2.0 SYNOPSIS

Name of the Sponsor: Nektar Therapeutics	**Individual Study Table Referring to Part of the Dossier:**	**For National Authority Use Only**
Name of Finished Product: NKTR-255 Drug Product Erbitux®	**Volume:**	
Name of Active Ingredient: NKTR-255 Drug Substance Cetuximab	**Page:**	
Title of Study: A Phase 1b/2, Open-label, Multicenter, Dose Escalation, and Dose Expansion Study of NKTR-255 Monotherapy or in Combination with Cetuximab as a Salvage Regimen for Solid Tumors		
Investigator(s) and Study Center(s): Multicenter study which enrolled patients at 6 centers in the United States.		
Publication(s): None		
Study Period: First patient registered: 30 October 2020 Last patient, last visit: 30 March 2023 Database lock: 11 May 2023	**Development Phase:** 1b/2	

Objectives:

The primary objectives were:

Phase 1b (Dose Escalation):

- To evaluate the safety and tolerability, as well as define the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D), of NKTR-255 in combination with cetuximab in relapsed or refractory (R/R) head and neck squamous cell carcinoma (HNSCC) or colorectal carcinoma (CRC)

Phase 2 (Dose Expansion):

- To evaluate the safety and tolerability of NKTR-255 monotherapy and NKTR-255 in combination with cetuximab in R/R HNSCC, CRC, cutaneous squamous cell carcinoma (cSCC), anal squamous cell carcinoma (ASCC), and cervical cancer
- To evaluate the efficacy of NKTR-255 in combination with cetuximab in R/R HNSCC or CRC by assessing the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

The secondary objectives were:

- To evaluate the efficacy of NKTR-255 monotherapy in R/R cSCC, ASCC, and cervical cancer by assessing the ORR by RECIST 1.1
- To evaluate the efficacy of NKTR-255 in combination with cetuximab and NKTR-255 monotherapy by assessing progression-free survival (PFS) and overall survival (OS)
- To characterize the pharmacodynamic (PD) effects and change from baseline in immune cell populations (natural killer [NK] cells, cytotoxic T lymphocyte [CD8+] cells, and other immune populations), tumor cells,

cytokine levels, and changes in gene expression after administration of NKTR-255 in combination with cetuximab and NKTR-255 monotherapy

- To characterize the pharmacokinetics (PK) of NKTR-255 and cetuximab
- To assess development of antidrug antibodies (ADA) against NKTR-255 and cetuximab

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Methodology:

This study was a Phase 1b/2, open-label, multicenter, dose escalation, and dose expansion study in patients with R/R HNSCC, CRC, cSCC, ASCC, and cervical cancers.

In Phase 1b, patients received an intravenous (IV) loading dose of cetuximab alone, followed 7 days later by the first combination treatment of IV cetuximab and IV NKTR-255 on Cycle 1 Day 1 (C1D1). Thereafter, IV NKTR-255 was given in 21-day cycles in combination with weekly IV cetuximab.

Phase 2 cohorts were not enrolled in this study.

Phase 1b – Dose Escalation

- The NKTR-255 starting dose was CCI [redacted] IV, which had no safety concerns as defined by pre-specified dose-limiting toxicities (DLTs) in the first cohort of the ongoing first-in-human (FIH) study Protocol 18-255-02. The starting dose was based on ongoing safety data generated from the escalation cohorts and the RP2D determination from the FIH study.
- After an initial cetuximab loading dose of [redacted] during the study run-in period (Day -7), patients received IV NKTR-255 every 21 days (q21d) in combination with [redacted] IV cetuximab weekly. On days that NKTR-255 and cetuximab were both dosed, cetuximab was administered first, followed by NKTR-255 a minimum of 1 hour later but within 3 hours of completing the cetuximab infusion.

Beginning with Dose Level 1, successive dose levels of at least 3 patients were to receive ascending doses of NKTR-255 until the MTD and/or RP2D was determined. Approximately 30 patients were to be enrolled in the dose escalation phase of the study. A 2-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle (Neuenschwander, 2008) was used as a guide during the escalation phase of the study for dose level selection and for determination of the MTD and/or RP2D. For details, refer to Protocol Amendment 2.0 (Appendix 16.1.1).

