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Effect of Inclisiran on Atherosclerotic Cardiovascular Disease

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Global Thrombosis Forum

in collaboration with

Science Valley Research Institute, São Paulo, BR

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Condition being considered:

- In the Victorion-1 clinical trial, the condition concerned is Atherosclerosis, which is the thickening or hardening of the arteries due to the buildup of cholesterol plaque in arteries.



Figure 1

Burden of Atherosclerosis:

Atherosclerosis usually causes

symptoms such as:

- Shortness of breath
- Chest pain (angina)
- Heart palpitations
- Nausea

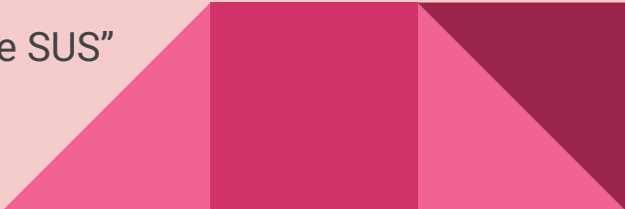


Figure 2

Puts an affected patient at risk for:

- Stroke
- Heart attack
- Vascular dementia
- Limb loss

Epidemiology

- In Brazil, cardiovascular disease has been the main cause of death since the end of the 1960s
 - Caused by the occurrence of lifestyle changes related to globalization and urbanization with higher caloric intakes occurring
 - Along with this, the rapid aging of population due to greater life expectancy and decreased fertility is another cause
 - Since the 1960s, cardiovascular disease has accounted for around 30% of the mortality rate in Brazil
 - According to the AHA journal, “Cardiac conditions accounted for 8.3% of all hospitalizations and for 18.6% of all reimbursement for hospital expenses by the SUS”
- 

Epidemiology

Table 1. Number of Deaths, and Crude and Standardized Mortality Rates for Cardiovascular Diseases, Brazil 2000 to 2011, All Ages

| Year | Deaths | | Population, N | Mortality Rate | |
|------|---------|-----------|---------------|---------------------------|-------------------------|
| | CVD, n | Total, N | | Proportional Mortality, % | Standardized* (/100000) |
| 2000 | 342 743 | 1 033 644 | 173 448 347 | 33.2 | 278 |
| 2001 | 344 875 | 1 043 753 | 175 885 229 | 33.0 | 272 |
| 2002 | 344 925 | 1 056 863 | 178 276 128 | 32.6 | 265 |
| 2003 | 349 685 | 1 074 157 | 180 619 108 | 32.6 | 260 |
| 2004 | 358 444 | 1 095 164 | 182 911 487 | 32.7 | 259 |
| 2005 | 346 363 | 1 076 611 | 185 150 806 | 32.2 | 242 |
| 2006 | 358 383 | 1 101 817 | 187 335 137 | 32.5 | 242 |
| 2007 | 360 605 | 1 115 275 | 189 462 755 | 32.3 | 235 |
| 2008 | 368 539 | 1 142 159 | 191 532 439 | 32.3 | 232 |
| 2009 | 368 542 | 1 163 796 | 193 543 969 | 31.7 | 223 |
| 2010 | 375 296 | 1 201 601 | 195 497 797 | 31.2 | 219 |
| 2011 | 384 615 | 1 238 708 | 197 397 018 | 31.0 | 216 |

