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SHORT REPORT

Haematological Malignancy – Clinical

Analysis of ventricular arrhythmias and sudden death from prospective, randomized clinical trials of acalabrutinib

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Summary

This analysis investigated the incidence of sudden deaths (SDs) and non-fatal and fatal ventricular arrhythmias (VAs) in five acalabrutinib clinical trials. In total, 1299 patients received acalabrutinib (exposure, 4568.4 patient-years). Sixteen (1.2%) patients experienced SD or VA (event rate, 0.350/100 patient-years). Non-fatal VAs occurred in 11 (0.8%) patients, nine (0.7%) of whom had premature ventricular contractions only. SD and fatal VAs occurred in five (0.4%) patients (event rate, 0.109/100 patient-years; median time to event: 46.2 months). SDs and VAs with acalabrutinib occurred at low rates, and there are insufficient data to point to an increased risk of SD or VA with acalabrutinib.

KEYWORDS
acalabrutinib, ibrutinib, sudden cardiac death, sudden death, ventricular arrhythmia

Approval of ibrutinib, the first covalent Bruton tyrosine kinase inhibitor (BTKi), caused a paradigm shift in the management of B-cell malignancies, providing a non-chemotherapy option for the treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL) and Waldenström macroglobulinaemia.[1] While ibrutinib is generally well tolerated, significant toxicities were observed in clinical studies, particularly cardiovascular adverse events (AEs) such as hypertension, atrial fibrillation and ventricular arrhythmias (VAs).[2,3] In a retrospective analysis, the rate of sudden death (SD) in ibrutinib-treated patients was 0.788 events per 100 patient-years.[4] In addition, a post hoc analysis of the phase 3 FLAIR trial in patients with previously untreated CLL reported a sudden unexplained or cardiac death rate of 0.5 patients per 100 patient-years (95% confidence interval [CI] 0.3, 1.0) with ibrutinib plus rituximab, and 0.1 (95% CI 0.0, 0.5) with the combination of fludarabine, cyclophosphamide and rituximab.[5] In a meta-analysis of studies including an ibrutinib regimen, the sudden unexplained or cardiac death rate in the FLAIR trial was consistent with other phase 3 studies, including the GENUINE trial (0.49 patients/100 patient-years [95% CI 0.12, 1.97]) and HELIOS trial (0.53 patients/100 patient-years [95% CI 0.26, 1.05]).[5] Since BTKis are typically administered continuously until disease progression, overall safety, particularly cardiovascular safety, is an important consideration in the treatment of CLL.[6]

The next-generation, highly selective, irreversible BTKi acalabrutinib was approved to treat relapsed/refractory MCL in 2017 and CLL/SLL in 2019.[7] Clinical trials evaluated the tolerability of acalabrutinib compared with chemoimmunotherapy and with ibrutinib.[8–10] The safety data reported in these trials demonstrated an improved

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safety profile with fewer cardiac events compared with ibrutinib.[8–10]

Recently, a retrospective analysis of a US-based Comprehensive Cancer Center cohort of 290 adult patients with B-cell malignancies treated with acalabrutinib was conducted to determine the rate of first-ever symptomatic VAs.[11] The authors concluded that long-term acalabrutinib treatment was associated with an increased risk of VA compared with idiopathic VA in the general population (relative risk 8.2; $p < 0.001$) and suggested this could be a class effect of BTKis.[11]

To provide a more comprehensive estimate of the risk of SD and VA in patients taking acalabrutinib, we analysed the incidence of SD and non-fatal and fatal VA using pooled data from five acalabrutinib trials. The acalabrutinib trials included three phase 3 trials and two non-randomized trials. The phase 3 trials, ASCEND, ELEVATE-TN and ELEVATE-RR, were prospective, randomized, comparative clinical trials comparing acalabrutinib to previous standard-of-care therapies.[8–10] The non-randomized trials were CL-001 and CL-003.[12,13] Events were identified using two methods: (1) a comprehensive data extraction of terms capturing events of SD and non-fatal and fatal VA (terms are defined in Table 1 footnote), and (2) manual clinical review to adjudicate the fatal events (Table 1).