The first patient (a sentinel patient) of each escalating NKTR-255 dose level was monitored for safety and tolerability for 7 days after the first dose of NKTR-255 before additional patients were dosed at the same dose level.

A composite of clinical information was to be used to select the RP2D based on safety and tolerability, PK, PD, and optimal biological response.

The dose-limiting toxicity (DLT) window was 21 days after the first dose of NKTR-255. Patients who achieved optimal response (partial response [PR] or complete response [CR] per RECIST 1.1) after at least 1 tumor assessment, as determined by the Investigator and in consultation with the Medical Monitor, were given the option to continue treatment with NKTR-255 as single agent for maintenance every 28 days (q28d) at the same dose as the patient's originally assigned dose.

NKTR-255 Sample Dose Escalation Scheme: Study Phase 1b

Dose Level[a]	Potential NKTR-255 Dose Levels[a]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

DLT = dose-limiting toxicity; FIH = first-in-human; PD = pharmacodynamic; PK = pharmacokinetic; SRC = Safety Review Committee

[redacted]

b. After the starting dose, dose levels for subsequent levels could adjusted (escalated or de-escalated) based on clinical safety, PK, or PD observations. The exact dose was confirmed based on review of safety data by the SRC after a minimum of 3 patients were enrolled at each dose level. The SRC or Sponsor could decide to enroll additional patients (ie, up to 12) to further understand the benefit/risk profile at a given dose level. Dose escalation could not exceed double the prior dose of NKTR-255.

c. If DLTs were observed at the starting dose, NKTR-255 could be de-escalated.

- Intermediate doses could be evaluated.
- No intra-patient dose escalation was allowed.
- Enrollment into a new dose level with an escalating dose of NKTR-255 could not begin until the DLT window had closed for at least 3 patients in the prior dose level.
- The Safety Review Committee (SRC)-assessed safety before opening dose escalation to the next level.
- [redacted]

Data from a minimum of 6 evaluable patients were required to define the RP2D.

- Dose reduction of NKTR-255 was not allowed during dose escalation within the DLT window. Outside of the DLT window in the dose escalation phase, and during dose expansion, dose levels of NKTR-255 could be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested (the dose level could be de-escalated in order to characterize RP2D for a specific dose level).
- The cetuximab dose could be reduced or adjusted based on review of available safety and tolerability data. Dose adjustment or discontinuation for cetuximab could be required based on emerging toxicities, and followed the guidelines specified in this protocol and in the current local prescribing information for cetuximab.

Phase 2 - Dose Expansion

Following enrollment of Phase 1b (Dose Escalation), the 19-255-03 study was closed at all sites due to Nektar decision. The 19-255-03 study was not closed due to risks to any subjects' safety. The study did not proceed past Phase 1b and no patients were enrolled in Phase 2 (Dose Expansion).

NKTR-255 was to be further evaluated in the following expansion cohorts upon reaching Phase 2:

- Cohort A: HNSCC patients; NKTR-255 in combination with cetuximab
- Cohort A1: HNSCC patients; NKTR-255 monotherapy
- Cohort B: CRC patients; NKTR-255 in combination with cetuximab
- Cohort B1: CRC patients; NKTR-255 monotherapy

- Cohort C: cSCC patients; NKTR-255 monotherapy
- Cohort C1: cSCC patients; NKTR-255 in combination with cetuximab
- Cohort D: ASCC patients; NKTR-255 monotherapy
- Cohort D1: ASCC patients; NKTR-255 in combination with cetuximab
- Cohort E: cervical cancer patients; NKTR-255 monotherapy
- Cohort E1: cervical cancer patients; NKTR-255 in combination with cetuximab

Cohorts A and B were to combine NKTR-255 at the RP2D and cetuximab in patients with R/R HNSCC and R/R CRC, respectively, to further characterize safety and tolerability. Each cycle of NKTR-255 was to be 21 days during dose expansion, and cetuximab was given weekly.

