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### Additional file 3: Detailed adverse event outcomes in each trial

**GI-related:**
- Placebo 17/219 (2.5%)
- Cele 0/73 (0%)
- Naprox 12/216 (5.6%)

**Serious CV:**
- Placebo 4/219 (2%)
- Cele 1/218 (0.5%)
- Naprox 6/216 (2.8%)

**GI Haemorrhage:**
- Placebo 2/219 (1.4%)
- Cele 0/217 (0.5%)
- Naprox 12/216 (5.6%)

**Diabetes:**
- Placebo 2/219 (1.4%)
- Cele 0/217 (0.5%)
- Naprox 6/216 (2.8%)

**Hypertension:**
- Placebo 4/219 (2%)
- Cele 1/218 (0.5%)
- Naprox 6/216 (2.8%)

**Heart failure:**
- Placebo 2/219 (1.4%)
- Cele 1/218 (0.5%)
- Naprox 6/216 (2.8%)

**Peripheral vascular disease:**
- Placebo 1/219 (0.5%)
- Cele 0/217 (0.5%)
- Naprox 6/216 (2.8%)

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### Double dummy design

- **Participants:** 1,000 patients with OA
- **Duration:** 24 weeks
- **Randomization:** 2:1
- **Placebo group:** 12 patients with OA

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#### Treatment groups

- **Active A:** Celecoxib 100mg/day
- **Active B:** Celecoxib 200mg/day

#### Placebo group

- **Placebo:** Placebo

#### Assessments

- **Baseline:** 0 weeks
- **Follow-up:** 6 weeks, 12 weeks

#### Efficacy Measures

- **Primary Outcome:** Pain intensity

#### Safety Measures

- **Adverse Events:** Diarrhea, nausea, abdominal pain

#### Other

- **Double dummy washout:** 2 weeks
- **Randomization:** 2:1

---

### Double dummy washout

- **Duration:** 2 weeks
- **Participants:** 1,000 patients with OA

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#### Efficacy Measures

- **Primary Outcome:** Pain intensity

#### Safety Measures

- **Adverse Events:** Diarrhea, nausea, abdominal pain

#### Other

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### Double dummy washout

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### Double dummy washout

- **Duration:** 2 weeks
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- **Follow-up:** 6 weeks, 12 weeks

#### Efficacy Measures

- **Primary Outcome:** Pain intensity

#### Safety Measures

- **Adverse Events:** Diarrhea, nausea, abdominal pain

#### Other

- **Double dummy washout:** 2 weeks
- **Randomization:** 2:1

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### Double dummy washout

- **Duration:** 2 weeks
- **Participants:** 1,000 patients with OA

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#### Assessments

- **Baseline:** 0 weeks
- **Follow-up:** 6 weeks, 12 weeks

#### Efficacy Measures

- **Primary Outcome:** Pain intensity

#### Safety Measures

- **Adverse Events:** Diarrhea, nausea, abdominal pain

#### Other

- **Double dummy washout:** 2 weeks
- **Randomization:** 2:1
### Study Design

- **Objective:** Evaluate the efficacy and safety of investigational drug (ID) vs. placebo in OA/RA patients.
- **Duration:** 12 weeks for washout and 6 months for treatment.
- **Randomization:** Double dummy method.

### Patient Population

- **Inclusion Criteria:** ≥ 18 years, OA/RA, treatment-naive or ≥ 6 months off NSAID.
- **Exclusion Criteria:** Major comorbidities, etc.

### Treatment Groups

- **ID (n=330):**
  - Diclofenac: 2x100mg/day
  - Celecoxib: 2x200mg/day
- **Placebo (n=221):**
  - Naproxen: 2x200mg/day

### Assessments

- **Baseline:** Demographic, clinical data.
- **30 days:** Washout period.
- **6 months:** Weekly assessments up to washout and monthly thereafter.

### Outcomes

#### Primary Outcome

- **Clinical:** Disease activity scores, pain intensity.

#### Secondary Outcomes

- **Safety:** Adverse events, laboratory values, vital signs.

### Adverse Events

- **GI Ulcers:** Diclofenac: 27/387, Celecoxib: 2208/3987, Placebo: 2/221.
- **GI-related:** Diclofenac: 35/387, Celecoxib: 22/365, Placebo: 1/345.
- **Serious:** Diclofenac: 92/327, Celecoxib: 118/326, Placebo: 12/221.

### Laboratory Changes

- **Creatinine:** ≥ 1.3xULN: Diclofenac: 33/1996, Celecoxib: 4/3701, Placebo: 0/221.
- **Hb:** ≥ 5% decrease: Diclofenac: 97/329, Celecoxib: 28/365, Placebo: 0/221.

### Conclusion

The study concluded that ID was superior to placebo in terms of efficacy and safety in OA/RA patients, with minimal risk of serious or GI-related adverse events.

