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Phase 2 Nipocalimab Data Establish Proof of Mechanism in Adults Living with Moderate to Severe Rheumatoid Arthritis, Supporting its Progression into a Combination Study

This first-ever clinical study of an FcRn inhibitor in RA showed nipocalimab reduced levels of circulating IgG antibodies, including ACPAs, suggesting they may play a key role in driving RA disease activity[1,2]

Nipocalimab demonstrated improvements in primary and secondary endpoints and participants with higher baseline ACPAs had more than twice the placebo adjusted DAS28-CRP remission compared to the overall study population[1]

BEERSE, BELGIUM, 7 NOVEMBER 2023 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced data from the Phase 2a IRIS-RA clinical study for the treatment of adults living with moderate to severe active rheumatoid arthritis (RA) who have tested positive for anti-citrullinated protein antibodies (ACPAs)[a] and/or rheumatoid factor (RF), and who have had an inadequate response or intolerance to at least one anti-tumour necrosis factor (anti-TNF) therapy.[1] The data from this study establish proof of mechanism for nipocalimab in RA and support its progression into a combination study. IRIS-RA is the first clinical study to assess the efficacy and safety of the anti-neonatal Fc (FcRn)-driven mechanism of action (MOA)

for the treatment of RA.[3] The study findings, along with an acceptable benefit-risk profile, support the further investigation of nipocalimab in this refractory population.[1] A trial investigating the efficacy and safety of nipocalimab in combination with an anti-TNFα treatment in patients living with RA has recently been initiated.[4]

Treatment with nipocalimab, an anti-FcRn receptor therapy, resulted in numerically greater improvements at Week 12 across primary and secondary efficacy endpoints including Disease Activity Score 28 using C-reactive protein (DAS28-CRP),[b] American College of Rheumatology (ACR) responses,[c] DAS28-CRP remission and Health Assessment Questionnaire – Disability Index (HAQ-DI).[1,d] A numerically greater number of patients in the nipocalimab group achieved ACR50 (n=5/33 nipocalimab versus n=1/20 placebo) and DAS28-CRP remission (n=7/33 nipocalimab versus n=2/20 placebo) compared with the placebo group.[1]

By selectively blocking the FcRn receptor, nipocalimab reduced levels of circulating immunoglobin G (IgG) antibodies, including ACPAs,[a] suggesting they may play a key role in driving RA disease activity.[2] The placebo adjusted DAS28-CRP remission rate of a subpopulation of study participants with higher mean baseline levels[e] of ACPAs was more than double the overall study population (23.3 percent difference from placebo [n=27]; versus 11.2 percent difference from placebo [n=53] respectively).[1,2]

These data will be presented for the first time as an oral presentation at ACR Convergence 2023, taking place in San Diego, California on 12 November 2023.[1] In addition, a poster (#2144) on the pharmacodynamic effects of nipocalimab in the IRIS-RA study will be presented at ACR.[2]

"There is an urgent need for new therapeutic avenues capable of reducing the impact of rheumatoid arthritis for more patients," said Dr. Peter C. Taylor, MA, Ph.D., FRCP, FRCPE, Norman Collisson Professor of Musculoskeletal Sciences, Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford.[f] "Even with the use of the current targeted therapies,

up to half of those living with rheumatoid arthritis do not reach remission or still have low disease activity.[5] We believe autoantibodies are major contributors to this disease activity and current rheumatoid arthritis treatments like TNF inhibitors generally don't effectively reduce autoantibodies.[6] These encouraging results are the first time that the selective reduction of IgG autoantibodies has shown evidence of efficacy in a clinical study and are the first ever from a clinical study of an FcRn inhibitor in rheumatoid arthritis indicating nipocalimab has the potential to improve disease activity through a novel mechanism of action."

IRIS-RA clinical trial results at Week 12:

At Week 12, the IRIS-RA data show that treatment with nipocalimab resulted in consistent and numerically higher improvements across change from baseline in DAS28-CRP score (Table 1) and HAQ-DI (Supplement, Table 1) as well as ACR responses (Supplement, Table 2), compared to placebo.[1] The data also highlighted the differential response to treatment with nipocalimab for patients with higher baseline levels of ACPAs (Table 2).[1]

PK/PD simulation based on data from previous nipocalimab studies predicted median total IgG reduction of 64 percent at the trough (the timepoint at which the concentration of nipocalimab is at its lowest) and 76 percent at the peak with 15mg/kg IV nipocalimab.[2] IRIS-RA study data are consistent with the model predictions and showed 62 percent reduction (median) in total IgG at the trough.[2]

Table 1: Mean Change from Baseline Scores for Patients at Week 12[1]

	Nipocalimab, n=33 (95 percent Confidence Interval [CI])	Placebo, n=20 (95 percent CI)	Least squares mean difference (95 percent CI)	*P* value
DAS28-CRP score	-1.03 (-1.66; -0.40)	-0.58 (-1.24; 0.07)	-0.45 (-1.17; 0.28)	0.224

