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Novartis' secukinumab expected to have successful Phase III ankylosing spondylitis trial - rheumatologists

Safety profile good, efficacy expected to meet bar

Market potential hinges on efficacy differentiation from TNFs

PsA potential is better for dermatology endpoints; RA remains uncertain

Novartis' (VTX:NOVN) secukinumab is expected to have positive Phase III results in ankylosing spondylitis (AS), according to rheumatologists. The biggest factor for its market success will be whether it can improve upon the efficacy of TNF inhibitors, they noted.

In arthritis (PsA) Phase III trials, the IL-17 is expected to impact dermatologic endpoints more than joints. Success in crowded rheumatoid arthritis (RA) is less likely, the experts agreed.

Treatments in AS are sparse and inadequate in comparison to rheumatoid arthritis (RA), and secukinumab will likely be a welcome addition for treating the indication, specialists agreed. Secukinumab has a solid safety profile, and the efficacy bar for Phase III AS success is lower in comparison to RA where radiographic progression is key, experts explained. TNF inhibitors demonstrate convincing benefits for bone progression in RA, while their ability to improve ankylosing in AS remains debatable.

Phase III AS and PsA results are expected in 2014, according to a 9 July press release. Secukinumab's 550-patient Phase III NURTURE 1 RA trial lists February 2015 as its primary completion date.

Novartis did not respond to a request for comment.

Safety reassuring, efficacy likely enough since AS bar is low

Secukinumab's safety has been very positive so far, and IL-17 inhibitors are widely seen as very safe, said Dr Petros Efthimiou, associate chief of rheumatology, New York Methodist Hospital. Safety profiles for the IL-17s are thought to be at least in line with other biologics like TNFs or better, added Dr Diane Horowitz, director, The Arthritis Center, North Shore-LIJ Medical Group, Great Neck, New York.

ClinicalTrials.gov lists injection site reactions, ECG outcomes and the detection of immunogenicity as key safety measures. Infections rates for the immunosuppressive agent have been impressive across secukinumab's trials and will remain closely watched, experts agreed. Unlike RA patients generally in their 50s, AS patients are much younger and could potentially be on biologic therapies for substantially longer periods of time, they said.

Secukinumab would likely show sufficient efficacy in Phase III to gain approval in AS where treatment options are limited, rheumatologists agreed. The primary endpoint measuring 16-week Assessment of Spondyloarthritis International Society criteria (ASAS 20) against placebo is standard and achievable given Phase II results, experts agreed.

Phase II results for secukinumab in AS were very promising, and the field will welcome additional treatments and targets, said Dr Nigil Haroon, assistant professor, Division of Rheumatology, University of Toronto, Canada.

Data from a Phase II trial showed that secukinumab met ASAS 20 endpoints at six weeks, though the trial size of just 30 patients would have to be expanded on, the experts agreed.

There is a lot of excitement for secukinumab to add another mechanism to the toolkit for AS, agreed Dr Muhammad Nisar, rheumatologist, Addenbrookes Hospital, Cambridge, UK. There are not many options in AS after the TNF inhibitors, he added. Because patients continue to get worse, there is certainly a need for more targets for treating AS, said Efthimiou.

Novartis' Phase III MEASURE program can include TNF inhibitor exposed patients but they must have experienced an inadequate response.

The 222-patient MEASURE 3 trial (NCT02008916) looking at 16-week ASAS-20 and three-year safety and tolerability has an August completion date, according to ClinicalTrials.gov. The firm's 372-patient MEASURE 1 trial (NCT01358175) is listed as ongoing but not recruiting, with February 2015 as its completion date. ClinicalTrials.gov also lists a MEASURE 4 trial, which is not yet recruiting, and MEASURE 2 which is recruiting.

The bar for showing efficacy is low in AS, as even TNF inhibitors are not completely effective, said Efthimiou.

