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Aprea presents preliminary clinical Phase Ib/II results in ovarian cancer with APR-246 – a 'first-in-class' compound reconverting mutant to wild-type p53 protein

STOCKHOLM – October 23, 2015. Aprea AB, a Karolinska Development AB (Nasdaq Stockholm: KDEV) portfolio company, announces updated preliminary data from its ongoing Phase Ib/II clinical study in collaboration with The European Network for Translational Research in Ovarian Cancer (EUTROC). The data will be presented on Saturday, October 24, at the European Society of Gynaecological Oncology (ESGO) International Meeting in Nice, France and reinforces the indicative conclusions presented from the study on April 20, 2015; that APR-246 can be combined with standard of care chemotherapy and that preliminary efficacy data of the combination regimen show activity in treatment of recurrent ovarian cancer.

Aprea's Phase Ib/II PiSARRO trial investigates the safety and efficacy of APR-246 in combination with carboplatin and doxorubicin in second-line treatment of patients with high grade serous ovarian cancer. Today, preliminary results for the first 24 patients in the Phase Ib part of the study are announced of which 8 patients have completed all 6 cycles of combination therapy with APR-246.

At cut-off, all patients treated in the study have stable disease or better according to RECIST criteria. In addition, 13 out of 14 evaluable patients have GCIG CA-125 (tumor antigen biomarker) response after 3 treatment cycles. Hence the preliminary efficacy data indicate that APR-246 in combination with chemotherapy has activity in patients with partially platinum sensitive as well as patients with platinum sensitive disease.

APR-246 showed linear pharmacokinetics with no accumulation and low intra patient variability and no indication of interaction between APR-246 and chemotherapy was seen. This indicates that APR-246 can be combined with carboplatin and doxorubicin at relevant doses.

No new safety concerns have emerged in the study. The main treatment-emergent adverse events have been low grade gastrointestinal and central nervous system related events. One dose limiting toxicity (DLT) of ruptured diverticulum occurred at the second dose level leading to expansion of this cohort to 6 patients. A possible increase in hematological side effects over those expected with the chemotherapy alone cannot be ruled out at this stage.

Mikael von Euler, CMO of Aprea comments: "We continue to be encouraged by the preliminary results emerging from the Phase Ib part of the study. Firstly, the safety and pharmacokinetic data indicate that APR-246 can be combined with chemotherapy at full dose in the ovarian cancer setting. Secondly, the early efficacy data from the evaluable patients indicate that the combination regimen with APR-246 has activity in ovarian cancer patients that are either partially or platinum sensitive. While we are careful not to draw definite conclusions from these preliminary results, we are encouraged by the data indicating that APR-246 has the potential to improve treatment for ovarian cancer patients."

The poster *Preliminary Results from EUTROC PiSARRO: a Phase Ib Study Combining APR-246 with Standard Chemotherapy in Platinum Sensitive Relapsed High Grade Serous Ovarian Carcinoma (HGSOC)* will be presented at the ESGO on Saturday, October 24, in an e-poster session that will start at 07.00 CEST and the poster is also attached to this press release and available at Aprea's website www.aprea.com

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TO THE EDITORS

About Aprea AB
Aprea AB is a Swedish biotech company focusing on discovery and development of novel anticancer compounds targeting the tumor suppressor protein p53. The main owner of Aprea is KDev Investments AB, part of Karolinska Development AB (publ). The other main owners are Östersjöstiftelsen, Praktikerinvest and KCIF Co-Investment Fund KB. For more information, please visit www.aprea.com

About APR-246
APR-246 has been developed based on results from Professor Klas Wiman and colleagues at Karolinska Institutet, and has been shown to reactivate non-functional tumor suppressor protein p53 and induce programmed cell death in many human cancer cells. Preclinical studies have confirmed that APR-246 can activate mutated p53 and demonstrated single agent efficacy and very strong synergy with conventional anti-cancer agents in vitro and in vivo. A clinical Phase Ib/II study in hematological malignancies and prostate cancer has been completed, demonstrating a favorable safety profile and both biological and clinical responses. A Phase Ib/II proof-of-concept study in ovarian cancer patients carrying mutant p53 is currently ongoing.

