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Tofacitinib in the Treatment of Rheumatoid Arthritis and Chronic Plaque Psoriasis

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ABSTRACT

Tofacitinib is an oral immunosuppressant approved for the treatment of rheumatoid arthritis (RA) and is currently undergoing investigation (Phase III trials) for treating chronic plaque psoriasis. Tofacitinib inhibits Janus kinases (JAKs), which are essential for the signaling of multiple inflammatory pathways and have been implicated in the pathogenesis of RA and psoriasis. The efficacy and safety of tofacitinib in the treatment of RA and psoriasis have been demonstrated in Phase III trials. Across all studies, the efficacy of tofacitinib in alleviating symptoms of RA and psoriasis were superior to placebo. Moreover, treatment was generally well-tolerated, with the most frequently reported adverse events, for both RA and psoriasis, being nasopharyngitis and upper respiratory tract infection. As such, tofacitinib proves to be an effective therapeutic option for RA and a promising new therapy for psoriasis.

Key words: tofacitinib, rheumatoid arthritis, chronic plaque psoriasis, JAK inhibitor, inflammation

Introduction

Tofacitinib (CP-690,550; trade name: Xeljanz®) is an oral immunosuppressant developed by Pfizer[1] that is currently approved for the treatment of rheumatoid arthritis (RA)[2,3] and is undergoing Phase III trials for the treatment of chronic plaque psoriasis.[4-6] Tofacitinib is a pan-Janus-activated kinase (JAK) inhibitor, which works by inhibiting JAK3, JAK1, and, to a lesser extent, JAK2.[7] Members of the JAK family play a key role in the signaling pathways of multiple cytokines (e.g., tumour necrosis factor [TNF]), growth factors, and hormones.[2] Activation of these immune pathways involving JAKs have been implicated in the pathogenesis of RA2,[8] and psoriasis.[9]

Since its FDA approval in 2012, tofacitinib has demonstrated promising results in Phase III clinical trials by significantly reducing RA associated symptoms such as synovial inflammation and structural joint damage.[10] Moreover, ongoing Phase III studies are demonstrating that tofacitinib could emerge as a valuable therapy for psoriasis.[11] The focus of this paper is to evaluate the efficacy and safety of tofacitinib in the treatment of RA and psoriasis by reviewing recent clinical trials.

Tofacitinib for Rheumatoid Arthritis

Phase III Trials

Six Phase III trials (belonging to the Oral Rheumatoid Arthritis triaLs [ORAL] series) have been conducted to assess the efficacy of tofacitinib in the treatment of RA in various patient groups.[12-17] A summary of the details from each Phase III trial and two long-term open extension trials[18] can be found in Table 1. Three primary efficacy outcomes were similar between the five Phase III trials: 1) American College of Rheumatology (ACR) 20 (≥20% reduction in the number of both tender and swollen joints and ≥20% improvement in three of five other criteria: the patient's assessment of pain, level of disability, C-reactive protein level or erythrocyte sedimentation rate, global assessment of disease by the patient, and global assessment of disease by the physician) response criteria; 2) changes from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI; range of score 0-3, "no difficulty" to "unable to do"); and 3) percentage of patients with Disease Activity Score for 28 joint counts based on erythrocyte sedimentation rate (DAS28-4 [ESR]) of less than 2.6 (range 0-9.4). The sixth trial (ORAL Start) used the primary efficacy outcome of ARC 70 response and the modified total Sharp

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score (mTSS) from baseline. In the groups receiving tofacitinib treatment, ARC 20 or 70 (for the ORAL Start trial) response rates and the HAQ-DI scores were significantly higher compared to the placebo groups. Most studies also showed significant changes from baseline in the DAS28-4 (ESR) score in the tofacitinib group(s) compared to placebo and the ORAL Start trials showed that the change in mTSS from baseline was significantly smaller in the tofacitinib groups. The most common adverse event (AE) throughout the studies was upper respiratory tract infection. During the first 3 months of tofacitinib therapy, significant decreases in neutrophil counts and increases in low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol counts were observed compared to placebo groups. Safety and tolerability data for these studies are summarized in Table 2.

Data from Phase II and Phase III Trials

A study using pooled data from tofacitinib Phase II, Phase III and long-term extension studies was conducted to determine the rate of infection and all-cause mortality across studies in patients receiving tofacitinib monotherapy or tofacitinib in conjunction with methotrexate or other non-biologic disease-modifying antirheumatic drugs (DMARDs).[19] The overall rate of serious infection in 4,789 patients was 3.09 events per 100 patient-years, with the overall rates of mortality and infection being similar in the tofacitinib groups and groups being treated with biological agents. A recent Phase II randomized control study was conducted to test the efficacy of tofacitinib monotherapy vs. placebo for the treatment of RA in Japanese patients.[20] Similar to the Phase III ORAL studies, dose-dependent decreases were observed in neutrophil and platelet counts, with a significant increase in low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol levels compare to placebo groups.[20] The significant decrease in neutrophil counts led to moderate-severe neutropenia in seven patients that was not life threatening.[20] Furthermore, 23.3% of patients across all groups had a decrease in absolute lymphocyte counts, however, this did not lead to an increase in severe infections.[20] Of note, RA patients from Asia may be at increased risk for herpes zoster when undergoing tofacitinib treatment. An open-label, long-term extension study of tofacitinib in Japanese patients reported herpes zoster in 19.3% of patients,[21] while analysis of tofacitinib patients from the worldwide clinical program identified Asia as an enrollment center to be an independent risk factor for developing herpes zoster.[22]

Another study conducted using data from the Phase III trial ORAL Step assessed patient-reported outcomes for tofacitinib.[23] Patients reported improvements in patient global assessment of disease activity ($p<0.0001$) and the physical and mental component of the Short Form 36 Health Survey version 2 scores ($p<0.05$) for both tofacitinib doses compared with placebo. Furthermore, improvements were more frequently reported by tofacitinib treated patients vs. placebo for pain ($p<0.0001$). The results are consistent with recently published data from the ORAL Solo trial, demonstrating statistically significant improvements in pain, Medical Outcome Survey (MOS) for Physical and Mental health, and Functional Assessment of Chronic Illness Therapy-Fatigue in patients receiving tofacitinib (5 mg or 10 mg) vs. placebo ($p<0.0001$ for all).[24]

A systematic review of randomized Phase II and III controlled trials concluded that tofacitinib, at dosages of 5 mg and 10 mg twice daily, is effective in patients with active RA who show an inadequate response to methotrexate or DMARDs.[25] The ACR 20 response rates were significantly higher in the tofacitinib 5 mg and 10 mg groups than in the placebo groups in all studies. Moreover, the safety outcomes did not differ between the tofacitinib groups and placebo groups, with the exception of infection in the tofacitinib 10 mg group.

