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Placebo Adverse Events in Non-alcoholic Steatohepatitis Clinical Trials: A Pooled Analysis of 2,944 Participants

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CONFLICTS OF INTEREST

Potential competing interests: D.Q.H. has served as an advisory board member for Eisai. M.N. has advised 89BIO, Abbott, Allergan, Blade, EchoSens, Fractyl, Gilead, Intercept, Novartis, Novo Nordisk, OWL, Roche Diagnostics, Siemens, and Terns; he received research support from Allergan, Bristol-Myers Squibb, Conatus, Enanta, Galectin, Galmed, Genfit, Gilead, Madrigal, Novartis, Shire, Viking, and Zydus; he is a shareholder of or has stock in Anaetos and Viking. R.L. serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, Astra-Zeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc. All other authors have no conflicts of interests.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C716, http://links.lww.com/AJG/C716, http://links.lww.com/AJG/C716

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Abstract

INTRODUCTION: In the absence of an effective treatment for non-alcoholic steatohepatitis (NASH), a randomized, placebo-controlled trial (RCT) remains the current gold standard study design in NASH. As NASH is a largely asymptomatic disease, the side effects of potential therapies require careful evaluation, therefore a pooled rate of the adverse events (AEs) in placebo-treated patients serves as a useful comparator for safety. Therefore, we performed a systematic review and meta-analysis to estimate the rate of AEs among participants in the placebo arm of NASH RCTs.

METHODS: Medline, Embase and Cochrane Central Register of Controlled Trials were searched to include clinical trials in phase 2–4 NASH RCTs with placebo treatment arms. A pooled proportions of AEs were analyzed using a generalized linear mixed model with Clopper-Pearson intervals.

RESULTS: A total of 41 RCTs (2,944 participants on placebo) were included in this meta-analysis. A total of 68% (confidence interval [CI] 55%–77%) of participants on placebo experienced an AE, 7.8% (5.7%–10%) experienced serious AEs and 3.1% (CI: 1.9%–5.1%) experienced AEs leading to discontinuation. A significantly higher proportion of participants experienced serious AEs in phase 3 studies compared to in phase 2 studies ($P < 0.01$) and in pharmaceutical funded studies as compared to studies which were federal-funded studies ($P < 0.01$). An analysis of clinical trials evaluating bile acid modulating agents determined that 10% (CI: 5.5%–18%) of participants receiving placebo developed pruritus.

DISCUSSION: The present study summarizes the AEs with NASH placebo. Among participants in the placebo arm in NASH, two-third experienced an AE, and nearly 10% experienced a serious AE.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease affecting one quarter of the global population and represents a spectrum of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) (1-5). An estimated 20% of NAFL will progress to NASH (3,6) and the latter is characterized by the presence of lobular inflammation, hepatocellular ballooning with or without fibrosis. The presence of NAFLD is associated with a significant increase in the risk of hepatic and extrahepatic morbidity and mortality (7-9). Despite the significant burden posed by NAFLD, there are currently no approved drugs by the US Food and Drug Administration for use in NASH (10,11) and liver transplantation is often the only therapeutic option available to patients with NASH cirrhosis (12).

There has been however significant headway made into the study of pharmacological therapies in NASH (13). Recent evidence from phase 2 and 3 clinical trials including Obeticholic acid, Semaglutide and Lanifibranor have shown significant improvements in NASH (14-17). However, there is currently an absence of an approved pharmaceutical treatment for NASH and a double-blind placebo-controlled randomized clinical trial is the gold standard study design in the assessment of treatment options (13). A pooled analysis of the placebo arms of these trials can offer significant insights into NASH (18,19). While studies on the placebo effect in NASH have focused on the natural history of the disease, the rate of adverse events (AEs) in the placebo arm will provide a useful comparator for safety but have not been systematically assessed (18,20). In addition, the interim analysis from an ongoing phase III trial of obeticholic acid, a Farnesoid X receptor agonist trial reported positive results but highlighted a substantial rate of pruritus among participants who received treatment, prompting the US Food and Drug Administration to request for more data before approval of the treatment (16). A careful analysis of the pooled rate of pruritus in the placebo arm among studies of bile acid modulating agents, which likely performed careful assessments for pruritus, will provide useful data for clinical trial design. As NASH is largely an asymptomatic disease, a deeper understanding of the side effects of any proposed therapeutic agent is essential prior to approval, which requires clear benchmarks for the rate of AEs in placebo-treated patients. In light of these considerations, we conducted a systematic review and meta-analysis to quantify the AEs in the Placebo arms of phase 2–4 trials conducted in NASH.