About the PiSARRO trial
The Phase Ib/II trial is designed to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of APR-246 in combination with carboplatin (AUC 5) and pegylated doxorubicin (30 mg/m2), a second line standard of care chemotherapy for relapsed platinum sensitive high grade serous ovarian cancer. The Phase Ib/II trial is a two-part study that will enroll approximately 180 patients. Part A is an open-label, multiple ascending dose study. The primary objectives of Phase Ib are to evaluate the safety and tolerability of APR-246 in combination with carboplatin and pegylated doxorubicin, and to confirm the dose of APR-246. Pending successful completion of this phase, Aprea expects to initiate Part B of the trial, which will be a randomized, controlled study investigating the safety and antitumor activity of APR-246 administered in combination with carboplatin and pegylated doxorubicin, compared with carboplatin and pegylated doxorubicin alone. Primary end point of Phase II will be Progression Free Survival (PFS). For details on the PiSARRO trial please visit: www.ClinicalTrials.gov.

About EUTROC
The European Network for Translational Research in Ovarian Cancer (EUTROC) was established to improve the current and future management in ovarian cancer and to bring the complex matrix into a single multidisciplinary, transnational framework for ovarian cancer. EUTROC aims to define and give direction to the clinical, scientific, and technological unmet needs by performing activities such as a European-wide tumour bank and technological platforms which will provide a roadmap for the identification and prioritisation of suitable biomarkers. EUTROC's network includes institutions with broad experience in clinical and scientific work in ovarian cancer that are dedicated to improving the long-term clinical outcome of patients within an integrated collaboration across Europe.

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About Karolinska Development AB
Karolinska Development AB is an investment company focused on identifying medical innovation and investing in the creation and growth of companies developing these assets into differentiated products that will make a difference to patients' lives and provide an attractive return on investment.

Karolinska Development has access to world-class medical innovations at the Karolinska Institutet and other leading universities and research institutes in the Nordic region. The Company aims to build companies around scientists who are leaders in their fields, supported by experienced management teams and advisers, and co-funded by specialist international investors, to provide the greatest chance of success.

Karolinska Development has established a portfolio of 12 companies targeting opportunities in innovative treatment for life-threatening or serious debilitating diseases.

The Company is led by a team including investment professionals with strong venture capital backgrounds, experienced company builders and entrepreneurs, with access to a strong global network.

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Preliminary Results from EUTROC PiSARRO: a Phase Ib Study Combining APR-246 with Standard Chemotherapy in Platinum Sensitive Relapsed High Grade Serous Ovarian Carcinoma (HGSOC)

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PiSARRO, p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, is a recently commenced Aprea/ EUTROC Phase Ib/II study of APR-246, the first clinical-stage compound that reactivates mutant p53, in combination with carboplatin and pegylated liposomal doxorubicin (PLD) in recurrent p53 mutant platinum sensitive high grade serous ovarian cancer.

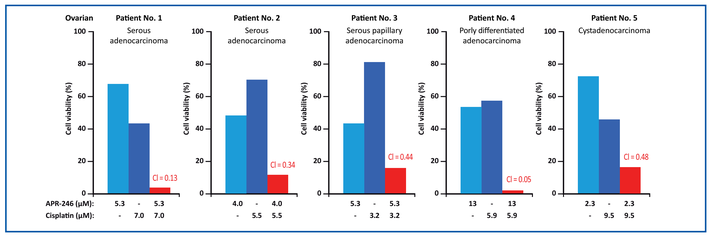
Introduction

- p53 is a key tumour suppressor that induces cell cycle arrest, senescence and/or apoptosis upon cellular stress, eliminating tumour cells. p53 mutations are found in more than 50% of cancers and are associated with increased resistance to chemotherapy and correlate with duration of remission and reduced survival across many tumour types[1].
- Despite high response rates from carboplatin in combination with paclitaxel in first-line treatment of ovarian cancer, most patients relapse and develop resistance.
- In High Grade Serous Ovarian Cancer (HGSOC) 96% of patients have p53 mutations[2].

