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EFFICACY AND SAFETY OF DUAL GLP-1/GIP RECEPTOR AGONISTS FOR GASTROINTESTINAL AND HEPATIC OUTCOMES IN ADULTS WITH OBESITY AND TYPE 2 DIABETES: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To evaluate the efficacy and safety of dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonism for gastrointestinal tolerability and hepatic outcomes in adults with obesity and type 2 diabetes.

Study design: Systematic review of randomized controlled trials, prespecified imaging sub studies and recent meta-analyses.

Place and duration of the study: Global evidence was reviewed between February 2025 to may 2026.

Methodology: MEDLINE/PubMed was searched for tirzepatide or dual GIP/GLP-1 agonism combined with gastrointestinal, liver, MASLD, MASH or NAFLD outcomes. Adult randomized studies and quantitative syntheses were eligible. Overlapping reports were identified by trial programme and were not pooled as independent participants. Published effects were synthesized without recalculation.

Results: The search identified 797 records and 24 focused reports were included. In SURPASS-3 MRI 296 participants had a baseline mean liver fat content of 15.71% ± 8.93%. At week 52 pooled tirzepatide 10/15 mg reduced liver fat by −8.09% ± 0.57 compared with −3.38% ± 0.83 with insulin degludec; estimated treatment difference −4.71% (95% CI −6.72 to −2.70, $p<0.0001$). In SYNERGY-NASH 190 participants were randomized. MASH resolution without worsening fibrosis occurred in 10% with placebo and 44%, 56% and 62% with tirzepatide 5, 10 and 15 mg ($p<0.001$ for each comparison). A 10-trial meta-analysis involving 6,836 participants reported dose-dependent gastrointestinal adverse events of 39% (95% CI 35–43), 46% (95% CI 42–49) and 49% (95% CI 38–60) at 5, 10 and 15 mg.

Conclusion: Tirzepatide improves liver fat and MASH activity and may improve fibrosis. Gastrointestinal adverse events are frequent, dose-dependent and usually mild to moderate. Gradual escalation and monitoring for dehydration, gallbladder disease and persistent symptoms are required.

KEYWORDS: tirzepatide; dual incretin agonist; obesity; type 2 diabetes; gastrointestinal adverse events; metabolic dysfunction-associated steatotic liver disease

INTRODUCTION

Obesity and type 2 diabetes are closely linked to gastrointestinal symptoms and metabolic dysfunction-associated steatotic liver disease (MASLD). Insulin resistance, excess adiposity and ectopic lipid deposition can progress from steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis and cirrhosis. Weight reduction improves metabolic and hepatic risk but durable non-surgical weight loss is difficult to achieve. Dual incretin receptor agonism has therefore become a major therapeutic strategy [1].

Tirzepatide activates glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. It lowers glucose, reduces appetite and produces substantial weight loss. These effects can reduce hepatic substrate delivery, visceral adiposity and insulin resistance [2]. The same mechanisms slow gastric emptying and alter gut motility. Nausea, diarrhoea, vomiting, constipation and abdominal discomfort are therefore common during dose escalation. The clinical question is not simply whether the drug is efficacious. It is whether hepatic benefit is achieved with acceptable gastrointestinal tolerability [3].

The evidence base spans obesity trials, type 2 diabetes trials, magnetic resonance imaging substudies and a recent biopsy-confirmed MASH trial. Trial populations differ in diabetes status, baseline body mass index, comparator, dose and duration [4]. Hepatic endpoints also differ: liver fat measured by MRI-proton density fat fraction is not equivalent to histological MASH resolution or fibrosis improvement. Safety reports may combine symptoms or present individual events. Direct pooling without addressing overlapping SURPASS and SURMOUNT reports can therefore overstate precision [5].

Pakistan faces a growing burden of obesity, diabetes and fatty liver disease but access, affordability and monitoring remain variable. Evidence synthesis can support patient selection and counseling. This systematic review assessed gastrointestinal safety and hepatic efficacy of dual GIP/GLP-1 receptor agonists in adults with obesity or type 2 diabetes. Secondary objectives were to examine dose response, discontinuation and serious hepatobiliary or pancreatic events [6-13].