Cohorts C, D, and E were to evaluate NKTR-255 monotherapy in patients with R/R cSCC, ASCC, and cervical cancer, respectively, to characterize safety and tolerability. The dose was to be further optimized according to Section 5.3.1.3 of Protocol Amendment 2.0 (Appendix 16.1.1), and the starting dose of the monotherapy was not to be higher than any previous dose level tested during dose escalation. Each cycle of NKTR-255 was to be 21 days during dose expansion.

Following review of safety, tolerability, and efficacy data from Cohorts A through E, Cohorts A1 through E1 could be opened for enrollment (Figure 1). If opened, Cohorts A1 and B1 were to evaluate NKTR-255 monotherapy in patients with HNSCC and/or CRC, respectively. If opened, Cohorts C1, D1, and E1 were to evaluate NKTR-255 in combination with cetuximab in patients with cSCC, ASCC, and/or cervical cancer, respectively.

Patients in Cohorts A, B, C1, D1, and E1 (combination cohorts) who achieved optimal response (PR or CR per RECIST 1.1) were to be given the option to continue treatment with NKTR-255 as single agent, at the same dose as originally assigned, for maintenance q28d.

The RP2D for any cohort could be adjusted based on review of safety, tolerability, and efficacy findings. A staggered adaptive randomization design was to be used to guide enrollment. Patients who received NKTR-255 monotherapy in Cohorts C, D, E, A1, or B1 (monotherapy cohorts) who, after at least 1 tumor assessment, did not experience PR or CR per RECIST 1.1, were to have the option to receive cetuximab as “add-on” therapy.

The dose of NKTR-255 for Cohorts C, D, and E could be adjusted according to Section 5.3.1.3 of Protocol Amendment 2.0 (Appendix 16.1.1).

Number of Patients Planned:

Phase 1b Dose Escalation: Approximately 30 patients

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Number of Patients Enrolled:

A total of 25 patients were enrolled in the study and received at least 1 dose of any study drug:

- Phase 1b Dose Escalation: 25 patients
- Phase 2 Dose Expansion: no patients were enrolled

Sex:	**Age, median (range):**
17 (73.9%) male; 6 (26.1%) female	61.0 years (34 to 81 years) for the 23 patients in Safety Population

Ethnicity (Race):

For the 23 patients in the Safety Population: White, 15 (65.2%); Not reported, 3 (13%); Black or African American, 2 (8.7%); Unknown, 2 (8.7%); Asian, 1 (4.3%); American Indian or Alaska Native, 0; Native Hawaiian or Other Pacific Islander, 0

Diagnosis and Main Criteria for Eligibility:

Adults at least 18 years of age having R/R cancer of one of the following tumor types:

- HNSCC
- CRC
- cSCC (not opened)
- ASCC (not opened)
- Cervical cancer (not opened)

Test Product, Dose and Mode of Administration, Batch Number:

NKTR-255 was administered intravenously as a 30-minute infusion q21d or q28d. NKTR-255 was administered as monotherapy and in combination with cetuximab q21d, and q28d as single-agent maintenance for patients previously treated with NKTR-255 in combination with cetuximab.

During dose escalation (Phase 1b), NKTR-255 was administered CCI [redacted]

The dose expansion (Phase 2) cohorts were not enrolled during this study.

All patients who received NKTR-255 received batch number [redacted]

Administration of cetuximab was according to the current local prescribing information. Cetuximab was administered IV weekly [redacted] as an initial loading dose alone, then at a dose of [redacted] IV in combination with NKTR-255).

The following cetuximab batch numbers were used in this study: [redacted] CCI [redacted] and [redacted]

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable; the study did not include a comparator or placebo

Duration of Treatment:

Patients were to remain on treatment until disease progression per RECIST 1.1, unacceptable toxicity, pregnancy, death, or one of the other criteria for discontinuation of treatment in Section 9.1.3.2.3.

Criteria for Evaluation:

Efficacy:

Tumor measurements were performed every 9 weeks + 7 days.