Figure 3A

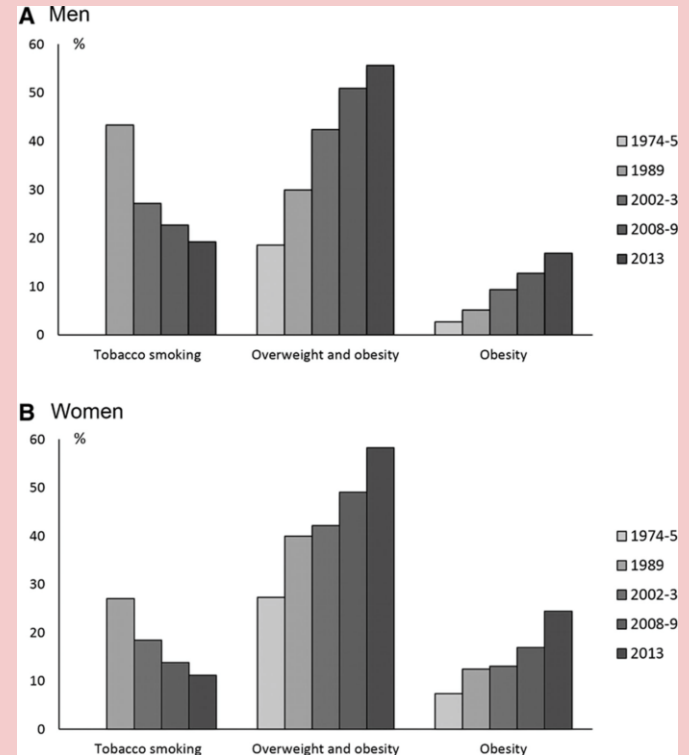


Figure 3B

Current Treatments Available:

- Statins: Lower LDL cholesterol
- Aspirin: Thins the blood to prevent blood clots
- Blood pressure medications: Treat other effects of atherosclerosis
- PCSK9 Monoclonal Antibodies: An injection which blocks the action of PCSK9 and prevents LDL cholesterol buildup



Figure 4A



Figure 4B



Figure 4C

Limitations/Harms:

- Risk of intestinal bleeding with taking aspirin
- Blood pressure medications only helping to treat side effects

Current Treatments Available: (contd.)

Other Non-Medication Treatments:

- Angioplasties or stents: Open the clogged artery
- Endarterectomy: The removal of plaque from the affected artery
- Coronary artery bypass graft surgery (also known as CABG surgery): A healthy blood vessel from another part of the body is taken to create a new path for blood flow for the heart
- Although these surgeries all come with their risks, they are very effective in cases not treatable by medications to clear up plaque buildup.



Figure 5A

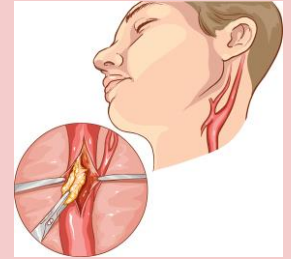


Figure 5B

Pharmacology of Inclisiran

- Inclisiran is a double stranded RNA molecule which works complementary to a segment of the PCSK9 mRNA
- Inclisiran blocks the actions of the protein called PCSK9, which is released by liver cells and raises cholesterol
 - By inhibiting the action of this, cholesterol levels are maintained and buildup of cholesterol plaque in arteries does not occur
- As opposed to other PCSK9 inhibitors which inhibit circulating PCSK9, inclisiran inhibits the initial production of PCSK9 through it's Small interfering (siRNA) which silences specific genes that code for PCSK9

Pharmacology of Inclisiran, contd.

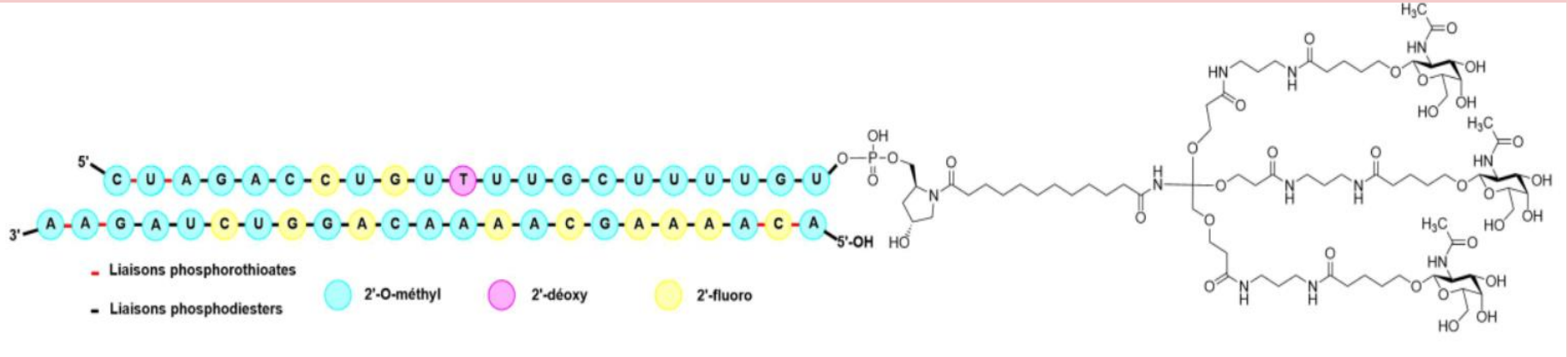
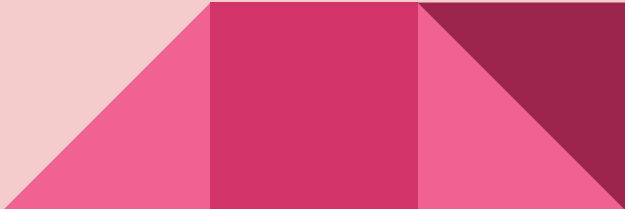


