Clinical Memorandum

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SUBJECT: PAS-Labeling Supplement

PRODUCT: YESCARTA (YESCARTA®) (Kite Pharma, a Gilead Company)

BLA: STN 125643/362

RECOMMENDATION: Approval

Executive Summary

This PAS supplement requests changes to the Prescribing Information (PI), primarily to the safety sections, based on results from Cohort 6 from Study ZUMA-1. The changes to the PI are based on data demonstrating a reduction in rate of CRS and/or neurotoxicities associated with YESCARTA® following prophylactic treatment with dexamethasone at a dose of 10 mg once daily administered on Days 1-3 post infusion of YESCARTA® to 39 evaluable subjects. The study was conducted as an add-on cohort (Cohort) to ZUMA-1, which was the primary study supporting marketing of YESCARTA® in large B cell lymphoma. Thus, while the initial approval of YESCARTA® was based on management of CRS mostly Grade 2 or later, a subsequent cohort (Cohort 4) was included in ZUMA-1 to evaluate the benefits of early intervention with tocilizumab and corticosteroids at lower grades of CRS including intervention at Grade 1 for prolonged fever in 40 subjects. The data from that cohort formed the basis for recommendations to the management of CRS in Section 2 of the existing label. The

results of the safety data from Cohort 6 were evaluated in the context of any improvements in the incidence of CRS and neurotoxicities based on the findings from Cohort 3 via descriptive statistics to provide a recommendation as to whether the benefits of prophylactic corticosteroids outweigh the risks of such therapy and whether a risk-based approach to individualize the management with prophylactic steroids is warranted. Cohort 6 was not designed to evaluate efficacy or compare efficacy with Cohort 4.

The review of the data demonstrates that with regard to CRS in Cohort 6, there was an absence of Grade 3 or greater CRS, delayed onset of CRS and reduction in the median duration of CRS. These benefits were offset by an increase in Grade 4 neurological toxicities, and late onset event of toxic/metabolic encephalopathy. Since the occurrence of CRS or neurotoxicities cannot be predicted for the individual patient and the data from Cohort 6 suggests limited benefit with regard to CRS counterbalanced by an increased risk of severe neurotoxicities, the recommendation of the review team is to consider the use of prophylactic therapy with corticosteroids on an individualized basis taking into consideration risks associated with co-morbidities that may exacerbate risks (e.g., diabetes mellitus that may exacerbate increased blood sugar requiring additional monitoring and management) or confound assessment of neurotoxicities (e.g., underlying psychiatric conditions). In addition, the conclusion in relation to CRS and neurotoxicities are derived from a small cohort and without direct comparison across Cohort 4 and Cohort 6 and should be interpreted with caution and remains a limitation of this safety analysis.

The labeling recommendations in Section 5 provide prescribers advice to administer prophylactic corticosteroids based on an individualized basis and describes the findings in terms of rates, severity, duration and time of onset of neurological and CRS events. Section 6 provides information regarding the study design and dose. Section 2 removes the advice to avoid prophylactic corticosteroids as the data from pharmacokinetic assessments of CAR T cell expansion do not suggest an inhibition of CAR T cell activity or expansion in the presence of corticosteroid administration.

Background:
YESCARTA® is an engineered autologous T cell immunotherapy. The original Biologics License Application (BLA) was approved on October 18, 2017 for the indication of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Approval was based on results from the Phase 1 study and Phase 2 pivotal study cohorts, Cohorts 1 and 2, from Study KTE-C19-101 (ZUMA-1).

ZUMA-1 is a Phase 1 / 2 single arm multicenter, open-label study evaluating the safety and efficacy of YESCARTA® in subjects with r/r large B-cell lymphoma. ZUMA-1 has 3

phases: Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (Cohorts 3 through 6).

