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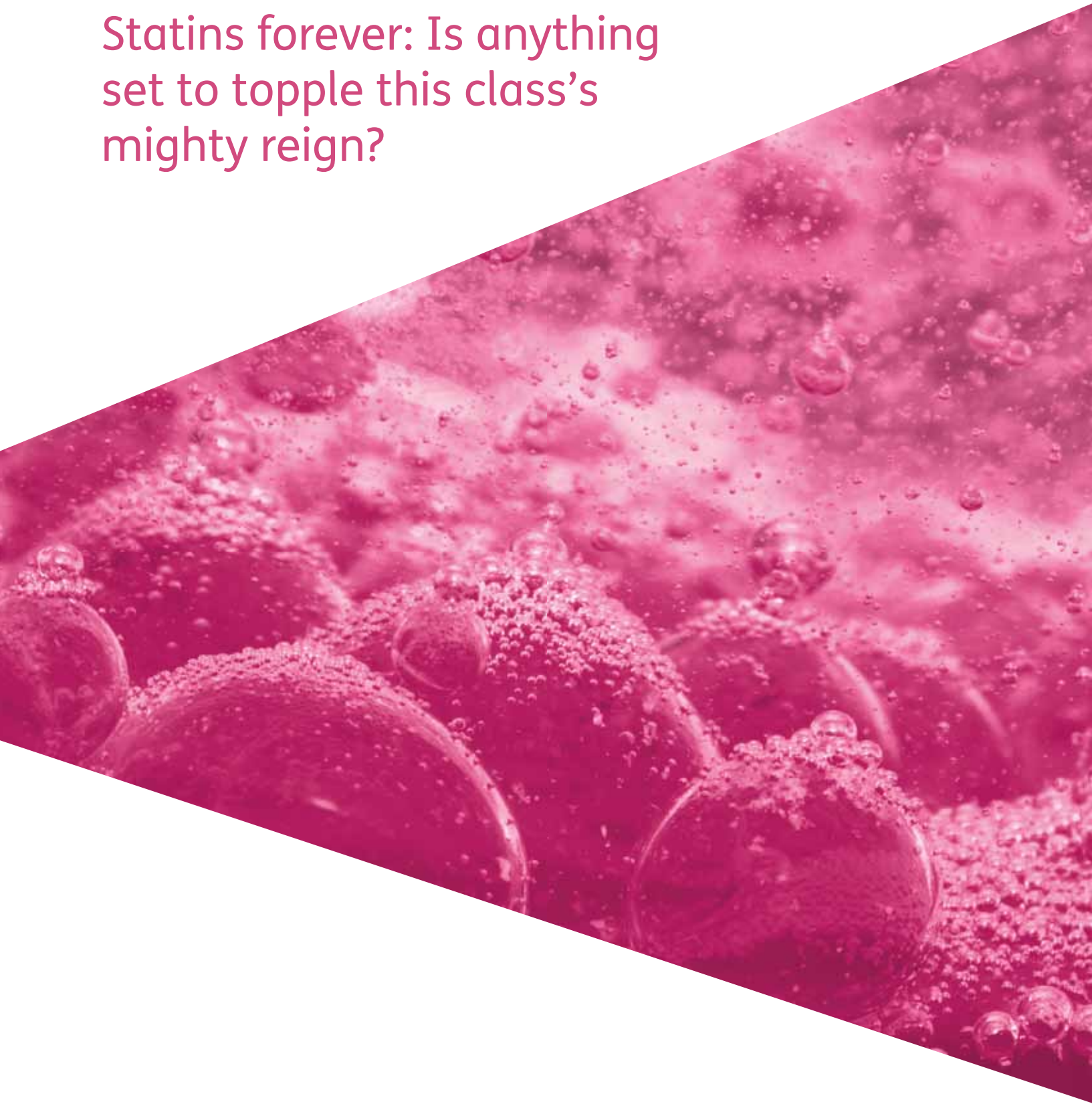
# Statins forever: Is anything set to topple this class's mighty reign?