Figure 6

Victorion-1 Clinical Trial:

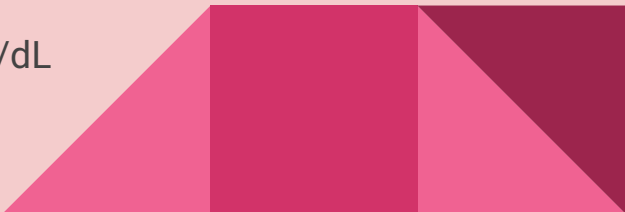
- The Victorion-1 clinical trial evaluates this condition and how it can be initially prevented with Inclisiran in patients at risk for atherosclerosis
- Sponsor: Novartis Pharmaceuticals
- Victorion-1 Research Question:
 - What is the effect of Inclisiran in preventing cardiovascular events in high risk primary prevention patients?

Target Population

- Target Audience for inclisiran: Patients with hypercholesterolemia and patients who are trying to prevent further buildup of cholesterol in their arteries
 - Targeted towards those that have a familial history of high cholesterol amounts as well as those with heightened LDL levels
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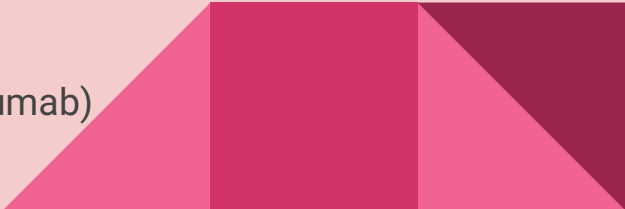
Eligibility Criteria

Main Inclusion Criteria:

- 40 - 79 years old
 - At an increased risk for a first Major cardiovascular event
 - Diabetes
 - Obesity
 - Hypercholesterolemia
 - Use of a statin
 - CAC score obtained by CT-scan ≥ 100 Agatston units
 - LDL-C levels greater than or equal to 70 mg/dL but less than 90 mg/dL
- 

Eligibility Criteria, contd.

Main Exclusion Criteria:

- History of a Major ASCVD
 - Heart attack
 - Stroke
 - Liver dysfunction
 - Myocardial infarction
 - History of procedures such as a Revascularization or an Amputation
 - Conditions such as Intermittent claudication or Acute coronary syndrome
 - Pregnant
 - Usage of monoclonal antibody treatments (ie. Evolocumab or Alirocumab)
 - Active Hepatic Dysfunction
- 

Intervention/Study Design

- Inclisiran is subcutaneously injected in a pre-filled syringe in 300 mg amounts on Day 1, Day 90, and every 6 months after that
- The study is designed with these being randomized in a 1:1 ratio along with the placebo
- It is a double blinded trial
 - Researchers and participants do not know if they are receiving the placebo or the intervention