METHODS

Search strategy

This study was conducted with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (21,22). Medline, Embase and Cochrane Central Register of Controlled Trials were searched with on February 1, 2022 without a lower limit on the date filter with assistance of a medical librarian for randomised controlled trials (RCTs) conducted in NASH. The full search strategy is detailed in Supplementary Digital Content (see Supplementary Material 1, http://links.lww.com/AJG/C716) and has been previously described (17,19). Duplicates were removed following the import of all references into Endnote X9.

Eligibility criteria and data extraction

Six authors (S.Y.L., P.W.L.T., C.H.N., J.X., W.H.L., Y.H.C.) each carried out an independent sieve of abstracts, followed by full text review for the inclusion of articles according to the eligibility criteria. Any discrepancies were resolved by consensus or in consultation with a senior author (M.M.). The eligibility criteria consisted of: (i) RCT by study design, (ii) clinical trials conducted in phase 2–4, (iii) studies which evaluated participants with NASH randomised to placebo treatment and (iv) reported AEs. We included only clinical trials from phase 2–4 as studies in these categories were conducted with close monitoring and detailing of AEs. Only original articles written in English were included while reviews, commentaries, and editorials were excluded. Studies conducted in the pediatric population were excluded. In the presence of overlapping studies which inferred results from the same

databases, only the most updated study was retained in the analysis. Six authors (S.Y.L., P.W.L.T., C.H.N., J.X., W.H.L., Y.H.C.) in 2 pairs independently extracted data including but not limited to (i) study characteristics such as author, year, country, and study design, (ii) patient characteristics such as sample size, age, gender, body mass index, presence of metabolic conditions including diabetes mellitus, hypertension, and hyperlipidemia (iii) AEs occurring in the placebo arm. Transformation of values were carried out using pre-existing formulae, in which mean and SDs were estimated from median and range using the widely adopted formula by Wan et al (23).

Definitions

Where possible, AE severity and Grade were defined according to the Common Terminology Criteria for AEs version 5.0 (24). Grade 1 AEs were defined as asymptomatic or mild symptoms; by clinical or diagnostic observations only; where intervention is not indicated. Grade 2 AEs were defined as moderate; minimal, local or non-invasive intervention indicated; with limiting age-appropriate instrumental Activities of Daily Living. Grade 3 AEs were defined as severe or medically significant but not immediately life-threatening, with hospitalization or prolongation of hospitalization indicated; or disabling; limiting patient's self-care Activities of Daily Living. Serious AEs were defined as AEs that resulted in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal functions, or a congenital anomaly/birth defect, or important medical events that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Mild and moderate AEs were defined per individual respective studies.

Statistical analysis and quality assessment

All analysis were conducted in RStudio (R version 4.0.3). Pooled proportions of AEs were analyzed using a generalized linear mixed model with Clopper-Pearson intervals (25,26). Random effects model was used in all analyses regardless of heterogeneity measures as evidence has demonstrated more robust effect estimates with random effect compared to fixed effect models (27,28). Statistical heterogeneity was assessed via I2 and Cochran's Q test values, with I2 values of 25%, 50% and 75% corresponding with low, moderate, and high degrees of heterogeneity respectively and a Cochran's Q test with P-value ≤0.10 was considered heterogeneous (29,30). Risk of bias was independently assessed by 4 authors (P.W.L.T., C.H.N., S.Y.L., J.L.X.). Quality assessment of included articles was assessed using the Cochrane Risk-of-Bias 2 Tool, which evaluates studies based on their random sequence generation, allocation concealment, masking of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias (31).

RESULTS

Summary of included articles

The initial search from Medline and Embase yielded a total of 1,353 articles, from which 187 duplicates were removed. The remaining 1,166 articles underwent a title-abstract sieve, which yielded 172 studies eligible for the full text screening. Finally, 41 RCTs were included in this meta-analysis (Figure 1), comprising a total of 2,944 trial participants on placebo. Twenty studies originated from USA (11,32-50), 2 each from Japan (51,52) and the United Kingdom (10,53), and one each from Brazil (54), Israel (55), France (56), and Taiwan (57) while 13 were multinational RCTs (14-16,58-67). There were 34 phase 2, 6 phase 3 and 1 phase 4 RCTs. When multiple studies shared the same institutional database, only the most recent study was included in the final analysis. Thirteen studies had a study duration of less than 6 months, 15 lasted between 6 and 12 months, while 13 studies exceeded 12 months (see Supplementary Material 2, http://links.lww.com/AJG/C717) Characteristics of the included studies have been summarised in Supplementary Digital Content (see Supplementary Material 2, http://links.lww.com/AJG/C717). Majority of the RCTs were assessed to be of low concern for risk of bias (n = 24), and few with moderate concern (n = 17; see Supplementary Material 3, http://links.lww.com/AJG/C718).

