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.

Syk Inhibitors

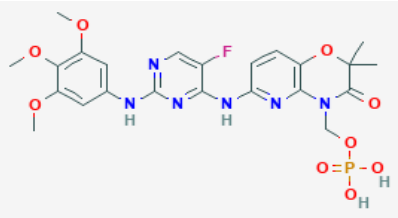
Evidence Summary

Syk inhibitors reduce immune cell activation and associated pathological inflammation, but so far clinical efficacy is limited to rare autoimmune diseases. Safety is good short-term, but long-term is unknown.

Neuroprotective Benefit: Syk inhibition may protect against Aβ-mediated neuroinflammation and microglial dysfunction, as well as promote tau degradation, but more studies in human tissue are needed.

Aging and related health concerns: Most efficacious in autoimmune diseases, but benefits are marginal. Limited effects as a monotherapy in hematological cancers, but may work in combination therapies. There are potential anti-fibrotic and senolytic effects.

Safety: In clinical trials, the most common adverse effects were gastrointestinal issues, headache, and hypertension. The risk for infection is not significantly increased in the short term, but long-term safety has not been established.

Availability: Rx or in clinical trials	**Dose**: 100mg BID Oral (for chronic ITP)	**Fostamatinib** **Chemical formula:** $C_{23}H_{26}FN_6O_9P$ **MW**: 580.5 g/mol  Source: PubChem
Half-life: 15 hours	**BBB**: Not known	
Clinical trials: Phase 3 RCTs for fostamatinib in autoimmune diseases ITP (n=76, n= 74) and RA (n=923, n=913, n=323). Phase 2 trials for fostamatinib, entospletinib, cerdulatinib, and mivavotinib in hematological malignancies.	**Observational studies**: None	

What is it?

Spleen tyrosine kinase (Syk) is a non-receptor tyrosine kinase, and is a member of the Src kinase family. It contains Src-homology 2 (SH2) domains which bind to phosphorylated immunoreceptor tyrosine-based activation motif (ITAM) sequences, leading to the recruitment and activation of additional adaptor proteins, leading to the induction of intracellular signaling cascades [1]. It is highly expressed in hematological cells, and plays important roles in B cell maturation, and immune cell signaling and activation. Consequently, **clinical development for Syk inhibitors has focused on autoimmune diseases and hematological cancers**. Two Syk inhibitors (fostamatinib and entospletinib) have undergone clinical testing, and two dual target receptors (cerdulatinib and mivavotinib) have been tested in clinical trials for cancer [2].

Fostamatinib is an oral Syk inhibitor that is marketed under the trade name Tavalisse® by Rigel Pharmaceuticals, and was licensed to Grifols for commercialization in Europe and Turkey. It was approved by the FDA in April 2018, and by the EMA in 2020 for chronic immune thrombocytopenia purpura, an autoimmune condition, in individuals with inadequate response to prior therapy. It has also been tested in clinical trials for rheumatoid arthritis, IgA nephropathy, autoimmune hemolytic anemia, and hematological malignancies. Development for cancer has been hampered by dose-limiting toxicities due to off-target kinase inhibition. Fostamatinib is a prodrug, which is cleaved to its active metabolite R406 by intestinal alkaline phosphatase [3].

Entospletinib (GS-9973) is a highly selective oral Syk inhibitor, with 14-fold selectivity for Syk over other kinases [4]. It is being developed by Gilead Sciences for hematological malignancies.

Cerdulatinib is a dual Syk/JAK inhibitor being developed by Portola Pharmaceuticals (part of Alexion) primarily for hematological malignancies.

Mivavotinib (TAK-659) is a dual Syk/Flt3 inhibitor being developed by Millennium/Takeda Oncology for hematological malignancies.

Neuroprotective Benefit: Syk inhibition may protect against Aβ-mediated neuroinflammation and microglial dysfunction, as well as promote tau degradation, but more studies in human tissue are needed.

