AASLD THE LIVER MEETING 2026

Residual Hepatic, Neurologic, and Psychiatric Disease Burden in Treatment-Experienced Patients with Wilson Disease

Baseline Findings from the FoCus Phase 3 Trial

Frederick Askari, MD, PhD (Presenter)

Valentina Medici, MD, FAASLD · Thomas D. Sandahl, MD, PhD · Chandler Robinson, BA/BS, MD, MS · Andrew Cittadine, MS · Declan Tuffy, PharmD · Karl Heinz Weiss, MD · Aftab Ala, MBBS, MD, FRCP, PhD

November 8, 2026



Disclosures

- Arbor Med, Advisor
- Monopar, Advisor
- Orphalan, Research Support and Advisor
- ETON Pharmaceutical, Advisor
- Alexion Pharmaceuticals, Research Support
- Arcturus, Advisor
- Astra Zeneca, Research Support
- Ultragenyx, Research Support and Advisor
- Prime Medicine, Advisor and Research Support
- Vivet, Research Support

AASLD The Liver Meeting®

Wilson Disease: A Rare, Serious Genetic Copper Disorder That Requires Lifelong Treatment

Overview of Wilson Disease

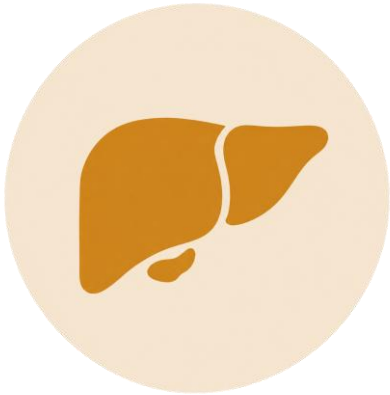
- Caused by mutations in the **ATP7B** gene that lead to copper accumulation in the liver and brain[1]
- Devastating **hepatic, neurologic,** and **psychiatric** consequences[2]
- Paradoxical **neurologic worsening** can occur with standard of care[3]
- Approximately **~7000 patients** with Wilson Disease in the US (based on prevalence of 21.2 per million[4])

Clinical Manifestation



Neuropsychiatric[5]

- Tremor
- Dystonia
- Depression



Hepatic[5]

