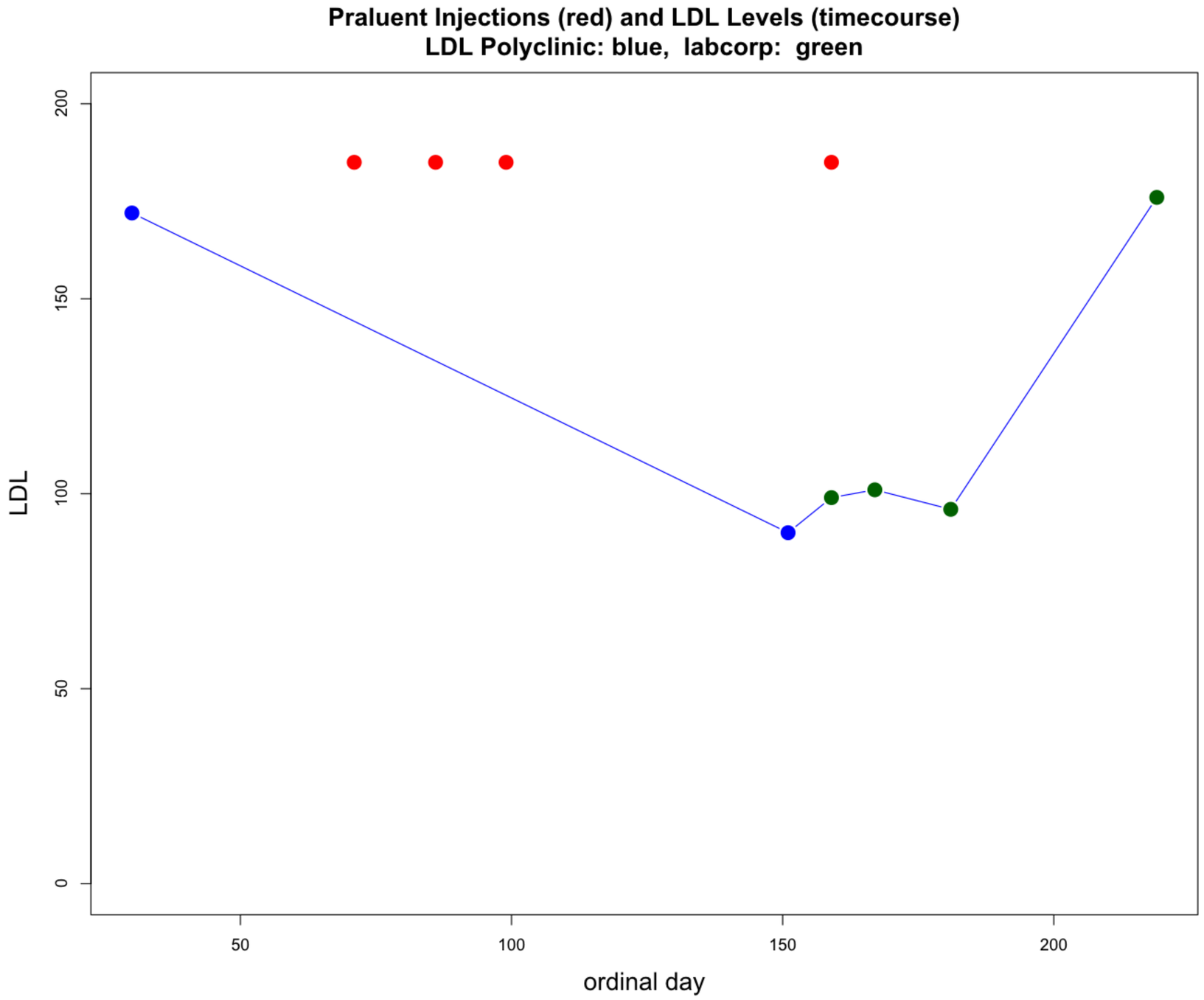
Frequency/Response Curve
Praluent 75 mgvs LDL



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Investigating the potential impact of PCSK9-inhibitors on mood disorders using eQTL-based Mendelian randomization

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(30 jan 2023): LDL = 172
(31 may 2023): LDL = 90
(08 jun 2023): LDL = 99 (labcorp)
(30 jun 2023): LDL = 101 (labcorp)
(08 jun 2023): at least 2 weeks without fatigue, no mild depression, no
                need to nap
(08 jun 2023, thursday): injection 4, after 8.5 weeks
               30 minute nap, seemingly related (though just hours after
               injection)
(09 jun 2023): daylong depression.  fatigue
(10 jun 2023): milder depression, washed out feeling, afternoon nap,
                felt very poorly when up for an hour at 130am

(11 jun 2023): washed out feeling, somewhat reduced on waking.  depression gone.
               afternoon nap required.  difficult waking.  early fatigued night
(12 jun 2023): morning good.  obligatory nap 4pm
(13 jun 2023): morning good.  obligatory nap 2pm
(14 jun 2023): pretty good all day
(15 jun 2023): pretty good all day
(16 jun 2023): LDL = 96  (labcorp)
(17 jun 2023): good
(18 jun 2023): good
(30 jun 2023): LDL = 101 (labcorp)
(07 aug 2023): LDL = 176 (labcorp)
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Despite the main role of PCSK9 in lipid metabolism being established primarily in the liver, the gene has detectable levels of expression in non-hepatic tissues, including the brain [5].

There is recent evidence of an association between *PCSK9*, both protein level [5] and genetic variation in the *PCSK9* locus [6], and mood disorders and related traits, including depressive symptoms and neuroticism. Mendelian randomization (MR) studies have provided evidence, using genetic risk scores of variants within the *PCSK9* locus, that this gene is associated with an increased risk of major depressive disorder (MDD) but not neuroticism [7].

In vivo experiments have also demonstrated that overexpression of LDLR (which is targeted for degradation by PCSK9), in mice brains led to neuroinflammatory responses, suggesting that inhibition of PCSK9 may also lead to neuroinflammation [8]. MR studies have also found LDL-C to be associated, albeit weakly, with MDD-related traits [9]. Moreover, mental illnesses including MDD have well-established comorbidity with CVD [10]. In contrast to medications like statins, which have over 40 years of clinical data for analyses of ADRs and off-target effects [11], clinical data on the long-term effects of PCSK9i do not yet exist, with the first PCSK9i being approved by the FDA only in 2015 [12]. In such instances, statistical methods like MR can estimate potential ADRs, or off-target effects using genetic data, akin to ‘natural randomised control trial’ [13].

Bulk tissue gene expression for PCSK9

https://www.gtexportal.org/home/gene/PCSK9