In total, 1299 patients received acalabrutinib (exposure, 4568.4 patient-years). Considering all SDs and non-fatal and fatal VAs combined, 16 (1.2%) patients treated with acalabrutinib had an event. Baseline characteristics for the 16 patients with an event are provided in Table S1. When adjusting for treatment exposure, the event rate per 100 patient-years was 0.350 with acalabrutinib (Figure 1; Table 1). Median time to event with acalabrutinib was 23.5 months. Results were similar after event adjudication through manual clinical review.

TABLE 1 Summary of SD events and non-fatal and fatal VA events from pooled acalabrutinib clinical trials ASCEND, ELEVATE-TN, ELEVATE-RR, CL-001 and CL-003.

	Comprehensive data extraction criteria[a,b] Pooled acalabrutinib (including crossover) *N* = 1299	Adjudicated SD and VA events[c] Pooled acalabrutinib (including crossover) *N* = 1299
Combined SD and fatal and non-fatal VA events		
Patients with event, *n* (%)	16 (1.2)	13 (1.0)
Event rate per 100 patient-years (95% CI)[d]	0.350 (0.215, 0.572)	0.285 (0.165, 0.490)
Patient-years	4568.4	4568.4
Time to event, median (range), months	23.5 (1.2–71.7)	21.4 (1.2–55.4)
SD and fatal VA events		
Patients with event, *n* (%)	5 (0.4)	2 (0.2)
Event rate per 100 patient-years (95% CI)[d]	0.109 (0.046, 0.263)	0.044 (0.011, 0.175)
Patient-years	4568.4	4568.4
Time to event, median (range), months	46.2 (30.5–71.7)	39.7 (31.3–48.1)
Non-fatal VA events excluding PVCs		
Patients with event, *n* (%)	2 (0.2)	-
Event rate per 100 patient-years (95% CI)[d]	0.044 (0.011, 0.175)	-
Patient-years	4568.4	-
Time to event, median (range), months	22.4 (1.4–43.4)	-
Non-fatal VA events including PVCs		
Patients with event, *n* (%)	11 (0.8)	-
Event rate per 100 patient-years (95% CI)[d]	0.241 (0.133, 0.435)	-
Patient-years	4568.4	-
Time to event, median (range), months	11.8 (1.2–55.4)	-

Abbreviations: AEPTCD, adverse event preferred term code; CI, confidence interval; CTCAE, common terminology criteria for adverse events; MedDRA, medical dictionary for regulatory activities; NOS, not otherwise specified; PT, preferred term; PVC, premature ventricular contraction; SD, sudden death; SMQ, standardized MedDRA queries; TEAE, treatment-emergent adverse event; VA, ventricular arrhythmia.

[a]Data extraction criteria for cardiac events: Fatal=TEAE with either PT of: cardiac death, death, death NOS, death from unknown, sudden cardiac death, sudden death, unwitnessed/unexplained death and CTCAE grade 5 or high-level terms of ventricular arrhythmias and cardiac arrest with outcome of death.

[b]MedDRA narrow sub-SMQs for ventricular tachyarrhythmias were used to identify the following non-fatal AEPTCDs: parasystole, rhythm idioventricular, torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachycardia, accelerated idioventricular rhythm, ventricular pre-excitation, ventricular parasystole, cardiac fibrillation, ventricular tachyarrhythmia, arrhythmic storm and early repolarization syndrome.

[c]Subset of events from comprehensive data extraction identified by manual clinical review of data.

[d]Only the first event is counted.