Background

- APR-246 (PRIMA-1^{MET}) is a pro-drug that is converted to the active form MQ, which restores mutant p53 to the wild type conformation[3].
- APR-246 is the first clinical-stage compound that reactivates mutant p53.
- In the first-in-human Phase Ia study, APR-246 monotherapy was found to have a satis-factory safety and pharmacokinetic profile allowing it to be combined with full dose chemotherapy. Signs of single agent clinical activity were observed in several patients, and p53-dependent biological effects in patient tumor cells were demonstrated. APR-246 was considered safe in patients, with infrequent fully reversible CNS related side effects (dizziness, dyskinesia and ataxia). No bone marrow toxicity was seen[4].
- APR-246 has been shown *in vitro* to reduce glutathione levels, increase ROS levels and ER stress, and to re-sensitize ovarian cancer cells to platinum drugs and doxorubicin[5,6].
- APR-246 displays strong synergy with conventional chemotherapeutic drugs in primary ovarian cancer cells *ex vivo* [5,7] (Figure 1).
- It is proposed that through reactivation of p53, APR-246 resensitizes tumor cells to cisplatin, forming a strong rationale for combination treatment with APR-246 and platinum-based chemotherapy.

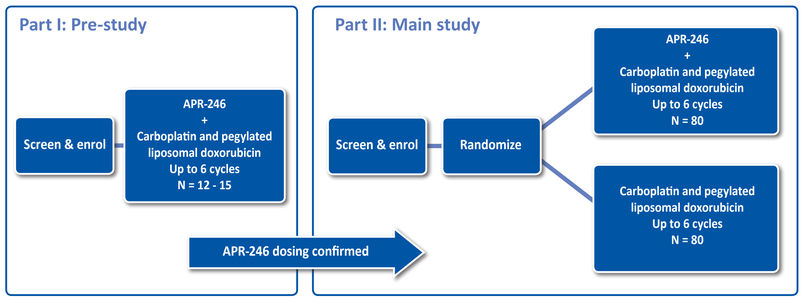
Fig. 1. Synergistic effect of APR-246 with cisplatin on primary cancer cells from 5/5 examined ovarian cancer patients.



Clinical study design

- The ongoing Phase Ib/II study is enrolling patients with recurrent partially platinum sensitive (PFI 6-12 mo) and platinum sensitive (PFI 12-24 mo) HGSOC with positive p53 staining on immunohistochemistry.
- APR-246 is administered as a 6h *i.v.* infusion on 4 consecutive days every 4 weeks for 6 cycles. On day 4, APR-246 is given concomitantly with carboplatin AUC 5 and PLD 30 mg/m^2.
- The Phase Ib part has a 3+3 dose escalation design with 3 planned dose levels (Figure 2) based on safety evaluation after cycle one for dose escalation.
- Phase II dose selection will be based on short and long term safety as well as preliminary efficacy data.
- In the Phase II part, patients with up to two prior lines of platinum based therapy with a PFI of 6-24 months with measurable disease available for pre- and on treatment biopsies will be randomized to standard chemotherapy with or without APR-246.
- Patients are followed for safety, response (Recist 1.1 and CA125 (GCIG criteria)), progression and survival as well as several exploratory endpoints.

Fig. 2 PiSARRO has a straight forward study design with PFS as primary endpoint



Translational studies

- A comprehensive exploratory translational science program with repeat tumour biopsies is included in the study as part of the EUTROC investigators group. The key objectives are to identify potential biomarkers for patient selection and for monitoring response to treatment and to further our understanding of the MOA.
- p53 will be sequenced in tumour biopsies. Mutations will be classified structurally, and the possible correlation of treatment response with mutations and/or type of mutant p53 structure will be assessed.
- p53 will also be sequenced from circulating free tumor DNA.
- Circulating cytokeratin 18 in serum will be measured by ELISA, to follow epithelial cell death and apoptosis.
- ER stress biomarkers will be analyzed in tumour biopsies using IHC.
- Multiple markers will be studied using reverse Phase protein array and mRNA micro-array analyses.

