LETTER TO THE EDITOR

Phase I trials of the lysine-specific demethylase 1 inhibitor, GSK2879552, as mono- and combination-therapy in relapsed/refractory acute myeloid leukemia or high-risk myelodysplastic syndromes

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Outcomes remain poor for patients with advanced myelodysplastic syndrome (MDS) or relapsed/refractory acute myeloid leukemia (AML) [1,2] due to a lack of effective treatment regimens [3,4], highlighting an unmet clinical need for novel treatments for these patients. Preclinical studies suggest that the lysine-specific demethylase 1 (LSD1) inhibitor GSK2879552 [5], a potent differentiating agent and epigenetic modifier, has therapeutic potential in MDS and AML [5,6]. Additionally, the activity of LSD1 inhibitors may be enhanced when combined with differentiation-inducing drugs such as all-trans retinoic acid (ATRA) or azacitidine [7,8]. Here, we present results from two Phase I, open-label studies conducted in patients with relapsed/refractory AML (study 200200; NCT02177812) or high-risk MDS (study 205744; NCT02929498) to determine the safety, recommended Phase II dose, clinical activity, pharmacokinetics (PK), and pharmacodynamics (PD) of GSK2879552 alone or in combination with ATRA or azacitidine. Both studies were terminated during dose escalation due to an unfavorable risk-to-benefit ratio.

Study 200200 (NCT02177812) was a Phase I, open-label, 2-arm, 2-part study of GSK2879552 in adult patients with relapsed/refractory AML by World Health Organization classification, for whom no standard therapies were available. The study was conducted at centers in Australia (n = 1), Canada (n = 1), and the USA (n = 3) between 2 September 2014 and 19 December 2017. Part 1 comprised a dose-escalation phase to determine the safety and tolerability of GSK2879552, given orally every day, alone or in combination with ATRA. GSK2879552 monotherapy was investigated in six dose-escalation cohorts (1, 2, 4, 8, 12, and 20 mg) and in the PK/PD expansion group at 20 mg. Patients in the combination arm received GSK2879552 2 mg daily + ATRA 45 mg/m²/day.

Study 205744 (NCT02929498) was a Phase I/II, open-label, 2-arm, 2-part study of GSK2879552 in patients with high-risk MDS who had failed hypomethylating treatment, conducted at centers in Spain (n = 2) and the USA (n = 1) between 3 July 2017 and 18 December 2017. Part 1 comprised a dose-escalation phase to determine the safety of GSK2879552 2 mg daily, alone or in combination with azacitidine (Vidaza®; 75 mg/m²/day for 7 days) [9]. Written informed consent was obtained from each participant. The studies were conducted in accordance with the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice, applicable country-specific requirements, and the Declaration of Helsinki. The studies were approved by the appropriate institutional review boards and independent ethics committees. Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Patient demographics and baseline characteristics for both studies are provided in Supplementary Table 1 and patient disposition is shown in Supplementary Figure 1. An expansion phase (Part 2) was planned for both...
studies but not initiated due to early study termination. Briefly, endpoints assessed in study 200200 included safety (primary endpoint), clinical response rate (secondary endpoint), PK parameters (secondary endpoint), and PD markers (exploratory endpoint, including expression of CD11b, CD86, and CD71 cell surface markers). Endpoints assessed in study 205744 included safety (primary endpoint) and clinical activity (secondary assessments). Full details of inclusion criteria, study endpoints, assessments and statistical analyses are provided in the Supplementary materials.

### Table 1. Safety in study 200200: serious adverse events by MedDRA Preferred Term (All-Treated population).

| SAEs | 1 mg (N = 1) | 2 mg (N = 2) | 4 mg (N = 7) | 8 mg (N = 5) | 12 mg (N = 6) | 20 mg (N = 4) | PK/PD expansion (N = 6) | 2 mg + ATRA 45 mg/m² (N = 10) | Total (N = 41) |
|-------|--------------|--------------|--------------|--------------|--------------|--------------|------------------------|-----------------------------|----------------|
| Any SAE | 1 (100) | 2 (100) | 7 (100) | 5 (100) | 6 (100) | 3 (75) | 5 (83) | 8 (80) | 37 (90) |
| SAEs | 2 | 6 | 16 | 13 | 14 | 9 | 9 | 6 | 15 |
| Drug-related SAEs | 0 | 0 | 1 | 0 | 2 | 1 | 1 | 0 | 2 |
| Fatal SAEs | 0 | 0 | 1 | 0 | 3 | 1 | 0 | 2 | 7 |
| Drug-related fatal SAEs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |

