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.

P021

Evidence Summary

Studies in 3xTg-AD mice suggest that chronic treatment with P021 restores cognitive function, increases neurogenesis and synaptic markers, and reduces Aβ and tau. No studies have tested P021 in humans yet.

Neuroprotective Benefit: Chronic treatment with P021 in a mouse model of Alzheimer's disease restores cognitive function, increases neurogenesis, BDNF, and synaptic markers, and reduces phosphorylated tau and soluble Aβ.

Aging and related health concerns: P021 appears to prevent pathologies of age-related macular degeneration and decrease mortality in a mouse model of Alzheimer's disease. In rodents, P021 does not have anorectic effects and may increase body weight.

Safety: Safety in humans has not been assessed. Numerous studies in rodents have shown that P021 treatment for up to 18 months does not result in weight loss, tumors, or signs of pain seen with treatment with the full-length CNTF.

Availability: not available; in clinical development	**Dose**: Dose has not been established. In mouse studies, 60 nM per gram of feed was typically used.	**Chemical formula:** Ac-DGGL^{A}G-NH2 **MW**: 578.3
Company: Phanes Biotech		
Half life: plasma half-life of over 3 hours in mice	**BBB**: penetrant in rats/mice	
Clinical trials: none	**Observational studies**: none	

What is it? P021 is a tetra-peptide (Ac-DGGL^{A}G-NH2) derived from the biologically active region of the human ciliary neurotrophic factor (CNTF; amino acid residues 148–151) (Li et al., 2010). P021 has an adamantylated glycine added at the C-terminal to increase its lipophilicity and blood-brain permeability while decreasing its degradation by exopeptidases. P021 is under clinical development by Phanes Biotech (PA, USA) as a disease-modifying drug for Alzheimer's disease and other neurodegenerative diseases.

P021 competitively inhibits the leukemia inhibitory factor (LIF) signaling, which inhibits the formation of neural progenitor cells from stem cells. P021 also increases expression of the neurotrophic factor BDNF, promoting neurogenesis.

CNTF is a member of the IL-6 family of cytokines. CNTF has pleiotropic effects and is a pluripotent neurotrophic factor that drives the development and maintenance of the nervous system, promoting neuronal survival and differentiation (Pasquin et al., 2015). CNTF plays an important role in adult hippocampal and subventricular zone neurogenesis, and the differentiation of neural stem cells (Kazim and Iqbal, 2016). CNTF also exerts myotrophic activities, modulates osteoblast function, promotes oligodendrocyte maturation and survival, and has potent effects on retinal cells and adipocytes (Pasquin et al., 2015). CNTF signaling occurs through a tripartite complex of CNTF receptor α (CNTFRα), LIF β receptor (LIFR), and gp130. There are three main signaling pathways activated by CNTF: the JAK/STAT3, MAPK, and Akt pathways (Pasquin et al., 2015). CNTF activation of STAT3 induces the transcription of specific target sequence responsible for CNTF's neuroprotective properties, neurite outgrowth, and neuronal migration. CNTF-induced PI3K/Akt pathway is important in survival and neurite growth of neuroblastoma cells (Wang et al., 2014) and responsible for CNTF's effects on skeletal muscle glucose uptake (Steinberg et al., 2009). CNTF activation of MAPK-ERK1/2 pathway may play an important role in neuronal survival, based on a study in hypothalamic cultures (Askvig and Watt, 2015).

Overall, CNTF's neuroprotective effects are well established and administration of CNTF in preclinical models have alleviated cognitive impairment, increased neurogenesis, and stabilized synaptic protein levels. The administration of the full-length human recombinant CNTF protein in clinical trials has been hindered by poor blood-brain barrier permeability, short half-life (2.9 minutes), poor plasma stability, and adverse effects; a clinical trial in amyotrophic lateral sclerosis patients reported significant adverse events including anorexia, skeletal muscle loss, hyperalgesia, severe cramps, and muscle pain (ALS CNTF Treatment Study Group, 1996). Side effects of CNTF treatments are thought to be linked to their ability to activate the alternative IL6Rα-LIFRβ-gp130 receptor.