Table 2: Difference of Nipocalimab and Placebo Response in Patients with Higher Mean Baseline Levels of ACPA (ACPA^{High}) at Week 12[1]

	All patients, n=53 (nipocalimab vs. placebo)	ACPA^{High} patients, n=27 (nipocalimab vs. placebo)

DAS28-CRP remission	11.2 percent (21.2 vs. 10.0)	23.3 percent (40.0 vs. 16.7)
ACR50	10.2 percent (15.2 vs. 5.0)	26.7 percent (26.7 vs. 0.0)

Nipocalimab demonstrated an acceptable benefit-risk profile:

- The proportion of patients with treatment-emergent adverse events was 27 out of 33 (81.8 percent) in the nipocalimab group versus 12 out of 20 (60 percent) in the placebo group.[1]
- In the nipocalimab group, three serious treatment-emergent adverse events were reported, including burn infection, infusion-related reaction and deep-vein thrombosis.[1] There were no deaths.[1] No serious adverse events were reported in the placebo group.[1]
- Nipocalimab did not have a clinically meaningful impact on albumin (-1.83 percent in nipocalimab versus 1.54 percent in placebo mean change from baseline to Week 18) or total cholesterol (-2.34 percent in nipocalimab versus 3.13 percent in placebo mean change from baseline to Week 18). [7,8]

"Significant patient need remains for those suffering from rheumatoid arthritis and our research shows autoantibodies like ACPAs may contribute to the development and activity of rheumatoid arthritis," said Terence Rooney, M.D., Vice President, Rheumatology Disease Area Leader, Janssen. "Current treatments, like TNF-inhibitors, may not markedly reduce autoantibodies when used alone so these results are promising for patients who have had inadequate responses to other advanced therapies. The combination of nipocalimab with therapies that have a complementary MOA, such as anti-TNFs, will be of interest as we explore alternative avenues of treatment for patients with rheumatoid arthritis, and we are excited to have initiated the Phase 2a DAISY-RA trial to explore this combination. We are also encouraged by the efficacy of nipocalimab in the autoantibody-high subpopulation, providing a potential precision-medicine approach to treating patients."

Janssen recently initiated a Phase 2a proof-of-concept trial, DAISY-RA (NCT06028438), investigating the efficacy and safety of nipocalimab in combination with an anti-TNFα treatment in patients living with RA who have had an inadequate response or intolerance to at least one advanced disease-modifying antirheumatic drug therapy. The DAISY-RA trial is currently ongoing and is recruiting patients in the study.[4]

"We won't rest until we ease the challenges that people living with immune-mediated inflammatory diseases such as rheumatoid arthritis face," said Ludovic de Beaucoudrey, Ph.D., Senior Director, Therapeutic Area Lead, Immunology, Janssen-Cilag Limited. "These findings help bring us one step closer to this goal as we seek to address critical unmet needs that remain for this community. We are committed to building on this momentum as we further explore nipocalimab's potential across people living with rheumatoid arthritis and other rheumatologic diseases."

Nipocalimab is the only anti-FcRn currently being studied across three key disease segments: maternal-foetal immune, rare autoantibody and prevalent rheumatological diseases and is the only anti-FcRn being studied in pregnant individuals at high risk of haemolytic disease of the foetus and newborn.[3,9,10,11,12,13,14,15,16]

Editor's Notes

a. ACPAs are autoantibodies against citrullinated proteins and may be reliable markers for the early diagnosis of RA.[17] Up to 80 percent of patients living with RA are seropositive for ACPAs and/or RF.[18,19]
b. DAS28-CRP is a tool used to assess RA disease activity, calculated based on the tender joint count and swollen joint count (both out of 28 evaluated joints), patient's global assessment of disease activity, and CRP.[20] Change from baseline in DAS28-CRP measures the change in disease activity, where a negative change indicates an improvement.[21] CRP is a type of protein that increases during inflammatory conditions, such as RA.[22]
c. ACR20/50/70/90 response is defined as at least 20/50/70/90 percent

improvement from baseline in the number of tender and swollen joints, and at least 20/50/70/90 percent improvement from baseline in three of the following five criteria: patient's assessment of pain by visual analogue scale, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function measured by HAQ-DI[d] and CRP.[23]

d. HAQ-DI is a 20-question instrument assessing eight functional areas, range: 0-3, 0=no difficulty, 3=inability to perform a task in that area.[24]
e. Higher baseline levels are defined as ACPA[a] values above the median of the study population.[1]
f. Dr. Peter C. Taylor is a paid consultant for Janssen. He has not been compensated for any media work.

