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Efficacy and Safety of GAD- alum Immunotherapy in recent onset Type-1 diabetes: A systematic review and meta-analysis

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Systematic Review

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Abstract

Background

GAD-alum (glutamic acid decarboxylase adsorbed to aluminium hydroxide) is an antigen-specific immunotherapy for recent-onset type 1 diabetes mellitus (T1DM). Randomized controlled trials (RCTs) have reported inconclusive results, potentially due to differences in HLA genotype, route of administration, and dosing regimens. This systematic review and meta-analysis evaluated the efficacy and safety of GAD-alum and explored these effect modifiers.

Methods

PubMed, Embase and Scopus were searched from inception to January 2026. RCTs comparing GAD-alum with placebo in T1DM were included. Primary outcomes were stimulated C-peptide area under the curve (AUC), HbA1c, and daily insulin requirement. Prespecified subgroup analyses were performed by HLA haplotype, route of administration, dosing frequency, and follow-up duration.

Results

Five RCTs comprising 708 participants were included. Overall, GAD-alum showed a modest but non-significant preservation of beta-cell function (pooled ratio of means [RoM] for stimulated C-peptide AUC (1.07, 95% CI 0.98–1.15; I^2=7.6%). No significant effects were observed on HbA1c (MD 0.00, 95% CI − 0.22 to 0.23) or daily insulin requirement (MD − 0.01 U/kg/day, 95% CI − 0.06 to 0.03). Significant benefit was observed in HLA-DR3-DQ2-positive individuals (RoM 1.56, 95% CI 1.13–2.15) and at 12–15 months of follow-up (RoM 1.11, 95% CI 1.00–1.24). GAD-alum was well tolerated, with no increase in serious or treatment-emergent adverse events.

Conclusions

GAD-alum does not provide significant benefit in unselected individuals with recent-onset T1DM. However, preservation of beta-cell function in HLA-DR3-DQ2-positive individuals suggests a potential role for genotype-guided precision immunotherapy. Future trials should adopt genotype-based patient selection and standardized outcome reporting.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a T-cell mediated chronic autoimmune disease resulting in progressive beta-cell destruction and absolute insulin dependence [1]. The recent regulatory approval of anti-CD3 monoclonal antibody therapy, teplizumab, for delaying progression to stage 3 T1DM has renewed interest in immunomodulatory strategies aimed at preventing disease progression [2, 3]. Glutamic acid decarboxylase 65 (GAD65) is a major pancreatic autoantigen, with autoantibodies detectable in 70–80% of individuals at

T1DM onset [1]. GAD-alum (recombinant human GAD65 adsorbed to aluminium hydroxide) restores antigen-specific immune tolerance by shifting pathogenic Th1 responses towards a bifunctional Th1/Th2 regulatory phenotype, characterised by expansion of GAD65-specific IL-13$^+$ CD4$^+$ T cells co-secreting IFN-γ, induction of GAD65-specific CD4$^+$CD25(high)FoxP3$^+$ regulatory T cells, and a sustained Th2-associated cytokine shift, reducing autoreactive beta-cell destruction [4, 5, 6]. Randomised controlled trials (RCTs) of GAD-alum have produced inconclusive results. Early subcutaneous trials demonstrated C-peptide preservation, whereas subsequent trials failed to confirm efficacy in unselected populations [7, 8]. Secondary analyses suggest that the response may depend on HLA-DR3-DQ2 genotype, route of administration, and dosing schedule. More recently, intralymphatic delivery has shown promising C-peptide preservation, particularly in HLA-DR3-DQ2 positive individuals [12]. With growing interest in precision immunotherapy for T1DM and the increasing number of RCTs employing different study designs, a comprehensive pre-registered systematic review and meta-analysis is needed. By examining outcomes according to HLA genotype, route of administration, and dosing strategy, such an analysis can provide a clearer understanding of the efficacy of GAD-alum and help identify patient subgroups most likely to benefit.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to the procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [21]. The protocol was registered in PROSPERO (CRD420251079327).

Search strategy

A systematic search was conducted across PubMed, Embase and Scopus with no date restriction and restricted to English-language publications. The full search strategy for each database is provided in Table 1.

Study Selection: Studies were eligible for inclusion if they met the following PICO criteria. The *population* comprised individuals of any age, sex, or ethnicity with a confirmed diagnosis of T1DM (or at high risk of developing T1DM) based on standard clinical criteria (hyperglycaemia, ketosis, insulin dependence) and/or immunological markers (GADA, IA2, IAA, ZnT8). The *intervention* was GAD-alum administered via subcutaneous (SC) or intralymphatic (IL) routes, at any dose or schedule, as monotherapy or as an isolable arm in combination studies. The *comparator* was placebo or standard care. Only RCTs were included. Studies were excluded if they enrolled patients with Type 2 diabetes, monogenic diabetes, latent autoimmune diabetes in adults (LADA), or secondary diabetes; used GAD-alum concurrently with other immunomodulatory agents where outcomes could not be separated; employed non-GAD65 antigen-based vaccines; or were observational, cross-sectional, or non-human studies.

Study screening and data extraction: Titles and abstracts of all retrieved records were independently screened by two reviewers (VK and SAK), followed by full-text assessment of potentially eligible studies by two reviewers (MAMA and KSA). Discordances at each stage were resolved through discussion and consensus. The selection process is summarised in a PRISMA 2020 flow diagram (Fig. 1). Data were extracted independently by two reviewers (MTI and UB) using a standardised, pre-piloted extraction form.

Variables collected included: study design, country, sample size, participant age and sex distribution, diabetes duration at enrolment, HLA genotype distribution, route of administration, GAD-alum dose and regimen, follow-up duration, funding source, and all reported outcomes. Disagreements were resolved by consensus; authors were not contacted for additional data.

Risk of Bias Assessment: The risk of bias in each included RCT was independently assessed by two reviewers (VK and SAK) using the Cochrane Risk of Bias 2 (RoB-2) tool, evaluating five domains: randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results [22]. Overall judgements were classified as low, some concerns, or high risk of bias.

