CT Application(s) Summary Report

- **Protocol title:** A randomized, double-blind, placebo- and active controlled multicentre trial to demonstrate efficacy of subcutaneous Secukinumab compared to placebo and etanercept (in a single blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from 6 to less than 18 years of age with severe chronic plaque psoriasis
- **Protocol code number:** CAIN457A2310
- **Public Registry Number: EudraCT:** 2014-005663-32
- **Version:** Amended Protocol Version 4
- **Date:** 18 September 2020

- **Investigational Medicinal Product being tested:**

Biological ■ **Pharmaceutical** ☐ **Innovative** ☐
Herbal medicine ☐ **Medical device** ☐

- **Sponsor:** Novartis
- **Indication: :** pediatric patients with severe chronic plaque psoriasis
- **Investigator's brochure (IB)**

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- **EDA approval date:**
1. Initial approval on Amendment Protocol version 4.0 dated 18\09\2022 and IB version 21 dated 05 August 2021 on 04\12\2022
2. Amendment approval of IB version 22 dated 04 August 2022 on 09\03\2023

- **Summary of pre-clinical studies:**

The non-clinical development program for Secukinumab included comprehensive **pharmacology**, **pharmacokinetic**, and **toxicology** studies conducted in accordance with ICH S6 guidance for biotechnology-derived pharmaceuticals.
The **cynomolgus monkey** was identified as the relevant species for evaluating human safety due to its pharmacological responsiveness to IL-17A inhibition.

Pharmacology studies confirmed that Secukinumab is a fully human monoclonal antibody that selectively

binds and neutralizes IL-17A, thereby inhibiting its pro-inflammatory activity.

Tissue cross-reactivity studies demonstrated no relevant off-target tissue binding, supporting the specificity of the antibody.

Pharmacokinetic studies showed characteristics typical of IgG monoclonal antibodies, including limited distribution, low clearance, dose-proportional exposure, and a prolonged elimination of half-life.

Drug-drug interaction studies were not considered necessary because monoclonal antibodies are not metabolized through cytochrome P450 enzymes or UGT pathways, and clinically relevant metabolic interactions are not expected.

The **toxicology program** included **safety pharmacology**, **single-dose** and **repeated-dose toxicity**, **reproductive toxicity**, and other specialized safety studies performed under GLP conditions.

Secukinumab was generally well tolerated, with the no-observed-adverse-effect level (NOAEL) established at the highest tested dose of 150 mg/kg/week in repeated-dose studies. No biologically relevant off-target effects or significant safety findings were identified. Reproductive and developmental toxicity studies demonstrated no evidence of teratogenicity, embryotoxicity, impairment of fertility, or adverse effects on reproductive organs. Studies using the mouse surrogate antibody (BZN035) similarly showed no adverse effects on fertility or pre- and postnatal development.

Although no dedicated juvenile toxicity studies were conducted, no treatment-related adverse findings were observed in developmental or reproductive toxicity studies, and ongoing pediatric clinical development has not identified unexpected non-clinical safety concerns. Genotoxicity and conventional carcinogenicity studies were not performed, consistent with ICH recommendations for biotechnology-derived products. Available scientific evidence indicates that IL-17A neutralization is not associated with increased tumor-promoting potential, Secukinumab is not considered a potent immunosuppressant, and the IgG1 antibody structure does not present an inherent carcinogenic risk.

Overall, the preclinical data confirmed the pharmacological activity and mechanism of action of Secukinumab and demonstrated a favorable non-clinical safety profile. The absence of relevant toxicity, together with acceptable reproductive safety and low carcinogenic risk, supports the continued clinical use of Secukinumab through both intravenous and subcutaneous administration at the proposed therapeutic doses.

• Summary of previous clinical studies:

-Phase I \early efficacy studies Clinical Studies of Secukinumab:

Study Code	Indication/Population	Status	Study Design	Key Results
CAIN457A2101	Patients with rheumatoid arthritis (First-in-human)	Completed	First-in-human clinical study evaluating the safety, pharmacokinetics, and preliminary efficacy of intravenous Secukinumab in patients with rheumatoid arthritis.	Demonstrated acceptable safety, pharmacokinetics and preliminary efficacy, supporting further clinical development.
CAIN457A2104	Healthy volunteers	Completed	Double-blind, placebo-controlled, parallel-group study with an open-label	Secukinumab inhibited IL-17A-mediated inflammatory

			corticosteroid reference arm evaluating the effect of intravenous Secukinumab	responses but produced limited inhibition of ozone-induced airway neutrophilia compared with corticosteroid treatment. The study confirmed biological activity and demonstrated an acceptable safety profile without unexpected adverse events.
CAIN457A2105	Healthy volunteers	Completed	Randomized, double-blind, placebo-controlled, single-dose study evaluating three subcutaneous formulations	All dose levels were safe and well tolerated. Pharmacokinetic analysis demonstrated dose-proportional exposure and comparable bioavailability across formulations, supporting selection of the commercial subcutaneous formulation for subsequent Phase II and III clinical studies.

