

Clinical and Molecular Differentiation of Efgartigimod in Generalized Myasthenia Gravis

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KEY TAKEAWAYS



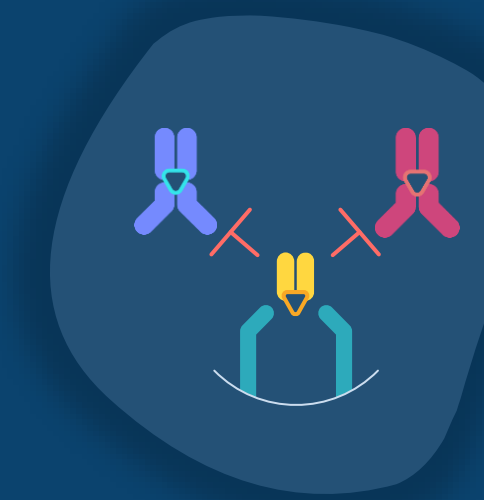
Patients with MG have a considerable CV disease burden, supporting the need for aggressive CV risk factor management, including caution with use of MG treatments that may exacerbate CV risk factors and comorbidities such as dyslipidemia



In preclinical studies, unlike the efgartigimod analog (ARGX-113), the analogs of anti-FcRn mAbs nipocalimab and batoclimab (N027 and HL161BK) altered cellular trafficking of FcRn and reduced cellular levels of FcRn in vitro¹



Across efgartigimod clinical studies, no reductions in albumin and no increases in LDL cholesterol were observed

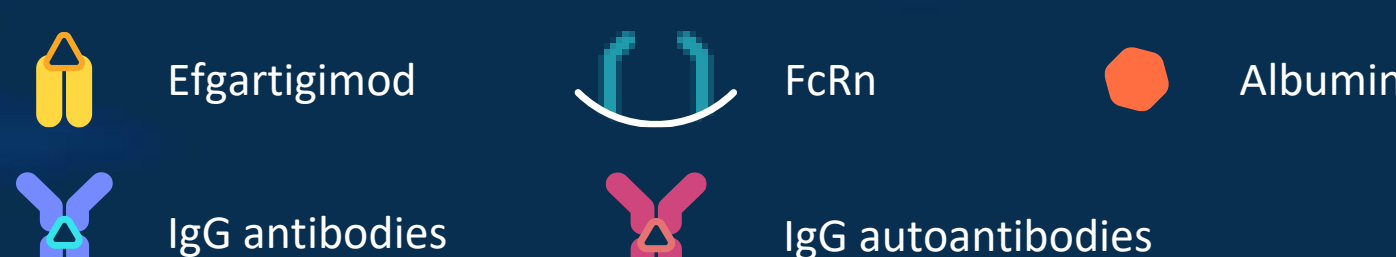


Efgartigimod's unique structure as a fully human Fc fragment avoids reductions in albumin and associated indirect effects on lipid parameters, making it a differentiated therapeutic option that effectively targets IgG without increasing CV burden in patients with MG

BACKGROUND

Efgartigimod Mechanism of Action²⁻⁴

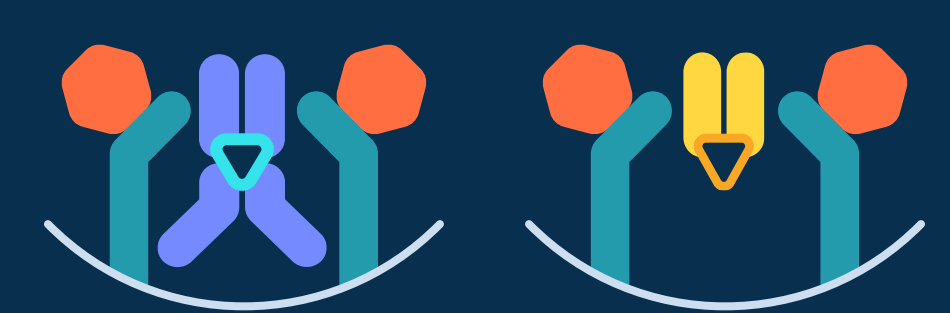
- 1 Efgartigimod and IgG are internalized into the cell
- 2 Efgartigimod outcompetes endogenous IgG antibodies, including pathogenic IgG autoantibodies, for binding to FcRn, due to increased affinity to FcRn. When bound to FcRn, efgartigimod and IgG escape lysosomal degradation
- 3 Remaining unbound IgG and efgartigimod are degraded in the lysosome
- 4 Efgartigimod and fewer IgG are recycled back into circulation