Outcomes and data synthesis: The primary outcome of interest was the preservation of beta-cell function as measured by ratio of means (RoM) stimulated C-peptide area under the curve (AUC). RoM was used for analysis of stimulated C-peptide because baseline values and reporting scales varied across studies, and RoM provides a clinically interpretable measure while minimizing distortion from differing absolute units and assay methods. The other outcomes were mean differences (MD) in HbA1c and daily insulin requirement (U/kg/day). Safety, comprising serious adverse events (SAEs), treatment emergent adverse events (TEAEs), and autoimmune side effects were looked into. Sub-group analyses were performed by HLA- status, route of administration (SC vs. IL), and dosing frequency (2 dose,3 dose and 4 dose). All analyses were performed using R (version 4.6.0; *metafor* package 5.0–1). For dichotomous outcomes (adverse events, HLA subgroup responders), risk ratios (RR) with 95% CI were used. Statistical heterogeneity was assessed using the I^2 statistic, with values > 50% considered substantial; a DerSimonian–Laird random-effects model was applied when I^2 exceeded 25%.

Results

A total of 73,462 articles were found on systematic literature search. The details of the search are shown in Table 1 and Fig. 1. 13,759 duplicates were removed. Following the review of the title and abstracts, the search was narrowed down to 5 RCTs, which fulfilled the inclusion and exclusion criteria that were analysed in this study. The study design, interventions and baseline patient characteristics are shown in Table 2 (Table 2a and 2b). Data from a total of 708 patients were analysed.

Table 1
Database Search Strategies

Database	Search String	Items founds
PubMed	1. ((((((((((((((((((((((((Type 1 Diabetes) OR (Diabetes, Type 1)) OR (Diabetes Mellitus, Insulin-Dependent)) OR (Diabetes Mellitus, Insulin Dependent)) OR (Insulin-Dependent Diabetes Mellitus)) OR (Diabetes Mellitus, Juvenile-Onset)) OR (Diabetes Mellitus, Juvenile Onset)) OR (Juvenile-Onset Diabetes Mellitus)) OR (IDDM)) OR (Diabetes Mellitus, Type I)) OR (Diabetes Mellitus, Sudden-Onset)) OR (Diabetes Mellitus, Sudden Onset)) OR (Sudden-Onset Diabetes Mellitus)) OR (Type 1 Diabetes Mellitus)) OR (Diabetes Mellitus, Insulin-Dependent, 1)) OR (Insulin-Dependent Diabetes Mellitus 1)) OR (Insulin Dependent Diabetes Mellitus 1)) OR (Juvenile-Onset Diabetes)) OR (Diabetes, Juvenile-Onset)) OR (Juvenile Onset Diabetes)) OR (Diabetes, Autoimmune)) OR (Autoimmune Diabetes)) OR (Diabetes Mellitus, Brittle)) OR (Brittle Diabetes Mellitus)) OR (Diabetes Mellitus, Ketosis-Prone)) OR (Diabetes Mellitus, Ketosis Prone)) OR (Ketosis-Prone Diabetes Mellitus) 2. ((((((Decarboxylase, Glutamate) OR (Glutamate Carboxy-Lyase)) OR (Carboxy-Lyase, Glutamate)) OR (Glutamate Carboxy Lyase)) OR (Glutamic Acid Decarboxylase)) OR (Acid Decarboxylase, Glutamic)) OR (Decarboxylase, Glutamic Acid) 3. Immunotherapies 4. (Vaccine Adjuvants) OR (Vaccine Adjuvant) 5. Compounds, Alum 6. (((((((Autoantigen) OR (Autologous Antigen)) OR (Antigen, Autologous)) OR (Self-Antigen)) OR (Self Antigen)) OR (Self-Antigens)) OR (Self Antigens)) OR (Autologous Antigens)) OR (Antigens, Autologous) 7.((((((((((((Hydroxide,Aluminum) OR (Hydrated Alumina)) OR (Alumina, Hydrated)) OR (Algeldrate)) OR (Alhydrogel)) OR (Amphojel)) OR (Aldrox)) OR (Basalgel)) OR (Dialume)) OR (Brasivil)) OR (Nephrox)) OR (Pepsamer)) OR (Rocgel)) OR (Alugel) 8. (((((#2) OR (#3)) OR (#4)) OR (#5)) OR (#6)) OR (#7) 9. (#1) AND (#8)	9062
Embase	#1 AND #8 #2 OR #3 OR #4 OR #5 OR #6 OR #7 'aluminum hydroxide'/exp OR 'aluminum hydroxide' 'aluminum potassium sulfate'/exp OR 'aluminum potassium sulfate' 'autoantigen'/exp OR 'autoantigen' 'immunotherapy'/exp OR 'immunotherapy' 'glutamate decarboxylase'/exp OR 'glutamate decarboxylase' 'insulin dependent diabetes mellitus'/exp OR 'insulin dependent diabetes mellitus'	12361
Scopus	((ALL ("type 1diabetes") or ALL ("diabetes, type 1") or ALL ("diabetes mellitus,insulin-dependent") or ALL ("diabetes mellitus, insulin dependent") or ALL ("insulin-dependent diabetes mellitus") or ALL ("diabetes mellitus, juvenile-	52040

Database	Search String	Items founds
	onset") or ALL ("diabetes mellitus, juvenile onset") or ALL ("juvenile-onset diabetesmellitus") or ALL ("iddm") or ALL ("diabetes mellitus, type i") or ALL ("diabetesmellitus, sudden-onset") or ALL ("diabetes mellitus, sudden onset") or ALL ("sudden-onset diabetes mellitus") or ALL ("type 1diabetes mellitus") or ALL ("diabetes mellitus, insulin-dependent, 1") or ALL ("insulin-dependent diabetesmellitus 1") or ALL ("insulin dependent diabetes mellitus 1") or ALL ("juvenile-onset diabetes") or ALL ("diabetes, juvenile-onset") or ALL ("juvenile onsetdiabetes") or ALL ("diabetes, autoimmune") or ALL ("autoimmune diabetes") orALL ("diabetes mellitus, brittle") or ALL ("brittle diabetes mellitus") or ALL ("diabetes mellitus, ketosis-prone") or ALL ("diabetes mellitus, ketosis prone") orALL ("ketosis-prone diabetes mellitus"))) and (((ALL ("decarboxylase,glutamate") or ALL ("glutamate carboxy-lyase") or ALL ("carboxy-lyase,glutamate") or ALL ("glutamate carboxy lyase") or ALL ("glutamic aciddecarboxylase") or ALL ("acid decarboxylase, glutamic") or ALL ("decarboxylase,glutamic acid"))) or (ALL ("immunotherapies")) or ((ALL ("vaccine adjuvants")or ALL ("vaccine adjuvant"))) or ((ALL ("autoantigen") or ALL ("autologousantigen") or ALL ("antigen, autologous") or ALL ("self-antigen") or ALL ("selfantigen") or ALL ("self-antigens") or ALL ("self antigens") or ALL ("autologousantigens") or ALL ("antigens, autologous"))) or (ALL ("compounds, alum")) or ((ALL ("hydroxide, aluminum") or ALL ("hydrated alumina") or ALL ("alumina,hydrated") or ALL ("algeldrate") or ALL ("alhydrogel") or ALL ("amphojel") or ALL("aldrox") or ALL ("basalgel") or ALL ("dialume") or ALL ("brasivil") or ALL ("nephrox") or ALL ("pepsamer") or ALL ("rocgel") or ALL ("alugel")))))	
Date restriction: Inception to 20 July 2025. **Language restriction**: English only. **Deduplication**: Performed in excel prior to screening. tiab = title/abstract field; MeSH = Medical Subject Headings.		

