3
36	Toki-shakuyaku-san[58,59]	Herbal	Active	Drugs	Repurposed	Unknown	Pharmaceutical	Undefined	Symptom management	TRL 3
37	Grape seed extract[60]	Polyphenol	Active	Dietary supplements	Repurposed	Multiple (i.e. aromatase)	Academic	Undefined	Symptom management	TRL 3
38	SB203580[61,62]	Small molecule	Active	Drugs	Novel	p38 MAPK	Pharmaceutical/ Academic	Undefined	Treatment	TRL 3.5
39	Euterpe oleracea[63,64]	Herbal	Active	Dietary supplements	Repurposed	Unknown	Academic	Undefined	Symptom management	TRL 3
40	Tempol[65]	Antioxidant	Inactive	Drugs	Novel	Unknown	Academic	Undefined	Treatment	TRL 3
41	VG 1177[66]	Amino acid-peptide	Inactive	Biologics	Novel	Class II-associated invariant chain peptide	Pharmaceutical/ Academic	Undefined	Prevention/Treatment	TRL 3.5
42	Boiogito[67]	Herbal	Inactive	Dietary supplements	Unknown	Non-specific	Pharmaceutical	Undefined	Treatment	TRL 3
43	Gelsolin[68]	Amino acid-peptide	Inactive	Biologics	Novel	Cytoplasmic actin	Pharmaceutical/ Academic	Undefined	Prevention/Treatment	TRL 3
44	Carveol[69]	Vascular agents	Active	Drugs	Novel	L-type Ca2+ ion channels	Academic	Undefined	Treatment	TRL 3
45	Saireito[67]	Herbal	Inactive	Drugs	Repurposed	Unknown	Pharmaceutical	Undefined	Treatment	TRL 3
46	Pirmagrel[70]	Vascular agents	Inactive	Drugs	Novel	Thromboxane synthase	Academic	Undefined	Treatment	TRL 3
47	Sofalcone[71]	Small molecule	Inactive	Drugs	Repurposed	Heme oxygenase-1	Academic	Undefined	Treatment	TRL 3
48	Thymus schimperi[72,73]	Herbal	Active	Dietary supplements	Novel	Unknown	Academic	Undefined	Symptom management	TRL 3
49	Vitis labrusca/vinifera extract[74-76]	Polyphenol	Active	Dietary supplements	Repurposed	NO synthase	Academic	Undefined	Symptom management	TRL 3
50	Regulatory T cells[77]	Cell therapy	Inactive	Biologics	Novel	Multiple (i.e. normal pregnant Tregs)	Academic	Undefined	Symptom management	TRL 3
51	BMS582949[61]	Small molecule	Inactive	Drugs	Novel	p38 MAPK	Pharmaceutical/ Academic	Early onset	Treatment	TRL 3

52	Doramapimod[61]	Small molecule	Inactive	Drugs	Novel	p38 MAPK	Pharmaceutical/Academic	Early onset	Treatment	TRL 3
53	Ad-VEGF[78,79]	DNA, siRNA, mRNA	Inactive	Biologics	Novel	VEGFR-1	Academic	Undefined	Prevention	TRL 3

Supplementary Data 2. Medium and low potential candidates.

Medium potential candidates

Of the 53 candidates analysed, 37 were identified as medium potential having a final score between 41 and 54 (Supplementary Table 3). These candidates tend to score lower in product development due to insufficient safety and efficacy studies (Supplementary Data 1). These candidates tend to also score lower in implementability due to route of administration and cold chain requirements (Supplementary Data 1). Five (13.5%) of these candidates are being investigated by pharmaceutical companies and 27 (73.0%) by academic institutes, while the remaining five (13.5%) are being explored by both (Supplementary Table 3). Three (8.1%) medium potential candidates are being investigated for pre-eclampsia prevention, 18 (48.6%) candidates are being explored for treatment, and seven (18.9%) candidates are for symptom management (Supplementary Data 1). The remaining nine (24.3%) candidates are being investigated for both the prevention and treatment of pre-eclampsia (Supplementary Table 3). The majority of medium potential candidates are at a TRL 3.5 meaning they need further research into the efficacy of the candidates (Supplementary Table 3).