MATERIALS AND METHODS

A systematic review was conducted using PRISMA 2020 principles. Eligible populations were adults with obesity, overweight with a weight-related complication, type 2 diabetes or biopsy/imaging-confirmed MASLD/MASH. The intervention was a dual GIP/GLP-1 receptor agonist. Because tirzepatide was the only agent with mature phase 3 and hepatic clinical evidence, the effectiveness synthesis focused on tirzepatide. Comparators included placebo, insulin, semaglutide or other active therapy.

MEDLINE/PubMed was searched.Terms combined tirzepatide or 'dual GIP GLP-1' with gastrointestinal, nausea, vomiting, diarrhoea, constipation, gastric emptying, hepatic, liver, MASLD, MASH or NAFLD. The broad search returned 797 records. Reference lists of recent systematic reviews, regulatory-era clinical reviews and MASLD guidelines were checked for missing randomized reports and prespecified hepatic substudies. Review work occurred from February 2025 to may 2026.

Randomized controlled trials, prespecified substudies and quantitative systematic reviews were eligible when they reported at least one gastrointestinal or hepatic endpoint. Hepatic endpoints included MRI liver fat, liver enzymes, non-invasive fibrosis markers, MASH resolution without fibrosis worsening and fibrosis improvement without MASH worsening. Safety endpoints included individual gastrointestinal adverse events, any gastrointestinal event, discontinuation, pancreatitis and gallbladder or biliary disease. Paediatric studies, animal experiments, case reports and reports without relevant outcomes were excluded.

A structured form captured study programme, sample size, diabetes status, dose, comparator, duration, baseline characteristics, endpoint definition, numerical effect, confidence interval and p-value. Trial reports from the same programme were linked to prevent double counting. MASH resolution and fibrosis improvement were kept as separate outcomes. Absolute change in liver fat was not converted to relative change. Gastrointestinal events were retained as reported because ascertainment and grouping differed across trials.

Risk of bias was assessed through randomization, allocation concealment, masking, missing data, outcome measurement and selective reporting. Open-label trials and post hoc studies were considered at higher risk for subjective symptoms. Meta-analyses were examined for duplicate trial reports, comparator mixing and heterogeneity. A new meta-analysis was not performed because the objective covered non-equivalent hepatic and gastrointestinal endpoints and several reports reused trial cohorts. Descriptive statistics were presented as n (%), mean ± SD or published effect estimates. $p<0.05$ was considered statistically significant when specified by the original analysis. No participant-level data were accessed. Ethical approval and consent were not required for published aggregate evidence [14].

RESULTS

The database search identified 797 records and 24 focused reports were included. The evidence comprised phase 3 obesity and diabetes trials, one MRI hepatic substudy, one biopsy-confirmed MASH trial and systematic reviews of gastrointestinal, pancreatic and biliary safety. Adult participants ranged from insulin-naïve patients with type 2 diabetes to adults with obesity without diabetes and patients with F2–F3 MASH fibrosis. Figure 1 summarizes selection and outcome domains.

SURPASS-3 MRI provided the clearest quantitative steatosis result. Of 502 people assessed, 296 were included in the MRI population: tirzepatide 5 mg n=71, 10 mg n=79, 15 mg n=72 and insulin degludec n=74. Mean baseline liver fat content was 15.71% ± 8.93%. At week 52 pooled tirzepatide 10/15 mg reduced liver fat by −8.09% ± 0.57 compared with −3.38% ± 0.83 with insulin degludec. The estimated treatment difference was −4.71% (95% CI −6.72 to −2.70, $p<0.0001$). Liver fat reduction correlated with baseline liver fat ($\rho=-0.71$), visceral adipose tissue reduction ($\rho=0.29$), subcutaneous adipose tissue reduction ($\rho=0.33$) and weight reduction ($\rho=0.34$); $p\leq0.0006$ for each reported correlation.

SYNERGY-NASH randomized 190 participants with biopsy-confirmed MASH and F2 or F3 fibrosis. Week-52 biopsy was evaluable in 157. MASH resolution without worsening fibrosis occurred in 10% with placebo and 44%, 56% and 62% with tirzepatide 5, 10 and 15 mg. Differences versus placebo were 34 percentage points (95% CI 17–50), 46 (95% CI 29–62) and 53 (95% CI 37–69); $p<0.001$ for all comparisons. Improvement of at least one fibrosis stage without worsening MASH occurred in 30% with placebo and 55%, 51% and 51% with tirzepatide. Differences were 25 points (95% CI 5–46), 22 (95% CI 1–42) and 21 (95% CI 1–42).