All MEASURE trials list the 16-week ASAS 20 as primary endpoints with overall safety and tolerability of varying time frames. Looking at radiographic progression using MRI in AS is more controversial and would be much harder to meet in AS compared to RA where radiographic progression is required for approval, experts noted. XRAY and MRI endpoints are not listed as endpoints in the MEASURE trials.

Drug will be compared to TNFs

There is a question whether TNFs do anything to improve the radiographic progression associated with AS, in contrast to RA where TNF agents have shown radiographic progression and the measure is required for any new agent trying to crack the RA market, experts noted.

Yet, noted Nisar, these drugs certainly help structural changes. Patients receiving TNFs feel better, he added. The problem is

Company

Amgen, Inc.

Eli Lilly & Co.

Novartis AG

Drug(s)

Brodalumab

Enbrel

Secukinumab

Topic

Other

Product Development

Indications

Ankylosing Spondylitis

Arthritis

Psoriasis

Rheumatoid Arthritis

Mechanism(s)

Interleukin-17 (IL-17) Binder

Interleukin-17 (IL-17) Binder

Interleukin-17 (IL-17) Blocker

Tumor Necrosis Factor - Alpha (TNFa) Antagonist

Tumor Necrosis Factor - Alpha (TNFa) Antagonist

Sub-sectors

Drug development

Country

USA

Clinical Trials

NCT01358175

NCT02008916

Intelligence Grade

Strong evidence

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that physicians are using old ways of looking at XRAYs and MRIs to assess progression, said Nisar.

The question for secukinumab in AS will be whether it can be as efficacious as TNF inhibitors have been for the indication, Nisar said. The 61% ASAS 20 rate versus 17% placebo response rate in the Phase II trial look similar to TNF inhibitors for efficacy but whether it can stand out against them is unclear, he added.

Additionally, though TNF inhibitors are thought to improve symptoms and inflammation in AS, there is some debate as to whether they alter the natural history of the disease, added Efthimiou.

AS is a slow-progressing disease starting off with inflammatory symptoms that over time result in ankylosing, so targeting the disease early with antinflammatory treatments will be important, said Dr Vasileios Kyttaris, assistant professor, medicine, Harvard Medical School, Beth Israel Deaconess Medical, Boston, Massachusetts. It will be very interesting to look at IL-17 targeting early in the progression of the disease, he added.

PsA chances better than in RA

Secukinumab and the other IL-17 inhibitors, which include Amgen's (NASDAQ:AMGN) brodalumab and Eli Lilly's (NYSE:LLY) ixekizumab, have produced exciting results in psoriasis and have a good chance at showing better results than TNF inhibitors, said Efthimiou. Psoriasis Phase III trials for secukinumab have shown up to 70% of secukinumab 300 mg patients experienced clear PASI 100 or almost clear skin, PASI 90, during the first 16 weeks of treatment, according to a 9 July 2014 release. Secukinumab has also demonstrated superiority to Amgen's Enbrel (etanercept) in a head-to-head Phase II trial, according to a 8 July 2013 release.

IL-17 inhibitors are viewed favorably for treating moderate-to-severe psoriasis but are not expected to show much clinical differentiation despite some variations in IL-17 inhibition, this service reported in July 2013.

IL-17s have been very positive in psoriasis where they seem to "melt" the plaques away, added Haroon.

When it comes to PsA, though, secukinumab failed to meet six-week ACR 20 in Phase II, but may be more effective for dermatologic symptoms than joints, noted Efthimiou.

Efficacy in RA has been more modest, failing to meet efficacy endpoints of ACR20 responders at week 16 with varying secukinumab doses ranging from 25-300mg, added Efthimiou. Phase II results for secukinumab in RA have not been overly positive and failed at even higher doses to meet ACR20, added Horowitz.

Novartis' Phase III trials testing secukinumab in RA are recruiting, though the other IL-17s, brodalumab and ixekizumab, have exited the RA field, which is already a crowded market, noted Kyttaris. It is unclear how big of a player IL-17 inhibitors can be in RA, he added.

Novartis' market cap is CHF 237.4bn (USD 255bn).

by Casey McDonald in New York

About Casey McDonald

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