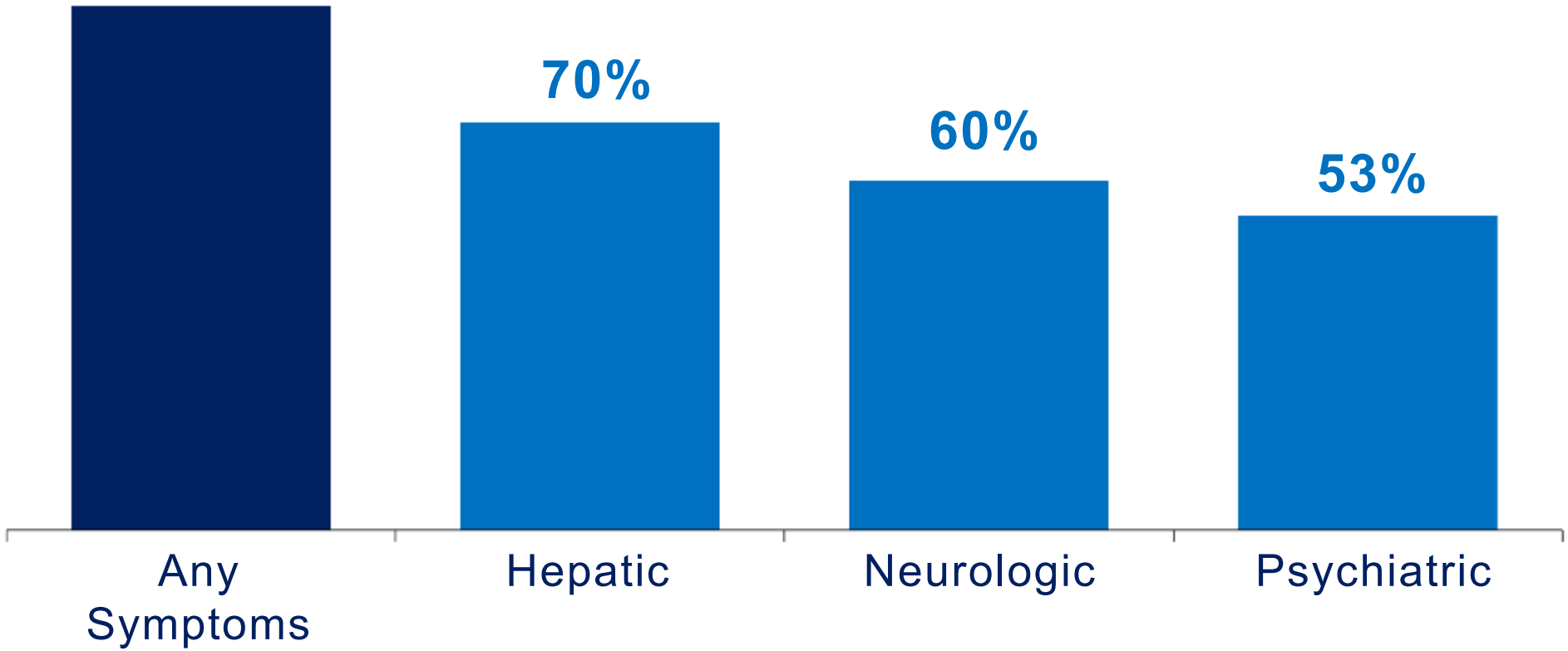
- Hepatitis
- Cirrhosis
- Liver failure

1 Gomes A, et al. Ann Hum Biol. 2016.; 2 Poujois A, et al. Eur J Neurol. 2017.; 3 Litwin T, et al. J Neurol Sci. 2015.; 4 Fang S, et al. BMJ Open. 2024.; 5 Merle U, et al. Gut. 2007.

SOURCE: Askari F et al., AASLD. 2026; Xelay Acumen; Updated as of 10/13/2026

Patients Often Present with Multidomain Symptoms, and Diagnosis May Be Delayed

Patients with Symptoms in Each Disease Domain at Diagnosis[1]



53%
have both **hepatic and neurologic/psychiatric** symptoms[1]

53%
have **liver cirrhosis** at diagnosis[2]

Many patients already have advanced liver disease at diagnosis

27 months
from neurologic symptoms to diagnosis[3]

Diagnosis is often delayed by more than 2 years

1 Medici V, et al. Front Gastroenterol. 2024.; 2 Moores A, et al. Can J Gastroenterol. 2012.; 3 Antos A, et al. Diagnostics. 2025.
SOURCE: Askari F et al., AASLD. 2026; Xelay Acumen Analysis; Updated as of 10/13/2026

Wilson Disease: Currently Available Treatments Reflect Absence of Innovation in Decades

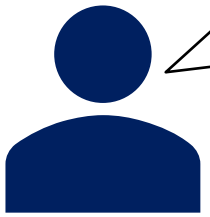
		Penicillamine	Trientine	Zinc
Approval Year		1970[1]	1985[2]	1997[3]
Overview		First FDA-approved therapy; promotes urinary copper excretion[4]	Chelator, like penicillamine, that promotes urinary copper excretion	Blocks intestinal copper absorption[4,5]
Limitations	Typical Use	Used both to de-copper and as maintenance	Used both to de-copper and as maintenance	Used as maintenance; Ineffective when symptomatic; doesn't remove accumulated copper[4,5]
	Safety	✗ Frequent side effects[6] ✗ Risk of neurologic worsening[7] ✗ Fatal aplastic anemia and agranulocytosis[6] ✗ Renal and hepatic reactions[6] ✗ Copper and iron deficiency[4,6]	✓ Better tolerated vs. penicillamine[4] ✗ Risk of neurologic worsening[5] ✗ Copper and iron deficiency[4,9]	✓ Fewer side effects than chelators[5] ✗ GI intolerance[5] ✗ Risk of inadequate treatment of accumulated copper[4,5] ✗ Copper deficiency[4]
	Dose Burden	Multiple daily doses; away from food[4]	Multiple daily doses; away from food[4]	Multiple daily doses; away from food[4]
	Refrigeration	No[6]	Yes for 2HCl; No for 4HCl (Cuvrior)[8,9]	No[10]
Dose Frequency		1-4x[4,6]	2-4x[8]	3x[10]

