D2d Safety Review

November 17, 2014

Safety Planning and Monitoring

Minimizing Risk Prior to Enrollment

* Inclusion/exclusion criteria
  * Medical history
  * Laboratory evaluation

Minimizing Risk: Screening

2052 Screened

879 did not meet eligibility criteria

- 711 Did not meet pre-diabetes criteria
- 33 Ineligible age or BMI
- 23 Vitamin D supplement use
- 40 Abnormal labs
  - 16 High serum Ca, 3 high urine Ca/Cr
  - 7 Low GFR, 14 Anemia
  - 3 Abnormal liver test
- 72 Other

As of 10/15/2014

Minimizing Risk: Safety monitoring

Algorithm for monitoring serum calcium

Exclude Ca ≥ ULN at screening → 16
Enrolled mean 9.5 mg/dl
Assess M03, M12, yearly, end of study
M03, n=383, mean 9.4 mg/dl
381 Ca ≤ ULN, 2 > ULN but ≤ ULN + 1, 0 > ULN + 1
Query those 2: Ca intake, HCTZ use, rpt in 6 wks
1 pending
1 repeat Ca lower
if repeat is high: d/c study pills, refer to HCP, no unmasking, continue to follow in study
n = 382 continuing in study per protocol

Minimizing Risk: Safety monitoring

Algorithm for monitoring serum creatinine and GFR

Exclude GFR < 50 ml/min at screening → 7
Enrolled mean 88.2 ml/min
Assess M03, M12, yearly, end of study
M03, n=383, mean 85.5 ml/min
383 GFR ≥ 40 ml/min
if lower, repeat within 4 weeks
if ≤ 30 ml/min → d/c study pills, refer to HCP, no unmasking, continue to follow pt in study
n = 383 continuing in study per protocol

Minimizing Risk: Safety monitoring

Algorithm for monitoring urine Ca/creatinine ratio

Exclude Ca/creat > 0.275 → exclude 3
Enrolled mean 0.083
Assess M03, M12, yearly, end of study
M03, n=381, mean 0.088
379 with ratio ≤ 0.375, 2 with ratio > 0.375
query the 2: Ca intake, Ca supplements, repeat within 4 weeks
→ both ≤ 0.375 on repeat
(if still high → d/c study pills, refer to HCP, no unmasking, continue to follow in study)
n = 381 continuing in study per protocol

Minimizing Risk: During Participation

Adverse event monitoring → safety signals/trends

Adverse event → serious vs. nonserious?

Standard event assessment:

unexpected in nature, severity, frequency?
possibly, probably, definitely related?
participants at increased risk of harm?
all 3 (+) = <u>unanticipated problem (UAP)</u>

UAP: asap → EDC, document in 2 business days

Non-UAP: → EDC, routine report as IRB requires

Adverse Events

AEs among randomized	All AEs	Onset p randomized
Subjects with AEs - n (%)	117 (5)	84 (14)
AEs in randomized, n	183[1]	131
Post-OGTT Intolerance (malaise, diarrhea, tremor)	1	0
Emesis during OGTT	1	0
Vasovagal in OGTT	1	0
Headache in OGTT	1	0
Kidney stone	1	1
(all considered “expected”)		

*As of 10/15/2014

Serious Adverse Events

- **Zero unanticipated problems (UAPs)**
- **Seven SAEs, six began post-randomization**
  - None (0) were classified as possibly, probably or definitely related to study; all unexpected
  - All classified as serious because of hospitalization
- **Post randomization events:**
  1. Urinary tract infection (1)
  2. Congestive heart failure (1)
  3. Bowel perforation (during colonoscopy) (1)
  4. Acute pancreatitis (1)
  5. Hip pain, arthroplasty (1)
  6. Heat exhaustion (1)

*As of 10/15/2014