

Rapidity of clinical response to adalimumab and improvement of quality of life in luminal Crohn's disease. RAPIDA study.

Supplementary Material

1. Patient diagnosis and Main Inclusion/Exclusion Criteria

6.3. Main Inclusion criteria

1. Active Crohn's disease with documented clinical symptoms and endoscopic/radiological findings.
2. Crohn's disease diagnosed within at least the previous 4 months.
3. Patients with moderately-to-severely active (Harvey-Bradshaw Index ≥ 8) luminal Crohn's disease.
4. 18 to 75-year-old patients.
5. No response to a complete and adequate course of therapy with a corticosteroid and/or an immunosuppressant.
6. Concomitant treatments for Crohn's disease will be allowed at stable dose.
7. Patient must understand and voluntarily sign an informed consent form prior to the conduct of any study related assessment/procedures.
8. If receiving any of the following treatments, their dose should be stable during the periods indicated:
 - Amino salicylates for, at least, the last 4 weeks
 - Probiotics for, at least, the last 4 weeks
 - Analgesics for, at least, the last 4 weeks
 - Antidiarrheal for, at least, the last 4 weeks
 - CD-related antibiotics for, at least, the last 4 weeks
 - Azathioprine, 6-mercaptopurine or methotrexate for, at least, the last 2 weeks.
9. If receiving any of the following treatments, their dose should not have been increased in the past two weeks (dose reduction is permitted):
 - Oral budesonide (maximum dose of 9 mg/day)

- Oral prednisone or equivalent (maximum dose of 40mg/day)

10. Able to adhere to the study visit schedule and other protocol requirements.

11. Male subjects (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in activity in which conception is possible while on study medication and for at least 28 days after taking the last dose of study medication.

12. Females of Childbearing Potential* (FCBP) must have a negative urine pregnancy test at Screening and Baseline and must be willing to use one medically approved form of birth control when engaging in activity in which conception is possible while on study medication and for at least 28 days after taking the last dose of study medication.

*A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral ovariectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).

6.3. Main Exclusion criteria

A patient **could not** be recruited into this study if any of the following criteria was met:

1. Any formal contraindication for the use of adalimumab described at the medical label.
2. Hypersensitivity to adalimumab or to any of the excipients.
3. Previous treatment with any anti-TNF agent.
4. Suspicion of ulcerative colitis, indeterminate colitis, ischemic colitis, radiation colitis, symptomatic obstructive strictures, diverticular disease-associated colitis as well as microscopic colitis. Evidence of toxic megacolon.
5. Surgical bowel resection within the previous 6 months, ostomy, extensive bowel resection (> 100 cm), short bowel syndrome.
6. Fistulizing Crohn's disease, both perianal fistulae and B3 category.
7. Treatment with any non-marketed drug substance or experimental therapy is prohibited within 30 days or 5 half-lives prior to Baseline (whichever is longer) and during the study.

8. Infection:

- Active infections less than 4 weeks from successful completion of antibiotic treatment for routine bacterial infection
- Febrile viral infection within 4 weeks of entry into the clinical trial
- Less than 12 weeks from conclusion of therapy for systemic fungal infections
- Hospitalized or treated with intravenous antibiotics for an infection within 3 months before screening

9. Treatment with cyclosporine or tacrolimus within the previous 8 weeks.

10. Treatment with NSAIDs within the previous 14 days, except for patients treated with salicylic acid ≤ 100 mg.

11. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months from screening, congestive heart failure of worse than grade II New York criteria (NYHA Functional Classification).

12. Febrile ($> 38^{\circ}\text{C}$).

13. Subject with an ostomy or ileoanal pouch. (Subjects with a previous ileo-rectal anastomosis are not excluded).

14. Presence of a severe bleeding or thrombotic disorder.

15. Anticipated need for surgery within 16 weeks.

16. Known obstructive diseases of the gastrointestinal system: Patients with symptomatic stenosis.

17. Proctocolectomy, total colectomy, ileostomy, stoma or ileal pouch-anal anastomosis.

18. Known infection with enteric pathogens, pathogenic ova or parasites, *C. difficile* toxin or CMV.

19. Received any of the following treatments within 2 years prior to study entry: anti-cancer therapy (e.g. alkylating agents, anti-metabolites, purine analogues used for anti-cancer therapy, monoclonal antibodies for malignancy).

