*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.*

# A3R Agonists

**Evidence Summary**

Protects tissues against hypoxia and other metabolic stressors. Likely offers clinical benefits for inflammatory and fibrotic diseases and cancer. Clinically tested agonists have a good safety profile.

**Neuroprotective Benefit:** Blood-brain barrier penetrant A3R agonists may protect against metabolic stress-related neurodegeneration by mitigating inflammation and excitotoxicity.

**Aging and related health concerns:** Clinical studies show benefits in diseases characterized by inflammation and fibrosis including arthritis and fatty liver disease. Preclinical studies show cytoprotection during ischemia and mitigation of neuropathic pain.

**Safety:** Clinically tested A3R agonists are well-tolerated and have a good safety profile. Very high doses may elevate heart rate.

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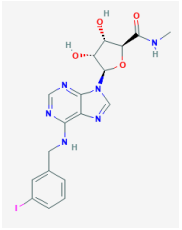
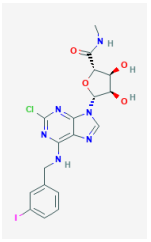
|---|---|---|
| **Availability**: In clinical trials | **Dose**: Not established | CF101 (IB-MECA)<br>**Chemical formula:** $C_{18}H_{19}IN_6O_4$<br>**MW**: 510.3 g/mol<br>  <br>Source: PubChem |
| **Half-life**:<br>CF101 $T_{1/2}$= 9 hours<br>CF102 $T_{1/2}$=12 hours | **BBB**: Varies<br>CF101/CF102 projected to have no/minimal penetrance | |
| **Clinical trials**:<br>CF101: Rheumatoid arthritis (Phase 2 n=79, 253, 254; Phase 3 n=525); Plaque-psoriasis (Phase 2 n=76; Phase 2/3 n=293; Phase 3 n=407); Dry eye (Phase 2 n=80; Phase 3 n=236); Glaucoma (Phase 2 n=89)<br>CF102: Hepatocellular carcinoma (Phase 1/2 n=19, 32; Phase 2 n=78); NAFLD/NASH (Phase 2 n=60) | **Observational studies**: None | CF102 (2-Cl-IB-MECA)<br>**Chemical formula:** $C_{18}H_{18}ClIN_6O_4$<br>**MW:** 544.7 g/mol<br>  <br>Source: PubChem |

**What is it?**

Adenosine is an endogenous purine nucleoside that can modulate a variety of physiological processes. The cellular response to adenosine is dependent on the expression pattern of the adenosine receptor subtypes in a given tissue [1]. The adenosine receptors include A1, A2A, A2B, and A3. The A3 receptor (A3R) is the least well characterized subtype, as it plays a limited role in normal physiological function. The adenosine receptors are G-protein coupled receptors (GPCRs). A3R preferentially couples to Gi to inhibit adenyl cyclase leading to a decrease in cyclic AMP (cAMP) levels, and an inhibition of cAMP-dependent signaling kinases/signaling. However, in some cell types and conditions A3R couples to Gq to stimulate the kinase phospholipase C (PLC), and increase levels of intracellular $Ca^{2+}$. Consequently, the effects of A3R activation are cell-type and context dependent. The expression pattern and dynamics of

A3R is species dependent, thus any studies assessing receptor function in animal models need to be confirmed in human tissue.

A3R is widely expressed, but at a low level under basal conditions, and has a much lower affinity for adenosine than the other receptor subtypes. The concentration of adenosine in the interstitial fluid is typically in the range of 30-300 nM, and in contrast to the A1 and A2 receptors with low nanomolar range affinity, A3R typically has micromolar range affinity for adenosine [2]. Therefore, **A3R function is most relevant under conditions that stimulate adenosine release, such as metabolic stress** [1]. A variety of A3R agonists have been developed with nanomolar affinity to the receptor. These agonists tend to exhibit bell-shaped dose response curves because at high doses they can activate multiple adenosine receptors, which may have counteracting effects. Several A3R agonists have been developed, however, only two have been tested in clinical trials thus far. A3R agonists are in clinical development for inflammatory autoimmune diseases (rheumatoid arthritis and plaque psoriasis), glaucoma, hepatocellular carcinoma with liver cirrhosis, and non-alcoholic fatty liver disease [3].