Phase II Studies:

- **Psoriasis Studies**

Study Code	Study Code	Study Code	Study Code
CAIN457A2102	Completed	Phase II, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study in patients with moderate-to-severe plaque psoriasis evaluating multiple intravenous Secukinumab dose regimens.	Demonstrated significant clinical efficacy compared with placebo, with rapid improvements in PASI responses. The study identified effective dose levels and confirmed an acceptable safety profile, supporting progression to Phase III development.
CAIN457A2211	Completed	Phase II, randomized, double-blind, placebo-controlled,	Demonstrated superior PASI75, PASI90, and PASI100 responses

		multicenter dose-ranging study evaluating subcutaneous Secukinumab induction and maintenance regimens in patients with moderate-to-severe plaque psoriasis.	compared with placebo. The study established the optimal induction and maintenance dosing schedules that were subsequently adopted in the Phase III psoriasis program. Safety findings were consistent with the known safety profile of Secukinumab.
CAIN457A2212	Completed	Phase II, randomized, double-blind, placebo-controlled, multicenter study evaluating subcutaneous Secukinumab dose-response in moderate-to-severe plaque psoriasis.	Confirmed a clear dose-response relationship, with higher Secukinumab doses producing greater clinical efficacy while maintaining an acceptable safety profile. The results contributed to selection of the 150 mg and 300 mg regimens for confirmatory Phase III studies
CAIN457A2220	Completed	Phase II, randomized, double-blind, placebo-controlled, multicenter dose-finding study in patients with moderate-to-severe plaque psoriasis.	Demonstrated rapid onset and sustained improvement in psoriasis severity with Secukinumab treatment. The study further confirmed the efficacy and safety of the selected dosing regimens and supported dose optimization for the Phase III clinical development program.

The four randomized Phase II studies (CAIN457A2102, CAIN457A2211, CAIN457A2212, and CAIN457A2220) demonstrated robust efficacy and an acceptable safety profile of Secukinumab in patients with moderate-to-severe plaque psoriasis. Collectively, these studies established the optimal induction and maintenance dosing regimens (150 mg and 300 mg) that were subsequently carried forward into the global Phase III psoriasis development program.

➢ Psoriatic Arthritis (PsA)

Study Code	Study Code	Study Code	Study Code
CAIN457F2206	Completed	Phase II, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy, safety, and tolerability of intravenous Secukinumab in patients with active psoriatic arthritis.	The study met its primary efficacy endpoint, demonstrating significantly greater ACR20 responses compared with placebo. Improvements were also observed in ACR50/70 responses, disease activity, physical function, and skin manifestations. Secukinumab was generally well tolerated, with a safety profile

			consistent with IL-17A inhibition.
CAIN457F2206E1	Completed	Open-label extension study evaluating the long-term efficacy, safety, and tolerability of Secukinumab in patients completing study CAIN457F2206. Patients were treated for up to 5 years, with dose escalation permitted after Week 156 where clinically indicated.	Clinical improvements achieved during the core study were maintained or further improved throughout the extension. Sustained responses were observed for ACR20/50/70, PASI75/90, DAS28-CRP, Minimal Disease Activity (MDA), dactylitis, enthesitis, physical function, and quality of life. Long-term treatment remained well tolerated without new or unexpected safety signals.

The Phase II PsA development program demonstrated that Secukinumab produced rapid and sustained improvements in joint and skin manifestations of psoriatic arthritis while maintaining an acceptable long-term safety profile. These findings supported advancement into the pivotal FUTURE Phase III clinical program.

- **Rheumatoid Arthritis**

Study Code	**Study Code**	**Study Code**	**Study Code**
CAIN457A2206	Completed	Phase II, randomized, double-blind, placebo-controlled, dose-ranging study evaluating intravenous Secukinumab in patients with active rheumatoid arthritis receiving stable methotrexate therapy.	Secukinumab demonstrated improvements in ACR responses and disease activity compared with placebo. The study confirmed biological activity and an acceptable safety profile, supporting further clinical development in RA.
CAIN457A2208	Completed	Phase II, randomized, double-blind, placebo-controlled study evaluating different intravenous dose regimens of Secukinumab in patients with active rheumatoid arthritis.	Demonstrated clinical improvements in disease activity with an acceptable safety profile. Results contributed to dose selection for subsequent Phase III studies.
CAIN457A2209	Completed	Phase II, randomized, double-blind, placebo-controlled, multicenter study in patients with active rheumatoid arthritis inadequately controlled with conventional therapy.	Confirmed clinical efficacy across multiple disease activity measures with no unexpected safety findings. Data supported advancement to confirmatory Phase III studies.

The Phase II RA studies demonstrated that Secukinumab had biological and clinical activity in patients

with active rheumatoid arthritis and showed an acceptable safety profile. These findings supported progression to large Phase III trials. However, although later Phase III studies met some efficacy endpoints, Secukinumab demonstrated lower clinical efficacy than the active comparator (abatacept). Consequently, Novartis discontinued the rheumatoid arthritis development program for strategic efficacy reasons rather than due to safety concerns.