The primary efficacy measurement was ORR by RECIST 1.1. Other efficacy outcomes included:

- BOR
- DOR
- CBR
- TTR
- PFS
- OS
- ORR by Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

Safety:

Assessment of safety included ongoing review of the following:

- incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs)
- clinical laboratory tests (blood and urine sampling)
- vital signs
- electrocardiograms (ECGs) and cardiac function tests
- physical examination

Pharmacokinetics:

Blood samples for NKTR-255 and/or cetuximab PK analyses were collected from patients (respective to treatment) at multiple scheduled sampling times. Plasma concentrations of NKTR-255 and cetuximab were determined using validated methods.

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Statistical Methods:

Following enrollment of Phase 1b (Dose Escalation), the study was closed at all sites due to Nektar decision. The 19-255-03 study was not closed due to risks to any subjects' safety. The study did not proceed past Phase 1b and no patients were enrolled in Phase 2 (Dose Expansion).

Efficacy:

Objective response rate, CBR, and each BOR category were calculated along with the 95% confidence intervals (CIs) based on the exact method. [redacted]

Safety:

Safety assessments included TEAEs, incidence of SAEs, clinical laboratory tests, vital signs, physical examinations, cardiac function tests, and ECGs. The incidence of DLTs was evaluated for each dose level. All TEAEs were to be summarized by system organ class and preferred term, incidence severity, and relationship to the study drug(s) for each dose level or cohort in the dose escalation and dose expansion phases of the study separately.

Clinical laboratory tests and vital signs were to be summarized descriptively for each dose level in the dose escalation phase and separately for the dose expansion phase of the study. All abnormal findings in clinical laboratory test results, vital signs, physical examination, cardiac function tests, and ECGs were listed.

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Summary and Conclusions:

This study was a Phase 1b/2, open-label, multicenter, dose escalation, and dose expansion study in patients with R/R HNSCC and CRC. In Phase 1b, patients received an IV loading dose of cetuximab alone, followed 7 days later by the first combination treatment of IV cetuximab and IV NKTR-255 on C1D1. Thereafter, IV NKTR-255 was given in 21-day cycles in combination with weekly IV cetuximab. Phase 2 cohorts were not enrolled in this study.

In total, 25 patients were enrolled and received at least one dose of any study drug (10 patients with HNSCC and 15 patients with CRC). Of these, 23 patients were dosed with NKTR 255: CCI [redacted] and were included in the Safety Population. Two additional patients received 1 dose of cetuximab, but no dose of NKTR-255.

In the HNSCC Safety Population, the median age for the 8 patients was 64.5 years, ranging from 50 to 81 years. Half the patients (50.0%) were less than 65 years of age, 3 patients (37.5%) were ≥ 65 and < 75 years of age, and only 1 patient (12.5%) was ≥ 75 years of age. No patients were ≥ 85 years of age. The majority of patients (87.5%) were men, and the most commonly reported race was White (50.0%). The majority of patients (75.0%) had metastatic disease and only 2 patients (25.0%) had locally advanced or recurrent disease. The median number of prior lines of therapy was 4.0 (range: 1 to 5 lines).

In the CRC Safety Population, the median age for the 15 patients was 58.0 years, ranging from 34 to 72 years. Most patients (66.7%) were less than 65 years of age, 5 patients (33.3%) were ≥ 65 and < 75 years of age, and no patients were ≥ 75 years of age. The majority of patients (66.7%) were men and most (73.3%) were White. All 15 patients had metastatic disease, none had locally advanced or recurrent disease, none had any prior history of brain metastases, and the median number of lines of prior therapy was 3.0 (range: 2 to 8 lines).

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Safety Results:

Dose-limiting Toxicities:

A single DLT (infusion-related reaction [IRR] in the NKTR-255 CCI [redacted], assessed as related to NKTR-255) was reported in 1 patient (5.0%), and no delayed DLTs were reported.

Adverse Events:

The most frequently reported TEAEs were dermatitis acneiform and IRR. Dermatitis acneiform was reported in 12 patients (52.2%), 11 of which experienced dermatitis acneiform which was Grade 1 or 2 in severity. Infusion-related reaction was reported in 10 patients (43.5%), the majority (8) of which experienced an IRR that was Grade 1 or 2 in severity.