Safety management Cohort 3 evaluated the effect of prophylactic use of tocilizumab on the rate and severity of cytokine release syndrome (CRS) and neurologic events. Results suggested that compared with subjects in Cohorts 1 and 2, subjects in Cohort 3 had a numerically lower incidence of Grade 3 or higher CRS, but no difference in the incidence of Grade 3 or higher neurologic events. Cohort 4 examined the effect of earlier intervention with corticosteroids and/or tocilizumab on the incidence and severity of CRS and neurologic events. Results suggested that compared with subjects in Cohorts 1 and 2, subjects in Cohort 4 had numerically lower incidences of Grade 3 or higher CRS and Grade 3 or higher neurologic events. Notably, in both Cohort 3 and Cohort 4, the use of corticosteroids and/tocilizumab did not appear to compromise the efficacy or CAR T-cell expansion after Yescarta infusion.

Cohort 6 was designed to assess the effect of prophylactic corticosteroids (oral dexamethasone 10 mg given daily for 3 days starting on Day 0 prior to Yescarta infusion) and levetiracetam starting on Day 0, in addition to the same earlier interventions with corticosteroids and/or tocilizumab as described for Cohort 4, on the incidence and severity of CRS and neurologic events. Of note, prophylactic tocilizumab was not used in Cohort 6 because the rates of Grade 3 or higher neurologic events were not improved with this approach. Similarly, as with Cohort 4, the subjects enrolled in Cohort 6 were allowed bridging therapy administration between the leukapheresis and the lymphodepletion at the discretion of the investigator.

Key study procedures were identical for Cohort 6 and Cohort 4. Bridging therapy was allowed in both Cohort 4 and 6. Therefore, the subjects enrolled and treated in Cohort 6 are comparable to subjects in Cohort 4. Of note, the subjects treated during Phase 1 and Phase 2 Cohorts 1 and 2 were not allowed to receive bridging therapy, and hence could have relatively higher tumor burden at baseline compared to Cohorts 4 and 6. The primary analysis was to be performed when a minimum of 40 treated subjects had had the opportunity to be followed up for at least 6 months after the infusion of Yescarta. Furthermore, the disease response assessment in Cohort 6 was not based on blinded independent review committee (IRC) review; and no formal hypothesis testing was pre-specified or conducted. Therefore, any conclusion from Cohort 6 regarding efficacy should be interpreted with caution, and we concluded that the data were insufficient to support any change in the efficacy section of the label.

The purpose of this Prior Approval Supplement (PAS) is to update the existing United States Prescribing Information (USPI) for YESCARTA® with safety results from ZUMA-1 Phase 2 Safety Management Cohort 6, which assessed the effect of prophylactic corticosteroids administered on Day 0, Day 1, and Day 2 and levetiracetam starting on Day 0, on the incidence and severity of CRS and neurologic events.

Clinical: Safety
A total of 42 subjects were enrolled and underwent leukapheresis in Cohort 6. Of those 42 subjects, 40 subjects (95%) received lymphodepletion, and all 40 subjects were treated with YESCARTA®. Of the 2 (5%) subjects who did not receive lymphodepletion, one no longer met the eligibility criteria, and one did not have the product available (manufacturing failure: transduction results was below the limit of quantification and failed to meet the prespecified lot release criteria). Twenty-one subjects (53%) received bridging therapy after leukapheresis and prior to lymphodepletion chemotherapy. The most commonly used regimens were corticosteroids (9 subjects, 23%), and rituximab+bendamustine+corticosteroids (4 subjects, 10%).

The primary safety population for ZUMA-1 Cohort 6 included a total of 40 enrolled subjects, of which there were 39 evaluable subjects who were treated with YESCARTA®, received all three doses of corticosteroids as planned and were followed-up for at least 6 months after the infusion. One subject (Subject ID: (b) (6) received only one dose of prophylactic dexamethasone on Day 0. The subject developed Grade 1 CRS on Day 10 that ended on Day 12). At the 6-month primary analysis, the median potential follow up was 8.9 months (range: 6.0 to 12.1 months), with all treated subjects having a minimum of 6 months of follow up from treatment with YESCARTA. At the 12-month data cutoff, the median potential follow-up from YESCARTA infusion was 14.9 months (range: 12.1 to 18.1 months).