Gastrointestinal events were dose-dependent. A meta-analysis of 10 trials involving 6,836 participants reported any gastrointestinal adverse event in 39% (95% CI 35–43) at 5 mg, 46% (95% CI 42–49) at 10 mg and 49% (95% CI 38–60) at 15 mg. Nausea and diarrhoea were the most frequent events. Discontinuation due to adverse events was highest at 15 mg (10%). Fatal events, severe hypoglycaemia, acute pancreatitis, cholelithiasis and cholecystitis were each ≤1% across doses in that synthesis.

In SURPASS-2 nausea occurred in 17%–22% with tirzepatide and 18% with semaglutide. Diarrhoea occurred in 13%–16% and 12% and vomiting in 6%–10% and 8%. Serious adverse events were reported in 5%–7% with tirzepatide and 3% with semaglutide. SURMOUNT-1 reported discontinuation due to adverse events in 4.3%, 7.1%, 6.2% and 2.6% with tirzepatide 5, 10, 15 mg and placebo. Most gastrointestinal events were mild to moderate and concentrated during dose escalation.

A nine-trial meta-analysis involving 9,871 participants found no significant association with pancreatitis (RR 1.46, 95% CI 0.59–3.61; p=0.436). The composite of gallbladder or biliary disease was increased against placebo or basal insulin (RR 1.97, 95% CI 1.14–3.42) although individual cholelithiasis, cholecystitis and biliary outcomes were not significantly increased. A 13-trial obesity analysis reported overall gastrointestinal risk for tirzepatide versus placebo of RR 2.94 (95% CI 2.61–3.32) and did not find a significant hepatic or pancreatic adverse-event increase. Tables 1–3 present population, hepatic and safety findings.

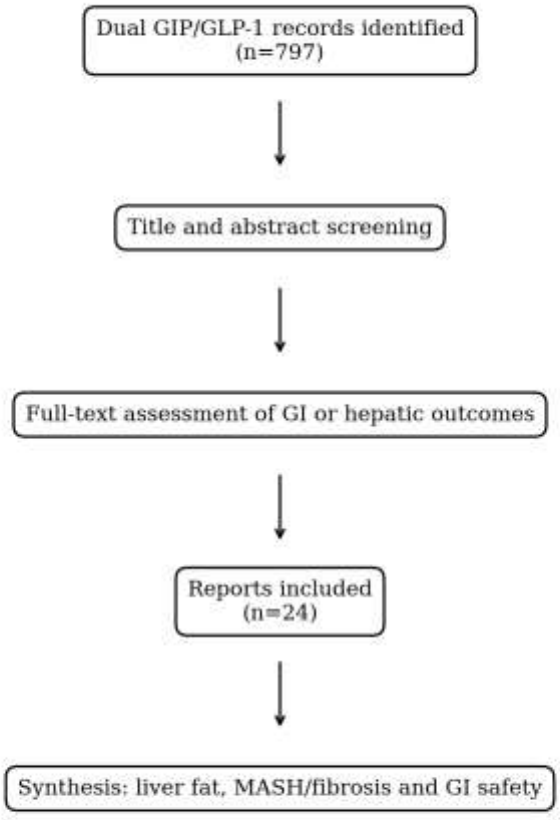

Figure 1. Study selection and evidence-synthesis flow.

