Cobomarsen is a chemically synthesized, phosphorothioate oligonucleotide, 14 nucleotides in length, that contains a mixture of deoxyribonucleotides and 2′-O, 4′-C-methylene-β-d-ribofurans. It is designed to specifically target microRNA miR155 involved in the pathogenesis of CTCL (cutaneous T-cell lymphoma). A subset of these genes has been identified as potentially translatable biomarkers to monitor increased gene expression in pathways involved in apoptosis and tumour cell death. Cobomarsen activity in clinical samples was assessed to be related.

### CLINICAL TRIAL DESIGN

#### Open-label, dose-ranging, multiple dose, study of intra-tumoral, subcutaneous, and intravenous administration of cobomarsen, an oligonucleotide inhibitor of microRNA miR155-5p in subjects with CTCL, MF subtype.

#### Primary Objective

- To investigate the safety and tolerability of multiple intra-tumoral (IT), subcutaneous (SC), and intravenous (IV) administrations of cobomarsen.

#### Secondary Objectives

- To characterize the pharmacokinetic profile, the recommended Phase 2 dose and route, and to evaluate the efficacy of cobomarsen in this population.

#### Main Inclusion/Exclusion Criteria

- Biopsy proven MF, Clinical Stage I-III, Large Cell Transformation included.
- Subjects refractory to or intolerant to established therapies.
- Subjects should remain on stable doses of background therapy.
- No evidence of clinically meaningful visceral, hepatic, or renal dysfunction related to CTCL.
- No clinically significant laboratory, cardiac, renal, hepatic, or other medical conditions.

### IMMUNOPHENOTYPING

No Evidence of Immunosuppression in Subjects Treated with Cobomarsen for up to 23 Months. No evidence of immunosuppression was observed in subjects treated with cobomarsen for up to 23 months. Mean duration of response is 276 days (range: 48 – 582+ days). A change in mSWAT score was proven with IT injection in 92% of subjects at any dose with systemic mode of administration showing improvement in mSWAT score. Modulation was proven with IT injection based on mSWAT. Mean duration of response is 276 days (range: 48 – 582+ days) of ADAs in these patients. 5 of 42 (12%) subjects subsequently screened were positive for ADAs.

### PHARMACOKINETICS

- Plasma concentration curves are multi-compartmental with a long elimination phase.
- Cobomarsen displays linear kinetics, with dose proportional increases in Cmax and AUC across dose groups.
- No evidence of accumulation at the highest doses tested for any route of administration.
- Plasma trough values reach steady state in 12-16 weeks of dosing suggesting a terminal half life of approximately 2.5 to 3 weeks.
- Increased trough values were observed in 3 patients that were later identified as having IgG anti-miRNA antibodies (ADAs); no effects on safety or efficacy were correlated with the presence of ADA in these patients. 5 of 42 (12%) subjects subsequently screened were positive for ADAs.

### SAFETY

- No serious AEs have been attributed to cobomarsen. Eight serious adverse events (SAEs) have been reported in 2 subjects. These SAEs were either unrelated to underlying disease (known complications of the CTCL patient population) or related to other concomitant therapies in these subjects, and unrelated to study drug.
- Thirty-nine subjects (90.7%) have reported at least one non-serious AE, for a total of 307 unique AEs.
- The maximum severity of AEs has been Grade 1/2 Grade 2 of 375 of 307 events (98.9%); 6/307 events (2.0%) were Grade 3/4 events.
- Of the 32 Grade 3/4 events, 14 events in 6 subjects (all in Part B) were assessed to be related.

### Efficacy

#### Part A: Systemic administration by subcutaneous (SC) injection or intravenous (IV) infusion in 300, 600, or 900 mg or IV bolus (300 mg only). Loading dose (3x/week) for 1 week followed by weekly dosing.

#### Part B: Systemic administration by subcutaneous injection or intravenous infusion of cobomarsen, an oligonucleotide inhibitor of microRNA miR155 in subjects with CTCL. Durations of response (days) are indicated by the number of evaluable patients (N=36) across dose groups.

**Figure 2**

- **A**) Cobomarsen tissue concentration detected by mass spectrometry in each biopsy. BLOQ = below the level of quantitation for the assay.

**Figure 3**

- **A**) mSWAT score represents best score achieved while on study for 38 patients who had evaluable mSWAT scores at the dosing cohort (300/600/900 mg). Duration of response (days) as assessed by the investigator is indicated at each dosing cohort. *P < 0.05 vs placebo (log-rank test).
- **B**) Cobomarsen treatment duration by dose level for evaluable patients (N=36). Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

**Figure 4**

- **A**) mSWAT score represents best score achieved while on study for 38 patients who had evaluable mSWAT scores at the dosing cohort (300/600/900 mg). Duration of response (days) as assessed by the investigator is indicated at each dosing cohort. *P < 0.05 vs placebo (log-rank test).
- **B**) Cobomarsen treatment duration by dose level for evaluable patients (N=36). Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

**Figure 5**

- **A**) Mean % change from baseline (green bars) and total scores (mean, error bars) for SKI scores in 300 mg IV-infusion cohort. Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

**Figure 6**

- **A**) Mean % change from baseline (green bars) and total scores (mean, error bars) for SKI scores in 300 mg IV-infusion cohort. Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

**Figure 7**

- **A**) Skindex-29 total scores: maximal % change from baseline (green bars) and total scores (mean, error bars) for SKI scores in 300 mg IV-infusion cohort. Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

#### Part A and B (N=43)

- **SOC PT = System Organ Class Preferred Term

**Figure 8**

- **A**) Mean % change from baseline (green bars) and total scores (mean, error bars) for SKI scores in 300 mg IV-infusion cohort. Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

**Figure 9**

- **A**) Mean % change from baseline (green bars) and total scores (mean, error bars) for SKI scores in 300 mg IV-infusion cohort. Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

**Figure 10**

- **A**) Mean % change from baseline (green bars) and total scores (mean, error bars) for SKI scores in 300 mg IV-infusion cohort. Duration of response (days) is indicated by the number of evaluable patients (N=36) across dose groups.

#### Conclusions

- Cobomarsen is well tolerated at doses ranging from 300-900 mg in CTCL. The doses studied after systemic administration appear to represent the top of the dose response curve based on mSWAT. Mean duration of response is 276 days (range: 48 – 582+ days). A change in mSWAT score was proven with IT injection in 92% of subjects at any dose with systemic mode of administration showing improvement in mSWAT score. Modulation was proven with IT injection based on mSWAT. Mean duration of response is 276 days (range: 48 – 582+ days) of ADAs in these patients. 5 of 42 (12%) subjects subsequently screened were positive for ADAs.

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