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# The Clinical Trials Landscape in Immunoglobulin Light Chain Amyloidosis: A Systematic Review

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## Abstract:

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#### The Clinical Trials Landscape in Immunoglobulin Light Chain 1 **Amyloidosis: A Systematic Review** 2

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## 1 To the editor,

2 Immunoglobulin light chain (AL) amyloidosis is a rare hematologic disorder characterized by end-organ damage from deposition of fibrillar aggregates of unstable light chains<sup>1</sup>. The key to 3 4 successful management of AL is rapid and profound reduction of amyloidogenic FLCs using 5 plasma cell clone-directed therapies<sup>2</sup>. The treatment armamentarium in AL is therefore mostly 6 borrowed from that of multiple myeloma. However, while drug development in myeloma has 7 proceeded rapidly, with >15 new therapies approved since 2010, just one therapy has received 8 FDA accelerated approval specifically for AL amyloidosis: anti-CD38 monoclonal antibody 9 daratumumab (2021)<sup>3</sup>. Potential reasons for this discrepancy include the rarity of AL 10 amyloidosis and its historically poor prognosis, especially patients with cardiac amyloid with baseline N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) >8500 pg/mL<sup>4,5</sup>, who often 11 12 have early mortality or cardiac adverse events that might deter pharmaceutical companies from 13 investing in this space.

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Furthermore, the lack of contemporary criteria to standardize assessment of hematologic 15 16 progression complicates trial design in AL, especially in the relapsed/refractory setting. The 17 2005 International Society of Amyloidosis (ISA) criteria for hematologic progression requires 18 the iFLC (involved FLC) to be at least 10mg/dL to define hematologic progression in most 19 patients<sup>6</sup>. However, a recent survey of global amyloidosis experts revealed their discomfort to 20 wait until such an iFLC elevation<sup>7</sup>. Another challenge is that clinical trials often exclude patients 21 with advanced cardiac and renal dysfunction. We performed a systematic review to define the 22 current landscape of clinical trials in AL amyloidosis and highlight unmet needs in this 23 population.

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A search on clinicaltrials.gov was performed on September 2023, using the term 'Amyloidosis'
under the field Condition/disease. We included all trials in AL amyloidosis testing a

pharmaceutical agent and that are currently ongoing, defined as having an enrollment status of
'Not yet recruiting', 'Recruiting', 'Active, not recruiting', and 'Enrolling by Invitation'. We
excluded studies that had 'suspended', 'withdrawn', or of 'unknown' status. Data on key
elements of the study design (inclusion/exclusion criteria, intervention, endpoints, sponsor)
were extracted by two independent reviewers (R.R. and V.S.), and discrepancies were resolved
by a third reviewer (R.C.).

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8 Our search generated 280 unique entries, among which 32 trials that tested a pharmaceutical 9 agent in systemic AL amyloidosis were included for analysis. The PRISMA flowchart is shown in 10 Supplementary Appendix I. The characteristics of included trials are summarized in Table I. 11 Notably, the majority of trials were in patients with previously-treated AL amyloidosis (17/32; 12 53%), followed by the newly-diagnosed setting (12/32; 38%). Just 9/32 trials (28.1%) tested 13 novel agents for AL amyloidosis rather than those approved for myeloma. Most trials (23/32); 14 71.9%) were multi-center and just a minority were industry-sponsored (8/32; 25%). Among the 15 5 phase III trials, 3 were industry-sponsored registrational trials. The mean estimated sample size for industry-sponsored vs non-industry-sponsored trials was 143 (±28.8) vs 59 (±16.6) 16 17 patients respectively (p=0.0174). The mean sample size of multi-center trials was significantly 18 higher than that of single-center trials  $[95\pm18 \text{ vs } 42\pm29 \text{ respectively; } p=0.025]$ . Industrysponsored trials had a substantially higher likelihood of being in newly diagnosed setting 19 20 (62.5%) compared to non-industry-sponsored trials (29.2%) (p=0.146). Of 32 trials, 31 reported 21 the cut-off in difference between involved and uninvolved FLC (dFLC) used for trial inclusion. 22 The most common cut-off was 5 mg/dL (16/31; 52%), followed 2 mg/dL (8/31; 26%). Of two 23 trials which had no dFLC cut-off, one evaluated different durations of daratumumab 24 maintenance (NCT05898646) and one tested siltuximab to reduce symptom-burden after auto-25 transplant (NCT03315026). Serum M-spike was allowed as measurable disease in 10 trials, with 26 the most common cut-off being 0.5 g/dL (n=9). Among 27 trials with available data on the