- **Ankylosing Spondylitis**

Study Code	Study Code	Study Code	Study Code
CAIN457F2305 (MEASURE 1)	Completed	Phase II/III randomized, double-blind, placebo-controlled, multicenter study evaluating intravenous loading doses followed by subcutaneous maintenance doses (75 mg and 150 mg) in patients with active ankylosing spondylitis.	The study met its primary endpoint, demonstrating significantly higher ASAS20 response rates with secukinumab 150 mg compared with placebo at Week 16. Improvements were also observed in ASAS40, BASDAI, ASDAS-CRP, spinal mobility, physical function, and quality of life. Clinical responses were sustained during long-term follow-up, with a favorable safety profile.
CAIN457F2305E1	Completed	Open-label extension study evaluating the long-term efficacy and safety of Secukinumab in patients completing the core MEASURE 1 study. Patients were treated for up to 5 years, with dose escalation permitted after Week 156 where clinically indicated.	Sustained improvements in disease activity, physical function, and patient-reported outcomes were maintained for up to 5 years. Long-term treatment remained well tolerated without new or unexpected safety findings.

Those studies demonstrated that Secukinumab provided rapid, clinically meaningful, and sustained improvements in patients with active ankylosing spondylitis. The long-term extension confirmed durable efficacy for up to five years and a consistent safety profile, supporting progression to the broader Phase III ankylosing spondylitis development program.

- **Uveitis**

Study Code	Study Code	Study Code	Study Code
CAIN457C2302 (INSURE)	Completed	Phase II, multicenter, randomized, double-masked, placebo-controlled, dose-ranging study	The study did not demonstrate a significant clinical benefit over placebo in preventing uveitis

		evaluating intravenous Secukinumab for inducing and maintaining uveitis suppression in adults with active non-infectious intermediate, posterior, or panuveitis requiring immunosuppressive therapy.	recurrence. The efficacy results did not support further development of the intravenous regimen in this indication. Secukinumab was generally well tolerated, with no new safety concerns identified.
CAIN457C2302E1	Completed	Extension study of CAIN457C2302 designed to assess the long-term safety and efficacy of Secukinumab.	The extension was terminated after completion of the core study. No additional efficacy conclusions beyond those of the parent study were established, and no new safety signals were observed.
CAIN457C2303 (SHIELD)	Completed	Phase II, multicenter, randomized, double-masked, placebo-controlled study evaluating subcutaneous Secukinumab as adjunctive therapy in patients with Behçet's disease-associated posterior or panuveitis receiving standard immunosuppressive therapy.	The study failed to demonstrate superiority over placebo in reducing recurrent uveitis exacerbations. The safety profile remained consistent with previous Secukinumab experience.
CAIN457C2303E1	Completed	Extension study of CAIN457C2303 evaluating long-term safety and efficacy.	Long-term follow-up did not demonstrate additional efficacy beyond the core study. Safety findings remained consistent with the known safety profile of Secukinumab, without unexpected adverse events.

The Phase II uveitis development program **did not demonstrate sufficient efficacy for Secukinumab** in the treatment of non-infectious uveitis or Behçet's disease-associated uveitis. Consequently, development in these indications was discontinued. Despite the lack of efficacy, the safety profile remained consistent with that observed across other Secukinumab clinical studies, with no new or unexpected safety concerns.

- **Other Indications**

Study Code/ indication	**Study Code**	**Study Code**	**Study Code**
CAIN457ADE11C (TitAIN)	Completed	Phase II, randomized, double-blind, placebo-controlled, multicenter trial evaluating	The study met its primary endpoint. Sustained remission was achieved in 70.4% of Secukinumab-treated

newly diagnosed or relapsing giant cell arteritis (GCA)		Secukinumab 300 mg plus a 26-week prednisolone taper versus placebo plus prednisolone in patients with newly diagnosed or relapsing giant cell arteritis (GCA).	patients at Week 28 and 59.3% at Week 52 compared with 24.0% and 8.0%, respectively, in the placebo group. The safety profile was consistent with previous Secukinumab experience, with no new safety signals identified.
CAIN457X2201 **Active overuse tendinopathy refractory to NSAIDs, physiotherapy, or corticosteroid injections**	Completed	Phase II, randomized, double-blind, placebo-controlled, parallel-group study evaluating Secukinumab in patients with active overuse tendinopathy refractory to NSAIDs, physiotherapy, or corticosteroid injections.	Secukinumab did not demonstrate sufficient clinical efficacy compared with placebo. No new or unexpected safety findings were observed, and the overall safety profile remained consistent with previous studies.
CPJMR0092202 **Dry eye syndrome**	Completed	Phase II, randomized, double-blind, placebo-controlled proof-of-concept study evaluating intravenous Secukinumab or ACZ885 in patients with dry eye syndrome.	The study did not demonstrate clinically meaningful efficacy for Secukinumab in dry eye syndrome. Safety findings were consistent with the known safety profile of Secukinumab, and no new safety concerns were identified.

The exploratory Phase II studies demonstrated variable outcomes across different immune-mediated diseases. Secukinumab showed positive proof-of-concept in giant cell arteritis, achieving significantly higher sustained remission rates than placebo. In contrast, studies in overuse tendinopathy and dry eye syndrome did not demonstrate sufficient clinical efficacy to justify further development. Across all studies, Secukinumab maintained a favorable and consistent safety profile without unexpected adverse events.