1 Ogbru, Omudhome. "Penicillamine." MedicineNet, www.medicinenet.com/penicillamine/article.htm. Accessed 30 Sept. 2026.; 2 "Search Orphan Drug Designations and Approvals: Trientine HCl (Syprine)." U.S. Food and Drug Administration, www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=4884. Accessed 30 Sept. 2026.; 3 "Search Orphan Drug Designations and Approvals: Zinc Acetate (Galzin)." U.S. Food and Drug Administration, www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=11185. Accessed 30 Sept. 2026.; 4 Schilsky ML, et al. Hepatology. 2023.; 5 Socha P, et al. J Hepatol. 2025.; 6 Cuprimine (Penicillamine) Prescribing Information. 2022.; 7 Brewer GJ, et al. Arch Neurol. 1994.; 8 "Trientine (Oral Route)." Mayo Clinic, 1 Feb. 2026, www.mayoclinic.org/drugs-supplements/trientine-oral-route/description/drg-20066488. Accessed 30 Sept. 2026.; 9 Syprine (Trientine) Prescribing Information. 2020.; 10 GALZIN (Zinc Acetate) Capsules Prescribing Information. 2024

SOURCE: Askari F et al., AASLD. 2026; Xelay Acumen; Updated as of 10/13/2026

Patients Report Debilitating Side Effects They Have to Endure with Wilson Disease Treatment

Patient Perspectives

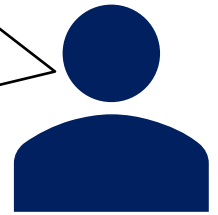


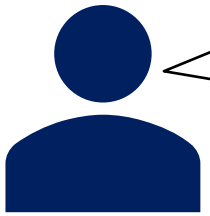
*"[My siblings and I] took D-penicillamine… spent almost two years in the hospital with **spasms and cramps** throughout our bodies, which we could not control. We **no longer walked or talked** and could only eat by a direct tube to the stomach."*

Eugeni, 37 – diagnosed at 11; hepatic and neurologic

*"My experience with Wilson disease would have been far less traumatic if the **treatment hadn't worsened my neurologic symptoms** to the point where I was a shell of a human being… I had **lost the ability to talk**, walk, eat, and drink completely, relying on a feeding tube."*

Emma, 20 – diagnosed at 17; neurologic and psychiatric





*"The biggest downside of my treatment is **nausea**. All the medication I've ever taken for Wilson disease makes me nauseated, and the complex dosing schedule is really challenging."*

Jean Marie, 62 – diagnosed at 16; neurologic and psychiatric

SOURCE: Askari F et al., AASLD. 2026; Wilson Disease Association – Voice of the Patient Report July 2026; Xelay Acumen; Updated as of 10/13/2026

FoCus (ALXN1840 Phase 3 Trial), the Largest Controlled Wilson Disease Trial Ever, Included Both Treatment-Naïve and Treatment-Experienced Patients

- **Largest single controlled Wilson disease trial** conducted
- Designed to **examine the efficacy and safety of ALXN1840** (tiomolibdate choline, TMC) versus SOC
- Enrolled both treatment-experienced and treatment-naive patients
- Patients **aged ≥12 years** with an established diagnosis of Wilson disease
- **Assessed at baseline and over 48 weeks plus extension**
  - **Hepatic Status**
  - **Neurologic Status**
  - **Psychiatric Status**
  - **NCC Status**