Figure 1. **PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only**

Table 2: **Baseline Characteristics of Included Studies**

Table 2
A .Study Design and Intervention Characteristics

Parameter	Johnny L et al. 2008[7]	Wherrett DK et al. 2011[8]	Johnny L et al. 2012[9]	Johnny L et al. 2021[12]	Helena EL et al. 2017[15]
Trial name	Phase II Sweden	TrialNet GAD	Phase III Europe	DIAGNODE-2	DiAPREV-IT
Study design	RCT, double-blind	RCT, double-blind	RCT, double-blind	RCT, double-blind	RCT, double-blind
Country/Setting	Sweden; 8 paediatric centres	USA/Canada; 15 TrialNet sites	9 European countries; 63 clinics	Czech Republic, Netherlands, Spain, Sweden; 18 clinics	Sweden; single centre
Inclusion criteria	T1DM ≤ 18 months; GADA+; fasting C-peptide > 0.1 nmol/L; age 10–18 yr	T1DM < 100 days; GADA+; stimulated C-peptide ≥ 0.2 nmol/L; age 3–45 yr	T1DM < 3 months; GADA+; fasting C-peptide > 0.1 nmol/L; age 10–20 yr	T1DM ≤ 6 months; GADA+; fasting C-peptide > 0.12 nmol/L; age 12–24 yr	Non-diabetic; GADA+ + ≥1 other islet autoantibody; age 4–17.9 yr
Total randomised (n)	70	145	334	109	50
GAD-alum arm (n)	35	97 (×2 and ×3 combined)	219 (×2 and ×4 combined)	57	25
Placebo arm (n)	34†	48	115	52	25
Route	Subcutaneous	Subcutaneous	Subcutaneous	Intralymphatic	Subcutaneous
GAD-alum dose	20 µg	20 µg	20 µg	4 µg	20 µg
Dosing schedule	2 injections (Day 1 + Day 30)	2 injections (Day 1 + Day 28) or 3 injections (Day 1 + 28 + 56)	2 injections (Day 1 + 30) or 4 injections (Day 1 + 30 + 90 + 270)	3 injections (Day 30 + 60 + 90) + oral Vitamin D 2000 IU/day × 120 days	2 injections (Day 1 + Day 30)
Comparator	Alum alone	Alum alone	Alum alone	Alum alone + oral placebo	Alum alone
Primary outcome	Change in fasting C-peptide at 15 months	Stimulated C-peptide AUC at 12 months	Change in stimulated C-peptide AUC at 15 months	Change in stimulated C-peptide AUC at 15 months	Time to onset of T1DM at 5 years; Safety
Follow-up duration	15 months and 30 months	12 months (primary);24 months (secondary)	15 months	15 months	5 years

Table 2
B: Baseline Clinical Characteristics of Participants

Parameter	Johnny L et al. 2008 (7) GAD (n = 35)	Wherrett DK et al. 2011 (8) GAD (n = 97)	Johnny L et al. 2012 (9) GAD (n = 219)	Johnny L et al. 2021 (12) GAD (n = 57)	Helena EL et al. 2017(15) GAD (n = 25)
Age (years), mean ± SD	13.8 ± 2.3	17.9 ± 10.4 (×3); 14.9 ± 8.72 (×2)	12.9 ± 2.4 (4-dose); 12.9 ± 2.1 (2-dose)	16.2 ± 3.8	6.0 (median; range 4.1–15.1)
Female, n (%)	23 (66%)	14 (29.2%) / 31 (63.3%)	58 + 48=106 (48.4%)	21 (36.8%)	11 (44%)
Duration of diabetes / disease at enrollment	9.9 ± 5.3 months	83.9–87.1 days	73.6–76.9 days	147.6 ± 54.7 days	N/A (pre-diabetic; GADA+ only)
BMI (kg/m²), mean ± SD	19.5 ± 2.4	22.3 ± 4.69	NR (percentile reported)	NR	NR (Z-score 0.22 ± 0.75)
Fasting C-peptide (nmol/L), mean ± SD	0.33 ± 0.19	NR	0.289 ± 0.152 (2-dose); 0.288 ± 0.179 (4-dose)	0.329 ± 0.165	0.21 ± 0.10
Stimulated C-peptide AUC (nmol/L/2hr), mean ± SD	1.24 ± 0.57	0.710 ± 0.362 (×3); 0.655 ± 0.374 (×2)	0.681 ± 0.310 (2-dose); 0.661 ± 0.348 (4-dose)	0.793 ± 0.381	1.22 ± 0.46 (2-hr OGTT)
HbA1c (%), mean ± SD	6.3 ± 1.3	6.63 ± 1.19 (×3); 6.63 ± 0.965 (×2)	7.10 ± 1.20 (4-dose); 6.98 ± 1.05 (2-dose)	6.39 ± 0.96	5.26% (32.76 ± 3.13 mmol/mol)
Insulin dose (U/kg/day), mean ± SD	0.66 ± 0.30	0.386 ± 0.229 (×3); 0.331 ± 0.219 (×2)	0.599 ± 0.345 (2-dose); 0.539 ± 0.276 (4-dose)	0.393 ± 0.228	N/A
GADA titre (median)	601 U/ml	0.230 (index units, ×3)	199.2 U/ml (4-dose)	76.2 IU/ml	369 U (median)

Parameter	Johnny L et al. 2008 (7) GAD (n = 35)	Wherrett DK et al. 2011 (8) GAD (n = 97)	Johnny L et al. 2012 (9) GAD (n = 219)	Johnny L et al. 2021 (12) GAD (n = 57)	Helena EL et al. 2017(15) GAD (n = 25)
HLA genotype reported	HLA-DQ risk classification (High/Moderate/Low)	DR3: 31.2%; DR4: 27.1%; DR3 + DR4: 27.1%.	Very high/High/Moderate/Low risk (%)	DR3-DQ2+: 51.8%	DQ2/8: 40%

Risk of bias and quality assessment of the analysed studies: Risk of bias assessment in RCTs was done using ROB2 and was low (Fig. 2). Publication bias assessment was not performed due to the presence of few studies.

