Leveraging Real-World Data to Support Trial Diversity Action Plans: A Fit-for-Purpose Assessment in Waldenström Macroglobulinemia

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CONCLUSIONS

- Real-world databases can be used to assess the safety of zanubrutinib in patients with Waldenström macroglobulinemia from ethnic and racial minority groups in the postmarketing setting
- In studies using real-world data for pharmacovigilance, a database fit-for-purpose assessment must be performed to ensure both the relevance and quality of the data for the intended purpose
- Leveraging real-world data can be an effective strategy to support trial diversity plan objectives, particularly when some patient groups are underrepresented in clinical studies or study enrollment of patients with rare diseases is challenging

INTRODUCTION

- The US Food and Drug Administration's (FDA's) draft guidance on diversity action plans emphasizes the importance of enrolling participants from underrepresented populations in clinical studies[1]
- Rare diseases such as Waldenström macroglobulinemia (WM) present unique challenges for achieving diversity goals due to their low incidence rates, particularly in ethnic and racial minority patients (eg, 0.18 per 100,000 per year in African Americans)[2]
- These challenges highlight the potential of real-world data (RWD) to augment clinical trials by assessing safety and effectiveness outcomes in minority populations
- Recently, the FDA released additional guidance with recommendations for collecting safety and effectiveness data in historically underrepresented populations in the postmarketing setting, when appropriate[3]
- The objective of this assessment was to evaluate the feasibility of leveraging RWD to assess the safety of zanubrutinib in ethnic and racial minority patients diagnosed with WM in the postmarketing setting

METHODS

- A fit-for-purpose (FFP) assessment was conducted to evaluate the distribution of patients with WM treated with zanubrutinib (2021-2024) by ethnic and racial group at three time points: October 2023, April 2024, and October 2024
- Per FDA guidance for assessing RWD to support regulatory decision-making,[4] the FFP criteria focused on database completeness, representativeness, and granularity in identifying racial and ethnic minority groups and ability to identify relevant safety endpoints
- Data were sourced from commonly used oncology research databases, identified through literature and expert insights, including Symphony Health Solutions claims data, TriNetX electronic health records, and eight additional claims or electronic health record databases that cannot be named due to contractual restrictions at the time of this assessment
- Assessment metrics included patient distribution by racial and ethnic group and the availability of data on safety outcomes, such as atrial fibrillation, hypertension, and second primary malignancy

RESULTS

- Across all databases, the data lag time varied from 1-6 months; see **Table 1** for the feasibility assessment of the data sources
- In the most recent assessment conducted in October 2024, Symphony Health Solutions recorded 438 patients initiating zanubrutinib as of July 31, 2024, including 22 African American (5.0%), 12 Hispanic (2.7%), and 9 Asian (2.1%) patients
- TriNetX identified 622 patients with WM initiating zanubrutinib as of September 16, 2024, including 23 Asian (3.7%), 20 African American (3.2%), and 11 Hispanic (1.8%) patients
- Other databases (ie, databases 1, 2, 4, and 5) also reported >500 zanubrutinib-treated patients with WM. For example, database 2, an oncology practice electronic health record database, recorded 32 African American (2.9%), 31 Hispanic (2.8%), and 27 Asian patients (2.4%)
- Accrual rates (reflecting an increase in patients since the last assessment) in minority groups varied by database. During the most recent data refreshments in April and October 2024, overall 6-month accrual rates were 10% in Symphony and 29% in TriNetX
- Most databases could identify select safety outcomes through diagnosis, procedure, or prescription records, but differences in granularity were observed. For example, in database 2—sourced from oncology practices; primarily community oncology clinics—noncancer safety endpoints such as cardiovascular diseases may have been underestimated
- The overall feasibility assessment—based on (1) the availability of race and ethnicity variables in each dataset, (2) the number of racial and ethnic minority patients as of October 2024, and (3) the ability to evaluate safety and efficacy outcomes of interest—indicated that several databases, including Symphony, TriNetX, and database 1, may be suitable for describing safety endpoints in patients with WM treated with zanubrutinib

