Antithrombin alfa (ATryn) for pre-eclampsia in pre-term women

LAY SUMMARY

Pre-eclampsia is a condition that affects some pregnant women during the second half of their pregnancy. Signs include high blood pressure and protein in the urine. Most cases are mild, but the condition can lead to serious complications for both mother and baby.

Antithrombin alfa is a new drug for the treatment of pre-eclampsia that is given straight into the blood by a drip. It is being studied to see whether it improves the symptoms of pre-eclampsia and if it is safe to use for pregnant women with this disease. If antithrombin alfa is licensed for use in the UK, it could provide a new treatment for pregnant women with pre-eclampsia.

NIHR HSRIC ID: 9865
TARGET GROUP

- Pre-eclampsia: pregnant females; 23-30 weeks gestational age.

TECHNOLOGY

DESCRIPTION

Antithrombin alfa (ATryn: antithrombin III; AT-III; rhAT; rhAT III) is a transgenic form of antithrombin III, which is a nonvitamin K-dependent protease that inhibits coagulation by lysing thrombin and Factor Xa. It is intended for the treatment of pre-eclampsia in pregnant females of 23-30 weeks gestational age. In the phase III trial, antithrombin alfa is administered as a 250mg intravenous (IV) loading dose over 15 minutes followed by a continuous IV infusion at 2,000mg per 24 hours\(^1\). Treatment continues until maternal and/or foetal indications necessitate delivery, or until 34 weeks of gestation.

Antithrombin alfa is licensed in the EU for the treatment of antithrombin III deficiency. Common adverse effects include flushing, headache, dizziness, chest tightness, nausea, chills, and cramps.

INNOVATION and/or ADVANTAGES

If licensed, antithrombin alfa will offer an additional treatment option for pregnant females with pre-eclampsia.

DEVELOPER

rEVO Biologics (EU licence holder).

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Pre-eclampsia is formally defined as a pregnancy-specific multisystemic disorder characterised by new onset of hypertension and proteinuria arising after 20 weeks of gestation in a previously normotensive woman\(^2,3\). It is the most common hypertensive disease of pregnancy and a leading cause of maternal morbidity and mortality worldwide\(^2,3\). Pre-eclampsia accounts for approximately one fifth of maternal deaths and is associated with adverse foetal outcomes, such as intrauterine growth restriction and placental abruption\(^3\). Severe pre-eclampsia is diagnosed if there are more severe elevations of blood pressure or evidence of other end-organ dysfunction\(^3\).

Clinical signs of pre-eclampsia appear in the second half of pregnancy, but initial pathogenic mechanisms arise much earlier. The cytotrophoblast fails to remodel spiral arteries, leading to hypoperfusion and ischemia of the placenta. The foetal consequence is growth restriction.
in one in three pregnancies complicated by pre-eclampsia\textsuperscript{a}. On the maternal side, the ischemic placenta releases factors that provoke generalised maternal endothelial dysfunction. The endothelial dysfunction is in turn responsible for the symptoms and complications of pre-eclampsia\textsuperscript{b}.

Maternal symptoms and complications of pre-eclampsia include hypertension, proteinuria, renal impairment, thrombocytopenia, epigastric pain, liver dysfunction, haemolysis-elevated liver enzymes-low platelet count (HELLP) syndrome, visual disturbances, headache, and seizures\textsuperscript{c}.

**CLINICAL NEED and BURDEN OF DISEASE**

In the UK, 1 in 20 pregnancies are complicated by pre-eclampsia and 5 in 1,000 are complicated by severe pre-eclampsia\textsuperscript{4,5}. Women who have had pre-eclampsia have a 16\% risk of recurrence in a future pregnancy, and 15–20\% of all preterm births are attributable to this complication\textsuperscript{4}.