The two clinically tested A3R agonists have been developed by the Israeli biopharmaceutical company, Can-Fite Biopharma.
CF101, which is also called Piclidenoson, is an orally bioavailable formulation of the A3R agonist IB-MECA, which shows approximately 50X selectivity for A3R relative to the A1 and A2 receptors. It has been tested in clinical trials for dry eye, glaucoma, rheumatoid arthritis, and plaque-psoriasis. Phase 3 RCTs are currently underway for the latter two indications.
CF102, which is also called Namodenoson, is an orally bioavailable formulation of the A3R agonist 2-Cl-IB-MECA, which has approximately 2500X and 1400X selectivity for A3R relative to the A1 and A2A receptors, respectively. It has been tested in clinical trials for hepatocellular carcinoma with underlying liver cirrhosis, and non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis.

FM101 is a biased A3R agonist, which acts as an agonist toward G-protein mediated signaling, but acts as an antagonist toward β-arrestin mediated signaling. It is being developed by the South Korean company, Futuremedicine Co. for glaucoma and non-alcoholic steatohepatitis.

**Neuroprotective Benefit:** Blood-brain barrier penetrant A3R agonists may protect against metabolic stress-related neurodegeneration by mitigating inflammation and excitotoxicity.

*Types of evidence:*

- Several 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)
Studies from Alzheimer's disease (AD) patients and animal models suggest that adenosine signaling is disrupted in the context of AD. The analysis of hippocampal postmortem tissue indicates a decrease in levels of adenosine receptor A1 and an increase in A2AR, but little is known about A3R in AD patients [4]. While there is currently no conclusive evidence indicating whether A3R expression or function is altered in the brain in patients with AD, evidence from AD animal models and human data from other conditions suggest that modulation of A3R signaling may be beneficial for AD. It will be necessary to determine whether there is a particular subset of AD patients who would preferentially benefit from A3R modulation, such as those with high brain inflammation or hypometabolism.

The A3R agonist IB-MECA (0.1 mg/kg i.p.) was shown to reduce scopolamine-induced memory impairment on a passive avoidance task in mice when administered immediately after scopolamine [5]. Similarly, the A3R agonist 2-Cl-IB-MECA (200 µg/kg i.p.) protected against streptozotocin-induced memory deficits on object recognition, water maze, and passive avoidance tasks in mice [6]. Conversely, a cell culture study found that use of the A3R agonist 2-Cl-IB-MECA promoted the neuronal internalization of LDL-cholesterol and an associated production of Aβ [7].
However, caution is warranted when interpreting and extrapolating these studies because the tissue profile of expression for A3R varies across species, and the expression is sensitive to environmental conditions [8]. Consequently, the results from *in vitro* cell culture studies are not always consistent with those from *in vivo* animal model studies, and in some cases have been contradictory [9]. This is because

the downstream effects of A3R engagement depend on the level of A3R expression, as well as the presence and engagement of other adenosine receptors in a given cell or tissue type [1].

A3R agonists have been shown to be neuroprotective with respect to several interrelated aspects of pathophysiology that may be relevant for AD.

***Ischemia:*** The function and regulation of **A3R is best understood for its cytoprotective role under the metabolically unfavorable condition of hypoxia** (see Aging section) [1]. A3R is normally expressed at a low level in the brain, but expression has been shown to be upregulated in the context of inflammation and hypoxia in numerous preclinical studies [10; 11; 12; 13; 14]. The loss of A3R exacerbates ischemic injury, whereas treatment with A3R agonists is associated with a reduction in inflammation, neuronal loss, and neurological impairment. The protective effect is thought to be mediated by reducing inflammation and excitotoxicity (see below).
One study in the APP23tg AD mouse model found that A3R was upregulated in the hippocampus of pre-symptomatic mice [15]. Since A3R increases under metabolically unfavorable conditions, it suggests that the brain has already adapted to a state of impaired energy metabolism (i.e. oxidative phosphorylation) in the pre-symptomatic phase, thus this upregulation could be a potential marker of future cognitive decline. When facing a hypoxic challenge these AD mice were unable to further upregulate this neuroprotective program. This adaptation, then, reduces the capacity of the brain to protect itself against additional metabolic/hypoxic insults, leading to an exacerbation of neurodegeneration.
However, the use of A3R agonists in other indications, such as arthritis and cancer, has shown that the upregulation of A3R is critical to the therapeutic response of the agonists, suggesting that AD patients with elevated A3R expression may also be more likely to benefit from A3R agonists [3]. In this context, the agonists could potentially restore the neuroprotection associated with elevated A3R signaling.

