Institution: Imperial College London

Unit of Assessment: 02 Public Health, Health Services and Primary Care

Title of case study: Inclisiran, a new therapeutic class for cardiovascular disease: pivotal studies underpin a multi-billion dollar sale to Novartis.

Period when the underpinning research was undertaken: 2015-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Kausik (Kosh) Ray	Professor of Public Health	2015 – present
Julia Brandts	Visiting Researcher Research Associate	9 Jul 2019 – 30 Sep 2020 26 Oct 20 – present

Period when the claimed impact occurred: Jan 2020 - present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Hypercholesterolaemia remains under-treated worldwide. Inclisiran is a first-in-class, siRNA-based therapeutic that lowers LDL cholesterol by targeting PCSK9 mRNA. Professor Ray at Imperial College designed and led the clinical trials that demonstrated that inclisiran, given as two injections/year, reduces LDL cholesterol by 50%. It is well tolerated and addresses the challenge of non-adherence to oral lipid-lowering drugs. The safety and efficacy data and benefits evident to healthcare resulted in Novartis buying The Medicines Company, the manufacturers of inclisiran, for $9.7 billion and an NHS partnership with Novartis to make the drug available to the NHS for evaluation in 300,000 patients.

2. Underpinning research (indicative maximum 500 words)

Hypercholesterolemia is a major risk factor for cardiovascular disease (CVD) and reducing low-density lipoprotein cholesterol (LDL-C) significantly reduces CVD risk. Statins are the standard therapy, but intolerance and reliance on long-term adherence limit their population impact. Professor Ray and colleagues at Imperial evaluated the association of adherence and treatment intensity with cardiovascular outcomes in patients with documented CVD. The lowest cardiovascular risk was observed among adherent patients receiving high-intensity therapy, and the highest risk was observed among non-adherent patients receiving low-intensity therapy. Suboptimal cholesterol lowering and non-adherence to treatments requiring daily dosing resulted in 12,000 excess cardiovascular events annually (1).

Proprotein convertase subtilisin-kexin type 9 protease (PCSK9) is an attractive alternative target for reducing LDL-C levels; loss-of-function mutations in the gene encoding PCSK9 are associated with low LDL-C levels and reduced risk of heart attack. For over 15 years, PCSK9 has been viewed as intractable to small molecule discovery. Monoclonal antibodies to PCSK9 have been developed to lower LDL-C but require 26 injections annually and are expensive. Inclisiran is a small interfering (si)RNA developed by The Medicines Company that inhibits PCSK9 synthesis.

In 2015, The Medicines Company approached Professor Ray to design the clinical development programme for inclisiran. He led the design and implementation of the Phase 2 ORION 1 trial, a multi-centre, double-blind, multiple-ascending-dose trial of inclisiran, administered as a subcutaneous injection to patients at high-risk for CVD. A total of 501 patients were recruited to compare (a) a single dose of placebo with 200/300/500 mg of

inclisiran, or (b) two doses of placebo with 100/200/300 mg of inclisiran at days 1 and 90. The primary end-point was the change in LDL-C level from baseline at 180 days. Results demonstrated that two doses of 300mg of inclisiran maintained a 50% cholesterol reduction over six months (2). Further analyses and modelling suggested after two doses 90 days apart, a 6-monthly dosing regimen could maintain this level of 50% cholesterol reduction (3). Professor Ray led the communication of data at conferences and in peer-review journals, New England Journal of Medicine and JAMA Cardiology, putting forward the concept of time-averaged reductions in LDL-C with infrequent dosing (2, 3).

Professor Ray then designed, with the sponsors, three pivotal Phase 3 trials which enrolled approximately 3,600 patients and was the PI of the largest of these, ORION 11. The latter demonstrated that a 6-monthly dosing schedule sustained a 50% reduction in cholesterol over 18 months (4), which was validated by ORION 9 and 10 (5). These data showed that this first-in-class therapy was effective, safe and well tolerated. The publications reporting this were voted by the Oligonucleotide Therapeutics Society as joint papers of the year and the publication of ORION 10 and 11 was voted by NEJM editors among the 13 top papers they published in 2020 and likely to transform clinical medicine.

Professor Ray and Dr Brandts then assessed the population benefits from cumulative exposure to lower cholesterol. Projecting over a 50-year therapeutic window the cumulative benefits of maintaining the same LDL-C differences, one might expect a 31.2% relative risk reduction for statins, 41.6% relative risk reduction for monoclonal antibodies to PCSK9, and 52% relative risk reduction for siRNAs (6).

3. References to the research (indicative maximum of six references)

(1) Khunti, K., Danese, M.D., Kutikova, L., Catterick, D., Sorio-Vilela, F., Gleeson, M., Seshasai, S.R.K., Brownrigg, J. and Ray, K.K. (2018). Association of a combined measure of adherence and treatment intensity with cardiovascular outcomes in patients with atherosclerosis or other cardiovascular risk factors treated with statins and/or ezetimibe**.** *JAMA Network Open*, 1(8), pp.e185554-e185554. DOI.