1 upper limit of NT pro-BNP cut-off for exclusion, the most common cut-off was 8500 pg/mL (17/27; 63%), followed by 1800 (2/27; 7%), 5000 (2/27; 7%), and 7500 (1/27; 4%). Of 5 trials 2 3 that did not exclude patients based on NT-proBNP, four were specifically targeted to patients 4 with stage IIIb disease, and one was a pragmatic trial that included all-comers. Notably, 23 trials 5 excluded patients with renal function below a specified eGFR cut-off: most commonly 40 6 ml/min/1.73m<sup>2</sup> (6 trials), 30 (6 trials), and 20 (6 trials). Only two trials with an eGFR cut-off 7 tested experimental drugs that are excreted renally (lenalidomide [NCT03252600] and 8 pomalidomide [NCT04270175]).

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10 The most common primary endpoints were hematologic response rate (13/32; 41%) and safety-11 related endpoints (13/32; 41%); overall survival (OS) was a primary endpoint in just 4/32 (13%) 12 trials. Industry-sponsored trials had a higher incidence of having safety as primary endpoint 13 compared to non-industry-sponsored trials (75% vs 29.2% respectively; p=0.022). Healthrelated quality of life (HRQoL) was measured as a pre-specified endpoint in just 12/32 trials 14 15 (38%). The majority of interventions were fixed-duration (26/31; 84%); industry-sponsored 16 trials were significantly more likely to treat until progression than non-industry sponsored trials 17 (50% vs 4.4%; *p*=0.0045).

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19 We demonstrate substantial heterogeneity in the eligibility criteria and definitions of 20 measurable disease used in current AL clinical trials. Two-thirds of trials continue to exclude 21 patients with NT-proBNP >8500 pg/mL, despite an improved prognosis for these patients in 22 the daratumumab era<sup>8,9</sup>. As early mortality in the era of Dara-VCd frontline therapy 23 predominantly occurs in patients with stage IIIb disease (i.e. baseline NT-proBNP>8500 24 pg/ml)<sup>10</sup>, it will be more difficult for emerging therapies to demonstrate an OS benefit in a 25 reasonable time-frame without including this high-risk group. Additionally, trials in 26 relapsed/refractory setting shouldn't exclude patients with stage IIIb disease at diagnosis since the steep drop in survival slope is limited to the 1<sup>st</sup> year after diagnosis. Despite the availability
of validated PRO instruments in AL and a well-defined HRQoL trajectory<sup>11-15</sup>, only one third of
trials measured a PRO endpoint.

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We also observed discordance in the dFLC cut-offs used for measurable disease. Notably, the 5 6 current hematologic response criteria in AL amyloidosis defines very good partial response 7 (VGPR) as dFLC<4 mg/dl, and requires a baseline dFLC  $\geq 5$  mg/dl to be considered response-8 evaulable<sup>16</sup>. However, several seminal studies have now demonstrated the strong prognostic 9 impact of achieving dFLC<1 mg/dl at the end of treatment, highlighting that even small 10 amounts of persistent clonal light chain can lead to ongoing organ damage<sup>17-20</sup>. Additionally, 11 several groups had proposed a new response category named "low-dFLC PR" for patients with 12 baseline dFLC of 2-5 mg/dl, defined as a post-treatment dFLC<1 mg/dl without achieving a 13 CR<sup>21-23</sup>. Since hematologic response evaluation is now feasible for all patients with dFLC≥2 14 mg/dl (due to creation of the new response category-low-dFLC PR), regulatory authorities 15 should encourage inclusion of these patients in clinical trials. Furthermore, novel assays to 16 check light chain burden such as mass spectrometry-based FLC assays<sup>24</sup> should be evaluated in 17 clinical trials. While significant advances have been made in clone-directed therapy – in large part thanks to successful development in myeloma – therapies targeting light chain cytotoxicity 18 19 and deposited amyloid fibrils in vital organs remain an unmet need, and should be tested in 20 RCTs. Furthermore, since patients with AL are frailer compared to myeloma, trials should be 21 designed with the shortest possible treatment duration needed to achieve the desired efficacy. 22 Table 2 highlights some suggestions in clinical trial design in AL, along with areas of unmet 23 need.