A meta-analysis of 10 randomized controlled studies evaluating the efficacy and safety of tofacitinib in patients with active RA showed that tofacitinib, at dosages of 5 mg and 10 mg twice daily, in combination with methotrexate, was the most effective therapy for active RA and was not associated with a significant risk for withdrawal due to AEs.[26]

From an economic/societal perspective, studies conducted in Korea[27] and Brazil[28] showed that incorporating tofacitinib into the treatment regime or as a first-line therapy for patients with moderate to severe RA is a cost-effective alternative to the current standard of care.

Tofacitinib for Psoriasis

Phase II Trials (NCT00678210)

A 12 week, Phase IIb multicenter, randomized, double-blind, parallel-group, placebo-controlled trial was conducted to evaluate the efficacy and safety of various doses of oral tofacitinib (2 mg, 5 mg, or 15 mg twice daily) in 197 patients with moderate-to-severe psoriasis.[29] At week 12, Psoriasis Area and Severity Index 75 (PASI 75; the percentage of patients who have achieved a 75% or more reduction in their PASI score from baseline) responses were observed in 25% (2 mg; $p<0.001$), 40.8% (5 mg; $p<0.0001$), and 66.7% (15 mg; $p<0.0001$) of the patients in the tofacitinib groups compared with 2% in the placebo group. The most common AEs were upper respiratory tract infections, nasopharyngitis, and headache. Moreover, mild dose-dependent decreases in hemoglobin and neutrophil counts, and increased total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol occurred over the duration of treatment compared to placebo.[29] In this same study cohort, outcome questionnaires were completed by the patient[30] and showed that treatment with tofacitinib resulted in significant, dose-dependent improvements in several patient-reported outcomes compared with placebo. In the same study cohort, the efficacy of tofacitinib was evaluated in four body regions (head and neck, upper limbs, trunk, and lower limbs).[31] Mean improvements in PASI 75 and body surface area (BSA) values were significantly improved with tofacitinib vs. placebo across all four body regions.

Data from the Phase IIb trial was also used to elucidate the correlation between pruritus (a severe and bothersome symptom of psoriasis which is not assessed by the PASI or Physician's Global Assessment [PGA] rating of 'clear' or 'almost clear' using a 5-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe)[32] and the clinical signs of psoriasis (erythema, induration and scaling).[33] This study showed that tofacitinib acts directly to improve patient-reported pruritus and this effect is independent from improvements in clinician-reported psoriasis severity signs.

Study	Duration	Participant Inclusion Criteria	Demographics	Intervention	Primary Outcomes	Results
ORAL Solo[12] (NCT00814307)	6 months	Active RA patients with inadequate response to at least one DMARD (biologic or nonbiologic)	n=611 Age: 49.7-52.4 Male: 13.3% Duration of RA: 7.7-8.6 years Baseline HAQ-DI: 1.50-1.53 Baseline DAS-28: 6.65-6.71	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Placebo for 3 months then tofacitinib 5 mg or 10 mg bid	ACR 20 response at month 3; DAS28-4 (ESR) <2.6 at month 3; HAQ-DI at month 3 (change from baseline)	ARC 20 response rates were sig. higher (p<0.001) and HAQ-DI score were sig. improved in tofacitinib groups (p<0.001).
ORAL Step[13] (NCT00960440)	6 months	Moderate to severe RA patients with inadequate response to TNFα inhibitors	n=399 Age: 54.4-55.4 Male: 16.7%-86.36% Duration of RA: 11.3-13.0 years Baseline HAQ-DI: 1.5-1.6 Baseline DAS-28: 6.4-6.5	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Placebo for 3 months then tofacitinib 5 mg or 10 mg bid	ACR 20 response at month 3; DAS28-4 (ESR) <2.6 at month 3; HAQ-DI at month 3 (change from baseline)	ARC 20 response and HAQ-DI score were sig. improved in both tofacitinib groups (p<0.0001). DAS28-4 (ESR) score <2.6 was sig. with tofacitinib 5 mg (p=0.049) and 10 mg (p=0.011).
ORAL Standard[14] (NCT00853385)	12 months	Active RA patients receiving stable doses of methotrexate	n=717 Age: 51.9-55.5 Male: 19.8% Duration of RA: 6.9-9.0 years Baseline HAQ-DI: 1.4-1.5 Baseline DAS-28: 6.3-6.6	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Adalimumab 40 mg SC every 2 weeks; Placebo for 6 months then tofacitinib 5 mg or 10 mg bid	ACR 20 response at month 6; DAS28-4 (ESR) <2.6 at month 6; HAQ-DI at month 3 (change from baseline)	ARC 20 responses were sig. higher in treatment groups compared to placebo (p<0.001). Sig. changes from baseline in DAS28-4 (ESR) and HAQ-DI in the active treatment groups were seen over time (p≤0.05).
ORAL Sync[15] (NCT00856544)	12 months	Active RA patients with inadequate response to one or more DMARD	n=792 Age: 50.8-53.3 Female: 20.85% Duration of RA: 8.1-10.2 years Baseline HAQ-DI: 1.24-1.45 Baseline DAS-28: 6.14-6.44	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Placebo	ACR 20 response at month 6; DAS28-4 (ESR) <2.6 at month 6; HAQ-DI at month 3 (change from baseline)	ARC 20 response and HAQ-DI score were sig. improved in both tofacitinib groups (p<0.001). DAS28-4 (ESR) <2.6 was sig. in both tofacitinib groups (p=0.005).
ORAL Scan[16] (NCT00847613)	24 months	Active RA patients receiving background methotrexate	n=797 Age: 52.0-53.7 Male: 14.3% Duration of RA: 8.8-9.5 years Baseline HAQ-DI: 1.23-1.41 Baseline DAS-28: 6.25-6.34	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Placebo for 3 months then tofacitinib 5 mg or 10 mg bid	ACR 20 response at month 6; DAS28-4 (ESR) <2.6 at month 6; HAQ-DI at month 3 (change from baseline); SHS at month 6 (change from baseline)	ARC 20 response rates were sig. higher in both tofacitinib groups compared to placebo (p<0.0001). Sig. changes from baseline in DAS28-4 (ESR) and HAQ-DI were seen in the tofacitinib 10 mg group (p<0.0001).
ORAL Start[17] (NCT01039688)	24 months	Methotrexate naïve patients with active RA	n=952 Age: 49.3-50.3 Male: 20.1% Duration of RA: 2.7-3.4 years Baseline HAQ-DI: 1.5 Baseline DAS-28: 6.5-6.6 Baseline TSS: 16.51-20.30	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Methotrexate 10 mg per week with 5 mg increments every 4 weeks up to 20 mg per week	Modified TSS at month 6; ACR 70 response at month 6	ARC 70 response rates were sig. higher in both tofacitinib groups compared with methotrexate (p<0.001). Change in modified TSS from baseline was sig. smaller in the tofacitinib groups (p≤0.05).
Long-Term Open Extension[18] (NCT00413699, NCT00661661)	60 months	Completed participation in a prior qualifying Phase I, II, or III study for RA	n=4102 Mean age: 53.2 Male: 17.0% Mean (max) duration: 531 (1844) days	Tofacitinib 5 mg or 10 mg bid + background DMARD; Tofacitinib 5 mg or 10 mg bid monotherapy	Safety; ACR 20, ACR 50, ACR 70, DAS28-4 (ESR), HAQ-DI	Safety consistent with Phase III; ACR response rates maintained, both DAS28-4 (ESR) decreased and mean HAQ-DI score improved at month 48.