***Inflammation:*** A3R is overexpressed in the context of inflammation, and has been shown to be involved in both pro- and anti-inflammatory responses, depending on the cell type and environmental conditions [3]. However, in the majority of *in vivo* studies, **A3R agonism is associated with anti-inflammatory responses**. A3R is expressed in nearly all immune cells, where it mediates the role of adenosine in inflammation. Extracellular adenosine is released through the breakdown of ATP, and increases in the context of metabolic stress, which typically serves to limit cellular damage [1]. Inflammatory cytokines modulate A3R expression in an autocrine manner, such that increased levels of the cytokines leads to an upregulation of A3R, then activation of A3R by its endogenous agonist adenosine limits further inflammation via the inhibition of NF-kB and TNFα, thereby creating a feedback loop [16]. A3R activation

also modulates the behavior of immune cells, particularly with respect to chemotaxis and migration [17]. For example, in rats subject to brain ischemic injury, treatment with the A3R agonist LJ529 (1 or 2 mg/kg i.p.) prevented the infiltration of immune cells by inhibiting the microglial chemotaxic response to the chemokine MCP-1 (CCL2) [11].

***Excitotoxicity:*** Adenosine plays a role in regulating neuronal excitability [8]. This is best understood via A1R mediated depression of excitability; however, recent work suggests that A3R may play a similar role in a context-dependent manner. A3R signaling may protect against excitotoxicity-related neuronal loss following metabolic stress. A study in rats suggest that differential expression of A3R may underlie the differential vulnerability to ischemic damage in different regions of the hippocampus [12]. Hippocampal CA1 pyramidal neurons are highly susceptible to damage, whereas CA3 pyramidal neurons are less vulnerable. A3R mediated signaling facilitated neuroprotective synaptic plasticity leading to a decrease in glutamatergic neurotransmission following metabolic stress (ischemia) in CA3 neurons, but this neuroprotective upregulation of A3R did not occur in CA1 neurons. This suggests that vulnerable brain regions may be protected from neurodegeneration by boosting A3R signaling.

*APOE4 interactions*:

It is not known whether the efficacy for A3R agonists would vary based on ApoE4 status, however, various studies have shown that E4 carriers have a higher degree of metabolic disturbances in the brain, and an associated increase in hyperexcitability even prior to the onset of AD pathology [18]. Since these are conditions that typically trigger the upregulation of A3R and associated cytoprotective responses, it suggests that the endogenous adenosine-A3R system may be dysregulated, such that E4 carriers may preferentially benefit from treatment with A3R agonists.

**Aging and related health concerns:** Clinical studies show benefits in diseases characterized by inflammation and fibrosis including arthritis and fatty liver disease. Preclinical studies show cytoprotection during ischemia and mitigation of neuropathic pain.

*Types of evidence:*

- 8 clinical trials (RCTs for CF101 in rheumatoid arthritis, dry eye, glaucoma; RCTs for CF102 in hepatocellular carcinoma and NAFLD/NASH)
- Numerous laboratory studies

A3R has been found to be overexpressed in a variety of inflammatory autoimmune disorders and cancer. A3R agonists have been shown to **have benefits in numerous preclinical models of inflammatory diseases**, and have shown evidence for therapeutic benefit in clinical trials for rheumatoid arthritis, psoriasis, liver cancer, and liver disease [3].

