# A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating, Phase 2a Safety, Tolerability, and Pharmacodynamic Study of Two Doses of an Histone Deacetylase Inhibitor (FRM-0334) in Subjects with Prodromal to Moderate Frontotemporal Dementia with Granulin Mutation

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2.1 Primary Objectives• Evaluate the safety and tolerability of 2 fixed doses of FRM-0334 (300 and 500 mg daily in 2 sequential periods) over 28 days in subjects with prodromal to moderate FTD-GRN• Assess the PD effects of FRM-0334 on the change...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Neurological disorders congenital |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON40735

**Source**
ToetsingOnline

**Brief title**
studying on patients with Prodromal-Moderate FTD with Granulin Mutation

### Condition

- Neurological disorders congenital
- Structural brain disorders

- Dementia and amnestic conditions

**Synonym**
inherited, memory loss

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** FORUM Pharmaceuticals Inc.
**Source(s) of monetary or material Support:** FORUM Pharmaceuticals Inc.

## Intervention

**Keyword:** Dementia, Frontotemporal, Granulin, Mutation

## Outcome measures

### Primary outcome

1) Evaluate the safety and tolerability of 2 fixed doses of FRM-0334 (300 and

500 mg daily in 2 sequential periods) over 28 days in subjects with prodromal

to moderate frontotemporal dementia with granulin mutation (FTD-GRN)

2) Assess the pharmacodynamic (PD) effects of FRM-0334 on the change from

baseline in plasma concentrations of progranulin (PGRN) after 28 days

### Secondary outcome

1) Assess the PD effects of FRM-0334 on the change from baseline in

cerebrospinal fluid (CSF) concentrations of PGRN after 28 days

2) Characterize the plasma and CSF concentrations of FRM-0334 and metabolites

following once daily dosing after 28 days

3) Characterize the intra- and inter-individual variability in plasma and CSF

concentrations of PGRN

# Study description

**Background summary**

The potential clinical indication for FRM-0334 is the treatment of a subset of inherited frontotemporal dementia (FTD) that is due to mutations in the granulin (GRN) gene (FTD-GRN). FTD-GRN is part of the heterogenous frontotemporal lobar degeneration (FTLD) syndrome. The various disease entities of the FTLD syndrome have an early onset (<65 years) and account for 5 to 10% of all dementia and 10 to 20% of early onset dementia (Eriksen and Mackenzie, 2008).
In general, FTD is characterized by changes in personality, cognition (eg, language impairment and executive dysfunction), and behavior (eg, disinhibition, apathy, and compulsivity) (van Swieten and Heutink, 2008). Common FTLD syndromes include: behavioral variant FTD, semantic dementia, progressive apraxia of speech, agrammatic aphasia, progressive supranuclear palsy syndrome, cortico-basal syndrome, amyotrophic lateral sclerosis with dementia, FTD with motor neuron disease, and other less common syndromes. In particular, the clinical phenotype of FTD-GRN is highly variable. The clinical phenotype is usually a combination of behavioral abnormalities and language disturbances that is most often a form of primary progressive aphasia. Mild Parkinsonism is common, but motor neuron disease is notably rare. Marked variation in the disease course and clinical features are common, not only between families with different mutations, but also within individual families. This degree of clinical variability makes it difficult to predict which cases of familial FTD will turn out to have a GRN mutation (Mackenzie, 2007). Approximately 10 to 50% of FTD cases are inherited in an autosomal dominant fashion, with mutations in several genes causing pathogenesis (Eriksen and Mackenzie, 2008; Gass et al, 2012). These include mutations in the genes encoding microtubule-associated protein tau, progranulin (PGRN), valosin containing protein, charged multivesicular body protein 2B, transactive response deoxyribonucleic acid (DNA) binding protein 43 (TDP-43), and fused in sarcoma, and most recently in the repeat expansion of the chromosome 9 open reading frame 72 gene (C9Orf72) (Dobson-Stone et al, 2012). Neuropathologically, the FTLD syndrome can be divided into 2 major groups that have a clear correlation with their genetic background, including those with tau-positive inclusions and those with ubiquitin- and TDP-43-positive inclusions. Recently, mutations in GRN on chromosome 17q21 were found to cause an FTLD variant with ubiquitin- and TDP-43-positive inclusions (Cruts et al, 2006; Baker et al, 2006; Gass et al, 2012). Seventy pathogenic GRN mutations in over 230 families have been described for FTD-GRN to date. These mutations include frameshift, splice-site, and nonsense mutations that are predicted to

produce a premature stop codon. The mutations result in haploinsufficiency and a greater than 50% reduction in expression of PGRN in plasma (Ghidoni et al, 2012). At present, there are no drugs available to treat GRN haploinsufficiency and the resulting neurodegeneration and dementia of FTD-GRN.