Table 1. Feasibility Assessment of Data Sources

	Symphony Health	TriNetX Dataworks-USA	Database 1[a]	Database 2[a]	Database 3[a]	Database 4[a]	Database 5[a]	Database 6[a]	Database 7[a]	Database 8[a]
Data source	Claims	EHR (can be supplemented by claims)	Claims	Oncology practice EHR (including structured, unstructured, and select curated elements); primarily community oncology	Oncology practice EHR (including structured, unstructured, and select curated elements); primarily community oncology	Oncology practice EHR (including structured, unstructured, and select curated elements); primarily community oncology	Oncology practice EHR with billing and payor data	EHR linked with claims	EHR	EHR
Sample size	**Outer dark blue circle is the October 2024 DCO sample size; inner light blue circle is the April 2024 DCO sample size;** the percentage indicates the change of sample size between the two DCO dates									
Adult patients with WM treated with zanubrutinib after FDA approval	438 400 10%	622 481 29%	536 408 31%	1118 732 53%	391 325 20%	864 293 195%	738 242 205%	416 205 103%	160 97 65%	413 316 31%
Race[b]	**October 2024 n** (April 2024 n; % change)									
Asian	**9** (8; 13)	**23** (17; 35)	**17** (16; 6)	**27** (17; 59)	**<10** (6; NE)	**24** (prev <10; NE)	**11** (4; 175)	**10** (6; 67)	**0** (0)	**8** (7; 14)
African American	**22** (20; 10)	**20** (18; 11)	**29** (17; 71)	**32** (23; 39)	**16** (8; 100)	**25** (12; 108)	**14** (8; 75)	**9** (4; 125)	**6** (3; 100)	**12** (8; 50)
White	**305** (277; 10)	**519** (399; 30)	**401** (308; 30)	**809** (543; 49)	**303** (250; 21)	**724** (266; 172)	**400** (139; 188)	**327** (163; 101)	**140** (83; 69)	**369** (283; 30)
Ethnicity	**October 2024 n** (April 2024 n; % change)									
Non-Hispanic-Latino	**389**[c]	**520** (408; 27)	**510**[d]	**825** (548; 51)	**319** (258; 24)	**458** (>278; NE)	**425** (149; 185)	**289** (148; 95)	**143** (84; 70)	**365** (280; 30)
Hispanic-Latino	**12** (11; 9)	**11** (10; 10)	**26**[d]	**31** (18; 72)	**4** (5; −20)	**11** (prev <10; NE)	**17** (4; 325)	**8** (5; 60)	**11** (10; 10)	**20** (15; 33)
Selected AESIs										
AF, flutter, ventricular fibrillation, other arrhythmias	✓ (DC)[e]	✓ (DC + MC)[e]	✓ (DC)[e]	◐ (MC)	◐ (MC)	◐ (MC)	◐ (MC)	✓ (DC + MC)[e]	✓ (DC + MC)[e]	✓ (DC + MC)[e]
Hypertension	✓ (DC)[f]	✓ (DC + MC)[f]	✓ (DC)[f]	◐ (MC)	◐ (MC)	◐ (MC)	◐ (MC)	✓ (DC + MC)[f]	✓ (DC + MC)[f]	✓ (DC + MC)[f]
Second primary malignancies	✓ (DC)	✓ (DC)	✓ (DC)	◐ (MC)	◐ (MC)	◐ (MC)	◐ (MC)	✓ (DC + MC)	✓ (DC + MC)	✓ (DC + MC)
RWD suitable for describing safety endpoints in patients with WM treated with zanubrutinib (as of October 2024)[g]	**Treated with zanubrutinib (as of October 2024)[g]**									
	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗

✓ Yes ◐ Partial yes ✗ No

[a]The database name cannot be disclosed due to contractual restrictions at the time of this assessment. [b]Due to the limited sample size of zanubrutinib patients, only three racial categories were included in this feasibility report. [c]Previously not available. [d]Previously unknown. [e]Atrial fibrillation/flutter is defined as ≥1 inpatient or ≥2 outpatient diagnosis codes. Ventricular arrhythmia is defined with principal diagnosis in inpatient or emergency room setting. [f]Incident hypertension is defined as ≥2 outpatient hypertension diagnoses (in any position) within 183 days or 1 inpatient hypertension diagnosis in any position, per the algorithms adopted by the FDA's Sentinel System. [g]The overall feasibility assessment results were determined by (1) the presence of race and ethnicity variables in each dataset, (2) the count of racial and ethnic minority of patients as of October 2024, and (3) the ability to assess the safety and efficacy outcomes of interest in each dataset.

Abbreviations: AESIs, adverse events of special interest; AF, atrial fibrillation; DC, diagnosis codes; DCO, data cut off; EHR, electronic health record; FDA, US Food and Drug Administration; NE, not estimable; MC, medical charts; RWD, real-world data; WM, Waldenström macroglobulinemia.

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