**Rheumatoid Arthritis:** POTENTIAL BENEFIT
The A3R agonist CF101 (an oral formulation of IB-MECA also known as Piclidenoson) has been tested in Phase 2 clinical trials for active rheumatoid arthritis, in which it showed efficacy as a monotherapy, but not when used in combination with methotrexate (NCT00280917, NCT00556894) [19]. The discrepancy relates to the dependence on A3R overexpression for clinical efficacy. In a non-placebo-controlled Phase 2 trial (NCT01034306) (n=74) when used as a monotherapy at a dose of 1 mg BID, 55.6%, 33.3%, and 11.5% of the CF101 treated patients achieved at least 20%, 50%, and 70% improvement, respectively, on the American College of Rheumatology (ACR) joint scores [20]. There were significant correlations between the baseline A3R expression level and the ACR50% and ACR70% responses, such that those with the highest baseline levels had the best responses to CF101. Chronic methotrexate use was found to reduce A3R expression levels, which is thought to account for the lack of therapeutic benefit of A3R agonists in this pretreated population [19]. Can-Fite, the biopharmaceutical company developing CF101 has also developed an A3R predictive biomarker kit to identify patients with high A3R who are most likely to respond to the drug (Press Release). CF101 is currently being tested in a Phase 3 RCT for rheumatoid arthritis.

**Osteoarthritis**: POTENTIAL BENEFIT (Preclinical)
Synoviocytes are fibroblast-like cells that produce synovial fluid in joints. In the context of joint diseases, such as arthritis, these cells proliferate and take on an altered phenotype involving the production of pro-inflammatory mediators which promote the destruction of cartilage in the joint. A study of synoviocytes from patients with osteoarthritis (n=35) found that adenosine receptors, particularly A2AR and A3R, are expressed and involved in mediating the inflammatory response in these cells by inhibiting p38 MAPK and NF-κB pathways [21]. Treatment of the human synoviocytes with A3R agonists reduced their production of pro-inflammatory cytokines (TNFα, IL-8), suggesting that the agonists may exert protective anti-inflammatory activity in the context of osteoarthritis.
In a rat model of osteoarthritis (monosodium iodoacetate induced), CF101 treatment (100 µg/kg oral 2x/day) starting upon disease onset prevented cartilage damage, osteoclast formation, and bone destruction [22]. CF101 inhibited NF-kB mediated inflammatory signaling, reduced the production of

inflammatory cytokines (TNFα), reduced the infiltration of lymphocytes, and promoted the apoptosis of inflammatory immune cells within the joint.
A Phase 2 RCT for CF101 in osteoarthritis was registered (NCT00837291), but subsequently withdrawn by the sponsor. Can-Fite announced that they have been granted a patent for the use of CF101 for the treatment of osteoarthritis in mammals, and appears to be interested in developing it for veterinary use (Press Release). It is unclear whether they will re-initiate clinical development for this indication in humans.

**Cancer**: POTENTIAL BENEFIT (Preclinical)
*In vitro* studies have been mixed as to whether A3R agonists or antagonists are more effective at inhibiting cancer cell proliferation, however, *in vivo* models overwhelmingly support the therapeutic efficacy for A3R agonists in cancer [3]. **A3R is highly expressed in solid tumors**, and A3R expression on neutrophils and lymphocytes in the blood has been shown to reflect receptor status in the tumors [23]. The hypoxic conditions of the tumor drive the production of adenosine and alters the expression of the adenosine receptors. This process promotes immune suppression and thus fosters tumor growth. In preclinical animal models, A3R agonists have been shown to inhibit tumor growth, inhibit tumor metastasis, and potentiate the anti-cancer effects of chemotherapeutics. The beneficial effects stem from the ability of the A3R agonists to induce different effects on cancer cells and the immune system. In cancer cells, the signaling pathway triggered by A3R activation involves coupling through Gi, which lowers levels of cAMP, and thus inhibits kinase signaling pathways dependent on cAMP such as PKA/PKB/AKT. This ultimately leads to the downregulation of the Wnt/β-catenin signaling pathways that drive tumor growth. Meanwhile, within the context of the cancer environment, A3R agonists activate the ability of the immune system to seek out and destroy cancer cells. Thus far, A3R agonists have only been clinically tested in the context of hepatocellular carcinoma (see below), but preclinical studies suggest they may also be useful for other tumor types characterized by high expression of A3R.

