Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Thyromimetics

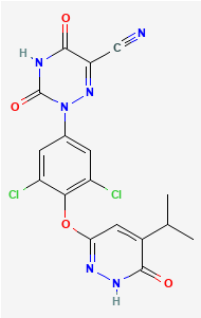
Evidence Summary

Liver-targeted, THRβ-selective thyromimetics improve lipid metabolism in metabolic disorders, including fatty liver disease. Clinical studies suggest a good safety profile as long as the drugs act only in the liver.

Neuroprotective Benefit: CNS-penetrating thyromimetics may improve myelin repair, cerebral metabolism, and inflammation. But it is unclear if safe ones could be developed due to the central role of thyroid hormone regulation in the brain.

Aging and related health concerns: Liver-targeted THRβ-selective thyromimetics have been found to improve hepatic lipid metabolism to benefit dyslipidemias and fatty liver disease in clinical trials. Resmetirom is the first drug approved for NASH.

Safety: Liver-targeted THRβ-selective thyromimetics show good safety, without evidence of cardio or musculoskeletal toxicity. Adverse events are primarily gastrointestinal related. Long-term studies are needed to fully assess the potential for systemic risks.

Availability: Rx (Rezdiffra™) for NASH; VK2908 and ALG-055009 are being tested in clinical trials.	**Dose**: Dosing for resmetirom for NASH with fibrosis is weight dependent. <100 kg, the recommended dosage is 80 mg orally once daily. ≥100 kg, the recommended dosage is 100 mg orally once daily.	**Resmetirom** **Chemical formula:** $C_{17}H_{12}Cl_2N_6O_4$ **MW**: 435.2g/mol  Source: PubChem
Half-life: Resmetirom: median terminal plasma half-life is 4.5 hours VK2809: 13-41 hours in Phase 1 trial ALG-055009: 20-24 hours in Phase 1 trial	**BBB**: Sobetirome and Sob-AM2 are penetrant, others are liver-targeted	
Clinical trials: Resmetirom has been tested in Phase 1 (n=120), Phase 2 (n=125), Phase 3 RCTs (n=966) in NAFLD/NASH, and Phase 2 RCT (n=76) in hypercholesterolemia. VK2809 has been tested in Phase 1 (n=56) and Phase 2 (n=59), and Phase 2b RCTs (n=229) in NAFLD/NASH. ALG-055009 has been tested in a Phase 1 trial (n=98) in healthy volunteers and patients with mild hyperlipidemia.	**Observational studies**: Hypothyroidism is associated with metabolic disorders and is a risk factor for fatty liver disease.	

What is it?

Thyroid hormone is an important regulator of metabolism [1]. Thyroid hormone levels are under the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Thyroxine (T4) and triiodothyronine (T3) are the major thyroid hormones released from the thyroid gland. Iodine deficiency or excess can impact thyroid function because thyroid hormones contain iodine. The majority of thyroid hormone released by the thyroid gland is in the form of T4, such that in humans the ratio between T4 to T3 is typically in the range of 13:1 to 20:1 [2]. Additionally, most of the thyroid hormone is protein bound, with only a small fraction of free circulating T4 or T3, which can be taken up into cells via transporters. Once inside cells,

thyroid hormone binds to thyroid hormone receptors (THR), which are nuclear hormone receptors that act as ligand-gated transcription factors. These THR transcription factors bind to thyroid hormone response elements to regulate gene expression. They can also interact with other nuclear hormone receptors, such as the retinoid X receptor (RXR). While the general effect of thyroid hormone is to increase the metabolic rate, the specific effect in any given cell type depends on the expression of specific THR isoforms as well as the expression of interacting receptors. While both T4 and T3 can bind to THRs, the affinity of T3 is around 10 to 15 fold higher, so the level of free T3 tends to be the major driver of THR activity, and is considered the active form of thyroid hormone [3]. The iodination of thyroid hormone, which is controlled by the activity of deiodinases, influences its degree of activity [2]. T4 is converted to T3 by type I and II deiodinases. Consequently, the type and expression level of the different deiodinases in a given tissue can also influence the degree of thyroid hormone activity.

The dysregulation of thyroid hormone leads to metabolic disorders. In cases of global hypothyroidism, supplementation with exogenous thyroid hormone can be a medically viable intervention. However, there is evidence for local thyroid hormone dysregulation in a variety of different disorders, in which case traditional thyroid hormone supplementation is not feasible due to the high risk for side effects in other organ systems. High systemic levels of thyroid hormone can induce organ toxicity, especially to heart, bone, and muscle. Thyromimetics were developed to try to circumvent this issue.

Different cell types preferentially express different THR isoforms [4]. The liver is critical in the regulation of lipid metabolism, and predominantly expresses the THRβ isoform. The cardiovascular and musculoskeletal toxicities associated with thyroid hormone primarily stem from the THRα isoform. Therefore, thyromimetics were developed which show preferential activity for THRβ, and in most cases also preferentially localize to the liver. These are primarily being developed for lipid-related metabolic disorders including dyslipidemia and non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis (NAFLD/NASH).

Sobetirome: Sobetirome, also called GC-1, was the first THRβ thyromimetic in clinical development [5]. The selectivity for THRβ over THRα has been estimated to be 3 to 10 fold based on *in vitro* binding assays, however, more physiologically relevant assays suggest it has only marginal (0 to 2 fold) selectivity [6]. It was being developed by QuantRx Pharmaceuticals and was tested in a Phase 1 trial, however development was discontinued [5]. Trials for adrenoleukodystrophy were also planned (NCT01787578, NCT03196765), but withdrawn, due to lack of funding.

Sob-AM2: Sob-AM2 is an amide prodrug of sobetirome with increased CNS penetrance. It has a 60-fold increase in the brain: serum ratio, related to sobetirome, and results in a nine-fold increase in brain exposure levels to sobetirome (the active compound) [7]. It is currently being tested in preclinical models for CNS disorders.

Eprotirome: Eprotirome, also called KB2115, was an early generation thyromimetic that was being developed by Karo Bio for dyslipidemia [8]. It has relatively weak selectivity for THRβ, and instead relies on liver specific localization. Development was discontinued due to evidence for extra hepatic effects in a dog study, and evidence of potential liver toxicity in clinical trials.

Resmetirom: Resmetirom, also known as MGL-3196, is a next generation thyromimetic, a highly selective THRβ thyromimetic [9]. In functional assays, it shows a 12-to-15-fold selectivity for THRβ [6]. Additionally, it shows preferentially localization and retention in the liver due to low hepatic clearance [10]. It is being developed by Madrigal Pharmaceuticals for NAFLD/NASH. Based on positive data from the Phase 3 MAESTRO-NASH RCT (NCT03900429) in patients with biopsy-proven NASH with fibrosis (stage F1B, F2, or F3), resmetirom recently received accelerated approval by the FDA as the first approved therapeutic for noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) (Press release). Full approval is contingent on long-term patient outcomes being assessed in the continuation of the MAESTRO-NASH trial along with the Phase 3 MAESTRO-NAFLD1RCT (NCT04197479), and open-label extension studies (MAESTRO-NAFLD-OLE) (NCT04951219). Resmetirom is marked under the tradename Rezdiffra™.

VK2809: VK2809, also known as MBO7811, is a next generation thyromimetic [8]. It is more potent than resmetirom, but is less selective for THRβ, showing approximately two-fold selectivity in functional assays, and relies on its liver specificity [6]. VK2809 is a prodrug that is cleaved by the cytochrome P450 enzyme CYP3A into the active compound, VK2809A, following first pass hepatic metabolism, and is rapidly eliminated in the bile. VK2809 is being developed by Viking Therapeutics for NAFLD/NASH, and has been tested in Phase 2 RCTs for this indication.

TG68: TG68 is a novel next generation thyromimetic showing good selectivity for THRβ and hepato-specificity [11]. It is a prodrug of IS25, a halogen-free THRβ agonist. It is currently in preclinical testing in models of NAFLD/NASH.

***ALG-055009*:** ALG-055009 is a second generation THRβ agonist derived from the parent compound VK2809A. It has undergone preclinical testing in models of NAFLD/NASH and is currently in clinical development for this indication by Aligos Therapeutics. It has been tested in a Phase 1 trial in healthy volunteers and patients with mild hyperlipidemia, and has been cleared for testing in a Phase 2 trial in NASH (Press release).

Neuroprotective Benefit: CNS-penetrating thyromimetics may improve myelin repair, cerebral metabolism, and inflammation. But it is unclear if safe ones could be developed due to the central role of thyroid hormone regulation in the brain.

Types of evidence:

- 2 meta-analyses of case-control studies on the association of thyroid hormones/function and dementia
- 11 observational studies on the association of thyroid hormone and dementia
- 7 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Thyroid hormone plays important roles in nervous system development, and numerous studies have found associations between thyroid dysfunction and cognitive impairment, suggesting that thyroid hormone is also required for the maintenance of CNS functions throughout the lifespan [12]. Thyroid dysfunction, manifest as clinical hypothyroidism or hyperthyroidism, is an established cause of reversible cognitive impairment. There are additional studies to suggest that euthyroid individuals with levels that fall within the extreme ends of the normal range (subclinical) may also be at elevated risk for dementia. Thyroid stimulating hormone (TSH), can be considered a rheostat of thyroid hormone levels, as it is produced by the pituitary gland when thyroid hormone levels are low. High TSH levels are indicative of hypothyroidism, while low levels are indicative of hyperthyroidism. They are typically within the range of 0.5-5 mU/L (UCLA Health).