- 1 In conclusion, our study highlights the urgent need to harmonize definitions of measurable
- 2 disease and hematologic progression criteria in AL clinical trials, greater inclusion of patients
- 3 with advanced organ involvement, and increased use of PRO endpoints.

## 6 Contributions

7 R.R abstracted the data and wrote the first draft of the manuscript. D.S. participated in writing the

- 8 manuscript along with R.R. C.L. and V.S. abstracted the data. R.C. designed the research, edited the
  9 manuscript, and approved the final version. V. Sanchoralwala, S.L., and E.C. provided critical input and
  10 approved the final draft of the manuscript.

# 12 Conflicts of Interest

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- 14 Sanofi, Adaptive Biotech

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# 8 Table 1. Characteristics of clinical trials in AL Amyloidosis

Variable	Number of trials (%), except			
	where indicated			
Disease Setting:				
Newly Diagnosed	12 (37.5)			
Previously Treated	17 (53.1)			
Mixed	3 (9.4)			
Trial Sponsor:				
Investigator-sponsored	17 (53.1)			
Industry-sponsored	8 (25.0)			
Co-operative group	7 (21.9)			
Trial Phase:				
I	7 (21.9)			
II	14 (43.8)			
I/II	6 (18.8)			
III	5 (15.6)			
Randomized	11 (34.4)			
Estimated sample size, median (range)	45 (12-416) patients			
Trial location:				
US	17 (53.1)			
Ex-US	10 (31.3)			
Both US and ex-US	5 (15.6)			

Primary endpoint:			
Safety	13 (40.6)		
Overall survival	4 (12.5)		
Hematologic response rate	13 (40.6)		
HRQoL measured:	12 (37.5)		
Nature of investigational agent:			
Clone directed	27(84.4)		
Fibril-directed	2/(04.4)		
Other	4(12.3)		
	1 (3.1)		
Biomarker-selected*	5 (15.6)		
dFLC cut-off for inclusion (mg/dl):			
2	8 (25.0)		
4	2 (6.3)		
4.5	1 (3.1)		
5	16 (50.0)		
18	2 (6.3)		
No cut-off	2 (6.3)		
Not available	1 (3.1)		
United the Contract DVD (and all for			
Upper limit of N1-proBNP (pg/ml) for			
exclusion			
1800	2 (6.3)		
5000	2(6.3)		
7500	1(3.1)		
8500	17 (53.1)		
No upper limit	5 (15.6)		
Not available	5 (15.6)		
NYHA class for exclusion@:			
III or higher	10 (55.6)		
III or higher	10 (00.0) 6 (00.0)		
	(33.3)		
1 V	2 (11.1 <i>)</i>		

	Lower limit of ANC for exclusion <sup>\$</sup> :	
	1000/cc	21 (91.3%)
	1500/cc	2 (8.7%)
	Treatment duration#:	
	Fixed-duration (n; %)	26 (83.9)
	Treatment until progression (n; %)	5 (16.1)
1 2 3 4	*All biomarker-selected trials were in patients wi @Data available for 18 trials \$Data available for 23 trials #Data available for 31 trials	th t(11;14) cytogenetic abnormality
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# Table 2. Suggestions for Clinical Trial Design in AL Amyloidosis

Key considerations in trial design:

• Uniform implementation of measurable disease criteria in trials of relapsed/refractory AL amyloidosis

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- Preference for time-limited therapy to reduce physical and financial toxicity
- Response-driven de-escalation strategies
- Inclusion of patients with advanced disease (e.g. NT-proBNP>8500 pg/mL, ESRD, and autonomic neuropathy)
- Incorporate correlative studies on novel assays for measuring tumor burden (e.g. free light chain-mass spectrometry)
- Incorporate patient-reported outcome (PRO) assessment to measure health related quality of life
- Functional assessment (6MWT) with clinically meaningful differences

Key areas of unmet need:

- Standardization of supportive care regimens
- Rare entities such as IgM amyloidosis
- Treatment and natural history studies of localized AL amyloidosis
- Determine the most appropriate imaging modalities for assessing disease burden and response, considering factors such as sensitivity, specificity, and feasibility
- Therapies targeting amyloid fibrils and misfolded light chains

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