Phase III Studies:

- **Plaque Psoriasis**

Study Code	Study Code	Study Code	Study Code
CAIN457A2302 (ERASURE)	Completed	Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy, safety, and tolerability of subcutaneous Secukinumab (150 mg and 300 mg) in patients with moderate-to-severe plaque psoriasis for up to 52 weeks.	The study met its primary endpoints. Both Secukinumab doses demonstrated significantly higher PASI 75 and IGA mod 2011 0/1 response rates than placebo at Week 12. Clinical responses were rapid, durable through Week 52, and accompanied by a safety profile

			consistent with previous studies, with no new safety signals.
CAIN457A2303 (FIXTURE)	Completed	Phase III, randomized, double-blind, double-dummy, placebo- and active-controlled multicenter study comparing Secukinumab (150 mg and 300 mg) with etanercept and placebo in patients with moderate-to-severe plaque psoriasis.	Secukinumab was superior to both placebo and etanercept in achieving PASI 75, PASI 90, PASI 100, and IGA 0/1 responses at Week 12. Clinical responses were sustained through Week 52, and Secukinumab demonstrated a favorable safety profile comparable to previous clinical experience.
CAIN457A2304 (SCULPTURE)	Completed	Phase III, randomized, double-blind study evaluating fixed-interval maintenance dosing versus retreatment-as-needed after an initial open-label induction period in patients responding to Secukinumab.	Fixed-interval maintenance dosing every 4 weeks was significantly more effective than retreatment-as-needed in maintaining PASI 75, PASI 90, and PASI 100 responses over 52 weeks. Safety remained consistent with the established profile of Secukinumab.
CAIN457A2307 (CLEAR)	Completed	Phase IIIb, randomized, double-blind, active-controlled multicenter study comparing secukinumab 300 mg with ustekinumab in patients with moderate-to-severe plaque psoriasis.	Secukinumab demonstrated superior efficacy to ustekinumab, with significantly higher PASI 90 response rates at Week 16. Improvements were maintained through one year, with a comparable safety profile between treatment groups.
CAIN457A2308 (FEATURE)	Completed	Phase III, randomized, double-blind, placebo-controlled multicenter study evaluating the efficacy and usability of Secukinumab administered using a prefilled syringe in patients with moderate-to-severe plaque psoriasis.	Secukinumab significantly improved PASI and IGA responses compared with placebo while demonstrating successful self-administration using the prefilled syringe. The safety profile was consistent with previous studies.
CAIN457A2309 (JUNCTURE)	Completed	Phase III, randomized, double-blind, placebo-controlled multicenter study evaluating Secukinumab administered using an autoinjector device in patients with moderate-to-severe plaque psoriasis.	The study confirmed significant efficacy versus placebo and demonstrated that self-administration with the autoinjector was feasible, effective, and well tolerated, with no new safety concerns.
CAIN457A2313	Completed	Phase IIIb, randomized, double-	Secukinumab demonstrated superior

(CLARITY)		blind, head-to-head study comparing Secukinumab with ustekinumab in patients with moderate-to-severe plaque psoriasis.	skin clearance, with significantly greater PASI 90, PASI 100, and IGA 0/1 responses compared with ustekinumab. Safety profiles were comparable between the two treatments.

The Phase III psoriasis development program consistently demonstrated that Secukinumab provides rapid, robust, and sustained clinical efficacy in patients with moderate-to-severe plaque psoriasis. Across placebo-controlled, active-comparator, and device usability studies, Secukinumab achieved superior PASI and Investigator's Global Assessment responses while maintaining a favorable and consistent safety profile. These studies established the efficacy of the 150 mg and 300 mg dosing regimens and supported the global regulatory approval of Secukinumab for plaque psoriasis.

- **Psoriatic Arthritis**

Study Code	Study Code	Study Code	Study Code
CAIN457F2306 (FUTURE 1)	Completed	Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating intravenous loading doses followed by subcutaneous Secukinumab (75 mg and 150 mg) in patients with active psoriatic arthritis.	The study met its primary endpoint, with significantly higher **ACR20** response rates at Week 24 compared with placebo. Significant improvements were also observed in ACR50/70, PASI responses, HAQ-DI, resolution of dactylitis and enthesitis, inhibition of radiographic progression, and quality of life. Clinical responses were maintained through long-term extension, with a favorable safety profile.
CAIN457F2312 (FUTURE 2)	Completed	Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating subcutaneous Secukinumab (75, 150, and 300 mg) without intravenous loading in patients with active psoriatic arthritis.	Secukinumab significantly improved ACR20, ACR50, ACR70, PASI75/90, physical function, and disease activity compared with placebo. Clinical benefits were sustained over long-term follow-up, with safety findings consistent with previous studies.
CAIN457F2318 (FUTURE 5)	Completed	Phase III, randomized, double-blind, placebo-controlled study evaluating secukinumab (150 mg and 300 mg) with or without loading doses in patients with	The study demonstrated significant improvements in ACR20 responses and significantly inhibited radiographic progression compared with placebo. Improvements in joint