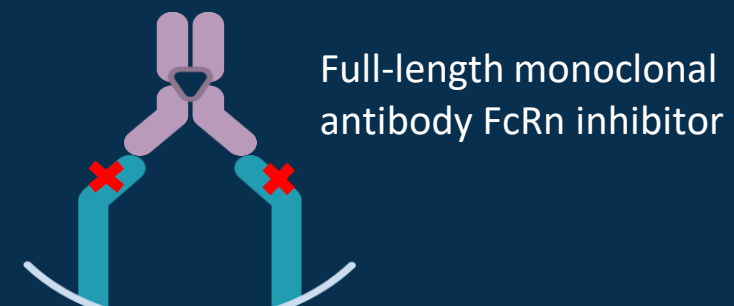
Efgartigimod is a human IgG fragment engineered for increased affinity to FcRn and is uniquely composed of only the part of the IgG antibody that normally binds FcRn^{2,5}



Efgartigimod binds to FcRn in the pH-dependent manner characteristic of endogenous IgG and blocks IgG binding without affecting the binding of albumin to FcRn^{2,6} or the cellular fate of FcRn¹



Some anti-FcRn mAbs, which bind primarily via the Fab arms, may reduce FcRn levels or impair binding of albumin to FcRn, which could impact albumin levels and may be associated with increased risk of hypercholesterolemia^{1,6}



- By blocking FcRn, efgartigimod selectively reduces IgG antibodies and pathogenic autoantibodies, and does so without impacting antibody production (including other Ig antibodies) or other parts of the immune system^{2,7}
- FcRn also recycles albumin (the most abundant plasma protein), which binds FcRn at a site distinct from IgG antibody binding. FcRn recycling of albumin results in a long half-life that is comparable to that of IgG^{2,6}
- Among its many other functions, albumin plays important roles in cholesterol efflux, lipid homeostasis, and regulation of platelet function and coagulation^{6,8,9}
- Low serum albumin levels are associated with increased total and LDL cholesterol levels and may lead to increased CV and all-cause mortality risk^{6,10}

RESULTS

CV RISKS AND COMORBIDITIES IN US PATIENTS WITH MG

- A retrospective cohort study used the anonymized Optum[®] Market Clarity claims dataset to provide a comprehensive overview of the CV comorbidities and CV risk factors in adults living with MG in the US
- Adult patients (aged ≥18 years) with ≥2 MG-related claims via ICD-9 or ICD-10 codes and who had continuous insurance enrollment during the 2-year assessment period from 1/1/2022 to 12/31/2023 were identified
- Subgroup analyses based on demographic factors (eg, age) were performed
- Patient attrition based on study criteria and patient demographics and clinical characteristics can be accessed via the QR code below