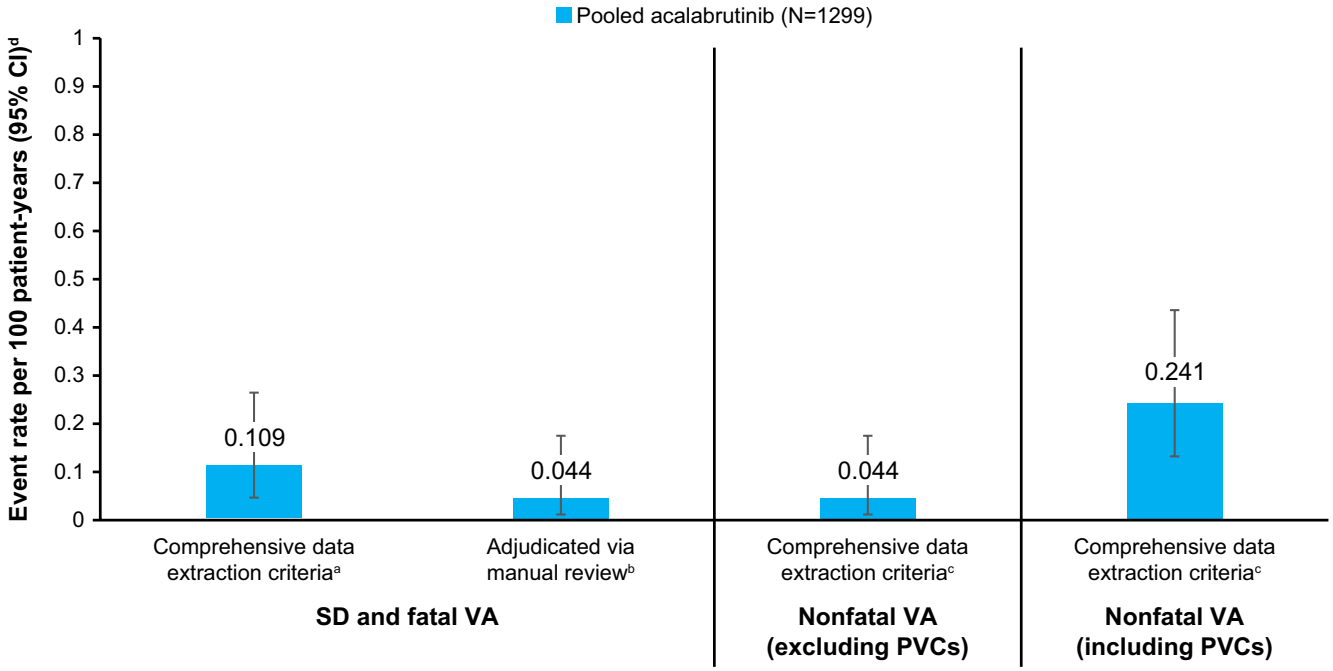

FIGURE 1 SD and VA event rate per 100 patient-years. [a]Data extraction criteria for cardiac events: Fatal = TEAE with either PT of: cardiac death, death, death NOS, death from unknown, sudden cardiac death, sudden death, unwitnessed/unexplained death and CTCAE grade 5 or high-level terms of ventricular arrhythmias and cardiac arrest with outcome of death. [b]Subset of events from comprehensive data extraction identified by manual clinical review of data. [c]MedDRA narrow sub-SMQs for ventricular tachyarrhythmias were used to identify the following non-fatal AEPTCDs: parasystole, rhythm idioventricular, torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachycardia, accelerated idioventricular rhythm, ventricular pre-excitation, ventricular parasystole, cardiac fibrillation, ventricular tachyarrhythmia, arrhythmic storm and early repolarization syndrome. [d]Only the first event is counted. AEPTCD, adverse event preferred term code; CI, confidence interval; CTCAE, common terminology criteria for adverse events; MedDRA, medical dictionary for regulatory activities; NOS, not otherwise specified; PT, preferred term; PVC, premature ventricular contraction; SD, sudden death; SMQ, standardized MedDRA queries; TEAE, treatment-emergent adverse event; VA, ventricular arrhythmia.

Across all clinical trials considered, among the total of 16 patients with an event, only five (0.4%) treated with acalabrutinib had SD or fatal VAs as identified via comprehensive data extraction, for an event rate of 0.109 per 100 patient-years. The rate of SDs and fatal VAs remained low when events were adjudicated through manual clinical review (Table 1). The remaining 11 (0.8%) patients experienced non-fatal VAs, of whom nine (0.7%) experienced premature ventricular contractions (PVCs) only (seven grade 1 events and two grade 2 events reported once in each patient, none of which were considered serious by the investigator); therefore, when excluding PVCs, two (0.2%) patients had non-fatal VAs, both of which were events of ventricular fibrillation (grade 2 and grade 4).

Narratives on the patients who experienced SD or fatal VA while receiving acalabrutinib are provided in Table S2. Of the five fatal cases included in this analysis, one involved a patient who had crossed over from chlorambucil plus obinutuzumab to acalabrutinib after disease progression (72 years of age); the other four cases were reported in patients aged 74, 84, 85 and 86 years, all with significant comorbidities or complications. In total, three patients were excluded during adjudication, including two patients due to a history of extensive cardiac disease and one additional patient due to a traumatic brain injury 2 days before death. No temporal pattern was observed regarding time from acalabrutinib initiation to the reported events. Median time to a non-fatal VA event was 11.8 months when PVCs were included and 22.4 months when PVCs were excluded. Median time to a fatal event was 46.2 months (39.7 months for adjudicated events).