Neuroprotective Benefit: Chronic treatment with P021 in a mouse model of Alzheimer's disease restores cognitive function, increases neurogenesis, BDNF, and synaptic markers, and reduces phosphorylated tau and soluble Aβ.

Types of evidence:

- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function: None available.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
The neuroprotective properties of P021 have been extensively evaluated in rodent models of Alzheimer's disease, normal aging, and Down syndrome. Many of these studies used very long-term treatments, some of which were started *in utero*.

Alzheimer's models: Several studies have examined the neuroprotective properties of P021 in a mouse model of Alzheimer's, the 3xTg-AD mice. One study examined P021 treatment initiated at 9-10 months of age, after amyloid pathology, but before tau pathology had emerged (Kazim et al., 2014). Two studies examined P021 treatment started at 3 months of age (before any pathology) and continued for 18 months (Baazaoui and Iqbal, 2017; Baazaoui and Iqbal, 2017). And the most recent study examined P021 treatment initiated *in utero* and continued until postnatal day 21 (Wei et al., 2020).

Treatment started at 9-10 months of age: In female Alzheimer's mice (3xTg-AD mice), P021 treatment (60 nmol/g feed) started at 9-10 months of age and continued for 6-12 months significantly reduced levels of phosphorylated tau while rescuing deficits in cognitive function, neurogenesis, and synaptic plasticity (Kazim et al., 2014). In 3xTg-AD mice, tau pathology occurs at around 12 months; therefore, the P021 treatment was initiated before this pathology occurred. Decreased levels of phosphorylated tau (labeled with AT8, PHF1, and 12E8) were observed after 6 months of treatment (15-16 months of age) and after 12 months of treatment (21-22 months of age) when compared to the vehicle-treated group. P021 treatment did not alter the levels of total tau.

Amyloid pathology was evaluated in the same study (Kazim et al., 2014). In 3xTg-AD mice, intraneuronal Aβ first appears in neocortical regions at 3-4 months of age and subsequently in CA1 pyramidal neurons by 6 months. P021 treatment for 6 months started at 9-10 months of age resulted in a significant reduction in soluble Aβ40 and Aβ42 in 15-16-month-old 3xTg-AD mice, but this treatment effect was not seen after 12 months of treatment in 21-22-month-old mice. No effects of P021 treatment (6 or 12 months) were seen for insoluble (aggregated) Aβ40 and Aβ42.

BDNF expression was also evaluated (Kazim et al., 2014). BDNF expression was decreased in 3xTg-AD mice at 15-16 and 21-22 months of age, but 6 or 12 months of P021 treatment started at 9 months of age, significantly increased BDNF levels. P021 treatment also significantly increased Ser9 phosphorylated-GSK3β (the inactive form of an enzyme that phosphorylates tau) in 3xTg-AD mice both in 15–16-month-old and 21–22-month-old animals. The effect of P021 on tau pathology was likely due to increased BDNF expression, leading to activation of TrkB-PI3K-Akt signaling pathway that induces an inhibition of GSK-3β activity via phosphorylation at Ser9 by Akt (Kazim and Iqbal, 2016).

P021 treatment (60 nmol/g feed) started at 9-10 months of age and continued for 6-12 months also increased neurogenesis in 15-16-month-old and 21-22-month-old 3xTg-AD mice (Kazim et al., 2014). P021 treatment significantly increased (and rescued) the number of Ki-67+ cells and DCX+ cells in the dentate gyrus of the hippocampus compared to vehicle treated 3xTg-AD mice. The data showed that the markedly impaired neurogenesis in 3xTg-AD mice was rescued to the level of wild-type control mice.

P021 treatment (60 nmol/g feed) in 3xTg-AD mice started at 9-10 months of age and continued for 6 months also significantly restored synaptic markers (Kazim et al., 2014). P021 treatment restored levels of MAP2 and synaptophysin in CA1, CA3, and dentate gyrus regions of the hippocampus, increased GluA1 in the dentate gyrus, and increased GluN1 in the CA1 and CA3. However, P021 treatment did not

restore the deficit in GluA2/3 density in the dentate gyrus in 3xTg-AD mice. Also, Western blot analysis showed that P021 treatment did not alter protein levels of GluN1 or GluA2/3 in 3xTg-AD mice.