Outcomes

Nine treatment arms from four RCTs [7, 8, 9, 12, 15] were included in the meta-analysis.

Stimulated AUC-C-peptide

GAD-alum immunotherapy was associated with a modest, but statistically non-significant preservation of beta-cell function compared to placebo, with a pooled RoM of 1.07 (95% CI 0.98–1.15 = 7; p = 0.371; Fig. 3a). Heterogeneity was negligible (I^2 = 7.6%; τ^2 = 0.0015), indicating a highly consistent treatment effect across the trial arms despite differences in dose regimen and follow-up duration. Individual arm estimates were uniformly directional, with RoM values ranging from 0.84 (12 months, 2-dose) to 1.30 (15 months ,2 dose). Notably, only the two-dose arm at 12 months showed a numerically lower C-peptide in the treatment group (RoM 0.84 [0.60–1.17]), though this did not reach statistical significance. Excluding studies which used unadjusted means did not significantly alter the analysis (Fig. 3b).

HbA1c

No statistically significant effect of GAD-alum on glycated haemoglobin was observed across five treatment arms (pooled MD 0.00 [− 0.22 to + 0.23]; p = 0.435; I^2 = 0.0%; Fig. 4a). Individual estimates were directionally mixed, with the 4-dose arm showing a marginal numerical reduction (MD -0.20[-0.57 to + 0.18]) and the 2-dose arm showing a marginal numerical increase (MD + 0.25 [-0.12 to + 0.63]). The intralymphatic arm (MD − 0.91 [-5.51 to + 3.70]) had negligible weight (0.35%) owing to its very wide confidence interval. (The null HbA1c finding is consistent with the modest, non-significant primary C-peptide result and reflects the limited endogenous secretory reserve preserved at the population level in trials with mixed HLA backgrounds.)

Insulin Requirement

GAD-alum did not significantly alter exogenous insulin requirements compared to placebo (pooled MD − 0.01U/kg/day [− 0.06 to + 0.03]; p = 0.404; I^2 = 0.3%; Fig. 4b). Individual arm estimates were directionally

mixed and uniformly crossed zero.

Subgroup Analysis

Follow-up Duration: In studies with **s**hort-term follow-up (12–15 months), GAD-alum therapy showed a significant improvement in AUC C-peptide compared with controls (RoM 1.11, 95% CI 1.00–1.24; I^2 = 0.0%) (Fig. 5a). In contrast, among studies with long-term follow-up (24–30 months**)**, no significant benefit was observed (RoM 1.01, 95% CI 0.82–1.23; I^2 = 34.2%). No statistically significant subgroup interaction was observed between short- and long-term follow-up durations (p = 0.38)

HLA Risk Subgroup: Among participants with high-risk HLA haplotypes, GAD-alum treatment was associated with a significant preservation of C-peptide secretion (Fig. 5b). The pooled effect from HLA-enriched studies showed a 34% higher AUC C-peptide compared with controls (RoM 1.34, 95% CI 1.05–1.71; I^2 = 34.2%). Specifically, patients with HLA DR3-DQ2 positivity exhibited a stronger response (RoM 1.56, 95% CI 1.13–2.15) compared with the broader HLA moderate-to-high risk subgroup (RoM 1.21, 95% CI 0.95–1.53).

Route of Administration

SC GAD-alum yielded a modest but statistically significant benefit in preserving β-cell function (RoM 1.07, 95% CI 0.96–1.19) [7, 8, 9], whereas IL administration showed a comparable effect estimate (RoM 1.09, 95% CI 0.85–1.41) [12] (Fig. 5c). However, IL data were limited to a single study, precluding firm conclusions. No significant subgroup differences were observed by route of administration (p = 0.57).

Dose Regimen

Dose-based subgroup analysis (Fig. 5d) suggested heterogeneity in treatment response according to dosing frequency. Studies using a 2-dose regimen demonstrated a trend toward improved β-cell preservation (RoM 1.06, 95% CI 0.89–1.28; I^2 = 45.6%), whereas 3-dose regimens showed a similar but non-significant effect (RoM 1.05, 95% CI 0.90–1.21; I^2 = 0.0%). The 4-dose regimen (single study) showed numerically greater benefit (RoM 1.18, 95% CI 0.96–1.45), although statistical significance was not reached. No statistically significant interaction was observed among dose subgroups (p = 0.64).

Safety

Serious Adverse Events (SAE)

The pooled risk of serious adverse events was numerically lower in the GAD-alum arm compared to placebo (RR 0.73 [0.47–1.13]; p = 0.160; I^2 = 0.0%) (Fig. 6a), representing a 27% relative risk reduction that did not reach statistical significance. Heterogeneity was absent (I^2 = 0%), indicating a consistent pattern across trials. DiAPREV-IT was a T1DM prevention trial with a 5-year follow-up which was not included in the meta-analysis due to the heterogeneous population. In this trial a total of 12 adverse events were recorded in the treatment arm over the five-year follow-up period; 11 were mild and one was of moderate severity. No SAEs or TEAEs were reported, and no acceleration of autoimmune progression was observed in the GAD-alum group.

Treatment-Emergent Adverse Events (TEAE)

The risk of treatment-emergent adverse events was virtually identical between GAD-alum and placebo (RR 1.01 [0.85–1.19]; p = 0.948; I^2 = 1.6%;) (Fig. 6b), confirming the favourable and placebo-equivalent tolerability profile of GAD-alum across all routes, doses, and follow-up durations evaluated.

DISCUSSION

This systematic review and meta-analysis evaluated the efficacy and safety of GAD-alum immunotherapy in recent-onset type 1 diabetes mellitus (T1DM) using evidence from randomized controlled trials spanning both conventional subcutaneous and newer intralymphatic approaches. While the pooled analysis did not demonstrate a clear overall benefit across all participants, findings from subgroup analyses suggest that treatment response may not be uniform and could vary according to genetic background and timing of intervention. [8, 12]

One of the consistent observations across the included studies was the heterogeneity in treatment response. Earlier studies reported preservation of residual β-cell function following GAD-alum administration, [7] whereas subsequent larger trials yielded less encouraging results [9]. This divergence has contributed to uncertainty regarding the clinical role of GAD-alum and likely reflects differences in patient selection, disease stage, and underlying immunological characteristics rather than complete absence of therapeutic effect. The relatively low heterogeneity in our pooled analysis despite variation in study design suggests that treatment effects, although modest, were directionally consistent.

