Cobomarsen (MRG-106) mir-155-5p Inhibitor

Cobomarsen is an RNAi-based investigational therapeutic identical oligonucleotide. 14 nucleotides in length, that contains a mixture of four phosphorothioate backbone modifications [26].-C4 methyl O-d-ribose modifications (LNA) which stabilize the oligomer’s structure and function. Three different sequences of cobomarsen are used in clinical trials, containing numerous genes implicated in cell cycle and apoptosis, conserved with the pharmacology impact on cell survival.

A subset of these genes has been identified as potentially translatable biomarkers to monitor cobomarsen activity in clinical samples.

Role of MicroRNA-155 in CTCL

Epigenetic alterations have been implicated in the pathogenesis of lymphomas and leukemias including CTCL. miR-155 plays a role in B cell development and proliferation with high expression.

miR-155 is upregulated in CTCL skin lesions and is involved in tumor progression. miR-155 targets BCL2, and other microRNA pathways are regulated by mir-155 and are activated in CTCL leading to uncontrolled cell expansion.

SAFETY

No serious AEs were observed in all cohorts. Eight serious adverse events (SAEs) have been reported to date. These SAEs were either related to underlying disease, adverse events in the CTCL population, or related to other co-morbidities in these subjects, and unrelated to study treatment.

Thirty-nine subjects (50%) have reported at least 1 non-serious AE, for a total of 307 unique AEs. The majority of AEs have been resolved or resolved with no residual effects. The most common AEs include decreases in gene expression in key CTCL disease pathways (PKB/AKT, JAK/STAT and NFkB pathways) as well as increased gene expression in pathways promoting tumor cell survival.

No evaluable Part A lesions directly injected with cobomarsen had improved CALS scores (Fig. 2B) and decreased tumor cells over time were observed by FCM sequencing on Study Day 0 (Fig. 2C).

EFFICACY

Part A: Lesion Biopsies Have Expected Gene Expression Changes and Lower Calcinosis and ULN Lesion Calcinosis Lesion Improvement to Treated CALS

Figure 2. miR-155 Expression in miR-155-5p treated CTCL tumor lesions. miR-155 detection in Frozen biopsies from healthy donors, participant skin samples from Parts A and B, and commercial cell lines (HH137, S2, and HS683). All evaluated lesions were treated with cobomarsen as a once weekly dermal injection.

Table 1: Most common AEs reported in ≥ 10% of subjects treated with cobomarsen in Parts A and B (N=43).

Table 2: Most common AEs reported in ≥ 10% of subjects treated with cobomarsen in Parts A and B (N=43).

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. Cobomarsen displays linear pharmacokinetics, with dose proportional increases in Cmax and AUC across dose groups.

The efficacy of cobomarsen in the treatment of CTCL is supported by the significant reductions in CALS scores observed in this study. The reductions in CALS scores were consistent with the observed reductions in tumor cell populations in other studies.

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No evidence of Immunomodulatory Treated Subjects with cobomarsen for up to 23 Months

There were no clinically significant changes in T or B cell subsets (including CD4, CD8, Treg, and B cells), or in monocytes or eosinophils.

No T cell counts increased in several patients treated with the highest cobomarsen dose (900 mg), though the relationship to drug administration is unclear with the small data set. Subtle innate immunocompromise (IRIS) by the study showed normal levels in T and B cell expansion and concomittant PR.

Immunophenotyping

There were no significant differences in the immunophenotypic profiles of PB and skin lymphocytes in patients treated with cobomarsen. The data suggest that cobomarsen has a minimal effect on the peripheral blood lymphocyte population.

In the skin, there was a trend towards a decrease in the number of CD8+ T cells, while the number of CD4+ T cells remained constant. There was also a decrease in the number of CD19+ B cells, although this change was not statistically significant.

In conclusion, cobomarsen appears to have a minimal impact on peripheral blood and skin lymphocyte subsets. Further studies are needed to confirm these findings and to elucidate the mechanisms of action of cobomarsen in CTCL.

Baseline demographics

There were no significant differences in baseline demographics between the cobomarsen-treated and control groups. The two groups were well matched in terms of age, gender, race, and disease duration.

Table 1: Baseline demographics and characteristics of the cobomarsen-treated and control groups.

Table 2: Baseline demographics and characteristics of the cobomarsen-treated and control groups.

Pharmacokinetics

Plasma concentration curves were multi-compartamental with a long terminal elimination phase. Cobomarsen displays linear pharmacokinetics, with dose proportional increases in Cmax and AUC across dose groups.

In vitro activity of cobomarsen at the highest dose tested for any route of administration.

Table 3: Pharmacokinetic parameters for 200 mg (Part A) and 600 mg (Part B) doses.

Table 4: Pharmacokinetic parameters for 200 mg (Part A) and 600 mg (Part B) doses.

Table 5: Pharmacokinetic parameters for 200 mg (Part A) and 600 mg (Part B) doses.