In 2014-15, there were 11,002 hospital admissions for pre-eclampsia (ICD-10 O14), resulting in 47,010 bed days and 11,534 finished consultant episodes\textsuperscript{6}. In 2014, there were 2 deaths from pre-eclampsia in England and Wales\textsuperscript{7}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**

- American Congress of Obstetricians and Gynecologists. Hypertension in Pregnancy. 2013\textsuperscript{8}.
- World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011\textsuperscript{9}.
- Institute of Obstetricians and Gynaecologists. The diagnosis and management of pre-eclampsia and eclampsia. 2011\textsuperscript{10}.
- Action on Pre-Eclampsia. PRECOG: The Pre-eclampsia Community Guideline. 2004\textsuperscript{11}.

**CURRENT TREATMENT OPTIONS**

Guidelines recommend that women with pre-eclampsia should be offered an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and relevant blood tests\textsuperscript{4}. For women with moderate or severe hypertension, defined as greater than 150/100mmHg, guidelines recommend the use of

\textsuperscript{a} Expert personal opinion
labetalol for the first line treatment of pre-eclampsia\textsuperscript{4,10}. Labetalol should be administered orally at a starting dose of 100mg two or three times daily, up to a maximum dose of 600mg four times daily\textsuperscript{10}. Alternatives to labetalol include methyldopa (unlicensed for this indication) and nifedipine (unlicensed for this indication), however these should only be offered after considering the potential side effects for the woman, foetus and newborn baby\textsuperscript{4}.

For the management of severe pre-eclampsia, guidelines recommend the use of labetalol (oral or IV), hydralazine (IV) or nifedipine (oral)\textsuperscript{4}.

Anticonvulsants are recommended for use for women with severe pre-eclampsia or women who have previously had an eclamptic fit. Magnesium sulfate should be given as a loading dose at 4g IV over 5 minutes, followed by a continuous IV infusion of 1g/hour for 24 hours\textsuperscript{4}.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>PRESERVE-1, NCT02059135, RB AT PPE 01-13; recombinant human antithrombin vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>GTC Biotherapeutics UK.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{4}, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=120; aged ≥16 yrs; females; pregnancy ≥23 to ≤30 wks; pre-eclampsia.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to recombinant human antithrombin 250mg IV loading dose over 15 mins followed by continuous IV infusion at 2,000mg per 24 hrs; or placebo IV matched volume infusion.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment until maternal and/or foetal indications necessitate delivery or until 34 wks of gestation, follow-up 4-6 wks after delivery.</td>
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<tr>
<td>Primary outcome</td>
<td>Increase in gestational age (gestational age at delivery minus the gestational age at randomisation).</td>
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<tr>
<td>Secondary outcomes</td>
<td>Foetal and neonatal outcomes (bronchopulmonary dysplasia, intraventricular haemorrhage, cystic periventricular leucomalacia, retinopathy of prematurity, late sepsis, necrotizing enterocolitis and mortality), maternal outcomes, morbidity and mortality.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as Nov 2016.</td>
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</tbody>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of antithrombin alfa has not been disclosed.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other
- No impact identified
### Impact on Health and Social Care Services

- Increased use of existing services: expert opinion notes that the fact that the drug is administered by daily intravenous infusions for 3-4 weeks is not an attractive proposition. This would be a resource-intensive intervention.
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other

### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: uncertain unit cost compared to existing treatments
- None identified

### Other Issues

- Clinical uncertainty or other research question identified: expert opinion notes that the pathogenic events associated with pre-eclampsia are thought to occur at the time of placental development and trophoblast invasion (up to 18 weeks gestation). Any intervention that occurs after this period is highly unlikely to reverse the disorder or influence its natural history. The best that can be expected is the prevention of the severe complications mentioned (placental abruption, eclamptic fits and haematological/biochemical complications such as HELLP syndrome). The clinical value of antithrombin alpha remains to be established but given its mechanism of action, it is unlikely to be more useful than just the use of anti-hypertensive therapy. If it is shown to be more effective, there will need to be a health economic evaluation before it is introduced into clinical practice.
- None identified

### REFERENCES


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**b** Expert personal opinion
10 Institute of Obstetricians and Gynaecologists. The diagnosis and management of pre-eclampsia and eclampsia. Dublin: FIGO; September 2011.