An important finding of the present review was the relatively greater preservation of β-cell function among participants with HLA-associated susceptibility, particularly those carrying the HLA-DR3-DQ2 haplotype. [7, 12, 15] This observation is in agreement with the individual patient data meta-analysis, [16] which demonstrated that treatment responses to GAD-alum were not evenly distributed across all individuals with T1DM. Even with IL administration individuals carrying DR3-DQ2 experienced greater preservation of stimulated C-peptide. Our findings support this observation and further suggest that inconsistent results from earlier trials may partly be explained by enrolment of genetically heterogeneous populations in which only a subset of patients may be responsive to antigen-specific therapy.

The apparent influence of HLA status on treatment response is also consistent with current understanding of disease immunobiology. [1] T1DM is increasingly recognized as a heterogeneous autoimmune disorder rather than a single disease entity, with variation in dominant autoantigens, immune pathways, and genetic susceptibility [1]. Since GAD65 represents a major pancreatic autoantigen and is strongly linked to HLA class II antigen presentation, it is plausible that individuals with specific HLA backgrounds may be more amenable to antigen-specific immune modulation. [16] From a clinical perspective, this raises the possibility that future immunotherapy trials in T1DM may require more careful biological stratification instead of treating newly diagnosed T1DM as a homogeneous population.

Another notable finding in the present analysis was the tendency toward greater preservation of β-cell function during shorter follow-up periods compared with longer-term assessment. [7] Although interpretation should remain cautious, this pattern may suggest that the effect of GAD-alum is most apparent earlier in the

disease course, when residual β-cell mass remains sufficient for immune preservation to have measurable clinical relevance. Progressive autoimmune destruction over time may diminish any initial therapeutic effect, which could explain the attenuation of benefit seen in longer follow-up studies. [8] Similar temporal patterns have been observed with other immune-modifying interventions in T1DM, where preservation of endogenous insulin secretion is often greatest during the early months after diagnosis. [17]

Differences according to route of administration and dosing schedule were less definitive. [12] Intralymphatic administration demonstrated numerically favourable outcomes; however, available evidence remains limited to DIAGNODE programme [12, 18, 19]. The rationale for intralymphatic delivery is nevertheless appealing, as administration directly into lymphoid tissue may enhance antigen presentation and immune tolerance while reducing antigen dose requirements. Likewise, although higher or repeated dosing schedules appeared to show numerically greater preservation of β-cell function in some studies, no consistent dose-response pattern was evident. These findings indicate that optimization of treatment delivery remains an area requiring further study.

Recent findings add further perspective to the evolving evidence surrounding GAD-alum. [20] The study was designed as a genetically enriched phase III study evaluating intralymphatic GAD-alum in individuals carrying the HLA-DR3-DQ2 haplotype, based on encouraging findings from earlier subgroup analyses[12, 20].

Despite modest preservation of β-cell function, no meaningful improvement was observed in HbA1c or insulin dose requirement. [7, 9, 12] This finding is not unexpected and has been observed across several disease-modifying studies in T1DM. Glycaemic outcomes are influenced by numerous behavioural and clinical factors, including insulin adjustment, dietary intake, diabetes education, and use of glucose monitoring technologies. Consequently, preservation of stimulated C-peptide may occur without immediate or measurable differences in conventional glycaemic outcomes during relatively short periods of follow-up. The safety findings of the present review are reassuring. Across studies, GAD-alum was generally well tolerated and was not associated with excess serious adverse events or treatment-emergent adverse effects compared with placebo. [7, 8, 9, 12, 15] This favourable safety profile remains one of the attractive aspects of antigen-specific immunotherapy, particularly when compared with broader immunosuppressive approaches that may carry risks of infection or systemic adverse effects.

In summary, the findings of this systematic review suggest that GAD-alum is unlikely to provide a uniform therapeutic benefit across all individuals with recent-onset T1DM. However, the available evidence indicates that certain subgroups, particularly individuals with HLA-DR3-DQ2 positivity, may derive greater benefit. Future studies should focus on biologically stratified populations, standardized reporting of β-cell outcomes, and optimization of route and timing of administration to better define the place of antigen-specific immunotherapy in T1DM.

CONCLUSION

GAD-alum immunotherapy demonstrated modest preservation of β-cell function in recent-onset type 1 diabetes mellitus, although a consistent overall benefit was not observed in unselected populations. Subgroup analyses suggested relatively greater benefit among individuals with HLA-DR3-DQ2 positivity and

during earlier follow-up, supporting the possibility of differential treatment response based on genetic background. No significant improvement was observed in HbA1c or insulin requirement, but GAD-alum was well tolerated with a favourable safety profile. Future studies should focus on genotype-based patient selection and optimized treatment strategies to better define the role of GAD-alum in type 1 diabetes.

Strengths & Limitations: This review updates the evidence base for GAD-alum as trials have shifted from subcutaneous to intralymphatic delivery, and placing both generations side by side gives a clearer picture of how the field has moved. The subgroup analyses add clinical texture: stratifying by HLA genotype, route, dosing schedule, and follow-up length matters here because these variables plausibly change the biology, not just the statistics. The overall risk of bias was low, which at least means the estimates are worth arguing about.

The limitations of this review include a smaller number of studies. Differences in how trials defined and reported C-peptide, and the variation in follow-up lengths, make pooling imperfect. And with these few studies, a funnel plot would be uninformative, so publication bias remains an open question rather than a tested one.

Abbreviations

T1DM: Type 1 diabetes mellitus, *GAD-65*: Glutamic Acid Decarboxylase 65, *GAD-alum*: Glutamic Acid Decarboxylase-aluminium hydroxide, *RCTs*: Randomised controlled trial, *PRISMA*: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *SC*: Subcutaneous, *IL*: Intralymphatic, *LADA*: Latent autoimmune diabetes in adults, *RoM*: Ratio of means, *AUC*: Area under Curve, *MD*: Mean deviation, *SAEs*: Serious adverse reactions, *TEAEs*: Treatment-Emergent Adverse Events

Declarations

Human Ethics and Consent to Participate declarations: Not applicable.

Ethics committee approval: Not applicable, this study is a systematic review and meta-analysis of previously published literature and did not involve direct participation of humans or animals; therefore, ethics committee approval and informed consent were not required.

Competing interest:

None declared.

