# Safety of Mogamulizumab in Mycosis Fungoides and Sézary Syndrome: Final Results from the Phase 3 MAVORIC Study

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## Introduction

- Mogamulizumab is a defucosylated, humanized monoclonal antibody that selectively binds C-C chemokine receptor 4 (CCR4), using antibody-dependent cellular cytotoxicity[1,2]
- MAVORIC was an open-label, multicenter, randomized phase 3 study evaluating the safety and efficacy of mogamulizumab compared with vorinostat in patients with previously treated mycosis fungoides (MF) or Sézary syndrome (SS) (NCT01728805)[3]
- Primary results have been reported based on a data cutoff date of December 31, 2016[3]
  - The primary endpoint was progression-free survival (PFS); patients in the mogamulizumab treatment arm experienced significantly longer PFS compared with patients in the vorinostat treatment arm (median 7.7 months vs 3.1 months; *P*<0.0001)
  - The most common all-cause treatment-emergent adverse events (TEAEs) reported in patients randomized to mogamulizumab were:
    - Infusion-related reaction (33.2%)
    - Drug eruption (i.e., skin rash attributed to mogamulizumab [23.9%])
    - Diarrhea (23.4%)
    - Fatigue (23.4%)
  - In total, 19.0% (35/184) of mogamulizumab-treated patients and 23.1% (43/186) of vorinostat-treated patients discontinued due to TEAEs
    - The most frequent TEAEs leading to discontinuation were drug eruption (7.1% [13/184]) in mogamulizumab patients and fatigue (4.3% [8/186]) in vorinostat patients
- Overall, serious adverse events (SAEs) were reported in 37.5% (69/184) of mogamulizumab patients and 24.7% (46/186) of vorinostat patients; SAEs considered drug related were reported in 19.6% (36/184) of mogamulizumab patients and 16.1% (30/186) of vorinostat patients

## Objective

- Report final safety results of MAVORIC based on a data cutoff of January 3, 2019

## Methods

- Patients were randomized 1:1 to mogamulizumab 1.0 mg/kg administered intravenously on Days 1, 8, 15, and 22 of the first cycle (28-day length) and on Days 1 and 15 of subsequent cycles or to vorinostat 400 mg administered orally once daily
- Patients randomized to vorinostat were allowed to cross over to mogamulizumab upon progression or intolerable toxicity
- Final safety results were based on a data cutoff of January 3, 2019, approximately 2 years after the data cutoff date of December 31, 2016, that was used for the primary analysis[3]
- Safety was assessed by reported adverse events (AEs), changes in physical examinations, vital sign measurements, electrocardiograms, and laboratory analyses

## Results

- Of the 372 randomized patients, 370 received study drug and were included in the safety analysis:
  - 184 randomized and treated with mogamulizumab
  - 186 randomized and treated with vorinostat
- Overall, 319 patients were exposed to mogamulizumab during the course of the study:
  - 184 randomized and treated with mogamulizumab
  - 135 crossed over and treated with mogamulizumab
- Median duration of follow-up was 34.5 months (range, 0.13–70.0) in the randomized part of the study
- Median treatment exposure in the randomized part of the study was 170 days (range, 1–1813) for mogamulizumab and 84 days (4–1230) for vorinostat
  - In the primary analysis, median treatment exposure was 170 days (1–1379) for mogamulizumab and 84 days (4–1058) for vorinostat
- The types and frequencies of all-cause TEAEs in both treatment groups (**Table**) were similar in this analysis to those reported in the primary analysis
  - TEAEs that occurred at higher frequency in the mogamulizumab vs vorinostat arm included infusion-related reaction and drug eruption (defined as skin rashes that were assessed by the investigator or sponsor as possibly, probably, or definitely related to study drug); the majority (>80%) of these events were Grade 1 or 2
- TEAEs that were reported at similar rates in the 2 treatment groups included constipation, peripheral edema, headache, and anemia
- The most frequently reported (>15%) AEs attributable to mogamulizumab (per Investigator assessment) included infusion-related reaction (33.2% [61/184]), drug eruption (23.9% [44/184]), and fatigue (18.5% [34/184]) (**Figure 1**), and for vorinostat, diarrhea (55.4% [103/186]), nausea (38.2% [71/186]), and fatigue (33.3% [62/186])
- Discontinuation rates due to AEs were similar between treatment arms (mogamulizumab, 21.7% [40/184]; vorinostat, 23.7% [44/186]) (**Figure 2**)
- The most common AEs leading to discontinuation were drug eruption with mogamulizumab (7.1% [13/184]) and fatigue with vorinostat (4.3% [8/186]) (**Figure 3**); some mogamulizumab discontinuations due to drug eruption were mandated by the protocol, such as occurrence of Grade ≥3, or Grade 2 that was unresolved for 2 weeks on mogamulizumab re-challenge following initial drug eruption
  - In cutaneous diseases such as MF/SS, drug eruption can be difficult to distinguish from disease progression; to make a definitive diagnosis, and in order to avoid premature discontinuation of mogamulizumab, a biopsy is recommended[4]
- Overall, the rates of SAEs in each treatment arm were as follows: mogamulizumab, 39.7% (73/184), and vorinostat, 25.3% (47/186)
- The rates of drug-related SAEs were similar between treatment arms (mogamulizumab, 19.6% [36/184]; vorinostat, 16.7% [31/186]) (**Figure 4**)