Preliminary results

- At data cut off (8 September, 2015) patients have been enrolled to all 3 dose cohorts of the Phase Ib and 8 patients have completed all 6 cycles of combination therapy.
- Overall, 2/3 of patients are partially platinum sensitive (relapse 6-12 months following previous platinum) and 1/3 are platinum sensitive (relapse >12 months following previous platinum therapy).
- During the safety observation period over the first cycle, one Dose Limiting Toxicity (DLT) of ruptured diverticulum occurred at the 2nd dose level leading to expansion of this cohort to 6 patients.
- Main APR-246 related treatment-emergent adverse events (TEAEs) have been GI related (low grade nausea and vomiting) and low grade CNS related effects (dizziness, vertigo, nausea, dysgeusia). No new safety concerns have emerged (Table 1). A possible increase in hematological side effects over the expected with the chemotherapy alone cannot be ruled out at this stage.
- APR-246 showed linear pharmacokinetics with no accumulation and low inter- and intra- patient variability (Fig. 3). No indication of interaction between APR-246 and chemotherapy was seen.
- 13/14 eligible patients have rapid falls in CA125 and have GCIG CA125 response after 3 cycles (Fig. 4).
- All patients have stable disease or better (emerging data) (Fig. 5).

Table 1. Summary of Grade 3 or Greater, Treatment-Emergent Adverse Events (TEAE) by System Organ Class (N=24) [1]

	APR-246 Dose Cohort (mg/kg)			
MedDRA System Organ Class MedDRA Preferred Term [1][2]	35	50	67.5	Overall
Number of Patients	7	6	11	24
Number of Patients with Any Grade 3 or Greater, TEAEs [3]	3 (42.9%)	5 (83.3%)	7 (63.6%)	15 (62.5%)
Blood and lymphatic system disorders	3 (42.9%)	4 (66.7%)	4 (36.4%)	11 (45.8%)
Neutropenia	3 (42.9%)	4 (66.7%)	2 (18.2%)	9 (37.5%)
Anaemia	0	3 (50.0%)	2 (18.2%)	5 (20.8%)
Thrombocytopenia	0	2 (33.3%)	1 (9.1%)	3 (12.5%)
Febrile neutropenia	0	1 (16.7%)	0	1 (4.2%)
Leukopenia	0	0	1 (9.1%)	1 (4.2%)
Infections and infestations	0	4 (66.7%)	2 (18.2%)	6 (25.0%)
Device related infection	0	1 (16.7%)	1 (9.1%)	2 (8.3%)
Infection	0	1 (16.7%)	1 (9.1%)	2 (8.3%)
Abdominal infection	0	1 (16.7%)	0	1 (4.2%)
Influenza	0	1 (16.7%)	0	1 (4.2%)
Infusion site infection	0	1 (16.7%)	0	1 (4.2%)
Septic shock	0	1 (16.7%)	0	1 (4.2%)
Gastrointestinal disorders	0	1 (16.7%)	2 (18.2%)	3 (12.5%)
Vomiting	0	0	2 (18.2%)	2 (8.3%)
Abdominal pain	0	1 (16.7%)	0	1 (4.2%)
Ascites	0	0	1 (9.1%)	1 (4.2%)
Large intestine perforation	0	1 (16.7%)	0	1 (4.2%)
Nausea	0	0	1 (9.1%)	1 (4.2%)
Small intestinal obstruction	0	0	1 (9.1%)	1 (4.2%)
General disorders and administration site conditions	**0**	**0**	**3 (27.3%)**	**3 (12.5%)**
Fatigue	0	0	2 (18.2%)	2 (8.3%)
Pyrexia	0	0	1 (9.1%)	1 (4.2%)
Investigations	0	1 (16.7%)	1 (9.1%)	2 (8.3%)
Neutrophil count decreased	0	0	1 (9.1%)	1 (4.2%)
Weight increased	0	1 (16.7%)	0	1 (4.2%)
Metabolism and nutrition disorders	0	1 (16.7%)	1 (9.1%)	2 (8.3%)
Decreased appetite	0	0	1 (9.1%)	1 (4.2%)
Hypoalbuminaemia	0	1 (16.7%)	0	1 (4.2%)
Nervous system disorders	0	0	2 (18.2%)	2 (8.3%)
Dizziness	0	0	2 (18.2%)	2 (8.3%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (9.1%)	1 (4.2%)
Pulmonary embolism	0	0	1 (9.1%)	1 (4.2%)
Vascular disorders	0	0	1 (9.1%)	1 (4.2%)
Hypotension	0	0	1 (9.1%)	1 (4.2%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple TEAEs were counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs) were defined as all AEs that occurred after the first dose of study medication or within 30 day post-treatment period.
[3] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Fatal