Funding:

None

Author Contribution

V.K. and S.A.K contributed in designing the study and acquisition of data.U.B and M.T.I contributed in data extraction.V.K, S.A.K, M.A.M.A and K.S.A contributed in analysis and interpretation of data.V.K, S.A.K, M.A.M.A, K.S.A, M.T.I and U.B contributed in final approval of manuscript to be published.

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Data Availability

The data, code, and other materials underlying the results reported in this article are available from the corresponding author upon reasonable request. Access will be granted to researchers who submit a methodologically sound proposal, subject to approval by all authors.

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Figures

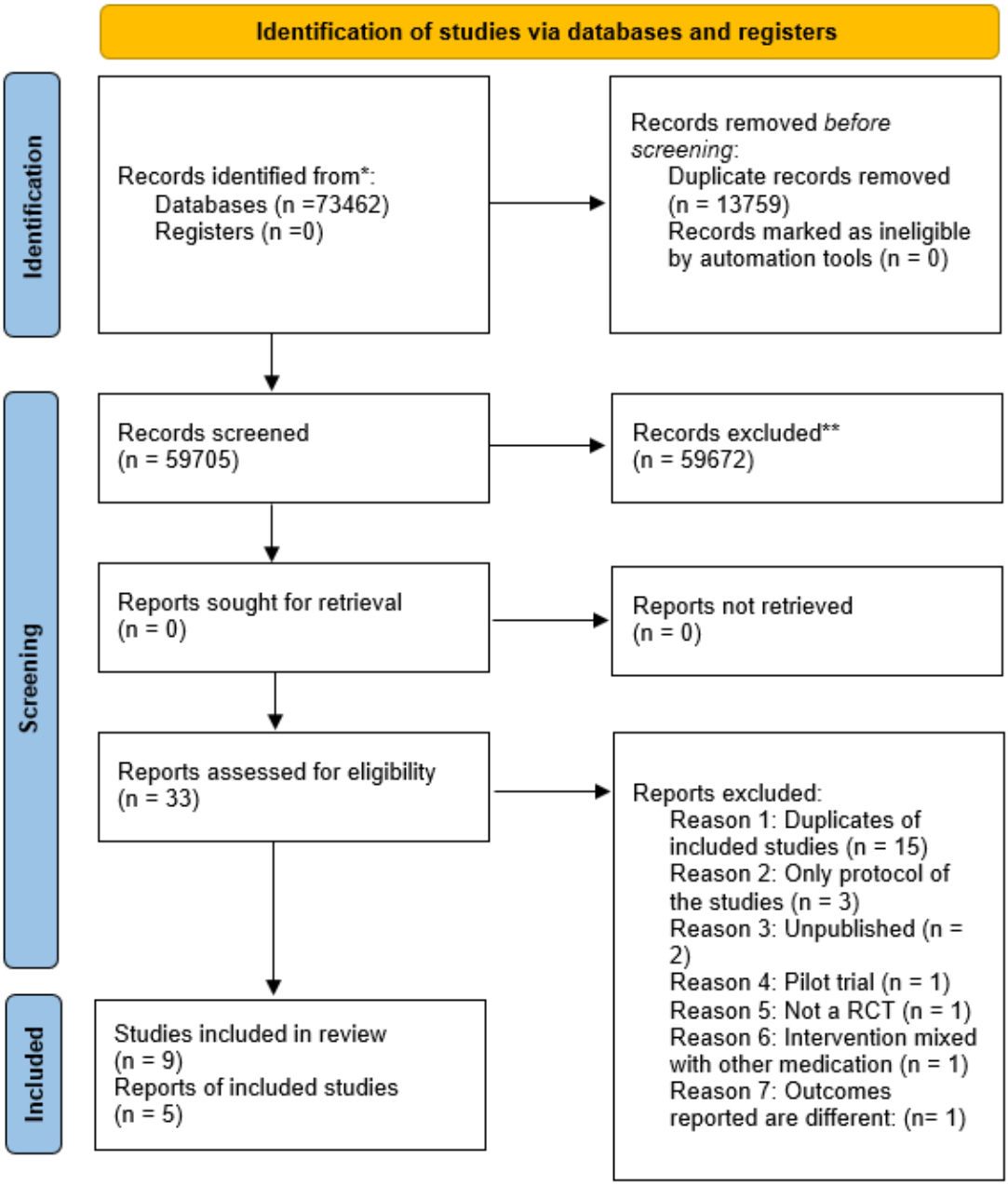


Figure 1

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

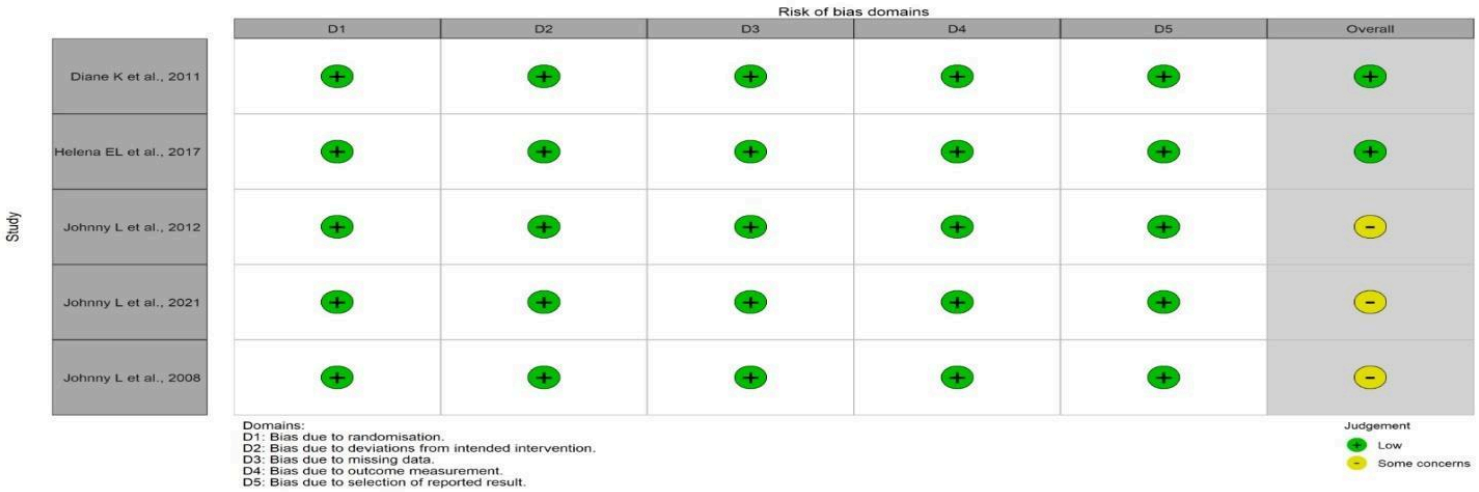


Figure 2

Risk of bias and quality assessment of the analysed studies by RoB2-tool.