207
Patients[1]

160
Tx Experienced

47
Tx Naïve Pts



52
sites

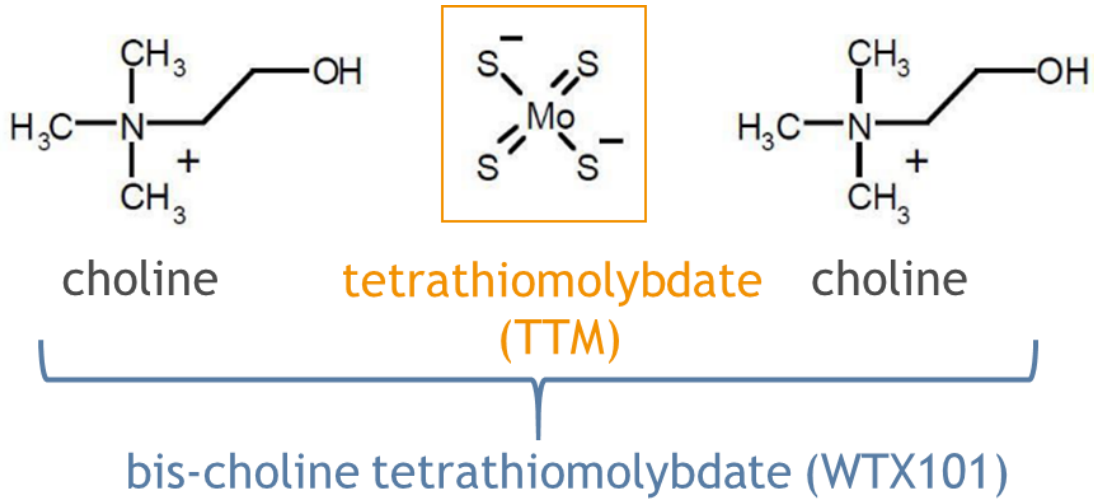
22
countries

6
in USA

1 214 patients were randomized and 207 patients received treatment

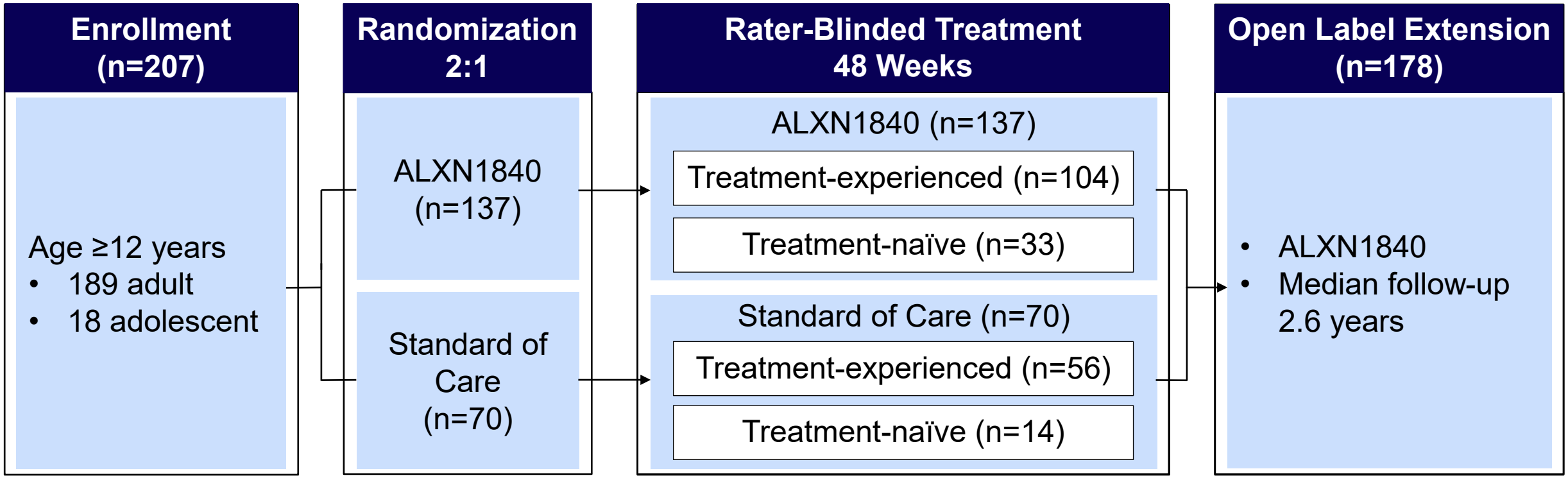
SOURCE: Askari F et al., AASLD. 2026; Data on file: CSR 301; Xelay Acumen; Updated as of 10/13/2026

Bis Choline tetrathiomolydbdate TTM ALXN1840/WTX 101- First in class



SOURCE:

FoCus – ALXN1840 Phase 3 Trial Design



Endpoints

Primary:
Copper mobilization (dNCC $AUEC_{0\text{-}48W}$)[1]

Secondary:
- Neurologic measures (UWDRS Part III)
- Global clinical improvement (CGI-I)