Medium potential candidates at a TRL 4

Three medium potential candidates performed well enough in efficacy and mechanism of action preclinical studies to warrant being at a TRL 4 (GYY4137, sFlt-1-targeting small interfering RNA (siRNA) and tetramethylpyrazine; Supplementary Table 3). GYY4137 is a novel slow releasing H^2S-releasing drug that has the ability to release H^2S in a slow and sustained manner more similar to endogenous production of H^2S.[90] This drug candidate is being investigated by Aston University and Sao Paulo State University for the treatment of pre-eclampsia targeting HO-1 and has produced two preclinical studies (Supplementary Data 1).[90,91] GYY4137 can deliver H^2S without potential toxicity, unlike fast-release sodium H^2S which delivers H^2S as a single concentrated burst.[90] GYY4137 was more advantageous to restore systolic blood pressure and protect against uteroplacental fetal growth restriction and oxidative stress.[90]

Another medium potential candidate at a TRL 4 is sFlt-1-targeting siRNA which utilises placenta-specific nanoparticle delivery.[60] This candidate is being investigated by Chinese academic institutes for the treatment of pre-eclampsia and has scored high in efficacy and mechanism of action studies resulting in a TRL 4 score (Supplementary Table 3). Two preclinical studies have been performed for this candidate, both *in vitro* and *in vivo*, finding significantly decreased sFlt-1 levels and improved pre-eclampsia outcomes without a toxic effect when administered with this siRNA.[92,93]

Tetramethylpyrazine is at TRL 4. It is a traditional Chinese medicine that has been used extensively for cardiovascular and cerebrovascular diseases.[60] This repurposed drug candidate is being investigated by academic institutes in China for the treatment of pre-eclampsia targeting CHOP and GRP78 miRNAs (Supplementary Table 3). Two preclinical studies have been performed on these candidates both in *in vitro* and *in vivo* pre-eclamptic models, finding the inhibition of CHOP and GRP78 miRNA resulted in downstream effects on increasing NO synthesis leading to improved placental and fetal weights.[94,95]

Despite being at a TRL 4, all three of these medium potential candidates scored low in implementability. GYY4137 and tetramethylpyrazine are both administered intravenously, and sFlt-1-targeting siRNA is administered subcutaneously or intramuscularly. All three candidates require cold chain to be transported and stored stably (Supplementary Data 1).

The remaining 30 medium potential candidates scored less than a TRL 4, due to lower scores in preclinical efficacy studies. Although some of these candidates may have scored higher than those at TRL 4, either the mechanism of action or efficacy of the candidate was not explored sufficiently, which has prevented them from progressing to a higher TRL. These candidates are therefore either at a TRL 3 or TRL 3.5.

Low potential candidates

Of the 53 candidates analysed, eight were identified as low potential having a final score of 40 or below (Supplementary Data 1). These candidates tend to score lower in quality of evidence and product development. Six (75.0%) of these candidates are being investigated by academic institutes and the two remaining (25.0%) are being explored by both (Supplementary Data 1). One (11.1%) candidate is being investigated for pre-eclampsia prevention, four (44.4%) are being explored for treatment, and four (44.4 %) candidates are for symptom management (Supplementary Table 3). Of the eight low potential candidates, two (22.2%) used a dosage in preclinical studies that was up to 25 times higher than the safe human dosage (Supplementary Data 1). All of the low potential candidates are at a TRL 3 meaning they need further research into the efficacy and mechanism of action of the candidates (Supplementary Table 3).