In a study examining the relationship between serum thyroid stimulating hormone (TSH) and incident dementia including participants from the Framingham Study (n=1,864), there was a U-shaped relationship between Alzheimer's disease (AD) risk and TSH levels (0.1 – 10 mU/L) in women [13]. The

risk for AD was elevated in women who had the lowest (TSH < 1.0 mU/L) (adjusted Hazard Ratio [HR] 2.39, 95% Confidence Interval [CI] 1.47 to 3.87), or the highest (TSH >2.10 mU/L) (HR 2.15, 95% CI 1.35 to 3.52) levels of serum TSH. Subsequent studies provide additional evidence to support these findings. Cerebral amyloid burden, based on 18F-florbetaben PET imaging, was found to be higher in individuals with serum TSH in the higher end of the normal range (≥ 2.5 ulU/L) [14]. Subclinical hypothyroidism, based on low free serum T3 and elevated TSH was found to be more prevalent in individuals with cognitive impairment relative to controls in a case-control study [15]. TSH levels were also inversely associated with Mini-Mental State Examination (MMSE) scores, suggesting increasing thyroid hormone dysfunction with worsening cognition. Similarly, a meta-analysis of seven studies including 1,189 AD patients and 72,711 controls found that hypothyroidism, particularly at a subclinical level, was more prevalent in AD cases relative to controls (6.4% vs 2.4%; odds ratio [OR]:1.50, 95% CI 1.09 to 2.07, P = 0.01) [16].

However, a large analysis of individual participant data from 23 cohorts (n= 74, 565) did not find a clear relationship between thyroid function and cognition or dementia risk [17]. There are numerous other studies indicating that low TSH is a risk factor for progression of cognitive impairment or that there is no relationship. This likely relates to the alteration of the hypothalamic-pituitary-adrenal (HPA) axis in AD, such that in more advanced stages of the disease there is a lack of correlation between TSH and thyroid hormone (T4 and T3) measures. AD patients with greater variation across these measures, indicative of a dysfunctional HPA axis, had reduced brain glucose uptake based on FDG-PET imaging [18]. Some studies have found that the T4/T3 ratio is altered in AD, suggesting that the conversion of thyroid hormone from its inactive (T4) to active (T3) form may be impaired [19]. In this way, different associations may vary with the stage of disease.

Additionally, since thyroid hormone gets taken up into cells and exerts its actions locally, local changes in active thyroid hormone (T3) signaling within the brain are more relevant than changes in systemic levels or surrogate markers. The inconsistencies across studies may stem from the extrapolation of brain thyroid hormone activity from systemic measures, as thyroid hormone signaling may be maintained in the brain in someone with low circulating levels, and there may be a brain-specific deficit in thyroid hormone signaling in someone with normal systemic levels. Notably, a study in postmortem tissue found that there were lower levels of active T3 relative to T4 within the brain itself at later Braak stages of AD [20].

Evidence that deficits in the activation of thyroid hormone from T4 to T3 may be a driver of dementia comes from a gene association study including 12,348 participants (3,054 African Americans and 9,304 European Americans) from the CHAP, ROS, and MAP cohorts [21]. A polymorphism (rs225014) in the deiodinase, DIO2, Thr92AlaD2, which appears to impair the conversion of T4 to T3, was found to be associated with 1.3 times (95% CI 1.07 to 1.58) increased odds of developing dementia, for African American carriers. There was also evidence of increased oxidative stress and mitochondrial dysfunction in brain tissue from these carriers. The mean allele frequency of this polymorphism was relatively high in both groups, but was significantly higher in African Americans than European Americans (43.9% vs 36.5%). A meta-analysis and systematic review of 32 case-control and cohort studies examined the relationship between thyroid hormones and AD status [22]. In this study, serum T4 levels were not significantly altered (Standardized mean difference [SMD]: 0.25, 95% CI −0.18 to 0.69, based on 974 AD and 670 controls), but AD patients had significantly lower levels of total T3 (SMD: −0.56, 95% CI −0.97 to −0.15; P = 0.008, based on 360 AD and 288 controls) and free T3 (SMD: −0.47, 95% CI −0.89 to −0.05; P = 0.03, based on 875 AD and 627 controls).

In early stages, such as mild cognitive impairment (MCI), an elevation in TSH may signify a strong compensatory response, while in later stages, free T3 levels within the brain may be the only relevant measure. Consistent with this, a study found that TSH was positively correlated with regional cerebral blood flow, based on SPECT imaging, in MCI patients, while in AD patients free T3 was positively correlated with cerebral blood flow [23]. Similarly, higher T3 levels were found to be associated with greater volumes in particular brain regions, such as the hippocampus and amygdala [19]. Due to potential discordance between serum T3 levels and brain T3 levels, the inconsistencies across studies using serum thyroid hormone markers are unsurprising. Until brain levels of T3 can be adequately assessed *in vivo*, the nature of the relationship between thyroid hormone and cognition/dementia risk will be unclear.

While the evidence is mixed, one study of individuals with atrial fibrillation in Sweden (n = 12,057) found that women treated with levothyroxine due to hypothyroidism had a lower rate of incident dementia (HR 0.61, 95% CI 0.41 to 0.90) [24]. A similar association was observed in a population-based cohort study of patients with newly diagnosed hypothyroidism using a nationwide database from the National Health Insurance Service in South Korea including 41,554 adults aged 50 and above [25]. Adherence to thyroid hormone medication was associated with a lower risk for dementia, such that those with the highest quartile of adherence based on the medication possession ratio (MPR) showed a 14% lower risk of overall dementia compared with the first quartile (lowest adherence) (adjusted HR: 0.86; 95% CI 0.76 to 0.97), and lower risk for AD (adjusted HR: 0.88, 95% CI 0.78 to 1.00) compared to those with the

lowest quartile of adherence, but there was no significant association for vascular dementia. However, overmedication leading to thyrotoxicosis is also associated with increased risk for dementia. A longitudinal cohort study using primary care electronic health records data from 65,931 adults found that thyrotoxicosis was significantly associated with increased risk of cognitive disorder diagnosis, including MCI and dementia (adjusted HR: 1.39, 95% CI 1.18 to 1.64; P < 0.001) [26].

Overall, the totality of evidence suggests that the dysregulation of thyroid hormone signaling in either direction has a negative impact on cognitive function, and that levels need to be maintained within a particular range. Regional hypothyroidism within the brain may be a common characteristic pattern associated with progression in AD, though it remains to be established whether it is a causal factor, or a byproduct of neuronal loss in critical brain regions. The loss of thyroid hormone activating deiodinase activity in the brain appears to be a contributor to this process, though it is not clear if tissue-selective deiodinase modulation is a viable therapeutic target. While their utility remains to be established, CNS-penetrant thyromimetics have the potential to act as a surrogate to maintain neuroprotective thyroid hormone-mediated signaling in the context of low T3.

Human research to suggest benefits to patients with dementia:

CNS-penetrant thyromimetics are not yet clinically available and have not been tested in the context of dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Thyroid hormone signaling plays numerous roles in the maintenance of brain function. Since both THRα and THRβ isoforms are expressed in the brain, thyromimetics with modest selectivity, such as sobetirome, may be preferable. A primary concern for the clinical development of these agents will be their potential effects on the central HPA axis [27].

Due to its important role in myelination, CNS thyromimetics have primarily been studied in the context of multiple sclerosis models. Sob-AM2 has been developed as a prodrug of sobetirome, which facilitates its entry into the CNS. In the rodent EAE model (MOG peptide-induced), treatment with Sob-AM2, prior to the onset of EAE symptoms, reduced the infiltration of CD4 T cells, microglial activation, and the degree of CNS pathology [28]. However, treatment starting after the onset of symptoms had no significant impact on disease course in this model. A separate study administering Sob-AM2 with the

same time course found that the effect on microglia was mediated by the induction of TREM2, which was identified as a thyroid hormone-regulated gene [29]. A TREM2-related microglial phenotype, such as increased phagocytosis and reduced pro-inflammatory cytokine expression, could be induced via the presence of T3 or a thyromimetic, such as Sob-AM2. TG68 was shown to promote the differentiation and maturation of oligodendrocyte precursor cells (OPCs) into oligodendrocytes in cell culture, even in the context of inflammatory cytokines, which typically interfere with this maturation process [30]. Sobetirome was also shown to promote the myelination potential of alpha-synuclein overexpressing oligodendrocytes based on the expression of myelin proteins and the myelination of nanofibers in cell culture [31]. This suggests that in addition to facilitating myelin repair by promoting the differentiation and survival of oligodendrocyte precursor cells, thyromimetics may also modulate the inflammatory profile within the CNS. These studies also suggest that thyromimetics may be best suited to early stages of disease, prior to significant neuronal loss, which may be more amenable to the normalization of thyroid hormone-mediated signaling.

