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Forigerimod plus standard of care for systemic lupus erythematosus

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LAY SUMMARY

Systemic lupus erythematosus (SLE) is a long-term condition causing inflammation to the joints, skin and other organs. Symptoms presented are usually very general: fever, joint pain, skin rash but can progress to the most severe: kidney failure. SLE typically has patterns of flare-ups where the condition gets worse for a period of time. The disease is likely to be caused by a combination of genetic and lifestyle factors and most commonly affects middle-aged women and those who belong to an ethnic minority group such as African-Caribbean.

Treatment for SLE is currently aimed at controlling or easing the symptoms associated with the disease. Forigerimod is being developed for the treatment of SLE in combination with standard of care. Forigerimod is being developed as an injection given every 4 weeks and may be considered beneficial compared to current treatments. It is expected to fight the body's dysfunctional immune system by the earlier activation of T-cells. Therefore if licensed it will be a potential additional treatment for SLE.

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TARGET GROUP

Systemic lupus erythematosus (SLE)

TECHNOLOGY

DESCRIPTION

Forigerimod (Lupuzur; IPP-201101; P140) is a 21-mer linear peptide which comes from the small nuclear ribonucleoprotein U1-70K and is phosphorylated at the Ser140 position.[1] Its unique mechanism of action involves modulating the activation of auto-reactive T-cells. In targeting upstream T-cell activation, forigerimod presents a novel approach in modulating this unwelcome autoimmune reaction. This targeted approach marks a paradigm shift in treating autoimmune disease. Instead of shutting down otherwise healthy immune responses the T-cells are suppressed, leaving the immune system deleted from unwanted deleterious cells but intact as normal, beneficial immune cells are concerned.[2]

Current treatment for SLE is often palliative rather than curative as corticosteroids and other immunosuppressive agents are generally given to control and ease the symptoms associated with condition.[1,3]

Forigerimod is currently in phase III clinical trial development (pivotal and extension) for the treatment of SLE.[4,5] In the pivotal phase III trial forigerimod is administered as a subcutaneous injection, in combination with standard of care at a dose of 200 mcg every 4 weeks, for 48 weeks in total. A total of 13 doses is expected to be administered.[4]

Forigerimod does not currently have Marketing Authorisation in the EU for any indication and is not being developed for any other indication.

INNOVATION and/or ADVANTAGES

Forigerimod has a novel mechanism of action which involves auto-reactive T-cell activation, specifically targeting the upstream of T-cell activation. This helps combat the body's compromised immune system.[2] Additionally forigerimod is distinctly different from other approved treatments for SLE as it is a small peptide as opposed to a monoclonal antibody and its dosing is relatively small and is only required every few weeks.[6]

Current treatments for SLE consists of drugs which have many side-effects and limited efficacy,[2] therefore if licensed, forigerimod could offer an additional treatment for SLE.

DEVELOPER

ImmuPharma

PATIENT GROUP

BACKGROUND

SLE is a complex autoimmune disease that affects numerous bodily systems and organs.[3,7] Mild SLE is marked by generalised symptoms such as headaches, fever, muscle and joint pain and skin rash, whilst severe SLE is characterised by significant morbidity such as renal damage, haemolytic anaemia, thrombocytopenic purpura and central nervous system abnormalities.[3, 8] SLE can involve various relapsing and remitting episodes which results in flare-ups that cause an accumulation of damage to the body's tissues, increasing the risk of infection, cardiovascular disease and even death.[3,8] Patients with late-onset SLE (≥50 years) tend to have a more insidious onset of disease with severe manifestations being infrequent, however they are also more likely to have greater damage at diagnosis, a higher frequency of comorbidities and a higher risk of premature mortality than those with an earlier onset of SLE.[9] Severe SLE may manifest into lupus nephritis, which is difficult to treat and can lead to permanent kidney damage, and end-stage renal disease.[8] Treatment aimed at controlling nephritis involves cytotoxic therapeutic regimes which consequently leads to significant morbidity and mortality.[1]