References:

1 Saif, J. *et al.* Hydrogen sulfide releasing molecule MZe786 inhibits soluble Flt-1 and prevents preeclampsia in a refined RUPP mouse model. *Redox Biol* **38**, 101814 (2021). https://doi.org/10.1016/j.redox.2020.101814

2 Rezai, H. *et al.* MZe786, a hydrogen sulfide-releasing aspirin prevents preeclampsia in heme oxygenase-1 haplodeficient pregnancy under high soluble flt-1 environment. *Redox Biol* **38**, 101768 (2021). https://doi.org/10.1016/j.redox.2020.101768

3 Hastie, R. *et al.* EGFR (Epidermal Growth Factor Receptor) Signaling and the Mitochondria Regulate sFlt-1 (Soluble FMS-Like Tyrosine Kinase-1) Secretion. *Hypertension* **73**, 659-670 (2019). https://doi.org/10.1161/hypertensionaha.118.12300

4 Huang, Q. *et al.* Cyclosporin A ameliorates eclampsia seizure through reducing systemic inflammation in an eclampsia-like rat model. *Hypertension Research* **43**, 263-270 (2020). https://doi.org/10.1038/s41440-019-0387-3

5 Eddy, A. C. *et al.* Biopolymer-Delivered, Maternally Sequestered NF-κB (Nuclear Factor-κB) Inhibitory Peptide for Treatment of Preeclampsia. *Hypertension* **75**, 193-201 (2020). https://doi.org/10.1161/hypertensionaha.119.13368

6 Yang, H. *et al.* Mangiferin alleviates hypertension induced by hyperuricemia via increasing nitric oxide releases. *J Pharmacol Sci* **137**, 154-161 (2018). https://doi.org/10.1016/j.jphs.2018.05.008

7 Huang, J. *et al.* Mangiferin ameliorates placental oxidative stress and activates PI3K/Akt/mTOR pathway in mouse model of preeclampsia. *Arch Pharm Res* **43**, 233-241 (2020). https://doi.org/10.1007/s12272-020-01220-7

8 Spradley, F. T. *et al.* Placental Growth Factor Administration Abolishes Placental Ischemia-Induced Hypertension. *Hypertension* **67**, 740-747 (2016). https://doi.org/10.1161/hypertensionaha.115.06783

9 Makris, A. *et al.* Placental Growth Factor Reduces Blood Pressure in a Uteroplacental Ischemia Model of Preeclampsia in Nonhuman Primates. *Hypertension* **67**, 1263-1272 (2016). https://doi.org/10.1161/hypertensionaha.116.07286

10 Lecarpentier, E. *et al.* Total Versus Free Placental Growth Factor Levels in the Pathogenesis of Preeclampsia. *Hypertension* **76**, 875-883 (2020). https://doi.org/10.1161/hypertensionaha.120.15338

11 Williamson, R. D. *et al.* L-(+)-Ergothioneine Significantly Improves the Clinical Characteristics of Preeclampsia in the Reduced Uterine Perfusion Pressure Rat Model. *Hypertension* **75**, 561-568 (2020). https://doi.org/10.1161/hypertensionaha.119.13929

12 Tinsley, J. H., Chiasson, V. L., South, S., Mahajan, A. & Mitchell, B. M. Immunosuppression improves blood pressure and endothelial function in a rat model of pregnancy-induced hypertension. *Am J Hypertens* **22**, 1107-1114 (2009). https://doi.org/10.1038/ajh.2009.125

13 Holwerda, K. M. *et al.* Hydrogen sulfide attenuates sFlt1-induced hypertension and renal damage by upregulating vascular endothelial growth factor. *J Am Soc Nephrol* **25**, 717-725 (2014). https://doi.org/10.1681/asn.2013030291

14 Possomato-Vieira, J. S., Gonçalves-Rizzi, V. H., Graça, T. U., Nascimento, R. A. & Dias-Junior, C. A. Sodium hydrosulfide prevents hypertension and increases in vascular endothelial growth factor and soluble fms-like tyrosine kinase-1 in hypertensive pregnant rats. *Naunyn Schmiedebergs Arch Pharmacol* **389**, 1325-1332 (2016). https://doi.org/10.1007/s00210-016-1296-5