Key Criteria

Inclusion:
Leipzig score ≥4

Exclusion:
- Decompensated cirrhosis
- MELD >13
- Significant neurologic disability

1 *Directly-measured non-ceruloplasmin-bound copper (dNCC) area under the effect-time curve from 0 to 48 weeks (AUEC), a measure of total copper mobilized

SOURCE: Askari F et al., AASLD. 2026; Data on file: CSR 301; Xelay Acumen Analysis; Updated as of 10/13/2026

Summary of Patient Demographics Across Treatment Groups

Overall Patient Demographics

Variable		Treatment Experienced (n = 160)	Treatment Naïve (n = 47)
Sex	Male, n (%)	84 (52.5)	35 (74.5)
	Female, n (%)	76 (47.5)	12 (25.5)
Race	White, n (%)	121 (75.6)	39 (83.0)
	Asian, n (%)	32 (20.0)	5 (10.6)
	Black or African American, n (%)	3 (1.9)	0 (0.0)
	Other / Not Reported, n (%)	4 (2.5)	3 (6.4)
Age (Years)	Mean (SD)	35.3 (14.1)	27.8 (9.5)
	Min-Max	12-71	15-56

SOURCE: Askari F et al., AASLD. 2026; Data on file: CSR 301; Xelay Acumen Analysis; Updated as of 10/13/2026

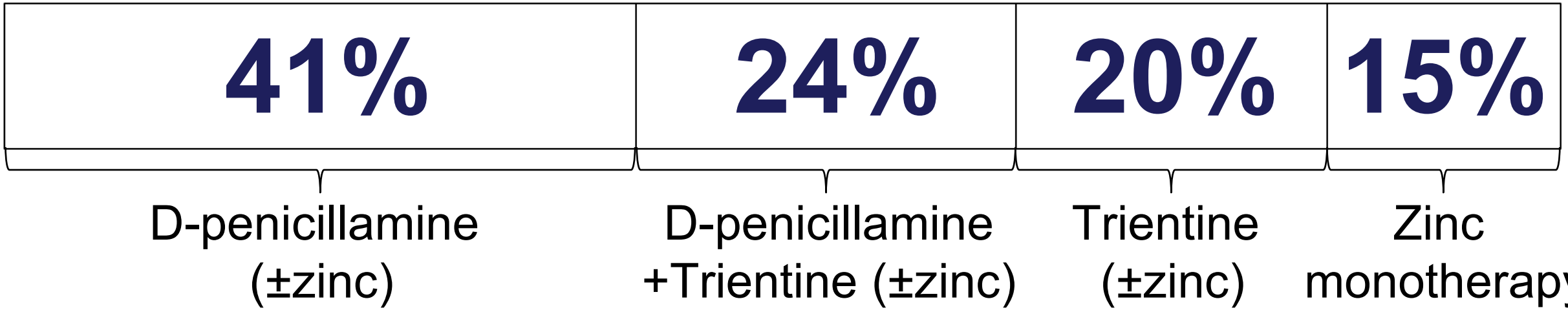
77% of the Patients Were Treatment Experienced with a Median of ~9.5 Years of Prior Wilson Disease (WD) Treatment

Prior WD Treatment Duration and Therapy Type Among Treatment-Experienced Patients

~9.5 years
Median prior WD treatment

77%
Treatment-experienced
(n=160)

Prior WD therapy options among treatment-experienced patients



SOURCE: Askari F et al., AASLD. 2026; Data on file: CSR 301; Xelay Acumen Analysis; Updated as of 10/13/2026

Unified Wilson's Disease Rating Scale (UWDRS)

The **Unified Wilson's Disease Rating Scale (UWDRS)** is a standardized clinical rating scale developed to assess the severity and progression of symptoms in patients with Wilson Disease

Structure & Core Items
The subscale spans two distinct components: a **patient/caregiver-reported section (Part II)** evaluating activities of daily living, and an **objective clinical examination (Part III)** performed by a neurologist.
The evaluation covers four core areas of motor dysfunction:

Bulbar Symptoms & Daily Functioning:

- Speech/dysarthria and clarity of voice
- Salivation and drooling
- Swallowing (dysphagia)
- Handwriting and dressing

Parkinsonian Symptoms (Bradykinesia & Rigidity):