FIGURE 1 Prevalence of CV Risk and Comorbidity in MG¹¹

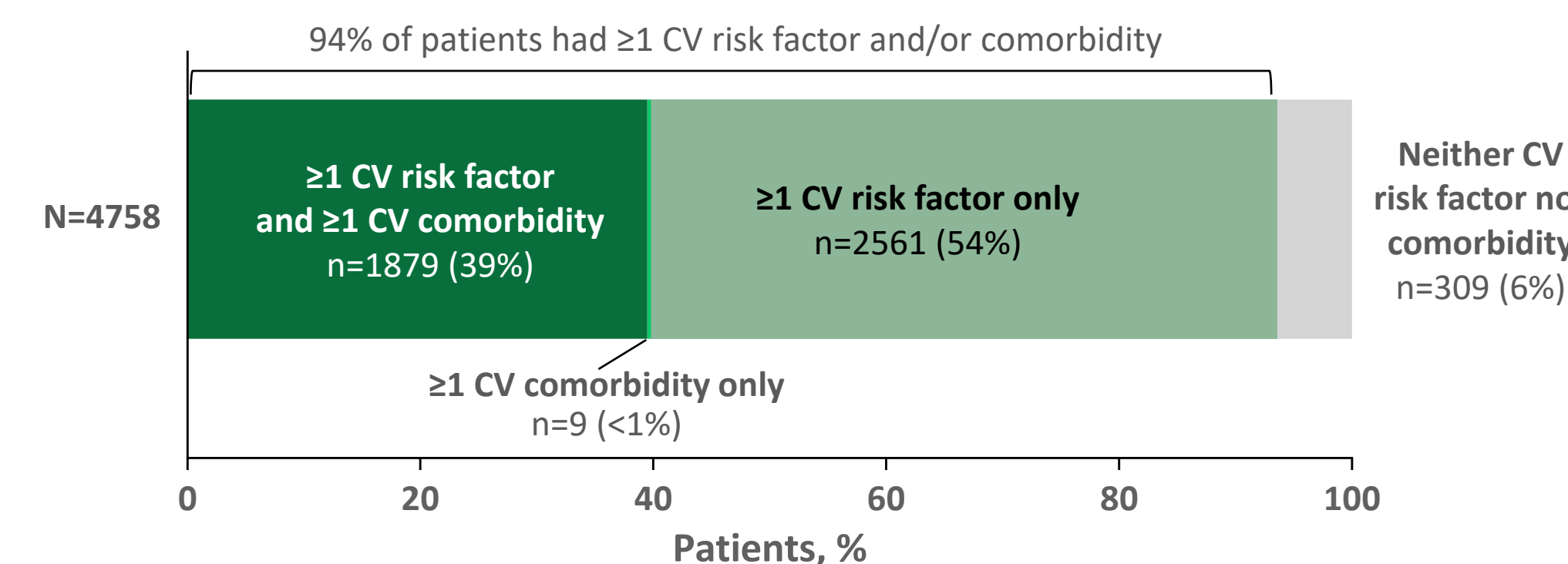


FIGURE 2 Prevalence of CV Risk Factors and Comorbidities Among Patients With MG¹¹ (N=4758)