Whilst the cause of SLE is not fully understood, genetics is considered to have a strong role in its development along with other lifestyle and environmental factors.[10] SLE is genetically complex and is characterised by the production of multiple autoantibodies which may contribute to the similarities being drawn between its own clinical manifestations and those of other inflammatory conditions such as arthritis.[2,11] This can create difficulty in the diagnosis and monitoring of the condition.[7] The role of gender and socioeconomic factors are further identified as being strong risk factors for developing SLE, with the disease being more prominent in ethnic minority groups and in women.[12]

CLINICAL NEED and BURDEN OF DISEASE

Gender is considered the strongest risk factor for SLE development, with most studies containing predominantly all-female (90%) populations.[12] Furthermore, the incidence in females is approximately 5.8 times that of males (8.34 per 100,000) per year compared to 1.44 per 100,000 per year. The peak age of incidence for females was between 40-49 years whilst SLE occurred much later in life in males at 60-69 years. In the UK, for 1999-2012, the incidence rate of SLE was 4.91 per 100,000 people and the prevalence rate was 97.04 per 100,000 people. As gender is a strong risk factor in the development of SLE, the highest incidence rates are observed in those of African-Caribbean descent: 31.4 per 100,000 people per year, compared with 6.7 per 100,000 per year for those of white European descent.[13]

In the UK, death from active lupus is rare, however a 10% mortality rate and a mean age of death at 53 years old, has recently been reported. Approximately one-third of patients with SLE go on to develop lupus nephritis.[9]

In 2016-2017 there were 4,734 admissions for SLE (ICD 10: M32) which resulted in 5,299 finished consultant episodes (FCE) and 7,608 FCE bed days.[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Systemic lupus erythematosus – prasterone (ID392). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (TA397). June 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.
- NHS England. 2013/14 NHS Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. A13/PS/a.

OTHER GUIDANCE

- British Society for Rheumatology (BSR). Guideline for the management of adults with Systemic Lupus Erythematosus. 2017[7]

CURRENT TREATMENT OPTIONS

Currently there is no cure for SLE, therefore the aim of treatment is to control and ease the symptoms associated with the disease.[3,15] Treatment is more successful when initiated at the earliest stage of the disease, and is dictated by the severity of the disease, the part of the body affected and depending on flare-ups.[15]

Standard therapy includes the use of non-steroidal anti-inflammatory drugs; corticosteroids such as prednisolone; disease-modifying drugs such as hydroxychloroquine; and immunosuppressants such as azathioprine, cyclophosphamide, methotrexate and mycophenolate mofetil. Rituximab is also considered as a treatment option, particularly in the case of more severe disease, and is covered by an interim clinical commissioning policy statement by NHS England for certain people with the disease. Belimumab is licensed for add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity.[3]

It is important to be able to manage immunosuppressive therapies and their potential toxicities in SLE patients, although it can be a considerable challenge due to the risk of infection, difficulties with attribution of cytopenias to lupus or cytotoxic drugs, and difficulties in distinguishing manifestations of lupus disease activity from damage and co-morbid conditions.[8]

EFFICACY and SAFETY		
Trial	LUPUZOR, NCT02504645; forigerimod plus standard of care vs placebo plus standard of care; phase III	IP-006, NCT03427151: forigerimod plus standard of care; phase III extension
Sponsor	ImmuPharma	ImmuPharma
Status	Complete but unpublished	Ongoing
Source of Information	Trial registry[4]	Trial registry[5]
Location	EU (not incl UK), USA and other countries	EU (not incl UK), USA and other countries
Design	Randomised, double-blind, placebo-controlled study	Non-randomised, open-label study
Participants	n=200; aged 18-70 years; active systemic lupus erythematosus	n=100 (planned); ≥18 years; active systemic lupus erythematosus
Schedule	Randomised to forigerimod at a dose of 200 mcg every 4 weeks in combination with standard of care for 48 weeks in total or placebo in combination with standard of care for 48 weeks in total. A total of 13 doses will be administered with the experimental or placebo product.	Receive forigerimod at a dose of 200 mcg every 4 weeks in combination with standard of care for 24 weeks.
Follow-up	Active treatment period for 48 weeks.	Active treatment period for 24 weeks.
Primary Outcomes	Assessment of SLE Responder Index (SRI) at week 52	• Occurrence of adverse events throughout the study [Time Frame: 7 months] • Clinical laboratory test results at each visit during the treatment extension period [Time Frame: 7 months] • Body weight measurements at each visit during the treatment period [Time Frame: 7 months] • Temperature measurements at each visit during the treatment period [Time Frame: 7 months] • Pulse measurements at each visit during the treatment period [Time Frame: 7 months] • Systolic and diastolic blood pressures measurements at each