In the adult brain, GRN messenger ribonucleic acid (mRNA) and PGRN immunoreactivity are located in certain neuronal populations (eg, pyramidal cells of cortex and hippocampus and cerebellar Purkinje cells) and in microglia (Eriksen and Mackenzie, 2008). In neuroinflammatory and neurodegenerative diseases, microglia appear to produce and secrete the majority of PGRN, which is taken up from the extracellular space by neurons (Sun and Eriksen, 2011). In FTD-GRN, GRN haploinsufficiency and decreased PGRN levels may result in an exaggerated neuroinflammatory response and/or loss of neurotrophic activities, leading to neurodegeneration.

A suggested approach for the treatment of FTD-GRN caused by GRN haploinsufficiency has been to increase PGRN levels. The histone deacetylase (HDAC) inhibitor (HDACi) suberoylanilide hydroxamic acid (SAHA) increased GRN mRNA transcription and PGRN levels (Cenik et al, 2011). While SAHA increased PGRN levels, it has limited central nervous system (CNS) penetration.

In the cell nucleus, DNA is tightly wound around proteins called histones, and this DNA/histone association is called chromatin (de Ruijter et al, 2003). Gene transcription depends on how tightly histones and DNA are associated; a looser association promotes gene transcription. Acetylation of histones results in a looser association of histone with DNA and therefore increases gene transcription. Addition of an acetyl group onto histones is catalyzed by a family of enzymes called histone acetyl transferases (HATs). Removal of acetyl groups from histones, with subsequent decreases in gene transcription, is catalyzed by a family of enzymes called HDACs. Thus inhibition of HDACs will result in retention of acetyl groups on histones, thereby maintaining a loose association between histone and DNA and increasing gene transcription. Although histone deacetylation is the best understood function of HDACs, other proteins in the cell can be deacetylated (Spange et al, 2009).

Furthermore, several lines of evidence indicate that HDACi may be useful for the treatment of memory loss in patients with dementia (Tully et al, 2003; Sweatt, 2007; Abel and Zukin, 2008; Fischer et al, 2010). In a transgenic mouse model that displays substantial atrophy in brain regions involved in cognition and memory, such as the hippocampus and cerebral cortex, HDACi restored memory function tested in associative learning and spatial learning memory tasks (Fischer et al, 2007). These results implicate HDACi as potential treatments for cognitive disorders that arise from neurodegeneration (Sweatt, 2007).

In conclusion, the effects of SAHA on GRN mRNA and PGRN levels suggest that a brain penetrant HDACi may be useful for treating FTD-GRN. FRM-0334 is a brain penetrant HDACi and has shown the potential to elevate GRN mRNA and PGRN levels in a variety of in vitro and in vivo models relevant to FTD-GRN due to GRN haploinsufficiency and to enhance cognition in animal models. Addressing the GRN haploinsufficiency associated with GRN mutations by increasing PGRN expression may offer a method to potentially treat these patients.

## Study objective

2.1 Primary Objectives
• Evaluate the safety and tolerability of 2 fixed doses of FRM-0334 (300 and 500 mg daily in 2 sequential periods) over 28 days in subjects with prodromal to moderate FTD-GRN
• Assess the PD effects of FRM-0334 on the change from baseline in plasma concentrations of PGRN after 28 days
2.2 Secondary Objectives
• Assess the PD effects of FRM-0334 on the change from baseline in CSF concentrations of PGRN after 28 days
• Characterize the plasma and CSF concentrations of FRM-0334 and metabolites following once daily dosing after 28 days
• Characterize the intra- and inter-individual variability in plasma and CSF concentrations of PGRN
2.3 Exploratory Objectives
• Assess the effects of FRM-0334 after 28 days on the change from baseline in function using the Frontotemporal Dementia Clinical Dementia Rating Sum of Boxes (FTD-CDR-SB) scale and the Alzheimer*s Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) scale, and activities of daily living using the Frontotemporal Dementia Rating Scale (FRS) in subjects requiring a support person
• Assess the PD effects of FRM-0334 after 28 days on the change from baseline in plasma concentrations of PGRN mRNA and the CSF concentrations of total tau (t-tau), tau phosphorylated at threonine 181 (p-tau181), 42 amino acid form of β-amyloid (Aβ42), neurofilament light chain (NF-L) and additional CSF biomarkers (eg, TDP-43), as technically feasible, and regional cerebral glucose metabolism using 18F-FDG-PET