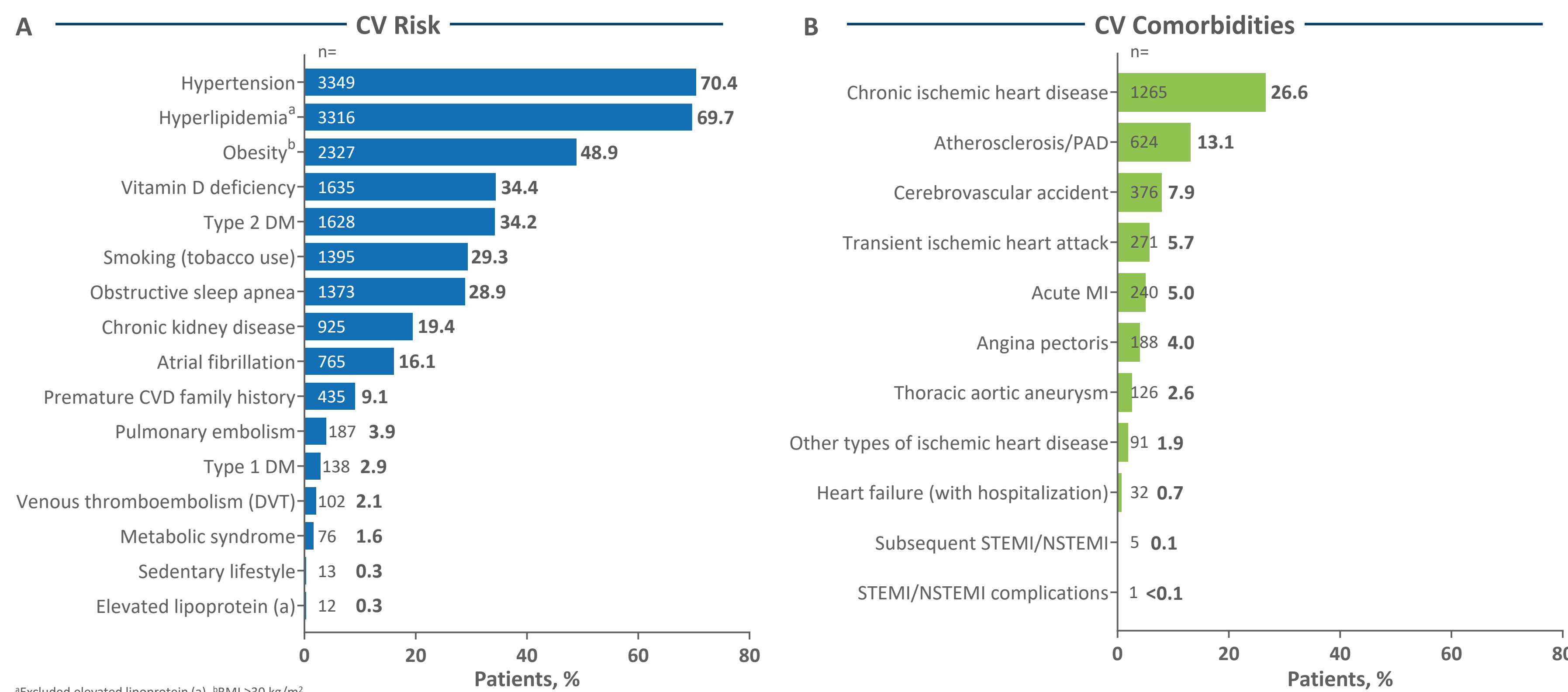
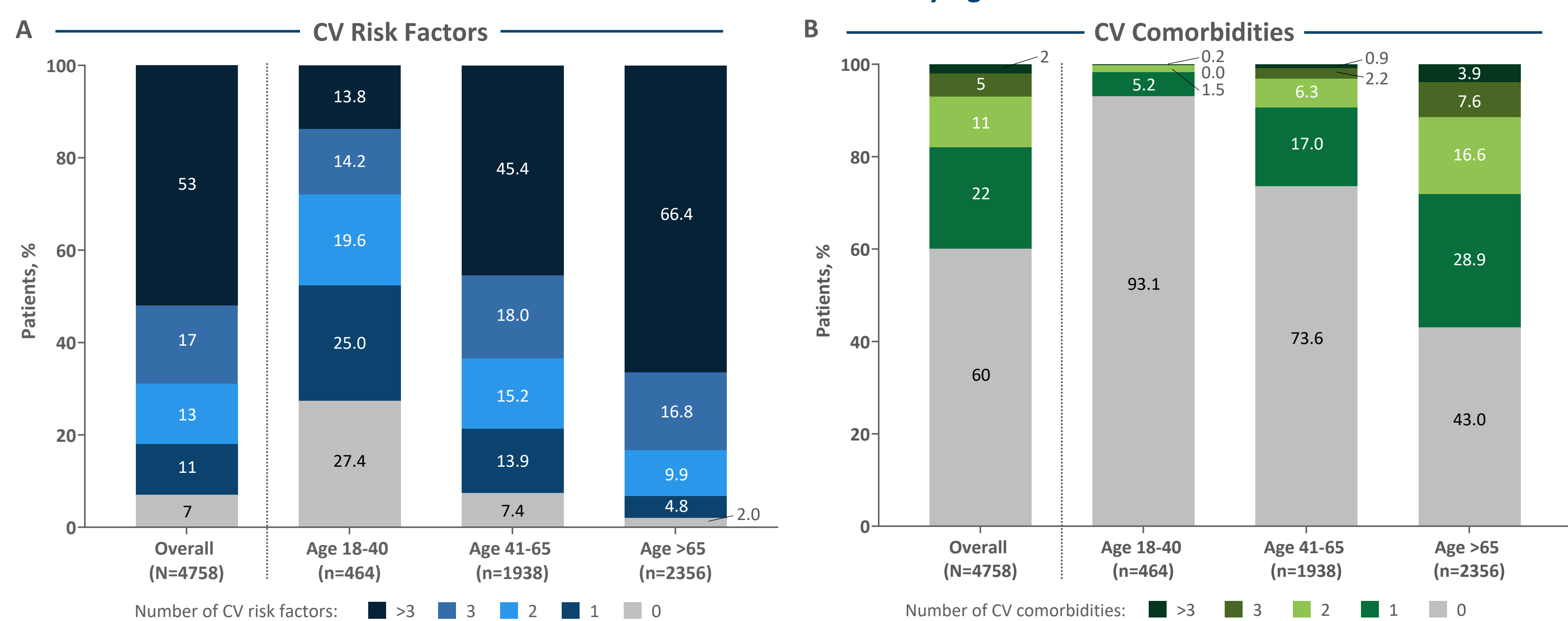