**Table. TEAEs Reported in ≥10% of Patients From Either Treatment Group During Randomized Treatment:[a] Results of the Final Safety Analysis**

| System organ class preferred term[b,c,d] | Mogamulizumab (n=184) | | Vorinostat (n=186) | |
|---|---|---|---|---|
| | All grades n (%) | Grade ≥3 n (%) | All grades n (%) | Grade ≥3 n (%) |
| **Gastrointestinal disorders** | **97 (52.7)** | **4 (2.2)** | **152 (81.7)** | **17 (9.1)** |
| Diarrhea | 48 (26.1) | 1 (0.5) | 115 (61.8) | 9 (4.8) |
| Nausea | 30 (16.3) | 1 (0.5) | 79 (42.5) | 3 (1.6) |
| Constipation | 23 (12.5) | 1 (0.5) | 34 (18.3) | 2 (1.1) |
| Vomiting | 13 (7.1) | 0 | 24 (12.9) | 1 (0.5) |
| Abdominal pain | 9 (4.9) | 0 | 22 (11.8) | 0 |
| **General disorders and administration site conditions** | **109 (59.2)** | **8 (4.3)** | **126 (67.7)** | **17 (9.1)** |
| Fatigue | 44 (23.9) | 3 (1.6) | 70 (37.6) | 11 (5.9) |
| Edema peripheral | 28 (15.2) | 0 | 27 (14.5) | 1 (0.5) |
| Pyrexia | 33 (17.9) | 1 (0.5) | 12 (6.5) | 0 |
| Asthenia | 10 (5.4) | 0 | 28 (15.1) | 4 (2.2) |
| **Infections and infestations** | **119 (64.7)** | **33 (17.9)** | **93 (50.0)** | **20 (10.8)** |
| Upper respiratory tract infection | 21 (11.4) | 0 | 10 (5.4) | 2 (1.1) |
| **Skin and subcutaneous tissue disorders** | **101 (54.9)** | **12 (6.5)** | **79 (42.5)** | **9 (4.8)** |
| Alopecia | 14 (7.6) | 0 | 36 (19.4) | 0 |
| Drug eruption | 46 (25.0) | 9 (4.9) | 2 (1.1) | 0 |
| **Nervous system disorders** | **70 (38.0)** | **3 (1.6)** | **101 (54.3)** | **7 (3.8)** |
| Dysgeusia | 8 (4.3) | 0 | 55 (29.6) | 1 (0.5) |
| Headache | 25 (13.6) | 0 | 29 (15.6) | 1 (0.5) |
| Dizziness | 12 (6.5) | 0 | 19 (10.2) | 0 |
| **Investigations** | **68 (37.0)** | **10 (5.4)** | **95 (51.1)** | **12 (6.5)** |
| Blood creatinine increased | 6 (3.3) | 0 | 52 (28.0) | 0 |
| Weight decreased | 11 (6.0) | 1 (0.5) | 33 (17.7) | 3 (1.6) |
| Platelet count decreased | 4 (2.2) | 0 | 19 (10.2) | 0 |
| **Metabolism and nutrition disorders** | **62 (33.7)** | **13 (7.1)** | **77 (41.4)** | **16 (8.6)** |
| Decreased appetite | 16 (8.7) | 2 (1.1) | 46 (24.7) | 2 (1.1) |
| **Musculoskeletal and connective tissue disorders** | **71 (38.6)** | **5 (2.7)** | **59 (31.7)** | **7 (3.8)** |
| Muscle spasm | 10 (5.4) | 0 | 29 (15.6) | 2 (1.1) |
| **Blood and lymphatic system disorders** | **49 (26.6)** | **3 (1.6)** | **77 (41.4)** | **19 (10.2)** |
| Thrombocytopenia | 22 (12.0) | 0 | 58 (31.2) | 13 (7.0) |
| Anemia | 21 (11.4) | 2 (1.1) | 20 (10.8) | 3 (1.6) |
| **Injury, poisoning, and procedural complications** | **82 (44.6)** | **9 (4.9)** | **28 (15.1)** | **2 (1.1)** |
| Infusion-related reaction | 61 (33.2) | 3 (1.6) | 1 (0.5)* | 0 |
| **Respiratory, thoracic, and mediastinal disorders** | **60 (32.6)** | **7 (3.8)** | **46 (24.7)** | **7 (3.8)** |
| Cough | 20 (10.9) | 0 | 16 (8.6) | 0 |
| **Vascular disorders** | **32 (17.4)** | **13 (7.1)** | **39 (21.0)** | **13 (7.0)** |
| Hypertension | 18 (9.8) | 9 (4.9) | 25 (13.4) | 12 (6.5) |