**Hepatocellular Carcinoma**: POTENTIAL BENEFIT
A3R has been shown to be overexpressed in both tumor tissue and peripheral blood mononuclear cells (PBMCs)(increased by 78% relative to healthy controls) in patients with hepatocellular carcinoma [24]. The expression level of A3R was correlated with levels of NF-kB, a transcription factor associated with pro-inflammatory signaling, which regulates A3R expression as part of a homeostatic feedback loop. CF102 (an oral formulation of 2-Cl-IB-MECA also known as Namodenoson) has been tested in hepatocellular carcinoma patients in Phase 1/2 (NCT00790218, NCT00790673) and Phase 2 (NCT02128958) clinical trials. In the Phase 1/2 open-label study (NCT00790218) (n=18), mean overall

survival of patients treated with CF102 (1, 5, or 25 mg orally BID in 28-day cycles) was 7.8 months [25]. Four patients had disease stabilization and one had regression of tumor metastases. A3R expression was predictive of therapeutic response, as there was a correlation between baseline A3R expression and overall survival following CF102 treatment during this study. A Phase 2 placebo-controlled RCT (n=78) testing CF102 (25 mg BID oral) as a 2nd line therapy in patients with advanced hepatocellular carcinoma and Child-Pugh B (CPB) liver cirrhosis failed to meet its primary endpoint of improved overall survival (median survival 4.1 months vs placebo 4.3 months), but showed a non-statistically significant increase in median survival (6.9 months vs 4.3 months) a significant increase in the 12 month survival rate (44% vs 18%) in the pre-specified subgroup of patients with CPB score 7 (CPB7) [26]. Based on these results, the FDA has approved Can-Fite's Phase 3 study design for this indication, and CF102 is available for patients in Israel as part of a compassionate use program (Press Release).
In preclinical models, CF102 has been shown to inhibit tumor cell growth through de-regulation of the PI3K-NF-kB and Wnt/β-catenin signaling pathways. De-regulation of PI3K-NF-kB is associated with the increased expression of pro-apoptotic proteins in cancer cells, while deregulation of Wnt decreased the expression/activity of proteins involved in cell proliferation, such as β-catenin, LEF/TCF, c-myc, and cyclin D [24; 27].

**NAFLD/NASH**: POTENTIAL BENEFIT
Non-alcoholic steatohepatitis (NASH) is an advanced form of non-alcoholic fatty liver disease (NAFLD), which involves a buildup of fat in the liver leading to inflammatory damage. Liver fibrosis is associated with canonical Wnt/β-catenin signaling.
CF102 (12.5 or 25 mg BID for 12 weeks) has been tested in an exploratory Phase 2 RCT for NAFLD/NASH (n=60) (NCT02927314). Topline results indicate that CF102 treatment reduced elevated liver enzymes in a dose-related manner, with 36.8% of patients achieving alanine aminotransferase (ALT) normalization in the 25 mg dose, and 23.8% in the 12.5 mg group, compared with 10% in the placebo (Press Release). Treatment was also associated with an increase in the anti-inflammatory/anti-fibrotic cytokine, adiponectin, and a trend toward decreased liver fat and fibrosis.
In mouse models of NAFLD and NASH, CF102 treatment (100 or 200 µg/kg i.p.) showed anti-inflammatory and anti-steatotic effects [28]. Consistent with the clinical study, treatment normalized ALT levels and improved adiponectin and leptin levels. Anti-inflammatory and anti-fibrotic effects were attributed to the de-regulation of the Wnt/β-catenin pathway in the liver, leading to a reduction in inflammatory NF-kB signaling and α-SMA-associated fibrosis.

The biased A3R agonist, FM101 (30 or 60 mg/kg/day), which has agonist activity toward Gi-mediated modulation (inhibition) of adenyl cyclase and cAMP, as well as antagonistic activity toward β-arrestin signaling, was also shown to inhibit steatofibrosis in a high-fat diet induced mouse model of NASH [29]. Treatment mitigated the elevation in liver enzymes and accumulation of fat within the liver, while enhancing mitophagic turnover of damaged mitochondria.

