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LETTER

# Cumulative review of cardiac failure with acalabrutinib in the treatment of chronic lymphocytic leukemia using data from clinical trials and postmarketing experience

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Bruton tyrosine kinase inhibitors (BTKis) have revolutionized the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). The first-generation BTKi, ibrutinib, has demonstrated efficacy in various CLL/SLL populations[1–3] but has been associated with cardiac toxicities, including atrial fibrillation, hypertension, and cardiac failure.[4,5] Acalabrutinib, a second-generation BTKi approved for CLL/SLL, has less off-target activity than ibrutinib,[6] with durable efficacy demonstrated in phase 3 trials of patients with treatment-naive (ELEVATE-TN)[7] and relapsed/refractory (ASCEND)[8] CLL/SLL. The head-to-head phase 3 ELEVATE-RR study in patients with relapsed/refractory CLL demonstrated noninferior efficacy and significantly lower incidences of any grade atrial fibrillation/flutter (9% vs. 16%) and hypertension (9% vs. 23%) with acalabrutinib versus ibrutinib,[9] consistent with findings from a pooled analysis of all sponsored clinical trials of acalabrutinib monotherapy in CLL (any grade atrial fibrillation/flutter, 5%; hypertension, 9%).[10]

Patients with CLL/SLL are typically older and therefore may have cardiovascular comorbidities that increase cardiac failure risk.[11,12] Hence, characterization of the cardiovascular safety profiles of BTKis is warranted, including data from sources other than clinical trials, which may recruit patients with fewer comorbidities than those seen in routine clinical practice. In this study, we report results from a cumulative review of the cardiac failure safety profile of acalabrutinib based on (1) clinical trial data from ELEVATE-RR, ELEVATE-TN, and ASCEND, and (2) real-world postmarketing data from the Global AstraZeneca Patient Safety Database (GAPSD) (Figure 1A). The GAPSD includes acalabrutinib safety data from all sponsored and unsponsored clinical trials and real-world postmarketing sources; only the real-world postmarketing data were used in this analysis. The three clinical trials were conducted according to the ethical principles derived from international guidelines; all patients provided written informed consent. Real-world postmarketing safety data were collected and reported according to global and local rules and regulations.

Exposure-adjusted incidence rates (EAIR) were reported for "cardiac failure" using the broad Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ, v25.0). SMQs are validated, predetermined groups of MedDRA terms used to support drug safety monitoring and analysis. The "cardiac failure" SMQ consists of 107 cardiac failure-specific and cardiac failure-related terms (Table S1). In the clinical trials analysis, EAIRs for the "cardiac failure" broad SMQ and for the most common MedDRA preferred terms from the SMQ were compared between the acalabrutinib arms and active comparators in the individual trials. A sensitivity analysis assessed EAIRs excluding the most common nonspecific cardiac failure-related preferred terms (i.e., peripheral edema, peripheral swelling, and edema) from the SMQ. Additionally, EAIR based on the "cardiac failure" single preferred term was analyzed from pooled data from the acalabrutinib monotherapy arms in the three trials. A cumulative search of the GAPSD was also performed using the "cardiac failure" broad SMQ and MedDRA preferred terms to report crude incidence and EAIR of cardiac failure events for acalabrutinib monotherapy from the postmarketing data.

EAIRs in the clinical trial analyses were reported as events/100 patient-months, which are calculated as:

$$\text{exposure adjusted incidence} = \frac{N \times 100}{\sum_i t_i}$$

where $N$ is the number of events in the treatment group, $t_i$ is the treatment period (in months) for the individual patient ($i$), and $\Sigma_i$ is the sum across all patients in the treatment group. The treatment-emergent period was defined as the time from the first study treatment dose until 30 days after the last study treatment dose or the start of new anticancer therapy for CLL, whichever occurred first.