15 Zochio, G. P., Possomato-Vieira, J. S., Chimini, J. S., da Silva, M. L. S. & Dias-Junior, C. A. Effects of fast versus slow-releasing hydrogen sulfide donors in hypertension in pregnancy and fetoplacental growth restriction. *Naunyn Schmiedebergs Arch Pharmacol* **392**, 1561-1568 (2019). https://doi.org/10.1007/s00210-019-01697-0

16 LaMarca, B. *et al.* Hypertension in response to chronic reductions in uterine perfusion in pregnant rats: effect of tumor necrosis factor-alpha blockade. *Hypertension* **52**, 1161-1167 (2008). https://doi.org/10.1161/hypertensionaha.108.120881

17 Cunningham, M. W. *et al.* Tumor necrosis factor alpha (TNF-α) blockade improves natural killer cell (NK) activation, hypertension, and mitochondrial oxidative stress in a preclinical rat model of preeclampsia. *Hypertens Pregnancy* **39**, 399-404 (2020). https://doi.org/10.1080/10641955.2020.1793999

18 Ebegboni, V. J., Balahmar, R. M., Dickenson, J. M. & Sivasubramaniam, S. D. The effects of flavonoids on human first trimester trophoblast spheroidal stem cell self-renewal, invasion and JNK/p38 MAPK activation: Understanding the cytoprotective effects of these phytonutrients against oxidative stress. *Biochem Pharmacol* **164**, 289-298 (2019). https://doi.org/10.1016/j.bcp.2019.04.023

19 Yang, S., Song, L., Shi, X., Zhao, N. & Ma, Y. Ameliorative effects of pre-eclampsia by quercetin supplement to aspirin in a rat model induced by L-NAME. *Biomed Pharmacother* **116**, 108969 (2019). https://doi.org/10.1016/j.biopha.2019.108969

20 Li, Q. *et al.* The bioflavonoid quercetin improves pathophysiology in a rat model of preeclampsia. *Biomed Pharmacother* **127**, 110122 (2020). https://doi.org/10.1016/j.biopha.2020.110122

21 Rana, S. *et al.* Ouabain inhibits placental sFlt1 production by repressing HSP27-dependent HIF-1α pathway. *Faseb j* **28**, 4324-4334 (2014). https://doi.org/10.1096/fj.14-252684

22 Gong, W., Wan, J., Yuan, Q., Man, Q. & Zhang, X. Ferulic acid alleviates symptoms of preeclampsia in rats by upregulating vascular endothelial growth factor. *Clin Exp Pharmacol Physiol* **44**, 1026-1031 (2017). https://doi.org/10.1111/1440-1681.12801

23 Chen, Y. *et al.* Ferulic acid ameliorated placental inflammation and apoptosis in rat with preeclampsia. *Clin Exp Hypertens* **41**, 524-530 (2019). https://doi.org/10.1080/10641963.2018.1516773

24 Xiao, S., Zhang, M., He, Z. & Wang, D. Celastrol attenuates symptoms of preeclampsia in rats by inhibiting matrix metalloproteinase-9. *Eur J Pharmacol* **830**, 33-38 (2018). https://doi.org/10.1016/j.ejphar.2018.04.025

25 Chatterjee, P. *et al.* Human placenta-derived stromal cells decrease inflammation, placental injury and blood pressure in hypertensive pregnant mice. *Clin Sci (Lond)* **130**, 513-523 (2016). https://doi.org/10.1042/cs20150555

26 Agnes Batmomolin, A. A., I. Wayan Arsana Wiyasa, Sanarto Santoso. *Ethanolic extract of Moringa oleifera leaves improve inflammation, angiogenesis, and blood pressure in rat model of preeclampsia*. Vol. Volume: 10 (Issue: 8, 2020).