Thyroid hormone has been implicated in amyloid precursor processing and regulation. In the context of *in vitro* assays, the thyromimetics sobetirome, IS25, and TG68, were found to inhibit transthyretin (TTR)-mediated amyloidosis [32]. Thyroid hormone levels can modulate Aβ clearance via impacts on the expression of ApoE and LDL receptors [33]. Under conditions of adequate T4, levels of LDL-R are increased in endothelial cells, allowing for efficient vascular uptake and clearance of Aβ, while under conditions of low T4, LDL-R and LRP1 expression is biased toward glial cells. The slower, less efficient, glial-based clearance may allow for greater levels of Aβ accumulation. Notably, sleep deprivation in rodents was found to reduce brain T4 levels and enhance Aβ deposition [33].

Alterations in thyroid hormone levels were found to be associated with altered patterns of microglial activation in the ADLP^{APT} AD mouse model [34]. Hippocampal levels of free T3 were found to be reduced in this model, stemming from a reduction in levels of iodothyronine deiodinase 2 (Dio2). Thyroid hormone depletion induced by an iodine-deficient diet resulted in the induction of a microglial activation signature characterized by the upregulation of pro-inflammatory chemokines and cytokines, including IL-1β and TNF-α, and the inhibition of CD73. These basally activated microglial failed to respond to inflammatory stimuli or Aβ. Treatment with T3 helped facilitate Aβ clearance by modulating the microglia toward a more productive activation state. This suggests that the hypothyroidism commonly observed in the AD brain may act as a driver of AD pathology by altering microglial responses.

APOE4 interactions: In observational studies, an interaction between T3 and ApoE4 has been identified with respect to cognitive function [35]. Some studies have found that ApoE4 was associated with higher levels of TSH and lower levels of free T3, indicative of hypothyroidism [36]. Furthermore, having low T3 has been associated with worse cognitive function in ApoE4 carriers [35]. Other studies suggest that hypothyroidism may promote ApoE4-related pathology, by driving the transport of liver-derived ApoE4-containing exosomes to the brain [37]. Together these studies suggest that ApoE4 carriers may be at increased risk for hypothyroid-related cognitive impairment, and thus may preferentially benefit from thyroid hormone normalizing therapies, such as thyromimetics.

Aging and related health concerns: Liver-targeted THRβ-selective thyromimetics have been found to improve hepatic lipid metabolism to benefit dyslipidemias and fatty liver disease in clinical trials. Resmetirom is the first drug approved for NASH.

Types of evidence:

- 1 clinical trial for Sobetirome
- 3 clinical trials for Eprotirome
- 4 clinical trials for Resmetirom
- 3 clinical trials for VK2809
- 1 clinical trial for ALG-055009
- 4 observational studies associating hypothyroidism with NAFLD/NASH
- Numerous laboratory studies

NAFLD/NASH: POTENTIAL BENEFIT

Thyroid hormone is an important regulator of hepatic lipid metabolism via the induction of hepatic autophagy, beta-oxidation of fatty acids, and mitochondrial biogenesis [9]. A reduction in thyroid function (hypothyroidism) is associated with metabolic syndrome. Hypothyroidism is associated with increased risk for NAFLD, including subclinical hypothyroidism, defined as thyroid-stimulating hormone (TSH) levels less than 4.5 milli-international units per liter (mIU/L) [38; 39]. NAFLD may be a manifestation of liver-specific hypothyroidism, even if systemic levels are within normal range. Liver biopsies from patients with NASH have shown that levels of the predominant hepatic thyroid hormone receptor, THRβ, is inversely associated with NASH disease severity, along with evidence for a liver-specific resistance to thyroid hormone [40]. A mutation in THRβ, R243Q, which leads to THRβ-related thyroid hormone resistance was found to be associated with increased incidence of hepatic steatosis in

a case-control study (n=21 cases; 22 controls). Since THRβ is most abundant in the liver, many THRβ-targeted thyromimetics have been tested in the context of NAFLD/NASH. The results of the clinical studies conducted thus far have been promising [9]. The development of early compounds was derailed by safety concerns, but newer compounds currently in development appear to have an improved therapeutic profile.

Resmetirom (MGL-3196): A Phase 2 RCT (NCT02912260) (n=84 resmetirom, n=41 placebo) was conducted testing resmetirom in biopsy-confirmed NASH (fibrosis stage 1-3 with hepatic fat fraction of at least 10%) [41]. The starting dose was 80 mg for the first four weeks, then it was adjusted down to 60 mg (n=37), up to 100 mg (n=5), or stayed at 80 mg (n=42) for the remainder of the 36-week study, based on the estimated AUC at week 2. The primary outcome was the change in MRI-proton density fat fraction (MRI-PDFF) at week 12, which is a measure of hepatic triglycerides. There was a greater reduction in hepatic fat with resmetirom relative to placebo at week 12 (−32.9% resmetirom vs −10.4% placebo; least squares mean difference [MD] −22.5%, 95% CI −32.9 to −12.2%), and at week 36 (−37.3% vs −8.5%; MD −28.8%, 95% CI −42.0 to −15.7%). A hepatic fat reduction of >29% correlates with a reduction in biopsy-based NASH resolution. A greater proportion of resmetirom-treated patients achieved a >30% reduction in liver fat at weeks 12 (60% vs 18%) and 36 (68% vs 30%), and unlike in the placebo group, these improvements could not be attributed to a substantial body weight loss. Patients with a resmetirom exposure of AUC ≥2700 ng*h/mL, which generally occurred at the 80 and 100 mg doses, showed greater hepatic fat loss. For these doses, there was a 50.5% relative and 10.8% absolute hepatic fat reduction. These doses also showed significant reductions in atherogenic lipoproteins (small LDL −34.3%, large VLDL >-50%). By 36 weeks, the average reduction in alanine aminotransferase was 40%, with 60% of resmetirom-treated patients achieving levels below 30 U/L (vs 30% in placebo). Fibrosis markers, including enhanced liver fibrosis (−0.48) and N-terminal type III collagen propeptide (−21.4 ng/ml), were also significantly reduced with treatment. MRI-PDFF responsiveness was associated with NASH resolution on biopsy. NAFLD activity scores (NAS) ≥5 are considered a marker of severe disease. Notably, none of the placebo patients with NASH resolution had NAS ≥5, while 39% (n=18) of resmetirom-treated patients with NASH resolution had NAS ≥5 at baseline. Health-related quality of life was also assessed via questionnaire (Short form-36). Resmetirom treatment was associated with improvements on bodily pain (+6.31 ± 2.67) and Short form-6D utility scores (+0.027 ± 0.012). Response on the MRI-PDFF was associated with greater improvements on physical function scores [42].
In an open-label extension study, non-responders (n=31) were re-randomized to 80 or 100 mg resmetirom for an additional 36 weeks [43]. In this population, all patients had at least a 20% relative reduction, and 85% had at least a 30% reduction in hepatic fat based on MRI-PDFF (mean: −52.3%

±4.4%). Relative to baseline, there were also significant reductions in LDL-c cholesterol (−26.1% ±4.5%), apolipoprotein B (−23.8% ± 3.0%), and a reduction of −46.1 ± 14.5 mg/dL in triglycerides (−19.6% ±5.4%). Additionally, there were reductions in fibrosis markers, and hepatic inflammation markers (reverse T3). The placebo-controlled Phase 3 MAESTRO-NASH RCT (NCT03900429) is testing resmetirom at a dose of 80 mg or 100 mg/day in patients with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 [44]. The planned duration of the study is 54 months, but the analysis of the primary endpoints of NASH resolution (including a reduction in the NAFLD activity score by ≥2 points) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score occurred at week 52. The key secondary end point of the trial was the percent change from baseline in LDL-c level at week 24. The primary analysis population consisted of 966 patients, 322 in the 80 mg group, 323 in the 100 mg group, and 321 in the placebo group. The trial achieved its primary outcome of NASH resolution with no worsening of fibrosis, which was achieved in 25.9% of patients in the 80-mg group, 29.9% in the 100-mg group, and only 9.7% in the placebo group, with differences relative to placebo of 16.4% (95% CI 11.0 to 21.8), and 20.7% (95% CI 15.3 to 26.2) for the 80 mg and 100 mg groups, respectively. Improvements in fibrosis by at least one stage with no worsening of the NAFLD activity score were also achieved in significantly more patients treated with resmetirom relative to placebo, with differences of 10.2% (95% CI 4.8 to 15.7), and 11.8% (6.4 to 17.2) for the 80 mg and 100 mg groups, respectively. Reductions in liver fat fraction based on MRI-PDFF at 52 weeks were also greater in resmetirom treated patients, with differences relative to placebo of 26.7% (95% CI −32.9 to −20.6), and −37.9% (95% CI −44.2 to −31.7) for the 80 mg and 100 mg groups, respectively. Similarly, there were significant reductions on levels of LDL-c at 24 weeks of −13.6% in the 80 mg group and −16.3% in the 100 mg group, but LDL-c was not significantly altered (0.1%) in the placebo group. Significant reductions with resmetirom relative to placebo were also observed in levels of liver enzymes (ALT, AST, GGT), triglycerides, apoB, and lipoprotein(a).
Based on the successful outcomes of this Phase 3 trial, resmetirom was granted accelerated approval by the FDA on March 14, 2024, for the treatment of noncirrhotic NASH in patients who have progressed to fibrosis (moderate to advanced F2 or F3), with full approval contingent on results from the ongoing studies on long-term patient outcomes (Press release). Resmetirom is the first drug to be approved for NASH.