Fig. 3. PK samples taken day 1 and day 4, cycle 1. Mean values (50 µg/L = 250 µM)

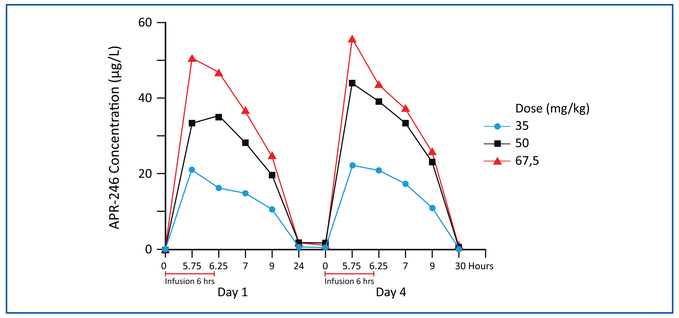


Fig. 4. Spider plot of CA125 change over the treatment period.

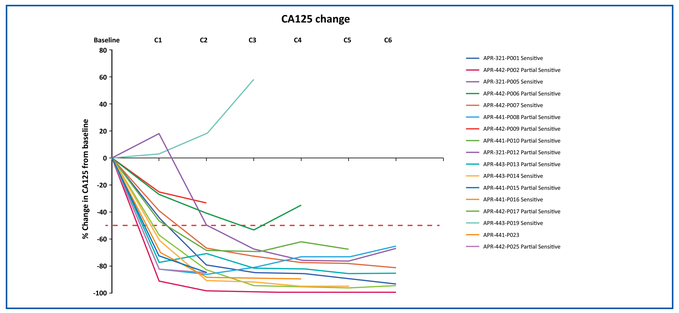
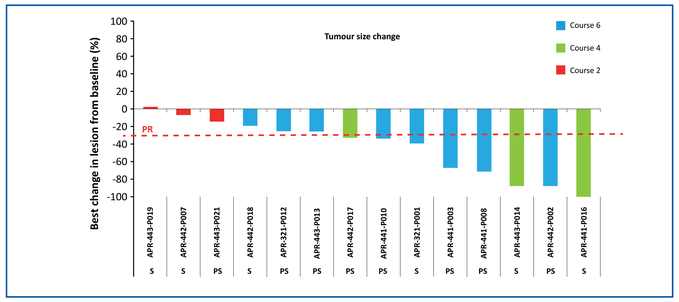


Fig 5. Waterfall plot of change in tumour size according to RECIST 1.1. At data cut off, all patients have SD or better.



Conclusions

- Preliminary data from the PiSARRO Phase Ib study indicate that APR-246 can be combined with carboplatin and PLD at relevant doses.
- A possible increase of the chemotherapy related hematological side effects cannot be ruled out at this stage.
- The preliminary efficacy data indicate that APR-246 in combination with chemotherapy has activity in patients with partially platinum sensitive as well as fully platinum sensitive disease.
- APR-246 in combination with chemotherapy has an encouraging safety and activity profile, supporting continuation of the study in Phase II.

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Disclosures:
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