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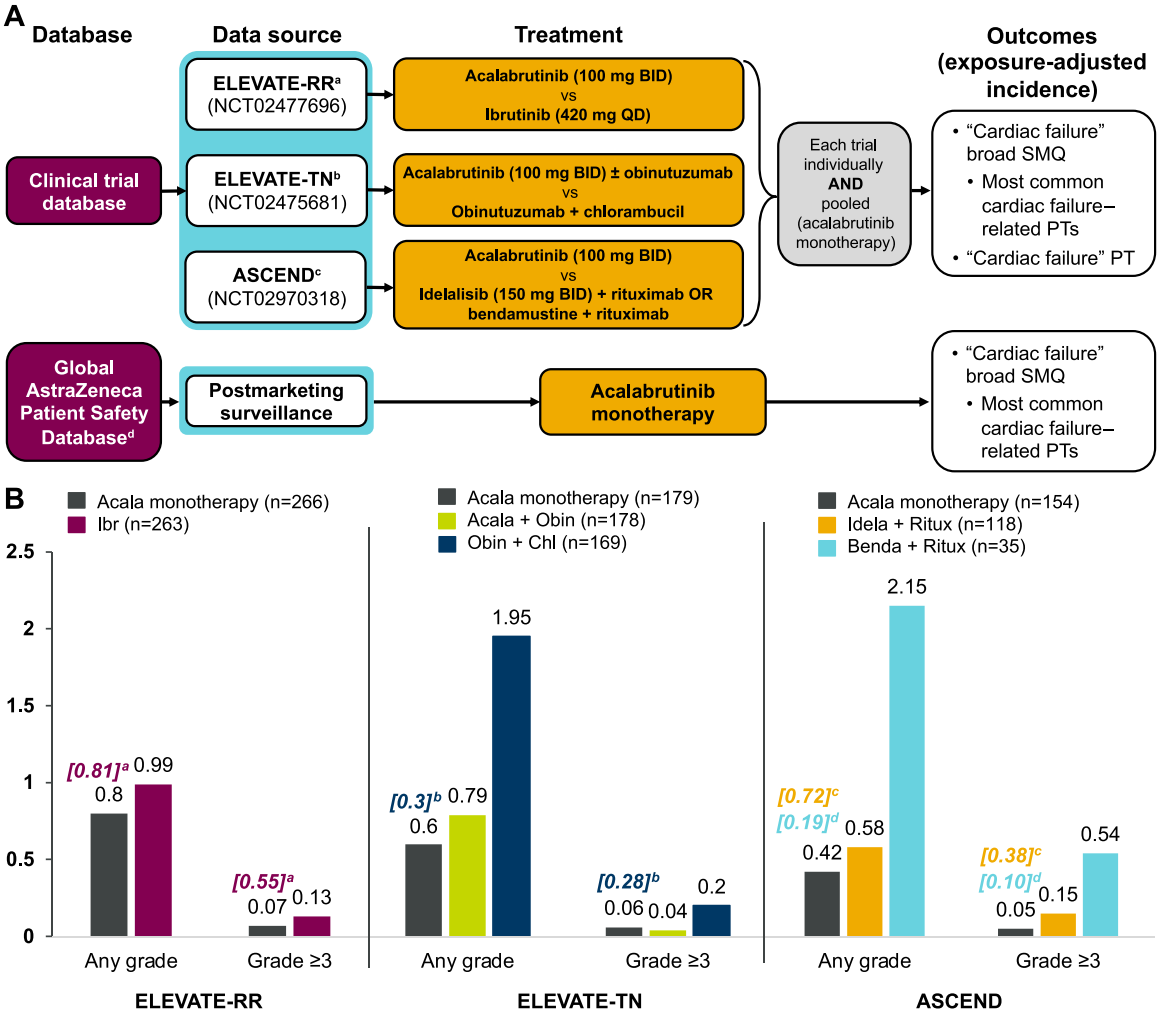


**FIGURE 1** **Overall analysis design and exposure-adjusted incidence rate of "cardiac failure" SMQ (broad) from the ELEVATE-RR, ELEVATE-TN, and ASCEND trials. (A)** The figure describes the methodology for the reported analyses, which included data from three clinical trials and postmarketing data from the Global AstraZeneca Patient Safety Database. [a]ELEVATE-RR is an ongoing, randomized, open-label, noninferiority study of acalabrutinib versus ibrutinib in patients with relapsed/refractory CLL and presence of either del(17p) or del(11q).[9] [b]ELEVATE-TN is an ongoing, randomized, open-label, three-arm study in which treatment-naive patients with CLL were randomized 1:1:1 to receive acalabrutinib, acalabrutinib plus obinutuzumab, or obinutuzumab plus chlorambucil.[7] [c]ASCEND was a randomized, open-label study in patients with relapsed/refractory CLL evaluating acalabrutinib monotherapy versus investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab.[8] **(B)** The graphs report the exposure-adjusted incidence rate of the "cardiac failure" broad SMQ. [a]Ratio of acalabrutinib (acala) monotherapy to ibrutinib (ibr). [b]Ratio of acala monotherapy to obinutuzumab (obin) + chlorambucil (chl). [c]Ratio of acala monotherapy to idelalisib (idela) + rituximab (ritux). [d]Ratio of acala monotherapy to bendamustine (benda) + ritux. BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; QD, once daily; SMQ, Standardized MedDRA Queries.

SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Across the three clinical trials, 599 patients were treated with acalabrutinib monotherapy, 178 with acalabrutinib plus obinutuzumab, and 585 with other targeted or nontargeted treatments (Table 1). Baseline characteristics were similar between the acalabrutinib and comparator arms (Table S2). In all three trials, overall EAIRs of any grade and grade ≥3 cardiac failure (broad SMQ) were numerically lower in the acalabrutinib arms versus the comparator arms (Figure 1B and Table 1), with EAIR ratios consistent with those observed in the sensitivity analysis excluding the most common nonspecific cardiac failure terms (Table 2). The most common cardiac failure-related preferred terms were also generally numerically lower in the acalabrutinib arms versus the comparator arms (Table 1). In the pooled analysis of acalabrutinib monotherapy across the three trials, the EAIR of any grade cardiac failure based on the single preferred term was 0.04/100 patient-months.

In the GAPSD postmarketing analysis, as of October 31, 2022, 727 cardiac failure (SMQ) events were captured based on 33,588 patient-years of acalabrutinib monotherapy exposure. The most common cardiac failure preferred terms reported were peripheral swelling ($n = 406$), edema peripheral ($n = 99$), edema ($n = 56$), pulmonary edema (n = 47), pulmonary congestion ($n = 33$), cardiac failure (n = 32), and cardiac failure congestive ($n = 32$). The estimated EAIR of any grade cardiac failure (SMQ) for acalabrutinib monotherapy from the GAPSD was 0.008/100 patient-months.

In this comprehensive, cumulative review of cardiac failure safety data, the low EAIRs of cardiac failure demonstrated with acalabrutinib in both the clinical trial and real-world settings using the broad SMQ add to the existing evidence supporting the favorable cardiac failure

**TABLE 1** Exposure-adjusted incidence rate of treatment-emergent cardiac failure events.

| | ELEVATE-RR | | | | ELEVATE-TN | | | | | | ASCEND | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Acala (*n* = 266) | | Ibr (*n* = 263) | | Acala (*n* = 179) | | Acala + Obin (*n* = 178) | | Obin + Chl (*n* = 169) | | Acala (*n* = 154) | | Idela + Ritux (*n* = 118) | | Benda + Ritux (*n* = 35) | |
| Treatment duration, median (range), months | 44.1 (0.3–80.2) | | 37.3 (0.2–82.5) | | 73.0 (0.3–94.8) | | 77.2 (1.4–94.0) | | N/A (six cycles max) | | 44.2 (1.1–54.2) | | Idela: 11.5 (0.1–52.3)<br>Ritux: 4.6 (0.0–7.6) | | Benda: 4.7 (0.1–6.2)<br>Ritux: 4.6 (0.0–6.2) | |
| **EAIR, events/100 patient-months [EAIR ratio of acala monotherapy vs. competitor]** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** |
| "Cardiac failure" broad SMQ | 0.80 [0.81] | 0.07 [0.55] | 0.99 | 0.13 | 0.59 [0.3][a] | 0.06 [0.28][a] | 0.79 | 0.04 | 1.95 | 0.20 | 0.42 [0.72][b] [0.19][c] | 0.05 [0.38][b] [0.10][c] | 0.58 | 0.15 | 2.15 | 0.54 |
| **Preferred terms under "cardiac failure" SMQ occurring at EAIRs of ≥0.02 in any arm** | | | | | | | | | | | | | | | | |
| Edema peripheral | 0.47 | 0 | 0.59 | 0.01 | 0.33 | 0.01 | 0.48 | 0.02 | 1.27 | 0 | 0.22 | 0 | 0.24 | 0 | 1.61 | 0 |
| Peripheral swelling | 0.15 | 0 | 0.12 | 0 | 0.15 | 0 | 0.15 | 0 | 0.39 | 0 | 0.05 | 0 | 0.10 | 0 | 0 | 0 |
| Cardiac failure | 0.06 | 0.06 | 0.09 | 0.08 | 0.03 | 0.02 | 0.04 | 0 | 0 | 0 | 0.05 | 0.02 | 0.10 | 0 | 0 | 0 |
| Edema | 0.05 | 0 | 0.10 | 0.01 | 0.03 | 0 | 0.02 | 0 | 0.10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Left ventricular failure | 0.03 | 0.01 | 0.01 | 0 | 0 | 0 | 0.02 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac failure chronic | 0.02 | 0.01 | 0.04 | 0.02 | 0 | 0 | 0.02 | 0 | 0.10 | 0.10 | 0.02 | 0 | 0.05 | 0.05 | 0 | 0 |
| Cardiac failure congestive | 0.02 | 0 | 0 | 0 | 0.03 | 0.02 | 0.01 | 0 | 0 | 0 | 0.04 | 0.02 | 0 | 0 | 0 | 0 |
| Pulmonary edema | 0 | 0 | 0 | 0 | 0.01 | 0.01 | 0.01 | 0 | 0.10 | 0.10 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiopulmonary failure | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.02 | 0.02 | 0.10 | 0.10 | 0 | 0 |
| Cardiac failure acute | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.54 | 0.54 |