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# Introduction

With the launch of Regeneron/Sanofi's first-in-class PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor, Praluent, in July 2015 and the following launch of Amgen's PCSK9 inhibitor, Repatha, shortly after, the treatment of dyslipidaemia has once again been thrust into the limelight, with efficacy and cost of novel treatment at the forefront of discussion.

In 2016, the US and UK had an estimated 97 million and 27 million cases of hypercholesterolemia, with prevalence expected to top 100 million and 30 million, respectively, by 2023. [1] Lifestyle modifications, such as weight loss, exercise and the introduction of a low-fat diet, can be an effective means of reducing blood lipid levels. In addition, there are also numerous pharmacological options when it comes to the treatment of dyslipidaemia. Owing to their low cost due to genericization and strong historical evidence of reducing cardiovascular disease and mortality in high risk patients (similar data won't be available for the PCSK9s until at least Q1 2017), statins are typically the first-line pharmacological intervention for the treatment of dyslipidaemia. [2] In 2012, Pfizer's blockbuster statin, Lipitor (atorvastatin) became the biggest selling drug of all time with sales of $140 billion worldwide since its launch in 1996. [3] Impressively, the drug still brought in almost $2 billion in 2015 for Pfizer despite being generically available since 2011.

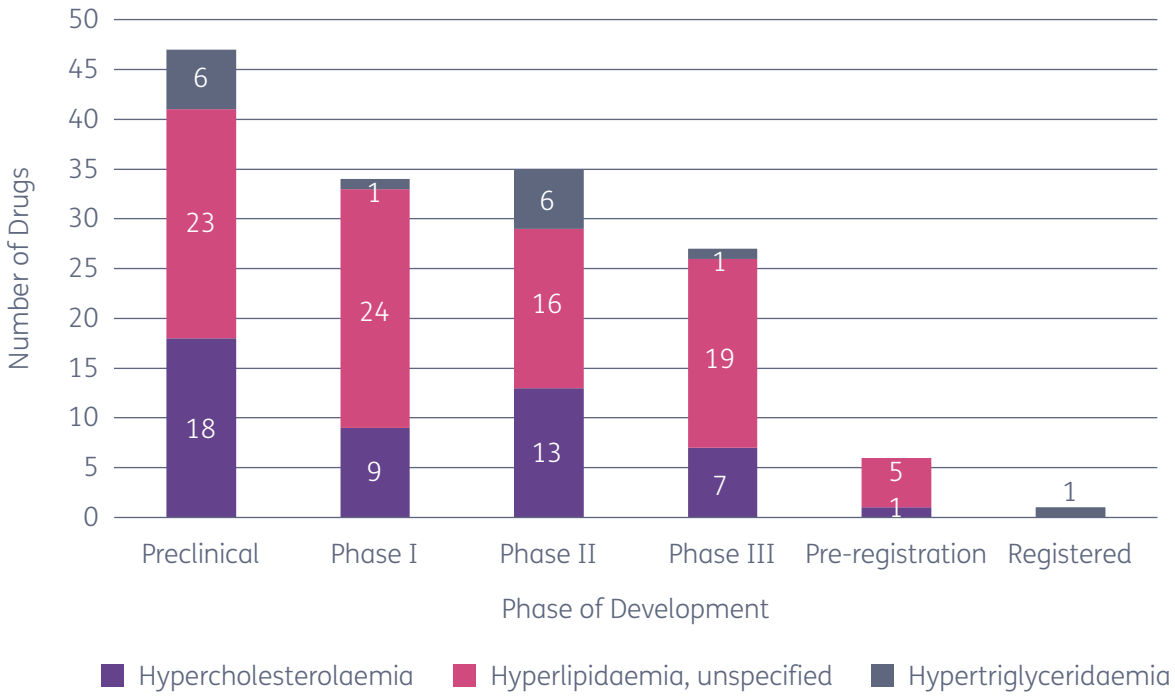
This analysis will discuss the current landscape of dyslipidaemia drugs from preclinical to pre-registration phases of development, focussing primarily on the alternatives to the PCSK9 inhibitors [4] to uncover whether there are currently any candidates that could challenge this novel class or the current first-line therapy, statins.