The effects seen in these studies are consistent with what has been seen with resmetirom in preclinical rodent models. In a diet-induced obesity NASH model, resmetirom treatment (3 mg/kg) for eight weeks reduced hepatic fat, alanine aminotransferase levels, plasma and liver cholesterol levels, as well as markers of hepatic fibrosis, without significantly affecting total body weight [45]. The expression levels

of genes involved in fatty acid synthesis and beta-oxidation were not significantly impacted, suggesting that the lipid lowering effects may involve post-transcriptional mechanisms. In human liver cells, resmetirom was found to be around 1000-fold less potent at activating thyroid hormone receptor-activated gene transcription, relative to the endogenous ligand, T3 [6]. While less potent than T3, resmetirom was still able to significantly reduce total cholesterol, LDL-c, and triglycerides, in a dose-dependent manner. In the AMLN mouse NASH model treatment with resmetirom restored the hepatic expression of RGS5, a protein involved in the regulation of inflammation and implicated in slowing NAFLD progression by preventing the activation of the JNK/p38 signaling cascade [46]. The liver specificity of resmetirom appears to stem from its preferential substrate specificity by the OATP1B1 transporter relative to other thyroid hormone transporters [47].

VK2809: VK2809 (5 mg daily, 10 mg daily, or 10 mg every other day, orally) was tested in a placebo-controlled Phase 2 RCT (n=59) in patients with primary hypercholesterolemia and NAFLD (NCT02927184). At week 16, four weeks after the completion of the treatment period, VK2809 treatment was associated with the maintenance of liver fat loss, relative to placebo (Press release) [48]. A significantly greater percentage of VK2809-treated patients had a reduction in liver fat ≥30% (70.4% vs 22%), as well as significantly greater relative fat reduction (-45.5% vs18.7%) and absolute fat reduction (-7.5% vs -2.0%) on MRI-PDFF, compared to placebo-treated patients. The response rate in the 5 mg daily dose group was 100%. Fifty-six percent of VK2809-treated patients maintained an absolute liver fat reduction ≥5%, compared to none in the placebo group. VK2809-treated patients also showed a greater mean change from baseline in alanine aminotransferase levels (-57.4% vs -2.1%), relative to placebo, at 12 weeks. Efficacy was not impacted by baseline blood glucose levels.
Based on these results, VK2809 (1 mg once daily (QD), 2.5 mg QD, 5 mg every other day (QOD), or 10 mg QOD, as oral capsules) is being tested in a Phase 2b 52-week placebo-controlled RCT (VOYAGE) in patients with biopsy proven NASH with fibrosis (F2 or F3) (n=229) (NCT04173065). The primary outcome is relative change in liver fat based on MRI-PDFF at week 12, and the secondary outcome is the change in NASH CRN fibrosis score at week 52. Topline results indicated that the trial met its primary outcome, with median changes in liver fat based on MRI-PDFF of -5.4%, -37.5%, 48.1%, 42.5%, and 55.1%, for the placebo (n=62), VK2809 1 mg QD (n=17), 2.5 mg QD (n=58), 5 mg QOD (n=36), and 10 mg QOD (n=56) groups, respectively (Press release). The percentage of patients achieving a ≥30% reduction in liver fat across the groups was 13.6%, 52.9%, 77.6%, 66.7%, and 84.9%, respectively. The efficacy was similar in patients with and without type 2 diabetes (Press release). Significant reductions in atherogenic plasma lipids, including LDL-c, apoB, triglycerides, apoC-III, and lipoprotein(a), were also observed with VK2809.

TG68: TG68 is the pro-drug of IS25, a novel halogen-free THRβ selective agonist, based on the scaffold of sobetirome, which was found to have a good toxicology profile [49; 50]. In a diet-induced mouse model of NAFLD, treatment with TG68 (2.8 or 9.35 mg/kg) was found to be comparable to resmetirom in reducing liver fat, ameliorating histopathological signs of NAFLD, and reducing aminotransferase liver enzymes [11]. The expression of genes involved in de novo lipogenesis were not affected, while there was an effect on genes involved in fatty acid oxidation.

CS271011: CS271011 is a THR-β agonist with higher *in vitro* potency relative to MGL-3196, with a 50% activation (AC50) of 0.65 µM relative to 3.11 µM [51]. The activation ratios of THR-α and THR-β were also higher for CS271011 (54.12 vs. 47.93), indicating that CS271011 also has higher THR-β activity. In the context of a high-fat diet induced NAFLD model, treatment with CS271011 (1 or 3 mg/kg by oral gavage) for ten weeks reduced serum levels of triglycerides and total cholesterol, as well as liver weight, with efficacy comparable to MGL-3196. Network expression analysis indicated that CS271011 impacts genes involved in lipid and steroid metabolism including Hmgcr, Cyp7a1, Sqle, LDLR, Cyp17a1, Srebp2, and Abcc3.

Dyslipidemia: POTENTIAL BENEFIT
Thyroid hormone plays an important role in metabolic homeostasis, as various critical steps in lipid metabolism are under thyroid hormone control [8]. The effects of thyroid hormone are cell-type specific based on the expression of transporters that allow for cellular uptake of thyroid hormone, as well as the subtype of thyroid hormone receptor expressed. THRβ, the predominant subtype in the liver, plays essential roles in mediating hepatic metabolism, and thus changes in THRβ signaling are implicated in liver-associated diseases. Thyromimetics targeting liver THRβ have been found to have lipid regulating properties. These include the plasma clearance of LDL-c via hepatic LDLR, reducing levels of hepatic fatty acid and triglyceride synthesis via SREBP-1c, and reducing hepatic cholesterol via the rate-limiting enzyme in the conversion of cholesterol into bile acids, CYP7A1. While seen in preclinical models, it is unclear which of these mechanisms are most relevant in the clinical lipid lowering effects of thyromimetics in humans. The specificity of these agents for liver THRβ is key to their therapeutic profile, as activity outside of the liver can derail clinical development, due to the emergence of systemic toxicity.

Sobetirome (GC-1): Sobetirome (SAD up to 450 ug; MAD up to 100 ug) was tested in a Phase 1 placebo-controlled RCT (SAD n=32; MAD n=24) (Press release). With single doses, LDL-c was reduced up to 22%, compared to 2% for placebo, while multiple doses over two weeks led to LDL-c reductions up to 41% (vs

5% for placebo). Despite a lack of evidence for toxicity in this study, development of sobetirome for this indication has been discontinued, likely due to the unanticipated evidence of toxicity that emerged in later clinical stages for other thyromimetics, at the time [8].

Eprotirome (KB2115): In a Phase 1 study in overweight individuals with hypercholesterolemia (n=24), treatment up to 200 μg for two weeks reduced LDL-c up to 40% (175 mg/dl to 105 mg/dl), compared to an up to 11% reduction with placebo [52]. No significant effects on HDL-c, lipoprotein(a), or serum triglycerides were seen, though a trend toward reduced triglycerides was seen in individuals with elevated levels at baseline. The effects were associated with an increase in the catabolism of cholesterol to bile acids, without significantly altering whole body cholesterol synthesis. In a 12-week Phase 2 RCT in statin-treated (simvastatin and atorvastatin) patients with hypercholesterolemia (n=189), the addition of eprotirome (25, 50, or 100 μg), further reduced serum LDL-c from 141 mg/dl to 113, 99, and 94 mg/dl, respectively, compared to a 7% reduction (to 127 mg/dl) with placebo + statin [53]. Dose-dependent reductions were also seen with apoB (20-30%), serum triglycerides (16-33%), and lipoprotein(a) (27-43%). Aside from mild and reversible elevations in alanine aminotransferase levels, no major adverse events were seen in these studies. However, in a Phase 3 trial in patients with familial hypercholesterolemia (n=236), in addition to significantly reducing plasma LDL-c, apoB, triglycerides, and lipoprotein(a), eprotirome showed evidence of liver toxicity, and the trial was terminated [54].