Compared with the previously published retrospective analysis of a cohort of 290 adult patients with B-cell malignancies treated with acalabrutinib,[11] this analysis of 1299 patients treated with acalabrutinib in clinical trials consistently demonstrated low risk of SD or VA in patients treated with acalabrutinib. When adjusting for treatment exposure, the event rate per 100 patient-years for all SD and VA events combined was 0.350 in this analysis compared with an event rate of 0.818 per 100 patient-years in the previous retrospective analysis, and time to event was longer in this analysis than the retrospective analysis (23.5 vs. 12.7 months). The proportions of SDs and fatal VAs were similar and low overall in this analysis and the retrospective analysis (0.4% and 0.3%, respectively). The event rate for SDs and fatal VAs was 0.109 per 100 patient-years in this analysis, compared with 0.5 per 100 patient-years for ibrutinib plus rituximab in the FLAIR study.[5] Low rates of non-fatal VAs excluding and including PVCs were reported in this analysis, 0.2% and 0.8%, respectively, compared favourably with a non-fatal VA rate of 3% in the retrospective analysis. It is important to note that PVCs

have limited clinical significance; they are common in the general population, with an estimated prevalence of >6% that further increases with age.[14] While the current analysis does not provide a direct comparison between acalabrutinib and other BTKis, a previous secondary analysis of ELEVATE-RR showed that ventricular arrhythmias and sudden cardiac death occurred in some patients with ibrutinib (3 and 1, respectively), but in none with acalabrutinib. Cardiac events were also lower with acalabrutinib versus ibrutinib, both in overall incidence and exposure-adjusted incidence.[15]

A limitation of this analysis is that, due to the more stringent inclusion/exclusion criteria of clinical trials, the current dataset may include more fit patients with fewer comorbid conditions compared with real-world retrospective studies. Conversely, data from controlled studies may provide a more accurate assessment of the impact of a treatment on a particular event.

In conclusion, this analysis of acalabrutinib clinical trials suggests that SD and VA with acalabrutinib occur at a low rate. Based on the prospective clinical trial data with more than 1200 patients treated with acalabrutinib reported here, as well as the totality of acalabrutinib clinical data already published, acalabrutinib has a favourable safety profile and a positive benefit–risk ratio in the intended patient population. There are insufficient data to point to an increased risk of SD or VA with acalabrutinib, but high-risk patients should still be closely monitored. Further characterization of the safety profile based on clinical and postmarketing data sources will continue.

AUTHOR CONTRIBUTIONS

PM designed the study. JPS, PG and JFS were study investigators and provided patients or study materials. NB and BS collected and assembled data. PM and BS performed data analysis. JPS, PG, PM, SR, NB, BS and JFS interpreted the data. All authors participated in the critical review and revision of this manuscript and provided approval of the manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

JPS has served as a consultant and as a study investigator for AstraZeneca, AbbVie, BeiGene and Lilly. PG has received research support and honoraria from AbbVie, AstraZeneca, Janssen and Bristol Myers Squibb, and has received honoraria from MSD, Loxo Oncology/Lilly and Roche. PM, NB and BS are employees of AstraZeneca and own stock. SR is an employee of AstraZeneca. JFS has served on advisory boards for AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Genor Bio, Gilead, Janssen and Roche; has served as a consultant for TG Therapeutics; has provided expert testimony for Bristol Myers Squibb, Roche and TG Therapeutics; has received research funding from AbbVie, Bristol Myers Squibb, Janssen and Roche; and has served on speakers' bureaus for AbbVie, Bristol Myers Squibb and Roche.

DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

ETHICS STATEMENT AND CONSENT TO PARTICIPATE

The institutional review board and independent ethics committee approved the protocols of the individual studies comprising this analysis. All patients provided written informed consent before enrolment. The studies were conducted in accordance with the protocol, applicable local regulations and the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practices principles.

CLINICAL TRIAL REGISTRATION

Clinicaltrials.gov identifiers: NCT02475681, NCT02477696, NCT02970318, NCT02029443 and NCT02296918.

PATIENT CONSENT STATEMENT

All patients provided written informed consent before enrolment.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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