P021 treatment also restored cognitive functions in 3xTg-AD mice (Kazim et al., 2014). In the one-trial object recognition task, 3xTg-AD mice treated with P021 (60 nmol/g feed) for 6 months (15-16-month-old) showed a clear preference for the novel object, as measured by % discrimination, which was equivalent to wild-type mice. In the Morris Water Maze test of spatial memory, 3xTg-AD mice needed significantly longer latencies to reach the platform than wild-type control mice and 3xTg-AD mice treated with P021. P021 treatment also showed a trend for a benefit in the probe trial that measures the strength of encoding the spatial information such that 3xTg-AD mice treated with P021 displayed better performance than vehicle-treated mice, though this was not statistically significant.

Treatment started at 3 months of age: Two studies examined P021 treatment started at 3 months of age and continued for 18 months in 3xTg-AD mice (Baazaoui and Iqbal, 2017a; Baazaoui and Iqbal, 2017b). P021 was administered 6-9 months before any overt Aβ or tau pathology, and during the period of synaptic compensation. Chronic P021 treatment was able to rescue dendritic and synaptic deficits, increase neurogenesis, and reverse cognitive impairment in 3xTg-AD mice (Baazaoui and Iqbal, 2017a).

After 9 months of P021 treatment in 3xTg-AD mice, PSD-95 was increased in the CA1, CA3, DG, and parietal cortex, GluN1 was increased in the CA3, but no changes were seen with MAP2 (Baazaoui and Iqbal, 2017a). After 15 months of P021 treatment, MAP2 was increased in CA1, CA3, DG, and parietal cortex, and GluA1 was increased in the CA1. After 18 months of treatment, synaptophysin and MAP2 were increased in the cortex with P021 treatment, but no changes were seen in pCREB/CREB, synapsin 1, or GluA1 in the cortex. After 18 months of treatment, PSD-95, GluA1, and pCREB/CREB were increased in the hippocampus, but not no changes were observed for synaptophysin or GluA2/3.

After 9 months of P021 treatment in 3xTg-AD mice, neurogenesis (DCX^+ and $Ki\text{-}67^+$ cells) was significantly increased by about 4-fold compared to vehicle-treated mice, and ~2-fold higher than wild type mice (Baazaoui and Iqbal, 2017a).

Nine months of P021 treatment started at 3 months of age also significantly reversed cognitive impairment in 3xTg-AD mice (Baazaoui and Iqbal, 2017a). In the Morris water maze task of spatial memory, P021-treated mice took a significantly shorter time (latency to escape) and a shorter distance to the hidden platform than vehicle-treated mice. In the probe trials to evaluate memory retention, P021 treated mice spent a significantly longer time in the target quadrant compared to vehicle-treated

mice. After 15 months of P021 treatment, the novel object location test was administered, and P021-treated mice spent more time exploring the novel location than the familiar one, whereas the vehicle-treated mice spent more time exploring the familiar location.

In a very similar study as above by the same authors, P021 treatment was started at 3 months of age and continued for 18 months in 3xTg-AD mice to evaluate neurodegeneration, Alzheimer's biomarkers, and object recognition (Baazaoui and Iqbal, 2017b). Compared to vehicle-treated 3xTg-AD mice, P021-treated mice showed significantly smaller areas occupied by degenerated neurons (labeled by Fluorojade C) in the CA3, dentate gyrus, parietal, and frontal cortices (comparable to wild-type mice) after 9 months of treatment; in the CA1, CA3, dentate gyrus, and parietal cortex after 15 months of treatment; and in the CA1, CA3, dentate gyrus, and parietal cortex after 18 months of treatment (Baazaoui and Iqbal, 2017b).