		active psoriatic arthritis.	and skin manifestations, dactylitis, enthesitis, and patient-reported outcomes were maintained through long-term treatment.
CAIN457F2336 (FUTURE 4)	Completed	Phase III, randomized, double-blind, placebo-controlled study evaluating subcutaneous secukinumab with and without loading regimens in patients with active psoriatic arthritis.	Secukinumab demonstrated clinically meaningful improvements across musculoskeletal and skin endpoints, with sustained efficacy during long-term follow-up. The safety profile remained favorable and consistent with previous clinical studies.
CAIN457F2366 (EXCEED)	Completed	Phase IIIb, randomized, double-blind, active-controlled study comparing secukinumab 300 mg with adalimumab in biologic-naïve patients with active psoriatic arthritis.	The primary endpoint (superiority for ACR20 at Week 52) was **not met**. However, secukinumab demonstrated comparable efficacy to adalimumab across musculoskeletal outcomes and superior skin responses (PASI90/PASI100), while maintaining its established safety profile.
CAIN457F3302 (MAXIMISE)	Completed	Phase IIIb, randomized, double-blind, placebo-controlled study evaluating secukinumab in patients with psoriatic arthritis and axial manifestations despite NSAID treatment.	Secukinumab significantly improved axial symptoms, achieving higher **ASAS20** response rates than placebo and demonstrating clinically meaningful improvements in spinal pain, function, and disease activity. Safety findings were consistent with the known safety profile.
CAIN457F3301 (ACHILLES)	Completed	Phase IIIb, randomized, double-blind, placebo-controlled study evaluating secukinumab in patients with spondyloarthritis and heel enthesitis.	Although the primary endpoint was not statistically significant, secukinumab demonstrated numerical improvements in heel enthesitis and other disease activity measures. The overall safety profile remained favorable and consistent with previous studies.
CAIN457F2306E1	Completed	Long-term open-label extension of FUTURE 1 evaluating sustained efficacy and safety.	Sustained improvements in ACR20/50/70 responses, inhibition of structural damage, skin disease, dactylitis, enthesitis, and physical function were maintained for up to **5**

			years, with no new safety signals identified.

The Phase III FUTURE program consistently demonstrated that Secukinumab provides significant and sustained improvements in the musculoskeletal and dermatological manifestations of psoriatic arthritis. Across placebo-controlled, active-comparator, and extension studies, Secukinumab improved joint symptoms, skin disease, enthesitis, dactylitis, physical function, and inhibited radiographic progression while maintaining a favorable long-term safety profile. These studies established Secukinumab as an effective treatment option for active psoriatic arthritis and supported its global regulatory approval.

- **Ankylosing Spondylitis**

Study Code	**Study Code**	**Study Code**	**Study Code**
CAIN457F2305 (MEASURE 1)	Completed	Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating intravenous loading doses followed by subcutaneous secukinumab (75 mg and 150 mg) in patients with active ankylosing spondylitis.	The study met its primary endpoint, demonstrating significantly higher ASAS20 response rates at Week 16 compared with placebo. Significant improvements were also observed in ASAS40, BASDAI, ASDAS-CRP, spinal mobility, physical function, quality of life, and MRI inflammation. Clinical efficacy was sustained through the long-term extension, with a favorable safety profile.
CAIN457F2310 (MEASURE 2)	Completed	Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating subcutaneous secukinumab (75 mg and 150 mg) without intravenous loading in patients with active ankylosing spondylitis.	Secukinumab demonstrated significantly greater **ASAS20 and ASAS40** responses than placebo, together with improvements in disease activity, function, pain, and quality of life. Benefits were maintained during long-term follow-up, with no new safety concerns.
CAIN457F2314 (MEASURE 3)	Completed	Phase III, randomized, double-blind, placebo-controlled study evaluating secukinumab 150 mg and 300 mg following intravenous loading in patients with active ankylosing spondylitis.	Both doses produced significant improvements in **ASAS20**, **ASAS40**, disease activity, spinal mobility, and patient-reported outcomes compared with placebo. The 300 mg dose provided greater improvements in some secondary endpoints while maintaining an acceptable safety profile.

CAIN457F2320 (MEASURE 4)	Completed	Phase III, randomized, double-blind, placebo-controlled study evaluating subcutaneous secukinumab 150 mg with and without loading doses.	Although the primary endpoint was **not statistically met** because of an unexpectedly high placebo response, efficacy outcomes generally favored secukinumab and were consistent with previous MEASURE studies. The safety profile remained favorable.
CAIN457F2322 (MEASURE 5)	Completed	Phase III, randomized, double-blind, placebo-controlled study conducted primarily in China evaluating secukinumab 150 mg in patients with active ankylosing spondylitis.	The study successfully met its primary endpoint, demonstrating significant improvements in **ASAS20**, disease activity, spinal function, and quality of life compared with placebo. Safety findings were consistent with the global secukinumab program.
CAIN457F2305E1	Completed	Long-term open-label extension of MEASURE 1 evaluating sustained efficacy and safety.	Clinical improvements achieved during the core study were maintained for **up to 5 years**, including sustained **ASAS20/40**, BASDAI, ASDAS, spinal mobility, and patient-reported outcomes. No cumulative toxicity or new safety signals were identified.
CAIN457F2310E1	Completed	Long-term extension study of MEASURE 2.	Confirmed durable efficacy and long-term safety, with sustained improvements in clinical and functional outcomes throughout follow-up. The safety profile remained consistent with previous studies.

The MEASURE clinical development program consistently demonstrated that Secukinumab provides rapid, clinically meaningful, and sustained improvements in patients with active ankylosing spondylitis. Across five pivotal studies and their long-term extensions, Secukinumab significantly improved disease activity, spinal mobility, physical function, pain, and health-related quality of life, with sustained efficacy for up to five years. Although MEASURE 4 did not achieve statistical significance for its primary endpoint due to a high placebo response, its efficacy trends were consistent with the overall program. The long-term safety profile remained favorable and supported the global approval of secukinumab for ankylosing spondylitis.