Table 1. Summary of Phase III tofacitinib studies for rheumatoid arthritis

DMARD: Disease-modifying antirheumatic drug; TSS: Total sharp score; TNF: Tumor necrosis factor; SHS: Sharp/van der Heijde Score; HAQ-DI: Health Assessment Questionnaire Disability Index; ARC 20 or 70 response: American College of Rheumatology response (≥20% or ≥70% reduction in the number of both tender and swollen joints and ≥20% or ≥70% improvement in three of five of other criteria: the patient's assessment of pain, level of disability, C-reactive protein level or erythrocyte sedimentation rate, global assessment of disease by the patient, and global assessment of disease by the physician; DAS 28-4 (ESR): Disease Activity Score for 28 joint counts based on erythrocyte sedimentation rate; sig.: significant(ly).

ORAL Solo[12]		**Placebo**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	
	TEAEs	55%	44%	48%	
	SAEs●	5%	1%	2%	
	Discontinuation of study●	4%	3%	2%	
ORAL Step[13]		**Placebo**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	
	TEAEs	57%	46%	49%	
	SAEs	5%	3%	3%	
	Discontinuation of study	5%	4%	5%	
ORAL Standard[14]		**Placebo**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	**Adalimumab 40 mg**
	TEAEs	40%	41%	40%	42%
	SAEs	2%	5%	4%	3%
	Discontinuation of study	2%	4%	4%	4%
Oral Sync[15]		**Placebo**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	
	TEAEs	62%	69%	68%	
	SAEs	4%	6%	6%	
	Discontinuation of study	2%	5%	8%	
ORAL Scan[16]		**Placebo**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	
	TEAEs	46%	48%	48%	
	SAEs	3%	4%	3%	
	Discontinuation of study	3%	4%	3%	
ORAL Start[17]		**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	**Methotrexate 10 mg**	
	TEAEs	80%	84%	79%	
	SAEs	11%	11%	12%	
	Discontinuation of study	11%	10%	13%	
Long-Term Open Extension[18]		**Tofacitinib 5 mg and 10 mg + DMARD**	**Tofacitinib 5 mg and 10 mg monotherapy**		
	TEAEs	56%	48%		
	SAEs	11%	10%		
	Discontinuation of study	8%	7%		

Table 2. Safety and tolerability of tofacitinib in RA patients: results from Phase III trials
TEAEs: treatment-emergent adverse events
SAEs: serious adverse events
Discontinuation of study due to treatment-emergent adverse events

Study	Duration	Participant Inclusion Criteria	Demographics	Intervention	Primary Outcomes	Results
OPT Retreatment[5] (NCT01186744)	56 weeks	≥18 years old, diagnosed with chronic plaque psoriasis for ≥12 months, were candidates for systemic therapies or phototherapy, had a PASI score ≥12, PGA score of 3 or 4 and psoriasis involvement of ≥10% of total BSA	n=666 Age: 18-83 Male: 68.8% Duration of disease (mean): 15.5 years	Initial treatment (24 weeks): tofacitinib 5 mg or 10 mg bid; Withdrawal (16 weeks): placebo or tofacitinib 5 mg or 10 mg bid; Retreatment (16 weeks): placebo or tofacitinib 5 mg or 10 mg bid	PASI 75 response and a PGA rating of 'clear' or 'almost clear'	Withdrawal period: sig. more patients maintained PASI 75 and PGA responses with both tofacitinib treatments vs. patients switched to placebo (p<0.0001). Retreatment: 48% and 52% and 72.5% and 64.2% of patients treated with placebo during withdrawal regained/ maintained PASI 75 and PGA response with tofacitinib 5 mg and 10 mg, respectively.
OPT Pivotal 1[4] (NCT01276639) and **OPT Pivotal 2**[4] (NCT01309737)	52 weeks	≥18 years old, diagnosed with chronic plaque psoriasis for ≥12 months, were candidates for systemic therapies or phototherapy, had a PASI score ≥12, PGA score of 3 or 4 and psoriasis involvement of ≥10% of total BSA	Pivotal 1, n=901 Age: 18-79 Male: 70.9% Duration of disease (mean): 16.2 years Average BSA affected: 25.2% Pivotal 2, n=960 Age: 18-82 Male: 68.6% Duration of disease (mean): 16.3 years Average BSA affected: 24.5%	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Placebo for 16 weeks then switch to tofacitinib 5 mg or 10 mg bid	PASI 75 response and a PGA rating of 'clear' or 'almost clear'	Sig. higher PASI 75 rates and PGA responses were seen with both tofacitinib treatments vs. placebo in both studies (p<0.001 for both studies).
OPT Compare[6] (NCT01241591)	12 weeks	≥18 years old, diagnosed with psoriasis for ≥12 months, were candidates for systemic therapies or phototherapy, had a PASI score ≥12, PGA score of 3 or 4 and psoriasis involvement of ≥10% of total BSA, and had failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic therapy for psoriasis	n=1101 Age: 18-81 Male: 70% Duration of disease (mean): 17 years Average BSA affected: 26.7%	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Etanercept 50 mg subcutaneously twice weekly; Placebo	PASI 75 response and a PGA rating of 'clear' or 'almost clear'	Sig. higher PASI 75 rates and PGA responses were seen with all active treatments (tofacitinib and etanercept) vs. placebo (p<0.0001).
OPT Extend (NCT01163253)		≥18 years old, diagnosed with plaque psoriasis, complete participation in a qualifying tofacitinib clinical study	n=3200 (estimate)	Tofacitinib 10 mg bid for first 3 months, then tofacitinib 5 mg bid or tofacitinib 10 mg bid at principal investigator's discretion	Evaluate long-term safety and tolerability	Ongoing

