J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

27/03/2022

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ולצרכן של התכשיר:

TREMFYA (Guselkumab) 100mg SfI (PFS, PFP)-
160-54-35346-00

המאושר להתוויה הבאה:

Plaque psoriasis
Tremfya is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Psoriatic arthritis
Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

א. השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

4.8 Undesirable effects

[…]

Description of selected adverse reactions

Transaminases Increased

[…]

Based on laboratory assessments, most transaminase increases (ALT and AST) were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency, occurring more often in the Tremfya q4w group compared with the Tremfya q8w group (Table 2). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase III psoriatic arthritis clinical study.

Table 2: Frequency of patients with transaminase increases post-baseline in two Phase III psoriatic arthritis clinical studies

	Through Week 24[a]			Through 1 Year[b]	
	Placebo N=370[c]	Tremfya 100 mg q8w N=373[c]	Tremfya 100 mg q4w N=371[c]	Tremfya 100 mg q8w N=373[c]	Tremfya 100 mg q4w N=371[c]
ALT					
>1 to ≤3 x ULN	30.0%	28.2%	35.0%	33.5%	41.2%
>3 to ≤ 5 x ULN	1.4%	1.1%	2.7%	1.6%	4.6%
>5 x ULN	0.8%	0.8%	1.1%	1.1%	1.1%
AST					
>1 to ≤3 x ULN	20.0%	18.8%	21.6%	22.8%	27.8%
>3 to ≤ 5 x ULN	0.5%	1.6%	1.6%	2.9%	3.8%
>5 x ULN	1.1%	0.5%	1.6%	0.5%	1.6%

[a] placebo-controlled period
[b] patients randomized to placebo ~~Tremfya~~ at baseline and cross over to Tremfya are not included
[c] number of patients with at least one post-baseline assessment for the specific laboratory test within the time period.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

Clinical efficacy and safety
[…]

Psoriatic arthritis (PsA)

DISCOVER 1 and DISCOVER 2
[…]
Signs and symptoms
[…]

Clinical response was maintained up to Week 100 as assessed by ACR 20/50/70, DAS 28 (CRP), MDA, IGA and PASI 90 response rates in DISCOVER 2 (see Table 10).

Table 10: Clinical Responses in DISCOVER 2 at Week 100[a]

	guselkumab 100 mg q8w	guselkumab 100 mg q4w
ACR 20		
N[b]	223	219
% Response	82.1%	84.9%
ACR 50		
N[b]	224	220
% Response	60.7%	62.3%
ACR 70		
N[b]	224	220
% Response	39.3%	38.6%
DAS 28 (CRP) change from baseline		
N[c]	223	219
Mean (SD)	-2.37 (1.215)	-2.36 (1.120)
MDA		
N[b]	224	220
% Response	44.6%	42.7%
Patients with ≥ 3% BSA and IGA ≥ 2 at baseline		
IGA Response		
N[b]	165	170
% Response	76.4%	82.4%
PASI 90		
N[b]	164	170
% Response	75.0%	80.0%

[a] There was no placebo arm beyond Week 24.
[b] Evaluable subjects with an observed response status.
[c] Subjects have an observed change from baseline.

Response over time
[…]
In DISCOVER 2, for subjects receiving continuous guselkumab treatment at week 24, ACR 20 response was maintained from Week 24 to Week 52 (see Figure 6). For subjects receiving continuous guselkumab treatment at week 52, ACR 20 response was maintained from Week 52 to Week 100 (see Figure 7).