Table 1. Characteristics of principal hepatic and safety evidence

Study	Population/sample	Comparator	Duration/outcome
SURPASS-3 MRI	296 adults with T2D and fatty liver index ≥60	Insulin degludec	52 weeks; MRI liver fat
SYNERGY-NASH	190 adults with biopsy-confirmed MASH and F2–F3	Placebo	52 weeks; histology
SURPASS-2	1,879 adults with T2D	Semaglutide 1 mg	40 weeks; efficacy and safety

Study	Population/sample	Comparator	Duration/outcome
GI adverse-event meta-analysis	10 trials; 6,836 participants	Mixed controls	Dose-specific adverse events
Pancreatic/biliary meta-analysis	9 trials; 9,871 participants	Placebo/active controls	Pancreatitis and biliary events

Table 2. Main hepatic efficacy outcomes

Outcome	Tirzepatide	Comparator	Reported comparison
Liver fat change	−8.09% ± 0.57, pooled 10/15 mg	−3.38% ± 0.83 degludec	Difference −4.71% (95% CI −6.72 to −2.70); p<0.0001
MASH resolution	44%, 56%, 62% at 5, 10, 15 mg	10% placebo	p<0.001 for each dose
Fibrosis improvement	55%, 51%, 51% at 5, 10, 15 mg	30% placebo	Differences 25, 22 and 21 percentage points
Liver fat/weight correlation	ρ=0.34	Not applicable	p≤0.0006

Table 3. Gastrointestinal and hepatobiliary safety

Outcome	Reported estimate	Clinical interpretation
Any GI event	39%, 46%, 49% at 5, 10, 15 mg	Dose-dependent; usually mild/moderate
SURPASS-2 nausea	17%–22% vs 18% semaglutide	Common in both groups
SURPASS-2 diarrhoea	13%–16% vs 12%	Common during escalation
Pancreatitis	RR 1.46 (95% CI 0.59–3.61); p=0.436	No significant increase
Composite gallbladder/biliary disease	RR 1.97 (95% CI 1.14–3.42)	Monitoring warranted
Discontinuation	10% at 15 mg in meta-analysis	Tolerability affects persistence

DISCUSSION

This review found clinically important hepatic improvement with dual GIP/GLP-1 agonism and a predictable gastrointestinal tolerability burden. Tirzepatide reduced MRI liver fat more than insulin degludec and produced dose-related MASH resolution in patients with F2–F3 fibrosis. Gastrointestinal events were common and increased with dose but were usually mild to moderate and occurred during escalation [15].

The hepatic evidence is biologically coherent. Weight loss reduces free-fatty-acid delivery to the liver. Improved insulin sensitivity decreases de novo lipogenesis and visceral adipose reduction lowers inflammatory signaling [16]. The SURPASS-3 MRI correlations show that liver fat change was linked to weight and adipose change but correlation values were modest apart from baseline liver fat. This suggests that benefit is partly mediated by weight reduction and partly by broader metabolic effects [17]. Imaging improvement is meaningful but does not alone establish prevention of cirrhosis or liver-related death.

SYNERGY-NASH advanced the evidence from imaging to histology. MASH resolution increased from 10% with placebo to 44%–62% across tirzepatide doses [18]. Fibrosis improvement occurred in 51%–55% with tirzepatide compared with 30% with placebo. The trial was phase 2, included 190 randomized participants and lasted 52 weeks. It therefore supports efficacy but does not establish long-term safety or decompensation benefit. Current MASLD guidance recognizes incretin-based therapies for obesity or diabetes indications and supports their metabolic value without treating every patient with steatosis as a drug candidate [19].

Recent network meta-analysis ranks tirzepatide among the stronger therapies for MASH resolution [20]. Such indirect rankings require caution because trials differ in fibrosis stage, endpoint adjudication and missing-biopsy handling. The most reliable interpretation remains within-trial comparison with placebo. Larger phase 3 studies should assess sustained histological response, fibrosis progression, cirrhosis and clinical liver outcomes. Pakistan-specific trials are absent. Local application should use standard fibrosis risk stratification rather than elevated aminotransferases alone [21].

Gastrointestinal adverse events were the principal tolerability limitation. Dose dependence across 5, 10 and 15 mg supports gradual escalation [22]. In clinical care, transient nausea or diarrhoea can often be managed with smaller meals, reduced dietary fat, hydration and delayed escalation. Persistent vomiting, severe abdominal pain, inability to maintain fluids or symptoms of obstruction require evaluation rather than automatic attribution to expected treatment effects [23]. Patients using insulin or sulfonylureas may also require glucose-lowering dose adjustment although severe hypoglycaemia is uncommon with tirzepatide alone.