*1 Datamonitor Healthcare®, 2016*
*2 Catapano AL, et al. (2016) 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J, 37 (39), 2999-3058.*
*3 King S (2013) The Best Selling Drugs Since 1996 – Why AbbVie's Humira Is Set To Eclipse Pfizer's Lipitor. Forbes. Available from: http://www.forbes.com/sites/simonking/2013/07/15/the-best-selling-drugs-since-1996-why-abbvies-humira-is-set-to-eclipse-pfizers-lipitor/#1b1f03982055 [Accessed 23 Nov 2016]*
*4 To learn more about this class of drugs, please refer to Natasha Boliter's article "PCSK9 Inhibitors: What does the future hold for this controversial new class?"*

## The Dyslipidaemia R&D Landscape

Figure 1 shows the number of drugs in development for dyslipidaemia by specific indication from preclinical through to registered phases of development. The split of compounds by phase follows a typical distribution; many compounds in the preclinical space that slowly tapers off to a single digit number of compounds in the pre-registration and registered phases of development. Again, referring to Figure 1, the majority of drugs between preclinical and pre-registration are indexed with the Pharmaprojects indication "Hyperlipidaemia, unspecified", meaning that companies have not specified any particular subtype of hyperlipidaemia. However, whether this is due to the enigmatic nature of the industry, or whether they are simply casting their net across as many dyslipidaemia indications as possible, is unclear.

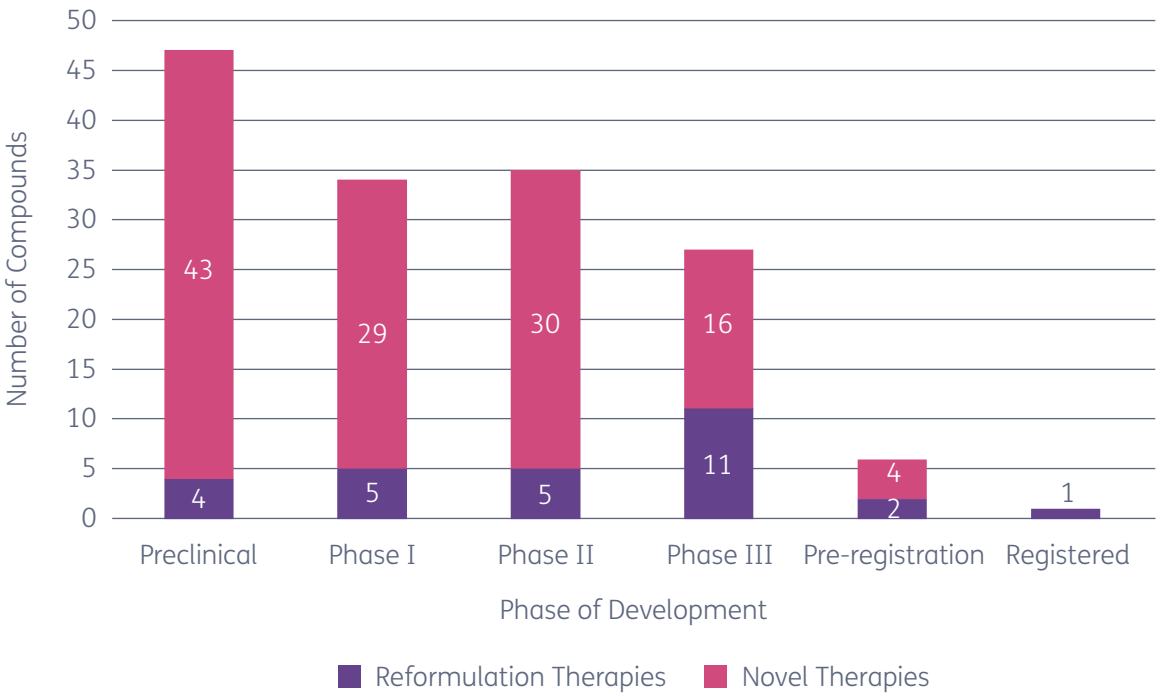
**Figure 1. Number of dyslipidaemia compounds under active development by phase**