➢ Non-radiographic Axial Spondyloarthritis (nr-axSpA)

Study Code	Study Code	Study Code	Study Code
CAIN457F2315 (PREVENT)	Completed	Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating subcutaneous secukinumab 150 mg with and without loading doses in patients with active non-radiographic axial spondyloarthritis who had an inadequate response or intolerance to NSAIDs.	The study met its primary endpoint, demonstrating significantly higher **ASAS40** response rates with secukinumab compared with placebo. Significant improvements were also observed in ASDAS-CRP, BASDAI, spinal pain, physical function, quality of life, and MRI evidence of inflammation. Clinical responses were sustained during long-term follow-up, and the safety profile was consistent with previous secukinumab studies.
CAIN457F2315E1	Ongoing/Extension	Open-label extension study evaluating the long-term efficacy and safety of secukinumab in patients completing the PREVENT study.	Long-term analyses demonstrated sustained improvements in disease activity, physical function, spinal pain, and patient-reported outcomes, with no new or unexpected safety signals observed during extended treatment.

The PREVENT study demonstrated that secukinumab significantly improved the signs and symptoms of active non-radiographic axial spondyloarthritis in patients with inadequate response to NSAIDs. Improvements in disease activity, function, pain, and MRI inflammation were sustained over long-term follow-up, while maintaining a favorable safety profile consistent with previous indications. These findings supported the approval of secukinumab for the treatment of active non-radiographic axial spondyloarthritis.

➢ Rheumatoid Arthritis

Study Code	Study Code	Study Code	Study Code
CAIN457A2306 (REASSURE 1)	Completed	Phase III, randomized, double-blind, placebo- and active-controlled, multicenter study evaluating intravenous loading doses followed by subcutaneous secukinumab (75 mg and 150 mg) versus placebo and abatacept in	Secukinumab demonstrated significant improvements in ACR responses compared with placebo; however, the magnitude of efficacy was lower than that observed with abatacept. The overall safety profile was favorable and consistent with

		patients with active rheumatoid arthritis and inadequate response to methotrexate.	previous studies, without new safety signals.
CAIN457A2306E1	Completed	Open-label extension study assessing the long-term efficacy and safety of secukinumab in patients completing REASSURE 1.	Long-term treatment demonstrated sustained clinical responses and a safety profile consistent with previous studies. No cumulative toxicity or unexpected adverse events were observed.
CAIN457A2317 (REASSURE 2)	Terminated	Phase III, randomized, double-blind, placebo- and active-controlled study evaluating secukinumab in patients with active rheumatoid arthritis.	The study was terminated following the strategic decision to discontinue secukinumab development for rheumatoid arthritis after review of the overall Phase III efficacy data. The decision was based on insufficient competitive efficacy rather than safety concerns.

The REASSURE program confirmed that secukinumab possesses biological activity and an acceptable safety profile in patients with active rheumatoid arthritis. Although significant clinical improvements over placebo were observed, efficacy was consistently lower than that of the active comparator, abatacept. Consequently, the rheumatoid arthritis development program was discontinued for strategic efficacy reasons, while no new safety concerns were identified.

- **Pediatric Plaque Psoriasis**

Study Code	**Study Code**	**Study Code**	**Study Code**
CAIN457A2310	Completed	Phase III, randomized, double-blind, placebo- and active-controlled (etanercept), multicenter study evaluating the efficacy, safety, and tolerability of weight-based subcutaneous secukinumab (low-dose and high-dose regimens) in children and adolescents aged **6 to <18 years** with severe chronic plaque psoriasis. Following a 12-week placebo-controlled period, patients entered a long-term treatment extension up to 236 weeks.	The study met its primary endpoint. Both low- and high-dose secukinumab demonstrated significantly higher **PASI75** and **IGA 0/1** response rates at Week 12 compared with placebo. High-dose secukinumab also showed numerically superior responses compared with etanercept for PASI75, PASI90, PASI100, and IGA 0/1. Clinical responses were rapid, durable through Week 52, and associated with significant improvements in quality of life (CDLQI). The safety profile was

			consistent with that observed in adults, with no new safety signals.
CAIN457A2311	Completed	Phase III, randomized, open-label, multicenter pharmacokinetic, efficacy, and safety study evaluating weight-based subcutaneous secukinumab in pediatric patients aged **6 to <18 years** with moderate-to-severe plaque psoriasis. The study also evaluated pharmacokinetic exposure-response relationships to support pediatric dose selection.	The study confirmed that weight-based dosing achieved drug exposures comparable to those observed in adults. High levels of efficacy were demonstrated, with sustained **PASI75, PASI90, PASI100, and IGA 0/1** responses throughout treatment. Pharmacokinetic analyses validated the proposed pediatric dosing algorithm, and the safety profile remained consistent with the established adult experience.