- Facial expression (hypomimia)
- Finger taps and hand movements
- Muscle rigidity (tested in major joints)

Tremor & Ataxia:

- Rest tremor
- Postural tremor (including the classic "wing-beating tremor" characteristic of Wilson's disease)
- Kinetic/action tremor
- Leg agility and coordination

Gait, Posture, and Dystonia:

- Walking gait and balance
- Postural stability
- Focal or generalized dystonia (abnormal muscle contractions)

AASLD The Liver Meeting®

Brief Psychiatric Rating Scale (BPRS)

The **Brief Psychiatric Rating Scale (BPRS)** is a clinician-administered assessment tool used to measure the presence and severity of psychiatric symptoms, particularly in patients with schizophrenia, psychotic disorders, and severe mood disorders.

Symptom Domains Measured

The standard 18-item BPRS evaluates a comprehensive array of psychiatric symptoms—encompassing positive, negative, affective, and general psychopathology dimensions—such as anxiety, depression, hallucinations, grandiosity, suspiciousness, conceptual disorganization, and blunted affect.

Length: The standard version consists of 18 items, though an expanded version (BPRS-E) features 24 items. [1]

Scoring Scale: Each symptom construct is rated on a 7-point scale—usually ranging from **1 (not present)** to **7 (extremely severe)**.

AASLD The Liver Meeting®

Most Patients Were Symptomatic at Baseline, With Multidomain Involvement in ~73%

Patient Distribution Across Individual and Overlapping Disease Domains (n=207[1])

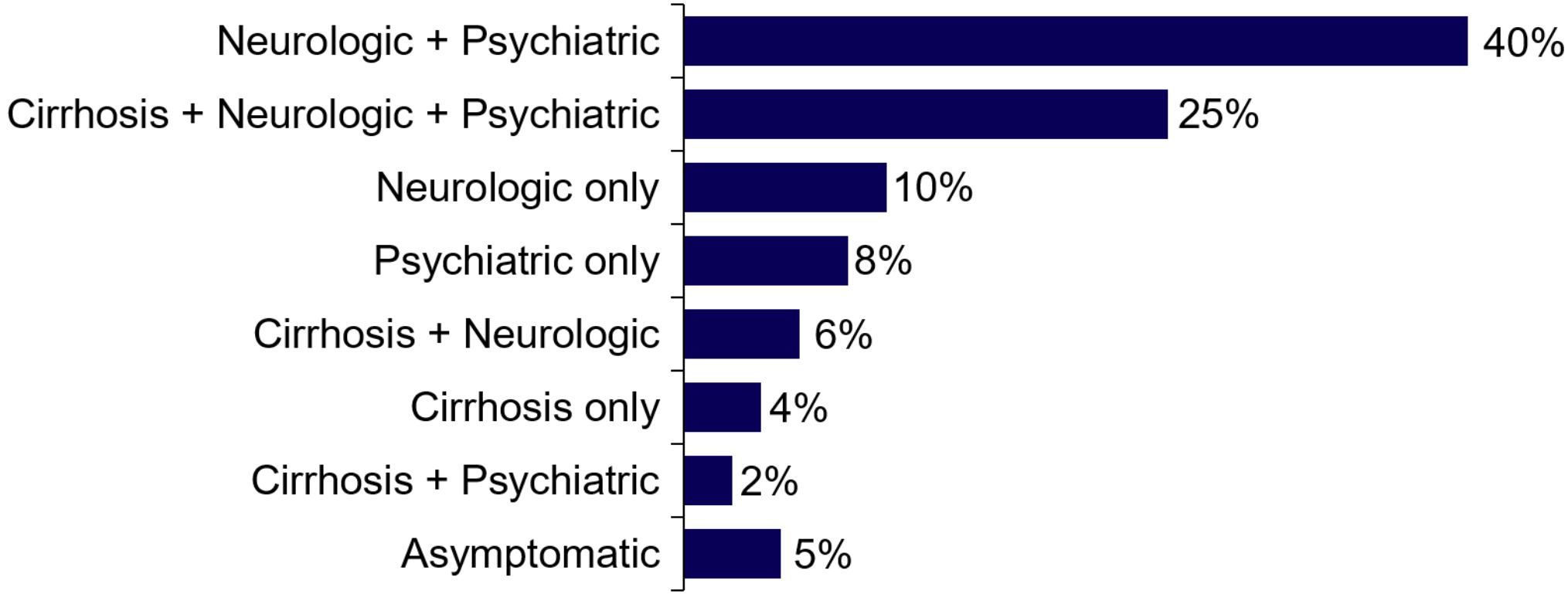
Percent[2]