20. Past or current malignancy, except for in situ cervical cancer, non-invasive basal cell and squamous cell skin carcinoma, superficial bladder tumors (Ta and Tis) with a complete response duration of > 10 years.

21. Previous or current systemic autoimmune diseases.
22. Systemic sclerosis.
23. Subjects with signs of latent TB can be included if they have started treatment according to local guidelines at least one month prior to starting investigational therapy. Screening for latent TB infection has to be conducted in accordance with local guidelines.
24. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral psychiatric disease, or evidence of demyelinating disease.
25. History of significant cerebrovascular disease.
26. Subjects with congenital or acquired immunodeficiencies.
27. Known human immunodeficiency virus (HIV) positive.
28. Screening laboratory values (according to central laboratory):
 - Hemoglobin <5.6 mmol/L (9.0 g/dL).
 - Neutrophils <1.5 × 10⁹/L.
 - Leukocytes <3.0 × 10⁹/L.
 - Platelets <100 × 10⁹/L.
 - Alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (ULN).
 - Total bilirubin >2 mg/dL.
 - Aspartate aminotransferase (AST) >1.5 times ULN.
 - Alkaline phosphatase (ALP) >2 times ULN.
 - Creatinine >133 mmol/L (1.5 mg/dL).
29. Known hepatitis C (HC) infection.
30. Serologic evidence of hepatitis B (HB) infection* based on the results of testing for HBsAg, anti-HBc and anti-HBs antibodies as follows:
 - Subjects positive for HBsAg are excluded.
 - Subjects negative for HBsAg but positive for both anti-HBc and anti-HBs antibodies were eligible to participate.
 - Subjects negative for HBsAg and anti-HBc antibody but positive for anti-HBs antibody are eligible to participate.
 - Subjects negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody required clarification of their status by testing for HB DNA which, if

positive, excludes the subject from participation.

*Patients with documented vaccination against hepatitis B (primary and secondary immunization and booster) are considered negative.

31. Receipt of any vaccination (live or attenuated) in 8 weeks prior to baseline.
32. Current participation in any other interventional clinical study.
33. Subjects known or suspected of not being able to comply with a study protocol (e.g. due to alcoholism, drug dependency or psychological disorder).
34. Subjects unable to undergo a radiological examination.
35. Pregnancy and breastfeeding.
36. Any other condition which the principal investigator considers would make the patient unsuitable for study participation.

2. Scheduled visits and procedures

3. Harvey Bradshaw Index score (HBI)¹

Please check one box per number (except for #5)

1. General well-being (yesterday)

- Very well = 0
- Slightly below par = 1
- Poor = 2
- Very poor = 3
- Terrible = 4

2. Abdominal pain (yesterday)

- None = 0
- Mild = 1
- Moderate = 2
- Severe = 3

3. Number of liquid or soft stools per day (yesterday) = _____

4. Abdominal mass

- None = 0
- Dubious = 1
- Definite = 2
- Definite and tender = 3

5. Complications

(check any that apply; score one per item except for first box)

- None
- Arthralgia
- Uveitis
- Erythema nodosum
- Aphthous ulcers
- Pyoderma gangrenosum
- Anal fissure
- New fistula
- Abscess

Please add scores of questions 1 through 5:

Remission <5

Mild disease 5-7

Moderate disease 8-16

Severe disease >16

¹Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet*. 1980;315(8167):514. 2. British Columbia Ministry of Health Services. Worksheet based on the Harvey-Bradshaw