Table 3. Summary of Phase III tofacitinib studies for psoriasis

PASI 75 response: Psoriasis Area and Severity Index (the percentage of patients who have achieved a 75% or more reduction in their PASI score from baseline); PGA rating: Physician's Global Assessment rating of 'clear' or 'almost clear' (using a 5-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe); BSA: body surface area; sig.: significant(ly); bid: twice daily.

OPT Retreatment[5]		**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	**Placebo + Tofacitinib 5 mg**	**Placebo + Tofacitinib 10 mg**		
	TEAEs	59%	66%	50%	48%		
	SAEs	2%	4%	2%	1%		
	Discontinuation of study	3%	4%	0%	1%		
OPT Pivotal 1, OPT Pivotal 2[4]		**Study 1**			**Study 2**		
		Placebo	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	**Placebo**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**
	TEAEs	50%	51%	61%	47%	56%	56%
	SAEs	3%	2%	3%	1%	3%	1%
	Discontinuation of study	6%	3%	3%	3%	4%	3%
OPT Compare[6]		**Placebo**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**	**Etanercept 50 mg**		
	TEAEs	51%	55%	60%	57%		
	SAEs	5%	2%	2%	2%		
	Discontinuation of study	4%	1%	3%	3%		

Table 4. Safety and tolerability of tofacitinib in psoriasis patients: results from Phase III trials
TEAEs: treatment-emergent adverse events; SAEs: serious adverse events; Discontinuation of study due to treatment-emergent adverse events

Phase III Trials

A summary of the details for the Phase III psoriasis trials can be found in Table 3. The most common AEs were nasopharyngitis and upper respiratory tract infection. Safety and tolerability data for these studies are summarized in Table 4. Laboratory findings were similar to those reported for tofacitinib for the treatment of RA. Two additional Phase III trials are undergoing clinical investigation: NCT01163253 (OPT Extend) is in the process of recruiting participants and is a long-term open label extension study available to patients enrolled in a qualifying clinical study, while NCT01815424 has been concluded and investigated the efficacy of tofacitinib 5 mg and 10 mg in Asian patients; results have not yet been published.

Treatment Withdrawal & Retreatment Study (NCT01186744)

A Phase III, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy of tofacitinib in three phases of treatment (OPT Retreatment).[5] At the end of the initial treatment, patients were classified as treatment responders if they achieved both PASI 75 response and a PGA rating of 'clear' or 'almost clear'. Responders entered the treatment-withdrawal period, and were re-randomized to placebo or their previous dose of tofacitinib. Patients who relapsed (defined as >50% reduction in the PASI improvement from baseline to week 24) entered the retreatment period. All remaining patients continued in the treatment-withdrawal period before entering the retreatment period. In the retreatment period, patients who received placebo during treatment withdrawal were retreated with the same dose of tofacitinib that they received during the initial treatment period. After initial treatment, 33.5% and 55.2% of patients achieved both PASI 75 and PGA responses with tofacitinib 5 mg and 10 mg, respectively, and were eligible to enter the treatment withdrawal phase. At the end of the withdrawal period, a greater number of patients receiving tofacitinib 5 mg (56.2%) and 10 mg (62.3%) maintained a PASI 75 response compared to patients who were switched to placebo (23.3%, p=0.008 and 26.1% p<0.0001). Moreover, 92.3% and 93.0% of patients receiving tofacitinib 5 mg and 10 mg, respectively, did not relapse compared with 32.8% and 42.9% of those who were switched to placebo. At the end of the retreatment period, 63.0% and 73.8% of patients who continued to receive tofacitinib 5 mg and 10 mg during the treatment-withdrawal period regained or maintained a PASI 75 response and 66.7% and 64.3% regained or maintained a PGA response. Moreover, 48.0% and 72.5% of the patients treated with placebo during the treatment-withdrawal period regained or maintained a PASI 75 response, and 52.0% and 64.2% regained or maintained a PGA response after 16 weeks of retreatment with tofacitinib 5 mg or 10 mg, respectively.

Pivotal Trials (NCT01276639 & NCT01309737)

Two similarly designed Phase III studies (OPT Pivotal 1, n=901 and OPT Pivotal 2, n=960) were conducted to evaluate the efficacy and safety of tofacitinib 5 mg and 10 mg twice daily.[4] At Week 16, higher PASI 75 rates were observed in both tofacitinib groups vs. placebo (OPT Pivotal 1: 39.9%, 59.2% and 6.2% for tofacitinib 5 mg and 10 mg, and placebo; OPT Pivotal 2: 46.0%, 59.6% and 11.4%; all p<0.0001). Moreover, higher PGA ratings were seen in patients receiving tofacitinib 5 mg and 10 mg vs. placebo (OPT Pivotal 1: 41.9% and 59.2% vs 9.0%; OPT Pivotal 2: 46.0% and 59.1% vs. 10.9%; all p<0.0001).

Tofacitinib vs. Etanercept (NCT01241591)

A Phase III, randomized, multicenter, double-dummy, placebo-controlled trial compared the non-inferiority of tofacitinib with etanercept (50 mg) subcutaneously twice weekly or placebo (OPT

Compare).[6] At week 12, a greater number of patients receiving active treatment (39.5% for tofacitinib 5 mg, 63.6% for tofacitinib 10 mg, and 58.8% for etanercept) achieved PASI 75 responses compared to placebo (5.6%, $p<0.0001$ for all treatments vs. placebo). Moreover, a PGA response was achieved by 47.1%, 68.2%, 66.3%, and 15.0% of the patients in the tofacitinib 5 mg, 10 mg, etanercept and placebo groups ($p<0.0001$ for all treatments vs. placebo).