Types of evidence:

- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None

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

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)

Syk is implicated in the microglial dysfunction that promotes neuroinflammation and facilitates tau propagation in the context of Alzheimer's disease (AD). In preclinical AD models, Syk inhibitors exhibit neuroprotection by reducing pathogenic neuroinflammation. In a study of changes in gene expression networks within the hippocampus across the lifespan, **Syk was found to be part of a dysregulated gene network that was elevated with aging**, and the effect was exacerbated in the context of AD [5]. Although there is evidence for pathological Syk activation in the human AD brain, species or disease-related differences in Syk processing and localization calls into question whether Syk inhibitors would offer similar therapeutic benefit in humans.

Tau pathology: In rodent AD models, Syk activation is present in a subset of microglia and Aβ-plaque associated dystrophic neurites [6; 7; 8]. Neurons with activated Syk had tau accumulation. Although, studies in rodents and cell culture suggest that Syk can facilitate tau phosphorylation, it appears not to be a major contributor to tau phosphorylation in the human hippocampus [7]. In postmortem AD brain tissue from the dorsolateral prefrontal cortex, activated Syk was detected in dystrophic neurites around

Aβ plaques and in tau containing neurons [8]. A separate study examining postmortem AD brain tissue from the hippocampus did not see a clear association of activated Syk with dystrophic neurites, but rather, Syk was primarily localized to stress granules and granulovacuolar degeneration (GVD) inclusions, which are associated with disturbed autophagy [7]. Microglia exposed to Aβ form stress granules, and Syk enhances the formation of stress granules [9]. Within the stress granules, activated Syk stimulates the production of neurotoxic reactive oxygen species (ROS) and reactive nitrogen species (RNS). The sequestration of Syk into the granules may be a neuroprotective response aimed at facilitating Syk clearance, but defective autophagic clearance may lead to the accumulation of Syk containing cytoplasmic aggregates [7]. In a rodent tauopathy model (Tau P301S), Syk inhibition (via BAY61-3606) promotes autophagic tau degradation, by inhibiting the Akt/mTOR pathway [10]. It is unclear whether the presence of activated Syk within cytoplasmic aggregates in the AD brain contributes to the defect in their clearance by autophagy. Within microglia, the sequestration of Syk within stress granules impairs phagocytic capacity, including Aβ uptake, in cell culture, and re-localization of Syk from the cytoplasm to the plasma membrane restores phagocytosis in these cells [9].

Phagocytosis: Syk is essential for phagocytosis in macrophages and microglia [9]. Many phagocytic receptors are associated with proteins with ITAM domains. The phosphorylation of the ITAM domains leads to the recruitment of Syk, which then initiates various intracellular signaling cascades, including those associated with phagocytosis. **TREM2 mediated phagocytosis in microglia involves Syk activation** and signaling through the P13K/Akt/PLCγ pathways [11]. In AD models, a TREM2 activating antibody activated Syk signaling and promoted phagocytic clearance of Aβ [12]. Therefore, Syk inhibition would be expected to impair the therapeutic efficacy of TREM activating antibodies.

Neuroinflammation: Syk plays multiple roles in microglia, which may have opposing impacts on AD-related pathology. Syk can promote phagocytic clearance, but it can also promote the secretion of pro-inflammatory cytokines. The outcome is likely determined by the composition of ITAM containing receptor complexes within a given cellular environment, and thus subject to conditional context. Syk is a downstream mediator of TREM2-related phagocytosis, but it does not participate in the anti-inflammatory effects of TREM2 [11]. In the absence of TREM2/DAP12, Syk activation primarily has a pro-inflammatory effect. This suggests that dysregulation of TREM2 or other Syk interacting proteins may drive a pathological dysregulation of Syk in AD. In organotypic brain slices from an AD model (Tau P301S), proinflammatory cytokine levels were elevated relative to wild type, including a 3 fold increase in IL-1β and 1.5 fold increase in IL-6, and these increases could be alleviated by Syk inhibition [6]. The increase in these cytokines in response to elevated Syk may derive from the **essential role of Syk in activation of the NLRP3 inflammasome**. Syk activation is also associated with the activation of NF-kB,

and in an AD mouse model (Tg19959), treatment with a Syk inhibitor (BAY61-3606) improved spatial memory, based on performance on the Morris water maze, and was neuroprotective against NF-kB associated neuronal loss [13].

Overall, Syk dysregulation may contribute to microglial dysfunction in AD, but whether Syk inhibition is therapeutically beneficial may depend on whether there is broader dysregulation of upstream Syk interacting receptors and downstream signaling pathways.