## Study design

This is a randomized, double-blind, placebo-controlled, dose-escalating, Phase 2a study to evaluate the safety, tolerability, PD, and PK of FRM-0334 for 28 days in subjects with prodromal to moderate FTD-GRN. For this study, the condition of *prodromal* does not require any clinically visible or measurable symptoms, but only the presence of the genetic mutation FTD-GRN. Subjects will receive FRM-0334 or placebo during 2 sequential periods (Group 1: 300 mg or placebo; Group 2: 500 mg or placebo [identical number of subjects per period]). After all subjects in Group 1 (300 mg [n=12] or placebo [n=3]) have been randomized and completed (or discontinued) double-blind treatment, safety, tolerability, and any available PK data will be reviewed in a blinded fashion. Randomization of subjects into Group 2 (500 mg [n=12] or placebo [n=3]) will begin only after the 28-day, double-blind safety, tolerability, and available PK data for Group 1 (300 mg or placebo) are deemed acceptable by the Medical Monitor and the Sponsor. Blinded safety, tolerability, and PK data for the 500 mg cohort will be reviewed on an ongoing basis. Enrollment will be competitive.

Recruitment will be terminated after randomization of 30 subjects.

### Intervention

Once daily oral dosing of 300 or 500 mg FRM-0334 as a white, opaque, size No. 1, hard gelatin capsule for 28 days, supplied as a 100 mg capsule that will be size- and color-matched to the placebo capsule. As a reference standard, once daily oral dosing of placebo for 28 days, supplied as a capsule that will be identical in appearance to the 100 mg FRM-0334 capsule.

### Study burden and risks

Risks Associated With FRM-0334
There is a risk of side effects (unwanted effects or health problems) from taking FRM 0334. Some of these risks may be serious or even life-threatening. If you take FRM-0334 and suffer lasting or serious side effects, it might affect your private medical insurance coverage.

Some effects are headache, muscle pain, diarrhea, and flatulence. Two subjects treated in a prior study of FRM-0334 had mild elevations of liver function tests which required further monitoring but no medical treatment and there was no liver damage

There is a risk of side effects (unwanted effects or health problems) from taking FRM*0334.
There has been 1 study with FRM-0334; 87 people have taken at least one dose of the FRM-0334. The most common side effects of FRM-0334 during this study were: headache, muscle pain, diarrhea, and gas. Two subjects in the study had increases in certain blood tests that measure how the liver functions. These changes were mild and required further monitoring but did not require treatment and there was no liver damage.

## Contacts

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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Informed consent form (ICF) signed by the subject or carer indicating that the subject or carer understands the purpose of and procedures required for the study before any studyspecific
procedures are performed
2. A carer may be required to participate in the study (in the judgment of the investigator at screening or as required by local regulations). The carer must sign an acknowledgement of responsibilities form at the study center before any study specific activities required for the carer are performed. The first required activity will be performed at screening. The carer will accompany the subject to the study center at screening and on Days 1 and 28 (or be available by telephone on Days 1 and 28), and if not living in the same household, interacts with the subject approximately 4 times per week, and be able to complete the study 3. Male or female subjects aged >=21 and <=75 years
4. Genotyped positive for a FTDGRN mutation criterion No. 2), a Clinical Dementia Rating Sum of the Boxes (CDRSB) score <16 at screening
5. Prodromal to moderate FTDGRN, and for subjects who require a care
score <16 at screening
6. Fertile, sexually active subjects (men and women) must practice true abstinence or use an effective method of contraception during the study. Female subjects and the female partner of male subjects must be surgically sterile (hysterectomy or bilateral salpingectomy/oophorectomy or bilateral tubal occlusion/ligation), postmenopausal for at least 1 year prior to screening, or willing to consistently and correctly practice adequate methods of contraception if of childbearing potential (defined as consistent use of combined effective methods of contraception [including at least 1 barrier method])
7. Women of childbearing potential must have a negative pregnancy test at screening and Day 1

8. Resides in a stable living situation, living at home, senior residential setting, or an institutional setting without the need for continuous (ie, 24hour) nursing care