27 Wang, K. *et al.* Dysregulation of hydrogen sulfide producing enzyme cystathionine γ-lyase contributes to maternal hypertension and placental abnormalities in preeclampsia. *Circulation* **127**, 2514-2522 (2013). https://doi.org/10.1161/circulationaha.113.001631

28 Gairard, A. *et al.* Effect of i1 imidazoline receptor agonist, moxonidine, in nitric oxide-deficient hypertension in pregnant rats. *J Cardiovasc Pharmacol* **43**, 731-736 (2004). https://doi.org/10.1097/00005344-200405000-00017

29 Kaga, M. *et al.* Liposome-encapsulated hemoglobin (hemoglobin-vesicle) is not transferred from mother to fetus at the late stage of pregnancy in the rat model. *Life Sci* **91**, 420-428 (2012). https://doi.org/10.1016/j.lfs.2012.08.021

30 Li, H. *et al.* Artificial oxygen carriers rescue placental hypoxia and improve fetal development in the rat pre-eclampsia model. *Sci Rep* **5**, 15271 (2015). https://doi.org/10.1038/srep15271

31 Ohta, H. *et al.* Potential New Non-Invasive Therapy Using Artificial Oxygen Carriers for Pre-Eclampsia. *J Funct Biomater* **8** (2017). https://doi.org/10.3390/jfb8030032

32 Charlton, F. *et al.* The protective effect of apolipoprotein in models of trophoblast invasion and preeclampsia. *Am J Physiol Regul Integr Comp Physiol* **312**, R40-r48 (2017). https://doi.org/10.1152/ajpregu.00331.2016

33 Liao, S., Wu, H. & Chen, R. Apolipoprotein A1 mimetic peptide ATI-5261 reverses arterial stiffness at late pregnancy and early postpartum in a COMT(-/-) mouse model

of preeclampsia. *Clin Hypertens* **24**, 11 (2018). https://doi.org/10.1186/s40885-018-0097-1

34 Gu, S. *et al.* Tetramethylpyrazine reduces the consequences of nitric oxide inhibition in pregnant rats. *J Cell Physiol* **234**, 19799-19806 (2019). https://doi.org/10.1002/jcp.28579

35 Yuan, Y., Zhao, L., Wang, X., Lian, F. & Cai, Y. Ligustrazine-induced microRNA-16-5p inhibition alleviates preeclampsia through IGF-2. *Reproduction* **160**, 905-917 (2020). https://doi.org/10.1530/rep-20-0309

36 Li, Z. *et al.* Recombinant vascular endothelial growth factor 121 attenuates hypertension and improves kidney damage in a rat model of preeclampsia. *Hypertension* **50**, 686-692 (2007). https://doi.org/10.1161/hypertensionaha.107.092098

37 Haase, N. *et al.* RNA interference therapeutics targeting angiotensinogen ameliorate preeclamptic phenotype in rodent models. *J Clin Invest* **130**, 2928-2942 (2020). https://doi.org/10.1172/jci99417

38 Younes, S. T., Maeda, K. J., Sasser, J. & Ryan, M. J. The glucagon-like peptide 1 receptor agonist liraglutide attenuates placental ischemia-induced hypertension. *Am J Physiol Heart Circ Physiol* **318**, H72-h77 (2020). https://doi.org/10.1152/ajpheart.00486.2019

39 Laufs, U., La Fata, V., Plutzky, J. & Liao, J. K. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation* **97**, 1129-1135 (1998). https://doi.org/10.1161/01.cir.97.12.1129

40 Putra, R. A., Effendi, J. S., Permadi, W., Bandiara, R. & Fauziah, P. N. Role of lovastatin on level of Soluble FMS-Like Tyrokenase-1 (sFlt-1), Placental Growth Factor (PlGF) in Preeclampsia-induced Human Umbilcal Vein Endhothelial Cell (HUVEC). *Bioscience Research* **15**, 967-974 (2018).