Resmetirom: In a Phase 1 trial (SAD n=72, MAD n=48), no significant effects on lipids were observed with single dose administration. With treatment for two weeks, doses of 50 to 200 mg led to significant reductions in LDL-c (up to 30%), non-HDL-c (up to 28%), and apoB (up to 24%), as well as a trend to triglycerides (up to 60%), with near maximal effects at the 80 mg dose [55]. Significant reductions in atherogenic lipoproteins were also seen in a Phase 2 RCT in NASH [41]. Resmetirom was tested in a Phase 2 placebo-controlled RCT in patients with heterozygous familial hypercholesterolemia (NCT03038022) (n=113) [56]. The starting dose of resmetirom was 100 mg, and was titrated down to 60 mg based on plasma levels at two weeks in a subset (22/76). By week 12, resmetirom reduced LDL-c by 18% (95% CI –27.8% to –9.8%) relative to placebo, with a mean difference of –27 mg/dL (95% CI –38.4 to –15.5 mg/dL). The reduction was dose dependent (100 mg -14.9%; 60 mg -9.7%). There were also significant reductions from baseline to week 12, compared to placebo in triglycerides (-18.3± 3.2% vs +4.4 ± 4.1%), apoB (-14.2 ± 1.7 vs +7.2 ± 4.6%), and lipoprotein(a) levels (-21.8 ± 2.9% vs 3.8 ±2.4%). In the primary analysis from the Phase 3 MAESTRO-NASH RCT (NCT03900429) in patients with biopsy-confirmed NASH with fibrosis (n=966), resmetirom was associated with a reduction in atherogenic blood lipids at week 24 [44]. Reductions with resmetirom were seen relative to placebo for LDL-c (80 mg:

−13.7%, 95% CI −17.5 to −10.0; 100 mg: −16.4%, 95% CI −20.1 to −12.6), non-HDL-c (80 mg: -15.4%, 95% CI -18.8 to -12.0; 100 mg: -17.9%, 95% CI -21.2 to -14.5), apoB (80 mg: 17.2%, 95% CI −20.0 to −14.4; 100 mg: −20.2%, 95% CI −22.9 to −17.4), apoC-III (80 mg: -18.7%, 95% CI -27.1 to -10.4; 100 mg: -22.2%, 95% CI -29.0 to -15.4), triglycerides (80 mg: −20.1%, 95% CI −28.3 to −11.8; 100 mg: −19.1%, 95% CI −27.8 to −10.3), and lipoprotein(a) (80 mg: −29.5%, 95% CI −37.6 to −21.5; 100 mg −35.1%, 95% CI −43.5 to −26.6). These changes were generally maintained at week 52.

VK2809: In a Phase 1 trial in individuals with mild hypercholesterolemia (n=56), treatment with VK2809 (0.25 to 40 mg) for 14 days led to significant reductions in atherogenic lipids [57]. At doses greater than 5 mg, there were placebo-adjusted reductions up to 41.2% in LDL-c, up to 78.6% in triglycerides, and up to 44.2% in non-HDL-c, as well as reductions in apoB and lipoprotein(a), without significantly affecting HDL-c. A Phase 2 RCT in patients with primary hypercholesterolemia and NAFLD (n=59), achieved its primary outcome of a significant reduction in LDL-c, relative to placebo, at 12 weeks (Press release). Patients were treated with oral doses of VK2809 5 mg daily, 10 mg daily, or 10 mg every other day. There was a 21.8% placebo-adjusted reduction in LDL-c with VK2809 treatment, as well as significant reductions in apoB and lipoprotein(a). In the Phase 2b VOYAGE trial conducted in patients with biopsy-confirmed NASH with fibrosis (n=229), topline results indicate that VK2809 was associated with placebo-adjusted reductions in LDL-c ranging from 11% to 20%, as well as significant reductions in apoB, triglycerides, apoC-III, and lipoprotein(a) (Press release).

ALG-055009: ALG-055009 was tested in a Phase 1 SAD study in healthy volunteers (n=40) and MAD study in patients with mild hyperlipidemia (LDL-c >110 mg/dL) (n=50) (NCT05090111). In the MAD study, participants were treated with doses of 0.3 mg, 0.5 mg, 0.6 mg, 0.75 mg, or 1 mg for 14 days (Corporate Presentation)(Poster). Dose proportional increases in SHBG, a marker of target engagement for thyromimetics, was observed in the MAD study. Dose proportional decreases in serum lipids, including LDC-c, apoB, and triglycerides, were also observed. Based on the results from the Phase 1 study, a randomized, double-blind, placebo-controlled Phase 2a trial testing up to four doses of ALG-055009 in patients with metabolic dysfunction-associated steatohepatitis (MASH, formerly called NASH) with liver fibrosis has been initiated.

Hepatocellular carcinoma: POTENTIAL BENEFIT (Preclinical)
Hypothyroidism has been identified as a risk factor for hepatocellular carcinoma (HCC)[58], and thyroid hormone signaling is altered in the context of HCC. In resected liver tissue from patients with HCC (n=45), the expression of THRβ was found to be downregulated in 66% of cases [59]. In rats, a short

course of T3 treatment was able to revert the expression profile of the cancerous tissue to that of normal liver tissue, particularly with respect to metabolic genes [59]. The induction of T3/THRβ signaling reverted the metabolic profile of the cells from Warburg (aerobic glycolysis) to oxidative phosphorylation, and had an anti-tumorigenic effect. The progression from NASH to cirrhosis of the liver is associated with increased risk for HCC [60]. In the diethylnitrosamine plus high-fat diet model of NAFLD, rats treated with TG68 (9.35 mg/kg in the drinking water for 3 weeks) achieved a near complete disappearance of preneoplastic lesions in the liver, as identified by the markers GSTP and G6PD, but was also associated with increases in heart and kidney weight [58]. Treatment with a lower dose (2.8 mg/mg) had similar efficacy in reducing preneoplastic lesions without exerting adverse effects on other organs. The effect is thought to stem from the ability of TG68 to promote the switch of preneoplastic hepatocytes towards a differentiated phenotype.

Anaplastic Thyroid Cancer: POTENTIAL BENEFIT (Preclinical)
Preclinical studies in anaplastic thyroid cancer models suggest that thyromimetics may offer therapeutic utility in this aggressive and dedifferentiated cancer. The TRβ agonist sobetirome reduced the tumorigenic phenotype, decreased cancer stem-like cell populations, and induced redifferentiation of anaplastic thyroid cancer cell lines with different mutational backgrounds (SW1736 and KTC-2) [61]. It also increased the efficacy of another class of antitumorigenic agents, PI3K inhibitors, in cell culture. In a mouse xenograft model with 8505C cells, sobetirome reduced tumor growth by 60% at day 16, which was similar efficacy to the PI3K inhibitor sorafenib, though a synergistic effect between the two agents was not apparent in this model.

Safety: Liver-targeted THRβ-selective thyromimetics show good safety, without evidence of cardio or musculoskeletal toxicity. Adverse events are primarily gastrointestinal related. Long-term studies are needed to fully assess the potential for systemic risks.

Types of evidence:

- 1 clinical trial for Sobetirome
- 3 clinical trials for Eprotirome
- 4 clinical trials for Resmetirom
- 3 clinical trials for VK2809
- 1 clinical trial for ALG-055009
- Numerous laboratory studies

The safety of clinically tested thyromimetics appears to depend on both their selectivity for THRβ, as well as their tissue localization profile. Thyromimetics were designed to circumvent the issues of systemic toxicity, particularly with respect to the cardiovascular system and musculoskeletal system, associated with systemic administration of thyroid hormone, which will activate all thyroid hormone receptor isoforms. These toxic effects are primarily mediated by THRα.

Sobetirome: Sobetirome was generally well-tolerated in Phase 1 clinical trials, at single doses up to 450 μg and multiple doses (for 14 days) up to 100 μg (Press release). There were no reported extra hepatic effects in these studies [8]. However, sobetirome has very low selectivity for THRβ, which increases its potential for toxicity, in conditions where it would be present outside of the liver [6].

Eprotirome: In Phase 1 trials, at single doses up to 2,000 μg, and multiple doses up to 200 μg (for 14 days), eprotirome was generally well tolerated, with no study withdrawals or serious adverse events [52]. There were no signs of musculoskeletal or cardiovascular side effects related to heart rate, ECG, QTc, or blood pressure. The most common drug-related adverse event was mild increases in liver aminotransferase enzymes (ALT and AST), with one patient having levels greater than three times the normal limit. In a Phase 2 RCT in patients with hypercholesterolemia taking statins, treated with 25, 50, or 100 ug eprotirome for 12 weeks, there were no significant effects on bone or heart-related measures [53]. There were no significant effects on body weight, heart rate, blood pressure, QTc, or ECG. There were no adverse effects on sexual function or testosterone levels. The majority of adverse events were mild or moderate, including transient increases in liver aminotransferase enzymes. Two patients had levels greater than three times the normal limit. A Phase 3 RCT in patients with primary hypercholesterolemia was terminated for safety concerns [54]. There were significant increases in the liver enzymes, ALT, AST, conjugated bilirubin, and gamma-glutamyl transpeptidase. Four patients discontinued due to aminotransferase elevations three to seven times the normal level. The trial had been terminated due to a toxicology finding in a preclinical study in dogs showing a toxic effect on cartilage. The cellular uptake of thyroid hormone and some thyromimetics relies on the expression of specific transporters. The transporter MCT8 is expressed in cartilage-forming cells, and may have mediated the effect seen in the dog study [62]. *In vivo*, the selectivity of many thyromimetics for THRβ appears to be lower than anticipated based on *in vitro* assays, and their capacity to enter into tissues outside of the target organ [6], which is generally the liver, is a major determinant of their toxicity potential.