AEs

Overall, 25 studies (2,049 trial participants on placebo) reported the occurrence of any AE. Pooled analysis determined that 68% (confidence interval [CI] 55%–78%) of participants on placebo experienced an AE, and 3.1% (CI: 1.9%–5.1%) of participants experienced AEs led to drug discontinuation (Table 1). The pooled proportion of mild, moderate, and severe AEs were 34% (CI: 26%–44%), 21% (CI: 11%–36%), and 7.8% (CI: 5.7%–11%) respectively. The pooled proportion of grade 1, 2, and 3 AEs were 39% (CI: 28%–50%), 29% (15%–49%), and 9.0% (CI: 4.3%–18%) respectively. Additional subgroup analysis was conducted to quantify factors associated with higher overall AEs, serious AEs or AEs leading to drug discontinuation (Table 2). In terms of reporting of overall AEs, a significantly higher proportion of participants experienced AEs in phase 3 studies (89%; CI: 83%–94%, Figure 2) compared to phase 2 studies (63%; CI: 49%–74%, Figure 2), $P < 0.01$. Likewise, a significantly higher proportion of participants experienced AEs in placebo administrated via injection (85%; CI: 78%–90%), as compared to studies involving oral placebo (63%; CI: 49%–75%), $P < 0.01$.

In terms of serious AEs, there was a greater proportion of serious AEs in phase 3 trials (13%, CI: 11%–15%) compared with phase 2 trials (6.5%, CI: 4.2%–9.9%), $P < 0.01$ (Table 2, Figure 3). Additional subgroup analyses were conducted to quantify study level variables that could result in more discontinuation events found no study related factors resulting in a higher rate of discontinuation (Table 2, Figure 4).

Systemic AEs

The AEs by organ system are summarized in Table 3 (Figure 5). Overall in the placebo arm, 11% (CI: 8.5%–13%) experienced symptoms of fatigue, and 7.7% (CI: 1.4%–34%) and 2.6% (0.96%–6.6%) of the population reported depression and anxiety respectively.

A total of 8.8% (CI: 6.6%–12%) of participants in the placebo arm developed diabetes during follow up in clinical trials and the pooled prevalence of rash, pruritus and injection site reaction was 2.7% (CI: 1.0%–7.2%), 9.1% (CI: 5.0%–16%), and 13% (CI: 3.4%–38%) respectively. An analysis of clinical trials evaluating bile acid modulating agents involving bile acid agents found a numerically higher estimate for pruritus (16%, CI: 14%–18%).

In gastrointestinal events, 8.6% (CI: 6.2%–12%) of placebo participants experienced nausea, while 4.3% (CI: 2.2%–8.5%) experienced vomiting. Among participants on placebo, 9.9% (CI: 7.1%–14%) had abdominal pain while 7.9% (CI: 6.0%–10%) had upper abdominal pain. Gallbladder-related conditions occurred in 0.45% (CI: 0.14%–1.5%) of participants on placebo. Neurological symptoms including headache and dizziness were experienced by 9.2% (CI: 7.1%–12%) and 6.00% (CI: 3.6%–9.9%) respectively. Cardiovascular events including cardiovascular death, myocardial infarction or stroke was reported by 2.5% (CI: 0.39%–14%) of participants, while chest pain was experienced by 5.5% (CI: 2.9%–10%) of participants on placebo. In respiratory events, 12% (CI: 8.4%–17%) of participants on placebo developed upper respiratory tract infection. In musculoskeletal events, pooled prevalence of myalgia, arthralgia and back pain was 5.7% (CI: 2.8%–11%), 8.3% (7.1%–9.7%) and 7.8% (5.9%–10%) respectively.