FIGURE 3 Number of CV Risk Factors and CV Comorbidities Overall and by Age¹¹



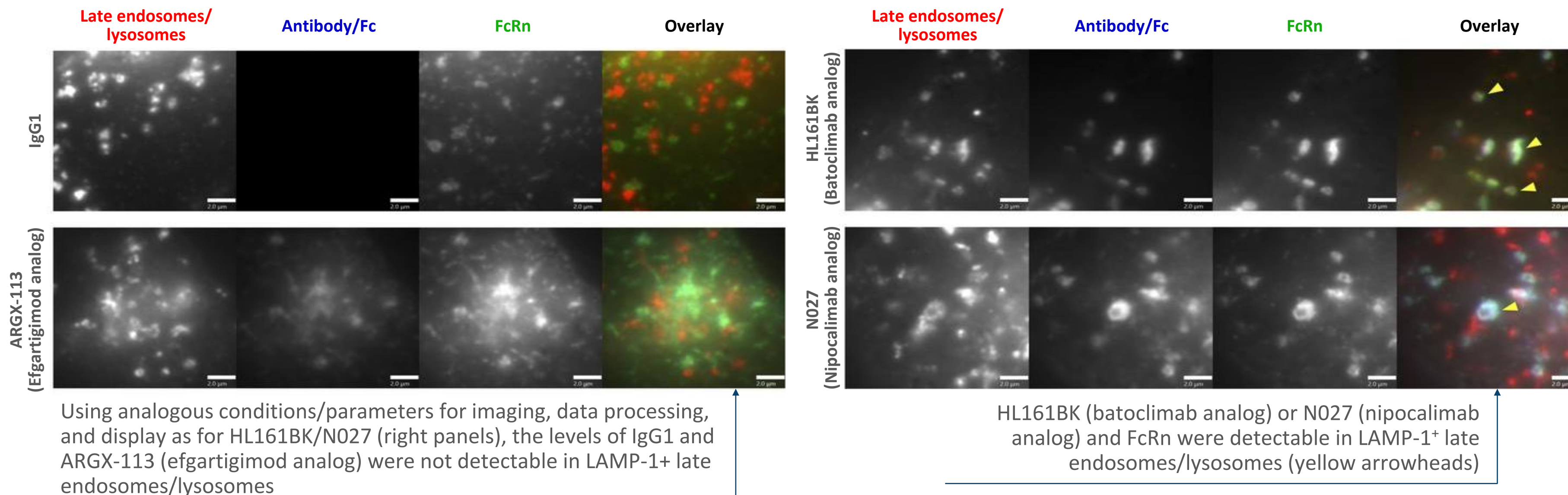
CV BURDEN IN PATIENTS WITH MG IN FRANCE AND JAPAN¹²

- Retrospective analyses of CV comorbidities and risk factors among adults with MG in France (using the French national health insurance database) and Japan (using Medical Data Vision database) were also conducted
- While the overall CV burden was highest in the US, most adults with MG in France and Japan had ≥1 CV comorbidity and/or CV risk factor
- Similar to the pattern in the US, the proportion of adults with MG in France and Japan who had CV comorbidities and/or CV risk factors was highest among patients aged >65 years, but was also substantial among younger age groups

PRECLINICAL DATA

FIGURE 4 Lysosomal Trafficking Analysis in HEK293-hFcRn-GFP Cells After 3-Hour Incubation¹