Abbreviations: Acala, acalabrutinib; Benda, bendamustine; Chl, chlorambucil; EAIR, exposure-adjusted incidence rate; Ibr, ibrutinib; Idela, idelalisib; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable; Obin, obinutuzumab; Ritux, rituximab; SMQ, Standardized MedDRA Queries.

[a]Ratio of acala monotherapy to obin + chl.

[b]Ratio of acala monotherapy to idela + ritux.

[c]Ratio of acala monotherapy to benda + ritux.

**TABLE 2** Exposure-adjusted incidence rate of treatment-emergent cardiac failure events excluding the most common non-specific preferred terms.

| | ELEVATE-RR | | | | ELEVATE-TN | | | | | | ASCEND | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Acala (*n* = 266) | | Ibr (*n* = 263) | | Acala (*n* = 179) | | Acala + Obin (*n* = 178) | | Obin + Chl (*n* = 169) | | Acala (*n* = 154) | | Idela + Ritux (*n* = 118) | | Benda + Ritux (*n* = 35) | |
| Treatment duration, median (range), months | 44.1 (0.3–80.2) | | 37.3 (0.2–82.5) | | 73.0 (0.3–94.8) | | 77.2 (1.4–94) | | N/A (6 cycles max) | | 44.2 (1.1–54.2) | | Idela: 11.5 (0.1–52.3)<br>Ritux: 4.6 (0.0–7.6) | | Benda: 4.7 (0.1–6.2)<br>Ritux: 4.6 (0.0–6.2) | |
| **EAIR, events/100 patient-months [EAIR ratio of acala monotherapy vs. competitor]** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** |
| "Cardiac failure" broad[a] SMQ | 0.14 [0.75] | 0.07 [0.66] | 0.18 | 0.11 | 0.08 [0.42][b] | 0.05 [0.24][b] | 0.15 | 0.02 | 0.20 | 0.20 | 0.15 [0.60][c] [0.27][d] | 0.05 [0.38][c] [0.10][d] | 0.24 | 0.15 | 0.54 | 0.54 |

Abbreviations: Acala, acalabrutinib; Benda, bendamustine; Chl, chlorambucil; EAIR, exposure-adjusted incidence rate; Ibr, ibrutinib; Idela, idelalisib; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable; Obin, obinutuzumab; Ritux, rituximab; SMQ, Standardized MedDRA Queries.

[a]Excluding peripheral edema, peripheral swelling, and edema.

[b]Ratio of acala monotherapy to obin + chl.

[c]Ratio of acala monotherapy to idela + ritux.