Thirteen of 23 patients (56.5%) experienced a Grade ≥ 3 TEAE. The only Grade ≥ 3 TEAEs reported for more than one patient were IRR and pneumonia, which were reported in 2 patients (8.7%). Infusion-related reaction was assessed as related to NKTR-255 in both patients, and pneumonia was assessed as not related to NKTR-255 in both patients. Other Grade ≥ 3 TEAEs assessed as related to NKTR-255 were gamma-glutamyl transferase (GGT) increased, lymphocyte count decreased, and pyrexia (each in 1 patient, 4.3%).

Ten patients (43.5%) reported a total of 14 SAEs. No SAEs were reported by more than 1 patient (4.3%). Two patients each had a single SAE that was assessed as related to NKTR-255: IRR (Grade 3), which led to discontinuation, and cytokine release syndrome (Grade 2).

Twenty-two of 25 patients (88.0%) experienced at least 1 extended TEAE assessed as related to study drug (NKTR-255 and/or cetuximab). The most frequently reported were dermatitis acneiform in 14 patients (56.0 none of which were assessed as related to NKTR-255, and IRR in 11 patients (44.0%), all of which had 1 or more IRRs assessed as related to NKTR-255.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events:

In total, 8 of 25 (32.0%) patients died during the study, with progressive disease being the most common cause of death (6/8 deaths).

A total of 3 (12.0%) patients died within the "extended" TEAE period (ie, period after first dose and up to 60 days after last dose or before starting new antineoplastic therapy), including 2 due to progressive disease and 1 due to adverse event (AE). The only TEAE leading to death (multiple organ dysfunction syndrome) occurred in 1 patient with CRC in the CCI [redacted] treatment group and was considered unrelated to study treatment. The remaining 5 deaths occurred during long-term follow-up (i.e., greater than 60 days following the last dose of NKTR-255) and were due to progressive disease (n = 4) or respiratory failure (n = 1) following progressive disease.

Four patients (16.0%) had extended TEAEs that led to study drug discontinuation. One patient experienced anaphylactic reaction (assessed as not related to NKTR-255), 1 patient experienced cellulitis (assessed as not related to NKTR-255), 1 patient experienced IRR (assessed as related to NKTR-255), and 1 patient had respiratory failure (assessed as not related to NKTR-255).

One patient (4.3%) experienced a TEAE of pyrexia leading to NKTR-255 dose reduction and 3 patients experienced at least 1 TEAE related to NKTR-255 which led to a dose delay. These TEAEs included cellulitis, peritonitis, pneumonia, sinusitis, and dermatitis acneiform, and each only occurred in 1 patient.

Clinical Laboratory Evaluation:

Worsening hematology toxicity grades that occurred in greater than 20% of patients included: decreased lymphocytes (95.7% of patients), decreased hemoglobin (Hgb; 65.2% of patients), decreased platelets (26.1% of patients), and decreased white blood count (21.7% of patients). Worsening postbaseline Grade 3 or 4 hematology abnormalities of decreased Hgb and decreased lymphocytes occurred in 13.0% and 87.0% of patients, respectively.

Hepatic impairment was normal (ie, not impaired) in 11 patients (50.0%) and mildly impaired in 11 patients (50.0%). Hepatic labs did not show moderate or severe hepatic impairment in any patients. No patients met the criteria for Hy's law.

Renal function was assessed as change from baseline based on both Levey and the Cockcroft and Gault equation. Based on Levey, the majority (72.7%) of patients had a normal estimated glomerular filtration rate (eGFR). Three patients (13.6%) had mild impairment, 3 (13.6%) had moderate impairment, and no patients had severe impairment

in eGFR. The results were similar based on the Cockcroft and Gault equation; 90.9% of patients had normal/mild, 9.1% had moderate impairment, and no patients had severe impairment in calculated creatinine clearance.