APOE4 interactions: ApoE stimulates Syk activation in a TREM2 dependent-manner [11]. In this way, ApoE acts as an agonist of TREM2-mediated phagocytic activation in microglia. However, in the absence of TREM2 and/or its associated ITAM-containing receptor DAP12, ApoE may stimulate Syk in an alternative manner which promotes pro-inflammatory signaling. ApoE4 has been shown to be a more potent activator of Syk than ApoE2, suggesting that Syk-mediated neuroinflammation may be enhanced in ApoE4 carriers.

Aging and related health concerns: Most efficacious in autoimmune diseases, but benefits are marginal. Limited effects as a monotherapy in hematological cancers, but may work in combination therapies. There are potential anti-fibrotic and senolytic effects.

Types of evidence:

- 2 meta-analyses for Fostamatinib (n=5; n=11) clinical trials for RA
- 4 clinical trials for Fostamatinib (Phase 2 for B cell malignancies, Two Phase 3 for ITP, Phase 2 for IgA nephropathy)
- 3 clinical trials for Entospletinib for hematological malignancies
- 1 clinical trial for Cerdulatinib for hematological malignancies
- 3 clinical trials for Mivavotinib for hematological malignancies
- Numerous laboratory studies

Cancer: CONTEXT DEPENDENT ROLE FOR SYK

Syk plays a context dependent role in cancer. It can either be pro-oncogenic or act as a tumor suppressor depending on the cell type of origin and stage [14]. Additionally, there are two alternatively spliced forms of Syk, which may have different effects on cancer growth properties, thus the relative level of the isoforms can influence its oncogenic effects. In the vast majority of hematological malignancies, Syk promotes cancer cell growth and survival. In non-hematological cancers, Syk appears

to preferentially act as a tumor suppressor in cancer cells of epithelial origin. The epithelial-to-mesenchymal transition is used by cancer cells to initiate invasion and metastasis, and Syk acts as a negative regulator of this process.

***Breast Cancer*:** Syk is expressed in healthy human breast tissue, but expression is low or absent in breast carcinoma tissue, particularly in cells with the most malignant, metastatic phenotype [15]. In breast cancer patients, low Syk expression is associated with increased risk for distant metastasis and poor prognosis [16]. The tumor suppressive effects are thought to be related to the modulation of cell adhesion signaling pathways and transcriptional repression of growth and proliferation related genes [14; 17].

Hepatocellular Carcinoma: Syk has opposing effects in hepatocellular carcinoma, depending on the isoform [18]. The full-length variant, Syk(L) inhibits metastasis, and its downregulation is associated with poor prognosis. While the shorter variant, Syk(S), which is not expressed in healthy liver tissue, promotes metastasis and its upregulation is associated with poor survival. Therefore, overall prognosis is associated with the balance of the Syk variants in a given tumor.

Retinoblastoma: Syk, which is not normally expressed in retinal cells, was found to be highly upregulated in retinoblastoma tumor tissue, stemming from epigenetic modulation in these tumor cells [19]. Syk inhibitors had anti-tumorigenic effects towards retinoblastoma cells *in vitro* and in xenograft models [19].

Glioma: Syk expression was found to be upregulated in glioblastoma tissue, particularly in patients with the mesenchymal subtype, relative to healthy brain tissue, and was found to be a driver of the of inflammatory P13K-NF-kB pathway [20; 21]. Syk expression is associated with worse prognosis in glioblastoma, and Syk inhibitors (BAY 61-3606, R406) have anti-tumorigenic properties in xenograft and *in vitro* models [22].

Hematological malignancies: POTENTIAL BENEFIT IN COMBINATION THERAPY

Syk inhibitors have been tested in clinical trials for hematological malignancies, particularly in cancers of B cell origin. Syk plays a critical role in the amplification of B cell receptor (BCR) signaling, which is an important therapeutic target for B cell malignancies [2]. But **in order to prevent resistance, BCR signaling inhibitors will likely need to be used in combination**. Some dual inhibitors are also being developed which target BCR signaling in conjunction with another oncogenic signaling pathway.