Conclusion

Numerous Phase II and Phase III trials have shown that tofacitinib is safe and effective in alleviating RA symptoms, relieving pain, and improving physical and mental health, either when used as monotherapy in patients who show inadequate responses to TNF inhibitors, methotrexate or DMARDs, or as combination therapy with methotrexate or DMARDs. In addition, tofacitinib has been shown to be effective in the treatment of chronic plaque psoriasis in Phase II and III clinical trials, with continuous therapy resulting in better treatment prognosis than intermittent therapy. Efficacy of tofacitinib was comparable to etanercept and superior to placebo in improving the clinical symptoms of psoriasis. Moreover, tofacitinib was also shown to improve pruritus, a common and troublesome symptom of psoriasis not typically assessed in clinical studies. These studies provide support for tofacitinib as an innovative and valuable oral systemic therapy for the treatment of RA and psoriasis.

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A Review of Guselkumab, an IL-23 Inhibitor, for Moderate-to-Severe Plaque Psoriasis

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Conflicts of interest: Dr. Tyring has been an investigator for clinical trials sponsored by Abbvie, Amgen, Boehringer Ingelheim, Celgene, Coherus, Contravir, Cutanea, Dermira, Galderma, Genocea, Innovaderm, Janssen, Eli Lilly and Company, Leo Pharma, Merck, MSD, Medimmune, Novan, Novartis, Pfizer, Promius, Regeneron, Tolmar, Vitae, Watson-Actavis, and Xoma. Drs. Nawas, Tong and Peranteau have been sub-investigators on clinical trials sponsored by the same companies listed above. Hatch, Ramos, and Liu have no conflicts of interest to disclose.

ABSTRACT

Psoriasis is a chronic inflammatory skin disorder that affects 2% of the population. Evidence suggests that interleukin (IL)-23 plays a pivotal role in the pathogenesis of psoriasis. Guselkumab is a subcutaneously administered, humanized anti-IL23 monoclonal antibody indicated for the treatment of moderate-to-severe plaque psoriasis. Data from Phase I-III trials in this patient population reveal that guselkumab has proven to be superior to placebo or adalimumab based on achieving a Psoriasis Area and Severity Index (PASI) 90% reduction, or a static Physician Global Assessment (sPGA) score of 0 or 1 from baseline. This article reviews the current status of guselkumab as a therapy for moderate-to-severe plaque psoriasis.

Key words: biologics, cytokine, IL-23, interleukin-23 inhibitor, monoclonal antibody, psoriasis, Th17

Introduction

Psoriasis is the most common chronic autoimmune skin condition affecting about 2% of the population.[1] This disease has a significant impact on quality of life, mental health and work productivity, and it is linked to other comorbid conditions such as cardiovascular disease, metabolic syndrome, and arthritis.[2,3] Psoriasis is thought to arise from a combination of pathogenic factors including genetic susceptibility and environmental exacerbation, which results in activation of dendritic cells in the skin and differentiation of T cells.[4] In turn, these T cells produce cytokines that induce keratinocyte hyperproliferation and result in characteristic raised, well-demarcated erythematous lesions of psoriasis.

Accumulating evidence suggests that the proinflammatory cytokine interleukin (IL)-23 and its resulting T helper 17 (Th17) pathway play a more important role in mediating psoriasis than IL-12.[5,6] IL-23 induces differentiation and maintenance of Th17 cells, which produce the effector cytokines IL-17, IL-22, and tumor necrosis factor-alpha (TNFα).[7,8] IL-23 is a heterodimer composed of two subunits, p40 and p19.[8] While p40 is also present in IL-12, p19 is specific for IL-23.[8] Levels of IL-23p19 and IL-12/23p40 messenger RNA (mRNA) are upregulated in psoriatic plaques and decrease with effective treatment.[7-11]

This paper focuses on guselkumab, a fully human immunoglobulin G1 (IgG1) monoclonal antibody that specifically inhibits intracellular IL-23 and downstream signaling by targeting the p19 subunit.[12,13] Guselkumab decreases blood and skin lesion levels of effector IL-17A and decreases epidermal hyperplasia and inflammation by downregulating T cells and myeloid dendritic cells.[12] This evidence further establishes the IL-23/Th17 axis as the primary driver of psoriatic inflammation. Additionally, another goal for guselkumab is increased safety by maintaining the IL-12/Th1 axis, an important regulator of immune function, unlike the previous medications that targeted both IL-12 and IL-23. IL-12 is required for appropriate Th1 response and defense against intracellular pathogens due to its role in the production of interferon gamma (INFγ) by T- and natural killer (NK)-cells.[14] Animal studies have demonstrated that anti-p40 antibodies enhance mycobacterial growth, but that p19-deficient mice are indistinguishable from wild type animals as long as IL-12 is functional.[6] In contrast, patients deficient in the p40 subunit are more susceptible to low virulence nontuberculous *Mycobacterium* and *Salmonella*.[6]

Additional monoclonal antibodies targeting both IL-12/23 have been investigated for the treatment of psoriasis. Briakinumab, has been found to be associated with a significantly higher rate of major adverse cardiovascular events, infections, and non-melanoma skin cancers as compared with placebo. Resultantly, this drug has been withdrawn from the market.[15] Conversely, ustekinumab, has shown a safer profile with a similar rate of adverse events in comaparison to placebo.[12]

Clinical Trials

Phase I

This first-in-human, randomized, double-blind, placebo-controlled Phase I study showed that a single dose of guselkumab results in a significant clinical response. In this trial, 24 patients with moderate-to-severe plaque psoriasis received a single dose of guselkumab consisting of either 10 mg, 30 mg, 100 mg

or 300 mg or a placebo. At week 12, Psoriasis Area and Severity Index (PASI) 75 was achieved in 50%, 60%, 60% and 100% of patients, respectively, as compared with 0% in the placebo group. In addition, the trial reported a decrease in both psoriasis gene expression and serum IL-17A levels in the guselkumab-treated group. The overall incidence of adverse reactions was similar in the treatment (65%) and placebo arms (50%).[16]

Phase II - Efficacy

The efficacy of guselkumab was evaluated in a Phase II randomized, double-blind, placebo controlled, active-comparator trial (X-PLORE).[17] In this trial, the efficacy of guselkumab was compared with adalimumab, a TNFα inhibitor used to treat plaque psoriasis. Two hundred and ninety-three patients were randomized to receive either gusekumab, adalimumab, or placebo. A total of 39 patients in the placebo group were crossed over to receive guselkumab at week 16. After 16 weeks of treatment, the percentage of patients achieving a physician's global assessment (PGA, primary endpoint) of 0 or 1 was significantly higher in each guselkumab group than placebo (34% for 5 mg, 61% for 15 mg, 79% for 50 mg, 86% for 100 mg, 83% for 200 mg, and 7% for placebo). Likewise, the percentage of patients with at least a 75% improvement from baseline in PASI score was significantly higher in each guselkumab group.