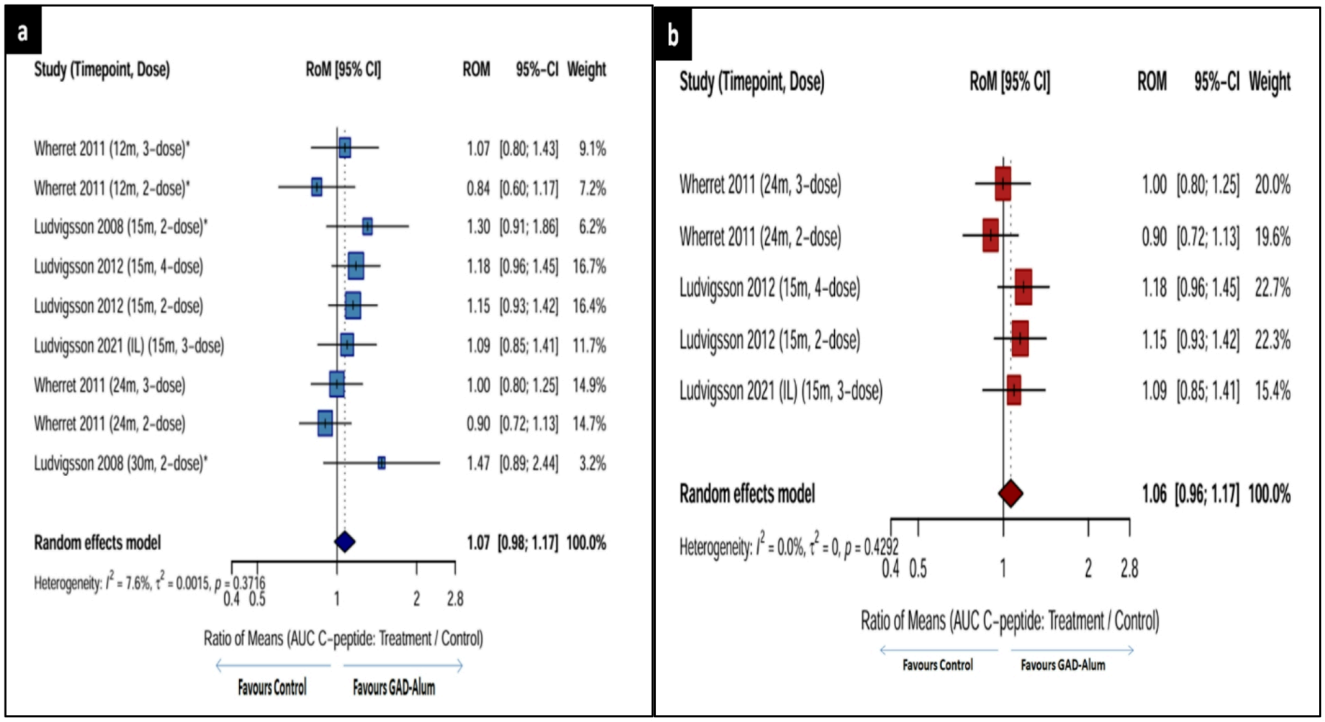


Figure 3

Forest Plot demonstrating the efficacy of GAD-Alum in comparison with controls. a) Depicts pooled RoM AUC C-peptide of all arms. b) Depicts pooled RoM AUC C-peptide of ANCOVA adjusted studies only. * = Unadjusted estimate (no ANCOVA)

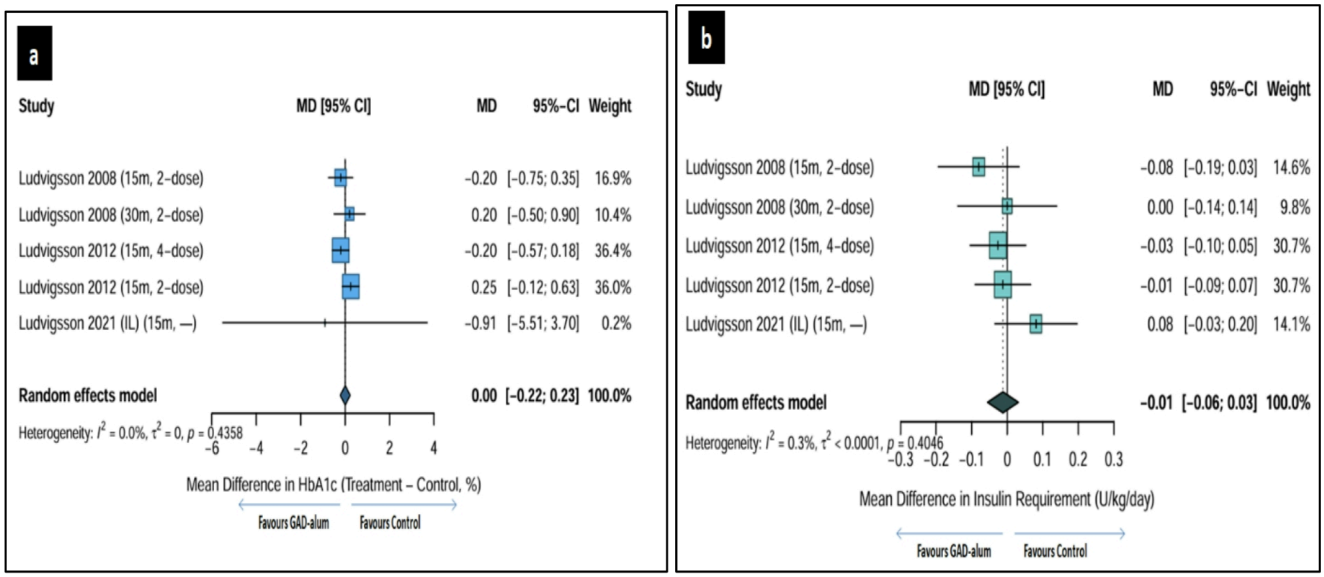


Figure 4

Forest Plot demonstrating the effect of GAD-Alum in comparison with controls on a) HbA1c and b) Insulin requirement. Negative values favour treatment.

