Anti-cancer activity in patients with advanced ovarian and biliary tract cancers treated with NUC-1031 and platinum agents

**Background**
- Platinum analogs and platinum agents remain cornerstone therapies for many solid malignancies
- Resistance to chemotherapy reduces patient survival
- Patients with advanced biliary tract cancer (BTC) or recurrent ovarian cancer (OC) have limited treatment options
- Effective new agents and rational combinations are required

**ProTides: Nucleotide Analogs**
- A new class of anti-cancer agents
- Transformative phosphoramide chemistry
- Increased intracellular levels of active anti-cancer metabolites
- Potential for broad clinical utility

**NUC-1031: The First Anti-Cancer ProTide**
- ProTide transformation of gemcitabine
- Overcomes gemcitabine resistance mechanisms associated with a poor survival prognosis
- Cellular uptake independent of nucleoside transporters (hENT1)
- Activation independent of deoxycytidine kinase (dCK)
- Protected from breakdown by cytidine deaminase (CDA)
- Increased intracellular generation of the active anti-cancer metabolite, dFdCTP 2-17 greater than gemcitabine

**Potential Mechanism of NUC-1031 + Platinum Synergy**
- NUC-1031 and platinum agents induce cancer cell death through a variety of different mechanisms
- Platinum forms DNA adducts
- Activates DNA damage response
- Attempted repair by removal of adducts and synthesis of new DNA strands
- Anti-cancer metabolite dFdCTP incorporated into DNA leading to cell death

**Ovarian Cancer: NUC-1031 + Carboplatin (PRO-002 study)**
- Phase Ib study of NUC-1031 (625 mg/m²) + carboplatin (AUC 5 or 6) in 25 patients with recurrent OC, who had exhausted all therapeutic options
- 23 patients evaluable for response (received ≥1 cycle)
- 7 platinum-resistant
- 10 platinum-sensitive
- 4 partially platinum-sensitive
- ≥2 platinum-sensitive
- High levels of disease control across all platinum status subgroups
- Combination is well-tolerated over multiple cycles

**Biliary Tract Cancer: NUC-1031 + Cisplatin (ABC-08 study)**
- Objective response rates
  - ABC-08: 26.1% (41/161) – cisplatin
  - ABC-02: 6% (4/67) – cisplatin
- Summary
  - High response rates achieved in difficult to treat patient populations
  - SVR: ORR in recurrent OC
  - 50% ORR in advanced BTC
  - NUC-1031 + platinum agents are well tolerated over multiple cycles
  - Clinical observations coupled with known mechanisms of action support hypotheses that NUC-1031 is synergistic with platinum agents
  - Future clinical studies will explore platinum combinations in
    - Recurrent OC: Phase II trial planned
    - Advanced BTC (Phase II, NuTide:121, to open in 2019)