DISCUSSION

In this systematic review and meta-analysis of 41 RCTs, two-third of participants in the placebo arm of NASH trials experienced AEs, 8% experienced serious AEs and 3% had an AE resulting in discontinuation. By organ system, the most common gastrointestinal AEs were abdominal pain and diarrhea which were present in 10% and 12% respectively, neurological AEs such as headache in 9%, and general AEs including fatigue in 11% of patients. Over a tenth of participants on the placebo arm in trials of bile acid modulators reported pruritic events. The current study found the rate of overall and serious AEs to be significantly higher in phase 3 trials compared with phase 2 trials, and overall AEs higher in pharmaceutical funded studies compared with government funded studies. These results may be partially explained by the longer duration of follow-up in phase 3 trials and possibly closer monitoring of participants in pharmaceutical sponsored studies.

As NASH is typically asymptomatic, the side effects of potential therapies in clinical trials require careful evaluation, therefore a pooled rate of the AEs in placebo-treated patients serves as a useful comparator for safety. The Placebo effect cannot be discounted and may result in a misrepresentation of safety in clinical trials (68). Studies have shown that adverse reactions emphasised by clinicians were more likely to be experienced by patients in clinical trials and standardized communication of information is essential to reduce reporter bias (69). A recent example can be drawn from the Self-Assessment Method for Statin Side-effects Or Placebo trial which found a similar proportion of reported AEs in both arms when patients who received placebo were told that they were included in the treatment arm (70). In particular, the unexpectedly high rates of pruritus in the placebo arm of RCTs involving bile acid modulating agents provide a useful comparator to gauge the impact of Farnesoid X receptor agonists on pruritus. The current study builds on existing meta-analyses of AEs in the placebo arm in other diseases (71-73).

The current analysis provides a novel and detailed analysis of the AEs in the placebo arm of NASH trials. There are, however, several limitations. Firstly, there was heterogeneity in the definition of AEs reported by included studies. Secondly, there were insufficient data to assess the factors associated with the development of AEs in the placebo arm. Additionally, reporting of AEs may have been subject to recall bias. Lastly, the analysis only included phase II–IV RCTs in NASH and excluded studies conducted outside of the clinical trial, in order to maintain the highest quality of included studies.

Among participants in the placebo arm, two-third experienced an AE, and nearly 10% experienced a serious AE. These data have value as a comparator for safety in future NASH trials and are informative for future references on tolerability and safety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability:

All articles in this manuscript are available from Medline and Embase.

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Study Highlights

WHAT IS KNOWN

- Obeticholic acid, Semaglutide and Lanifibranor have shown significant improvements in non-alcoholic steatohepatitis (NASH).
- Up to a fifth of participants in NASH trials can have a 1 point reduction and progression of NASH in the placebo arm despite the absence of therapeutics.

WHAT IS NEW HERE

- An important benchmark of the expected rate of adverse events in the placebo arm.
- In the placebo arm, two-third experienced an AE, nearly 10% experienced a serious AE, and 10% of participants in trials evaluating bile acid modulating agents experienced pruritus.