Fostamatinib: The overall response rate of patients with relapsed or refractory diffuse large B-cell lymphoma treated in a Phase 2 clinical trial with fostamatinib (100 mg or 200 mg BID) was only 3%, and was deemed to be ineffective for this indication (NCT01499303) [23]. The lack of therapeutic efficacy may have been related to dose limiting toxicities in this population [2].

Entospletinib: Entospletinib has been tested in a Phase 2 trial (n=326) for non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL) (NCT01799889). In NHL, entospletinib (800 mg BID) has very limited efficacy as a single agent, as indicated by a lack of complete responses, and continued disease progression in the majority of patients [24; 25]. In CLL (n=49), the overall response rate for entospletinib (400 mg BID) was 32.7% (95% Confidence Interval (CI) 21.7 to 45.3%) [26]. Due to limited single agent efficacy, subsequent trials have focused on using entospletinib in combination, however, it has been challenging to find a combination that is both safe and effective [2]. A trial for the use of entospletinib with vincristine and dexamethasone in relapsed or refractory acute lymphoblastic leukemia (ALL) was terminated due to lack of efficacy (NCT02404220). A trial for entospletinib in combination with idelalisib in relapsed or refractory hematological malignancies was terminated for safety due to an increased incidence of pneumonitis (NCT01796470). Trials for entospletinib in combination with chemotherapy have also been terminated (NCT02343939, NCT03135028, NCT02568683). Trials for additional combinations are ongoing (NCT03010358, NCT02983617).

Cerdulatinib: Cerdulatinib is a dual JAK/Syk inhibitor which has been tested in a Phase 1 trial (NCT01994382) for relapsed or refractory B-cell malignancies (n=43). In the dose escalation study, full inhibition of JAK and Syk was detected in the blood of patients treated with tolerable doses, and the inhibition of these pathways was correlated with tumor responses [27]. Treatment with cerdulatinib also reduced serum markers of inflammation and BCR activation. The Phase 2 portion of this trial is currently ongoing.

Mivavotinib (TAK-659): Mivavotinib is a dual Flt3/Syk inhibitor which has been tested in several clinical trials for hematological malignancies. In a Phase 2 trial for relapsed or refractory diffuse large B-cell lymphoma (n=49) (NCT03123393), 90% of patients discontinued treatment, due to disease progression, indicating a lack of efficacy in this population [28]. A trial for mivavotinib in combination with nivolumab in patients with solid tumors (NCT02834247) was also terminated due to lack of efficacy. The Flt3/Syk target combination is considered most applicable for acute myeloid leukemia (AML), for which it has been tested in a Phase 1/2 trial (NCT02323113), and is currently being tested in combination with the proteasome inhibitor ixazomib (NCT04079738).

Autoimmune disease

Syk plays a central role in mediating inflammatory immune responses. It is essential for the development of mature B cells and B cell antibody responses [1]. It mediates responses to integrin signaling and Fc immune complexes in myeloid cells [1; 29]. Antibody (IgG)-antigen bound immune complexes are recognized by ITAM containing Fc receptors, which leads to the activation of Syk, and induction of downstream processes that promote the phagocytosis of the complexes by activated macrophages and neutrophils [29]. In the context of autoimmune disease, immune complexes that aberrantly target endogenous proteins promote the inflammatory-mediated destruction of healthy tissue. Therefore, blocking the activation of Syk would be expected to protect against the immune mediated attack on healthy cells tagged by (auto)immune complexes.

***Immune thrombocytopenia purpura (ITP)**:* BENEFIT

The Syk inhibitor fostamatinib (Tavalisse®), is approved for the treatment of chronic ITP, which is an autoimmune disease involving antibody-mediated destruction of platelets, in individuals with insufficient response to prior therapy. In the pivotal Phase 3 RCTs (NCT02076399 and NCT02076412), the overall responses, defined retrospectively as ≥1 platelet count ≥50 000/μL within the first 12 weeks, occurred in 43% of patients on fostamatinib vs. 14% on placebo (P = .0006) [30].