**Neuropathic pain**: POTENTIAL BENEFIT (Preclinical)
Adenosine is involved in pain processing in the CNS by regulating neuronal excitability, neural signaling, and glial activation. A3R activation does not alter nociceptive thresholds, thus in preclinical models **A3R agonists inhibited pathological but not protective nociceptive responses** [30]. A3R agonists have been shown to inhibit mechanical allodynia and hyperalgesia in the context of neuropathic pain. Notably, A3R agonists are projected to lack the abuse potential of opioid-based pain medications because their therapeutic effects are not dependent on the endogenous opioid or endocannabinoid pathways [31]. A3R agonists have been shown to inhibit spinal nociception by decreasing the excitability of dynamic wide range neurons and activating serotoninergic and noradrenergic circuits [31]. In the context of chemotherapy induced peripheral neuropathy, A3R agonists have been shown to modulate spinal neuroinflammatory processes by attenuating astrocyte hyperactivation, reducing the production of pro-inflammatory mediators (TNFα, IL-1β), and increasing the production of anti-inflammatory mediators (IL-10, IL-4) [32; 33]. A3R agonists also modulate neurotransmission by inhibiting redox-mediated posttranslational tyrosine nitration and inactivation of glial proteins involved in synaptic glutamate homeostasis [33]. These studies generally involve treatment prior to or concurrent with the therapeutic agent, in which they mitigate the establishment of neuropathic pain. Based on preclinical studies suggesting that A3R agonists may augment the anti-cancer activity of chemotherapeutic agents, they may be particularly suited to use as adjuncts to chemotherapy, where they may have both anti-cancer and anti-neuropathy effects [30].

**Ischemia**: POTENTIAL BENEFIT (Preclinical)
The adenosine-A3R system has been shown to be cytoprotective in the context of ischemic-reperfusion injuries in a variety of organ systems, including the brain, heart, lung, and liver [11; 34; 35; 36]. A3R upregulation is associated with the protective effects of ischemic preconditioning, but it has also been found to exert protective benefits when administered during reperfusion, which is more relevant to clinical application [1]. Activation of A3R in the context of ischemia is associated with a reduction in cell loss within the ischemic tissue as well as reduced infiltration of pro-inflammatory mediator producing immune cell subsets.

**Cardiovascular:** POTENTIAL BENEFIT DURING ISCHEMIA (Preclinical)
A3R has low expression on cardiac tissue, but numerous preclinical studies indicate that A3R activation has cardioprotective effects [37], suggesting that its expression and function may be context dependent, and only contribute to cardiovascular function in a clinically meaningful manner during trauma. The low expression and apparent minimal function in the heart under basal conditions potentially improves the therapeutic profile of A3R agonists relative to A1R and A2R modulators by reducing the risk for cardiovascular side effects [30]. A3R activation is protective in the context of cardiac ischemia by regulating protein kinase C (PKC) activity and mitochondrial K(ATP) channels [37]. Rodent models suggest that A3R does not significantly contribute to atherogenesis or blood pressure regulation, though it is not known whether these findings are species specific or similar in humans. A3R is upregulated on neutrophils in the context of hemorrhagic shock, and the degree of upregulation was found to be correlated with the severity of injury in trauma patients [38]. It is not clear if this is part of a protective adaptive response. In a rodent study, hemorrhagic shock resulted in a decrease in A3R expression on vascular cells, which was associated with a loss of vasoreactivity [39]. Treatment with an A3R agonist (IB-MECA), partially restored vascular reactivity in this model.

**Colitis**: POTENTIAL BENEFIT (Preclinical)
A3R expression was found to be decreased on epithelial cells in the colon in patients with ulcerative colitis and in a mouse model of DSS-induced colitis [40; 41]. In ulcerative colitis patients (n=18), the decrease in A3R was associated with an upregulation of inflammatory mediators, TNFα, IL-1β, and NF-kB [40]. Treatment of cultured colon tissue from these patients with the A3R agonist 2-Cl-IB-MECA significantly reduced the production of these pro-inflammatory mediators. In the colitis mouse model, 2-Cl-IB-MECA reduced damage to the colonic mucosa and reduced levels of the same set of pro-inflammatory mediators as was seen in the patient tissue [41]. Additionally, A3R agonist treatment reduced the infiltration of neutrophils and levels of myeloperoxidase (MPO) [17; 41].