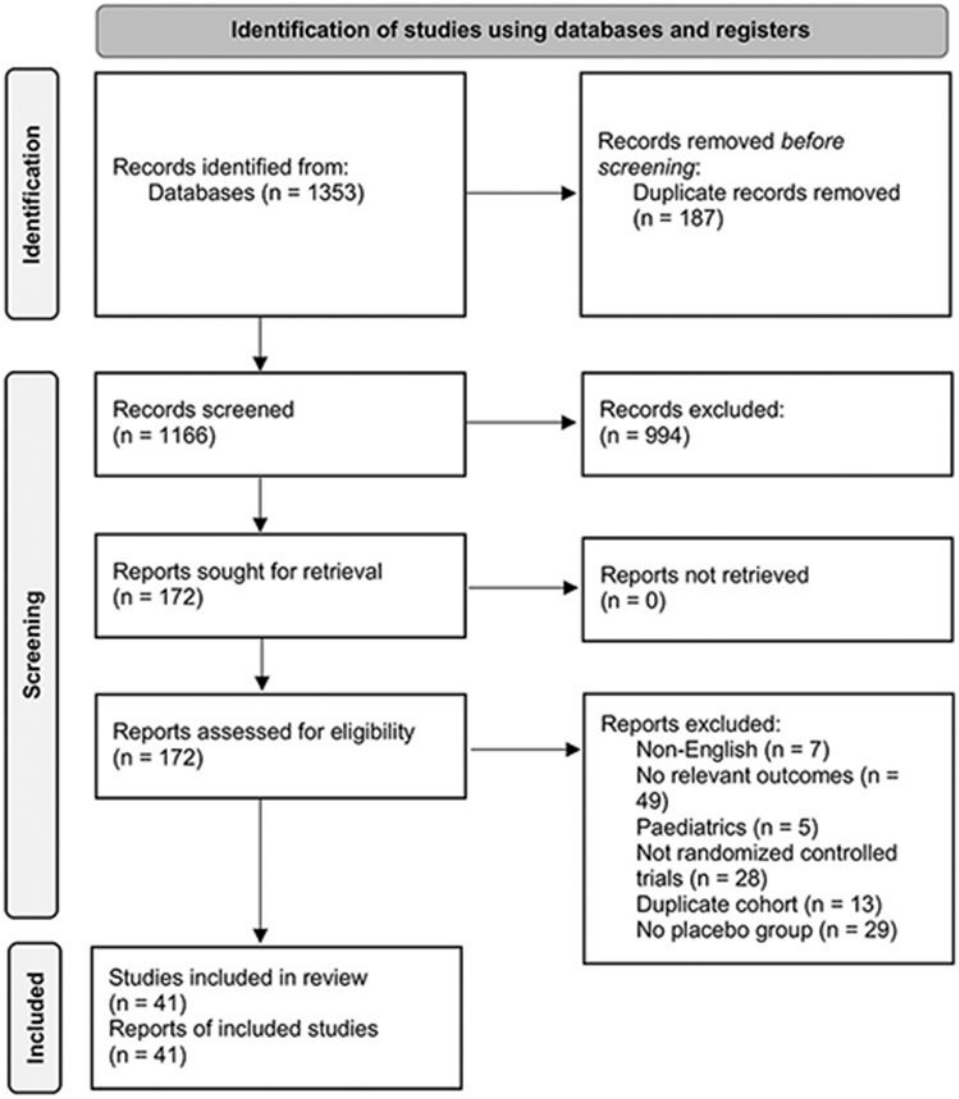

Figure 1.
PRISMA flowchart of included articles. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

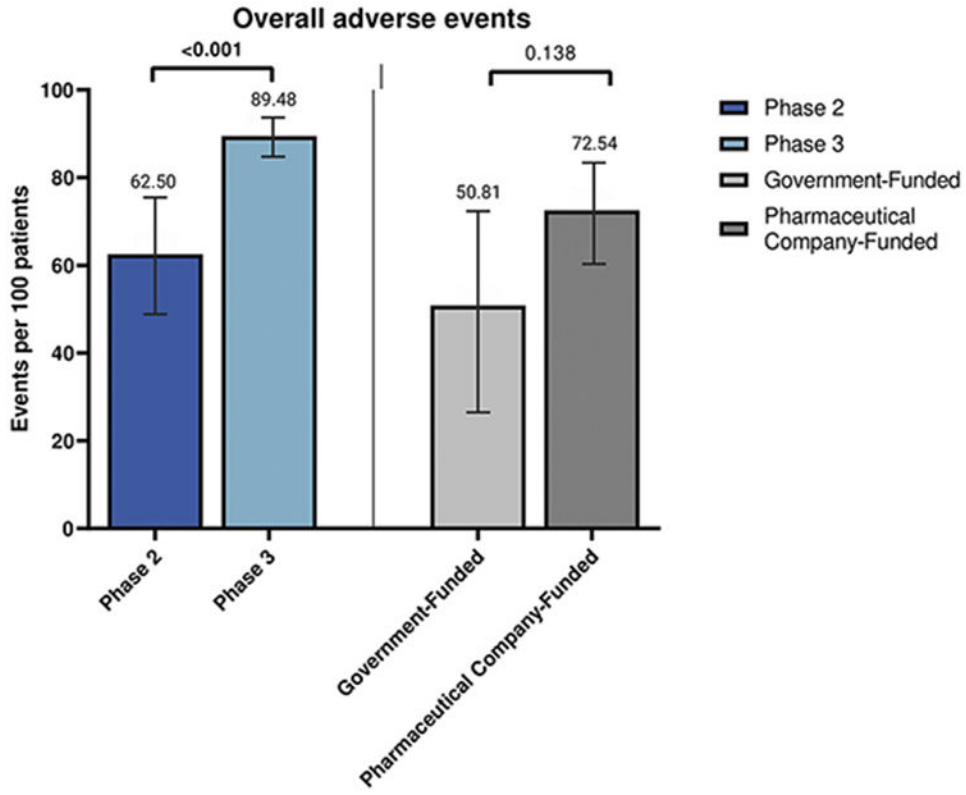

Figure 2.
Overall adverse events in phase 2 vs phase 3 trials and government vs pharmaceutical funded trials.