*Source: Pharmaprojects®, October 2016*

The dyslipidaemia pipeline includes a mixture of novel and reformulated compounds, which include previously launched drugs that have been reformulated as fixed dose combinations (FDCs), products with increased duration of action and formulations using novel delivery technologies. In comparison to the total number of drugs, the minority of products at the earlier stage of development are reformulations (9%, 14% and 14% for Preclinical, Phase I, and Phase II, respectively). At later stages of development, a much higher proportion of the pipeline is made up of reformulated compounds (40%, 33% and 100% for Phase III, Pre-Registration, and Registered, respectively). The industry appears to be pursuing more novel compounds at early stages of development, but this has not yet translated to more novel compounds at later stages of development. This does not necessarily mean, however, that industry is focusing on novel mechanisms of action.

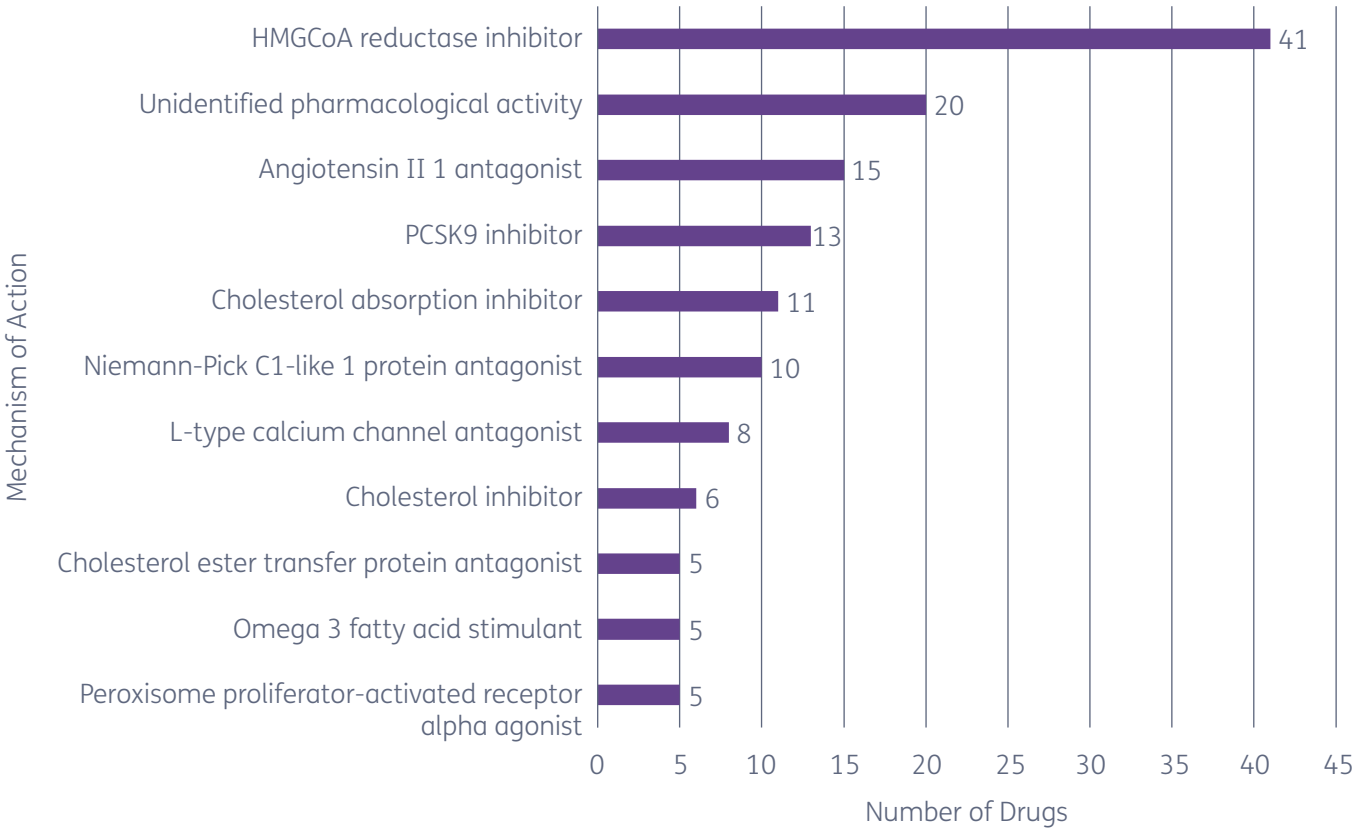
**Figure 2. Number of reformulations versus novel dyslipidaemia compounds**