80%
Neurologic

74%
Psychiatric

37%
Cirrhosis

5%
Asymptomatic



~73% of patients had symptoms in two or more domains

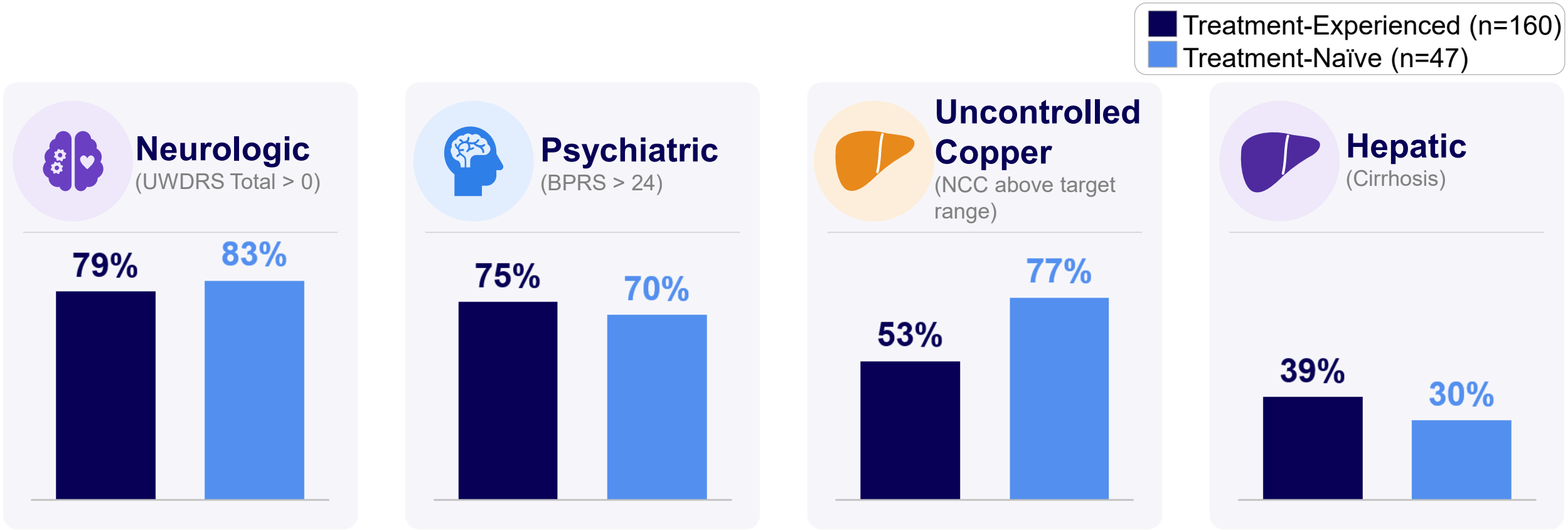
1 For overlapping disease domains, n was 204 since 1 patient without UWDRS & BPRS score and 2 patients without BPRS scores were excluded

2 Percentages are rounded to the nearest whole number

SOURCE: Askari F et al., AASLD. 2026; Data on file: CSR 301; Xelay Acumen Analysis; Updated as of 10/13/2026

Substantial Morbidity Persisted at Baseline Despite Prior Treatment, with Rates Comparable to Treatment-Naive Patients

Proportion of Patients with Baseline Morbidity – Treatment-Experienced vs. Treatment-Naive Patients (n=207)