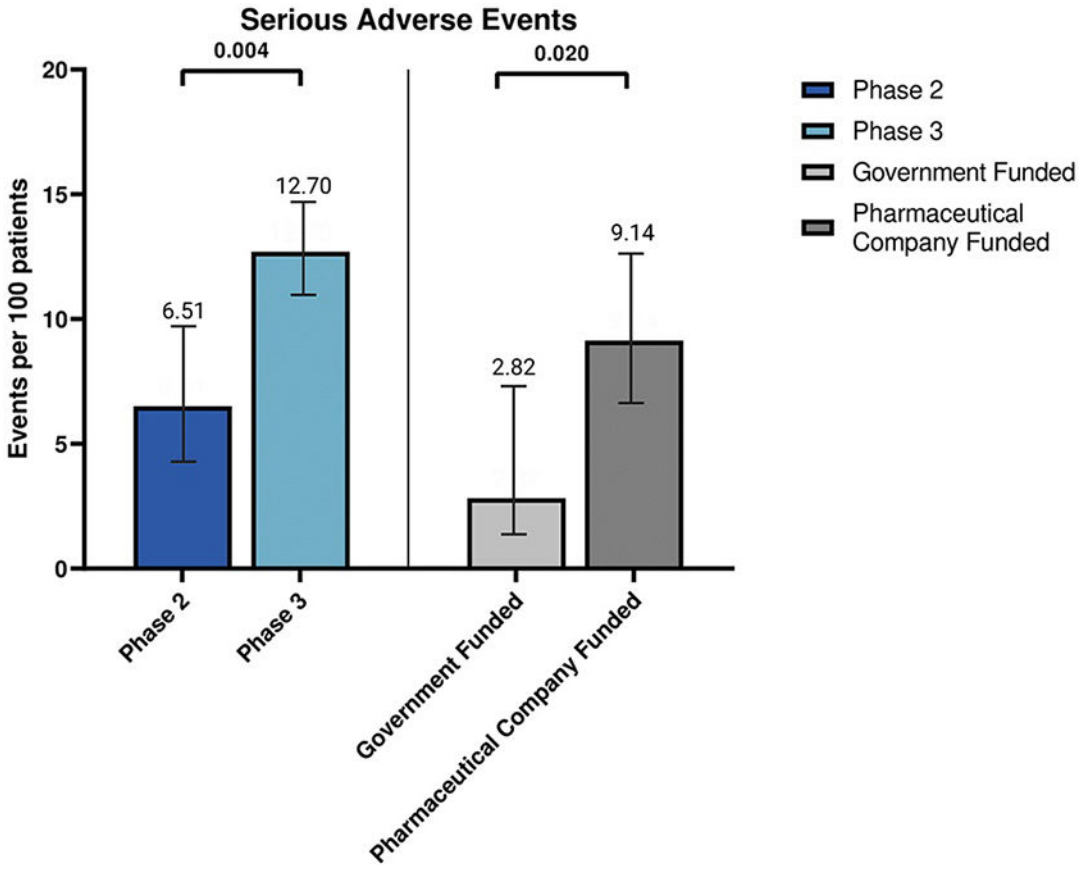

Figure 3.
Serious adverse events in phase 2 vs phase 3 trials and government vs pharmaceutical funded trials.