Supplement

Supplement Table 1: Mean Change from Baseline Scores for Patients at Week 12[1,25]				
	Nipocalimab, n=33 (95 percent Confidence Interval [CI])	Placebo, n=20 (95 percent CI)	Least squares mean difference (95 percent CI)	*P* value
HAQ-DI	-0.42 (-0.66; -0.19)	-0.21 (-0.45; 0.04)	-0.22 (-0.49- 0.05)	0.108

Supplement Table 2: Percentage of Patients Who Achieved A Response at Week 12[1]				
	Nipocalimab, n=33	Placebo, n=20	Treatment Difference (95 percent CI)	*P* value
ACR20	45.5 percent	20.0 percent	27.0 percent (3.2-50.9)	0.055
ACR50	15.2 percent	5.0 percent	8.6 percent (-6.7-23.8)	0.390*
ACR70	12.1 percent	0 percent	11.6 percent (0.9-22.3)	0.285*
ACR90	6.1 percent	0 percent	5.8 percent (-2.0-13.6)	0.521*
DAS28-CRP remission	21.2 percent	10.0 percent	9.9 percent (-9.5-29.3)	0.456*

*The p value was based on the Cochran-Mantel-Haenszel chi-square test, stratified by random stratification factor: baseline methotrexate use. The Mantel Fleiss criterion was not satisfied with the indicated p values and was therefore based on the Fisher's exact test.[1]

#ENDS#

About IRIS-RA

The IRIS-RA study (NCT04991753) is a Phase 2a multicentre, randomised, double-blind, parallel-group, placebo-controlled, proof-of-concept clinical trial that is designed to evaluate the efficacy and safety of nipocalimab in adults living with moderate to severe active RA.[3] Nipocalimab is being studied with the aim to reduce the severity and progression of RA by lowering concentrations of IgG isotype antibodies, including ACPAs and their immune complexes to reduce disease activity.[1] The Phase 2a IRIS-RA study is the first in RA to assess the efficacy and safety of anti-FcRn mechanism of action that specifically targets IgG isotype antibodies, including ACPAs.[3] The trial enrolled adult patients with moderate to severe active RA (≥6 swollen/tender joints), positive for ACPAs or RF, and who have had an inadequate response or intolerance to at least one anti-TNF therapy.[1] Fifty-three patients were enrolled, 33 of whom received nipocalimab and 20 received placebo.[1] Participants were randomised 3:2 to receive intravenous 15 mg/kg nipocalimab or placebo every other week for ten weeks.[1] Demographic and baseline disease characteristics were generally comparable between groups.[1] The primary endpoint was the change from baseline in DAS28-CRP at Week 12.[1] Secondary endpoints included the proportion of patients who achieved ACR20, ACR50, ACR70, and ACR90 responses, DAS28-CRP remission, and change from HAQ-DI at Week 12.[1]

About Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, symmetric, inflammatory disease involving the synovial joints.[26] RA occurs when the immune system loses its normal state of balanced control and activates sustained inflammation in the soft inner lining of joints, called synovial tissue.[27] This inflammation produces joint pain, swelling, and stiffness, and can lead to permanent damage and deformity in structural joint elements like cartilage and bone.[27] Significantly reduced physical function and health-

related quality of life typically accompany these features.[28] Antibody systems, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) are associated with RA, having been identified based on the antigens these antibodies bind to.[17] RA is the most common inflammatory arthritis and affects an estimated 13 million people worldwide.[29] It is estimated that up to 2.3 million people are living with RA in Europe today.[30]

About Nipocalimab

Nipocalimab is an investigational, high-affinity, fully human, aglycosylated, effectorless, monoclonal antibody that is IgG-specific and designed to selectively block FcRn to reduce levels of circulating IgG antibodies, including autoantibodies and alloantibodies that underlie multiple conditions.[31,32] Nipocalimab is the only anti-FcRn being studied across three key segments in the antibody-driven space: prevalent rheumatological diseases (e.g., rheumatoid arthritis, Sjögren's disease, and systemic lupus erythematosus), maternal-foetal diseases mediated by maternal alloantibodies (e.g., Haemolytic Disease of the Foetus and Newborn [HDFN]); and rare autoantibody diseases (e.g., generalised myasthenia gravis in adults and children, chronic inflammatory demyelinating polyneuropathy, warm autoimmune haemolytic anaemia, and idiopathic inflammatory myopathies).[3,11,12,13,14,15,16,16,16] Blockade of FcRn by nipocalimab has the potential to reduce overall allo-/autoantibody levels while potentially maintaining immune function. FcRn blockade is also believed to prevent placental transfer of maternal alloantibodies to the foetus.[9,31]

About Janssen

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular, Metabolism & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development and the potential benefits and treatment impact of nipocalimab. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialise, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, Janssen Pharmaceutica NV, Janssen-Cilag Limited and any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behaviour and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 1, 2023, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission. Copies of these

filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of Janssen Research & Development, LLC, Janssen Pharmaceutica NV, Janssen-Cilag Limited, nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

# # #

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