[d]Ratio of acala monotherapy to benda + ritux.

safety profile of acalabrutinib in CLL. In the individual clinical trials, numerically lower EAIRs of cardiac failure were seen with acalabrutinib monotherapy compared to ibrutinib monotherapy and the non-BTK-targeted and nontargeted combination therapies. The low EAIR of cardiac failure in the pooled acalabrutinib monotherapy clinical trial analysis based on the single preferred term also reinforces the low incidence of cardiac failure (any grade, 0.8%; grade ≥3, 0.4%) reported in a previous pooled analysis of 762 patients with CLL/SLL treated with acalabrutinib for a median duration of 24.9 months across four clinical trials.[10]

Notably, the EAIRs of any grade and grade ≥3 cardiac failure (broad SMQ) in the acalabrutinib monotherapy arms were numerically lower than those in the chemoimmunotherapy comparator arms (bendamustine plus rituximab in ASCEND and obinutuzumab plus chlorambucil in ELEVATE-TN). Cardiac failure has been reported as a serious adverse event with bendamustine in clinical trials, and rituximab carries warnings for cardiac arrhythmias and angina,[13,14] both of which may explain the higher incidence of cardiac failure in this treatment arm. However, neither obinutuzumab nor chlorambucil is associated with cardiotoxicities[15,16]; therefore, the reason for the high cardiac failure incidence in this arm is unknown.

While the mechanisms by which BTKis lead to cardiac failure are not well defined, evidence suggests off-target inhibition of the cardioprotective PI3K-Akt pathway plays a role.[17–19] Since acalabrutinib has less off-target kinase activity compared to ibrutinib, cardiotoxicities including cardiac failure may be lessened with acalabrutinib treatment.[6] In the primary report of ELEVATE-RR, at a median treatment exposure duration of 38.3 months for acalabrutinib and 35.5 months for ibrutinib, the overall incidence of "heart failure" (including four cardiac failure-related preferred terms) was low for both treatments, with numerically lower incidences of any grade and grade ≥3 "heart failure" in patients treated with acalabrutinib (any grade, 2.3% vs. 3.4%; grade ≥3, 1.9% vs 3.0%).[9] Results from the current, more comprehensive analysis of "cardiac failure" SMQ accounting for treatment duration demonstrated numerically lower EAIRs for acalabrutinib versus ibrutinib, in line with the primary report.[20]

Despite low levels of cardiac failure reported in clinical trials with acalabrutinib treatment, real-world evidence is sparse. The real-world CLL/SLL population tends to be older with a high prevalence of cardiovascular comorbidities (up to 43%) at the time of diagnosis, which may put them at higher risk for cardiac failure during BTKi treatment.[11,12] Although lower, the estimated prevalence of cardiac failure (defined by the single terms "cardiac failure" or "heart failure") in patients with CLL at the time of diagnosis ranges from 7% to 16%.[11,12] Analyses of real-world data from patients treated with ibrutinib have identified increased safety signals for or associations with cardiac failure events.[4,21,22] In contrast, our analysis of real-world safety data, which included 33,588 patient-years of acalabrutinib exposure, supports a favorable risk profile for cardiac failure with acalabrutinib treatment.

Limitations of this analysis include its retrospective and descriptive design. The analysis comparing EAIRs between the treatment arms of the individual trials was conducted post hoc and did not adjust for multiplicity testing, nor was it powered for assessment of statistical significance. A meta-analysis pooling data across these trials was not performed because it would require combining data across indications (relapsed/refractory and treatment-naive CLL), which include heterogeneous patient populations, making it less informative to the medical community. Statistical analysis comparing EAIRs between the pooled acalabrutinib monotherapy data from the clinical trials and the GAPSD also was not done since some data from the GAPSD contain sparse information on patient characteristics; thus, an accurate statistical comparison between the two data sets adjusting for differing methodologies and patient characteristics was not possible. Furthermore, AstraZeneca only receives postmarketing reports containing acalabrutinib data in the GAPSD; therefore, a control arm could not be included for that analysis.

Based on results from this analysis of clinical trials and real-world safety data, the risk of cardiac failure with acalabrutinib monotherapy in patients with CLL/SLL appears to be low. Patients at high risk for developing cardiac failure should still be monitored closely while receiving BTKi therapy, especially given the association of these treatments with an increased incidence of atrial fibrillation, which may further increase cardiac failure risk.[4]

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## AUTHOR CONTRIBUTIONS

Data analysis: Anthony J. Corry. Data interpretation: All authors. Manuscript review and revisions: All authors. Final approval of the manuscript: All authors.

## CONFLICT OF INTEREST STATEMENT

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## SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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