Inclisiran injection



Figure 7

Common Patient Concerns/Questions

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graph LR; A[Common Patient Concerns/Questions] --- B[How long does this trial last?]; A --- C[How does the intervention work? (Will I be injected or does it work through pills?)]; A --- D[How often do I have to take the intervention?]; A --- E[Can I drop out at any time?]; A --- F[Is my transportation covered?]; A --- G[Can I receive any benefits from this trial?]; A --- H[What other medications can I take/not take during this trial?]; A --- I[What are the possible side effects?];
```

How long does this trial last?

*How does the intervention work?
(Will I be injected or does it work through pills?)*

How often do I have to take the intervention?

Can I drop out at any time?

Is my transportation covered?

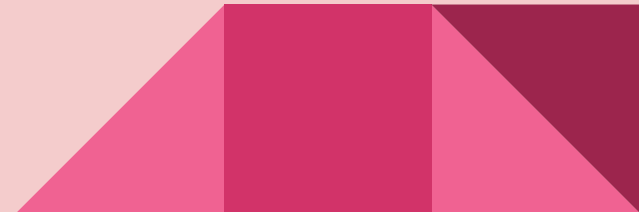
Can I receive any benefits from this trial?

What other medications can I take/not take during this trial?

What are the possible side effects?

Current Comparator

- The current gold standard of treatment for this condition is the use of statins
- However, statins can be used during the interventional study, making it that there is no possible comparator as statins are not being put in comparison with Inclisiran
- As statins work on patients with atherosclerosis and hypercholesterolemia, this drug works for patients at risk of atherosclerosis who do not have it yet



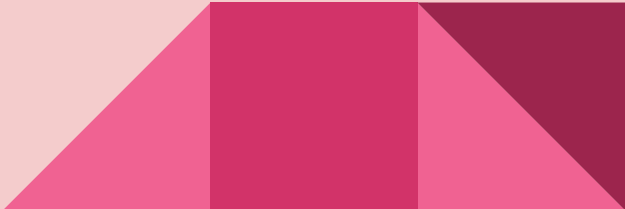
Outcomes

Primary Outcome:

- The primary outcome being measured in this study is the time to the first occurrence of a 4 point Major Cardiovascular Event
 - The 4 point MACE includes a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, and a CABG (Coronary Artery Bypass Graft) Surgery

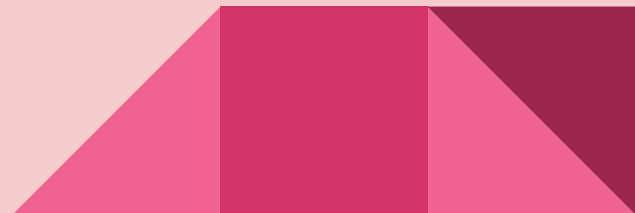
Outcomes

Secondary Outcome:

- Time to first occurrence of first 3 point MACE
 - 3 point Major cardiovascular event includes a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke
 - Total number of first or repeated 3 point or 4 point Major cardiovascular event
 - Time to occurrence of cardiovascular death
 - Time to occurrence of death
- 

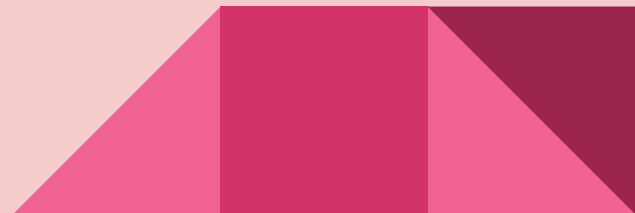
Outcomes

- All outcomes are measured within a time period of up to 75 months after the trial begins



Time

- Patients apart of this clinical trial come in once every 6 months to receive the randomized intervention
- Time is important because patients must come in on the scheduled date and time for the study to effectively take place