		visit during the treatment period [Time Frame: 7 months] • 2-lead electrocardiogram (ECG) findings at week 28 (or final assessment) [Time Frame: 7 months] • Physical examination findings, at specified time points at each visit during the treatment extension period [Time Frame: 7 months] • Concomitant medication usage throughout the study extension [Time Frame: 7 months]
Secondary Outcomes	• SLE Responder Index (SRI) response at each visit during the study [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Reduction in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) total score by at least 4 points at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Assessment of the British Isles Lupus Assessment Group (BILAG-2004) disease activity index, at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Status of disease by Physician's Global Assessment (PhGA scale) at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Reduction of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) total score by at least 5 points at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Reduction of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) total	• Effect in the Clinical SLEDAI-2K total score by at final visit compared to initial visit [Time Frame: at week 28] • Remission of the disease (i.e reduction of clinical SLEDAI-2K score to 0) [Time Frame: at week 28]

	score by at least 6 points at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Systemic Lupus Erythematosus Responder Index (SRI-5) response at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Systemic Lupus Erythematosus RI-6 response at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Assessment by the 28-joint count examination for pain and tenderness at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Incidence of disease flares at each visit during the treatment period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Occurrence of Systemic Lupus Erythematosus-induced organ damage at visits at weeks 24 and 52 (or final assessment) [Time Frame: baseline, weeks 24 and 52] • Assessment of health-related quality of life by completion of the Medical Outcome Survey Short Form 36 (SF-36) at visits at weeks 12, 24, 36, and 52 (or final assessment) [Time Frame: baseline, weeks 12, 24, 36 and 52] • Steroid dose over time throughout the study. [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Biologic markers of disease activity assessment at each visit during the treatment period	

	[Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Biologic markers of disease activity assessment at visits at weeks 4, 12, 24, 36, and 52 (or final assessment) [Time Frame: baseline, weeks 4, 12, 24, 36 and 52] • Biologic markers of disease activity assessment at visits at weeks 4, 12, 24, 36, and 52 (or final assessment) [Time Frame: baseline, weeks 4, 12, 24, 36 and 52] • Biologic markers of disease activity assessment at visits at weeks 4, 12, 24, 36, and 52 (or final assessment) [Time Frame: baseline, weeks 4, 12, 24, 36 and 52] • Biologic markers of disease activity assessment at visits at weeks 4, 12, 24, 36, and 52 (or final assessment) [Time Frame: baseline, weeks 4, 12, 24, 36 and 52] • Biologic markers of disease activity assessment at visits at weeks 4, 12, 24, 36, and 52 (or final assessment) [Time Frame: baseline, weeks 4, 12, 24, 36 and 52] • Assessment of fatigue using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale at visits at weeks 12, 24, 36, and 52 (or final assessment) [Time Frame: baseline, weeks 4, 12, 24, 36 and 52] • In vitro intracellular and cytokine response [Time Frame: baseline, weeks 4, 24 and 52] • Occurrence of adverse events throughout the study [Time Frame: baseline, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Clinical laboratory test results at each visit during the treatment	

	period [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Vital signs assessment at each visit [Time Frame: baseline, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • 12-lead electrocardiogram (ECG) findings at week 52 (or final assessment) [Time Frame: baseline and week 52] • Physical examination findings [Time Frame: baseline, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Evaluation for suicidality at each visit during the treatment period using the Columbia-Suicide Severity Rating Scale (C-SSRS) [Time Frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52] • Concomitant medication usage throughout the study [Time Frame: baseline, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52]	
Key Results	Not reported	-
Adverse effects (AEs)	Not reported	-
Expected reporting date	Results expected to be reported in Q1 2018[2]	Primary completion date reported as October 2018

ESTIMATED COST and IMPACT

COST

The cost of forigerimod is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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