## Exclusion criteria

Subjects who meet any of the following exclusion criteria are ineligible to participate:
Exclusion Criteria - Medical
1. Employees of the investigator or study center or their family members, or employees of FORUM Pharmaceuticals or Worldwide Clinical Trials who are directly involved in the conduct of the study
2. Female subjects who are pregnant, breastfeeding, or planning to become pregnant during the study
3. Unstable medical condition that is clinically significant (in the judgment of the investigator) within 30 days before screening
4. Untreated vitamin B12 or folate deficiency (must be stably treated for at least 6 months before screening)
5. Clinically significant untreated hypothyroidism (if treated, thyroid-stimulating hormone level and thyroid supplementation dose must be stable for at least 6 months before screening)
6. Clinically significant abnormal serum electrolytes (sodium, potassium, and magnesium) after repeat testing (in the judgment of the investigator)
7. Alanine transaminase (ALT) or aspartate transaminase (AST) >2.5 times the upper limit of normal
8. Renal insufficiency with serum creatinine >2.0 mg/dL, unless receiving current treatment with an angiotensin-converting enzyme (ACE) inhibitor in which case the Medical Monitor should be contacted
9. Insufficiently controlled diabetes mellitus (in the judgment of the investigator)
10. Clinically significant hematologic abnormalities including thrombocytopenia and leukocytosis (in the judgment of the investigator)
11. Malignant tumor within 3 years before screening with the exception of squamous and basal cell carcinoma or cervical carcinoma in situ or brachytherapy for localized prostate cancer
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9. Insufficiently controlled diabetes mellitus (in the judgment of the investigator)
10. Clinically significant hematologic abnormalities including thrombocytopenia and leukocytosis (in the judgment of the investigator)
11. Malignant tumor within 3 years before screening with the exception of squamous and basal cell carcinoma or cervical carcinoma in situ or brachytherapy for localized prostate cancer
12. Systemic infection of any kind or any acute, subacute or chronic inflammatory process (eg, rheumatoid arthritis, chronic obstructive pulmonary disease, or gastrointestinal inflammatory diseases)
Exclusion Criteria - Neurological
13. Magnetic resonance imaging (MRI) or computed tomography (CT) scan performed within 12 months before screening with findings consistent with a clinically significant comorbid pathology other than FTD. If the MRI or CT scan is unavailable or occurred >12 months before screening, an MRI scan must be completed and findings confirmed before the Day -7 procedures are performed and a copy of the digital imaging and communications in medicine (DICOM) standard image and report must be available
14. Diagnosis of motor neuron disease, including probable amyotrophic lateral sclerosis
15. History of brain tumor, subdural hematoma, or other clinically significant (in the judgment of the investigator) space-occupying lesion on CT or MRI
16. Stroke within 18 months before screening or history of a stroke concomitant with onset of dementia
17. Head trauma with clinically significant (in the judgment of the investigator) loss of consciousness within 12 months before screening or concurrent with the onset of dementia
18. Onset of dementia within 12 months before screening secondary (in the judgment of the investigator) to cardiac arrest, surgery with general anesthesia, or resuscitation
19. Specific degenerative CNS disease diagnosis other than FTD (eg, Parkinson*s disease, Alzheimer*s disease, Huntington*s disease, Creutzfeldt-Jakob disease, Down*s syndrome)
20. Wernicke*s encephalopathy
21. Epilepsy if present antiseizure therapy is required for seizure control
Exclusion Criteria - Psychiatric
22. Current diagnosis of severe major depressive disorder with psychotic features, if the present condition or treatment interferes with the subject*s ability to complete the study (in the judgment of the investigator)
23. Significant suicide risk as defined by 1) suicidal ideations as endorsed on items 4 or 5 on the C-SSRS within the past year at screening or baseline, 2) suicidal behaviors detected by the C-SSRS within 2 years before screening, or 3) investigator assessment
24. History or current diagnosis of psychosis
25. History within 2 years before screening or current evidence of substance abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 13-01-2015 |
| Enrollment: | 2 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Not Applicable. |
| Generic name: | not applicable |

# Ethics review

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|---|---|
| Approved WMO Date: | 23-09-2014 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 19-12-2014 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam |

| | |
|---|---|
| | (Rotterdam) |
| Approved WMO Date: | 19-02-2015 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 19-03-2015 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 26-11-2015 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 22-12-2015 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2014-001489-85-NL |

| Register | ID |
| --- | --- |
| ClinicalTrials.gov | NCT02149160 |
| CCMO | NL50361.078.14 |