After 9 months of P021 treatment, Aβ pathology was prevented in the subiculum region (decreased area occupied by half), but not in the CA1, and a trend toward an effect of P021 on preventing tau pathology was seen in the CA1 but not in the subiculum (Baazaoui and Iqbal, 2017b). After 15 months of treatment, there was a strong effect of P021 on Aβ plaque load in the subiculum, but not in the CA1; P021 treatment for 15 months also significantly reduced tau hyperphosphorylation (AT8 staining and PHF1) in both the CA1 and subiculum. After 18 months of treatment, P021 was able to partly prevent Aβ pathology in the CA1 (by ~20%) and in the subiculum (by ~40%), and reduce tau hyperphosphorylation (AT8 and PHF1 % area occupied, as well as Western blot of PHF1) by about 50%.

In the novel object recognition task, P021 treatment for 16-17 months slightly decreased the impairment seen in 3xTg-AD mice.

Treatment started *in utero*: In 3xTg-AD mice, P021 treatment (60 nmol/g feed) initiated *in utero* (through mother's milk) and continued until postnatal day 21 rescued cognitive deficits at 4 months of age, reduced abnormal hyperphosphorylation and accumulation of tau, and decreased Aβ plaque load at 22 months of age in 3xTg-AD mice (Wei et al., 2020). Prenatal to early postnatal treatment with P021 increased synaptic protein levels of GluN1, GluN2A, GluA1, pCREB/CREB, and PSD95, and decreased protein levels of GFAP when the 3xTg-AD mice were adults. However, no changes with P021 treatment were seen for levels of synapsin, synaptophysin, MAP2, or Iba1.

Aging models: In aged rats (19-21 months old), P021 treatment (289.15 µg/500 nM/10 ml saline/kg body weight) by oral gavage for 88 days reduced levels of total tau in the hippocampus but not in the

cortex (Khatoon et al., 2015). Phosphorylated forms of tau were not evaluated. Furthermore, chronic P021 treatment reduced cerebrospinal fluid (CSF) levels of total tau, but not Aβ/Aβ-protein-precursor (AβPP), to that of the levels found in young adult rats.

In aged rats (22-24-month-old), P021 treatment (500 nM, 289.15 µg/kg body weight per day) by oral gavage for 88 days restored neurogenesis in the hippocampal dentate gyrus, increased expressions of BDNF, TrkB receptor, and pCREB/CREB, and restored synaptic deficits (levels of GluN2A, GluN2B, GluA1, GluA2/3, synaptophysin)(Bolognin et al., 2014). Regional differences were seen with synaptic proteins: in the hippocampus, P021 treatment restored GluN2A levels and slightly increased GluN2B levels but had no effect on GluA1 or GluA2/3. In the cortex, P021 treatment restored levels of GluA1, fully restored levels of GluN2A and GluN2B, and increased levels of GluA2/3 compared to vehicle-treated old rats. However, a magnetic resonance spectroscopy study showed that P021 treatment did not alter levels of neurotransmitter metabolites in the hippocampus (GABA, glutamate, NAA, NAA+NAAG, and glutamine+glutamine). Glucose metabolism was also analyzed using FDG-PET but no effects of P021 were seen in uptake of FDG. Latency to reach the submerged platform on the Morris water maze task was significantly improved in old rats treated with P021, but error bars were overlapping with vehicle-treated old rats and the P021-associated improvement did not approach performance by young rats. Time in quadrant was also improved with P021 in old rats, but also did not reach the performance observed in young rats.

Down syndrome model: In a mouse model of Down syndrome (Ts65Dn mice), P021 treatment (200 nM/g formulated diet) from prenatal gestational day 8 to postnatal day 21 significantly rescued developmental delays in pups and Alzheimer's-like memory impairments when they became adults (Kazim et al., 2017). P021 treatment also prevented the deficit in synaptophysin levels, decreased the activity of GSK3β (enzyme that phosphorylates tau), and increased levels of synaptic plasticity markers including the neurotrophic factor BNDF by two-fold (comparable to that of wild-type vehicle-treated mice), and increased phosphorylated CREB, both in young (3-week-old) and adult (~ 7-month-old) Ts65Dn mice. However, P021 treatment did not affect levels of PSD-95, TrkB, CNTF, or CREB in Ts65Dn mice. Prenatal to early postnatal treatment with P021 also ameliorated long-term memory deficit in adult life in this mouse model. P021 treatment attenuated spatial reference learning and memory deficit (in the Morris water maze task) when they became adults. P021 treatment did not induce any significant changes in body weight, anxiety-like behavior, or activity level in adult Ts65Dn mice. Treatment with P021 in this mouse model rescued the delay in the development of surface righting, cliff aversion, and ear twitch.