**Ocular disease:** MARGINAL POTENTIAL BENEFIT
The preclinical literature has been mixed as to whether A3R agonists or A3R antagonists are more beneficial for ocular diseases, however the discrepancies are likely related to the context dependent nature of adenosine signaling, such that the effects of A3R activation may differ based on the experimental conditions [1; 42]. Early clinical trials of the A3R agonist CF101 suggested possible benefits for several ocular diseases, but subsequent trials failed to show clinical efficacy.

Glaucoma

Preclinical studies have been mixed as to whether A3R agonists are protective against optic nerve degeneration, but suggest the effects may be cell type dependent. The A3R agonist 2-Cl-IB-MECA exacerbated oligodendrocyte cell death and myelin loss in rat oligodendrocyte cell culture, but protected against retinal ganglion cell death when administered intravitreally in rat models of retinal ischemic injury and optic nerve injury. Increased intraocular pressure (IOP) is one of the major risk factors for glaucoma. It was noted in a Phase 2 RCT for dry eye that treatment with 1 mg CF101 BID for 12 weeks decreased IOP by 1.1 mmHg, which was a significant reduction relative to placebo [43]. However, oral CF101 failed to significantly reduce IOP in a Phase 2 RCT (NCT01033422) in patients with ocular hypertension or glaucoma [3]. Since preclinical and clinical studies used different routes of administration, it is unclear if the pleiotropic effects of systemic A3R agonism impact its efficacy in ocular disease, and whether targeted topical or intravitreal formulations of CF102 would offer higher therapeutic benefit.

Preclinical studies suggest that the biased A3R agonist, FM101, may be a more effective option for lowering IOP [44]. Topical formulations (500 and 750 uM) of FM101 lowered IOP in rabbits and in the DBA/2J glaucoma mouse model [45]. Systemic administration of FM101 (oral 10 or 20 mg/kg) also lowered IOP to a similar extent in a glucocorticoid-induced glaucoma mice model. The reduction to IOP was associated with the remodeling of the trabecular meshwork in a manner to increases outflow of fluid in the eye (aqueous humor).

Dry Eye

CF101 (oral 1mg BID for 12 weeks) significantly improved clinical symptoms of dry eye, including the proportion of patients with more than 25% improvement in corneal staining (CF101 84.6% vs placebo 52.2%), and an improvement in tear meniscus height, in a Phase 2 RCT (n=68) (NCT00349466) [43]. However, the Phase 3 RCT (NCT01235234) testing CF101 for dry eye did not meet its primary endpoint, and clinical development has been discontinued for this indication.

Uveitis

Uveitis is an inflammatory eye condition which can result in blindness. In a mouse model of autoimmune IRPB-induced uveitis, CF101 (10 µg/kg, 2x/day oral) improved pathological manifestations of uveitis such as the infiltration of immune cells, retinal folds and focal retinal detachments [46]. Treatment was associated with anti-inflammatory effects including, the inhibition of pro-inflammatory cytokines IL-2, TNFα, and IFNγ, along with the upregulation of the anti-inflammatory cytokine IL-10. A clinical trial

testing CF101 for uveitis was registered (NCT01905124), but was subsequently withdrawn by the sponsor.

**Safety:** Clinically tested A3R agonists are well-tolerated and have a good safety profile. Very high doses may elevate heart rate.

*Types of evidence:*

- 11 clinical trials (7 clinical trials for CF101, 4 clinical trials for CF102)
- Numerous laboratory studies

Since A3R expression is generally low at basal levels, and tends to only increase in the context of trauma, such as metabolic stress, the therapeutic safety profile of A3R modulators is expected to be superior to other modulators of adenosine signaling [3]. Preclinical and clinical safety studies provide further evidence of a good safety profile for A3R agonists.

The A3R agonists CF101 and CF102 have been shown to be **well-tolerated and have a good safety profile** in patients with rheumatoid arthritis, plaque psoriasis, dry eye, glaucoma, hepatocellular carcinoma, and NAFLD/NASH, as well as in healthy volunteers. The pharmacokinetics were linear, proportional to dose [47]. Can-Fite's annual Drug Safety Update Report for 2020, demonstrates favorable safety profiles for CF101 and CF102, based on clinical testing in over 1,500 patients (Press Release).