### Non-fatal SAEs, number of events

- Febrile neutropenia: 2
- Hematoma/subdural hematoma: 0
- Cellulitis: 0
- Bacteremia (Pseudomonal/Klebsiella): 0
- Hemorrhage (gastric/subarachnoid): 0
- Pneumonia: 0
- Acute kidney injury: 0
- Alanine aminotransferase increased: 0
- Anemia: 0
- Anorectal cellulitis: 0
- Arthralgia: 0
- Bone pain: 0
- Cardiomyopathy: 0
- Clavicle fracture: 0
- Cognitive disorder: 0
- Delirium: 0
- Fall: 0
- Hallucinations: 0
- Hypoxia: 0
- Influenza: 0
- Leukocytosis: 0
- Lung infection: 0
- Nausea: 0
- Oral pain: 0
- Pancreatitis: 0
- Parainfluenza: 0
- Pneumonia respiratory syncytial viral: 0
- Pulmonary mycosis: 0
- Pyrexia: 0
- Soft tissue infection: 0
- Thrombocytopenia: 0
- Troponin I increased: 0
- Upper respiratory tract infection: 0
- Viremia: 0
- Vomiting: 0

### Fatal SAEs, number of events

- Dyspnea: 0
- Encephalopathy: 0
- Escherichia sepsis: 0
- Febrile neutropenia: 0
- Pleural effusion: 0
- Septic shock: 0

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event.

*Drug-related SAEs, n = 1.*

*One AE of toothache (not included in the table) was recorded as Grade 5, which indicates a cause for fatality, but this could not be corrected as the database had been frozen.*

In study 200200, 41 patients with relapsed/refractory AML received treatment for a median duration of 4.0 (range 1.4–24.4) weeks. All patients reported at least one adverse event (AE), most frequently febrile neutropenia (54%), nausea (46%), hypokalemia (41%), and fatigue (34%) (Supplementary Table 2). Of special interest, eight (20%) patients experienced nine thrombocytopenia events, seven of which were Grade 4. Four thrombocytopenia events were considered treatment related. Twenty-four (59%) patients experienced 54 hemorrhagic events, nine of which were considered treatment related,
Figure 1. PK and PD analysis of GSK2879552: (A,B) mean plasma PK concentration–time curves for GSK2879552 after the first dose, and (C) changes in cell surface marker expression over time in the pooled GSK2879552 8 mg, 12 mg, and 20 mg dose groups in bone marrow aspirate and peripheral blood (study 200200). Data from evaluated dose levels (GSK2879552 8 mg, 12 mg, 20 mg) are pooled and shown with a 95% confidence interval in C. Number of patients included in the BMA analysis: 8 mg, n = 1; 12 mg, n = 6; 20 mg, n = 8. Number of patients included in the peripheral blood analysis: 8 mg, n = 1; 12 mg, n = 6; 20 mg, n = 9. BMA: bone marrow aspirate; D: day; SD: standard deviation; W: week.
including four Grade 2 (gingival, conjunctival, petechiae, and subdural) and two Grade 3 (subdural and epistaxis) events (Supplementary Table 2; Supplementary materials). Eight (20%) patients had AEs leading to permanent discontinuation of GSK2879552 (Supplementary materials). Thirty-seven (90%) patients had ≥1 serious AE (SAE), most commonly febrile neutropenia (n = 20 [49%]) (Table 1 and Supplementary Table 3). Seven (17%) patients had a treatment-related SAE and seven (17%) died due to fatal SAEs, one of which was considered treatment related (febrile neutropenia) (Table 1).