 - If a patient misses an appointment multiple times, the results of the clinical trial may be affected



AI Tool Recruitment Strategy

- Searched using the AI tool to identify patients who fit the eligibility criteria of the clinical trial

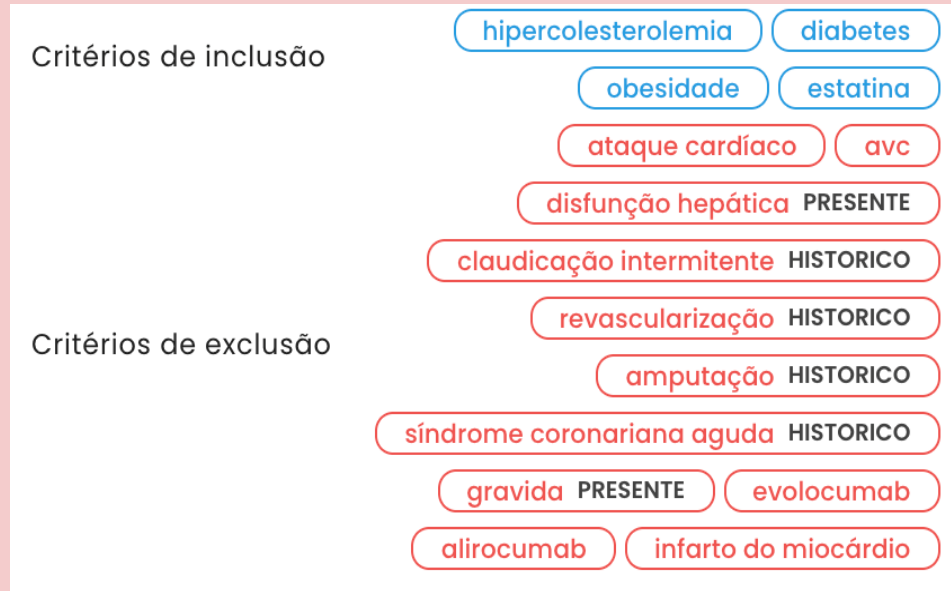


Figure 9

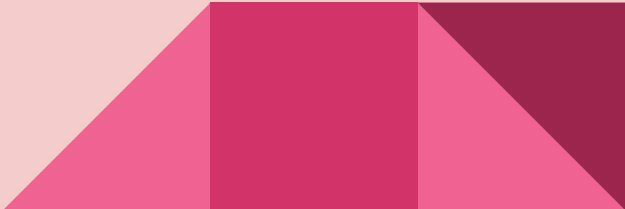
Demographics

- 9 Patients total

Gender:

- 3 male and 6 female
- Differed from initial search of all males

Age:

- Five out of the nine patients were aged 71 and older
 - Three were aged between 51 and 70
 - One patient was aged between 40 and 50
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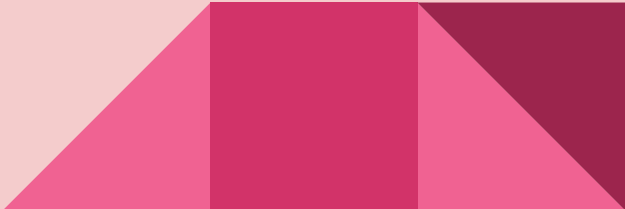
Demographics

- All of the 9 patients had been using statins prior to or during this event
- Seven out of the nine patients presently have hypercholesterolaemia.
- This has caused me to believe that the other 2 patients are at risk for hypercholesterolaemia, making them eligible for this study.

Main procedures or screenings:

- Coronary angiograms and ECGs

Main Symptoms:

- Edema
 - Dyspnea
 - Chest pain
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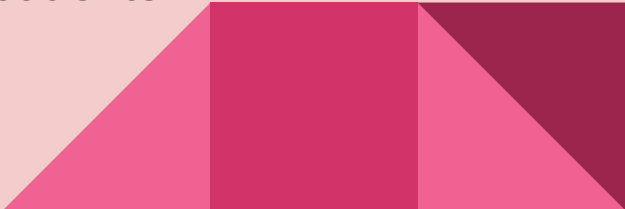
Demographics

Top drugs:

- Clopidogrel (antiplatelet drug)
- Statins

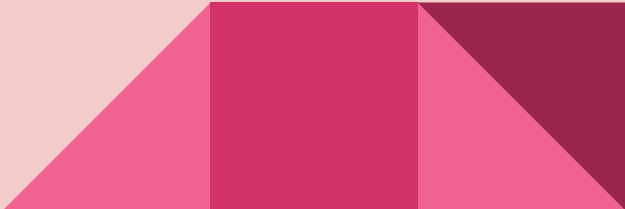


Future Recruitment Strategy Ideas

- Visiting Elderly Homes
 - Discuss with major caregiver companies on approaching patients who they find eligible for this study
 - Contact pharmacies in sending out QR code flyers with certain medications that would be used in a patient (ie. statins, insulin, etc.)
 - Communicate with endocrinologists specifically and other physicians about this trial and provide them with fliers to give to their patients
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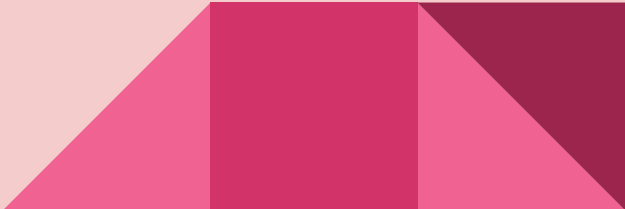
Research Question

Next Steps:

- What is the effect of the use of inclisiran in patients who have lipid profiles showing elevated triglyceride levels but normal cholesterol levels?
 - What is the cost-effectiveness of inclisiran compared to statins and other treatment drugs in managing patients' conditions?
- 

My Perspective on this Internship

Throughout this internship, I:

- Got to understand the basics of a clinical trial and was showed the realities of how hard it is to obtain patients who meet the criteria, convince those patients to get involved in the trial, and undergo the processes of a clinical trial