The percentage of patients with a PGA score of 0 or 1 reached a maximum at week 20 in most guselkumab groups, which was maintained through week 40. In addition, the group that crossed over from placebo to guselkumab at week 16 achieved similar PGA scores as the group that received 100 mg guselkumab. Finally, at both weeks 16 and 40, the percentage of patients with a PGA score of 0 or 1 was higher in most guselkumab groups (50 mg, 100 mg, and 200 mg) compared to the adalimumab group.

Phase II - Safety

Up to week 16, the proportion of patients with adverse events was similar in the different treatment groups (52% for placebo, 50% for guselkumab, 56% for adalimumab), and there was no demonstrable relationship between the guselkumab dose and rate of adverse events through to termination of the study. However, through week 52, a higher proportion of patients in the adalimumab group (61%) experienced an adverse event compared with guselkumab groups (49%). Of note, two serious infections, one case of grade 3 cervical intraepithelial neoplasia, and three major adverse cardiovascular events, including one death from myocardial infarction, occurred in the guselkumab group.

Trial ID	Title of Study	Primary Outcome Measure	Status
NCT02207231	A Study of Guselkumab and Active Comparator in the Treatment of Participants With Moderate to Severe Plaque-Type Psoriasis (VOYAGE 1)	Percentage of participants with an Investigator's Global Assessment (IGA) score of 0 or 1 comparing the guselkumab group and the placebo group on week 16 Percentage of participants with a PASI 90 response comparing the guselkumab group and the placebo group at week 16	Ongoing
NCT02207244	A Study of Guselkumab in the Treatment of Participants With Moderate to Severe Plaque-Type Psoriasis With Randomized Withdrawal and Retreatment (VOYAGE 2)	Percentage of participants with an IGA score of 0 or 1 comparing the guselkumab group and the placebo group on week 16 Percentage of participants with a PASI 90 response comparing the guselkumab group and the placebo group at week 16	Ongoing
NCT02343744	An Efficacy and Safety Study of CNTO1959 (Guselkumab) in the Treatment of Participants With Generalized Pustular Psoriasis or Erythrodermic Psoriasis	Percentage of participants with treatment success ("very much improved" in the Clinical Global Impression [CGI] scale) at week 16	Ongoing
NCT02325219	An Efficacy and Safety of CNTO 1959 (Guselkumab) in Participants With Moderate to Severe Plaque-Type Psoriasis	Number of participants who achieve an IGA score of 0 or 1 at week 16 comparing 50 mg, 100 mg of CNTO1959 or placebo	Ongoing
NCT02203032	A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Guselkumab for the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis and an Inadequate Response to Ustekinumab	The number of visits at which participants achieve an IGA response of 0 or 1 and at least a 2 grade improvement (from week 16) among randomized participants with an inadequate (IGA ≥2) response to ustekinumab at week 16	Completed – pending results

Table 1. Phase III clinical trials of guselkumab in psoriasis

Phase III

Preliminary results for the VOYAGE 1 and VOYAGE 2 trials have been published. In the VOYAGE 1 trial, patients were randomly assigned to three arms: guselkumab 100 mg at weeks 0 and 4, then every 8 weeks; placebo at weeks 0, 4 and 12 then guselkumab at week 16 and 20, then every 8 weeks; or adalimumab 80 mg at week 0, 40 mg week 1, then 40 mg every 2 weeks. At week 16, the patients exhibited improved responses to guselkumab as compared with placebo (PASI 90 response of 73.3% vs. 2.9%) and adalimumab at week 16 (73.3% vs. 49.7%). Furthermore, guselkumab comparisons to adalimumab were also significantly superior at weeks 24 and 48 (80.2% vs. 53%, and 76.3% vs. 47.9%, respectively). Adverse events were similar among all groups.

In the VOYAGE 2 trial, patients were randomized to identical comparison arms, however at week 28 PASI 90 responders were re-randomized to guselkumab or placebo with further crossover for those who lost response. The results showed that at week 16, 70.0% of patients receiving guselkumab had a PASI 90 as compared with 2.4% in placebo. When compared to adalimumab, guselkumab demonstrated 75% and 100% of PASI 90 improvement at 16 and 24 weeks, respectively. In addition, guselkumab showed improved outcomes in those who were adalimumab nonresponders.

Currently a Phase III, multicenter, randomized, double-blind study evaluating the efficacy and safety of guselkumab is ongoing.[16] This study examines patients with moderate-to-severe plaque-type psoriasis who experienced an inadequate response to ustekinumab. Results from the study are planned for presentation at upcoming scientific meetings according to a Janssen press release. Other Phase III trials of guselkumab are also currently underway (Table 1).[17-19]

Conclusion

Guselkumab is a monoclonal IL-23 antibody that treats psoriasis. Targeting IL-23 is believed to block a specific mediator of psoriatic inflammation. Data from a Phase II study shows that guselkumab is safe and efficacious. Preliminary results have demonstrated superiority of guselkumab over placebo and adalimumab. Guselkumab was superior to both placebo and adalimumab ($p<0.001$ for all comparisons of guselkumab with placebo and adalimumab). Further data from Phase III trials is expected to be available in the summer 2018.

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Skin Treatments Introduced in 2016

Skin Therapy Letter uses reasonable efforts to include accurate and up-to-date information, we make no warranties or representations as to the accuracy, completeness, timeliness or reliability of the content and assume no liability or responsibility for any error or omission.
The content primarily focuses on approvals issued by US and Canadian drug regulatory agencies.