Wild-type mice: One of the first preclinical studies with P021 used adult C57Bl6 mice (8-10 months old)(Li et al., 2010). P021 treatment (subcutaneous implants of extended-release depot pellets; 25 nM/day) for 35 days of continuous dosing improved performance on the one-trial object recognition task and the spatial reference memory task compared to vehicle-treated mice. P021 treatment also increased neurogenesis as measured by $BrdU^+$ cells in the granule cell layer and subgranular zone of the dentate gyrus. Significant increases in synaptophysin and synapsin I immunoreactivities were also observed in the dentate gyrus with P021 treatment. In cell culture, P021 treatment inhibited LIF-induced phosphorylation of STAT3 by ~30% (Li et al., 2010).

APOE4 interactions: Unknown.

Aging and related health concerns: P021 appears to prevent pathologies of age-related macular degeneration and decrease mortality in a mouse model of Alzheimer's disease. In rodents, P021 does not have anorectic effects and may increase body weight.

Types of evidence:

- Two laboratory studies

Lifespan: No studies have tested P021 in humans. In female 3xTg-AD mice, P021 treatment (60 nM/g feed) started at 3 months of age and continued until 18 months of age dramatically decreased mortality rate (Baazaoui and Iqbal, 2017). The survival rate of 3xTg-AD mice treated with vehicle at week 71 was significantly less (41%) than the survival rate of 3xTg-AD mice treated with P021 (87%). P021 treatment also decreased the incidence of hindlimb paralysis in 3xTg-AD mice; 5 (out of 34) vehicle-treated 3xTg-AD mice experienced hindlimb paralysis compared to only 1 (out of 32) P021-treated 3xTg-AD mice had hindlimb paralysis.

Age-related macular degeneration: In aged rats and in a mouse model of Alzheimer's (3xTg-AD mice), pathologies of age-related macular degeneration were observed, including photoreceptor degeneration, lipofuscin granules, vacuoles, atrophy in the retinal pigment epithelium, Bruch's membrane thickening, and microgliosis and astrogliosis in different retinal layers (Liu et al., 2019). Treatment with P021 (3xTg-AD mice, 60 nM/g formulated diet; aged rats, 500 nM/kg/day by gavage) for 3 months in old rats and for 18 months in 3xTg-AD mice prevented these pathological changes associated with age-related macular degeneration. One limitation of this study is that rodents do not have a macula/fovea and therefore do

not fully replicate the human degenerative condition. Also, no visual performance or electroretinography measures were obtained.

An intraocular CNTF delivery treatment called NT-501 (Renexus; Neurotech, Lincoln, RI) has been granted orphan drug designation by the FDA for retinitis pigmentosa and macular telangiectasia as well as fast-track designation for retinitis pigmentosa and dry age-related macular degeneration (Pasquin et al., 2015; Emerich and Thanos, 2008).

Obesity/metabolic dysfunction: No studies, preclinical or clinical, have tested P021 for obesity or metabolic dysfunction. In Alzheimer's mice (3xTg-AD mice) and in wild-type mice, P021 treatment (60 nmol/g feed) started at 9-10 months of age and continued for 6 months increased body weight compared to controls, without affecting food consumption (Kazim et al., 2014).

The findings above contrast with the full-length CNTF neuropeptide, which is known to have an anorectic effect; CNTF regulates energy homeostasis and adipocyte metabolism (Pasquin et al., 2016). A recombinant human CNTF derivative (Axokine; Regeneron Pharmaceuticals, Inc.) was tested in a phase II double-blind randomized clinical study in obese patients and a significant weight loss was experienced (Ettinger et al., 2003). Treatment with 1.0 µg/kg of Axokine for 12 weeks resulted in a 4.0 kg weight loss, representing a minimum of 5% change in total body weight for 30% of the patients. However, development of this intervention was halted during the phase III trial where peripheral side effects were seen in addition to the development of neutralizing antibodies (Pasquin et al., 2016). The anorectic effect of CNTF is suggested to be due to a hypothalamic inhibition of the neuropeptide Y (Pasquin et al., 2015;. In animal models, long-term anorectic effects of CNTF appear to be the result of neurogenesis in the hypothalamus.

