Response to "Drucebo effect – the challenge we should all definitely face!"

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We thank Professors Banach and Penson for their letter.

They make an excellent point that symptoms are, by definition, subjective, and therefore best recorded contemporaneously, for example through the app we used. We agree that only a minority of statin abandoners try 4 of more regimens, although the definition of statin intolerance does require *at least* two different statins, of which one must be at the lowest approved daily starting dose. This was reflected in our study, where 5/6 had tried 3 or fewer.

All participants had been through UK NHS processes which will have included counselling from their physicians. However, it is the number of drug regimens which is most straightforward to quantify, as a surrogate for extent of exploration and counselling. SAMSON provides the individual patient information specific to (and interpretable by) themselves.

We thank them for introducing the concept of "drucebo", to refer to the combination of genuine plus nocebo effects. However, we are sceptical of the advisability of reducing dose or frequency, for three reasons. First, it immediately reinforces the patient's belief that the drug is the cause. Second, these reductions are always carried out when symptoms are bad, and therefore tend to improve, while increases only occur when symptoms are absent, and therefore can only worsen. This causes a consistent temporal association between dose and symptoms, without any biological causation. Third, even if a strict schedule is implemented to prevent this phenomenon, without a placebo tablet, there is no way to partition the drucebo effect between drug and nocebo elements.

They should indeed ask why SAMSON recruited patients whose symptoms arose within 2 weeks of starting statins. The trial pivoted on having multiple periods of drug, placebo, and no tablets. To deliver 12 such periods, and not require more than a year of participation in a trial expecting intolerable side effects, required the periods to be only 1 month long. For 1 month periods to be enough, recruitment was limited to those whose symptoms characteristically arose within 2 weeks. We agree that patients with more slowly arising symptoms have not been studied. A corresponding protocol for patients with onset within 6 months (i.e. 1 year periods) would take 12 years.

We agree that symptoms with statins (and indeed without statins!) grow increasingly common with age. This may be why 87% of SAMSON participants were over 60.

We too are curious about reversible underlying causes of statin intolerance. To ensure maximum participation and representativeness, SAMSON had no mandatory blood tests. Despite this, symptoms on

statins were not significantly higher than those on placebo, and both were very significantly higher than those on no tablets. This means that genuine statin intolerance (whether having an underlying reversible cause or not), if present, was surprisingly small.

Conflict of interest

The authors declare no conflict of interest.