Type/Class of Therapy	Generic/Trade/ Company Names	Indication	Approving Regulatory Agency
Actinic Keratosis	**PDT for actinic keratosis** *Ameluz® gel + BF-RhodoLED®* Biofrontera AG	Approval was granted to the topical drug Ameluz® (aminolevulinic acid, a porphyrin precursor) for use in combination with the BF-RhodoLED® lamp for photodynamic therapy (PDT) treatment of mild to moderate actinic keratoses on the face and scalp. This approval covers lesion-directed as well as field-directed treatment.	US FDA
Anti-acne Agents	**Adapalene 0.1% gel** *Differin® Gel* Galderma Laboratories, L.P.	This approval makes Differin® Gel the first and only OTC acne product containing a full prescription-strength retinoid. It also marks the first new FDA-approved active ingredient to be introduced to the OTC acne category in over 3 decades.	US FDA
	Dapsone 7.5% gel *Aczone®* Allergan plc.	Dapsone 7.5% gel was approved for the once-daily topical treatment of acne in patients ≥12 years of age. This agent treats both inflammatory and non-inflammatory acne with a new concentration of dapsone.	US FDA
Antibacterial Agents	**Ceftaroline fosamil** *Teflaro®* Allergan plc.	A supplemental New Drug Application was granted to ceftaroline fosamil, an IV antibiotic, extending new indications for pediatric patients 2 months to <18 years of age with acute bacterial skin and skin structure infections.	US FDA
Anti-cancer Agents	**Cobimetinib + vemurafenib** *Cotellic™ + Zelboraf®* Hoffmann-La Roche Limited (Roche Canada)	Cobimetinib (MEK-inhibitor) was approved for use in combination with vemurafenib (BRAF-inhibitor), as an oral treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. European and US approvals were gained in 2015.	Health Canada
	Nivolumab + ipilimumab *Opdivo® + Yervoy®* Bristol-Myers Squibb Company	Approval was granted to nivolumab (Opdivo®, anti-PD-1 monoclonal antibody) in combination with ipilimumab (Yervoy®, anti-CTLA-4 monoclonal antibody) for the treatment of advanced (unresectable or metastatic) melanoma in adults.	European Commission Health Canada US FDA
	Pembrolizumab IV injection *Keytruda®* Merck & Co.	Pembrolizumab was approved for the treatment of patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Pembrolizumab is now the first and only anti-PD1 agent approved for first-line treatment regardless of BRAF mutation status.	Health Canada
Atopic Dermatitis	**Crisaborole 2% ointment** *Eucrisa™* (formerly AN2728) Pfizer Inc.	Crisaborole ointment was approved to treat mild-to-moderate eczema (atopic dermatitis, AD) in patients ≥2 years of age. Cisaborole is a novel non-steroidal topical anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor.	US FDA
Dermal Fillers	**Dermal filler with calcium** hydroxylapatite (CaHA) + integral 0.3% lidocaine *Radiesse® Lidocaine* Merz Pharma	CE mark certification was granted to Radiesse® Lidocaine, an injectable implant dermal filler that contains a small quantity of the local anesthetic lidocaine. In Europe, Radiesse® Lidocaine is indicated for plastic/reconstructive procedures, including deep dermal and subdermal soft tissue augmentation of the facial area and for restoration and correction of facial volume loss.	European Commission
	Hyaluronic acid (HA) gel filler *Juvéderm Volbella® XC* Allergan plc	Approval was granted to market Juvéderm Volbella® XC for use in the lips for lip augmentation and correction of perioral rhytids, commonly referred to as perioral lines, in adults >21 years of age.	US FDA
	HA dermal fillers *Restylane® Refyne* *Restylane® Defyne* Galderma Laboratories	These HA-based dermal fillers were approved for the treatment of nasolabial folds or "laugh lines" in patients >21 years of age. Restylane® Refyne was approved for moderate-to-severe facial wrinkles and folds, and Restylane® Defyne was approved for treating moderate-to-severe, deep facial wrinkles and folds.	US FDA

Hemangioma	**Propranolol hydrochloride oral solution 3.75 mg/ml** *Hemangiol®* Pierre Fabre Dermo-Cosmétique	The beta-adrenergic blocker propranolol hydrochloride was approved for the treatment of proliferating infantile hemangioma requiring systemic therapy. Treatment should be initiated in infants 5 weeks to 5 months. Age for treatment initiation should be corrected in case of prematurity.	Health Canada
Hereditary Angioedema	**C1 esterase inhibitor (human) for IV infusion** *Berinert®* CSL Behring	Approved indications of C1 esterase inhibitor (human) broadened to include the treatment of hereditary angioedema (HAE) attacks in pediatric patients. This expands the use of Berinert® into all age groups, making it the first and only approved HAE treatment available to patients <12 years of age.	US FDA
Hidradenitis Suppurativa	**Adalimumab for SC injection** *Humira®* AbbVie Inc.	Adalimumab was approved for the treatment of adults with active moderate to severe hidradenitis suppurativa (HS, acne inversa), who have not responded to conventional therapy (including systemic antibiotics). This follows approval from both the FDA and the European Commission in 2015.	Health Canada
Neuromodulator	**Botulinum toxin type A for injection (IncobotulinumtoxinA)** *Bocouture®* Merz Pharma	This formulation of botulinum toxin type A was approved for the treatment of upper facial lines, including horizontal frown lines, lateral periorbital lines and glabellar frown lines. Bocouture® is the only neurotoxin approved in Europe for the simultaneous treatment of upper facial lines.	European Commission
Psoriasis	**Betamethasone dipropionate 0.05% spray** *Sernivo™* Promius Pharma	Approval was granted to this topical corticosteroid spray formulation containing betamethasone dipropionate 0.05% for the treatment of mild to moderate plaque psoriasis in patients ≥18 years of age.	US FDA
	Calcipotriol + betamethasone dipropionate foam *Enstilar®* Leo Pharma	Scientific approval was granted to this fixed combination of calcipotriol/betamethasone dipropionate 50 micrograms/g / 0.5 mg/g for the treatment of psoriasis vulgaris in patients ≥18 years of age.	European Commission Health Canada
	Brodalumab for SC injection *Lumicef®* Kyowa Hakko Kirin	This fully human anti-interleukin-17 (IL-17) receptor A antibody was approved as a second-line treatment for psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and psoriatic erythroderma.	Japan's Ministry of Health, Labour and Welfare (MHLW)
	Ixekizumab for SC injection *Talz®* Eli Lilly and Company	Ixekizumab was approved for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. This humanized monoclonal antibody specifically targets interleukin (IL)-17A.	European Commission Health Canada US FDA
	Etanercept for SC injection *Enbrel®* Amgen Inc.	A supplemental Biologics License Application (sBLA) was approved for the expanded use of etanercept (Enbrel®), making it the first and only systemic therapy to treat pediatric patients aged 4 to 17 years with chronic moderate-to-severe plaque psoriasis.	US FDA
	Apremilast tablets *Otezla®* Celgene Corporation	This oral selective inhibitor of phosphodiesterase 4 (PDE4) was granted full marketing authorization for the treatment of adults with plaque psoriasis with an inadequate response to topical therapies, as well as adult patients with psoriatic arthritis.	MHLW (Japan)
	Ustekinumab for SC injection *Stelara®* Janssen Inc.	Ustekinumab, a fully human IL-12 and IL-23 antagonist, was approved for the treatment of chronic moderate-to-severe plaque psoriasis in adolescent patients aged 12 to 17 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. This marks the first biologic to gain regulatory approval for the treatment of moderate-to-severe psoriasis in adolescents.	Health Canada
	Adalimumab-atto for SC injection *Amjevita™* Amgen Inc.	The first biosimilar to adalimumab (Humira®), Amjevita™ was approved to treat seven inflammatory diseases, including psoriatic arthritis and moderate-to-severe chronic plaque psoriasis.	US FDA