Safety: Safety in humans has not been assessed. Numerous studies in rodents have shown that P021 treatment for up to 18 months does not result in weight loss, tumors, or signs of pain seen with treatment with the full-length CNTF.

Types of evidence:

- Numerous laboratory studies

P021 has not been tested in humans yet.

In a mouse model of Alzheimer's (3xTg-AD mice), treatment with P021 (60 nmol/g feed) started at 3 months of age and continued for 18 months did not result in any weight loss, tumors, or signs of pain (Baazaoui and Iqbal, 2017). In the same mouse model as well as in wild-type mice, P021 treatment (60 nmol/g feed) started at 9-10 months of age and continued for 6 or 12 months did not result in changes in the general physical state, including grooming, posture, and clasping reflex (Kazim et al., 2014). Although 3xTg-AD mice had lower body temperatures as compared to wild-type mice, P021 treatment did not significantly affect body temperature. Wild-type mice were heavier than 3xTg-AD mice, and P021 treatment increased body weight in both 3xTg-AD and wild-type mice. There was no treatment effect in food consumption over the 6 months. P021 treatment did not affect levels of anxiety as measured by the elevated plus-maze task or exploration of a new environment.

In adult C57Bl6 mice (8-10 months old), P021 treatment (subcutaneous implants of extended-release depot pellets; 25 nM/day) for 35 days of continuous dosing did not alter general physical state, body weight, exploratory behavior, or swim speed (Li et al., 2010).

In mice, P021 has a plasma half-life of over 3 hours, stability of over 95% in artificial intestinal fluid after 2 hours, and stability of over 90% in artificial gastric juice after 30 minutes (Kazim and Iqbal, 2016).

It is worth noting that treatment with the full-length CNTF has been associated with serious side effects such as anorexia, severe cramps, and muscle pain. In a clinical trial in amyotrophic lateral sclerosis patients, subcutaneous administration of human CNTF did not show beneficial effects on pulmonary function, motility, or survival, and in fact, some patients experienced a substantial weight loss (ALS CNTF Treatment Study Group, 1996). This was originally thought to be due to CNTF-induced activation of hypothalamic areas that regulate food intake and body weight. However, CNTF treatment resulted in lowered body weight sustained for weeks to months after the cessation of treatment, an effect not seen with leptin or other anti-obesity medications (Ding et al., 2013). Later, it was discovered that CNTF treatment in mice increased neurogenesis in the hypothalamus, which was responsible for the sustained long-term effects on food intake and body weight beyond the duration of the treatment (Kokoeva et al., 2005). Other adverse events associated with the full-length CNTF therapy included muscle weakness, nausea, cough, aphthous stomatitis (mouth ulcers), and fever (ALS CNTF Treatment Study Group, 1996).

Since the side effects of CNTF are thought to be linked to its ability to activate the alternative IL6Rα-LIFRβ-gp130 receptor (as opposed to the CNTFRα-LIFRβ-gp130 receptor), CNTFR-specific mutants of CNTF have been developed that bind to the CNTFRα-LIFRβ-gp130 receptor, and these developments may offer safer systemic applications of CNTF interventions (Pasquin et al., 2015).

Drug interactions: No published studies have examined drug interactions with P021.

Sources and dosing: P021 is under clinical development by Phanes Biotech, PA, USA, as a disease-modifying drug for Alzheimer's disease and other neurodegenerative diseases. Dosage for human use has not been established. In mice, 60 nM per gram of feed has been used (Kazim et al., 2014; Baazaoui and Iqbal, 2017).

Research underway: There are no clinical trials ongoing that are testing P021, based on ClinicalTrials.gov. There are no NIH-funded programs that are specifically investigating P021.

Search terms:
Pubmed, Google:

- P021, CNTF

Websites visited for P021:

- Clinicaltrials.gov (0)
- NIH RePORTER (0)
- DrugAge (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem (0)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)

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