VIP943 is a Novel CD123 Antibody Drug Conjugate (ADC) binding to the IL3Rα chain (CD123). VIP943 combines the new payload class of kinase spindle protein inhibitor (KSPi) with a novel legumain-cleavable linker, which is specifically cleaved in the lysosome. KSP inhibition results in the formation of characteristic monopolar spindles (monotetrad), and subsequent mitotic catastrophe. Consequently, KSP selectively acts on cells undergoing cell division. Our KSPi is a mitosis-specific drug optimized for significant retention in the tumor cell resulting in a favorable efficacy and safety profile. Current treatment options (e.g., cytoreduction with anthracyclines) for patients with acute myeloid leukemia (AML) are associated with severe toxicities, making these treatments unsuitable for elderly and vulnerable patients. For this patient population, the current standard of care (SOC) is a combination of venetoclax and azacitidine, yet novel therapies are still needed.

In the present study, we evaluated a novel ADC against CD123 (VIP943) for the treatment of AML. Here, legumain cleaves the linker and releases the payload.

Table 1. Summary of AML patient characteristics and no efficacy

Cytokine Release and Immunophenotyping Profile of VIP943

In a human PBMC cytokine release assay, VIP943 did not induce the release of cytokines, compared to positive controls (Fig. 3A). In an immunophenotyping study in non-human primates, one dose of VIP943 led to a reversible reduction in CD123+ basophils (Fig. 3B). Other blood cell populations showed no change.

Safety of VIP943 in Non-Human Primates (NHP) Compared to Gem-Oz

In a NHP toxicity study, VIP943 was compared with Gem-Oz. Additionally, we included a newly generated ADC using a gemtuzumab bispecific as the targeting antibody conjugated to our linker and payload (Gem-KSP-ADC). This allowed the direct comparison of the effector chemistry of Gem-Oz to our linker and payload since the target (cd133) was the same. The effect on hematology and serum chemistry after a single application of nontoxic doses was evaluated.

Figure 5. Cytokine release assay and Immunophenotyping. A) In vivo evaluation of reduction of cytokines vs vehicle by VIP943 in human PBMC. B) T lymphocytes were isolated from PBMC and stimulated with different concentrations of CD3 (1µM) and CD28 (1µM) a) VIP943 vs vehicle control (negative controls, IgG1 isotype control). b) Gemtuzumab (Gem)-KSP-ADC vs vehicle control (negative controls, IgG1 isotype control). c) CD123 expression was measured by flow cytometry in PBMC from healthy male and female donors. d) CD123 expression was measured by flow cytometry in PBMC from healthy male and female donors.

Gem-Oz Toxicity Ameliorated by Substituting Prophylactic Linker - Payload

VIP943 and Gem-Oz showed mild increase in liver enzymes (ALT and AST), which were normalized with VIP943 to pre-dose levels on day 14, whereas in the Gem-Oz group the elevated levels were persistent. At the end of the observation period total bilirubin levels are doubled in the Gem-Oz with no changes observed in the other treatment groups. A significant increase in urea nitrogen was detected only in the Gem-Oz group. One Gem-Oz treated animal died on day 13 (female) and the male animal showed signs of liver and kidney toxicity and a critical decrease in RBC count. A cat was euthanized due to morbidity.

CONCLUSIONS

- The novel cd123 ADC VIP943 demonstrates efficacy in an ex vivo AML patient-derived BM proliferation assay with various levels of CD123 cell surface expression.
- VIP943 is not expected to cause cytokine release syndrome based on results from an in vitro cytokine release assay.
- In a patient-derived xenograft model, the triple combination of VIP943 with the SCL AsaVax increased the number of complete responses and the overall survival.
- In a NHP toxicity study, VIP943 (20mg/kg) showed no signs of toxicity as measured by hematology, serum chemistry and survival. No adverse effects were observed other than a reversible decrease in bisphos. In contrast, VIP943 treated with Gem-Oz had significant toxicity including death and mandatory euthanasia. The toxicity of Gem-Oz was ameliorated by substituting our proprietary linker and payload on an cd133 antibody as measured by hematology, serum chemistry and survival.
- These results provide compelling evidence that VIP943 represents a substantial advancement in ADC technology and warrants evaluation in clinical trials.

REFERENCES

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ACKNOWLEDGMENTS

Special thanks to Dr. Gmbh for performing in vivo studies and Vivia Biotech Ltd. for in vivo support. Also special thanks to Dr. Clemens for assistance in performing the safety study.

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Presented at the American Society of Hematology, December 12, 2022, New Orleans, LA

Poster # 2650

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