Delayed gastric emptying has implications for procedures and oral medicines [24]. Guidance on withholding incretin therapy before anaesthesia has evolved toward individualized assessment based on symptoms, dose escalation and aspiration risk. A blanket interruption may worsen glycaemic control and does not guarantee an empty stomach. Patients with severe gastroparesis or recurrent vomiting need cautious selection. Contraceptive counseling may also be relevant during initiation because delayed absorption can affect oral drug exposure [25].
Pancreatitis was not significantly increased in the nine-trial synthesis but the confidence interval was wide [26]. Low event rates prevent a claim of zero risk. New persistent severe epigastric pain warrants discontinuation and assessment. Gallbladder or biliary events showed a significant composite signal against placebo or basal insulin. Rapid weight loss itself may contribute. Clinicians should ask about biliary history and evaluate right upper-quadrant pain, fever or jaundice [27]. Routine enzyme or ultrasound monitoring in asymptomatic patients is not established.
The obesity and diabetes evidence shows that benefit extends beyond liver endpoints. SURMOUNT-2 produced substantial weight reduction in adults with obesity and type 2 diabetes [28]. Long-term SURMOUNT-1 follow-up found sustained weight loss and reduced progression from prediabetes to diabetes [29]. Head-to-head obesity evidence found greater weight reduction with tirzepatide than semaglutide [30]. These outcomes can indirectly improve liver risk but should not be substituted for histological or fibrosis outcomes.
Real-world tolerability may differ from trials. Clinical cohorts include patients with multimorbidity, variable access and interrupted supply [31]. Cost and discontinuation may produce weight regain. Patient education should set expectations that gastrointestinal symptoms are most likely during escalation and that slower titration may be appropriate. In Pakistan, dehydration risk during hot weather or fasting and limited access to urgent assessment deserve attention. Therapy should be integrated with nutrition, physical activity, diabetes care and fibrosis assessment [32].
Evidence for hepatic safety was generally reassuring. A recent meta-analysis of GLP-1-based therapies found reduced liver fat and improved steatosis, ballooning and inflammation with no drug-related liver adverse signal [33]. Yet rare idiosyncratic injury cannot be excluded by trials. Baseline liver tests are clinically useful for disease assessment rather than because tirzepatide commonly causes hepatotoxicity. The strongest current benefit-risk profile is in patients who meet approved obesity or diabetes indications and may gain hepatic benefit at the same time [34].
Patient selection is central to benefit-risk balance. A person with poorly controlled diabetes, obesity and high liver risk may gain glycaemic, weight and hepatic benefit from one therapy. A person with mild steatosis, normal fibrosis markers and severe baseline gastrointestinal disease may have less favourable tolerability. Baseline review should include current medicines, previous pancreatitis or biliary disease, symptoms suggesting gastroparesis, renal vulnerability to dehydration and planned procedures. Pregnancy intention also matters because weight-management pharmacotherapy is not used during pregnancy and effective contraception may be required. Shared decisions should define the primary treatment goal and the symptoms that require contact or discontinuation.
Dose escalation should be treated as a clinical process rather than a fixed race to the maximum dose. The lowest effective tolerated dose may provide substantial metabolic benefit. Escalation can be delayed when nausea, diarrhoea or constipation remains troublesome. Dietary counseling should focus on smaller portions, slower eating and avoidance of large high-fat meals during symptomatic periods. Fluid intake and sick-day advice are especially important when vomiting or diarrhoea coexist with SGLT2 inhibitors, diuretics or renin-angiotensin system blockers. Renal function should be assessed when volume depletion is clinically significant.
Hepatic monitoring should match disease risk. Aminotransferases alone can be normal in advanced fibrosis and can fall with weight loss without proving fibrosis regression. Adults with obesity or type 2 diabetes should undergo structured case finding using a validated fibrosis score followed by elastography or specialist assessment when indicated. MRI liver fat is useful in research but is not required for routine initiation. Repeat fibrosis assessment can help determine whether metabolic improvement is accompanied by lower liver risk. Patients with cirrhosis need specialist care because trial evidence in decompensated disease is insufficient.
Future comparative research should separate tolerability from serious safety. Trials should report the timing, duration and severity of each gastrointestinal event, rescue medication, dose interruption and successful rechallenge. Hepatic trials need common definitions, central histology review and longer follow-up for cirrhosis and clinical events. Independent studies should evaluate affordability, discontinuation and outcomes after treatment interruption. Head-to-head comparisons with selective GLP-1 agonists should include patient-reported gastrointestinal burden and quality of life in addition to weight and glycated haemoglobin. These measures would make efficacy estimates more useful for real clinical decisions.
Treatment persistence deserves explicit attention. The clinical benefit observed in randomized trials assumes continuing access and adherence. Gastrointestinal symptoms, cost, medicine shortages or unrealistic expectations can lead to interruption. Rapid re-escalation after a prolonged gap may reproduce nausea or vomiting. Services should provide a contact point for dose advice and should document why treatment stopped. When benefit is inadequate at a tolerated dose, clinicians should reassess adherence, secondary causes of weight gain, concurrent medicines and the original goal before escalating or changing treatment.
Outcome interpretation should remain patient-centred. A reduction in liver fat is valuable because it indicates lower steatotic burden but patients may care more about energy, glucose control, avoidance of cirrhosis and ability to continue treatment. MASH resolution is a regulatory and histological endpoint that does not guarantee an