Psoriasis	**Etanercept-szzs for SC injection** *Erelzi*™ Sandoz Inc., a Novartis division	Erelzi™ (etanercept-szzs), a tumor necrosis factor blocker biosimilar to etanercept (Enbrel®) was approved for all indications included in the reference product label.	US FDA
	Biosimilar of infliximab *Flixabi*® Samsung Bioepis Co.	Flixabi® (also known as SB2), an infliximab biosimilar referencing Remicade®, was approved for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, and ankylosing spondylitis.	European Commission
	Infliximab-dyyb for IV infusion *Inflectra*™ Hospira/Celltrion	Multiple indications were approved for Inflectra™, a biosimilar to infliximab (Remicade®). Approved uses include chronic severe plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.	US FDA
Psoriatic Arthritis	**Brodalumab for SC injection** *Lumicef*® Kyowa Hakko Kirin	This fully human anti-interleukin-17 (IL-17) receptor A antibody was approved as a second-line treatment for psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and psoriatic erythroderma.	MHLW (Japan)
	Secukinumab for SC injection *Cosentyx*® Novartis AG	Expanded approval of secukinumab, a monoclonal antibody that inhibits IL-17A, was granted to include two new indications - the treatment of adult patients with active psoriatic arthritis and active ankylosing spondylitis.	US FDA
	Adalimumab-atto for SC injection *Amjevita*™ Amgen Inc.	The first biosimilar to adalimumab (Humira®), Amjevita™ was approved to treat seven inflammatory diseases, including psoriatic arthritis and moderate-to-severe chronic plaque psoriasis.	US FDA
	Etanercept-szzs for SC injection *Erelzi*™ Sandoz Inc., a Novartis division	Erelzi™ (etanercept-szzs), a tumor necrosis factor blocker biosimilar to etanercept (Enbrel®) was approved for all indications included in the reference product label.	US FDA
	Biosimilar of infliximab *Flixabi*® Samsung Bioepis Co.	Flixabi® (also known as SB2), an infliximab biosimilar referencing Remicade®, was approved for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, and ankylosing spondylitis.	European Commission
	Infliximab-dyyb for IV infusion *Inflectra*™ Hospira/Celltrion	Multiple indications were approved for Inflectra™, a biosimilar to infliximab (Remicade®). Approved uses include chronic severe plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.	US FDA
Urticaria	**Bilastine 20 mg tablet** *Blexten*™ Aralez Pharmaceuticals	Bilastine 20 mg oral tablet was approved for the treatment of symptoms of seasonal allergic rhinitis and chronic spontaneous urticaria (such as itchiness and hives). This is the first new antihistamine introduced in Canada in over 15 years.	Health Canada

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Update on Drugs

Name/Company	Approval Dates/Comments
Oxymetazoline hydrochloride 1% cream *Rhofade*™ Allergan plc.	The US FDA approved oxymetazoline hydrochloride 1% cream in January 2017 for the topical treatment of persistent facial erythema (redness) associated with rosacea in adults. Approval was based on two clinical trials that demonstrated once-daily application of oxymetazoline hydrochloride 1% cream (Rhofade™) reduced persistent facial erythema associated with rosacea through 12 hours. The primary efficacy endpoint was at Day 29 and defined as the proportion of patients with at least a 2-grade reduction in erythema from baseline (pre-dose on day 1) on both the clinician erythema assessment and subject self-assessment measured at hours 3, 6, 9 and 12 vs. vehicle. Rhofade™ was proven to be more efficacious compared with vehicle in reducing persistent facial erythema associated with rosacea in adults.
Brodalumab for SC injection *Siliq*™ Valeant Pharmaceuticals	In February 2017, the FDA approved brodalumab, a monoclonal antibody that targets the interleukin (IL)-17 receptor, for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. Administered as a subcutaneous injection, brodalumab binds to IL-17, inhibiting several pro-inflammatory cytokines from the IL-17 family, which are thought to contribute to the pathophysiology associated with psoriasis. Brodalumab's safety and efficacy were established in three randomized, placebo-controlled clinical trials involving a total of 4,373 adult participants with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy. More patients treated with brodalumab compared to placebo had skin that was clear or almost clear, as assessed by scoring of the extent, nature and severity of psoriatic changes of the skin. Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with brodalumab during clinical trials. Siliq™ users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior compared to patients without this history. A causal association between treatment with brodalumab and increased risk of suicidal ideation and behavior has not been established. Because of the observed risk of suicidal ideation and behavior, the labeling for Siliq™ includes a Boxed Warning and the drug is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Siliq™ REMS Program.
Device News	
Cryolipolysis for upper arm fat reduction *CoolAdvantage*™ *Petite applicator for CoolSculpting®* Zeltiq® Aesthetics, Inc.	In January 2017, the FDA granted clearance to CoolSculpting® for fat reduction of the upper arms with the CoolAdvantage™ Petite applicator. The CoolAdvantage™ Petite treatment comes with two interchangeable contours designed to uniquely treat the upper arm area in 35 minutes. CoolSculpting® is now FDA-cleared for the reduction of localized subcutaneous fat in the submental area, thigh, abdomen, flank, bra and back fat area, underneath the buttocks, and the upper arm.
Wound healing device *WoundShield*™ NanoVibronix	In December 2016, Health Canada granted marketing clearance to the WoundShield™. The WoundShield™ system is a novel, patch-based therapeutic ultrasound device that facilitates soft tissue regeneration and wound healing (for persistent wounds including diabetic foot ulcers), as well as disrupts biofilms and bacteria colonization, by using low-frequency ultrasound waves to increase local capillary perfusion and tissue oxygenation.