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

Figure 6: ACR 20 Response by Visit from Week 24 Through Week 52 in DISCOVER 2

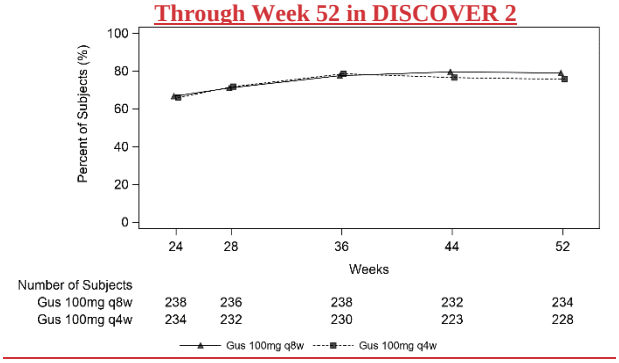
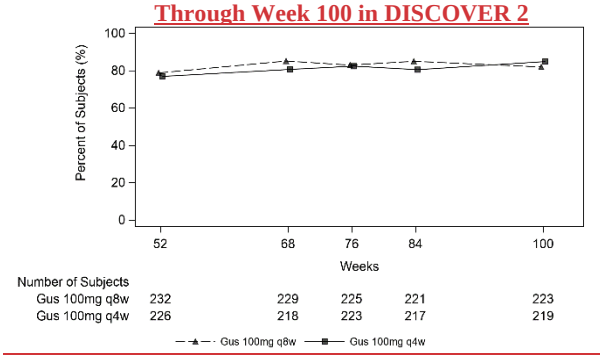
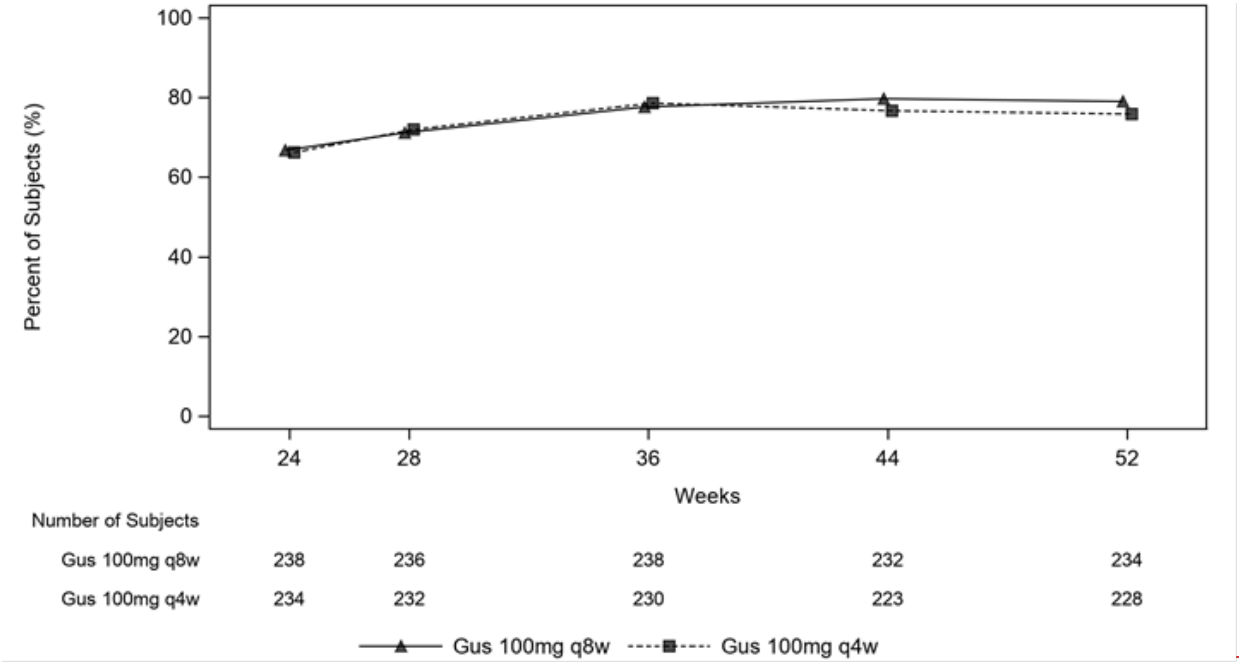