41 Wang, Y. *et al.* A potential role of Baicalin to inhibit apoptosis and protect against acute liver and kidney injury in rat preeclampsia model. *Biomed Pharmacother* **108**, 1546-1552 (2018). https://doi.org/10.1016/j.biopha.2018.09.107

42 Liu, Y., Xiong, M., Zhou, F., Shi, N. & Jia, Y. Effect of baicalin on gestational hypertension-induced vascular endothelial cell damage. *J Int Med Res* **48**, 300060520934288 (2020). https://doi.org/10.1177/0300060520934288

43 Yu, J., Jia, J., Guo, X., Chen, R. & Feng, L. Modulating circulating sFlt1 in an animal model of preeclampsia using PAMAM nanoparticles for siRNA delivery. *Placenta* **58**, 1-8 (2017). https://doi.org/10.1016/j.placenta.2017.07.360

44 Li, L. *et al.* Trophoblast-Targeted Nanomedicine Modulates Placental sFLT1 for Preeclampsia Treatment. *Front Bioeng Biotechnol* **8**, 64 (2020). https://doi.org/10.3389/fbioe.2020.00064

45 Quitterer, U. *et al.* Beta-Arrestin1 Prevents Preeclampsia by Downregulation of Mechanosensitive AT1-B2 Receptor Heteromers. *Cell* **176**, 318-333.e319 (2019). https://doi.org/10.1016/j.cell.2018.10.050

46 Violin, J. D. *et al.* Selectively engaging β-arrestins at the angiotensin II type 1 receptor reduces blood pressure and increases cardiac performance. *J Pharmacol Exp Ther* **335**, 572-579 (2010). https://doi.org/10.1124/jpet.110.173005

47 Li, Y. L. *et al.* Enhanced Protective Effect of the Combination of Uncaria and Semen Raphani on Vascular Endothelium in Spontaneously Hypertensive Rats. *Evid Based Complement Alternat Med* **2015**, 358352 (2015). https://doi.org/10.1155/2015/358352

48 Kim, J. H., Bae, C. H., Park, S. Y., Lee, S. J. & Kim, Y. Uncaria rhynchophylla inhibits the production of nitric oxide and interleukin-1β through blocking nuclear factor κB, Akt, and mitogen-activated protein kinase activation in macrophages. *J Med Food* **13**, 1133-1140 (2010). https://doi.org/10.1089/jmf.2010.1128

49 Wu, L. Z. & Xiao, X. M. Evaluation of the effects of Uncaria rhynchophylla alkaloid extract on LPS-induced preeclampsia symptoms and inflammation in a pregnant rat model. *Braz J Med Biol Res* **52**, e8273 (2019). https://doi.org/10.1590/1414-431x20198273

50 Yang, X., Guo, L., Sun, X., Chen, X. & Tong, X. Protective effects of hydrogen-rich saline in preeclampsia rat model. *Placenta* **32**, 681-686 (2011). https://doi.org/10.1016/j.placenta.2011.06.020

51 Ushida, T. *et al.* Molecular hydrogen ameliorates several characteristics of preeclampsia in the Reduced Uterine Perfusion Pressure (RUPP) rat model. *Free Radic Biol Med* **101**, 524-533 (2016). https://doi.org/10.1016/j.freeradbiomed.2016.10.491

52 Turgut, N. H. *et al.* Investigation of the role of the NO-cGMP pathway on YC-1 and DEA/NO effects on thoracic aorta smooth muscle responses in a rat preeclampsia model. *Can J Physiol Pharmacol* **91**, 797-803 (2013). https://doi.org/10.1139/cjpp-2013-0086

53 Brownfoot, F. C. *et al.* YC-1 reduces placental sFlt-1 and soluble endoglin production and decreases endothelial dysfunction: A possible therapeutic for preeclampsia. *Mol Cell Endocrinol* **413**, 202-208 (2015). https://doi.org/10.1016/j.mce.2015.06.033