### References

- OA/RA: Osteoarthritis and rheumatoid arthritis.
- ULN: Upper limit of normal.
- CHF: Congestive heart failure.
- MI: Myocardial infarction.
OA/RA (Documented), requiring NSAID
12 weeks
OA/RA (Documented), requiring NSAID
12 weeks
OA/RA (Documented), requiring NSAID
12 weeks

Assessment at baseline, 4, 8, 12 weeks
Assessment at baseline, 4, 8, 12 weeks
Assessment at baseline, 4, 8, 12 weeks

Endoscopy at baseline and 12 weeks
Endoscopy at baseline and 12 weeks
Endoscopy at baseline and 12 weeks

Double dummy method
Double dummy method
Double dummy method

Washout ≥ 30 days
Washout ≥ 30 days
Washout ≥ 30 days

Cele 2x100mg/day (n=63)
Cele 2x100mg/day (n=63)
Cele 2x100mg/day (n=63)

Diclo 2x50mg/day (n=61)
Diclo 2x50mg/day (n=61)
Diclo 2x50mg/day (n=61)

Cele 7/63
Cele 7/63
Cele 7/63

Diclo 11/61
Diclo 11/61
Diclo 11/61

Cele 1/63
Cele 1/63
Cele 1/63

Diclo 4/61
Diclo 4/61
Diclo 4/61

GI-related:
GI-related:
GI-related:

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 3/61
Diclo 3/61
Diclo 3/61

Any:
Any:
Any:

Cele 29/63
Cele 29/63
Cele 29/63

Diclo 37/61
Diclo 37/61
Diclo 37/61

GI-related:
GI-related:
GI-related:

Cele 9/63
Cele 9/63
Cele 9/63

Diclo 17/61
Diclo 17/61
Diclo 17/61

Serious:
Serious:
Serious:

Cele 2/63
Cele 2/63
Cele 2/63

Diclo 1/61
Diclo 1/61
Diclo 1/61

Serious UGI:
Serious UGI:
Serious UGI:

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 0/61
Diclo 0/61
Diclo 0/61

Dyspepsia:
Dyspepsia:
Dyspepsia:

None reported
None reported
None reported

Abdominal pain:
Abdominal pain:
Abdominal pain:

Cele 6/63
Cele 6/63
Cele 6/63

Diclo 10/61
Diclo 10/61
Diclo 10/61

Nausea:
Nausea:
Nausea:

Cele 2/63
Cele 2/63
Cele 2/63

Diclo 1/61
Diclo 1/61
Diclo 1/61

Diarrhoea:
Diarrhoea:
Diarrhoea:

Cele 2/63
Cele 2/63
Cele 2/63

Diclo 3/61
Diclo 3/61
Diclo 3/61

Vomiting:
Vomiting:
Vomiting:

None reported
None reported
None reported

Haemorrhagic gastric ulcer:
Haemorrhagic gastric ulcer:
Haemorrhagic gastric ulcer:

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 1/61
Diclo 1/61
Diclo 1/61

Mod/severe abdominal pain, nausea, dyspepsia:
Mod/severe abdominal pain, nausea, dyspepsia:
Mod/severe abdominal pain, nausea, dyspepsia:

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 2/61
Diclo 2/61
Diclo 2/61

"Mod/severe GI related":
"Mod/severe GI related":
"Mod/severe GI related":

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 6/61
Diclo 6/61
Diclo 6/61

Facial oedema:
Facial oedema:
Facial oedema:

Cele 2/63
Cele 2/63
Cele 2/63

Diclo 0/61
Diclo 0/61
Diclo 0/61

Peripheral oedema:
Peripheral oedema:
Peripheral oedema:

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 3/61
Diclo 3/61
Diclo 3/61

No reports of hypertension or CHF
No reports of hypertension or CHF
No reports of hypertension or CHF

Hct ≥ 5% decrease:
Hct ≥ 5% decrease:
Hct ≥ 5% decrease:

Cele 2/63
Cele 2/63
Cele 2/63

Diclo 2/61
Diclo 2/61
Diclo 2/61

Hb ≥ 20 g/L decrease:
Hb ≥ 20 g/L decrease:
Hb ≥ 20 g/L decrease:

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 0/61
Diclo 0/61
Diclo 0/61

Creatinine ≥ 1.3xULN:
Creatinine ≥ 1.3xULN:
Creatinine ≥ 1.3xULN:

Cele 0/63
Cele 0/63
Cele 0/63

Diclo 0/61
Diclo 0/61
Diclo 0/61

Cele 2/63
Cele 2/63
Cele 2/63

Diclo 13/44
Diclo 13/44
Diclo 13/44

Cele 7/44
Cele 7/44
Cele 7/44

Diclo 13/44
Diclo 13/44
Diclo 13/44

Abdom = abdominal; ACR = American College of Rheumatology; AE = adverse event; BP = blood pressure; Cele = celecoxib; CF = cardiac failure; CHF = chronic heart failure; Clin = clinically; CV = cardiovascular; Diclo = diclofenac; GI = gastrointestinal; GIH = gastrointestinal haemorrhage; GIH = gastrointestinal haemorrhage; Hct = haematocrit; Hb = haemoglobin; Ice = icepack; I.p. = intraperitoneal; I.v. = intravenous; IV = intravenous; K-L = Kellgren-Lawrence; Loxo = loxoprofen; MI = myocardial infarction; Mod = moderate; Nap = naproxen; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; Para = paracetamol; Plac = placebo; Plaq = plaquenil; Peripheral = peripher; Plav = plavix; QoL = quality of life; Rofe = rofecoxib; sig = significant; Trad = traditional; VAS = visual analogue scale; VS = validity score.