Worsening chemistry toxicity grades that occurred in greater than 20% of patients included: increased GGT (47.8% of patients), decreased albumin (43.5%), increased alanine aminotransferase (39.1%), increased lactate dehydrogenase (39.1%), decreased sodium (30.4%), and increased alkaline phosphatase, decreased calcium corrected for albumin, and decreased potassium (each 26.1%). Grade 3 or 4 worsening postbaseline chemistry abnormalities occurred as follows: increased lipase (13.0% of patients) and increased GGT and decreased sodium (each in 4.3% of patients).

Vital Signs and Other Observations:

No clinically meaningful pattern of vital signs changes was identified and no clinically meaningful changes in ECG were reported. No pregnancies were reported.

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Conclusions:

Nektar Study 19-255-03 was a Phase 1b/2, open-label, multicenter, dose escalation and dose expansion study planned in adults with R/R HNSCC, CRC, cSCC, ASCC, and cervical cancer. This study was to be run in 2 parts: Dose Escalation (Phase 1b) and Dose Escalation (Phase 2). However, following enrollment of Phase 1b, the study was closed at all sites due to Nektar decision.

In Phase 1b, patients received an IV loading dose of cetuximab alone, followed 7 days later by the first combination treatment of IV cetuximab and IV NKTR-255. Thereafter, IV NKTR-255 was given in 21-day cycles in combination with weekly IV cetuximab.

In total, 25 patients were enrolled and received at least one dose of any study drug (10 patients with HNSCC and 15 patients with CRC). Of these, 23 patients were dosed with NKTR-255: CCI [redacted]) and were evaluated for safety. The majority of the patients enrolled were men (73.9%).

Safety

Overall, NKTR-255 in combination with cetuximab was found to be well tolerated at all doses studied. As expected for this patient population with R/R CRC and HNSCC, most patients (96.0%) reported 1 or more extended TEAE. The most frequently reported TEAEs were dermatitis acneiform and IRR. Dermatitis acneiform was reported in 12 patients (52.2%), 11 of which experienced dermatitis acneiform which was low grade (Grade 1 or 2) and none of which were assessed as related to NKTR-255. Infusion-related reaction was reported in 10 patients (43.5%), the majority (8) of which experienced an IRR that was low grade (Grade 1 or 2), and all of which were assessed as related to NKTR-255.

No overlapping toxicities were noted between cetuximab and NKTR-255 based on the terms and reported relationship.

NKTR-255 was better tolerated at CCI versus CCI with lower frequency of SAEs and Grade ≥ 3 AEs. Therefore, it is expected that NKTR-255CCI is an optimal dose for combination with other antibody-dependent cellular cytotoxicity (ADCC) agents. Transient increase of inflammatory cytokines was observed at ~6 hours postdose, however, they returned to baseline around Day 2 to 3. In addition, the majority of patients (52.0%) reported at least 1 SAE, though only 12% of patients reported an SAE that was assessed as related to either study drug.

During the clinical conduct of the study only 2 serious adverse drug reactions were reported (IRR and cytokine release syndrome [CRS]). Both reactions were recovered/resolved, and CRS was assessed as serious due to hospitalization of the patient; however, the patient was hospitalized for observation only and not due to the severity of the episode. Only 1 fatal event was reported (multiple organ dysfunction syndrome occurring 33 days following last dose of NKTR-255), deemed unrelated to the study treatment but related to the disease progression. During the clinical conduct of the study no patient died or discontinued study treatment due to an AE.

The great majority of laboratory findings and treatment-related AEs, such as lymphopenia, neutropenia, and low platelet count, were transient by nature and in-line with the expected mechanism of action of cytokines, which includes rapid cellular marginalization of nucleated cells into the interstitial tissue. This rapid effect is well characterized with agnostic cytokines and poses no additional safety concerns or enhancement of any opportunistic infection as monitored on-study.

Overall, NKTR-255 in combination with cetuximab was considered safe and well tolerated with a positive benefit-risk balance.

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Pharmacokinetics

While there were some limitations in the PK dataset, overall, the study and resulting data were able to meet the study PK objectives. CCI

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Date of Report:	30 January 2024