Resmetirom: In Phase 1 studies in single and multiple doses (14 days) up to 200 mg, resmetirom was well-tolerated [55]. Adverse events were mild, and not considered drug related. There were no effects on vital signs, liver enzymes, or cardiovascular parameters (ECG, QTc, blood pressure). In a Phase 2 RCT in patients with NASH, with doses at 60 or 80 mg, adverse events were mild and moderate and the only events more common with resmetirom were nausea and diarrhea, which were transient during therapy initiation [41]. Vital signs were not affected, and there were no significant effects on bone or cardiovascular parameters. The decrease in liver enzymes was related to the therapeutic response. Resmetirom, at doses of 80 or 100 mg, had a similar safety profile during the open label extension trial, with no increased incidence of gastrointestinal events [43]. In a Phase 2 RCT in patients with familial hypercholesterolemia, treated with doses of 60 or 80 mg resmetirom, there was a similar adverse event profile to the NASH trial, with increased incidences of nausea (20.5%) and diarrhea (19.2%) [56]. Vital signs and cardiovascular parameters were not changed.
In the Phase 3 MAESTRO-NASH RCT in patients with biopsy-proven NASH and fibrosis (stages F1B, F2, or F3) (n=966), treatment with resmetirom at a dose of 80 mg or 100 mg/day for 52 weeks was generally well-tolerated, with equal levels of adverse events between the treatment and placebo arms, most of mild or moderate severity [44]. The adverse events that occurred more frequently with resmetirom were diarrhea (80 mg: 27%, 100 mg: 33.4%, placebo: 15.6%), and nausea (80 mg: 22%, 100 mg: 18.9%, placebo: 12.5%). These primarily occurred at the initiation of treatment and around half of the cases were exacerbations of pre-existing gastrointestinal conditions. There were two serious adverse events considered to be related to the trial regimen which occurred in the resmetirom group, along with one in the placebo group. Cancer incidence rates were similar across the groups, and there was no evidence of drug-induced liver injury with resmetirom.
The FDA prescribing label for resmetirom contains warnings for potential hepatotoxicity and gallbladder related adverse events, including cholelithiasis and cholecystitis. It is recommended for liver enzymes to be monitored while taking resmetirom, and resmetirom is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C). The most common adverse events are listed as diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.

VK2809: In a Phase 1 trial testing doses up to 40 mg for 14 days, VK2809 was well-tolerated with no serious adverse events [57]. There were no changes to vital signs or cardiovascular parameters, such as ECG or cardiac rhythm. The most common was a mild increase (up to 1.5 times normal levels) in ALT, primarily at the highest doses. In a Phase 2 RCT in patients with NAFLD, VK2809 (5 mg or 10 mg) for 12 weeks was well-tolerated and not associated with any serious adverse events [48]. In the Phase 2 VOYAGE trial in patients with at least 8% liver fat with F2 or F3 fibrosis (n=229), treatment emergent

adverse events were primarily mild or moderate (Press release). There were similar rates of drug-related treatment emergent adverse events, and events leading to study discontinuation across study arms at the 12-week timepoint. The most common treatment emergent adverse events were gastrointestinal related, including nausea and diarrhea, but the rates were similar across the placebo (18.5%) and VK2809 (range 2.7% to 23.5%) groups. Over the course of 12 weeks there were no significant changes in levels of liver enzymes (AST or ALT), levels of thyroid hormones, vital signs, blood pressure, heart rate, or body weight. There was one reported serious adverse event of a worsening of symptoms in a patient with a history of psychiatric disorders.

TG68: This novel, selective THRβ thyromimetic has not yet been clinically tested. It is the prodrug of IS25. Both compounds were found to have low potential for toxicity in *in vitro* cytotoxicity and ADME-Tox assays [49]. *In vivo*, TG68 administration did not show any evidence of hepatotoxicity [11; 50]. One study found that at a dose of 9.35 mg/kg in the drinking water for three weeks, TG68 treatment led to significant increases in heart and kidney weight, but at a dose of 2.8 mg/kg in the drinking water for two weeks, TG68 showed efficacy on liver-related outcomes without impacting the heart kidney, suggesting that TG68 may have some dose-related toxicities [58].

Sob-AM2: This sobetirome pro-drug has not yet been clinically tested, and the preclinical studies conducted thus far have not adequately addressed its safety potential [27]. A primary concern for Sob-AM2 will be its ability to impact the central HPA axis, which primarily relies on THRβ [27]. A study in mice found that Sob-AM2 is able to cross the blood-placental barrier and was able to influence thyroid hormone-related gene expression and brain development in the fetuses [63].

CS271011: In a diet-induced obesity mouse model, CS271011 exhibited a safety profile similar to MGL-3196, in not significantly impacting liver enzymes (ALT, AST, ALP and total bilirubin) [51]. It was also not associated with changes in heart weight, or cell viability in renal or cardiac cells, suggesting a lack of renal toxicity or cardiotoxicity.

ALG-055009: ALG-055009 was found to be well-tolerated in a Phase 1 trial with no serious adverse events (Corporate Presentation)(Poster). Transient, dose-dependent reductions in thyroid hormone were observed, but levels generally stayed within the normal range, and there was no evidence of clinical hypo- or hyperthyroidism. All treatment emergent adverse events were mild, Grade 1 or 2 in severity. A SAD study in healthy volunteers (n=40) tested single oral doses of 0.1 mg, 0.3 mg, 0.9 mg, 2.4 mg, and 4 mg, and found that the pharmacokinetics were dose proportional, and there were no dose

limiting toxicities. The plasma half-life of ~20-24 hours is consistent with once daily dosing. The most common treatment emergent adverse events were headache (n=2), and rhinopharyngitis (n=2). In the MAD study in patients with mild hyperlipidemia (n=50), the pharmacokinetics were also dose proportional, and consistent with what was seen in the SAD study. The most common treatment emergent adverse events in the MAD study were insomnia (n=2), headache (n=5), abdominal distension (n=4), and diarrhea (n=3). A formulation and food effect study was also conducted in 10 healthy volunteers, and no significant differences in bioavailability or pharmacokinetics were observed between 0.6 mg doses taken in fed or fasted states, or in liquid and gel capsule formulations. The most common treatment emergent adverse events in this part were nasopharyngitis (n=3) and diarrhea (n=2). Overall, there were no clinically relevant changes in laboratory tests, ECG, vital signs, or physical examination findings.

Drug interactions: The specific interactions will vary depending on the drug, for example, VK2809 will interact with CYP3A inhibitors, since that enzyme is critical for its mechanism of action. Other interactions will be common to the class, such as those that impact thyroid function or thyroid hormone levels. Resmetirom has drug interactions with strong or moderate CYP2C8 inhibitors, such as the fibrate gemfibrozil and the antiplatelet clopidogrel, OATP1B1 and OATP1B3 inhibitors, such as the immunosuppressant cyclosporine, and CYP2C8 substrates, such as loperamide, montelukast, or paclitaxel (Drugs.com) (FDA prescribing label). Resmetirom also interacts with the statins, atorvastatin, pravastatin, rosuvastatin and simvastatin, by increasing their exposure, thus the maximum daily dose may need to be limited to mitigate side effects.

Sources and dosing:

Resmetirom received accelerated approval in March 2024 for the treatment of noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), though full approval is contingent on long-term patient outcomes in ongoing clinical trials. It is being marketed under the tradename Rezdiffra™ by Madrigal Pharmaceuticals. It is currently priced at $47,400 per year. According to a cost effectiveness study based on the efficacy of resmetirom in NASH in Phase 2 trials, the incremental cost-effectiveness ratio for resmetirom is US$53,929 per quality-adjusted life-year (QALY) gained [64]. The dosing is based on weight, with recommended oral dosing for those <100 kg (~220 lbs) at 80 mg/day, and for those ≥100 kg, the recommended oral dose is 100 mg/day. VK2809 is being developed by Viking Therapeutics for NAFLD/NASH, and is in the process of completing Phase 2 clinical development. ALG-055009 is being developed by Aligos Therapeutics for NAFLD/NASH and is entering

Phase 2 clinical development. Sob-AM2 and TG68 are still in preclinical testing within academia. Sob-AM2 comes from the lab at Oregan Health and Science University which first tested sobetirome [7], while TG68 comes from labs at the University of Pisa [65]. The clinical development of sobetirome and eprotirome has been discontinued.

Research underway:

Resmetirom is being tested in a Phase 3 RCT (MAESTRO-NASH) to evaluate its safety and efficacy in NASH with fibrosis (NCT03900429), a Phase 3 RCT (MAESTRO-NAFLD1) to evaluate safety and biomarkers in NAFLD (NCT04197479), as well as Open-label extension of these studies (MAESTRO-NAFLD-OLE) (NCT04951219).

VK2809 is being tested in a Phase 2B RCT in biopsy-proven NASH (VOYAGE) (NCT04173065).

ALG-055009 will be tested in the Hepatic fat reduction with ALG-055009 in steatotic liver disease (HERALD) study, starting in 2024 (Press release).

Search terms:

Pubmed, Google: Thyromimetic, Sobetirome, Eprotirome, Resmetirom, VK2809

- Alzheimer's disease, neurodegeneration, NAFLD, dyslipidemia, clinical trials, safety

Websites visited for Thyromimetics:

- Clinicaltrials.gov (Sobetirome), (Eprotirome), (Resmetirom), (VK2809),
- PubChem (Sobetirome), (Eprotirome), (Resmetirom), (VK2809)
- Drugs.com (Resmetirom)
- DrugBank.ca (Sobetirome), (Eprotirome), (Resmetirom), (VK2809)

References:

1. Shahid MA AM, Sharma S (2022) Physiology, Thyroid Hormone. *StatPearls* https://www.ncbi.nlm.nih.gov/books/NBK500006/.