4. Baseline anthropometric measures and vital signs

	N	Mean (SD)	Median [Q1 , Q3]	Min , Max
Weight (kg)	85	69.30 (14.20)	67.85 [58.10 , 77.20]	36.50 , 102.00
Height (cm)	82	167.83 (8.75)	168.0 [161.0 , 174.0]	150.00 , 186.00
BMI (kg/m ²)	82	24.57 (4.42)	24.35 [20.96 , 27.64]	15.59 , 36.64
Temperature (°C)	82	36.02 (0.48)	36.0 [35.90 , 36.30]	34.00 , 36.90
Systolic Blood Pressure (mmHg)	86	116.67 (15.06)	113.0 [108.0 , 124.0]	91.00 , 179.00
Diastolic Blood Pressure (mmHg)	86	70.07 (11.85)	68.50 [62.0 , 76.0]	45.00 , 116.00
Respiratory Rate (bpm)	81	17.02 (3.01)	18.0 [15.0 , 19.0]	10.00 , 30.00
Heart Rate (bpm)	86	73.08 (11.13)	71.50 [65.0 , 80.0]	50.00 , 106.00

5. Harvey-Bradshaw scores during the study (ITT population)

	BL	W1	W2	W4	W12
N	85	84	83	78	73
Mean (SD)	9.32 (1.63)	4.81 (3.22)	4.31 (3.23)	3.45 (2.89)	3.42 (2.95)
Median	9.0	4.0	4.0	3.0	3.0
Q1, Q3	8.0 , 10.0	3.0 , 7.0	2.0 , 6.0	1.0 , 5.0	1.0 , 5.0
Min, max	6.0 , 17.0	0.0 , 17.0	0.0 , 12.0	0.0 , 16.0	0.0 , 16.0

BL, baseline; D, day; W, week.

6. Scores in Quality of Life measurements during the study (ITT population)

6.3. EuroQoL-5D

Index Score						
	BL	D4	W1	W2	W4	W12
N	84	84	81	79	79	71
Mean (SD)	0.62 (0.22)	0.69 (0.19)	0.70 (0.20)	0.74 (0.20)	0.76 (0.21)	0.76 (0.23)
Median	0.68	0.74	0.74	0.74	0.79	0.79
Q1, Q3	0.47 , 0.74	0.59 , 0.79	0.59 , 0.79	0.59 , 1.0	0.68 , 1.0	0.65 , 1.0
Min, Max	0.01 , 1.0	0.12 , 1.0	0.03 , 1.0	0.23 , 1.0	0.03 , 1.0	0.07 , 1.0

BL, baseline; D, day; W, week.

Visual Analogue Scale (VAS)						
	BL	D4	W1	W2	W4	W12
N	85	83	83	82	79	73
Mean (SD)	55.36 (18.52)	60.36 (18.61)	62.84 (18.90)	65.07 (19.34)	68.62 (20.72)	71.0 (22.42)
Median	55.0	60.0	60.0	66.0	70.0	72.0
Q1, Q3	40.0 , 70.0	50.0 , 70.0	50.0 , 80.0	50.0 , 80.0	58.0 , 87.0	54.0 , 90.0
Min, Max	15.0 , 94.0	9.0 , 100.0	15.0 , 100.0	15.0 , 100.0	16.0 , 100.0	15.0 , 100.0

BL, baseline; D, day; W, week.