The pediatric Phase III development program demonstrated that weight-based secukinumab provides rapid, robust, and sustained clinical efficacy in children and adolescents with moderate-to-severe plaque psoriasis. Both pivotal studies confirmed high rates of skin clearance, improved quality of life, and pharmacokinetic exposures comparable to adults, while maintaining a favorable safety profile with no new safety concerns. These findings supported the regulatory approval of secukinumab for pediatric patients aged 6 to <18 years with plaque psoriasis who are candidates for systemic therapy.

- **Juvenile Idiopathic Arthritis (JPsA and ERA)**

Study Code	**Study Code**	**Study Code**	**Study Code**
CAIN457F2304	Completed	Phase III, randomized, double-blind, placebo-controlled, multicenter withdrawal study evaluating the efficacy, safety, and tolerability of subcutaneous secukinumab in children and adolescents (2 to <18 years) with active **Juvenile Psoriatic Arthritis (JPsA)** or **Enthesitis-Related Arthritis (ERA)**. Following a 12-week open-label treatment period, responders were randomized to continue secukinumab or switch to placebo until disease flare or study completion.	The study met its primary endpoint. Secukinumab significantly **prolonged the time to disease flare** and **reduced the risk of flare by approximately 72%** compared with placebo. Sustained improvements were observed in disease activity, joint counts, physical function, and quality of life. The safety profile was consistent with that observed in adult indications, with no new safety concerns identified.

CAIN457F2304E1	Ongoing (Long-term Extension)	Open-label extension study evaluating the long-term efficacy, safety, and tolerability of secukinumab in patients completing CAIN457F2304.	Long-term follow-up demonstrated sustained disease control with maintenance of clinical responses and continued prevention of disease flares. No cumulative toxicity or unexpected adverse events were identified, confirming the favorable long-term safety profile in pediatric patients.

The Phase III JIA program demonstrated that secukinumab provides effective and durable disease control in pediatric patients with Juvenile Psoriatic Arthritis and Enthesitis-Related Arthritis. The pivotal withdrawal study showed a significant reduction in the risk of disease flare and sustained improvements in clinical outcomes, while long-term follow-up confirmed a favorable and consistent safety profile. These findings supported the regulatory approval of secukinumab for the treatment of active JPsA and ERA in pediatric patients.

- **Protocol: Phase:** III

-Psoriasis is an inflammatory, immune-mediated skin disease that causes a rash with itchy, scaly patches, most commonly on the knees, elbows, trunk and scalp, which is caused by inappropriate activation of cutaneous T cells and dendritic cells with subsequent release of inflammatory cytokines such as interleukin IL-1, IL-6, IL-12, IL-17, IL-23, and tumor necrosis factor a (TNF-α). These cytokines are responsible for keratinocyte hyperproliferation, the influx of neutrophils, and further propagation of inflammation.

-Psoriasis is a complex, potentially multisystem disease featuring extracutaneous manifestations (such as arthritis, heart disease, dyslipidemia, obesity, metabolic syndrome, and depression) in a subset of patients. Asthma has also been reported recently as a possible emerging comorbidity.

-The most common type of psoriasis is plaque psoriasis, which causes dry, itchy, raised skin patches (plaques) covered with scales. Although commonly involving the scalp, elbows, knees, and lower back in adolescents and adults, any area of skin may be involved, including the palms and soles. Children with psoriasis can present with unique distribution patterns, including isolated facial or genital involvement, particularly in infancy. The affected skin might heal with temporary changes in color (post inflammatory hyperpigmentation), particularly on brown or Black skin.

-Psoriasis Treatment in Pediatrics

Possible alternative treatments include the following:

Topical Treatments:

- Topical corticosteroids (frequently considered for localized disease)
- Vitamin D3 analogs (calcipotriene, calcipotriol,and calcitriol) used as immunotherapy which consider the first-line treatment for pediatric plaque psoriasis, although in practice they are frequently used in

combination with a topical steroid to gain initial control.
- Topical calcineurin inhibitors (pimecrolimus, tacrolimus, and cyclosporine)
- Topical anthralin
- Coal tar preparations can be used as a monotherapy or combined with other topical therapies for the treatment of pediatric psoriasis.
- Phototherapy and Photo chemotherapy Treatments

Non-biologic Systemic Treatments: Methotrexate, Cyclosporine, Systemic retinoid such as Acitretin, Systemic fumaric acid esters.

Biologic Systemic Treatments (Biologics may be safely combined with topical corticosteroids, with or without a Vitamin D analogue, to augment effectiveness for the treatment of moderate to severe plaque psoriasis): Etanercept, Adalimumab, Infliximab, Ustekinumab (an anti-p40 monoclonal antibody targeting both IL-12 and IL-23), Risankizumab, guselkumab, tildrakizumab (three anti-p19 monoclonal antibodies targeting IL-23).

Secukinumab

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human Interleukin-17A (IL-17A) antibody of the IgG1/kappa isotype. Secukinumab is marketed as Cosentyx and is available as a solution for subcutaneous (SC) injection in a prefilled syringe (PFS) and an autoinjector/pen (AI); or as a lyophilizate in vial (LYO) which is marketed in selected countries.

---Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

Secukinumab Mechanism of Action

Secukinumab (AIN457) selectively binds to Interleukin-17A (IL-17A) and inhibits its interaction with IL-17 receptor.