2. Gomes-Lima C, Wartofsky L, Burman K (2019) Can Reverse T3 Assay Be Employed to Guide T4 vs. T4/T3 Therapy in Hypothyroidism? *Frontiers in Endocrinology* **10**https://www.frontiersin.org/article/10.3389/fendo.2019.00856.

3. Pleasure JR, Pleasure D, Pleasure SJ (2017) 133 - Trophic Factor, Nutritional, and Hormonal Regulation of Brain Development. In *Fetal and Neonatal Physiology (Fifth Edition)*, pp. 1326-1333.e1323 [RA Polin, SH Abman, DH Rowitch, WE Benitz and WW Fox, editors]: Elsevierhttps://www.sciencedirect.com/science/article/pii/B9780323352147001335.

4. Iwen KA, Schröder E, Brabant G (2013) Thyroid hormones and the metabolic syndrome. *European thyroid journal* **2**, 83-92https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3821514/.

5. Scanlan TS (2010) Sobetirome: a case history of bench-to-clinic drug discovery and development. *Heart Failure Reviews* **15**, 177-182https://doi.org/10.1007/s10741-008-9122-x.

6. Luong XG, Stevens SK, Jekle A *et al.* (2020) Regulation of gene transcription by thyroid hormone receptor β agonists in clinical development for the treatment of non-alcoholic steatohepatitis (NASH). *PLOS ONE* **15**, e0240338https://doi.org/10.1371/journal.pone.0240338.

7. Meinig JM, Ferrara SJ, Banerji T *et al.* (2019) Structure-Activity Relationships of Central Nervous System Penetration by Fatty Acid Amide Hydrolase (FAAH)-Targeted Thyromimetic Prodrugs. *ACS medicinal chemistry letters* **10**, 111-116https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6331174/.

8. Jakobsson T, Vedin LL, Parini P (2017) Potential Role of Thyroid Receptor β Agonists in the Treatment of Hyperlipidemia. *Drugs* **77**, 1613-1621https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613055/.

9. Alkhouri N (2020) Thyromimetics as emerging therapeutic agents for nonalcoholic steatohepatitis: rationale for the development of resmetirom (MGL-3196). *Expert Opinion on Investigational Drugs* **29**, 99-101https://doi.org/10.1080/13543784.2020.1708899.

10. Kelly MJ, Pietranico-Cole S, Larigan JD *et al.* (2014) Discovery of 2-[3,5-Dichloro-4-(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yloxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-carbonitrile (MGL-3196), a Highly Selective Thyroid Hormone Receptor β Agonist in Clinical Trials for the Treatment of Dyslipidemia. *Journal of Medicinal Chemistry* **57**, 3912-3923https://doi.org/10.1021/jm4019299.

11. Caddeo A, Kowalik MA, Serra M *et al.* (2021) TG68, a Novel Thyroid Hormone Receptor-β Agonist for the Treatment of NAFLD. *Int J Mol Sci* **22**, 13105https://www.mdpi.com/1422-0067/22/23/13105.

12. Rivas M, Naranjo JR (2007) Thyroid hormones, learning and memory. *Genes, Brain and Behavior* **6**, 40-44https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1601-183X.2007.00321.x.

13. Tan ZS, Beiser A, Vasan RS *et al.* (2008) Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Arch Intern Med* **168**, 1514-1520https://pubmed.ncbi.nlm.nih.gov/18663163

14. Choi BW, Kim S, Kang S *et al.* (2020) Relationship Between Thyroid Hormone Levels and the Pathology of Alzheimer's Disease in Euthyroid Subjects. *Thyroid* **30**, 1547-1555https://doi.org/10.1089/thy.2019.0727.

15. Elbadawy AM, Mansour AE, Abdelrassoul IA *et al.* (2020) Relationship between thyroid dysfunction and dementia. *The Egyptian Journal of Internal Medicine* **32**, 9https://doi.org/10.1186/s43162-020-00003-2.

16. Salehipour A, Dolatshahi M, Haghshomar M *et al.* (2023) The Role of Thyroid Dysfunction in Alzheimer's Disease: A Systematic Review and Meta-Analysis. *The journal of prevention of Alzheimer's disease* **10**, 276-286https://pubmed.ncbi.nlm.nih.gov/36946455/.

17. van Vliet NA, van Heemst D, Almeida OP *et al.* (2021) Association of Thyroid Dysfunction With Cognitive Function: An Individual Participant Data Analysis. *JAMA Internal Medicine* **181**, 1440-1450https://doi.org/10.1001/jamainternmed.2021.5078.

18. Chiaravalloti A, Ursini F, Fiorentini A *et al.* (2017) Functional correlates of TSH, fT3 and fT4 in Alzheimer disease: a F-18 FDG PET/CT study. *Scientific Reports* **7**, 6220https://doi.org/10.1038/s41598-017-06138-7.

19. Quinlan P, Horvath A, Eckerström C *et al.* (2020) Altered thyroid hormone profile in patients with Alzheimer's disease. *Psychoneuroendocrinology* **121**, 104844https://www.sciencedirect.com/science/article/pii/S0306453020302663.

20. Davis DJ, Podolanczuk A, Donahue EJ *et al.* (2008) Thyroid Hormone Levels in the Prefrontal Cortex of Post-Mortem Brains of Alzheimers Disease Patients. *Current Aging Science* **1**, 175-181http://www.eurekaselect.com/article/40134.

21. McAninch EA, Rajan KB, Evans DA *et al.* (2018) A Common DIO2 Polymorphism and Alzheimer Disease Dementia in African and European Americans. *The Journal of Clinical Endocrinology & Metabolism* **103**, 1818-1826https://doi.org/10.1210/jc.2017-01196.

22. Dolatshahi M, Salehipour A, Saghazadeh A *et al.* (2023) Thyroid hormone levels in Alzheimer disease: a systematic review and meta-analysis. *Endocrine* **79**, 252-272https://pubmed.ncbi.nlm.nih.gov/36166162/.

23. Nomoto S, Kinno R, Ochiai H *et al.* (2019) The relationship between thyroid function and cerebral blood flow in mild cognitive impairment and Alzheimer's disease. *PLOS ONE* **14**, e0214676https://doi.org/10.1371/journal.pone.0214676.

24. Wändell P, Carlsson AC, Sundquist J *et al.* (2019) Effect of Levothyroxine Treatment on Incident Dementia in Adults with Atrial Fibrillation and Hypothyroidism. *Clin Drug Investig* **39**, 187-195https://pubmed.ncbi.nlm.nih.gov/30552650

25. Han S, Jeong S, Choi S *et al.* (2023) Association of Thyroid Hormone Medication Adherence With Risk of Dementia. *The Journal of clinical endocrinology and metabolism* **109**, e225-e233https://pubmed.ncbi.nlm.nih.gov/37515589/.

26. Adams R, Oh ES, Yasar S *et al.* (2023) Endogenous and Exogenous Thyrotoxicosis and Risk of Incident Cognitive Disorders in Older Adults. *JAMA Intern Med* **183**, 1324-1331https://pubmed.ncbi.nlm.nih.gov/37870843/.

27. Ferrara SJ, Bourdette D, Scanlan TS (2018) Hypothalamic-Pituitary-Thyroid Axis Perturbations in Male Mice by CNS-Penetrating Thyromimetics. *Endocrinology* **159**, 2733-2740https://doi.org/10.1210/en.2018-00065.

28. Chaudhary P, Marracci GH, Calkins E *et al.* (2021) Thyroid hormone and thyromimetics inhibit myelin and axonal degeneration and oligodendrocyte loss in EAE. *J Neuroimmunol* **352**, 577468-577468https://pubmed.ncbi.nlm.nih.gov/33422763

29. Ferrara SJ, Chaudhary P, DeBell MJ *et al.* (2022) TREM2 is thyroid hormone regulated making the TREM2 pathway druggable with ligands for thyroid hormone receptor. *Cell Chemical Biology* **29**, 239-248.e234https://doi.org/10.1016/j.chembiol.2021.07.014.

30. Baldassarro VA, Quadalti C, Runfola M *et al.* (2023) Synthetic Thyroid Hormone Receptor-β Agonists Promote Oligodendrocyte Precursor Cell Differentiation in the Presence of Inflammatory Challenges. *Pharmaceuticals (Basel, Switzerland)* **16**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10534456/.

31. Mészáros L, Himmler M, Schneider Y *et al.* (2024) Sobetirome rescues α-synuclein-mediated demyelination in an in vitro model of multiple system atrophy. *The European journal of neuroscience* **59**, 308-315https://pubmed.ncbi.nlm.nih.gov/38086536/.

32. Kim B, Ko YH, Runfola M *et al.* (2021) Diphenyl-Methane Based Thyromimetic Inhibitors for Transthyretin Amyloidosis. *Int J Mol Sci* **22**, 3488https://pubmed.ncbi.nlm.nih.gov/33800546

33. da Luz MHM, Pino JMV, Mônico-Neto M *et al.* (2023) Sleep deprivation modulates APOE and LDL receptor-related protein 1 through thyroid hormone T4 and impairs Aβ clearance in hippocampus of rats. *Biochimica et biophysica acta Molecular basis of disease* **1869**, 166729https://pubmed.ncbi.nlm.nih.gov/37137431/.