6.3. Inflammatory Bowel Disease Questionnaire IBDQ-36

Global	BL	D4	W1	W2	W4	W12
N	78	75	76	74	73	68
Mean (SD)	145.15 (35.83)	161.95 (35.86)	171.86 (35.96)	180.35 (35.79)	191.51 (38.35)	191.53 (46.20)
Median	142.50	158.0	170.0	184.50	198.0	201.0
Q1, Q3	118.0 , 170.0	135.0 , 188.0	147.0 , 197.5	156.0 , 208.0	173.0 , 224.0	164.0 , 230.5
Bowel symptoms						
N	78	75	76	74	73	68
Mean (SD)	31.56 (8.16)	35.77 (7.86)	38.04 (8.57)	40.43 (8.44)	42.59 (8.62)	43.12 (10.10)
Median	30.50	35.0	37.0	41.0	45.0	45.0
Q1, Q3	25.0 , 38.0	30.0 , 42.0	31.0 , 45.0	34.0 , 46.0	39.0 , 49.0	37.0 , 51.0
Min, Max	17.0 , 53.0	19.0 , 54.0	16.0 , 56.0	18.0 , 56.0	18.0 , 55.0	15.0 , 56.0
Systemic symptoms						
N	78	75	76	74	73	68
Mean (SD)	27.19 (6.87)	30.24 (6.97)	31.78 (7.52)	33.28 (7.23)	34.82 (8.38)	35.43 (9.71)
Median	26.50	30.0	32.50	34.0	37.0	37.50
Q1, Q3	22.0 , 31.0	25.0 , 35.0	27.0 , 38.0	28.0 , 39.0	30.0 , 42.0	30.0 , 45.0
Min, Max	15.0 , 44.0	16.0 , 47.0	16.0 , 49.0	16.0 , 49.0	17.0 , 46.0	13.0 , 49.0
Emotional function						
N	78	75	76	74	73	68
Mean (SD)	31.68 (10.42)	33.81 (10.67)	36.82 (10.06)	38.80 (10.02)	41.70 (10.05)	41.44 (11.91)
Median	32.0	33.0	37.0	38.50	44.0	45.50
Q1, Q3	23.0 , 40.0	25.0 , 42.0	29.0 , 42.0	33.0 , 46.0	34.0 , 49.0	33.0 , 51.0
Min, Max	8.0 , 53.0	14.0 , 56.0	17.0 , 56.0	17.0 , 56.0	20.0 , 56.0	16.0 , 56.0
Functional impairment						
N	78	75	76	74	73	68
Mean (SD)	26.44 (9.43)	31.16 (9.69)	32.93 (9.41)	34.76 (9.59)	37.64 (9.77)	37.38 (10.78)
Median	27.0	31.0	33.0	37.0	40.0	41.0
Q1, Q3	21.0 , 33.0	25.0 , 40.0	28.0 , 42.0	28.0 , 43.0	31.0 , 45.0	30.0 , 45.0
Min, Max	9.0 , 48.0	11.0 , 48.0	9.0 , 47.0	8.0 , 49.0	8.0 , 49.0	12.0 , 49.0

Global	BL	D4	W1	W2	W4	W12
Social impairment						
N	78	75	76	74	73	68
Mean (SD)	28.28 (7.43)	30.96 (6.90)	32.29 (6.49)	33.08 (5.94)	34.75 (6.40)	34.16 (7.08)
Median	29.0	32.0	32.50	34.0	36.0	36.0
Q1, Q3	23.0 , 35.0	26.0 , 37.0	27.0 , 37.50	29.0 , 38.0	32.0 , 39.0	32.0 , 40.0
Min, Max	14.0 , 42.0	15.0 , 42.0	16.0 , 42.0	19.0 , 42.0	11.0 , 42.0	11.0 , 42.0

BL, baseline; D, day; W, week.

