PROGNOSIS
Prediction of short-term outcome in pregnant women with suspected preeclampsia study using the angiogenic biomarkers sFlt-1/PIGF

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Introduction
The current “gold-standard” for the diagnosis of preeclampsia involves blood pressure measurement and determination of protein in urine. The prognostic performance of the current diagnostic standard in determining which women will develop preeclampsia/eclampsia/HELLP syndrome is quite poor.²
As a consequence, many pregnant women with signs and/or symptoms of preeclampsia are often unnecessarily hospitalized for observation, resulting in significant additional costs related to pregnancy care.

The PROGNOSIS study is addressing this unmet need and represents the first clinical study demonstrating short-term prediction of preeclampsia using fully automated Elecsys sFlt-1/PIGF maternal blood testing in pregnant women with clinical suspicion of preeclampsia. Preeclampsia may be caused by an imbalance of angiogenic factors. It has been demonstrated that high serum levels of sFlt-1, an anti-angiogenic protein, and low levels of PIGF, a pro-angiogenic protein, predict subsequent development of preeclampsia. The sFlt-1/PIGF ratio was markedly elevated before the onset of clinical preeclampsia.³⁴
Roche Professional Diagnostics has developed the first fully automated Elecsys® sFlt-1 and PIGF immunoassays for use on the cobas® modular platform currently CE IVD approved for “aid in diagnosis of preeclampsia”.

Key conclusion
We expect that PROGNOSIS will demonstrate ruling out of preeclampsia/eclampsia/HELLP syndrome for one week with a high negative predictive value.

We expect that PROGNOSIS will demonstrate ruling in of preeclampsia/eclampsia/HELLP syndrome within four weeks in women with suspected preeclampsia.
**Study design**

PROGNOSIS is a multicenter, prospective, double-blind, non-interventional study evaluating the short-term prediction of preeclampsia/eclampsia/HELLP syndrome in pregnant women with suspected preeclampsia.

**Primary study objectives**

- Demonstrate that low ratios of sFlt-1/PlGF predict absence of preeclampsia/eclampsia/HELLP syndrome within one week.
- Demonstrate that high ratios of sFlt-1/PlGF predict diagnosis of preeclampsia/eclampsia/HELLP syndrome within four weeks.

**Secondary study objectives**

PROGNOSIS includes a number of secondary study objectives correlating the sFlt-1/PlGF ratio to

- Adverse outcomes
- Time to delivery
- Disease severity
- Health economics benefits

**Inclusion criteria**

- Age of ≥18 years
- Gestational week: 24+0 to 36+6
- Signed written informed consent
- **Suspicion of clinical diagnosis of preeclampsia:**
  - New onset of elevated blood pressure
  - Aggravation of pre-existing hypertension
  - New onset of protein in urine
  - Aggravation of preexisting proteinuria
  - Preeclampsia-related symptoms (epigastric pain, excessive edema, severe swelling, headache, visual disturbances, sudden weight gain)
  - Preeclampsia-related findings (e.g. abnormal uterine Doppler sonography)

**Exclusion criteria**

- Manifest preeclampsia
- Eclampsia
- HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome

**Study size**

1000 eligible subjects have to complete 5 study visits once a week over 4 weeks, a visit at delivery and postpartum data collection. At each visit clinical data relating to the mother’s health, preeclampsia status and the health of the foetus/child as well as study samples for biomarker testing will be collected.

<table>
<thead>
<tr>
<th>Patients enrolled</th>
<th>Samples collected</th>
<th>Clinical study visits completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1250</td>
<td>4500</td>
<td>7000</td>
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Study location
The study started enrolling in December 2010. In 2012, the study covered globally 14 countries in 4 regions and 32 sites.

Contributing sites
Sites that have recruited eligible patients to study

<table>
<thead>
<tr>
<th>Site/location</th>
<th>Site/location</th>
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<tbody>
<tr>
<td>Medical University of Vienna, Austria</td>
<td>Mater Medical Research Institute, Australia</td>
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<tr>
<td>Centre Hospitalier Universitaire (CHU) de Liège, Belgium</td>
<td>The Royal Women’s Hospital, Australia</td>
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<td>Charité University Medicine Berlin, Germany</td>
<td>CHUM (Centre Hospitalier de L’Université de Montreal), Canada</td>
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<td>CHUQ-Pavillon CHUL, Canada</td>
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<tr>
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<td>Hospital Base Osorno, Chile</td>
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<td>Karolinska University Hospital, Stockholm, Sweden</td>
<td>Hospital Regional de Concepcion, Chile</td>
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<tr>
<td>Uppsala University, Sweden</td>
<td>Instituto Chileno de Medicina Reproductiva, Chile</td>
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<tr>
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<td>Christchurch Hospital, New Zealand</td>
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<td>Wellington Hospital, New Zealand</td>
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<tr>
<td>CEMIC, Argentina</td>
<td>Instituto de Ginecologia y Reproduccion, Peru</td>
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<td>Clinica Internacional Sede San Borja, Peru</td>
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<td>Hospital Maria Auxiliadora, Peru</td>
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<td>Liverpool Hospital, Australia</td>
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Acknowledgement
A special thank you to all PROGNOSIS investigators at the various locations for performing the study and to Prof. Holger Stepan for supporting as medical advisor. Thanks also to the Roche colleagues for their dedicated support.

Abbreviations
sFlt-1 = soluble fms-like tyrosine kinase-1
PIGF = placental growth factor
HELLP = Hemolysis, Elevated Liver enzymes and Low Platelets

References
1 Hund M et al. poster presented at the 18th World Congress on Controversies in Obstetrics, Gynecology and Infertility (COGI), Vienna, Austria, 24–27 October 2013
2 Steegers EAP et al. 2010 Lancet 2010; 376: 631–44