(2) Ray, K.K., Landmesser, U., Leiter, L.A., Kallend, D., Dufour, R., Karakas, M., Hall, T., Troquay, R.P., Turner, T., Visseren, F.L., Wijngaard, P., Wright, R.S., Kastelein, J.J. (2017). Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. *New England Journal of Medicine***;** 376(15): 1430-1440. DOI.

(3) Ray, K.K., Stoekenbroek, R.M., Kallend, D., Nishikido, T., Leiter, L.A., Landmesser, U., Wright, R.S., Wijngaard, P.L.J., Kastelein, J.J.P. (2019). Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels: One-Year Follow-up of the ORION-1 Randomized Clinical Trial. *JAMA Cardiology*; 4(11): 1067-1075. DOI.

(4) Ray, K.K., Wright, R.S., Kallend, D., Koenig, W., Leiter, L.A., Raal, F.J., Bisch, J.A., Richardson, T., Jaros, M., Wijngaard, P.L.J., Kastelein, J.J.P., for the ORION-10 and ORION-11 Investigators. (2020). Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *New England Journal of Medicine;* 382: 1507-1519. DOI.

(5) Raal, F.J., Kallend, D., Ray, K.K., Turner, T., Koenig, W., Wright, R.S., Wijngaard, P.L.J., Curcio, D., Jaros, M.J., Leiter, L.A., Kastelein, J.J.P., for the ORION-9 Investigators. (2020). Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *New England Journal of Medicine***;** 382: 1520-1530. DOI.

(6) Brandts, J., and Ray, K.K. (2020). Low Density Lipoprotein Cholesterol–Lowering Strategies and Population Health: Time to Move to a Cumulative Exposure Model. *Circulation*; 141: 873-876. DOI.

4. Details of the impact (indicative maximum 750 words)

CVD is the number one cause of mortality globally. LDL-C lowering is pivotal to reducing cardiovascular events (such as heart attacks), with international guidelines recommending lower LDL-C targets for those at highest risk.

The central approach to achieving these targets has relied upon the use of statins, alone or in combination with other small molecule drugs, which requires patient adherence to a daily dosing regimen. The ORION trials developed and led by Professor Ray at Imperial College represent a paradigm shift in treatment strategy. Inclisiran is a siRNA that inhibits PCSK9 synthesis. siRNA is a novel technology and there was limited experience of its use as a therapeutic agent in humans. By providing compelling evidence that inclisiran is well tolerated and safe when given 6 monthly and that it results in a sustained and clinically important reduction in cholesterol, the ORION trials have opened a new class of therapeutics. Furthermore, by avoiding daily dosing, it enables adherence and the opportunity to meet guidelines for LDL-C reduction, which translate into a reduction in CVD. A competitor approach, namely monoclonal antibodies to PCSK9, requires 26 injections per year.

In 2020, the European Medicines Agency and Committee for Medicinal Products for Human Use approved inclisiran (brand name Leqvio) [**A**]. The data from the ORION studies designed and led by Professor Ray were key to the regulatory approval of inclisiran for hypercholestrolaemia: [redacted]

The potential of this novel first-in-class therapy, together with Professor Ray and Dr Brandts' demonstration of the major population health impact if adopted by healthcare systems, resulted in Novartis buying The Medicines Company and inclisiran for **$9.7 billion**, completed in Jan 2020 [**C**]. Novartis highlighted specifically the results of the comprehensive Phase 3 inclisiran program, which showed potent and durable reduction of >50% in LDL-C on top of standard of care with an excellent safety profile, as the basis for this acquisition [**C**]. [redacted]

Professor Ray's report on how the cumulative effects of long-term uncontrolled LDL-C placed millions of people at increased cardiovascular risk shaped stakeholder acceptance of inclisiran's unique value proposition. With this understanding, Professor Ray together with The Medicines Company, put forward the proposition that a treatment administered by healthcare professionals in line with clinical practice that overcomes non-adherence could address some of the healthcare challenges for the NHS in its Long-Term NHS plan. This has led to a unique partnership between Novartis and the NHS to enable the drug to be made available for 300,000 NHS patients to understand how to best implement this therapy in primary care where the bulk of "at risk patients" are managed [**D**]. This collaboration has the potential to prevent 55,000 heart attacks and strokes and save up to 30,000 lives over the next ten years.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Leqvio market authorisation approval document:
https://www.ema.europa.eu/en/medicines/human/EPAR/leqvio#assessment-history-section
(archived here).

[redacted]

[**C**] Confirmation of Novartis acquisition of The Medicines Company for $9.7 billion:

https://www.novartis.com/news/media-releases/novartis-acquire-medicines-company-usd-97-bn-adding-inclisiran-potentially-transformational-investigational-cholesterol-lowering-therapy-address-leading-global (archived here).

[**D**] NHS/Novartis partnership to make inclirisan available to patients: https://www.gov.uk/government/news/new-heart-disease-drug-to-be-made-available-for-nhs-patients (archived here).