***Rheumatoid arthritis**:* POTENTIAL MINOR BENEFIT (but development discontinued)

Meta-analyses of RCTs using fostamatinib for the treatment of rheumatoid arthritis indicate that fostamatinib treatment was associated with a significant improvement on the American College of Rheumatology 20% response (weighted mean difference (WMD) vs placebo: 1.96, 95% CI 1.46 to 2.61, based on 11 studies; Odds ratio (OR): 1.86, 95 % CI 1.32 to 2.62, based on 5 studies) and disease activity score (WMD: 4.70, 95% CI 3.14 to 7.03) [31; 32]. However, the results from the Phase 3 trials were mixed, and efficacy was not better than currently available disease-modifying anti-rheumatic drugs. Consequently, AstraZeneca, which had licensed fostamatinib from Rigel for this indication, discontinued development for this indication (Press release).

IgA Nephropathy: POTENTIAL MINOR BENEFIT FOR SEVERE DISEASE

IgA nephropathy is the most common type of primary glomerulonephritis (kidney inflammation), which often progresses to kidney failure [33]. It involves the abnormal deposition of IgA immune complexes in the kidney, leading to a destructive inflammatory response. Total Syk expression is correlated to the severity of active IgA nephropathy and proteinuria (levels of protein in the urine), and inversely

correlated with renal function [34]. Preclinical data suggest that Syk activation contributes to the inflammatory processes downstream of IgA immune complex deposition [33]. In preclinical models, treatment with fostamatinib before or after the induction of glomerulonephritis reduced renal pathology [33; 35]. However, the proof-of-principal Phase 2 (NCT02112838) clinical trial for fostamatinib (100 or 150 mg BID) in IgA nephropathy failed to meet its primary endpoint of reducing proteinuria (Press release). There was a trend toward improvement in a pre-specified subgroup with the greatest risk of disease progression (proteinuria >1g/day).

Diabetes-associated complications: POTENTIAL BENEFIT (Preclinical)

In preclinical type 1 diabetes models, targeting Syk is protective against autoimmune pancreatic beta cell destruction, as well as diabetes-associated complications related to high glucose-induced inflammation [1]. The deletion of Syk from antigen presenting dendritic cells can block the generation of diabetogenic T cells in mice [36]. In the streptozotocin-induced model of diabetes in male rats, hyperglycemia induces activation of the NLRP3 inflammasome and downstream pro-inflammatory cytokine IL-1β [37; 38]. This inflammation may contribute to diabetic complications, such as cardiopathy and nephropathy. High glucose-related activation of the inflammasome is downstream of Syk-mediated JNK activation, and can be inhibited through the use of Syk inhibitors in cell culture [37; 38]. Treatment with a Syk inhibitor (R406 10 mg/kg oral for 12 weeks) was protective against inflammation, edema, and vessel distortion in a model of diabetic retinopathy [39]. It also reduced leakiness by increasing the integrity of the blood-retinal-barrier.

Liver disease: POTENTIAL BENEFIT (Preclinical)

Syk activation is positively correlated with disease severity in a variety of liver diseases, including fibrosis, viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease [40]. Syk mRNA expression was shown to be significantly up-regulated in liver tissue with hepatitis B virus infection (by 7.52 fold), hepatitis C virus infection (by 2.19 fold), alcoholic liver disease (by 1.96-fold) and non-alcoholic steatohepatitis (by 1.34 fold) in comparison to heathy liver [41]. In fibrotic livers, the increase in Syk was primarily localized to hepatocytes and hepatic stellate cells. Syk promotes the activation of hepatic stellate cells, as well as their expression of pro-fibrotic genes, such as TGFβ and Wnt/β-catenin [41]. Syk inhibition can reduce the induction of pro-fibrotic genes *in vitro*. Treatment with a Syk inhibitor (GS-9973 10 mg/kg oral) reduced elevated liver enzyme levels and improved hepatic function in male rodent models of liver fibrosis (the CCl_4 mouse, diethyl nitrosamine rat and bile duct ligation rat models) [41].

Cardiovascular

Syk activation has been shown to promote vascular smooth muscle cell (VSMC) proliferation, and in a high-throughput screen, the Syk inhibitor BAY61-360 was found to be a potent inhibitor of VSMC proliferation and migration [42]. In aged (18 months old) male rats, treatment with a micro-RNA that targets Syk (mir-542-3p) inhibited neointimal formation in a balloon angioplasty model [43].