34. Kim DK, Choi H, Lee W *et al.* (2024) Brain hypothyroidism silences the immune response of microglia in Alzheimer's disease animal model. *Science advances* **10**, eadi1863https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10942107/.

35. Lee JS, Soh Y, Kim H-G *et al.* (2020) Interactive Effects of Apolipoprotein E ε4 and Triiodothyronine on Memory Performance in Patients With Subjective Cognitive Decline. *Frontiers in Medicine* **7**https://www.frontiersin.org/article/10.3389/fmed.2020.00298.

36. Bojar I, Stasiak M, Cyniak-Magierska A *et al.* (2016) Cognitive Function, APOE Gene Polymorphisms, and Thyroid Status Associations in Postmenopausal Women in Poland. *Dementia and Geriatric Cognitive Disorders* **42**, 169-185https://www.karger.com/DOI/10.1159/000449373.

37. Zhang M, Gong W, Zhang D *et al.* (2022) Ageing related thyroid deficiency increases brain-targeted transport of liver-derived ApoE4-laden exosomes leading to cognitive impairment. *Cell Death & Disease* **13**, 406https://doi.org/10.1038/s41419-022-04858-x.

38. Pagadala MR, Zein CO, Dasarathy S *et al.* (2012) Prevalence of hypothyroidism in nonalcoholic fatty liver disease. *Digestive diseases and sciences* **57**, 528-534https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3922233/.

39. Kim D, Kim W, Joo SK *et al.* (2018) Subclinical Hypothyroidism and Low-Normal Thyroid Function Are Associated With Nonalcoholic Steatohepatitis and Fibrosis. *Clinical Gastroenterology and Hepatology* **16**, 123-131.e121https://doi.org/10.1016/j.cgh.2017.08.014.

40. Krause C, Grohs M, El Gammal AT *et al.* (2018) Reduced expression of thyroid hormone receptor β in human nonalcoholic steatohepatitis. *Endocrine connections* **7**, 1448-1456https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6300861/.

41. Harrison SA, Bashir MR, Guy CD *et al.* (2019) Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet* **394**, 2012-2024https://doi.org/10.1016/S0140-6736(19)32517-6.

42. Younossi ZM, Stepanova M, Taub RA *et al.* (2022) Hepatic Fat Reduction Due to Resmetirom in Patients With Nonalcoholic Steatohepatitis Is Associated With Improvement of Quality of Life. *Clinical Gastroenterology and Hepatology* **20**, 1354-1361.e1357https://doi.org/10.1016/j.cgh.2021.07.039.

43. Harrison SA, Bashir M, Moussa SE *et al.* (2021) Effects of Resmetirom on Noninvasive Endpoints in a 36-Week Phase 2 Active Treatment Extension Study in Patients With NASH. *Hepatology communications* **5**, 573-588https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8034581/.

44. Harrison SA, Bedossa P, Guy CD *et al.* (2024) A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *The New England journal of medicine* **390**, 497-509https://pubmed.ncbi.nlm.nih.gov/38324483/.

45. Kannt A, Wohlfart P, Madsen AN *et al.* (2021) Activation of thyroid hormone receptor-β improved disease activity and metabolism independent of body weight in a mouse model of non-alcoholic steatohepatitis and fibrosis. *British Journal of Pharmacology* **178**, 2412-2423https://doi.org/10.1111/bph.15427.

46. Wang X, Wang L, Geng L *et al.* (2023) Resmetirom Ameliorates NASH-Model Mice by Suppressing STAT3 and NF-κB Signaling Pathways in an RGS5-Dependent Manner. *Int J Mol Sci* **24**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10058113/.

47. Hönes GS, Sivakumar RG, Hoppe C *et al.* (2022) Cell-Specific Transport and Thyroid Hormone Receptor Isoform Selectivity Account for Hepatocyte-Targeted Thyromimetic Action of MGL-3196. *Int J Mol Sci* **23**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9691000/.

48. Lian B, Loomba R, Neutel J *et al.* (2020) VK2809, a novel liver-directed thyroid receptor agonist, produces durable reductions in liver fat in patients with non-alcoholic fatty liver disease: Results of 4-week follow-up assessment from a 12-week Phase 2 randomized, placebo-controlled trial. *Journal of Hepatology* **73**https://www.journal-of-hepatology.eu/article/S0168-8278(20)30652-8/pdf.

49. Runfola M, Sestito S, Bellusci L *et al.* (2020) Design, synthesis and biological evaluation of novel TRβ selective agonists sustained by ADME-toxicity analysis. *European Journal of Medicinal Chemistry* **188**, 112006https://www.sciencedirect.com/science/article/pii/S0223523419311638.

50. Perra A, Kowalik MA, Cabras L *et al.* (2020) Potential role of two novel agonists of thyroid hormone receptor-β on liver regeneration. *Cell Proliferation* **53**, e12808https://onlinelibrary.wiley.com/doi/abs/10.1111/cpr.12808.

51. Lin S, Huang S, Deng Z *et al.* (2023) Discovery of a novel, liver-targeted thyroid hormone receptor-β agonist, CS271011, in the treatment of lipid metabolism disorders. *Front Endocrinol (Lausanne)* **14**, 1109615https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9896003/.

52. Berkenstam A, Kristensen J, Mellström K *et al.* (2008) The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. *Proceedings of the National Academy of Sciences* **105**, 663-667https://www.pnas.org/doi/abs/10.1073/pnas.0705286104

53. Ladenson PW, Kristensen JD, Ridgway EC *et al.* (2010) Use of the Thyroid Hormone Analogue Eprotirome in Statin-Treated Dyslipidemia. *New England Journal of Medicine* **362**, 906-916https://www.nejm.org/doi/full/10.1056/NEJMoa0905633.

54. Sjouke B, Langslet G, Ceska R *et al.* (2014) Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. *The Lancet Diabetes & Endocrinology* **2**, 455-463https://www.sciencedirect.com/science/article/pii/S2213858714700063.

55. Taub R, Chiang E, Chabot-Blanchet M *et al.* (2013) Lipid lowering in healthy volunteers treated with multiple doses of MGL-3196, a liver-targeted thyroid hormone receptor agonist. *Atherosclerosis* **230**, 373-380https://doi.org/10.1016/j.atherosclerosis.2013.07.056.

56. Hovingh GK, Klausen IC, Heggen E *et al.* (2022) Resmetirom (MGL-3196) in Patients With Heterozygous Familial Hypercholesterolemia. *Journal of the American College of Cardiology* **79**, 1220-1222https://www.sciencedirect.com/science/article/pii/S0735109722001899.

57. Lian B, R H, Schoenfeld S (2008) A Phase 1 Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate Safety, Tolerability and Pharmacokinetics of the Liver-Selective TR-Beta Agonist VK2809 (MB07811) in Hypercholesterolemic Subjects. . *ENDO Meeting 2008*https://www.vikingtherapeutics.com/wp-content/uploads/2016-ACC-VK2809-Poster-Final.pdf.

58. Caddeo A, Serra M, Sedda F *et al.* (2023) Potential use of TG68 - A novel thyromimetic - for the treatment of non-alcoholic fatty liver (NAFLD)-associated hepatocarcinogenesis. *Frontiers in oncology* **13**, 1127517https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9996294/.

59. Kowalik MA, Puliga E, Cabras L *et al.* (2020) Thyroid hormone inhibits hepatocellular carcinoma progression via induction of differentiation and metabolic reprogramming. *Journal of Hepatology* **72**, 1159-1169https://doi.org/10.1016/j.jhep.2019.12.018.

60. Dhamija E, Paul SB, Kedia S (2019) Non-alcoholic fatty liver disease associated with hepatocellular carcinoma: An increasing concern. *The Indian journal of medical research* **149**, 9-17https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6507546/.

61. Gillis NE, Cozzens LM, Wilson ER *et al.* (2023) TRβ Agonism Induces Tumor Suppression and Enhances Drug Efficacy in Anaplastic Thyroid Cancer in Female Mice. *Endocrinology* **164**https://pubmed.ncbi.nlm.nih.gov/37702560/.

62. Kersseboom S, van Gucht ALM, van Mullem A *et al.* (2017) Role of the Bile Acid Transporter SLC10A1 in Liver Targeting of the Lipid-Lowering Thyroid Hormone Analog Eprotirome. *Endocrinology* **158**, 3307-3318https://doi.org/10.1210/en.2017-00433.

63. Valcárcel-Hernández V, Guillén-Yunta M, Scanlan TS *et al.* (2023) Maternal Administration of the CNS-Selective Sobetirome Prodrug Sob-AM2 Exerts Thyromimetic Effects in Murine MCT8-Deficient Fetuses. *Thyroid* **33**, 632-640https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10171952/.

64. Javanbakht M, Fishman J, Moloney E *et al.* (2023) Early Cost-Effectiveness and Price Threshold Analyses of Resmetirom: An Investigational Treatment for Management of Nonalcoholic Steatohepatitis. *PharmacoEconomics - open* **7**, 93-110https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9929016/.

65. Runfola M, Sestito S, Gul S *et al.* (2020) Collecting data through high throughput in vitro early toxicity and off-target liability assays to rapidly identify limitations of novel thyromimetics. *Data in Brief* **29**, 105206https://www.sciencedirect.com/science/article/pii/S2352340920301001.