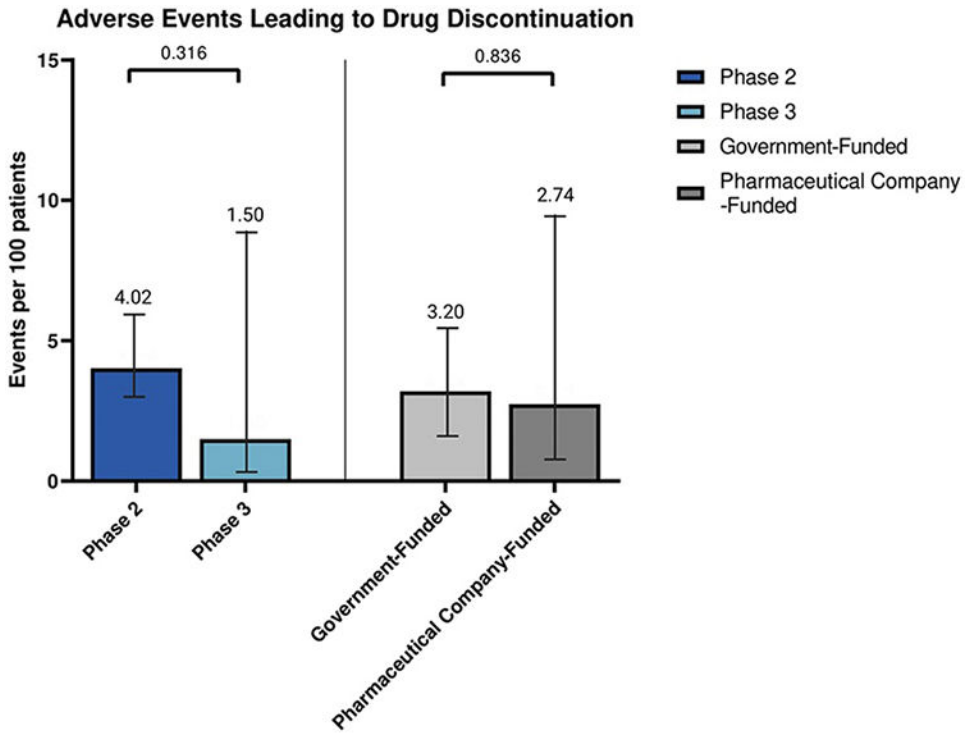

Figure 4.

Discontinuation events in phase 2 vs phase 3 trials and government vs pharmaceutical funded trials.

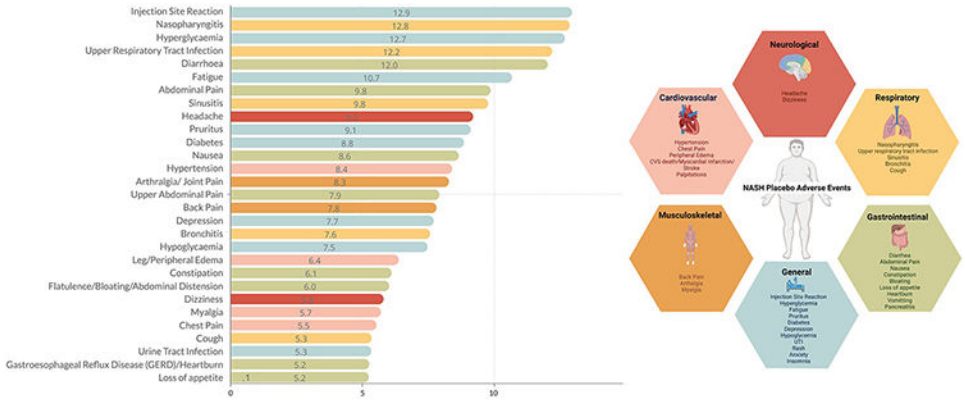

Figure 5.
Summary of systematic adverse events.

Table 1.

Summary of overall adverse events in placebo patients

	Sample size	Pooled proportion (%)	95% CI	I^2
Overall	2,049	67.59	55.15–77.96	93.00%
Adverse event leading to drug discontinuation	1,550	3.14	1.94–5.05	0.00%
By severity				
Mild	963	34.44	26.02–43.97	86.10%
Moderate	963	20.87	10.98–36.04	90.40%
Serious	2,119	7.82	5.66–10.71	49.70%
By CTCAE grading				
Grade 1	83	38.52	28.29–49.76	38.30%
Grade 2	83	29.18	14.84–49.35	75.80%
Grade 3	78	8.97	4.34–17.65	0.50%

CI, confidence interval; CTCAE, common terminology criteria for adverse events.

Table 2.