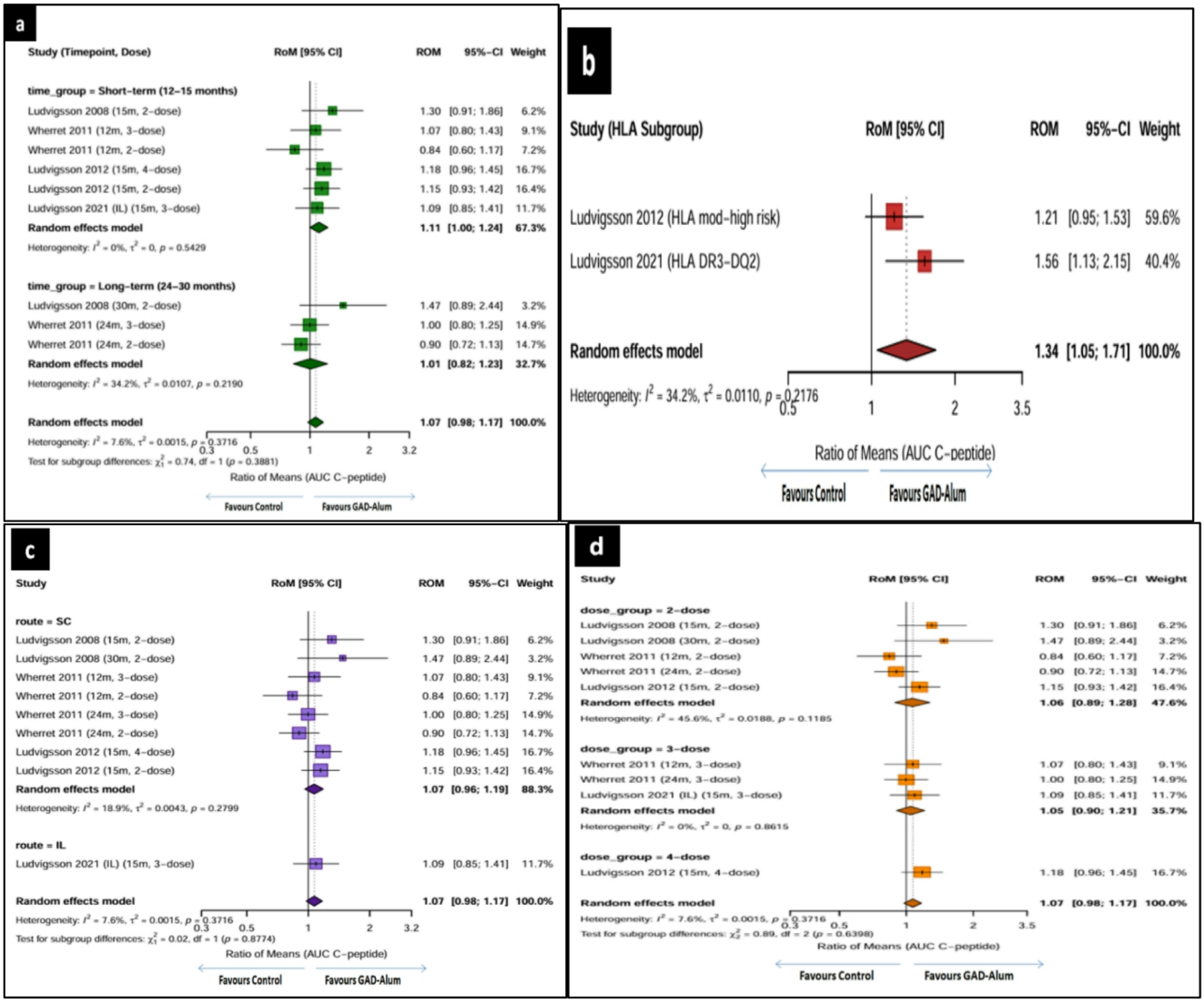


Figure 5

Subgroup Analysis by a) Timepoint: Short−term (12–15m) vs Long−term (24–30m) , b)HLA-grouping , c) Route (Subcutaneous vs Intralymphatic) and d) dosing frequency(2-dose,3-dose and 4 dose).Note: Only 2 studies reported HLA−stratified data.

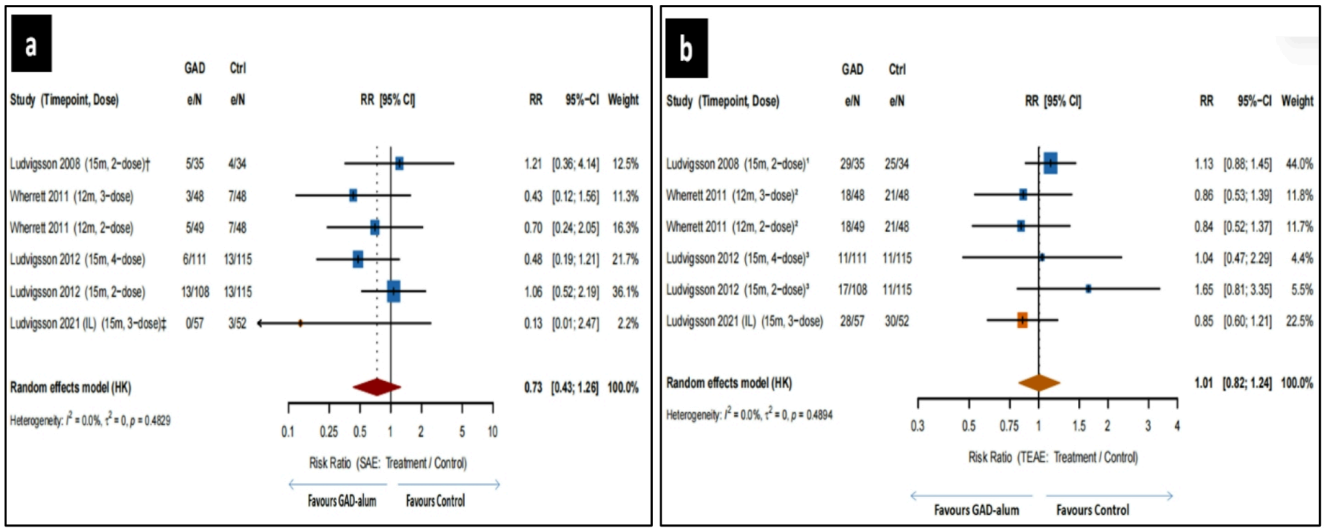


Figure 6

Forest plot depicting safety of GAD-Alum, a) pooled risk ratios of SAE, and b) pooled RR for TEAE.