6.3. Daily Fatigue impairment scale (ITT population)

N (%)	BL	D4	W1	W2	W4	W12
Overall score						
N	83	81	80	81	76	70
Mean (SD)	14.51 (8.40)	12.17 (7.98)	11.20 (8.33)	10.41 (7.98)	8.76 (8.50)	8.47 (9.06)
Median	15.00	11.00	9.00	9.00	5.50	4.50
Q1, Q3	7.00 , 21.00	6.00 , 18.00	5.00 , 16.00	4.00 , 16.00	2.00 , 15.00	1.00 , 14.00
Min, Max	0.00 , 32.00	0.00 , 31.00	0.00 , 31.00	0.00 , 31.00	0.00 , 32.00	0.00 , 32.00
I feel less alert						
No problem	14 (16.28)	17 (19.77)	22 (25.58)	32 (37.21)	37 (43.02)	21 (24.42)
Small problem	18 (20.93)	23 (26.74)	31 (36.05)	22 (25.58)	13 (15.12)	26 (30.23)
Moderate problem	27 (31.40)	29 (33.72)	18 (20.93)	16 (18.60)	14 (16.28)	23 (26.74)
Big problem	21 (24.42)	14 (16.28)	9 (10.47)	4 (4.65)	6 (6.98)	11 (12.79)
Extreme problem	5 (5.81)	1 (1.16)	2 (2.33)	4 (4.65)	3 (3.49)	3 (3.49)
I have to reduce my workload or responsibilities						
No problem	17 (19.77)	15 (17.44)	21 (24.42)	28 (32.56)	30 (34.88)	22 (25.58)
Small problem	17 (19.77)	26 (30.23)	25 (29.07)	22 (25.58)	18 (20.93)	25 (29.07)
Moderate problem	14 (16.28)	23 (26.74)	18 (20.93)	15 (17.44)	13 (15.12)	18 (20.93)
Big problem	24 (27.91)	11 (12.79)	13 (15.12)	8 (9.30)	7 (8.14)	9 (10.47)
Extreme problem	12 (13.95)	8 (9.30)	5 (5.81)	5 (5.81)	5 (5.81)	8 (9.30)
I am less motivated to do anything that requires physical effort						
No problem	7 (8.14)	12 (13.95)	18 (20.93)	22 (25.58)	32 (37.21)	14 (16.28)
Small problem	14 (16.28)	20 (23.26)	24 (27.91)	23 (26.74)	18 (20.93)	29 (33.72)
Moderate problem	24 (27.91)	24 (27.91)	21 (24.42)	13 (15.12)	9 (10.47)	19 (22.09)
Big problem	30 (34.88)	22 (25.58)	17 (19.77)	14 (16.28)	10 (11.63)	17 (19.77)
Extreme problem	10 (11.63)	5 (5.81)	2 (2.33)	4 (4.65)	4 (4.65)	4 (4.65)
I have trouble maintaining physical effort for long periods						
No problem	9 (10.47)	10 (11.63)	13 (15.12)	22 (25.58)	22 (25.58)	11 (12.79)
Small problem	11 (12.79)	20 (23.26)	25 (29.07)	24 (27.91)	20 (23.26)	25 (29.07)
Moderate problem	19 (22.09)	23 (26.74)	19 (22.09)	13 (15.12)	13 (15.12)	15 (17.44)
Big problem	30 (34.88)	23 (26.74)	18 (20.93)	14 (16.28)	11 (12.79)	22 (25.58)
Extreme problem	16 (18.60)	8 (9.30)	7 (8.14)	6 (6.98)	7 (8.14)	11 (12.79)
I find it difficult to make decisions						
No problem	34 (39.53)	36 (41.86)	43 (50.00)	50 (58.14)	43 (50.00)	41 (47.67)
Small problem	16 (18.60)	19 (22.09)	17 (19.77)	13 (15.12)	16 (18.60)	21 (24.42)
Moderate problem	20 (23.26)	19 (22.09)	14 (16.28)	9 (10.47)	6 (6.98)	14 (16.28)

Big problem	13 (15.12)	6 (6.98)	5 (5.81)	3 (3.49)	6 (6.98)	6 (6.98)
Extreme problem	2 (2.33)	3 (3.49)	2 (2.33)	3 (3.49)	1 (1.16)	2 (2.33)
I am less able to finish tasks that require thinking						
No problem	28 (32.56)	33 (38.37)	40 (46.51)	45 (52.33)	41 (47.67)	36 (41.86)
Small problem	16 (18.60)	20 (23.26)	17 (19.77)	15 (17.44)	15 (17.44)	24 (27.91)
Moderate problem	26 (30.23)	20 (23.26)	18 (20.93)	10 (11.63)	6 (6.98)	12 (13.95)
Big problem	12 (13.95)	9 (10.47)	5 (5.81)	4 (4.65)	8 (9.30)	9 (10.47)
Extreme problem	3 (3.49)	2 (2.33)	2 (2.33)	4 (4.65)	3 (3.49)	3 (3.49)
I feel slowed down in my thinking						
No problem	30 (34.88)	35 (40.70)	41 (47.67)	45 (52.33)	41 (47.67)	36 (41.86)
Small problem	15 (17.44)	21 (24.42)	18 (20.93)	17 (19.77)	16 (18.60)	21 (24.42)
Moderate problem	24 (27.91)	15 (17.44)	14 (16.28)	6 (6.98)	5 (5.81)	13 (15.12)
Big problem	11 (12.79)	9 (10.47)	7 (8.14)	7 (8.14)	5 (5.81)	10 (11.63)
Extreme problem	5 (5.81)	4 (4.65)	2 (2.33)	3 (3.49)	4 (4.65)	3 (3.49)
I have to limit my physical activities						
No problem	10 (11.63)	12 (13.95)	16 (18.60)	23 (26.74)	23 (26.74)	14 (16.28)
Small problem	14 (16.28)	24 (27.91)	25 (29.07)	22 (25.58)	20 (23.26)	27 (31.40)
Moderate problem	22 (25.58)	22 (25.58)	22 (25.58)	15 (17.44)	12 (13.95)	15 (17.44)
Big problem	23 (26.74)	16 (18.60)	12 (13.95)	11 (12.79)	11 (12.79)	17 (19.77)
Extreme problem	15 (17.44)	10 (11.63)	7 (8.14)	7 (8.14)	6 (6.98)	11 (12.79)