Figure 7: ACR 20 Response by Visit from Week 52 Through Week 100 in DISCOVER 2



~~**Figure 6: ACR 20 Response by Visit Through Week 52 in DISCOVER 2**~~



In DISCOVER 1 and 2, improvements were shown in all components of the ACR scores including patient assessment of pain. At Week 24 in both studies, the proportion of patients achieving a modified PsA response criteria (PsARC) response was greater in the guselkumab groups compared to placebo. PsARC responses were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Dactylitis and enthesitis were assessed based on pooled data from DISCOVER 1 and 2. At Week 24, among patients with dactylitis at baseline, the proportion of subjects with dactylitis resolution was greater in the guselkumab q8w group (59.4%, nominal $p < 0.001$) and q4w group (63.5%, $p = 0.006$) compared to placebo (42.2%). At Week 24, among patients with enthesitis at baseline, the proportion of subjects with enthesitis resolution was greater in the guselkumab q8w group (49.6%, nominal $p < 0.001$) and q4w group (44.9%, $p = 0.006$) compared to placebo (29.4%). At Week 52, the proportions of subjects with dactylitis resolution (81.2% in q8w group and 80.4% in q4w group) and enthesitis resolution (62.7% in q8w group and 60.9% in q4w group) were maintained. In DISCOVER 2, among subjects with dactylitis and enthesitis at baseline, the proportion of patients with dactylitis resolution (91.1% in q8w group and 82.9% in q4w group) and enthesitis resolution (77.5% in q8w group and 67.7% in q4w group) were maintained at Week 100.

In DISCOVER 1 and 2, patients treated with guselkumab who had spondylitis with peripheral arthritis as

their primary presentation, demonstrated greater improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) compared to placebo at Week 24. Improvement in BASDAI was maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Radiographic response
[…]

(Table ~~10~~11). The observed benefit with the guselkumab q4w dosing regimen on inhibition of radiographic progression (ie, smaller mean change from baseline in total modified vdH-S score in the q4w group versus placebo) was most pronounced in subjects with both a high C-reactive protein value and high number of joints with erosions at baseline.

Table ~~10~~11: Change from baseline in total modified vdH-S score at Week 24 in DISCOVER 2

	N	LSMean change[c] (95% CI[d]) from baseline in modified vdH-S score at Week 24
Placebo	246	0.95 (0.61, 1.29)
Guselkumab 100 mg q8w	248	0.52 [a] (0.18, 0.86)
Guselkumab 100 mg q4w	245	0.29 [b] (-0.05, 0.63)

[a] not statistically significant p = 0.068 (major secondary endpoint)
[b] p = 0.006 (major secondary endpoint)
[c] LSmean change = least squares mean change
[d] CI = confidence interval

At Week 52 and Week 100, the mean change from baseline in total modified vdH-S was similar in the guselkumab q8w and q4w groups (Table ~~11~~12).

Table ~~11~~12: Change from baseline in total modified vdH-S score at Week 52 and weel 100 in DISCOVER 2

	N[a]	Mean change (SD[b]) from baseline in total modified vdH-S score
Week 52		
Guselkumab 100 mg q8w	235	0.97 (3.623)
Guselkumab 100 mg q4w	229	1.07 (3.843)
Week 100		
guselkumab 100 mg q8w	216	1.50 (4.393)
guselkumab 100 mg q4w	211	1.68 (7.018)

[a] ~~52 Based on observed data at Week 52~~Evaluable subjects have observed change for the specified time period
[b] SD = standard deviation
Note: no placebo group beyond Week 24

Physical function and health-related quality of life
In DISCOVER 1 and 2, guselkumab treated patients showed significant improvement ($p < 0.001$) in physical function compared to placebo as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24. Improvements in HAQ-DI were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

A significantly greater improvement from baseline in the SF-36 Physical Component Summary (PCS) score was observed in guselkumab treated patients compared to placebo at Week 24 in DISCOVER 1 ($p < 0.001$ for both dose groups) and DISCOVER 2 ($p = 0.006$ for q4w group). At Week 24, a greater increase from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score was observed in guselkumab treated patients compared to placebo in both studies. In DISCOVER 2, greater improvements in health-related quality of life as measured by the Dermatology Life Quality Index (DLQI) were observed in guselkumab treated patients compared to placebo at Week 24.
Improvements in SF-36 PCS, FACIT-F and DLQI scores were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

העלון לרופא/לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפס בפניה אלינו לטלפון 09-9591111.

בברכה,

מירי חזן

רוקחת ממונה