Among the 10 patients who received GSK2879552 + ATRA combination therapy, treatment-related Grade 2 pruritus led to treatment discontinuation due to investigator discretion in one patient. In addition, eight Grade 1/2 cognitive disorder, confusional state and disturbance in attention events were reported in five patients (50%; 5/8 events were resolved); correspondingly, two of these patients had a decrease of ≥3 in their Montreal Cognitive Assessment (MoCA) scores compared with baseline, which required treatment discontinuation per protocol (although treatment was not discontinued for one patient due to a protocol deviation). A third patient on GSK2879552 + ATRA combination therapy also had a decrease of ≥3 in their MoCA score, correlating with a Grade 3 AE of delirium. An additional patient had a 6-point drop in MoCA score, but it occurred before the first dose was administered.

Two patients had Grade ≥3 increases in clinical laboratory evaluations from baseline deemed to be related to study treatment (Grade 3 hypophosphatemia and hypertriglyceridemia), and two patients had clinically significant changes in electrocardiogram readings from baseline.

Minor clinical responses were observed in 2/41 (5%) patients. Two patients achieved a morphologic leukemia-free state at the 12 mg dose level and with GSK2879552 + ATRA combination therapy, and improvement in leukemia cutis was observed in one patient following treatment with GSK2879552 12 mg (Supplementary Figure 2). Following single and repeated dosing in study 200200, GSK2879552 was rapidly absorbed with maximum plasma drug concentration (C\text{max}) achieved within the first hour and showed slow elimination, with a half-life (t\text{1/2}) of 17 h (Figure 1(A,B) and Supplementary Table 4). C\text{max} and area under the curve tended to increase dose-proportionally and the moderate accumulation seen with daily administration corresponded with t\text{1/2}. Co-administration with ATRA did not alter the PK of GSK2879552. Evaluation of cell-differentiation-related [8] cell surface markers demonstrated an increase in CD11b+ cells, consistent with monocytic differentiation, and a decrease in CD71+ cells, consistent with the maturation of hematopoietic progenitors, over time in blood and bone marrow aspirate, with minimal changes (<10%) in CD86+ cells following treatment with GSK2879552 (Figure 1(C)).

In study 205744, five patients with MDS received GSK2879552 monotherapy; no patients received combination with azacitidine (Supplementary Figure 1). All five patients reported a total of 40 AEs (Supplementary Table 5), most of which were isolated Grade 1/2 episodes not attributed to study treatment. However, for the single events of parosmia (Grade 1), decreased appetite (Grade 1), and fatigue (Grade 2), a causal relationship to study treatment was reported by the investigator. Grade 2 fatigue (3 events in 3/5 patients) and Grade 1/2 rash (2 events in 2/5 patients) were the only AEs that were reported in >1 patient. Atrial fibrillation (Grade 2) was reported twice in the same patient. Three non-fatal SAEs were reported in one patient: Grade 3 sinusitis, subdural hematoma, and transfusion reaction. No AEs led to permanent discontinuation of study treatment. No clinical responses were observed. GSK2879552 plasma concentrations in study 205744 were in line with those observed in study 200200.

In this Phase 1 study of GSK2879552 in relapsed/refractory MDS and AML, PK profiles and exposure of the investigational agent were similar to those seen in a parallel clinical study in patients with small cell lung cancer (SCLC) (NCT02034123) [10]. As predicted, GSK2879552 induced markers of differentiation in a small subset of patients with relapsed/refractory AML, providing evidence for target engagement. However, no significant responses or clinical benefit were observed with GSK2879552 and treatment was associated with toxicity, including hemorrhage in 24 patients (treatment-related in 5/24) and Grade 3/4 thrombocytopenia in eight patients (treatment-related in 4/8) in study 200200, respectively. Thrombocytopenia is an on-target effect of GSK2879552 previously observed in preclinical studies [5,10] and the parallel clinical study in SCLC [10]. While it is difficult to attribute causality in the context of active leukemia, compromised marrow function, and with a significant background rate of bleeding events (8–11% Grade 3 and 2% Grade 4) in comparable AML populations [11,12], the frequency of hemorrhagic events, other toxicities, and lack of clinical benefit, led to the early termination of the GSK2879552 studies. Of interest, laboratory models continue to support further evaluation of LSD1 inhibitors in AML and MDS, possibly in other AML settings, such as maintenance therapy [7].

Authorship Contributions

Conception or design: MB, AD, HPM, RGK, NOK, GF-B, AA, TC

Acquisition of data: AFB, GS, AV, AHW, GJR, KY, GB, NOK

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Disclosure statement

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