Abdominal Aortic Aneurysm: POTENTIAL BENEFIT (Preclinical)

B cells are implicated in the pathogenesis of abdominal aortic aneurysms (AAA) through the production of immunoglobulins and proinflammatory cytokines [44]. There is an increased level of immune cell infiltrate and Syk activation, particularly on B cells, in AAA tissue relative to normal abdominal aortic tissue [45; 46]. In mice, AAA formation is inhibited in the absence of B cells, while the addition of IgG can stimulate inflammatory AAA formation and expansion [45]. These IgG-induced effects could be suppressed by treatment with a Syk inhibitor (fostamatinib). In *ex vivo* culture from human AAA tissue, treatment with a Syk inhibitor (P505-15) also suppressed IgG-induced inflammatory cytokine production [46].

Stroke: POTENTIAL BENEFIT (Preclinical)

Syk activation is increased in response to hypoxic-ischemic/reperfusion injury. This activation can promote oxidative damage and mitochondrial dysfunction by inducing NADPH oxidase (Nox)-driven production of ROS [47]. Syk is also a critical signaling mediator for immune cell receptors, including the platelet collagen receptor glycoprotein VI (GPVI), which influences arterial thrombosis formation and stroke outcome [48]. Syk also activates signaling pathways downstream of the inflammation-inducing pattern recognition receptor, dectin-1, via its ITAM domain, which promotes microglial activation and inflammatory cytokine production in the context of stroke [49]. Treatment with an oral Syk inhibitor (BI1002494 100 mg/kg) prior or immediately after the focal ischemic stroke model of transient middle cerebral artery occlusion (tMAO) in mice, reduced infarct size and improved neurological outcome [48]. Syk inhibition (piceatannol 20 mg/kg/day i.p. 1hr after stroke and 1x/day for 2 days) also reduced expression of inflammatory and oxidative stress mediators, reduced infarct size, and improved neurological function in a photothrombotic mouse model of ischemic stroke [49].

Senescence: POTENTIAL BENEFIT (Preclinical-cell culture)

The Syk inhibitor R406 was identified in a high throughput screen as having selective toxicity for senescent cells [50]. The screen used a model of replicative senescence in human diploid fibroblasts and

validated in a stress-induced (etoposide or H_2O_2) premature senescence model cell model. R406 mediated apoptosis of senescent cells (p16+, p21+) was associated with the inhibition of FAK and MAPK, suggesting that its senolytic effects may be partially mediated by off-target kinase (non-Syk) effects.

Safety: In clinical trials, the most common adverse effects were gastrointestinal issues, headache, and hypertension. The risk for infection is not significantly increased in the short term, but long-term safety has not been established.

Types of evidence:

- 1 meta-analysis of RCTs (n=12) for Fostamatinib
- 1 clinical trial for Fostamatinib in B cell malignancies
- 3 clinical trials for Entospletinib (Phase 1 in healthy volunteers, Phase 2 in B cell malignancies)
- Numerous laboratory studies

The prescribing information for fostamatinib carries precautions/warnings for hypertension, hepatotoxicity (liver enzyme elevation), diarrhea, neutropenia, and embryo-fetal toxicity (FDA label). In a meta-analysis for Phase 2 and 3 RCTs for fostamatinib (n=12 studies with 1,444 cases and 1,188 controls) fostamatinib was associated with 19% higher risk of any adverse event compared to placebo (9 studies, Relative Risk (RR): 1.19, CI 1.07 to 1.33, I^2 = 40%) [51]. **The most common adverse events were diarrhea** (10 studies, RR: 2.23, CI 1.46 to 3.41, I^2 = 45%), **headache, nausea and hypertension** (9 studies, RR: 2.23, CI 1.61 to 3.09, I^2 = 13%), though few patients required medication adjustment for the hypertension. Although Syk is involved in immune activation, there were no significant increases in upper respiratory tract infections, urinary tract infections, or serious infections, relative to placebo. Fostamatinib significantly **increased the risk for neutropenia** (ANC < 1500/uL) (8 studies, RR: 4.34, CI 1.82 to 10.31, I^2 = 30%), but not for febrile neutropenia. Fostamatinib treatment also significantly **increased the risk for liver enzyme elevation** (9 studies, RR: 2.21, CI 1.18 to 4.14, I^2 = 0%). Notably, although there were more bleeding events in the fostamatinib group, as would be projected from the role of Syk in platelets, the difference was not significant relative to placebo, suggesting that bleeding is not a significant risk for fostamatinib.

