NOX66 is under development as a sensitizer of chemotherapy and radiotherapy across a range of tumour types. The active ingredient, idronoxil, has been well studied, with in vitro evidence of increased cytotoxicity of agents including cisplatin, carboplatin, paclitaxel, gemcitabine, topotecan, docetaxel and captothecin. The mode of action of idronoxil is summarized below (Figure 1). Early phase studies of an IV formulation showed that idronoxil has a short half-life, with significant and rapid Phase 2 metabolism to inactive conjugates. It was concluded that for idronoxil to have maximum effect it must be administered in a manner to allow constant availability of active drug to the cells (high bioavailability of active drug). A phase 2 study of IV idronoxil (dose 2 days per week) in combination with cisplatin or paclitaxel in patients with ovarian cancers showed efficacy signals in some patients, however a Phase 3 study of oral idronoxil in combination with carboplatin was terminated early due to slow recruitment and lack of efficacy. The rapid and complete metabolism of idronoxil is believed to be a primary reason for lack of results seen.

NOX66 has been developed to specifically address the challenges of phase 2 metabolism and allow active (unconjugated) idronoxil to bind ENOX2. Formulation in a fatty acid environment is believed to be a primary reason for lack the results seen.

Cascade of events in Figure 1 is as follows:

1. Idronoxil binds to ENOX2 → inhibition of the transmembrane electron pump → accumulation of proton ions.
2. Accumulation of protein disrupts sphingomyelin pathway → blockage of serine/threonine conversion to SIP → ΔSIP and ΔCeramide.
3. ΔSIP → ΔAkt → up regulation of the intrinsic (mitochondrial) pathway of apoptosis, via ΔCaspase 9 and ΔCaspase 3, → cell death.
4. ΔAkt → inhibition of FLIP → Caspase 8 (activated via the Death Receptor on the Protein Membrane) → Caspase 3 → apoptosis.
5. ΔSIP and ΔAkt prevents down regulation of Caspase 9 and Caspase 3, supporting apoptosis.

End Stage, metastatic disease (no further therapy options) with solid tumours of type: breast, head and neck, lung, prostate and ovarian.

Each patient undertakes 3 sequential phases of treatment:
- Monotherapy: 21 day cycle where NOX66 is administered for daily for 14 days.
- Low Dose Carboplatin (reported here): 3 × 28 day cycles; NOX66 is administered Day 1-7, IV carboplatin (AUC4) Day 2
- High Dose Carboplatin: 3 × 28 day cycles; NOX66 is administered Day 1-7, IV carboplatin (AUC6) Day 2

19 Patients recruited, 18 patients received at least one dose of NOX66 (safety population)

Preliminary response on CT images by investigator per RECIST 1.1. Following completion of low dose and high dose carboplatin and allow active (unconjugated) idronoxil to bind ENOX2. Formulation in a fatty acid environment is believed to be a primary reason for lack the results seen. 4. of the eighteen patients commencing Low Dose (AUC4) therapy in combination with NOX66

• 8 patients received NOX66 400mg, 10 patients received NOX66 800mg
• 13 patients completed 3 cycles of combination therapy - these patients continue in the study, receiving up to 3 cycles of High Dose Carboplatin (AUC6)
• 13 patients were evaluable for radiological assessment of response following third dose of carboplatin (9-12 weeks from baseline)

⇒ Of the these, 12 showed stable disease compared with baseline, with one patient (800mg NOX66, prostate cancer) showing a partial response and one patient with progressive disease (800mg NOX66, lung cancer).

No patient discontinuations were due to NOX66 administration (either adverse events or practical issues). Reasons for discontinuation were: due to patient decision (n=3) and due to SAE (n=1)(see Table 1)

• Total of 19 Adverse events were reported by 11 patients during this phase of study (Table 1).

⇒ One adverse event (Grade 2 anemia, breast cancer), receiving 800mg NOX66 was considered possibly related to NOX66. This event resolved while continuing therapy.

⇒ Two [2] events led to withdrawal, one was a serious.

**CONCLUSIONS**

This interim analysis shows that, in patients with End Stage Metastatic Cancer of varying primary origin, NOX66 in combination with low dose (AUC4) carboplatin is well tolerated, with no Serious Adverse Events or patient withdrawals considered related to NOX66 therapy. Furthermore, efficacy signals – from evaluable patients during this phase of the study – provides support for further investigation of NOX66 combined with low dose carboplatin as a therapeutic option for patients with solid tumours.

The study is continuing to the NOX66 / high dose carboplatin phase, with last patient visit scheduled for May 2018. Final results, including relationship to prior therapy and disease progression at study entry, will be reported soon after.

**RESULTS - Low Dose Carboplatin**

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>ADVERSE EVENTS</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and Neck Type</td>
<td>Med 1: 400mg</td>
<td>Med 2: 800mg</td>
</tr>
<tr>
<td>Median Age</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Gender</td>
<td>F 5 (65.0%)</td>
<td>M 3 (37.5%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian 8 (100%)</td>
<td>Other 0 (0%)</td>
</tr>
<tr>
<td>Tumour Type</td>
<td>Breast 3 (37.5%)</td>
<td>Head and Neck 0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Prostate 1 (12.5%)</td>
<td>Ovarian 1 (12.5%)</td>
</tr>
<tr>
<td></td>
<td>Lung 3 (37.5%)</td>
<td>Total of 19 Adverse events were reported by 11 patients during this phase of study (Table 1).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>⇒ One adverse event (Grade 2 anemia, breast cancer), receiving 800mg NOX66 was considered possibly related to NOX66. This event resolved while continuing therapy.</td>
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<tr>
<td></td>
<td></td>
<td>⇒ Two [2] events led to withdrawal, one was a serious.</td>
</tr>
</tbody>
</table>

**REFERENCES**

This page is a summary of the study results and conclusions. The full study report is available upon request.

**FINANCIAL DISCLOSURE**

The authors are employees of NaxosPharm Ltd, the sponsor company of this study.