Of all the subjects enrolled, median age was 64.5 years (range: 37 to 85 years), 58% were male, 95% were non-Hispanic/Latino, 85% were white, and majority (63%) were from the United States. Majority of the subjects had DLBCL (60%), the rest were transformed follicular lymphoma (23%) and high-grade B cell lymphoma (18%). At enrollment, 95% of the subjects had received ≥2 prior lines of chemotherapy.

The median weight-adjusted dose of YESCARTA was 2.00 x 10e6 CD19 CAR T cells/kg (range: 1.30 to 2.00 x 10e6 CD19 CAR T cells/kg). One subject weighing 85 kg received 120 x 10e6 total CAR T cells. Thirty-nine treated subjects received ± 10% of the planned dose of YESCARTA (2 x 10e6 CD19 CAR T cells/kg or 2 x 10e8 CD19 CAR T cells).

All subjects experienced at least one adverse event (AE) following YESCARTA infusion. All forty subjects (100%) had at least one worst Grade 3 or higher events.

Deaths: At the 6-month analysis, 7 of the 40 subjects (18%) who received YESCARTA infusion had died. None of the deaths occurred within 30 days of YESCARTA infusion. Six of those deaths occurred “on study” while one subject died after withdrawal of consent. The primary causes of death were progressive disease in 4 subjects (10%) and adverse events in 3 subjects (8%).

Subject ID (b) (6) was a 66-year-old white male with relapsed refractory DLBCL, who died on Day 107 of study due to urosepsis. The investigator felt that the causality of

the urosepsis was unrelated to YESCARTA, and the causality was not reported for the conditioning chemotherapy.

Subject (b) (6) was a 67-year-old white male with relapsed transformed follicular lymphoma (Stage IV DLBCL) who died on day 91 due to respiratory failure.

Subject ID (b) (6) was a 71-year-old white male who died on Day 212. The subject had withdrawn consent from the study on Day 210. Therefore, as per the sponsor, no additional information was collected on the cause of death, nor any events leading to the death.

At 12-month analysis, 2 additional subjects died: one due to progressive disease and other due to grade 5 toxic metabolic encephalopathy considered related to YESCARTA.

Subject (b) (6) was an 80-year-old while male with relapsed stage III DLBCL. On Day 351, the subject experienced an SAE (serious NE) of toxic encephalopathy (Grade 4). The event changed to Grade 5 on Day 369. The event was considered related to axicabtagene ciloleucel and was unresolved at death**.** MRI done on Day 351/352 was abnormal and showed mild area of restricted diffusion in the left frontal lobe with extensive surrounding edema (differential considerations included toxic metabolic etiologies as well as infection including progressive multifocal leukoencephalopathy). On Day 369, the subject died due to toxic/metabolic encephalopathy**.** Per the sponsor, the analysis of this subject's cause of death was limited as a result of subject's family decision. The investigator considered the death to have likely occurred due to acute CNS process. The subject did not have any evidence of CRS at the time of death.

The sponsor has agreed to including the information about this late and fatal event in the proposed label.

Adverse events of special Interest (AESI):
Adverse Events of Special Interest (AESI) included CRS, neurologic toxicities, serious infections, neutropenia, prolonged cytopenias lasting greater than 30 days, and hypogammaglobulinemia.

Cytokine Release Syndrome (CRS): CRS was graded as per 2014 Lee criteria. At the 6-month analysis, 31 out of 39 subjects (79%) developed CRS. However, no subject had Grade 3 or higher CRS. The median time to onset of CRS was 5.0 days (range: 1 to 15 days) after YESCARTA infusion. At the time of data cutoff, CRS had resolved in all subjects with median duration of 4.0 days (range: 1-10 days). There were no changes in CRS incidence, onset, or duration at the 12-month analysis. The most frequent CRS symptoms were fever, hypotension, tachycardia, fatigue, hypoxia, headache, and chills.