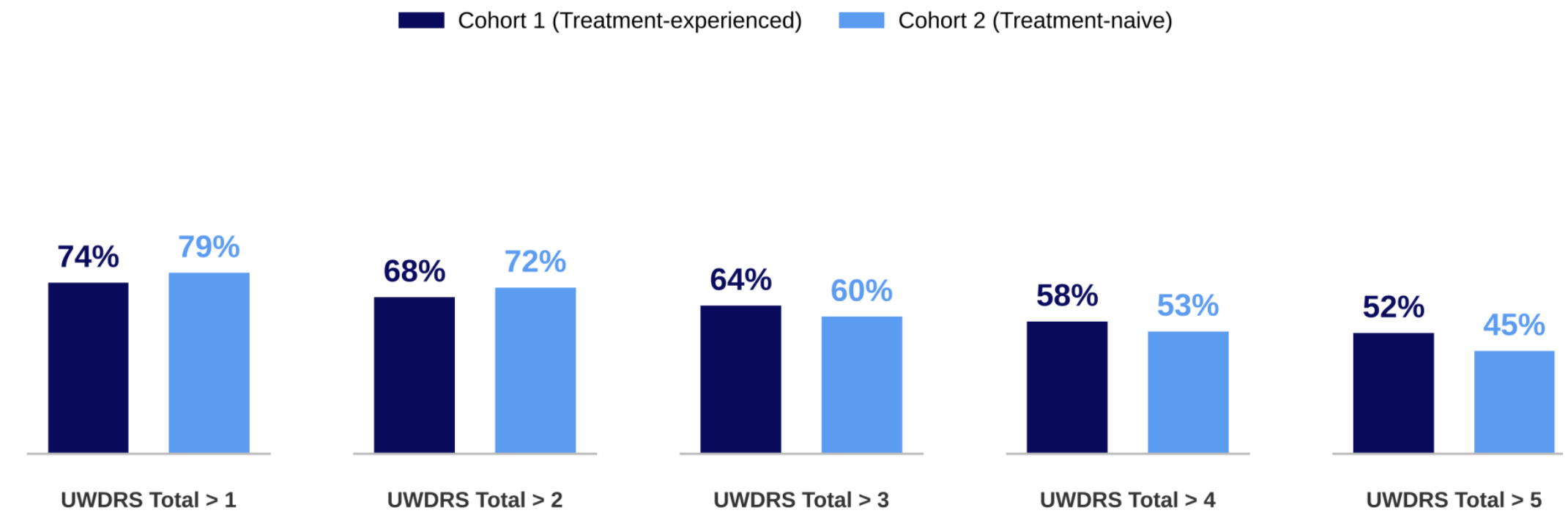


Even after a median of 9.5 years of prior treatment, a high proportion of patients had neurologic, psychiatric, uncontrolled copper, and hepatic morbidity at baseline, highlighting the unmet need with current standard of care

SOURCE: Askari F et al., AASLD. 2026; Data on file: CSR 301; Xelay Acumen Analysis; Updated as of 10/13/2026

UWDRS Baseline Cut-off Thresholds

Percent of Population Exceeding Threshold



SOURCE:

Conclusion: Study Limitation Includes Sudy Trial Enrollment Bias

1. FoCus trial baseline data provided a unique opportunity to evaluate **Wilson Disease burden cross-sectionally across a large patient population;**
2. The **majority of patients** had **significant hepatic, neurologic, and/or psychiatric symptoms at baseline**
3. **Symptom prevalence was similar among treatment experienced and treatment naïve patients**
4. Clinicians should direct significant **focus on the assessment and management of symptoms** in addition to routine laboratory assessments
5. A clear **unmet need** remains for newer modalities that **enhance efficacy, reduce adverse events, and improve tolerability and compliance**

SOURCE: Askari F et al., AASLD. 2026; Xelay Acumen; Updated as of 10/13/2026

Forward-Looking Thoughts

Despite clinical diligence, these observations of ongoing symptomatic disease reflect the **limitations of current therapies**

Diagnosis & Monitoring



Improved Diagnostics

Advances in diagnostic technology and specificity



Emerging Biomarkers

To monitor and manage disease



Non-invasive Imaging

Less invasive approaches to diseases assessment

New Therapies



Pharmacologic Therapies

Including ALXN1840 (tiomolibdate choline, TMC)



Genetic Therapies

Genetic therapy and gene editing

SOURCE: Askari F et al., AASLD. 2026; Xelay Acumen; Updated as of 10/13/2026

AASLD THE LIVER MEETING 2026

Thank You

With thanks to the patients, families, investigators, and study teams across 52 sites in 22 countries who made the FoCus trial possible.