While fostamatinib has a good safety profile in autoimmune conditions, it was associated with dose-limiting toxicities for diarrhea, neutropenia, and thrombocytopenia in heavily pre-treated patients (refractory or relapsed disease) with hematological malignancies [2]. However, fostamatinib is not completely selective for Syk, and these toxicities have been attributed to off-target kinases [52].

As a more selective Syk inhibitor, entospletinib is expected to have a more favorable therapeutic profile. In heathy volunteers (n=120, ages 18 to 45), entospletinib (from 25 up to 1200 mg) was generally well tolerated, with adverse events being mild or moderate [4]. The most common drug-attributed adverse events were headache, nausea, rhinorrhea, and oropharyngeal pain. In heavily pre-treated patients with hematological malignancies, common treatment-emergent adverse events were fatigue, nausea, decreased appetite, constipation, dyspnea, diarrhea, dehydration, cough, insomnia, and peripheral edema [25; 26]. Common laboratory abnormalities were anemia, neutropenia, and thrombocytopenia, as well as increases in aspartate transaminase, alanine transaminase, total bilirubin, and serum creatinine. Combination with the PI3K inhibitor idelalisib resulted in treatment-emergent pneumonitis in 18% of the study population, which was severe in the majority of cases, resulting in two fatalities [53]. This suggests that attempts to combine multiple agents targeting BCR signaling pathways need to be approached with caution.

Overall, there is good short-term safety for Syk inhibitors based on clinical trial data, but long-term safety, especially the risk for infections with chronic use, remains to be established. Since Syk expression is widespread, systemic inhibition is likely to produce side effects in non-targeted tissues.

Drug interactions: Fostamatinib has drug interactions with strong CYP3A4 Inhibitors, which will increase exposure to the active metabolite (R406), as well as strong CYP3A4 Inducers, which will decrease drug exposure (FDA label). According to Drugs.com, there are 40 major and 397 moderate drug interactions with fostamatinib. There is also a food/supplement interaction with St. John's wort.

Sources and dosing: Fostamatinib (Tavalisse®) is approved for chronic Immune thrombocytopenia purpura in individuals within insufficient response to prior therapy. It is marketed by Rigel Pharmaceuticals. For this indication, the starting dose is 100 mg orally twice a day, then increased to 150 mg orally twice a day after 4 weeks, if necessary (FDA label). Entospletinib, cerdulatinib, and mivavotinib are still in clinical development by Gilead Sciences, Portola Pharmaceuticals (acquired by Alexion Pharmaceuticals), and Takeda Oncology, respectively.

Research underway: According to Clinicaltrials.gov there are active clinical trials for fostamatinib for myelofibrosis with thrombocytopenia, ovarian cancer, renal transplant rejection, warm antibody autoimmune hemolytic anemia, hematological malignances, and ITP.

There are active clinical trials for entospletinib for B cell malignancies and CLL.

There are active clinical trials for cerdulatinib for hematological malignancies and vitiligo.

There are active clinical trials for mivavotinib for hematological malignancies.

Search terms:

Pubmed, Google: Syk inhibitor, Fostmatinib, entosplentinib, cerdulatinib, TAK-659

- Alzheimer's disease, neurodegeneration, stroke, cardiovascular, cancer, aging, fibrosis, diabetes, autoimmune, inflammation, clinical trials, meta-analysis, safety

Websites visited for Syk Inhibitors:

- Clinicaltrials.gov (Fostamatinib, Entospletinib, Cerdulatinib, Mivavotinib)
- Drugs.com (Fostamatinib)
- WebMD.com (Fostamatinib)
- PubChem (Fostamatinib, Entospletinib, Cerdulatinib, Mivavotinib, BAY 61-3606)
- DrugBank.ca (Fostamatinib, Entospletinib, Cerdulatinib,
- Cafepharma (Fostamatinib, Entosplentinib)

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