*Source: Pharmaprojects®, October 2016*

Figure 3 depicts the most popular mechanisms of action (MOA) attached to the dyslipidaemia drugs, across all phases of development. Notably, this list primarily consists of mechanisms which have previously been launched for the treatment of dyslipidaemia, with the exception of the CETP (cholesteryl ester transfer protein) antagonists. There are also a large number of drugs with unidentified pharmacological activities, some of which may be novel MOAs (which in this case, is unlikely). Alternatively, the undisclosed MOAs could be attributed to companies being secretive of their R&D pipelines. Given Figure 3 and the abundance of HMG-Co-A reductase inhibitors, it appears that the pharma industry is sticking with the tried and tested statin class for the treatment of dyslipidaemia for the foreseeable future. Considering the track record of non-statin failures in this space however, statin therapies are likely to be a safe bet.

**Figure 3. Top mechanisms of action for dyslipidaemia drugs in development**




*Source: Pharmaprojects®, October 2016*

## Failure in the dyslipidaemia space: a reason for caution?

With the recent controversy surrounding the approval and launch of the first wave of PCSK9 inhibitors (focussing mainly on the extremely high cost in comparison to statin therapies), it may be easy to forget that the dyslipidaemia space has also been plagued by a number of high profile and costly failures, mainly centred around the CETP inhibitor (CETPi) class. The most recent failures are seen in Table 1 below.

**Table 1. Recent failures in the dyslipidaemia space**

| Drug Name | Company | Mechanism of Action | Reason for Discontinuation | Phase of Discontinuation |
|---|---|---|---|---|
| torcetrapib | Pfizer | CETP Inhibitor | Adverse Events | Phase III |
| dalcetrapib | Roche | CETP Inhibitor | Efficacy | Phase II |
| evacetrapib | Eli Lilly | CETP Inhibitor | Efficacy | Phase III |
| bococizumab | Pfizer | PCSK9 inhibitor | Strategic | Phase III |

*Source: Pharmaprojects®, October 2016*

All three CETP inhibitors (torcetrapib, dalcetrapib and evacetrapib) listed in Table 1 failed in later phases of development (Phase II or Phase III). Adverse events played a part in the discontinuations of torcetrapib and with reasons including "excessive all-cause mortality in the treatment group receiving a combination of atorvastatin (Lipitor) and torcetrapib" [5] disclosed by Pfizer in a statement on the termination of this compound. On the other hand, efficacy stifled the success of dalcetrapib and evacetrapib, with Roche and Lilly both stating that discontinuation was down to "lack of clinically meaningful efficacy". [6,7] These discontinuations have seriously bought into question the suitability of inhibiting CETP as a treatment for dyslipidaemia.