Subgroup analysis of adverse events in placebo patients

	Sample size	Pooled proportion (%)	95% CI	Subgroup difference
Overall				**<0.001**
Phase				
2	1,054	62.50	49.34–74.04	
3	988	89.48	82.84–93.75	
Initiator				0.138
Federal funded	106	50.84	25.34–75.86	
Pharmaceutical company	1,393	72.54	60.36–82.09	
Route of administration				**0.001**
Injection	152	84.87	78.26–89.73	
Oral	1,890	62.85	48.62–75.15	
Risk of bias				0.063
Low concern	1,609	61.53	43.29–77.02	
Some concern	435	77.73	70.35–83.70	
Serious adverse events				
Phase				**0.004**
2	1,009	6.51	4.21–9.93	
3	1,071	12.70	10.83–14.83	
Initiator				0.02
Federal funded	142	2.82	1.06–7.26	
Pharmaceutical company	1,938	9.14	6.75–12.28	
Mode of administration				0.890
Injection	284	7.57	2.57–20.30	
Oral	1,816	8.17	6.04–10.96	
Risk of bias				0.976
Low concern	1,610	8.17	5.79–11.40	
Some concern	470	8.08	4.24–14.85	
Adverse events leading to drug discontinuation				
Phase				0.316
2	523	4.02	2.63–6.08	
3	988	1.50	0.22–9.46	
Initiator				0.836
Federal funded	1,438	3.20	1.86–5.46	
Pharmaceutical company	73	2.74	0.69–10.30	
Mode of administration				0.159
Injection	179	5.03	2.64–9.38	
Oral	1,332	2.51	1.92–5.15	

	Sample size	Pooled proportion (%)	95% CI	Subgroup difference
Risk of bias				0.184
Low concern	379	4.52	2.83–7.15	
Some concern	1,135	2.14	0.78–5.77	

Bolded *P* value <0.05 denotes statistical significance.

CI, Confidence Interval.

Table 3.

Adverse events by organ system

	Sample size	Pooled proportion (%)	95% CI	Subgroup difference
General				
Fatigue	2,077	10.65	8.45–13.34	52.60%
Urinary tract infection	1,563	5.32	2.70–10.21	84.90%
Pruritus	992	9.10	5.01–15.94	92.90%
Depression	111	7.69	1.35–33.70	88.50%
Anxiety	157	2.55	0.96–6.59	0.00%
Insomnia	157	0.92	0.01–47.65	0.00%
Hypoglycaemia	228	7.45	3.05–17.10	71.50%
Hyperglycemia	72	12.66	4.73–29.78	75.50%
Diabetes	464	8.84	6.57–11.78	36.50%
Rash	600	2.71	1.00–7.16	65.40%
Injection site reaction	74	12.94	3.44–38.23	79.20%
Gastrointestinal				
Nausea	2,237	8.64	6.20–11.92	63.40%
Vomiting	1,242	4.32	2.16–8.45	62.10%
Abdominal pain	2,132	9.85	7.05–13.61	82.70%
Upper abdominal pain	1,665	7.91	5.98–10.38	49.20%
Bloating	1,164	6.09	3.18–11.35	77.70%
Diarrhea	2,241	12.01	8.99–15.87	74.80%
Constipation	1,831	6.36	4.53–8.88	33.80%
Loss of appetite	223	5.23	0.64–32.11	84.60%
Increase appetite	48	2.08	0.29–13.36	0.00%
GERD/heartburn	286	5.24	3.19–8.52	0.00%
Gallbladder-related conditions	896	0.45	0.14–1.45	10.40%
Pancreatitis	278	1.08	0.35–3.29	0.00%
Neurological				
Headache	2,316	9.18	7.07–11.85	57.00%
Dizziness	1,281	6.00	3.58–9.90	66.50%
Cardiovascular				
CVS death/MI/stroke	306	2.48	0.39–14.15	85.70%
Chest pain	163	5.52	2.90–10.27	0.00%
Palpitations	79	2.53	0.63–9.56	0.00%
Hypertension	441	8.39	6.14–11.37	0.00%
Peripheral oedema	414	5.79	2.84–11.45	56.60%
Respiratory				
Sinusitis	680	9.76	7.22–13.07	36.20%
Nasopharyngitis	1,128	12.85	9.24–17.60	66.30%
Cough	1,105	5.33	3.211–8.7267	59.60%

	Sample size	Pooled proportion (%)	95% CI	Subgroup difference
Upper respiratory tract infection	1,300	12.18	8.43–17.29	77.80%
Bronchitis	628	7.55	2.18–23.09	89.60%
Musculoskeletal				
Myalgia	248	5.68	2.76–11.34	10.50%
Arthralgia	1,706	8.26	7.05–9.67	31.10%
Back pain	1,485	7.80	5.90–10.24	13.40%

CI, confidence interval; CVS, cardiovascular system; GERD, gastroesophageal reflux disease; MI, myocardial infarction.