Neurologic events (NE): NEs were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The NEs were identified and reported based on Method 1 or narrow search strategy (based on

known neurologic toxicities associated with CD19 directed immunotherapy, Topp MS et. al. Lancet Oncol 2015) and Method 2 or wide search strategy (based on MedRA system organ classes of psychiatric disorders and nervous system).

At the 6-month analysis, by narrow search strategy (Method 1), neurologic event of any grade occurred in 23 out of 39 subjects (59%): 5 subjects had Grade 3 or higher event (worst grade 3 event in 3 subjects and worst grade 4 event in 2 subjects). No subject experienced grade 5 neurologic event. The most frequent neurologic event of any grade was encephalopathy (53%), tremor (23%), aphasia (18%), delirium (15%) and seizure (8%). Whereas by broad search strategy (Method 2) which is consistent with FDA's approach to analysis of neurotoxicities for all labeling purposes, the neurologic event of any grade occurred in 33 out of 39 subjects (85%). Worst grade 3 or higher NE occurred in 5 subjects (3 subjects with worst grade 3 and 2 subjects with worst grade 4 NE). No subject had worst grade 5 NE. The most frequent NEs were encephalopathy (53%), headache (30%), tremor (23%), aphasia (20%), dizziness (18%), delirium (15%), insomnia (15%) and anxiety (10%). At 12-month analysis, one subject developed a grade 5 treatment emergent AE of toxic/metabolic encephalopathy. No subject in cohort 6 developed cerebral edema.

Collectively, Method 2 yielded more reports of NEs compared to Method 1, as expected. However, both methods yielded the same incidence of worst grade 3 or higher NEs. The median time to onset of NE was 6 days (range: 1-274 days) with a median duration of 12 days (range: 1 to 107 days).

Treatment of CRS and Neurotoxicity: Besides the prophylactic use, the corticosteroids were administered for treatment of toxicities: CRS (17 subjects, 43%), neurologic events (16 subjects, 41%), and for other reasons (1 subject, 3%). Twenty-three subjects (59%) who received corticosteroids also received tocilizumab. Tocilizumab was administered to 23 subjects (59%) for treatment of CRS and 1 subject for the treatment of neurologic events (3%). Twenty-three subjects received treatment with corticosteroid and tocilizumab for either CRS and/or neurologic toxicity. The median time to onset of therapeutic corticosteroid treatment was 5.0 days (range: 3 to 9 days) after Yescarta infusion, and the most frequent reason for treatment was Grade 2 CRS (9 of 24 subjects, 37.5%). Among the 40 subjects who received corticosteroids for prophylaxis, the median cumulative dose was 939.0 mg (range: 313 to 939 mg); 39 subjects (98%) received 3 doses and 1 subject received 1 dose.

Twenty-five subjects received corticosteroids for use other than prophylaxis; these subjects were treated with a median cumulative dose of 2504 mg (range: 313 to 4,240,710 mg). Fifteen subjects (6 subjects who did not have neurologic toxicity and 9 subjects who did have neurologic toxicity) did not report the use of additional corticosteroid doses between the time of prophylactic use and hospital discharge. Eight out of those 9 subjects with neurologic event who were not treated with additional corticosteroids, had Grade 1 NEs (headache, aphasia, dizziness, tremor, insomnia and confusional state), whereas 1 subject had grade 2 NE (headache). Of note, although the

management guideline as per table 2 in current USPI of Yescarta recommends using therapeutic corticosteroid to treat grade 1 neurologic toxicity, the ultimate decision was based on treating physician's clinical judgement.

Prolonged cytopenias (lasting 30 days or longer): At the 6-month analysis, 24 subjects (61%) had prolonged cytopenias of any grade. Eighteen subjects (46%) had worst grade 3 or higher cytopenia on or after Day 30. Worst Grade 3 or higher prolonged neutropenia (including febrile neutropenia) was reported for 12 subjects (30%). Worst Grade 3 or higher prolonged thrombocytopenia was reported for 8 subjects (20%), and worst Grade 3 or higher prolonged anemia was reported for 4 subjects (10%). Overall, the incidence of cytopenia did not change between the 6 month and 12-month analysis.