Despite these notable failures, Merck is still soldiering on with their Phase III CETPi, anacetrapib, which is scheduled to complete its REVEAL trial in early 2017. The REVEAL trial currently involves 30,000 patients with circulatory disease and is investigating whether those given anacetrapib are less likely to suffer heart attacks or death from heart or other vascular disease. Given the history of this class, the opinion of many seems to be that it is unlikely that the trial will meet its outcomes or gain approval. Biomedtracker estimates that its chances of approval are currently hovering just above 30%, which is 15% below the average likelihood of approval for Phase III drugs in this indication.[8] There are also a small number of early stage CETPi's still under active development, including Chong Kun Dang's Phase I compound, CKD-519, Kowa's Preclinical K-312 and Dexa Medica's DLBS-1449 (albeit, the only active trial, a Phase II/III, for this compound was recently withdrawn prior to enrolment, suggesting its possibly inevitable relegation to the CETPi scrapheap).

Removing the statins and CETPis from the equation, there are few disclosed classes left in the late stages of development. Indeed, the remainder of the Pre-registration and Phase III landscape is comprised of a smattering of lone drugs with different MOAs (Table 2). With the lack of diversity in late stage development and no new drugs close to approval, it seems unlikely that the statin-heavy market will change for some time.

*5 Press release, Pfizer (2006); In Interests of Patient Safety, Pfizer Stops All Torcetrapib Clinical Trials; Company Has Notified FDA and Is In The Process of Notifying All Clinical Investigators and Other Regulatory Authorities*
*6 Press release, Roche/Japan Tobacco (2012); Termination of all the studies of anti-dyslipidemia drug JTT-705 (dalcetrapib), JT's partner, F. Hoffmann-La Roche Ltd., has announced*
*7 Press release, Eli Lilly (2015); Lilly to Discontinue Development of Evacetrapib for High-Risk Atherosclerotic Cardiovascular Disease*
*8 Biomedtracker, 2016*

**Table 2. Late stage non-statin dyslipidaemia candidates**

| Drug name | Mechanism of Action | Company | Phase of Development |
|---|---|---|---|
| pemafibrate | Peroxisome proliferator-activated receptor alpha (PPAR-α) agonist | Kowa | Pre-Registration |
| volanesorsen | Apolipoprotein C inhibitor | Akcea Therapeutics | Phase III |
| TRIA-662 | Vitamin B3 agonist/ ADP ribose polymerase inhibitor | Pharmena | Phase III |
| hyzetimibe | Cholesterol absorption inhibitor | Zhejiang Hisun Pharmaceutical | Phase III |
| bempedoic acid | AMPK stimulant/ATP citrate pro 3S lyase inhibitor | Esperion Therapeutics | Phase III |

*Source: Pharmaprojects®, October 2016*

## Conclusion

Until the PCSK9 enclave can prove their worth [9] in their ongoing outcomes trials or anacetrapib manages to achieve the seemingly impossible as a CETP inhibitor to reach approval, it would seem that the statins are likely to continue to be the kings of the dyslipidaemia space for some time to come. Although it does seem that industry is starting to make investments into novel compounds in earlier stages of development, statins and reformulated drugs still have a strong foothold across the dyslipidaemia R&D landscape, especially in the later stages of development. In a world where low cost alternatives of lifestyle modification and generic statins can effectively treat dyslipidaemia and lead to a definitive reduction in cardiovascular disease and mortality, only time will tell whether the PCSK9s or something entirely novel will be able to infiltrate this tough space.

*9 On the 2nd Feb 2017, Amgen announced to their investors that Repatha had passed its cardiovascular outcomes test. Despite this, they also issued a warning that they foresee a continued slow uptake for their PCSK9i in 2017. Datamonitor Healthcare analyst, Kevin Shannon, stated "What matters next is how the cardiovascular impact compares to statins [alone]. If it's similar, Repatha is unlikely to be reimbursed. If it shows a big benefit, insurers will almost have to reimburse". So, although we now know that Repatha works, the question still remains, how well? (Jackson M (2017); Amgen's Repatha Passes CVOT Test, But Contribution To 2017 Sales Growth Unclear. Available from https://scrip.pharmamedtechbi.com/SC098166/Amgens-Repatha-Passes-CVOT-Test-But-Contribution-To-2017-Sales-Growth-Unclear [accessed 3 Feb 2017]).*

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