In a Phase 1 ascending dose study in healthy men (n=43) for CF101, single oral doses up to 5 mg and multiple doses up to 4 mg were safe and well-tolerated [47]. Single oral doses of 10 mg were associated with flushing, tachycardia, nausea and vomiting, while multiple doses of 5 mg were associated with headache, drowsiness, hot flushes and dizziness. Aside from elevated heart rate at the highest dose, there was no other evidence of adverse cardiac events, based on electrocardiogram (ECG) monitoring.

In reported Phase 2 and Phase 3 RCTs, the incidence of adverse events was typically similar to placebo. At the 4 mg dose of CF101, three rheumatoid arthritis patients discontinued treatment due to adverse events, including headache/nausea, atrial tachycardia, and an exacerbation of Parkinson's disease [20]. In RCTs testing the 1 to 2 mg dose range, adverse events were mild, and included headache, nausea, and rash [20; 43; 48; 49].

In a Phase 1/2 trial testing CF102 at oral doses up to 25 mg BID in hepatocellular carcinoma, there were no serious drug-related adverse events or dose related toxicities [25]. In a Phase 2 RCT in the same population, treatment related adverse events were primarily grade 1 or 2 for gastrointestinal events or

reductions in blood cell counts [26]. One grade 3 adverse event was reported for hyponatremia. No drug-related serious adverse effects or hepatotoxicity were reported in topline results for the Phase 2 RCT of CF102 in NAFLD/NASH.

The biased A3R agonist FM101 has been tested in acute and sub-chronic toxicology studies in rats and dogs [44; 45]. Abnormal posture, irregular respiration, decreased movement, loose stools, and ear flushing were observed during the early phase of dosing in rats that received 500 and 1000 mg/kg/day (orally). No adverse effects were observed related to ophthalmology, clinical chemistry, urine, organ weight, and histopathology [44]. The no evidence of adverse events level (NOAEL) was determined to be 1000 mg/kg/day in rats.

**Sources and dosing:**

CF101 (Piclidenoson) and CF102 (Namodenoson) are being developed by Can-Fite BioPharma for rheumatoid arthritis/plaque psoriasis and hepatocellular carcinoma/NASH, respectively, and are currently being tested in RCTs. CF102 is available in Israel for patients with advanced liver cancer as part of a compassionate use program. The derivative compounds IB-MECA (CF101) and 2-Cl-IB-MECA (CF102) are available for research use from commercial suppliers. A therapeutic dose has not yet been established, but CF101 has shown to have a good safety profile at an oral dose of 1 or 2 mg BID, and is currently being tested at oral doses ranging from 1 to 3 mg BID in Phase 3 RCTs. CF102 has been safely tested at oral doses up to 25 mg BID. FM101 is being developed by Futuremedicine Co. for glaucoma and NASH, and is currently being tested in a Phase 1 trial in healthy volunteers.

**Research underway:**

CF101 is currently being tested in the Phase 3 Comfort™ study for moderate to severe plaque-psoriasis (NCT03168256), which has an expected completion date in 2021.

CF101 is currently being tested in the Phase 3 ACRobat™ trial for active rheumatoid arthritis (NCT02647762), which has an expected completion date in late 2020.

Can-Fite has recently registered a trial for the use of CF101 in patients with Covid-19 (NCT04333472). Due to its anti-inflammatory activity, A3R agonists have been proposed to be good candidates for

immunotherapy associated cytokine release syndrome [50], and thus may be beneficial for patients with Covid-19 to prevent the induction of a cytokine storm.

FM101 is being tested in a Phase 1 trial in healthy volunteers (NCT03879928).

**Search terms:**

Pubmed, Google: A3R, CF101, CF102, IB-MECA, 2-Cl-IB-MECA

- Alzheimer's diease, neurodegeneration, ischemia, inflammation, cancer, arthritis, cardiovascular, neuropathy, glacuoma, clinical trial, safety

Websites visited for A3R agonists:

- Clinicaltrials.gov (CF101, CF102, FM101)
- PubChem (CF101, CF102)
- DrugBank.ca (CF101, CF102)
- Cafepharma (CF101, CF102)

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