- Cellular and molecular analyses of full-length and Fc-fragment FcRn blockers evaluated effects on cellular trafficking patterns of FcRn in vitro



Using analogous conditions/parameters for imaging, data processing, and display as for HL161BK/N027 (right panels), the levels of IgG1 and ARGX-113 (efgartigimod analog) were not detectable in LAMP-1+ late endosomes/lysosomes

HL161BK (batoclimab analog) or N027 (nipocalimab analog) and FcRn were detectable in LAMP-1+ late endosomes/lysosomes (yellow arrowheads)

Proposed Late Lysosomal Trafficking of Full-Length FcRn Blockers

High-affinity full-length anti-FcRn mAbs (batoclimab and nipocalimab analogs):

- 1 Bind FcRn independent of pH^{1,13,14}
- 2 Inhibit binding of endogenous IgG to FcRn¹
- 3 Are found bound to FcRn in late lysosomes and presumably degraded, along with unbound IgG^{1,4}



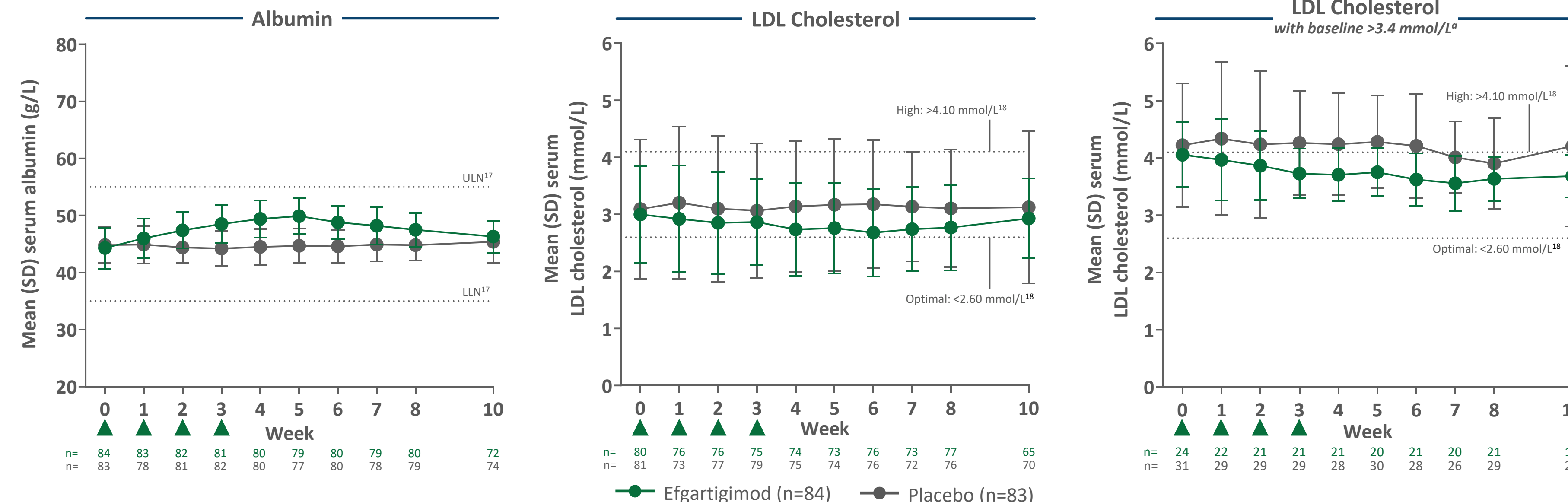
PRECLINICAL DATA CONCLUSIONS

- After 3-hour incubation, HL161BK (batoclimab analog) and N027 (nipocalimab analog) colocalized with both FcRn and late endosomes/lysosomes; no detectable IgG1 or ARGX-113 was observed in these compartments¹
- In separate in vitro experiments, HL161BK and N027 variably reduced FcRn levels; no FcRn reductions were observed with efgartigimod analog or control IgG1¹
- These data suggest that some full-length anti-FcRn mAbs (batoclimab analog HL161BK and nipocalimab analog N027) may increase delivery of FcRn to lysosomes, resulting in the reduced FcRn levels observed¹
- Unlike studies of efgartigimod, studies with full-length anti-FcRn mAbs batoclimab and nipocalimab have reported reduced albumin and increased LDL and total cholesterol levels, which may be an effect of decreased FcRn levels^{1,15,16}