IL-17A is one of the principal pro-inflammatory cytokines in autoimmune diseases such as psoriasis, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) and is thought to play a role in other inflammatory conditions. IL-17A belongs to the IL-17 cytokine family that includes six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F) and most resembles IL-17F, the only other member secreted by Th-17 cells. However, IL-17A has a higher binding affinity to IL-17 receptors than IL-17F leading to higher in vitro biological activity of IL-17A versus IL-17F. The widespread expression of the IL-17 receptors enables IL-17A to act on a variety of cell types, including epithelial cells (such as keratinocytes), dendritic cells, macrophages, fibroblasts, osteoblasts, endothelial cells, and astrocytes.

Objective(s):

- **Primary Objective** to demonstrate the superiority of Secukinumab in pediatric subjects with severe chronic plaque psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary

endpoints) at Week 12, compared to placebo.

- **Secondary Objectives:**

- To demonstrate superiority of Secukinumab (low and high dose) in subjects with severe chronic plaque psoriasis with respect to PASI 90 response at Week 12, compared to placebo.
- To assess efficacy of Secukinumab in subjects with severe chronic plaques psoriasis with respect to PASI 50 and PASI 100 at Week 12, compared to placebo.
- To assess efficacy of Secukinumab in subjects with severe chronic plaque psoriasis with respect to PASI 50, PASI 75, PASI 90 , PASI 100 and IGA mod 2011 0 or 1 at Week 16 and over time up to Week 52.
- To assess the efficacy of Secukinumab with respect to changes in PASI score and IGA mod 2011 score at Week 12, compared to placebo, and over time up to Week 52.
- To investigate the effects of treatment with Secukinumab with respect to changes in CDLQI at Week 12, compared to placebo, and over time up to Week 52.
- To investigate the effects of treatment of Secukinumab with respect to CDLQI 0 or 1 achievement at Week 12, compared to placebo, and over time up to Week 52.
- To evaluate the effects of treatment of Secukinumab on disability at Week 12 and over time up to Week 52 by use of the Childhood Health Assessment Questionnaire (CHAQ©), for subjects with history of psoriatic arthritis.
- To investigate the clinical safety and tolerability of Secukinumab as assessed by growth, weight gain, tolerability of s.c. injections, vital signs, clinical laboratory variables, ECGs, and adverse events monitoring, compared to placebo.

Rationale:

The efficacy and safety of Secukinumab have been demonstrated in adults in a comprehensive phase II/III program. It is now appropriate that a similar assessment is made in the pediatric population with a dosing regimen that can be extrapolated from the adult efficacious dose. The purpose of this trial is to demonstrate the efficacy and safety of Secukinumab compared to placebo and etanercept in children and adolescents aged 6 to less than 18 years with severe plaque psoriasis.

Design:

Multicenter, randomized, double-blind, parallel group, placebo-and active (etanercept)-controlled study. 12-week induction treatment period followed by a 40-week maintenance treatment period, a 184-week open-label extension treatment period and a 16-week follow-up off treatment period**.**
Pediatric subjects aged 6 years to less than 18 years with severe chronic plaque psoriasis.

Benefit/risk assessment

- Secukinumab is expected to provide significant clinical benefit in pediatric patients with severe plaque psoriasis based on its demonstrated efficacy and favorable safety profile in adult Phase II/III studies.
- Compared with conventional systemic therapies (e.g., methotrexate, cyclosporine, acitretin), Secukinumab offers less frequent dosing and has fewer potential end-organ toxicities due to its targeted mechanism of action.
- Weight-based dosing is implemented to achieve comparable drug exposure across pediatric weight groups.
- Based on available non-clinical and adult clinical data, no adverse effects on immune system maturation, linear bone growth, or development are anticipated in children aged 6 to <18 years.
- The known risks of Secukinumab include:
  - Increased susceptibility to infections, particularly **Candida infections**.
  - **Neutropenia** (generally mild, transient, and rarely leading to treatment discontinuation).
  - **Hypersensitivity reactions**.
  - Potential risks of **malignancies**, **major adverse cardiovascular events (MACE)**, **Crohn's disease**, **immunogenicity**, and reduced response to **live vaccines**.
- Participants are advised to complete age-appropriate immunizations before enrollment. Live vaccines should not be administered during Secukinumab treatment, and non-live vaccines may elicit a reduced immune response.
- The active comparator (etanercept) also carries risks including injection-site reactions, upper respiratory infections, headache, and a potential increased risk of infections and malignancy due to immunosuppression.

- ***Recommendation &/ or*** **Questions & Answers:-----**

- **Abbreviation**

CDLQI	Children's Dermatology Life Quality Index
CHAQ	Childhood Health Assessment Questionnaire
CT	Clinical Trial
EDA	Egyptian Drug Authority
ERA	Enthesitis-Related Arthritis
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for

	Human Use
IGA	Investigator's Global Assessment
IL	Interleukin
JIA	Juvenile Idiopathic Arthritis
LYO	Lyophilized
MACE	Major Adverse Cardiovascular Events
MRI	Magnetic Resonance Imaging
NOAEL	No-Observed-Adverse-Effect Level
PASI	Psoriasis Area and Severity Index
PFS	Prefilled Syringe
PI	Principal Investigator
RA	Rheumatoid Arthritis
SC	Subcutaneous
TNF	Tumor Necrosis Factor
UGT	Uridine 5′-Diphospho-Glucuronosyltransferase

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