immediate symptomatic change. Discussions should explain this difference. Weight, waist circumference, glycated haemoglobin, fibrosis risk and tolerability can be reviewed together. A therapy that produces slightly less weight loss but is sustainable may be preferable to a higher dose that causes recurrent symptoms and discontinuation.

Health systems should prepare for wider use. Primary care can identify appropriate patients and monitor routine tolerability. Diabetes and liver services can support complex cases. Pharmacists can reinforce injection technique, storage and escalation schedules. Standardized documentation should record dose, symptoms, weight, glycaemia and relevant liver risk. Supply continuity is important because intermittent access can undermine both outcomes and confidence. Where patients pay out of pocket, clinicians should discuss the likely duration of treatment before initiation so that early response is not followed by unavoidable cessation.

Regulatory indications should be separated from promising secondary benefits. Tirzepatide may be prescribed for approved diabetes or obesity indications and a patient with MASLD may gain additional hepatic benefit. The available evidence does not justify unsupervised use solely because ultrasonography shows fatty liver. Diagnosis should exclude other causes of liver disease and assess alcohol intake, viral hepatitis, medicines and fibrosis risk. Lifestyle support remains necessary because nutrition, physical activity and alcohol exposure influence outcomes independently of drug treatment. This framing avoids medicalizing uncomplicated steatosis while ensuring that high-risk MASH is not dismissed as a cosmetic consequence of weight.

The balance may change as new dual and triple agonists enter practice. Receptor activity, dose, escalation and molecular half-life may produce different hepatic and gastrointestinal profiles. Class-wide assumptions should therefore be avoided. Each agent requires outcome-specific evidence and active post-marketing surveillance. Comparative trials should include diverse ethnic groups and enough participants with advanced fibrosis to identify effect modification. They should also report outcomes after discontinuation because durability is relevant to a chronic disease. Until such evidence matures, tirzepatide findings are best regarded as agent-specific rather than proof for every future multi-receptor agonist.

This review had limitations. Tirzepatide dominated the evidence so conclusions cannot automatically be generalized to future dual agonists. Several reports arose from overlapping SURPASS or SURMOUNT programmes and a combined participant total would have double counted people. Gastrointestinal event definitions and ascertainment differed. Only one biopsy-confirmed MASH trial directly assessed histology and its duration was 52 weeks. Most trials were industry funded and excluded severe gastrointestinal disease or decompensated cirrhosis. The focused MEDLINE/PubMed search may have missed non-indexed studies. Heterogeneity prevented a new pooled analysis and evidence from Pakistan was absent [35].

CONCLUSION

Dual GIP/GLP-1 receptor agonism with tirzepatide reduces liver fat and produces clinically important MASH resolution with possible fibrosis improvement in adults with obesity or type 2 diabetes. Gastrointestinal adverse events are common, dose-dependent and usually mild to moderate. Gradual escalation, hydration advice and assessment of persistent or severe symptoms can improve tolerability. Pancreatitis was not significantly increased but gallbladder and biliary risk requires attention. Larger long-term trials should confirm fibrosis and clinical liver outcomes and include diverse low- and middle-income populations.

Declarations

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