54 Jiang, L. *et al.* 1-O-Hexyl-2,3,5-Trimethylhydroquinone Ameliorates the Development of Preeclampsia through Suppression of Oxidative Stress and

Endothelial Cell Apoptosis. *Oxid Med Cell Longev* **2021**, 8839394 (2021). https://doi.org/10.1155/2021/8839394

55 Covarrubias, A. E. *et al.* AP39, a Modulator of Mitochondrial Bioenergetics, Reduces Antiangiogenic Response and Oxidative Stress in Hypoxia-Exposed Trophoblasts: Relevance for Preeclampsia Pathogenesis. *Am J Pathol* **189**, 104-114 (2019). https://doi.org/10.1016/j.ajpath.2018.09.007

56 Korokin, M. *et al.* Erythropoietin Mimetic Peptide (pHBSP) Corrects Endothelial Dysfunction in a Rat Model of Preeclampsia. *Int J Mol Sci* **21** (2020). https://doi.org/10.3390/ijms21186759

57 Zheng, L. *et al.* Vitexin ameliorates preeclampsia phenotypes by inhibiting TFPI-2 and HIF-1α/VEGF in a l-NAME induced rat model. *Drug Dev Res* **80**, 1120-1127 (2019). https://doi.org/10.1002/ddr.21596

58 Takei, H. *et al.* The herbal medicine Toki-shakuyaku-san improves the hypertension and intrauterine growth retardation in preeclampsia rats induced by Nomega-nitro-L-arginine methyl ester. *Phytomedicine* **11**, 43-50 (2004). https://doi.org/10.1078/0944-7113-00332

59 Takei, H., Yamamoto, M., Kase, Y. & Takeda, S. The effect of herbal medicine Toki-shakuyaku-san on blood pressure in an Nomega-nitro-L-arginine methyl ester-induced pre-eclampsia rat model during pregnancy and the postpartum period. *J Pharmacol Sci* **98**, 255-262 (2005). https://doi.org/10.1254/jphs.fpj04043x

60 Tropea, T., Greenwood, S. L., Sibley, C. P. & Cottrell, E. C. Grape Seed Extract Polyphenols Improve Resistance Artery Function in Pregnant eNOS(-/-) Mice. *Front Physiol* **11**, 588000 (2020). https://doi.org/10.3389/fphys.2020.588000

61 Che, G. *et al.* Knockdown of Heparanase Suppresses Invasion of Human Trophoblasts by Activating p38 MAPK Signaling Pathway. *Dis Markers* **2018**, 7413027 (2018). https://doi.org/10.1155/2018/7413027

62 Fan, M. *et al.* LPS Induces Preeclampsia-Like Phenotype in Rats and HTR8/SVneo Cells Dysfunction Through TLR4/p38 MAPK Pathway. *Front Physiol* **10**, 1030 (2019). https://doi.org/10.3389/fphys.2019.01030

63 Rocha, A. P. *et al.* Endothelium-dependent vasodilator effect of Euterpe oleracea Mart. (Açaí) extracts in mesenteric vascular bed of the rat. *Vascul Pharmacol* **46**, 97-104 (2007). https://doi.org/10.1016/j.vph.2006.08.411

64 da Silva, A. S. *et al.* Açaí (Euterpe oleracea Mart) seed extract protects against maternal vascular dysfunction, hypertension, and fetal growth restriction in experimental preeclampsia. *Hypertens Pregnancy* **39**, 211-219 (2020). https://doi.org/10.1080/10641955.2020.1754850

65 Hoffmann, D. S. *et al.* Chronic tempol prevents hypertension, proteinuria, and poor feto-placental outcomes in BPH/5 mouse model of preeclampsia. *Hypertension* **51**, 1058-1065 (2008). https://doi.org/10.1161/hypertensionaha.107.107219