CLINICAL RESULTS

FIGURE 5 Laboratory Values in Cycle 1 of ADAPT

Safety Population



¹³ 3.4 mmol/L is the lower threshold for borderline high LDL cholesterol in people who do not have coronary artery disease and for high LDL cholesterol in people with coronary artery disease or other atherosclerosis.¹⁸

CLINICAL RESULTS CONCLUSIONS

- In ADAPT (gMG Phase 3 study), efgartigimod IV did not reduce serum albumin and did not increase LDL cholesterol levels in adult participants with gMG
- Approximately one-third of ADAPT participants had elevated LDL cholesterol (>3.4 mmol/L) at baseline, and efgartigimod did not increase LDL in this subgroup
- Across clinical studies in gMG (ADAPT+, ADAPT-SC, ADAPT-SC+, ADAPT NXT), CIDP (ADHERE), and ITP (ADVANCE IV), efgartigimod has consistently been observed to cause no decrease in serum albumin levels¹⁹⁻²³

ABBREVIATIONS

BMI, body mass index; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DVT, deep vein thrombosis; Fab, antigen-binding fragment (of IgG antibody); Fc, crystallizable fragment (of IgG antibody); FcRn, neonatal Fc receptor; GFP, green fluorescent protein; gMG, generalized myasthenia gravis; HEK, human embryonic kidney; hFcRn, human neonatal Fc receptor; ICD, International Classification of Diseases; Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune thrombocytopenia; LAMP-1+, lysosome-associated membrane protein 1+; LDL, low-density lipoprotein; LLN, lower limit of normal range; mAb, monoclonal antibody; MG, myasthenia gravis; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PAD, peripheral arterial disease; STEMI, ST-elevation myocardial infarction; ULN, upper limit of normal range.

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DISCLOSURES AND ACKNOWLEDGMENTS

LL, SS, EP, EL, JP, KH, KS, LH, IR, JVS, VB, and BB are employees of argenx. GM and ARC received funding from argenx. ESW received funding from argenx and has a financial interest in argenx. Medical writing and editorial support for this presentation were provided by Precision AQ and funded by argenx.