BL, baseline; D, day; W, week.

7. Safety data

7.1. Report of all adverse events by patient

SOC term	Preferred Term	Mild		Moderate		Severe	
		N	%	N	%	N	%
Blood and lymphatic system disorders	Anemia	1	1.16	-	-	-	-
Ear and labyrinth disorders	Ear pain	1	1.16	-	-	-	-
Eye disorders	Eyelid disorder	1	1.16	-	-	-	-
	Lacrimation increased	1	1.16	-	-	-	-
	Presbyopia	1	1.16	-	-	-	-
Gastrointestinal disorders	Abdominal mass	3	3.49	-	-	-	-
	Abdominal pain	3	3.49	-	-	-	-
	Aphthous ulcer	2	2.33	-	-	-	-
	Crohn's disease	-	-	1	1.16	1	1.16
	Diarrhea	3	3.49	-	-	-	-
	Hemorrhoids	1	1.16	-	-	-	-
	Subileus	1	1.16	-	-	-	-
	Vomiting	4	4.65	-	-	-	-
General disorders and administration site conditions	Asthenia	2	2.33	-	-	-	-
	Fatigue	1	1.16	-	-	-	-
	General physical health deterioration	-	-	1	1.16	-	-
	Pyrexia	2	2.33	1	1.16	-	-
Immune system disorders	Drug hypersensitivity	-	-	1	1.16	-	-
Infections and infestations	Cellulitis	-	-	1	1.16	-	-

SOC term	Preferred Term	Mild		Moderate		Severe	
		N	%	N	%	N	%
	Conjunctivitis	1	1.16	-	-	-	-
	Cystitis	1	1.16	-	-	-	-
	Folliculitis	1	1.16	-	-	-	-
	Herpes virus infection	2	2.33	-	-	-	-
	Influenza	4	4.65	-	-	-	-
	Nasopharyngitis	1	1.16	-	-	-	-
	Pharyngitis	3	3.49	-	-	-	-
	Pharyngotonsillitis	1	1.16	-	-	-	-
	Pneumonia	1	1.16	-	-	-	-
	Rash pustular	1	1.16	-	-	-	-
	Respiratory tract infection	2	2.33	-	-	-	-
	Rotavirus infection	1	1.16	-	-	-	-
	Tooth infection	1	1.16	-	-	-	-
	Urinary tract infection	-	-	1	1.16	-	-
Investigations	Blood triglycerides increased	1	1.16	-	-	-	-
	Transaminases increased	1	1.16	-	-	-	-
	Weight decreased	1	1.16	-	-	-	-
Musculoskeletal and connective tissue disorders	Arthralgia	2	2.33	1	1.16	-	-
	Arthritis	-	-	1	1.16	-	-
	Flank pain	1	1.16	-	-	-	-
	Muscular weakness	1	1.16	-	-	-	-
	Sacroiliitis	1	1.16	-	-	-	-
Nervous system disorders	Headache	1	1.16	-	-	-	-
	Migraine	-	-	1	1.16	-	-
Psychiatric disorders	Anxiety	-	-	1	1.16	-	-
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1	1.16	-	-	-	-
Skin and subcutaneous tissue disorders	Alopecia	2	2.33	-	-	-	-
	Eczema	1	1.16	-	-	-	-
	Erythema	1	1.16	-	-	-	-
	Psoriasis	-	-	2	2.33	-	-
	Rash	1	1.16	-	-	-	-
	Skin lesion	1	1.16	-	-	-	-
Vascular disorders	Hypertension	1	1.16	-	-	-	-