 - Worked with the AI tool for recruiting patients and attempted to find patients eligible
 - Saw the Victorion-2 clinical trial taking place with Dr. Valeria Aguiar, Isabel, and Raquel from the Science Valley Research Center in Santo Andre.
 - Saw blood samples being taken and intervention being administered for patients on their 9 month visit
 - Learned about eCRFs and other forms used in the clinical trial
 - Became GCP Certified
- 

My Perspective on this Internship



- Viewed various patient consultations with Dr. Ramacciotti
 - Saw many patients with DVTs, aneurysms, varicose veins, and other conditions
 - Saw the great bedside manner which Dr. Ramacciotti maintained with his patients
- Viewed multiple surgeries within the surgery center.
 - Multiple Vascular Surgeries (some with a laser), a Procto-surgery, a live C-section, a hernia removal, and an orthopedic knee surgery
- Presented my poster on the Role of Nurses in the Management of VTE to the nurses in Santo Andre
- Visited Santa Casa hospital in Santos where we got to see state of the art technology along with historical artifacts



Presenting Poster to Nurses



Working on the Summer Project



In the Surgery Center in Santo Andre



Presented GTF Experience to Physician Pharmaceutical Representatives



Using Da Vinci surgery Robot Training Simulator in Santa Casa



After Final Presentation with SVRI Team

Acknowledgements During My Internship

I greatly appreciate all of the time which Dr. Ramacciotti, Camilla, Leandro, everyone at SVRI Villa Olympia, the research center in Santo Andre, and those at the SVRI location in Santos at Santa Casa hospital took out of their busy work days to help guide us with our projects and teach us new things.

A stylized, handwritten-style graphic of the words "Thank You" in black ink. The text is surrounded by several short, radiating lines, giving it a sunburst or celebratory appearance. The background of the slide features a decorative footer with a blue horizontal bar at the bottom and a pink and purple geometric pattern of triangles above it.

References

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- https://safe.ihealthgroup.tec.br/auth/realms/shc/protocol/openid-connect/auth?client_id=shc-cp-cli&redirect_uri=https%3A%2F%2Fshc.ihealthgroup.tec.br%2Fapp%2Ffn%2Fdashboard&state=9d82b43e-b933-4297-842f-d358b6f145a0&response_mode=fragment&response_type=code&scope=openid%20profile%20email%20offline_access%20dcad15ce-47be-8eee-2d86e16a8be0