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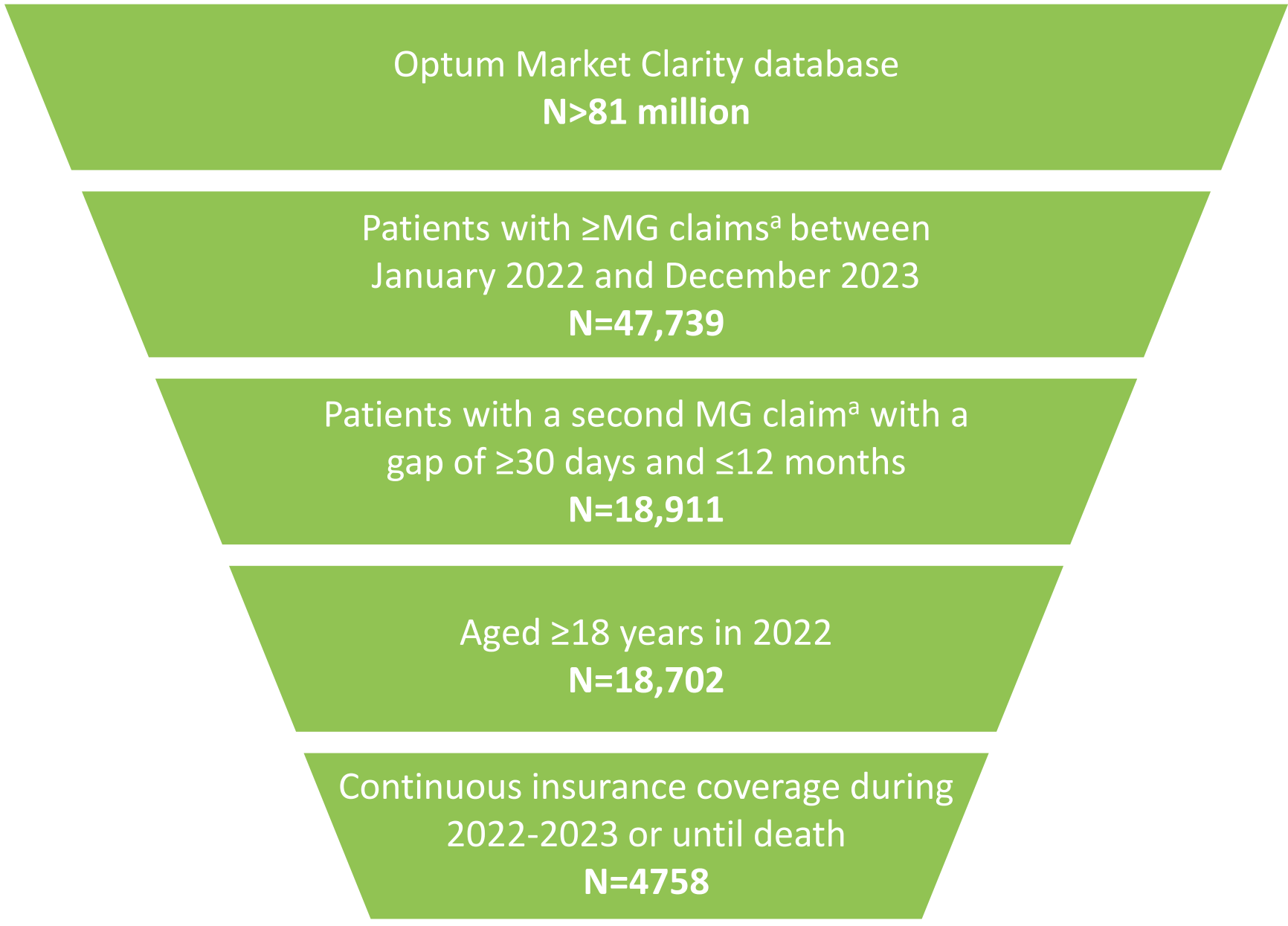
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SUPPLEMENTAL

CV RISKS AND COMORBIDITIES IN US PATIENTS WITH MG

FIGURE S1 Patient Attrition Based on Study Criteria¹²



^aICD-9: 358.0, 358.00, and 358.01; ICD-10: G70.0, G70.00 and G70.01.

TABLE S1 Patient Demographics and Clinical Characteristics¹²

	Overall (n=4758)
Age, years, mean (SD) ^a	63.4 (15.7)
Age category, years, n (%) ^a	
18-40	464 (9.8)
41-65	1938 (40.7)
>65	2356 (49.5)
Sex, n (%)	
Female	2537 (53.3)
Male	2221 (46.7)
CCI score, mean (SD) ^b	2.90 (2.97)
CCI category, n (%) ^b	
0	1023 (21.5)
1-2	1670 (35.1)
3-4	985 (20.7)
≥5	1080 (22.7)
Coexisting autoimmune condition, n (%) ^b	1581 (33.2)
Non-MG hospitalizations, n (%) ^b	1241 (26.1)

^aRecorded at the start of the assessment periods. ^bRecorded during the 2-year assessment periods.

ABBREVIATIONS

BMI, body mass index; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DVT, deep vein thrombosis; Fab, antigen-binding fragment (of IgG antibody); Fc, crystallizable fragment (of IgG antibody); FcRn, neonatal Fc receptor; GFP, green fluorescent protein; gMG, generalized myasthenia gravis; HEK, human embryonic kidney; hFcRn, human neonatal Fc receptor; ICD, International Classification of Diseases; Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune thrombocytopenia; LAMP-1+, lysosome-associated membrane protein 1+; LDL, low-density lipoprotein; LLN, lower limit of normal range; mAb, monoclonal antibody; MG, myasthenia gravis; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PAD, peripheral arterial disease; STEMI, ST-elevation myocardial infarction; ULN, upper limit of normal range.

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