[a]Defined as AEs that occurred from the first dose of randomized study drug through 90 days after the last dose of randomized study drug or the start of alternative CTCL therapy, whichever occurred first; AEs considered related to study drug that occurred >90 days after the last dose of randomized study drug were also counted as TEAEs during the randomized treatment period.
[b]MedDRA Version 15.1 was used for coding.
[c] The protocol was amended on May 31, 2018, to require only collection of study drug-related AEs/SAEs and implemented at individual sites upon institutional review board/ethics committee approval.
[d]For each system organ class, the overall rate includes specific AEs not listed in the table due to <10% occurrence.
*1 patient had an infusion reaction on Day 1 of crossover to mogamulizumab treatment (17 days after the last dose of vorinostat) that was indicated as possibly related to vorinostat (and mogamulizumab).
CTCL, cutaneous T-cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities.

**Figure 1. Drug-Related TEAEs Reported by ≥15% of All Patients Exposed to Mogamulizumab**

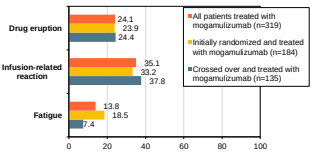



**Figure 2. Overall Discontinuation Rates due to AEs in the Randomized Population and in Crossover Patients**

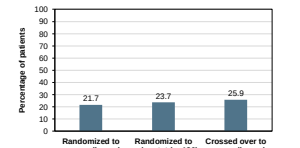



**Figure 3. TEAEs Leading to Discontinuation in ≥2.5% of Patients in Either Treatment Group During Randomized Treatment**

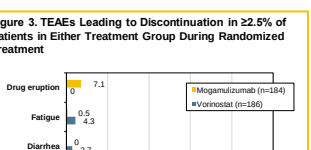
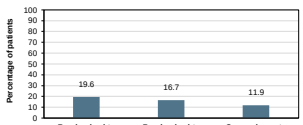



**Figure 4. Overall Rates of Drug-Related SAEs in the Randomized Population and in Crossover Patients**




- After the data cutoff for the primary analysis, 2 patients experienced TEAEs with an outcome of death; all were considered unrelated to study treatment per Investigator: 1 patient randomized to mogamulizumab (decreased appetite, general physical health deterioration, hypoalbuminemia) and 1 crossover patient (cerebral hemorrhage)

*Crossover patients*

- In patients who crossed over to mogamulizumab, the most frequently reported (>15%) AEs attributable to mogamulizumab were infusion-related reaction (37.8% [51/135]) and drug eruption (24.4% [33/135]) (**Figure 1**); other common AEs were fatigue, increased alanine aminotransferase, and increased aspartate aminotransferase (7.4% [10/135] each)
- The discontinuation rate due to AEs was 25.9% (35/135) (**Figure 2**)
- Overall, the rate of SAEs was 30.4% (41/135); the rate of drug-related SAEs was 11.9% (16/135) (**Figure 4**)
- Discontinuation rates by AEs and SAEs did not correlate in mogamulizumab and cross-over

## Conclusions

- **This final safety analysis from the MAVORIC study in patients with previously treated MF and SS demonstrated that mogamulizumab was generally well tolerated with long-term exposure, and no new safety issues emerged**
  - **Infusion-related reaction and drug eruption were the 2 most commonly reported AEs attributable to mogamulizumab**
- **With a longer follow-up (approximately 2 years after the data cutoff for the primary analysis; approximately 3 years of total follow-up including the primary analysis) and a broader range of treatment exposure (median exposure 170 days [range, 1–1,813+]), the current analysis did not identify any new safety signals with mogamulizumab treatment**

## References

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