66 Chatterjee, P. *et al.* Depletion of MHC class II invariant chain peptide or γ-δ T-cells ameliorates experimental preeclampsia. *Clin Sci (Lond)* **131**, 2047-2058 (2017). https://doi.org/10.1042/cs20171008

67 Takei, H. *et al.* The herbal medicines Saireito and Boiogito improve the hypertension of pre-eclamptic rats induced by Nomega-Nitro-L-arginine methyl ester. *Phytomedicine* **14**, 591-600 (2007). https://doi.org/10.1016/j.phymed.2007.01.009

68 Nadkarni, N. A. *et al.* Gelsolin is an endogenous inhibitor of syncytiotrophoblast extracellular vesicle shedding in pregnancy. *Pregnancy Hypertens* **6**, 333-339 (2016). https://doi.org/10.1016/j.preghy.2016.07.003

69 Evaristo Rodrigues da Silva, R. *et al.* Relaxant Effect of Monoterpene (-)-Carveol on Isolated Human Umbilical Cord Arteries and the Involvement of Ion Channels. *Molecules* **25** (2020). https://doi.org/10.3390/molecules25112681

70 Ding, Z. Q., Rowe, J., Ng, B., Sinosich, M. J. & Gallery, E. D. Modulation of prostacyclin and thromboxane secretion by cytotrophoblasts from normal and pre-eclamptic human pregnancies. *Placenta* **23**, 594-599 (2002). https://doi.org/10.1053/plac.2002.0851

71 Onda, K. *et al.* Sofalcone upregulates the nuclear factor (erythroid-derived 2)-like 2/heme oxygenase-1 pathway, reduces soluble fms-like tyrosine kinase-1, and quenches endothelial dysfunction: potential therapeutic for preeclampsia. *Hypertension* **65**, 855-862 (2015). https://doi.org/10.1161/hypertensionaha.114.04781

72 Haji, H., Makonnen, E., Debella, A. & Geleta, B. Evaluation of diuretic and antihypertensive activity of leaf extracts of Thymus schimperi in rats. *British Journal of Pharmacology and Toxicology* **7**, 1-8 (2016).

73 Mergiaw, K. *et al.* Effects of Aqueous Leaf Extract of Thymus schimperion Hematologic Profiles of Animal Models of Pre-eclampsia. 30-36 (2020).

74 Soares De Moura, R. *et al.* Antihypertensive, vasodilator and antioxidant effects of a vinifera grape skin extract. *J Pharm Pharmacol* **54**, 1515-1520 (2002). https://doi.org/10.1211/002235702153

75 de Moura, R. S., Resende, A. C., Moura, A. S. & Maradei, M. F. Protective action of a hydroalcoholic extract of a vinifera grape skin on experimental preeclampsia in rats. *Hypertens Pregnancy* **26**, 89-100 (2007). https://doi.org/10.1080/10641950601147960

76 da Costa, G. F. *et al.* Vitis vinifera L. Grape Skin Extract Prevents Development of Hypertension and Altered Lipid Profile in Spontaneously Hypertensive Rats: Role of

Oxidative Stress. *Prev Nutr Food Sci* **25**, 25-31 (2020). https://doi.org/10.3746/pnf.2020.25.1.25

77 Cornelius, D. C. *et al.* An increased population of regulatory T cells improves the pathophysiology of placental ischemia in a rat model of preeclampsia. *Am J Physiol Regul Integr Comp Physiol* **309**, R884-891 (2015). https://doi.org/10.1152/ajpregu.00154.2015

78 Miquerol, L., Langille, B. L. & Nagy, A. Embryonic development is disrupted by modest increases in vascular endothelial growth factor gene expression. *Development* **127**, 3941-3946 (2000). https://doi.org/10.1242/dev.127.18.3941

79 Woods, A. K. *et al.* Adenoviral delivery of VEGF121 early in pregnancy prevents spontaneous development of preeclampsia in BPH/5 mice. *Hypertension* **57**, 94-102 (2011). https://doi.org/10.1161/hypertensionaha.110.160242