Serious Infections: Twenty subjects (51%) had infection of any grade. Eight subjects (20%) had worst grade 3 or higher infection: 5 subjects (13%) with worst grade 3 infection, 2 subjects (5%) with worst grade 4 infection, and one subject (2%) with worst grade 5 infection (urosepsis leading to death as described above).

Hypogammaglobulinemia: At the 6 month-analysis, 6 subjects (15%) had hypogammaglobinemia. No subject developed grade 3 or higher hypogammaglobulinemia.

Key labeling changes

The applicant proposes the following changes based on data from ZUMA-1, Cohort 6:

1. To revise Section 2 Dosage and Administration, Subsection 2.2 Administration: Under Premedication, the applicant proposes to remove the statement "Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of Yescarta"
2. To include summaries of Cohort 6's rates and severity of CRS and neurologic toxicities in Section 5 Warnings and Precautions, Subsection 5.1 Cytokine Release Syndrome and 5.2 Neurologic Toxicities, respectively.
3. To update Section 6.1 Clinical Trial Experience with Safety data from Cohort 6.

Reviewer comments

The key change in the treatment of subjects in ZUMA-1 Cohort 6 compared with those in ZUMA-1 Cohort 4 was the prophylactic use of corticosteroids (oral dexamethasone 10 mg daily for 3 days starting on Day 0 before Yescarta infusion). Thirty-nine subjects received all three doses of corticosteroids. In Cohort 6, Grade 3 or higher CRS occurred in none of the subjects, compared with 2% subjects with Grade 3 or higher CRS in Cohort 4. The median time to onset was delayed: 5 days (range: 1-15 days) in Cohort 6 vs 2 days (range: 1-8 days) in Cohort 4. The median duration of CRS was shorter: 4 days (range: 1-10 days) in Cohort 6 vs 7 days (range: 2-16 days) in Cohort 4. Furthermore, In Cohort 6, Grade 3 or higher neurologic events occurred in 5 subjects (13%): 3 subjects with Grade 3 and 2 subjects with Grade 4 neurologic events. One additional subject in Cohort 6 developed late Grade 5 fatal event of toxic/metabolic

encephalopathy. In Cohort 4, 20% (8/41) subject developed Grade 3 neurologic toxicity with no subjects developing Grade 4 or 5 events. The median time to onset of neurologic toxicity was similar: 6 days (range: 1-274 days) in Cohort 6 vs 6 days (range: 1-193 days) in Cohort 4. However, the median duration was longer in Cohort 6: 12 days (range: 1-107 days) in Cohort 6 vs 8 days (range: 1-144 days) in Cohort 4.

Collectively, in this small cohort of subjects treated with Yescarta, the prophylactic use of corticosteroid prior to Yescarta infusion decreased the incidence of Grade 3 or higher CRS, delayed the onset and shortened the duration of CRS. However, such approach increased the incidence of Grade 4 neurologic events and prolonged the duration of neurologic events. Therefore, the treating physicians should consider the risks and benefits of prophylactic corticosteroids in the context of pre-existing comorbidities for the individual patient and the potential for increased risk of Grade 4 and prolonged neurologic toxicities.

The applicant’s proposed changes to Section 2, Section 5 and Section 6 of the USPI listed above are acceptable. ZUMA-1 Cohort 6 efficacy data are insufficient to support any change in the efficacy section of the label (Section 14). The APLB found the prescribing information (PI) changes to be acceptable. On 10 January 2022, revisions recommended to the USPI label were sent to the applicant. The applicant agreed to all FDA’s changes and made the requested revisions. A final, fully acceptable label was sent on 11 January 2022. This reviewer recommends approving this labeling supplement.